# Synthesis of 2-Arylquinolin-4(1*H*)-ones and Their Transformation to *N*-Alkylated and *O*-Alkylated Derivatives



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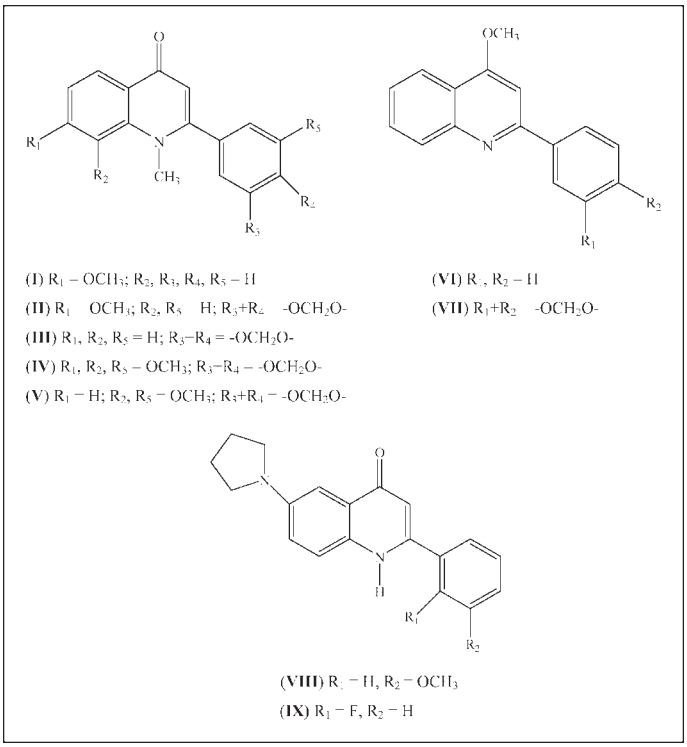


2-Aryl-4-quinolones are versatile synthetic intermediates and several articles continue to appear in literature describing their synthesis, chemical transformation, structural properties, and biological activities. Their versatility as synthetic intermediates is a consequence of 4-quinolone moiety, which contains several reactive centers (positions 1, 3, and 4) for possible functionalization and can also enable different degree of unsaturation. In this review, we describe methods developed to-date for the synthesis of 2-arylquinolin-4(1*H*)-ones and their *N*-alkylated and *O*-alkylated derivatives.

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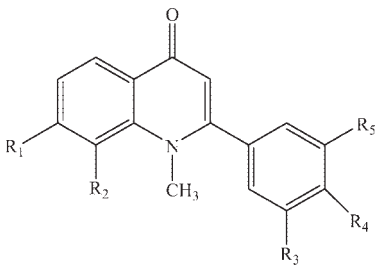
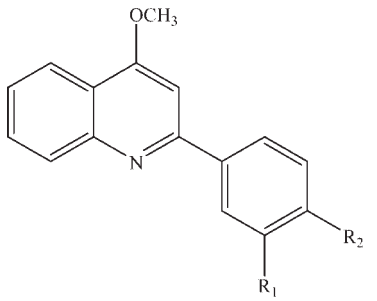
**Contents**

## 1. INTRODUCTION

2-Aryl-4-quinolone moiety constitutes important chemical unit in a large variety of naturally occurring compounds and it plays an extremely important role in synthetic and medicinal chemistry. Most of the 2-aryl-4-quinolones and their 2-arylquinoline derivatives are widely distributed in the plant family *Rutaceae*. Eduleine or 7-methoxy-1-methyl-2-phenylquinolin-4(1*H*)-one (**I**) ($R_1$ = $OCH_3$; $R_2$, $R_3$, $R_4$, $R_5$ = H), for example, was first isolated from the bark of the Mexican tree *Casimiroa edulis* [1] and the bark of *Lunasia quercifolia* (Warb) [2]. Eduleine and its 4-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)quinolin-4(1*H*)-one analogue (**II**) ($R_1$ = $OCH_3$; $R_2$, $R_5$ = H; $R_3$+$R_4$ = —$OCH_2O$—) were also isolated from the leaves of *Lunasia amara* Blanco of the Philippine origin [2]. Graveoline (**III**) ($R_1$, $R_2$, $R_5$ = H; $R_3$+$R_4$ = —$OCH_2O$—), on the other hand, was first isolated from *Ruta graveolens* and its substituted derivatives methoxygraveoline (**IV**) ($R_1$, $R_2$, $R_5$ = $OCH_3$; $R_3$+$R_4$ = —$OCH_2O$—) and 3,8-dimethoxygraveoline (**V**) (R = R′ = OMe) were isolated from the roots of the Brazilian plant *Esenbeckia grandiflora* [3]. The isomeric 4-methoxy-2-phenylquinoline (**VI**) ($R_1$, $R_2$ = H) and its 4-methoxy-2-(3,4-methylenedioxyphenyl)quinoline analogue (**VII**) ($R_1$+$R_2$ = —$OCH_2O$—) were also isolated from the leaves of *Lunasia amara* Blanco [2].



(**I**) $R_1 = OCH_3$; $R_2, R_3, R_4, R_5 = H$
(**II**) $R_1 = OCH_3$; $R_2, R_5 = H$; $R_3+R_4 = OCH_2O$—
(**III**) $R_1$, $R_2$, $R_5$ = H; $R_3+R_4$ = —$OCH_2O$—
(**IV**) $R_1$, $R_2$, $R_5$ = $OCH_3$; $R_3+R_4$ = —$OCH_2O$—
(**V**) $R_1 = H$; $R_2, R_5 = OCH_3$; $R_3+R_4 = $—$OCH_2O$—



(**VI**) $R_1$, $R_2$ = H
(**VII**) $R_1+R_2$ = —$OCH_2O$—

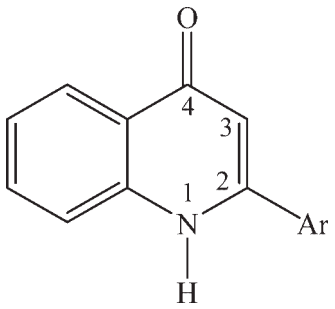
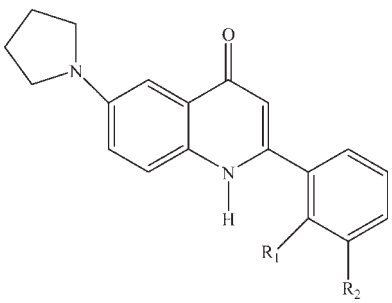


**Figure 1.** Generalized structure of 2-arylquinolin-4(1*H*)-one.

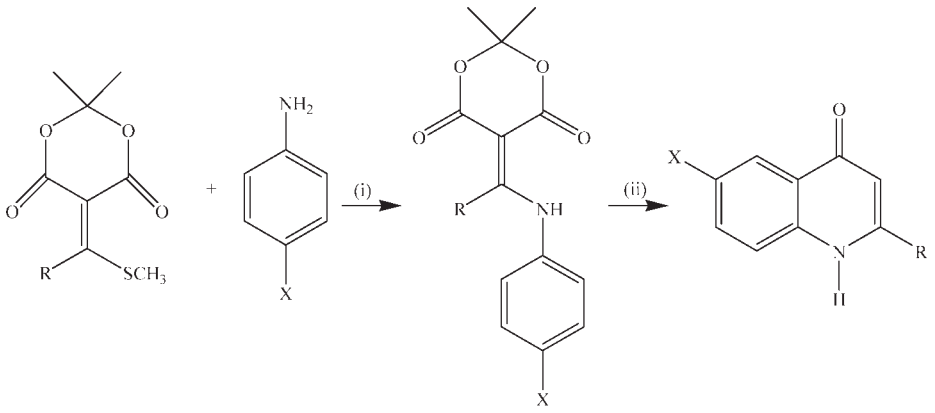
Over the last years, the interest in 2-arylquinolin-4(1*H*)-ones and their analogues have been the subject of extensive study as potential anti-tumor, anti-mitotic, and cytotoxic agents [4–8] as well as anti-platelet agents [9,10]. 2-(3-Methoxyphenyl)-6-(1-pyrrolinyl)quinolin-4(1*H*)-one (**VIII**) ($R_1$ = H, $R_2$ = $OCH_3$) and 2-(2-fluorophenyl)-6-(1-pyrrolinyl)quinolin-4(1*H*)-one analogue (**IX**) ($R_1$ = F, $R_2$ = H), for example, are potent inhibitors of tubulin polymerization ($IC_{50}$ = 0.44 μ*M* (**I**); 0.46 μM (**IX**)) and exhibit anti-mitotic anti-tumor activity at low concentrations having effects comparable to those of colchicine, podophyllotoxin, and combretastatin A-4 [4,5]. The 4-substituted quinoline moiety constitutes the framework for several nitrogen-containing heterocycles known to exhibit cytotoxic [11], anti-leishmanial [12], anti-malarial [13], and anti-bacterial properties [14]. Aryl substituted quinolines have also been reported to serve as estrogen receptor modulators [15] and also as potent inhibitors of tyrosine kinase PDGF-RTK [16]. The naturally occurring 4-methoxy-2-phenylquinoline (**VI**) and its 4-methoxy-2-(3,4-methylenedioxyphenyl)quinoline analogue (**VII**) [8] have recently been found to exhibit inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Rv$ [17].



(**VIII**) $R_1$ = H, $R_2$ = $OCH_3$
(**IX**) $R_1$ = F, $R_2$ = H

The 2-aryl-4-quinolones are also versatile synthetic intermediates and several articles continue to appear in literature describing their synthesis, chemical transformation, structural properties, and biological activities. Their versatility as synthetic intermediates is a consequence of 4-quinolone moiety (Fig. 1), which contains

**Scheme 1. Reagents**: (i) $(C_6H_5)_2O$, 140°C, 30 min or EtOH, heat, 2–4 h; (ii) $(C_6H_5)_2O$, 250–260°C.



**1** **2** **3** **4**

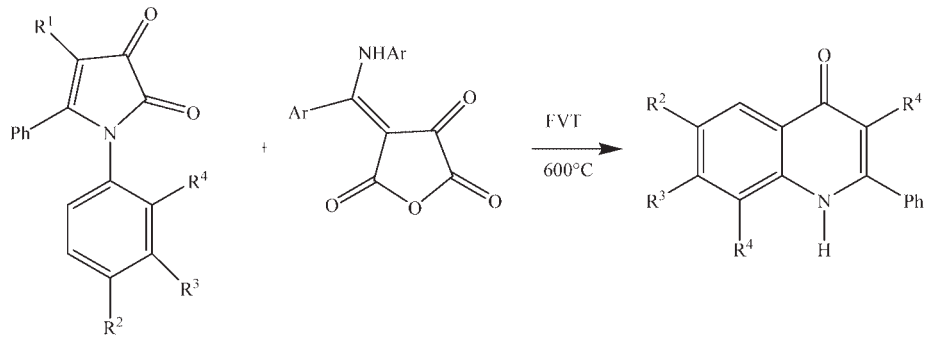
several reactive centers (positions 1, 3, and 4) for possible functionalization and can also enable different degree of unsaturation. They are known to undergo electrophilic substitution with alkyl derivatives to afford *N*- or *O*-alkylated derivatives or a mixture of the two isomers depending on the nature of the electrophile used and steric effect on the quinolone moiety. Aromatization of the 4-quinolone moiety with phosphorus oxychloride occurs with ease to afford 4-chloroquinolines which are important intermediates in the synthesis of 2-arylquinolines bearing a heteroatom group in the 4-position. Their α,β-unsaturated framework allows C-3 halogenation to yield 3-halogeno derivatives, which have been shown to undergo metal-catalyzed C—C formation to yield polysubstituted and polynuclear derivatives.

Although the popularity of variously substituted 2-arylquinolin-4(1*H*)-ones has been increasing over the years, their synthesis and transformation into *N*-alkylated or *O*-alkylated derivatives have never been reviewed. We wish to address this need by reviewing various methods developed to-date for the synthesis of 2-arylquinolin-4(1*H*)-ones and their transformation to *N*-alkylated and *O*-alkylated derivatives.

## 2. SYNTHESIS OF 2-ARYLQUINOLIN-4 (1*H*)-ONES

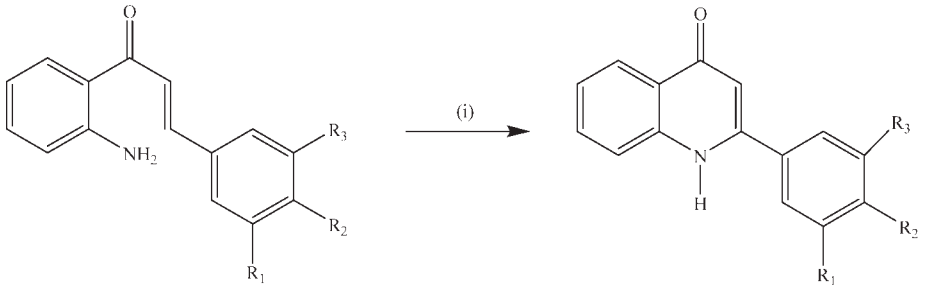
**2.1. From arylamines and carbonyl derivatives.** Several articles continue to appear in literature describing novel methods for the synthesis of 2-arylquinolin-4(1*H*)-ones. In one of the earliest methods, anthranilic acid or its ester derivative was heated with the acetal of an alkyl aryl ketone to yield the corresponding 2-arylquinolin-4(1*H*)-one [18]. Arylamines were also condensed with an ethyl benzoylacetate derivative in the presence of polyphosphoric acid (PPA) to afford 2-arylquinolin-4(1*H*)-ones [6,9,19]. Both these pathways are, however, not suitable for the synthesis of 2-arylquinolin-4(1*H*)-ones with multiple substituents. Anilinoarylidenemalonates derived from β-chloroarylidenemalonates and sodium diethyl malonate were previously cyclized at 250°C to afford 2-aryl-3(ethoxycarbonyl)-4-quinolones

**Scheme 2**



**5** **6** **7**

**Scheme 3. Reagents**: (i) $Pd(PPh_3)_2Cl_2$, THF, heat, 2 h.



**8** **9**

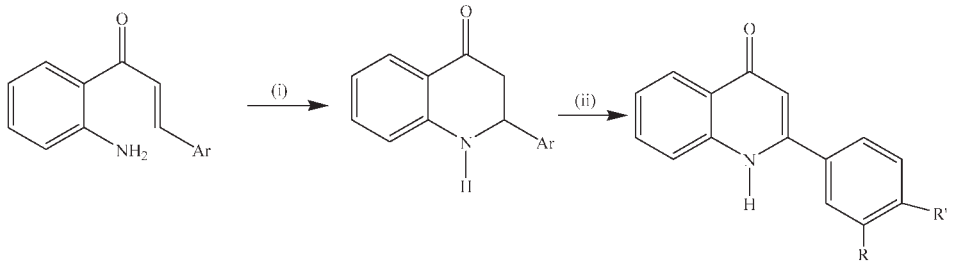
[20]. Lai and coworkers also subjected anilinoarylidenemalonates derived from carboxymidoyl chlorides to thermolysis at 170°C to afford 2-aryl-3(ethoxycarbonyl)-4-quinolones [8]. Thermolysis of the mono-ethoxycarbonyl vinyl derivatives, which are formed in comparable yields along with the anilinoarylidenemalonates afforded the 2-aryl-4-quinolones. In another development, 2,2-dimethyl-5-methylthioalkylidene-1,3-dioxane-4,6-diones **1** (R = Me, Et, Pr, Ph), which are easily prepared from Meldrum's acid (2,2-dimethyl[1,3]dioxane-4,6-dione) were condensed with substituted arylamines **2** (X = H, Me, $NO_2$, Br, Cl) in refluxing diphenyl ether or ethanol with (isolated yields: 54–57%) or without isolating the resulting intermediate **3** to afford 2-alkyl- and 2-arylquinolin-4(1*H*)-ones **4** (60–96%) upon cyclization in $Ph_2O$ at very high temperature (Scheme 1) [21].

2-Arylquinolin-4(1*H*)-ones were also prepared by condensing ethyl benzoylacetate with aniline in ethanol at 50°C followed by heating the resulting intermediate at 240–250°C in diphenyl ether [22,23]. A series of substituted 2-aryl-4-quinolones **7** has been synthesized in good yields (16–88%) from 1-aryl-5-phenylpyrrole-2,3-diones **5** substituted at the 4-position with cyano ($R^1$ = CN) or methoxycarbonyl group ($R^1$ = $CO_2Me$) and **6** *via* flash thermolysis (FVT) at 600°C (Scheme 2) [24].

**2.2. From 2-aminochalcones or 2-aryl-1,2,3,4,-tetrahydroquinol-4-ones.** 2′-Amonichalcones and their isomeric 2-aryl-1,2,3,4-tetrahydro-4-quinolone derivatives have also been used as substrates for the synthesis of 2-arylquinolin-4(1*H*)-ones. The 2′-amonichalcones **8**, which are readily accessible *via* Murphy-Watanism's aldol condensation of 2-aminoacetophenone with benzaldehyde derivative [25,26], have been found to undergo intramolecular cyclization in THF in the presence of dichloro-bis(triphenylphosphine)palladium(II) to afford the corresponding 2-arylquinolin-4(1*H*)-ones **9** in good yields (55–85%) (Scheme 3) [27]. The main disadvantage of this reaction is the use of stoichiometric amounts of the organometallic reagent and column chromatographic separation of the NH-4-oxo derivatives that are almost insoluble in many organic solvents.

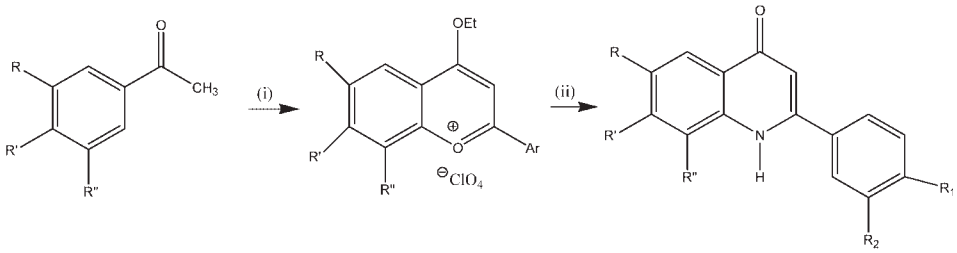
Thallium(III) *p*-tolylsulfonate (TTS) in dimethoxyethane (DME) [28] or iodobenzene diacetate in methanolic KOH [29,30] were used before to dehydrogenate 2-aryl-1,2,3,4-tetrahydro-4-quinolones **10** to 2-aryl-4-quinolones **9** (Scheme 4). The 2-aryl-1,2,3,4-tetrahydro-4-quinolones are themselves easily obtainable through acid-catalyzed cyclization of the isomeric 2-amonichalcones **8** [25,26]. Lee and Youn, recently used zinc chloride in acetonitrile to cyclize series of 2-amonichalcones to afford the corresponding isomeric 2-aryl-1,2,3,4-tetrahydro-4-quinolone derivatives in high yields (>85%) [30]. The 2-aryl-1,2,3,4-tetrahydro-4-quinolones bearing substituents on the fused benzo ring can also be prepared through direct one-pot acid-catalyzed condensation of substituted

**Scheme 4. Reagents**: (i) $H_3PO_4$, EtOH, heat; (ii) TTS, DME, heat or toluene, heat.



**8** **10** **9**

**Scheme 5. Reagents**: (i) ArCHO; $HClO_4$, $HC(OEt)_3$; (ii) 25% $NH_3$ (aq).



**11** **12** **13**

R = H, $CH_3$, t-Bu, $NHCOCF_3$

R' = H; R" = H, $NHCOCF_3$

$R_1$ = H, OH, $OCH_3$

$R_2$ = H, OH, $OCH_3$

aniline derivatives with ethyl benzoylacetate in refluxing toluene [22,23].

The other approach to 2-arylquinolones makes use of flavylium salts **12** derived from the condensation of 2-hydroxyacetophenones **11** with aryldehydes in ethyl orthoformate in the presence of potentially explosive perchloric acid (Scheme 5) [31]. The resulting flavylium salt is then treated with aqueous ammonia to release the corresponding 2-aryl-4-quinolone **13**. A modification of this procedure employs trifluoroacetic acid or trifluoromethanesulfonic acid in ethyl orthoformate or dichloromethane to afford flavylium salts in high yields, however, the expected 2-aryquinolones are isolated in relatively low yields (18–59%) [32].

**2.3. Synthesis from 2-aminoacetophenone and aroylchlorides.** The most convenient and high yielding method usually used for the synthesis of 2-arylquinolin-4(1*H*)-ones involves the use of 2-aminoacetophenones **14** and substituted benzoyl chlorides **15** as starting material [5,7,33,34]. The resulting *N*-benzoyl-2-aminoacetophenone **16** is cyclized under reflux using t-BuOK in t-BuOH to afford the corresponding 2-arylquinolin-4(1*H*)-one **17** in high yield (60–80%) and purity (Scheme 6).

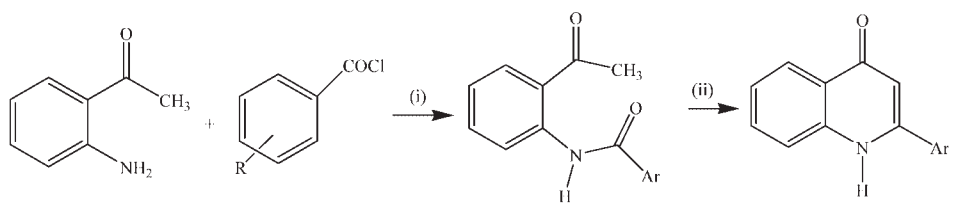
The reaction has also been carried out under microwave conditions involving irradiation of acylated 2′-aminoacetophenone in the presence of sodium hydroxide to afford 2-aryl-4-quinolones [35].

**2.4. Methods involving organometallic reagents.** Less traditional syntheses of 2-arylquinolin-4(1*H*)-ones, which make use of transitional metals have been developed. Palladium-catalyzed carbonylation of 2-haloaniline **18** in the presence of terminal acetylenes **19** under proper conditions (20 kg/cm$^2$ of CO at 120°C) afforded a variety of 2-substituted quinolin-4(1*H*)-ones **20** (Scheme 7) [36]. Carbonylation of series of *o*-iodoanilines and terminal alkynes in the presence of palladium catalyst [$PdCl_2$(dppf)] afforded 2-aryl-4-quinolones in good yields (62–83%) [37]. The reaction was found to proceed well in both secondary (diethylamine) and tertiary amines (triethylamine) and in benzene containing 4 equivalent of diethylamine.

Variously substituted 2-arylquinolin-4(1*H*)-ones **23** can also be obtained in appreciable yields (72–97%) *via* sequential Cu-catalyzed amidation of halophenones **21** followed by a base-promoted Camps cyclization of the resulting *N*-(2-ketoaryl)amides **22** (Scheme 8) [38].

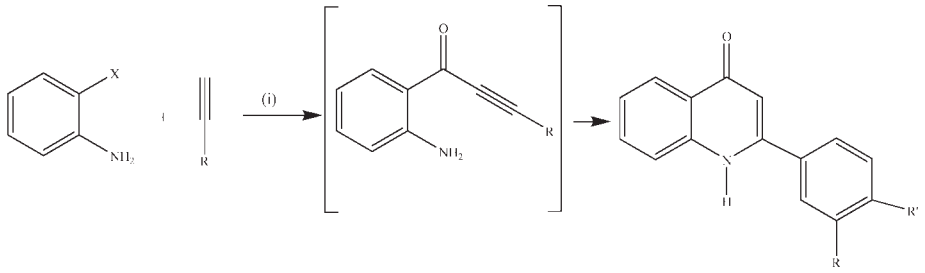
A mild and high yielding (>85%) one-pot synthesis of 2-arylquinolin-4(1*H*)-ones **26** *via* sequential palladium-catalyzed amidation of 2′-bromoacetophenone derivatives **24** followed by base-promoted intramolecular cyclization of **25** has been recently developed (Scheme 9) [39].

**Scheme 6. Reagents:** (i) $NEt_3$, THF, 0°C to r.t. 2 h; (ii) t-BuOK, t-BuOH, heat, 20 h.



**14** **15** **16** **17**

**Scheme 7. Reagents**: (i) CO, $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf), $NHEt_2$, 120°C.



**18** (X = Br, I) **19** **20**

R, R' = H (90%)

R = H, R' = -OMe (95%)

R = H, R' = -$CO_2$Et (85%)

R, R' = -$OCH_2O$- (88%)

These novel methods that make use of organometallic reagents are high yielding and allow synthesis of variously substituted potentially tautomeric 2-arylquinolin-4(1*H*)-ones [40].

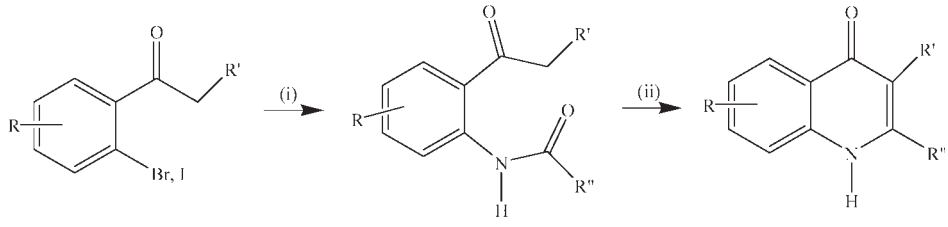
## 3. REACTIONS OF 2-ARYLQUINOLIN-4(1*H*)-ONES

New findings on the biological properties of 2-aryl-4-quiolones reveal a need to increase the diversity of substituents around the 4-quinolone framework. This moiety contains several reactive centers for possible functionalization to yield novel systems, which can themselves serve as substrates for further chemical transformation. The 2-arylquinolin-4(1*H*)-ones have been found to undergo C-3 halogenation, *N*- or *O*-alkylation, and oxidative aromatization.

**3.1. C-3 Halogenation.** Halogenated heterocyclic systems continue to attract considerable attention because of the profound effect a halogen atom can have on the physical, chemical, and biological properties of such substances. Iodine–$Na_2CO_3$ mixture in THF at room temperature was previously used to effect C-3 iodination of 2-arylquinolin-4(1*H*)-ones **27** to afford the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-ones **28** (X = I) in high yield and purity (Scheme 10) [41]. The NH-4-oxo derivatives can also be iodinated using iodine–ammonium cerium nitrate (CAN) mixture in acetonitrile at 70–80°C to afford 2-aryl-3-iodoquinolin-4(1*H*)-ones [42]. On the other hand, the analogous 2-aryl-3-bromoquinolin-4(1*H*)-ones **28** (X = Br) were prepared in high yield and purity from the corresponding 2-arylquinolin-4(1*H*)-ones using pyridinium tribromide in acetic acid at room temperature (Scheme 10) [41].

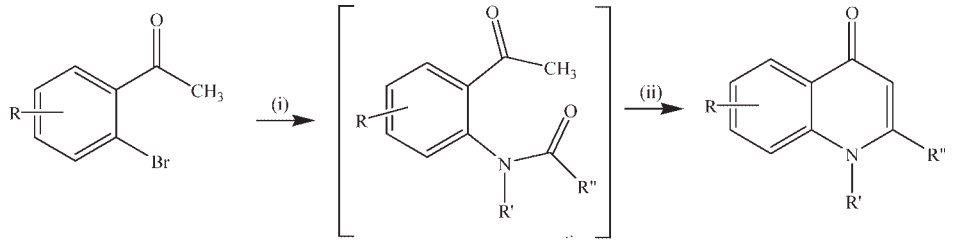
**3.2. Alkylation of 2-arylquinolin-4(1H)-ones and their derivatives.** The synthetic versatility of the potentially tautomeric 4-quinolone framework enables interconversion between the NH-4-oxo precursors and their *O*- or *N*-methylated derivatives. Comparison of spectroscopic data (IR, NMR, and ms) of these fixed derivatives (*O*- or *N*-alkylated) with those of the corresponding precursors (NH-4-oxo) has been used to resolve uncertainties on the 2-substituted 4-quinolone *versus* 2-substituted 4-quinolinol tautomeric equilibrium [40]. The naturally occurring 4-methoxy-2-phenylquinoline **29**

**Scheme 8. Reagents:** (i) Amide, CuI, ligand, toluene, heat; (ii) NaOH, 1,4-dioxane, heat.



**21** **22** **23**

**Scheme 9. Reagents**: (i) $Pd_2(dba)_3$, xantphos, amide, $Cs_2CO_3$, dioxane, heat; (ii) t-BuONa, t-BuOH, heat.



**24** **25** **26**

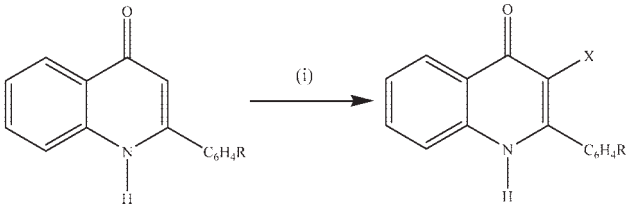
was previously treated with HCl in methanol under reflux to yield the 2-phenylquinol-4-one **30**, which was in turn converted to the NMe-4-oxo derivative **31** using dimethyl sulfate under basic conditions [43]. On the other hand, when heated with MeI, the 4-methoxyquinoline **29** yielded the dimethylated salt **32**, which upon treatment with a base afforded the isomeric 1-methyl-2-phenylquinoline **31** (Scheme 11).

The most classical method used for alkylation of 2-arylquinolin-4(1*H*)-ones involves subjecting the NH-4-oxo derivative to a base followed by quenching with the corresponding alkyl halide. Methylation of the 2-substituted-4(1*H*)-quinolones **33** using MeI-$K_2CO_3$ mixture in DMF was reported to afford a mixture of the *O*-methylated **34** and *N*-methylated derivatives **35** (Scheme 12) [44] while on the other hand, NaH and MeI in DMF afforded the *O*-methylquinoline derivatives, exclusively [45]. It was, however, discovered by Kuo and coworkers that the product mixture comprised of *N*- and *O*-methylated derivatives in the ratio 2:3 [46]. Alkylation of 2-phenylquinolin-4(1*H*)-one with methyl iodide or various primary alkyl, allyl, and benzyl halides in DMF in the presence of NaH, on the other hand, afforded the corresponding *N*-alkylated derivatives as sole products [47]. Enol ethers were also isolated as sole products when 2-(2-fluorophenyl)-6,7-methylenedioxyquinolin-4(1*H*)-one was treated with NaH in DMF followed by alkylation with ethyl chloroacetate or ethyl 4-chlorobutyrate [5]. Alkylation of 2-arylquinolin-4(1*H*)-ones with various alkyl halides also afforded the corresponding *O*-alkylated derivatives, exclusively [10]. Methylation was, however, found not to be regioselective under these conditions affording mixtures of *O*-methylated and *N*-methylated isomers.

It was also observed that the presence of substituent at C-5 or C-3 position has significant effect on the regioselectivity of alkylation of the quinolone derivatives. Treatment of 5,7-dimethoxy-2-phenylquinolin-4(1*H*)-one **36** (R, R′ = OMe) with MeI-$K_2CO_3$ mixture in DMF afforded *O*-methylated derivative **37** as the sole product (Scheme 13) [48]. On the other hand, under similar reaction conditions, 5-hydroxy-7-methoxy-2-phenyl-4-quinolone **36** (R = OH, R′ = OMe) afforded both *O*- **37** and *N*-methylated derivatives **38** [46] with *N*-methylated derivative as major product (ratio 9:1 *N*-alkylated *vs*. *O*-alkylated) [49]. Hadjeri *et al*. attributed the observed non-regioselectivity to the tautomeric equilibrium between the NH-4-oxo and its quinolinol isomer which is favored by chelation effect of the 5-OH group [48]. Treatment of the analogous 5-ethyl-2-phenylquinolin-4(1*H*)-one **36** (R = Et, R′ = H) with NaH-MeI mixture in THF afforded both *O*-methylated **37** (R″ = Me) and *N*-methylated isomers **38** (R″ = Me) in the ratio 1:5.4 [10]. On the other hand, under similar reaction conditions ethyl iodide and various ethoxycarbonylalkyl halides afforded only the corresponding *O*-alkylated products **37** (R = Et, R′ = H; R″ = Et, $CH_2CO_2Et$, $CH_2CO_2H$) [10].

The 3-halogenated NH-4-oxo derivatives **39** (R′ = Br, I) were treated with NaH in THF to afford the *N*-methylated derivatives **40** as the only products (Scheme 14) [41,50,51]. The observed regioselectivity was attributed to the preponderance of these derivatives as the NH-4-oxo tautomers in polar medium and solid state [40,51]. 2-Aryl-3-bromo-1-methylquinolin-4(1*H*)-ones **40** (X = Br) were also prepared directly from the corresponding 2-aryl-1-methylquinolin-4(1*H*)-one precursors in high yields (77–93%) using pyridinium tribromide in acetic acid at room temperature [41].

**Scheme 10. Reagents**: (i) $I_2$, $Na_2CO_3$, THF, heat for X = I; $C_5H_5NH.Br_3$, AcOH, r.t. for X = Br.

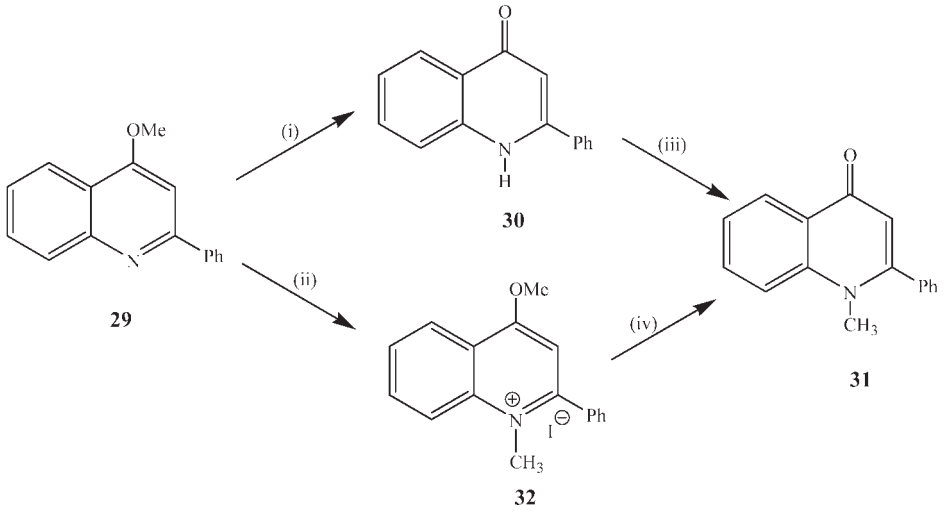


**27** **28**

X = I; R = H (85%), 4-F (83%), 4-Cl (90%), 4-OMe (83%)

X = Br; R = H (94%), 4-F (95%), 4-Cl (91%), 4-OMe (90%)

**Scheme 11. Reagents**: (i) HCl, MeOH, heat; (ii) MeI, heat; (iii) $Me_2SO_4$, NaOH; (iv) NaOH.




In another development, series of pharmaceutically important *N*-methylated 2-aryl-4-quinolone alkaloids **44** were prepared by methylation of 2-arylquinolines **43** with methyl trifluoromethanesulfonate followed by oxidation with potassium ferricyanate $[K_3Fe(CN)_6]$ (Scheme 15) [52]. 2-Arylquinoline **43** used as substrate in this investigation were, in turn, synthesized by Diels–Alder reaction of substituted 1,2,3-benzotriazine **41** prepared by oxidation of 1-amino-1*H*-indazole with lead tetraacetate, and pyrrolidine enamine of substituted acetophenone **42** in dry chloroform in the presence of zinc bromide under reflux [52].

Although primary alkyl halides and benzyl halides afforded the *O*-alkylated derivatives exclusively, the problem of non-regioselectivity with methylation necessitates the development of sure-fire methods for the direct and regioselective synthesis of either *N*- or *O*-methylated isomers. Very few methods have been developed to-date for the direct synthesis of *N*-alkyl 2-arylquinolin-4(1*H*)-ones.

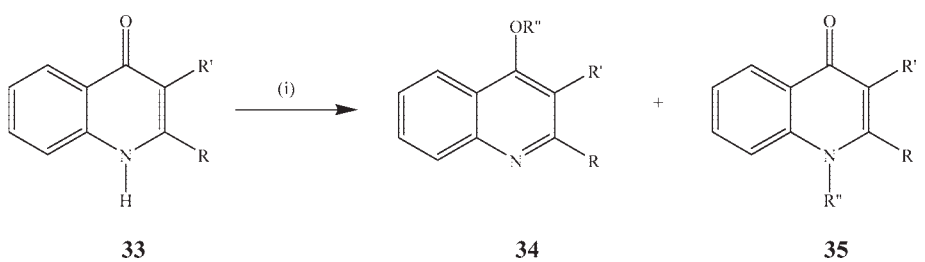
***3.2.1. Direct synthesis of N-alkylated 2-arylquino-linones.*** The shortest route (one-step synthesis) reported to-date for the synthesis of 2-aryl-1-methyl-4-quinolones **47** in appreciable yields involves the condensation of lithium enolates of acetophenone derivatives **46** with substituted *N*-methylisatoic anhydrides **45** (Scheme 16) [46,53]. Although the reaction is high yielding, each reaction when using different substrates has its unique temperature requirements for completion.

Several *N*-methylated 2-aryl-4-quinolinones were prepared in moderate yields by treatment of resin bound flavylium salts with methylamine following a similar procedure outlined in Scheme 5 [32]. In another development involving synthesis of *N*-alkylated 2-arylquinolone derivatives, 2-aminoacetophenone **48** was first condensed with various aldehydes followed by selective reduction using $NaBH_3CN$ to yield **49** (Scheme 17). The alkylated derivatives **49** were, in turn, acylated using various benzoyl chlorides and the resulting amides **50** were cyclized using t-BuOK in refluxing t-BuOH to afford 1-benzyl-2-arylquinolin-4(1*H*)-ones **51** [54].

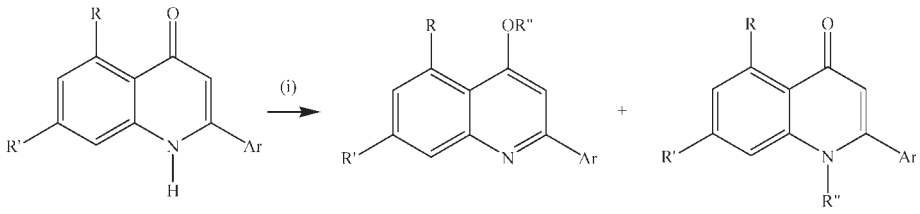
Palladium-catalyzed carbonylation of *N*-ethyl-2-iodoaniline **52** with phenylacetylene **53** in diethylamine afforded a mixture of enamine **54** (52%) and 2-phenylquinoline **55** (20%) (Scheme 18). Further heating of the enamine in THF in the presence of NaH effected smooth cyclization leading to quantitative yield of the quinolone [36].

A direct one-pot synthesis of 2-aryl-1-methylquinolin-4(1*H*)-ones **58**, which involves treatment of *N*-arylamidoacetophenone derivatives **56** with MeI in presence of

**Scheme 12. Reagents**: (i) MeI, NaH in THF or DMF; MeI, $K_2CO_3$ in DMF or Acetone.



**Scheme 13. Reagents**: (i) $K_2CO_3$, R″X, DMF or NaH, R″X, THF.



**36** **37** **38**

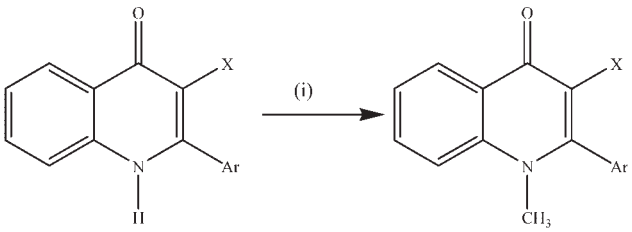
NaH in THF was recently described (Scheme 19) [40]. The corresponding *N*-methylated arylamidoacetophenone derivatives **57** were isolated in trace amounts (>5%).

Friedel-Crafts acylation of **59** using stannic chloride ($SnCl_4$) as catalyst afforded **60,** which upon cyclization with t-BuOK in t-BuOH yielded the corresponding 2-aryl-1-methylquinolin-4(1*H*)-ones **61** (Scheme 20) [55]. This cyclization previously worked well for the synthesis of 2-aryl-3,5,7-trimethoxy-4-quinolones from *N*-phenylamido methoxyacetophenones prepared, in turn, *via* stannic chloride-catalyzed Friedel-Crafts acylation of 3,5-dimethoxyphenyl-*N*-phenylamide with methoxyacetyl chloride in 1,2-dichloroethane [56].

Iodocyclization of the dimethylamino systems **62** using iodine in dichloromethane proved highly selective for the 6-endo-digonal pathway to afford 2-substituted 3-iodo-1-methylquinolin-4(1*H*)-ones **63** in high yield (94%, R = 4-MeO) (Scheme 21) [57].

***3.2.2. Direct synthesis of* O*-alkylated 2-arylquinolines.*** An alkoxide-mediated cyclization of Schiff bases **64** derived from the reaction of trifluoromethylaniline with alkyl or heterophenyl ketones is reported to afford 2-aryl-4-alkoxyquinoline **65**, exclusively [58,59]. In this reaction, the Schiff base is treated with t-KOBu in THF under reflux to afford the alkoxyquinoline derivative (OR = t-BuO) in high yield (83%) (Scheme 22) [58]. On the other hand, under similar reaction conditions, use of sodium or potassium ethoxide afforded the corresponding 4-ethoxy-2-phenylquinoline (R = Et) in lower yield (25%). The 2,3,4-trisubstituted quinoline (R′ = $CH_3$; R″ = t-Bu) was prepared in 52% yield following similar procedure [58].

**Scheme 14. Reagents**: (i) NaH, MeI, THF, r.t. 18 h.



**39** (X = Br, I) **40**

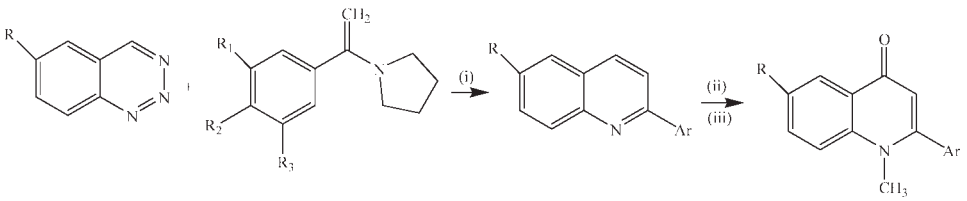
One of the recent developments in the synthesis of 4-alkoxyquinolines involved direct synthesis of the naturally occurring 4-alkoxy-2-arylquinoline derivatives from the corresponding 2-aryl-1,2,3,4-tetrahydro-4-quinolones using oxidative reagents (Scheme 23). Oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones **66** to 2-aryl-4-methoxyquinolines **67** was effected with either thallium(III) nitrate [60] or [hydroxyl(tosyloxy)iodo]benzene [61] in trimethyl orthoformate in the presence of catalytic amount of perchloric acid. Molecular iodine in refluxing methanol was also found to effect oxidative aromatization of 2-aryl-1,2,3,4-tetrahydro-4-quinolones **66** to 2-aryl-4-methoxyquinolines **67** [62]. Recently, Kumar and coworkers used $FeCl_3{\cdot}6H_2O$ in methanol to effect oxidative aromatization of series of 2-aryl-1,2,3,4-tetrahydroquinolin-4-ones to afford 2-aryl-4-methoxyquinolines in 70–85% yields [63]. $FeCl_3{\cdot}6H_2O$ in methanol was later used by these authors to effect direct one-pot synthesis of series of 2-aryl- and 2-heteroaryl-4-methoxyquinolines (55–72%) and their flavones derivatives from the corresponding 2-azachalcones and 2-hydroxychalcones, respectively [64].

Series of 2,4-disubstituted quinolines **69** (X = Br, I, SEt, SPh) including 4-alkoxy-2-arylquinolines (X = OEt, OMe, OAr) were prepared in moderate to high yields (33–98%) from the corresponding β-(2-aminophenyl)-α,β-ynones **68** using various nucleophiles (Scheme 24) [65].

The 4-alkoxy-2-arylquinolines **72** (R′ = Me, Et, i-Pr) were recently prepared in low to moderate yields (10–81%) from 2-(2-(trimethylsilyl)ethynyl)anilines **70** and aryldehydes **71** in the presence of sulfuric acid in alcohols (Scheme 25) [66].

Although simple and efficient, the above reagents used for direct oxidative aromatization of 2-aryl-1,2,3,4-tetrahydro-4-quinolones cannot be used for the synthesis of 2,3-disubstituted 4-alkoxyquinoline derivatives. On the other hand, the Skraup, Döbner-Miller, Friedländer and Combes reactions, which are well known classical methods for the synthesis of polysubstituted quinolines, cannot be adapted for the synthesis of quinoline derivatives bearing 4-alkoxy group [67]. Consequently, indirect methods remain the method of choice for the

**Scheme 15. Reagents**: (i) $ZnBr_2$, CHCl3, heat, 2 h; (ii) Methyl trifluoromethanesulfonate, heat, 1 h; (iii) $K_3Fe(CN)_6$, 20% NaOH, r.t. 2 h.



**41** **42** **43** **44**

$R = R^1 = R^2 = R^3 = H$

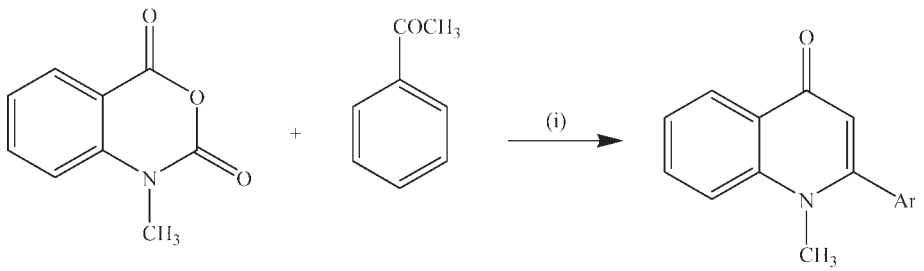
$R = R^3 = H$, $R^1 + R^2 = OCH_2O$

$R = R^1 = R^3 = H$, $R^2 = OH$

$R = OCH_3$, $R^1 = R^2 = R^3 = H$

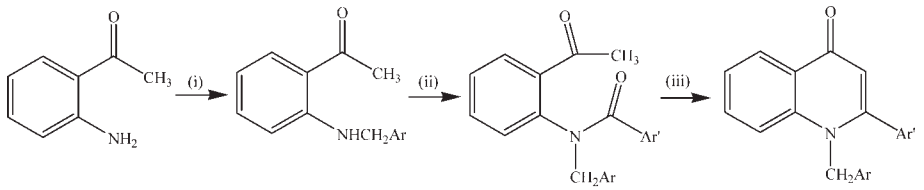
$R = R^1 = R^3 = H$, $R^2 = H$

**Scheme 16. Reagents**: (i) DIPA, n-BuLi, THF, −65°C, 3.5 h.



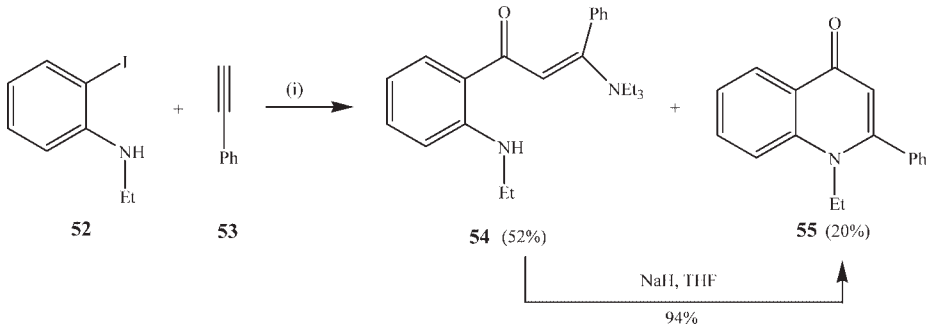
**45** **46** **47**

**Scheme 17. Reagents**: (i) *a*: PhCHO, $C_6H_6$; *b*: $NaCNBH_3$, PPTS, MeOH. (ii) ArC(O)Cl, $NEt_3$, $CH_2Cl_2$. (iii) t-BuOK, t-BuOH.



**48** **49** **50** **51**

**Scheme 18. Reagents**: (i) CO, $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf), $NHEt_2$, 120°C.

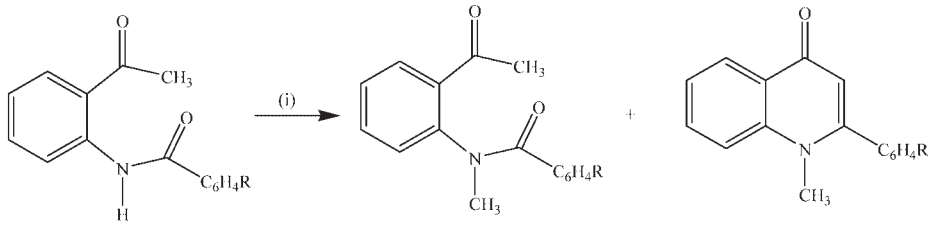


**52** **53** **54** (52%) **55** (20%)

NaH, THF

94%

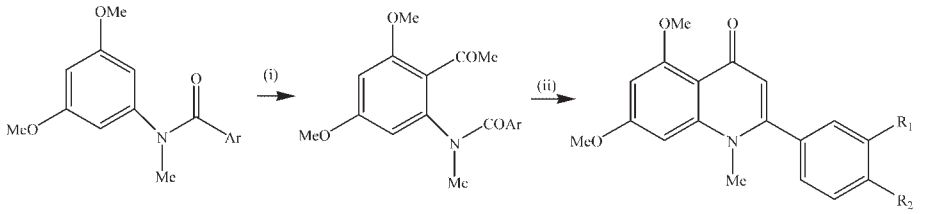
**Scheme 19. Reagents:** (i) NaH, MeI, THF, r.t.



**56** **57** (minor) **58** (major)

Major: R = H (52%), 4-F (54%), 4-Cl (61%), 4-OMe (51%)

**Scheme 20. Reagents**: (i) $MeCOCl$, $SnCl_4$, $CH_2Cl_2$, 0°C; (ii) t-BuOK, 30°C.

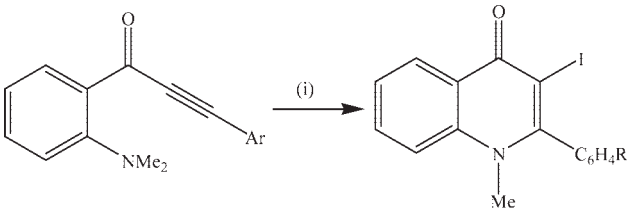


**59** **60** **61** ($R_1 = NO_2$, $R_2 = Cl$) ($R_1 = H$, $R_2 = OCOMe$)

synthesis of polysubstituted *O*-alkylated quinoline derivatives.

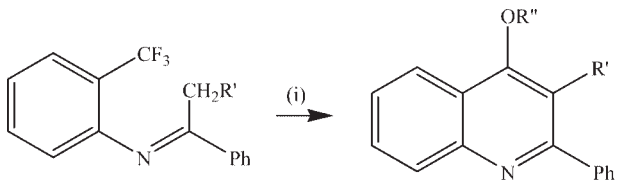
***3.2.3. Indirect synthesis of* O-*alkylated 2-arylquinolines.*** In this approach, the NH-4-oxo derivatives **73** are first converted to the corresponding 4-chloroquinoline derivatives **74** using phosphorus oxychloride under reflux. The C3 unsubstituted 2-aryl-4-chloroquinolines were also prepared by reaction of Vilsmeier reagent with 2′-azidochalcones, which are prepared in turn from the corresponding 2′-amonichalcones by diazotization followed by treatment with $NaN_3$ [68]. The 4-chloroquinolines **74** are then reacted with alkoxides or phenoxide ions to

**Scheme 21. Reagents**: (i) $I_2$, $CH_2Cl_2$.



**62** **63**

**Scheme 22. Reagents**: (i) KOR″, THF, heat, 2 h.

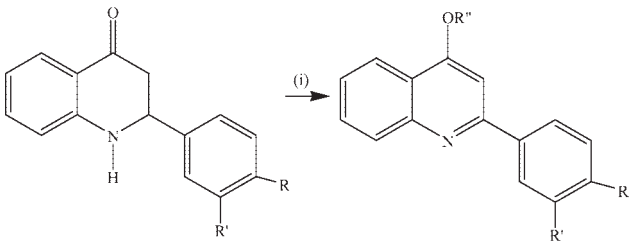


**64** **65**

R' = H; R" = t-Bu, Et

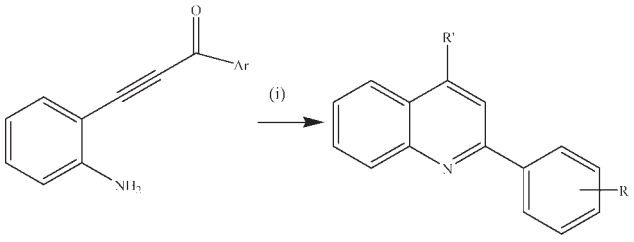
R' = $CH_3$; R" = t-Bu

**Scheme 23. Reagents**: (i) TTN, $CH(OR'')_3$, $HClO_4$, 1 h [60]; HTIB, $CH(OR'')_3$, $HClO_4$, 1.5 h [61]; $I_2$, MeOH, 2 h [62]; or $FeCl_3{\cdot}6H_2O$, MeOH, heat, 3 h [63].



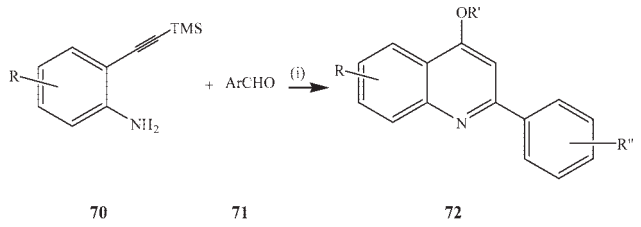
**66** **67**

**Scheme 24. Reagents**: (i) NaOR′, R′OH (R′ = Me, Et).



**68** **69** (R' = OMe, OEt)

**Scheme 25. Reagents**: (i) $H_2SO_4$, R′OH, heat, 17 h.



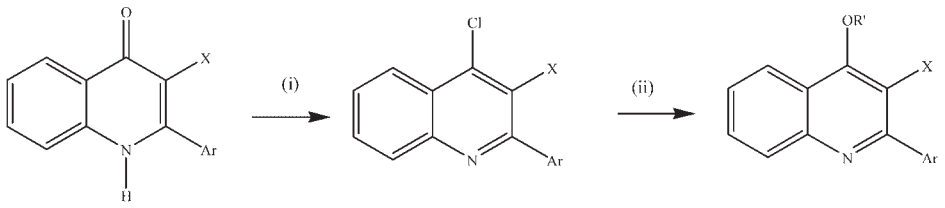

70 71 72

yield the expected 4-phenoxy- or 4-alkoxyquinoline derivatives **75** (Scheme 26) [69,70]. This approach, which takes advantage of the ease of displacement of 4-chlorine atom by nucleophiles has recently been used for the synthesis of 2,3-disubstituted 4-alkoxyquinoline derivatives (R′ = Me) that cannot be easily prepared otherwise. Series of 2-aryl-3-bromo/iodo-4-methoxyquinolines were prepared this way from the corresponding 2-aryl-4-chloro-3-halogenoquinolines [50,51,70].

This indirect approach has also been adapted to involve the use of organometalic reagents in the synthesis of 2,3-disubstituted 4-alkoxyquinolines. The synthesis of 3-aryl-2-(ethyl/phenyl)-4-phenoxyquinolines **78**, involved initial C-2 coupling of 3-aryl-2,4-dichloroquinolines **76** with alkyl- or aryl-zinc reagents ($R_2Zn$; R = Et, Ph) followed by displacement of the 4-chlorine atom from **77** with bromophenol derivative (Scheme 27) [71].

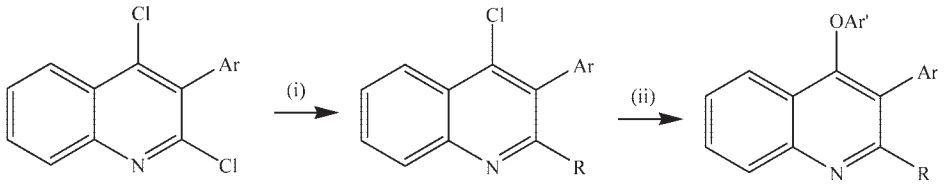
The results of sequential functionalization of 2-aryl-4-chloro-3-iodoquinolines **73** (X = I) *via* palladium-catalyzed cross-coupling with phenylboronic acid followed by displacement of the 4-chloro atom from the resulting 2,3-diaryl-4-chloroquinolines **78** with methoxide ion to yield 2,3-diaryl-4-methoxyquinolines **79** have recently been described (Scheme 28). Compounds **79** were also

**Scheme 26. Reagents**: (i) $POCl_3$, heat, 2 h; (ii) NaOMe, THF, heat, 18 h.



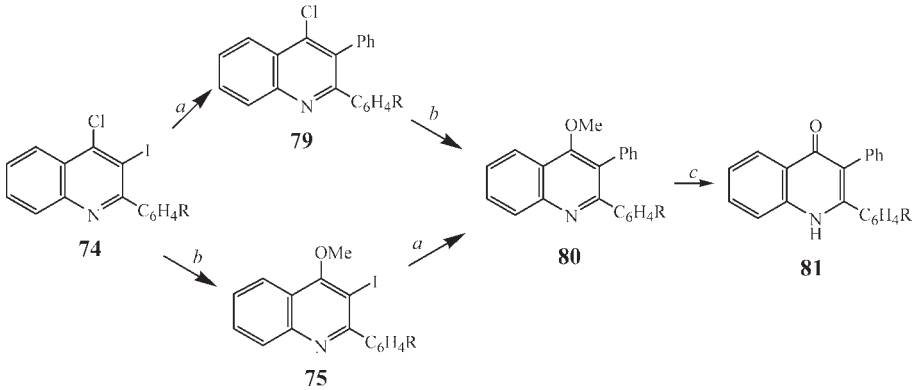

**73** (X = H, Br, I) **74** **75**

**Scheme 27. Reagents:** (i) $Zn(R')_2$, $PdCl_3(dppf)$, $K_2CO_3$, THF; (ii) *p*-$BrC_6H_4OH$, NaOH, DMF, 110°C.




**76** **77** **78**

**Scheme 28. Reagents**: (*a*) $Pd(PPh_3)_4$, $PhB(OH)_2$, $K_2CO_3$, DMF; (*b*) NaOMe, THF or DMF, heat; (*c*) $BBr_3$, $CH_2Cl_2$, r.t.



prepared *via* Suzuki–Miyaura cross-coupling of 2-aryl-3-iodo-4-methoxyquinolines **74** (R′ = Me, X = I) with phenylboronic acid [70]. Demethylation of the methoxy compounds **79** with $BBr_3$ in $CH_2Cl_2$ gave the 2,3-diaryl-4(1*H*)-quinolinones **80**.

This demethylation represents a convenient synthetic strategy for the construction of 2,3-diarylquinolin-4(1*H*)-ones of potential biological interest that can be obtainable only with difficulty otherwise.

## 4. CONCLUSIONS

Overall, the methods described in this review present another example showing the potential of 2-arylquinolin-4(1*H*)-ones in the synthesis of 2,3-substituted NH-4-oxo derivatives and their transformation into *N*-alkylated and *O*-alkylated derivatives. Interestingly, *O*-alkylated and *N*-alkylated quinolone derivatives do not feature at all in a recent review on quinolines by Kouznetsov *et al.* [72]. Despite the establishment of structural requirements and optimum reaction conditions suitable for the synthesis of *N*-alkylated quinolone derivatives, there is still a growing need for development of generalized methods for the synthesis of polysubstituted derivatives. On the other hand, indirect methods, which make use of 4-chloroquinolines and take advantage of the ease of displacement of the 4-chloro atom remain the best option for the synthesis of polysubstituted 4-alkoxyquinolines.

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### REFERENCES AND NOTES

[1] Sondheimer, F.; Meisels, A. J Org Chem 1958, 23, 762.

[2] Goodwin, S.; Smith, A. F.; Velasquez, A. A.; Horning, E. C. J Am Chem Soc 1959, 81, 6209.

[3] Michael, J. P. Nat Prod Rep 1997, 14, 605.

[4] Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Hackl, T.; Lee, K. H. J Med Chem 1998, 41, 1155.

[5] Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. J Med Chem 2001, 44, 3932.

[6] Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J. H.; Lee, K. H. Bioorg Med Chem Lett 2003, 13, 2891.

[7] Hadjeri, M.; Peiller, E.-L.; Beney, C.; Deka, N.; Lawson, M. A.; Dumontet, C.; Boumendjel, A. J Med Chem 2004, 47, 4964.

[8] Lai, Y.-Y.; Huang, l.-J.; Lee, K.-H.; Xiao, Z.; Bastow, K. F.; Yamori, T.; Kuo, S.-C. Bioorg Med Chem 2005, 13, 265.

[9] Huang, L.-J.; Hsieh, M.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C. Bioorg Med Chem 1998, 6, 1657.

[10] Ko, T. C.; Hour, M. J.; Lien, J. C.; Teng, C. M.; Lee, K. H.; Kuo, S. C.; Huang, L. J. Bioorg Med Chem 2001, 11, 279.

[11] Chun, M. W.; Olmstead, K. K.; Choi, Y. S.; Lee, C. O.; Kim, J. H.; Lee, J. Bioorg Med Chem Lett 1997, 7, 789.

[12] Fournet, A.; Barrios, A. A.; Munoz, R. H.; Hocquemiller, R.; Cave, A.; Bruneton, J. Antimicrob Agents Chemother 1993, 37, 859.

[13] Michael, J. P. Nat Prod Rep 2006, 24, 223.

[14] Alguinaldo, A. M.; Dalangin-Mallari, V. M.; Macabeo, A. P. G.; Byrne, L. T.; Abe, F.; Yamauchi, T.; Franzblau, S. G. Int J Antimicrobial Agents 2007, 29, 738.

[15] Hoekstra, W. J.; Patel, H. S.; Liang, X.; Blanc, J. E.; Heyer, D. O.; Willson, T. M.; Iannone, M. A.; Kadwell, S. H.; Miller, L. A.; Pearce, K. H.; Simmons, C. A.; Shearin, J. J Med Chem 2005, 48, 2243.

[16] Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. J Med Chem 1994, 37, 2129.

[17] Alguinaldo, A. M.; Dalangin-Mallari, V. M.; Macabeo, A. P. G.; Byrne, L. T.; Abe, F.; Yamauchi, T.; Franzblau, S. G. Int J Antimicrobial Agents 2007, 29, 738.

[18] Fuson, R. C.; Burness, D. M. J Chem Soc 1946, 68, 1270.

[19] Giardina, G. A. M.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Grugni, M.; Ravereglia, L. F.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Vecchietti, V.; Hay, D. W. P. J Med Chem 1997, 40, 1794.

[20] Hormi, O. E. O.; Peltonen, C.; Heikkilä, L. J Org Chem 1990, 55, 2513.

[21] Chen, B.; Huang, X. H.; Wang, J. Synthesis 1987, 482.

[22] Jaroszewski, J. W. J Heterocyclic Chem 1990, 27, 1227.

[23] Park, M.-S.; Lee, J.-I. Bull Korean Chem Soc 2004, 35, 1269.

[24] Rao, V. V. R.; Wentrup, C. J Chem Soc Perkin Trans 1 2002, 1232.

[25] Donnelly, J. A.; Farell, D. F. Tetrahedron 1990, 46, 885.

[26] Donnelly, J. A.; Farell, D. F. J Org Chem 1990, 55, 1757.

[27] Kasahara, A.; Izumi, T.; Watabe, H.; Takahashi, S. Chem Ind 1981, 121.

[28] Singh, O. V.; Kapil, R. S. Synth Commun 1993, 23, 277.

[29] Prakash, O.; Kumar, R. J.; Saini, R. J.; Singh, S. P. Synth Commun 1994, 24, 2167.

[30] Lee, J. I.; Youn, J. S. Bull Korean Chem Soc 2008, 29, 1853.

[31] Sato, S.; Kumagai, H.; Matsuba, S.; Kumazawa, T.; Onodera, J.-I.; Suzuki, M. J Heterocyclic chem 1999, 36, 1345.

[32] Sato, S.; Kubota, Y.; Kumagai, H.; Kumazawa, T.; Matsuba, S.; Kitamura, N.; Onodera, J. I.; Suzuki, M. Heterocycles 2000, 53, 1523.

[33] Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-C.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. J Med Chem 1994, 37, 1126.

[34] Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-C.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. J Med Chem 1994, 37, 3400.

[35] Ding, D.; Li, X.; Wang, X.; Du, Y.; Shen, J. Tetrahedron Lett 2006, 47, 6997.

[36] Torii, S.; Okumoto, H.; Xu, L. H. Tetrahedron Lett 1991, 32, 237.

[37] Kalanin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. Tetrahedron Lett 1992, 33, 373.

[38] Jones, C. P.; Anderson, K. W.; Buchwald, S. L. J Org Chem 2007, 72, 7968.

[39] Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. Org Lett 2008, 10, 2609.

[40] Mphahlele, M. J.; El-Nahas, A. M. J Mol Struct 2004, 688, 2159.

[41] Mphahlele, M. J.; Nwamadi, M. S.; Mabeta, P. J Heterocyclic Chem 2006, 43, 255.

[42] Venkataraman, S.; Barabge, D. K.; Pal, M. Tetrahedron Lett 2006, 47, 7317.

[43] Goodwin, S.; Smith, A. F.; Horning, E. C. J Am Chem Soc 1957, 79, 2239.

[44] Somanathan, R.; Smith, K. M. J Heterocyclic Chem 1981, 18, 1077.

[45] Jaroszewski, J. W. J Heterocyclic Chem 1990, 27, 1227.

[46] Kuo, S. C.; Lee, H. Z.; Juang, J. P.; Lin, Y. T.; Wu, T. S.; Chang, J. J.; Lednicer, D.; Paull, K. D.; Lin, C. M.; Hamel, E.; Lee, K. H. J Med Chem 1993, 36, 1146.

[47] Shim, S. C.; Chae, S. A.; Lee, D. Y.; Lim, H. S.; Kalinin, V. N. J Kor Chem Soc 1994, 38, 774.

[48] Hadjeri, M.; Mariotte, A.-M.; Boumendjel, A. Chem Pharm Bull 2001, 49, 1352.

[49] Pain, C.; Célanire, S.; Guillaumet, G.; Joseph, B. Tetrahedron 2003, 59, 9627.

[50] Mphahlele, M. J. J Chem Res 2002, 196.

[51] Mphahlele, M. J.; Fernandes, M. A.; Ottosson, H.; El-Nahas, A. M.; Ndlovu, S. M.; Sithole, H. M.; Dladla, B. S.; De Waal, D. J Chem Soc Perkin Trans 2 2002, 2159.

[52] Koyama, J.; Toyokuni, I.; Tagahara, K. Chem Pharm Bull 1999, 47, 1038.

[53] Coppola, G. M. J Heterocyclic Chem 1982, 19, 727.

[54] Niedzinski, E. J.; Lashley, M. R.; Nantz, M. H. Heterocycles 2001, 55, 623.

[55] Manfroni, G.; Gatto, B.; Tabarrini, O.; Sabatini, S.; Cecchetti, V.; Giaretta, G.; Parolin, C.; Del Vecchio, C.; Calistri, A.; Palumbo, M.; Fravolini, A. Bioorg Med Chem Lett 2009, 19, 714.

[56] Beney, C.; Hadjeri, M.; Mariotte, A.; Boumendjel, A. Tetrahedron Lett 2000, 41, 7037.

[57] Hessian, K. O.; Flynn, B. L. Org Lett 2006, 8, 243.

[58] Strekowski, L.; Wydra, R. L.; Cegla, M. T.; Czarny, A.; Harden, D. B.; Patterson, S. E.; Battiste, M. A.; Coxon, J. M. J Org Chem 1990, 55, 4777.

[59] Janda, L.; Nguyen, J.; Patterson, S. E.; Strekowski, L. J Heterocyclic Chem 1992, 29, 1753.

[60] Singh, O. V.; Kapil, S. Synlett 1992, 751.

[61] Varma, R. S.; Kumar, D. Tetrahedron Lett 1998, 39, 9113.

[62] Mphahlele, M. J.; Hlatshwayo, S. M.; Mogamisi, F. K.; Tsanwani, M.; Mampa, R. M. J Chem Res 1999, 706.

[63] Kumar, K. H.; Muralidharan, D.; Perumal, P. T. Tetrahedron Lett 2004, 45, 7903.

[64] Kumar, K. H.; Muralidharan, D.; Perumal, P. T. Tetrahedron 2007, 63, 9531.

[65] Acardi, A.; Marinelli, F.; Rossi, E. Tetrahedron 1999, 55, 13233.

[66] Wang, Y.; Peng, C.; Liu, L.; Zhao, J.; Su, L.; Zhu, Q. Tetrahedron Lett 2009, 50, 2261.

[67] Ryabukhin, S. V.; Volochnyuk, D. M.; Plaskon, A. S.; Naumchik, V. S.; Tolmachev, A. A. Synthesis 2007, 1214.

[68] Akila, S.; Selvi, S.; Balasubramanian, K. Tetrahedron 2001, 57, 3465.

[69] Andersen, K. E.; Lundt, B. F.; Jørgensen, A. S.; Braestrup, C. Eur J Med Chem 1996, 31, 417.

[70] Mphahlele, M. J.; Mtshemla, V. J Chem Res 2008, 437.

[71] Hoekstra, W. J.; Patel, H. S.; Liang, X.; Blane, J.-P. E.; Heyer, D. O.; Willson, T. M.; Iannone, M. A.; Kadwell, S. H.; Miller, L. A.; Pearce, K. H.; Simmons, G. A.; Shearin, J. J Med Chem 2005, 48, 2243.

[72] Kouznetsov, V. V.; Méndez, L. Y. V.; Gómez, C. M. M. Curr Org Chem 2005, 9, 141.

# Syntheses and Herbicidal Activity of Pyrazolyl Benzoxazole Derivatives

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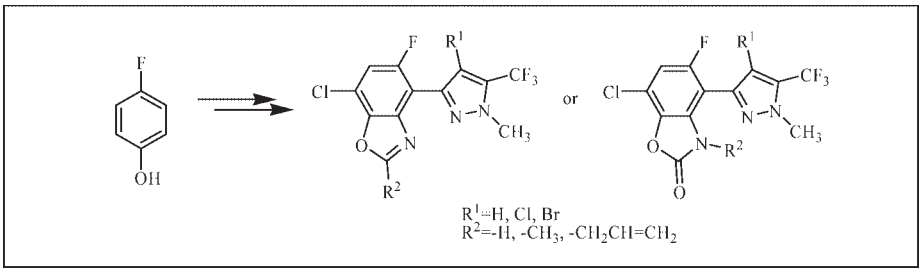


In recent years, protoporphyrinogen oxidase (Protox) inhibitor herbicides are developed rapidly, because of this type of herbicides shows high herbicidal activity and low toxicity. In this paper, we prepared a series of new substituted pyrazolyl benzoxazole derivative, which were synthesized from 4-fluorophenol, via a serial of reactions included chlorination, acylation, condensation, ring closure, methylation, nitration, and so on. All the structures are confirmed by $^1$H NMR, MS and element analysis. Preliminary bioassay shows that most substituted pyrazolyl benzoxazole derivatives exhibit high herbicidal activity to the tested gramineous weeds and latifoliate weeds.

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## INTRODUCTION

Herbicides play an important role in agricultural practices. In recent 30 years, herbicides targeting the enzyme protoporphyrinogen IX oxidase (Protox), which have been used commercially to control annual grasses and weeds in soybean, peanut, cotton, rice, and other crops, are developed rapidly [1–3], because this type of herbicides shows high bioactivity and low toxicity. Diphenyl ether (DPE) herbicides are the first widely used family of Protox inhibitor herbicides. Nitrofen was the leading compound of this kind [4].

The bicyclic nature of diphenyl ethers is similar to the structure of half of protoporphyrinogen IX, which allows competitive inhibition of Protox located in the plastid by occupying the binding site for protoporphyrinogen IX [5–7]. Besides, many other chemical structures belong to this family are reported, such as phenyl heterocycle (Heterocycle including triazolinone, oxazolidone, pyrazole, phthalamide, etc.) and benzoheterocycle. Many of them are commercial and of high bioactivity [8–11]. Some samples of commercial Protox inhibitors are shown in Figure 1.

As the development of Protox inhibitor, many benzoheterocyclic compounds have shown good herbicidal activity, which are effective at controlling grass and broadleaf weeds at low dose [12–14]. In recent years, benzoxazole derivatives were found to be high bioactivities [15–19]. Earlier work at our laboratory involved some pyrazole [20] and isoxazole [21] derivatives with high herbicidal activity. In this article, we described the syntheses and herbicidal activity of pyrazolyl benzoxazole derivatives. Preliminary bioassay showed that most of them had good herbicidal activity.

## RESULTS AND DISCUSSION

The syntheses of the compounds are described in the Schemes 1 and 2, and the yields were not optimized. The intermediates **10a–10c** and **11a–11c** were synthesized from 4-fluorophenol, via a serial of reactions included chlorination, acylation, condensation, ring closure, methylation, nitration, and so on (Scheme 1). The title compounds can be obtained through the different ring-close and alkyl reactions from compounds **10a–10c** or **11a–11c** (Scheme 2).

The synthesis of **11** is the key step, which involves reducing nitro group to amino group in the phenyl ring. At the beginning, we used sodium sulfide to reduce nitro group, the yield was only 10%. We also used the method of catalytic hydrogenation with Pt/C, but the selectivity was not good. Finally, we found reduction of **10** with iron and saturated ammonium chloride has the higher yield (86%) and selectivity. For the product **11** is sensitive to air, reaction should be carried out under

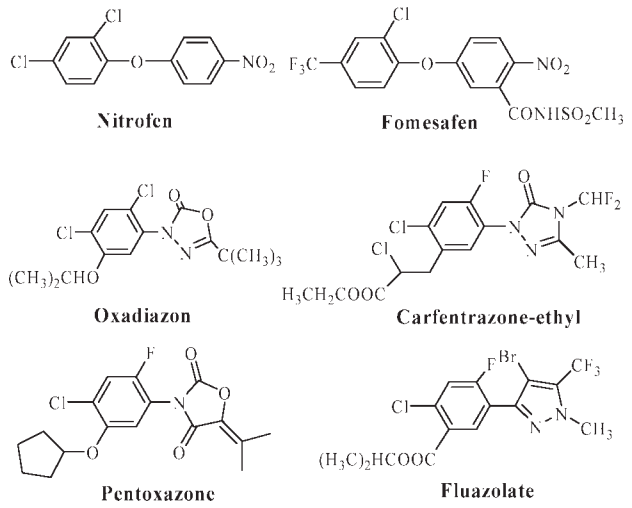



**Figure 1.** Samples of commercial protox inhibitors.

nitrogen, and the crude product is used directly in the next reaction without further purification.

**13** can be synthesized by stirring the mixture of compounds **11** and acetyl chloride or acetic anhydride at room temperature, but the selectivity was not satisfied. So we changed to another pathway. At first, **10** was acetylation to form **12**, then **12** was reduced with iron and subjected to ring-closed in acetic acid. By that way **13** was made in good yield.

**15** and **16** are isomers. The different reacting conditions lead to different products. When using base such as anhydrous potassium carbonate as the catalyst, and acetone as solvent, alkyl was attached to atom N. But when silver (I) oxide and methylene chloride were employed, alkyl was attached to atom O. The distinguishing of **15** and **16** can be determined by the shift of $^1$H NMR. For example, **15a:** δ: 3.18 (s, 3H, NC$H_3$); **16a:** δ: 4.31 (s, 3H, OC$H_3$).

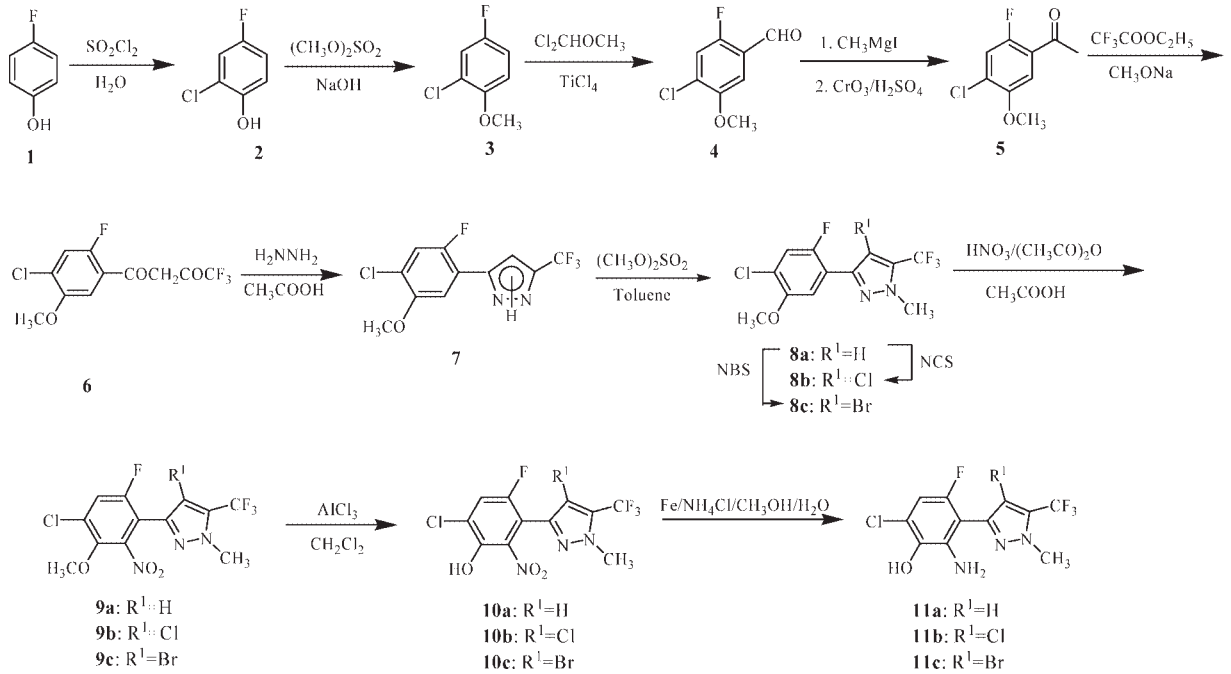
The herbicidal activity of the compounds were tested against *Setaria viridis, Ditaria sanguinalis* (monocot crops) and *Abutilon theophrasti* (dicot crops) using Fomesafen and Fluazolate for comparison. The results shown in Table 1 were the effect visual measurement treat after 10 days.

From Table 1 we can conclude that most of them had good herbicidal activity. When no substituent on pyrazole position 4, there is no herbicidal activity or low activity (**13a, 14a, 15a, 16a, 17a**), but when halogen (such as chlorine or bromine) is on pyrazole, most of them show good herbicidal efficacy. Similar results have been reported by Meazza *et al*. [22]. Their study on pyrroles showed that the halopyrrole nucleus is important for biological activity; if there is only hydrogen on pyrrole the compounds are virtually inactive.

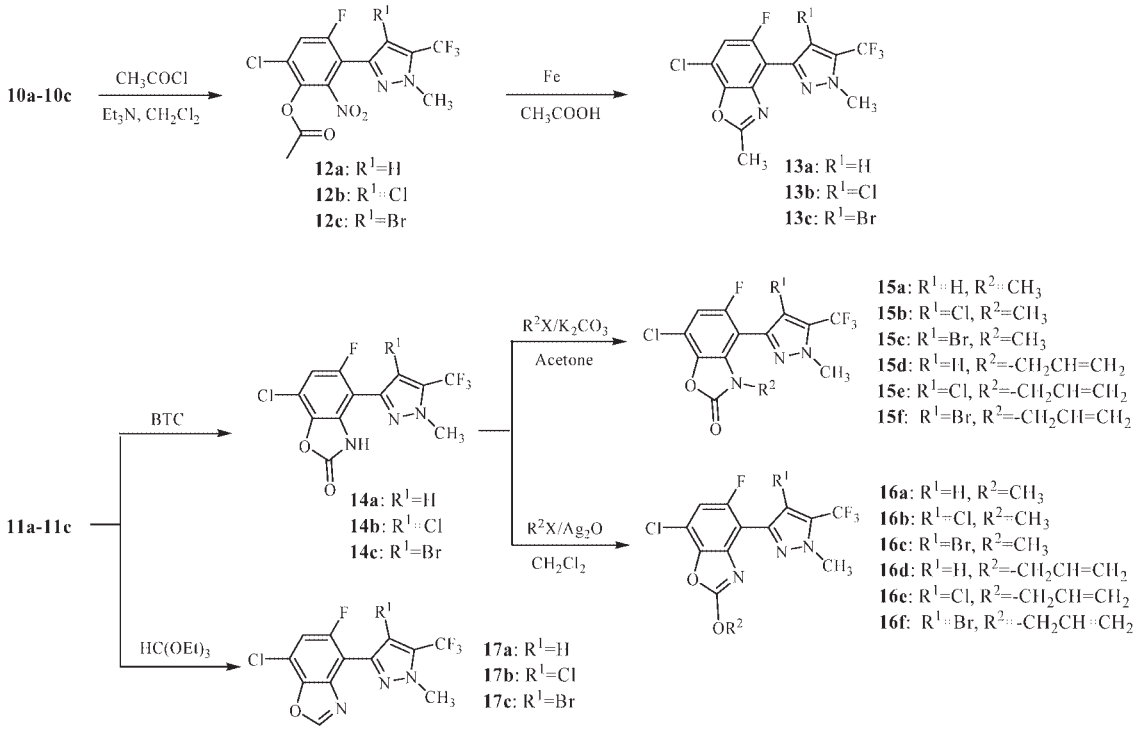
The herbicidal activity of compound **14** is not high, mainly because of its poor lipophilicity. When its lipophilicity is increased by introducing methyl or allyl to N or O atom, which form **15** or **16**, the activity is much increased.

Compared with corresponding compounds **15** (**b, c, e, f**) and **16** (**b, c, e, f**) , we can find that the herbicidal

**Scheme 1.** Syntheses of the intermediates.



**Scheme 2.** Syntheses of the aimed compounds.




activities of the compounds alkyl attached to atom O is higher than that of alkyl attached to atom N. And the activity of **16b** is all 100% even at the usage dose of 37.5 g/hm$^2$, so it is a valuable compound that fit for dicot crops and monocot crops. **15b** and **15e** are good for dicot crops, reached more than 80% at the usage

**Table 1**

Herbicidal activity of the title compounds.[a]

| | *Setaria viridis* | | | *Ditaria sanguinalis* | | | *Abutilon theophrasti* | | |
|---|---|---|---|---|---|---|---|---|---|
| Comp. | 37.5[b] | 150[b] | 600[b] | 37.5[b] | 150[b] | 600[b] | 37.5[b] | 150[b] | 600[b] |
| **13a** | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| **13b** | 4 | 7 | 8 | 5 | 7 | 8 | 6 | 6 | 7 |
| **13c** | 2 | 4 | 5 | 1 | 3 | 5 | 2 | 4 | 6 |
| **14a** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **14b** | 1 | 5 | 6 | 1 | 3 | 4 | 2 | 6 | 7 |
| **14c** | 0 | 1 | 2 | 0 | 1 | 2 | 1 | 3 | 4 |
| **15a** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **15b** | 1 | 3 | 8 | 1 | 4 | 8 | 9 | 10 | 10 |
| **15c** | 3 | 6 | 8 | 3 | 4 | 7 | 5 | 9 | 10 |
| **15e** | 2 | 4 | 5 | 2 | 5 | 6 | 8 | 10 | 10 |
| **15f** | 2 | 3 | 7 | 5 | 5 | 7 | 7 | 8 | 10 |
| **16a** | 1 | 2 | 4 | 3 | 3 | 5 | 3 | 6 | 9 |
| **16b** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **16c** | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 |
| **16e** | 5 | 5 | 6 | 3 | 5 | 6 | 5 | 8 | 9 |
| **16f** | 8 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 10 |
| **17a** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| **17b** | 3 | 7 | 9 | 5 | 6 | 9 | 7 | 10 | 10 |
| **17c** | 8 | 10 | 10 | 7 | 9 | 10 | 10 | 10 | 10 |
| Fomesafen | 4 | 9 | 10 | 4 | 9 | 10 | 6 | 9 | 10 |
| Fluazolate | 9 | 10 | 10 | 9 | 10 | 10 | 9 | 10 | 10 |

[a] 0 = no activity and 10 = total kill.
[b] The usage dose of compounds (g a.i./ hm$^2$).

dose of 37.5 g/hm$^2$, but for monocot crops, the activity not very high. The activity of **17c** is higher than **17b** for monocot crops, but for dicot crops, they are the same.

The activity of compounds **16b, 16c, 16f,** and **17c** is obviously higher than Fomesafen, **16b** and **16c** is even a little higher than Fluazolate.

## EXPERIMENTAL

Melting points were taken on a Micro melting point apparatus (X-6, Beijing Tech Instrument Co. Ltd.) and were uncorrected. $^1$H NMR spectra were measured in deuterochloroform on a Varian VA400 MHz spectrometer with TMS as an internal standard. Elemental analyses were performed on a Vario EL III (Elementar, German) elemental analysis instrumentation. MS were obtained with a HP1100 high Performance Liquid Chromatography/Mass Selective Detector.

**8** were synthesized from 4-Fluorophenol according to the existing methods [23,24].

**General procedure for 9a–9c.** ***3-(4-Chloro-6-fluoro-3-methoxy-2-nitrophenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (9a)*** A mixed acid (27 mL, V(acetic anhydride): V(fuming nitric acid)= 2:1) was added dropwise to a solution of **8a** ( 8 g, 0.026 mol) in acetic acid (25 mL) while maintaining the reaction solution at 0°C, and the resulting mixture was stirred at 0°C for 2 h. The reaction solution was poured into water, filtrated, and washed with water. The crude product was recrystallized with ethanol. **9a** was obtained in 83% yield as a faint yellow solid; m.p. 94.0–96.0°C; MS (API-ES, positive), *m*/*z*: 354 ([M+H]$^+$); **$^1$H NMR**, δ: 7.37 (d, 1H, $J$ = 9.6 Hz, Ph-*H*), 6.94 (d, 1H, $J$ = 3.2 Hz, Pyr-*H*), 4.02 (s, 3H, Pyr-C$H_3$), 3.98 (s, 3H, OC$H_3$). Anal. Calcd. for $C_{12}H_8ClF_4N_3O_3$ (353.7): C, 40.75; H, 2.28; N, 11.88. Found: C, 40.87; H, 2. 35; N, 11.67.

***4-Chloro-3-(4-chloro-6-fluoro-3-methoxy-2-nitrophenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (9b).*** The compound was orange pasty matter and was used directly in the next reaction without purification; MS (API-ES, positive), *m*/*z*: 388 ([M+H]$^+$); **$^1$H NMR**, δ: 7.42 (d, 1H, $J$ = 7.6 Hz, Ph-*H*), 4.02 (s, 3H, Pyr-C$H_3$), 4.01 (s, 3H, OC$H_3$). Anal. Calcd. for $C_{12}H_7Cl_2F_4N_3O_3$ (388.1): C, 37.14; H, 1.82; N, 10.83. Found: C, 36.87; H, 1.63; N, 10.67.

***4-Bromo-3-(4-chloro-6-fluoro-3-methoxy-2-nitrophenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (9c).*** The compound was orange pasty matter and was used directly in the next reaction without purification; MS (API-ES, positive), *m*/*z*: 432 ([M+H]$^+$); **$^1$H NMR**, δ: 7.42 (d, 1H, $J$ = 7.6 Hz, Ph-*H*), 4.03 (s, 3H, Pyr-C$H_3$), 4.01 (s, 3H, OC$H_3$). Anal. Calcd. for $C_{12}H_7BrClF_4N_3O_3$ (432.6): C, 33.32; H, 1.63; N, 9.71. Found: C, 32.99; H, 1.60; N, 9.62.

**General procedure for 10a-10c.** ***6-Chloro-4-fluoro-3-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-nitrophenol (10a).*** A mixture of **9a** (3.9 g, 11 mmol), anhydrous aluminium chloride (3.7 g, 27.7 mmol) and dichloromethane (70 mL) were stirred at room temperature for 2 h. The reaction solution was poured into icy hydrochloric acid and extracted with dichloromethane (20 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under vacuum. **10a** was obtained in 100% yield as a yellow powder and was used directly in the next reaction without purification. A sample suiting for analysis was obtained by recrystallization with a mixture of petroleum ether and ethyl acetate (3:1); m.p. 94.0–97.0°C; MS (API-ES, negative), *m*/*z*: 338 ([M-H]$^-$); $^1$H NMR, δ: 7.53 (d, 1H, $J$ = 9.6 Hz, Ph-*H*), 6.95 (d, 1H, $J$ = 3.2 Hz, Pyr-*H*), 4.01 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{11}H_6ClF_4N_3O_3$ (339.6): C, 38.90; H, 1.78; N, 12.37. Found: C, 38.84; H, 1.71; N, 12.42.

***6-Chloro-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-4-fluoro-2-nitrophenol (10b).*** The compound was a light yellow powder and was used directly in the next reaction without purification. The yield of two steps was 82%. A sample suiting for analysis was obtained by recrystallization with a mixture of petroleum ether and ethyl acetate (3:1); m.p. 85.2–87.1°C; MS (API-ES, negative), *m*/*z*: 372 ([M-H]$^-$); **$^1$H NMR**, δ: 7.58 (d, 1H, $J$ = 8.4 Hz, Ph-*H*), 4.03 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{11}H_5Cl_2F_4N_3O_3$ (374.1): C, 35.32; H, 1.35; N, 11.23. Found: C, 35.64; H, 1.43; N, 11.42.

***3-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-6-chloro-4-fluoro-2-nitrophenol (10c).*** The compound was a yellow powder and was used directly in the next reaction without purification. The yield of two steps was 83%. A sample suiting for analysis was obtained by recrystallization with a mixture of petroleum ether and ethyl acetate (3:1); m.p. 86.3–88.6°C; MS (API-ES, negative), *m*/*z*: 416 ([M-H]$^-$); **$^1$H NMR**, δ: 7.58 (d, 1H, $J$ = 8.4 Hz, Ph-*H*), 4.04 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{11}H_5BrClF_4N_3O_3$ (418.5): C, 31.57; H, 1.20; N, 10.04. Found: C, 31.69; H, 1.23; N, 10.25.

**General procedure for 11a–11c.** ***2-Amino-6-chloro-4-fluoro-3-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)phenol (11a).*** Under nitrogen a mixture of **10a** (3.7 g, 10.9 mmol), iron (3.8 g, 0.068 mol), a solution of saturated ammonium chloride (120 mL) and methanol (80 mL) were stirred at 55°C for 6 h. Then methanol was removed under vacuum. The reaction solution was filtrated and the filtrate was extracted with ethyl acetate (40 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under vacuum. **11a** was obtained in 86% yield as a brown solid and was used directly in the next reaction without purification.

***2-Amino-6-chloro-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-4-fluorophenol (11b).*** The crude product was obtained as brown paste and was used directly in the next reaction without purification. The yield of crude product was 95%.

***2-Amino-3-(4-bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-6-chloro-4-fluorophenol (11c).*** The crude product was obtained as brown paste and was used directly in the next reaction without purification. The yield of crude product was 90%.

**General procedure for 12a–12c.** ***6-Chloro-4-fluoro-3-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-nitrophenyl acetate (12a).*** A mixture of **10a** (650 mg, 1.91 mmol), acetyl chloride (0.2 mL, 2.96 mmol), triethylamine (0.3 mL, 2.16 mmol) and methylene chloride (25 mL) was stirred at 40°C for 1 h. The reaction solution was poured into water. The organic layer was washed with a solution of 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude product was recrystallized with ethanol. **12a** was obtained in 85% yield as a white powder; m.p. 137.5–139.2°C; MS (API-ES, positive), *m*/*z*: 382 ([M+H]$^+$), 404 ([M+Na]$^+$); **$^1$H NMR** δ: 7.45 (d, $J$ = 9.6 Hz, 1H, Ph-*H*),

6.95 (d, $J$ = 3.2 Hz, 1H, Pyr-*H*), 4.00 (s, 3H, Pyr-C$H_3$), 2.36 (s, 3H, COC$H_3$). Anal. Calcd. for $C_{13}H_8ClF_4N_3O_4$ (381.7): C, 40.91; H, 2.11; N, 11.01. Found: C, 40.62; H, 2.20; N, 11.25.

***6-Chloro-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-4-fluoro-2-nitrophenyl acetate (12b).*** The compound was obtained in 75% yield as a light brown powder; m.p. 103.8–105.3°C; MS (API-ES, positive), *m*/*z*: 416 ([M+H]$^+$), 438 ([M+Na]$^+$); **$^1$H NMR** δ: 7.51 (d, $J$ = 8.4 Hz, 1H, Ph-*H*), 4.02 (s, 3H, Pyr-C$H_3$), 2.37 (s, 3H, COC$H_3$). Anal. Calcd. for $C_{13}H_7Cl_2F_4N_3O_4$ (416.1): C, 37.52; H, 1.70; N, 10.10. Found: C, 37.69; H, 1.73; N, 10.27.

***3-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-6-chloro-4-fluoro-2-nitrophenyl acetate (12c).*** The compound was obtained in 72% yield as a brown powder; m.p. 107.9–109.0°C; MS (API-ES, positive), *m*/*z*: 460 ([M+H]$^+$); **$^1$H NMR** δ: 7.51 (d, $J$ = 8.0 Hz, 1H, Ph-*H*), 4.04 (s, 3H, Pyr-C$H_3$), 2.37 (s, 3H, COC$H_3$). Anal. Calcd. for $C_{13}H_7BrClF_4N_3O_4$ (460.6): C, 33.90; H, 1.53; N, 9.12. Found: C, 34.02; H, 1.68; N, 8.91.

**General procedure for 13a–13c.** ***7-chloro-5-fluoro-2-methyl-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-benzoxazole (13a).*** Under nitrogen a mixture of **12a** (680 mg, 1.78 mmol), iron (1.0 g, 0.017 mol), and acetic acid (35 mL) were stirred at 80°C for 3 h. The reaction solution was filtrated and the filtrate was poured into water, filtrated, and washed with water, recrystallized with ethanol. **13a** was obtained in 74% yield as a white solid; m.p. 124.9–126.9°C; MS (API-ES, positive), *m*/*z*: 334 ([M+H]$^+$), 356 ([M+Na]$^+$); **$^1$H NMR** δ: 7.27 (s, 1H, Pyr-*H*), 7.21 (d, $J$ = 10.8 Hz, 1H, Ph-*H*), 4.14 (s, 3H, Pyr-C$H_3$), 2.73 (s, 3H, Oxa-C$H_3$). Anal. Calcd. for $C_{13}H_8ClF_4N_3O$ (333.7): C, 46.79; H, 2.42; N, 12.59. Found: C, 46.84; H, 2.41; N, 12.72.

***7-Chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-2-methyl-benzoxazole (13b).*** The compound was obtained in 70% yield as a light yellow paste; MS (API-ES, positive), *m*/*z*: 368 ([M+H]$^+$), 390 ([M+Na]$^+$); **$^1$H NMR** δ: 7.23 (d, $J$ = 9.6 Hz, 1H, Ph-*H*), 4.11 (s, 3H, Pyr-C$H_3$), 2.70 (s, 3H, Oxa-C$H_3$). Anal. Calcd. for $C_{13}H_7Cl_2F_4N_3O$ (368.1): C, 42.42; H, 1.92; N, 11.41. Found: C, 42.53; H, 1.94; N, 11.40.

***4-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-2-methyl-benzoxazole (13c).*** The compound was obtained in 74% yield as a white powder; m.p. 139.4–140.9°C; MS (API-ES, positive), *m*/*z*: 412 ([M+H]$^+$); **$^1$H NMR** δ: 7.23 (d, $J$ = 9.6 Hz, 1H, Ph-*H*), 4.13 (s, 3H, Pyr-C$H_3$), 2.70 (s, 3H, Oxa-C$H_3$). Anal. Calcd. for $C_{13}H_7BrClF_4N_3O$ (412.6): C, 37.85; H, 1.71; N, 10.19. Found: C, 38.08; H, 1.71; N, 10.32.

**General procedure for 14a–14c.** ***7-Chloro-5-fluoro-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-3H-benzoxazol-2-one (14a).*** A solution of **11a** (600 mg, 1.94 mmol) in toluene (6 mL) was added dropwise to a solution of triphosgene (210 mg, 0.71 mmol) in toluene (2 mL). After the reaction solution was stirred at room temperature for 1 h, triethylamine (0.2 mL) was added. Stirred for 0.5 h, the reaction solution was poured into water. The organic layer was washed with a solution of 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate and concentrated under vacuum. After recrystallization with ethanol, **14a** was obtained in 69% yield as a light brown powder; m.p. 213.6–215.2°C; MS (API-ES, positive), *m*/*z*: 336 ([M+H]$^+$), 358 ([M+Na]$^+$); **$^1$H NMR** δ: 9.48 (s, 1H, N-*H*), 7.16 (d, $J$ = 3.6 Hz, 1H, Pyr-*H*), 6.97 (d, $J$ = 11.6 Hz, 1H, Ph-*H*), 4.11 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{12}H_6ClF_4N_3O_2$ (335.6): C, 42.94; H, 1.80; N, 12.52. Found: C, 43.12; H, 1.95; N, 12.58.

***7-Chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-3H-benzoxazol-2-one (14b).*** The compound was obtained in 59% yield as a white powder; m.p. 217.2–218.5°C; MS (API-ES, positive), *m*/*z*: 392 ([M+Na]$^+$); **$^1$H NMR** δ: 8.86 (s, 1H, N-*H*), 7.01 (d, $J$ = 10.4 Hz, 1H, Ph-*H*), 4.13 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{12}H_5Cl_2F_4N_3O_2$ (370.1): C, 38.94; H, 1.36; N, 11.35. Found: C, 38.78; H, 1.42; N, 11.36.

***4-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-3H-benzoxazol-2-one (14c).*** The compound was obtained in 84% yield as a brown powder; m.p. 217.1–219.8°C; MS (API-ES, negative), *m*/*z*: 412 ([M-H]$^-$), 450 ([M+Cl]$^-$); **$^1$H NMR** δ: 8.67 (s, 1H, N-*H*), 7.01 (d, $J$ = 10.4 Hz, 1H, Ph-*H*), 4.15 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{12}H_5BrClF_4N_3O_2$ (414.5): C, 34.77; H, 1.22; N, 10.14. Found: C, 35.03; H, 1.31; N, 10.32.

**General procedure for 15a–15f.** A mixture of Compound **14a** (600 mg, 1.62 mmol), a small amount of anhydrous potassium carbonate, dimethyl sulfate (0.5 mL, 5 mmol) or bromoallylene (0.3 mL, 3.1 mmol)and acetone (15 mL) was stirred at ambient temperature for 3 h. The reaction solution was poured into water and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel chromatography with eluent (petroleum ether:ethyl acetate = 6:1).

***7-Chloro-5-fluoro-3-methyl-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-3H-benzoxazol-2-one (15a).*** The Compound was obtained in 34% yield as a light yellow powder; m.p. 194–198°C; MS (API-ES, positive), *m*/*z*: 350 ([M+H]$^+$), 372 ([M+Na]$^+$); **$^1$H NMR** δ: 6.97 (d, $J$ = 10.0 Hz, 1H, Ph-*H*), 6.85 (s, 1H, Pyr-*H*), 4.09 (s, 3H, Pyr-C$H_3$), 3.18 (s, 3H, NC$H_3$). Anal. Calcd. for $C_{13}H_8ClF_4N_3O_2$ (349.7): C, 44.65; H, 2.31; N, 12.02. Found: C, 44.58; H, 2.45; N, 12.01.

***7-Chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-3-methy-3H-benzoxazol-2-one (15b).*** The compound was obtained in 29% yield as a light brown powder; m.p. 103.1–104.8°C; MS (API-ES, positive), *m*/*z*: 384 ([M+H]$^+$), 406 ([M+Na]$^+$); **$^1$H NMR** δ: 7.00 (d, $J$ = 10.0 Hz, 1H, Ph-*H*), 4.11 (s, 3H, Pyr-C$H_3$), 3.08 (s, 3H, NC$H_3$). Anal. Calcd. for $C_{13}H_7Cl_2F_4N_3O_2$ (384.1): C, 40.65; H, 1.84; N, 10.94. Found: C, 40.97; H, 2.00; N, 10.28.

***4-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-3-methy-3H-benzoxazol-2-one (15c).*** The compound was obtained in 28% yield as a light yellow powder; m.p. 126.8–128.9°C; MS (API-ES, positive), *m*/*z*: 428 ([M+H]$^+$), 450 ([M+Na]$^+$); **$^1$H NMR** δ: 6.99 (d, $J$ = 9.6 Hz, 1H, Ph-*H*), 4.13 (s, 3H, Pyr-C$H_3$), 3.05 (s, 3H, NC$H_3$). Anal. Calcd. for $C_{13}H_7BrClF_4N_3O_2$ (428.6): C, 36.43; H, 1.65; N, 9.80. Found: C, 36.46; H, 1.68; N, 9.55.

***3-Allyl-7-chloro-5-fluoro-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-3H-benzoxazol-2-one (15d).*** The compound was obtained in 33% yield as a white powder; m.p. 93.3–95.2°C; MS (API-ES, positive), *m*/*z*: 376 ([M+H]$^+$), 398 ([M+Na]$^+$); **$^1$H NMR** δ: 6.98 (d, $J$ = 10.0 Hz, 1H, Ph-*H*), 6.80 (s, 1H, Pyr-*H*), 5.44 (m, 1H, C*H*=CH$_2$), 4.96 (d, $J$ = 10.4 Hz, 1H, 1/2 C$H_2$=), 4.68 (d, $J$ = 17.2 Hz, 1H, 1/2 C$H_2$=), 4.47 (d, $J$ =

5.2 Hz, 2H, N-C$H_2$), 4.09 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{15}H_{10}ClF_4N_3O_2$ (375.7): C, 47.95; H, 2.68; N, 11.18. Found: C, 48.11; H, 2.69; N, 11.09.

***3-Allyl-7-chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-3H-benzoxazol-2-one (15e).*** The compound was obtained in 36% yield as a light brown powder; m.p. 89.4–91.3°C; MS (API-ES, positive), *m*/*z*: 410 ([M+H]$^+$), 432 ([M+Na]$^+$); **$^1$H NMR** δ: 7.02 (d, *J* = 10.0 Hz, 1H, Ph-*H*), 5.44 (m, 1H, C*H*=CH$_2$), 4.99 (d, *J* = 10.4 Hz, 1H, 1/2 C$H_2$=), 4.67 (d, *J* = 16.8 Hz, 1H, 1/2 C$H_2$=), 4.31 (d, *J* = 17.2 Hz, 2H, N-C$H_2$), 4.10 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{15}H_9Cl_2F_4N_3O_2$ (410.2): C, 43.93; H, 2.21; N, 10.25. Found: C, 44.33; H, 2.49; N, 9.86.

***3-Allyl-4-(4-bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-3H-benzoxazol-2-one (15f).*** The compound was obtained in 42% yield as a white powder; m.p. 130.2–132.0°C; MS (API-ES, positive), *m*/*z*: 454 ([M+H]$^+$), 476 ([M+Na]$^+$); **$^1$H NMR** δ: 7.01 (d, *J* = 9.6 Hz, 1H, Ph-*H*), 5.42 (m, 1H, C*H*=CH$_2$), 5.00 (d, *J* = 10.4 Hz, 1H, 1/2 C$H_2$=), 4.69 (d, *J* = 16.8 Hz, 1H, 1/2 C$H_2$=), 4.37 (m, 1H,1/2 N-C$H_2$), 4.19 (m, 1H,1/2 N-C$H_2$), 4.12 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{15}H_9BrClF_4N_3O_2$ (454.6): C, 39.63; H, 2.00; N, 9.24. Found: C, 39.41; H, 1.98; N, 9.19.

**General procedure for 16a–16f.** A mixture of **14a** (600 mg, 1.62 mmol), methyl iodide (0.51 g, 3 mmol), and sliver(I) oxide (417 mg, 1.80 mmol) in methylene chloride (50 mL) was stirred at ambient temperature for 24 h. Sliver(I) oxide was filtered and filtrate was concentrated under vacuum. The crude product was purified by silica gel chromatography with eluent (petroleum ether:ethyl acetate = 6:1).

***7-Chloro-5-fluoro-2-methoxy-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-benzoxazole (16a).*** The compound was obtained in 42% yield as a light yellow powder; m.p. 129.7–132.1°C; MS (API-ES, positive), *m*/*z*: 350 ([M+H]$^+$), 372 ([M+Na]$^+$); **$^1$H NMR** δ: 7.31 (s, 1H, Pyr-*H*), 7.08 (d, *J* = 11.6 Hz, 1H, Ph-*H*), 4.31 (s, 3H, OC$H_3$), 4.12 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{13}H_8ClF_4N_3O_2$ (349.7): C, 44.65; H, 2.31; N, 12.02. Found: C, 44.58; H, 2.45; N, 12.01.

***7-Chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-2-methoxy-benzoxazole (16b).*** The compound was obtained in 19% yield as a light yellow pasty matter. MS (API-ES, positive), *m*/*z*: 384 ([M+H]$^+$), 406 ([M+Na]$^+$); **$^1$H NMR** δ: 7.08 (d, *J* = 10.0 Hz, 1H, Ph-*H*), 4.24 (s, 3H, OC$H_3$), 4.10 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{13}H_7Cl_2F_4N_3O_2$ (384.1): C, 40.65; H, 1.84; N, 10.94. Found: C, 40.41; H, 1.89; N, 10.51.

***4-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-2-methoxy-benzoxazole (16c).*** The compound was obtained in 45% yield as a light yellow pasty matter. MS (API-ES, positive), *m*/*z*: 428 ([M+H]$^+$), 450 ([M+Na]$^+$); **$^1$H NMR** δ: 7.08 (d, *J* = 10.0 Hz, 1H, Ph-*H*), 4.24 (s, 3H, OC$H_3$), 4.13 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{13}H_7BrClF_4N_3O_2$ (428.6): C, 36.43; H, 1.65; N, 9.80. Found: C, 36.73; H, 1.79; N, 9.58.

***2-(Allyloxy)-7-chloro-5-fluoro-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)benzoxazole (16d).*** The compound was obtained in 19% yield as a white powder; m.p. 122.4–123.4°C; MS (API-ES, positive), *m*/*z*: 376 ([M+H]$^+$), 398 ([M+Na]$^+$); **$^1$H NMR** δ: 7.32 (s, 1H, Pyr-*H*), 7.08 (d, *J* = 11.2 Hz, 1H, Ph-*H*), 6.09 (m, 1H, C*H*=CH$_2$), 5.55 (d, *J* = 16.8 Hz, 1H, 1/2 C$H_2$=), 5.42 (d, *J* = 10.4 Hz, 1H, 1/2 C$H_2$=), 5.13 (d, *J* = 6.0 Hz, 2H, O-C$H_2$), 4.11 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{15}H_{10}ClF_4N_3O_2$ (375.7): C, 47.95; H, 2.68; N, 11.18. Found: C, 48.24; H, 2.86; N, 10.79.

***2-(Allyloxy)-7-chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-benzoxazole (16e).*** The compound was obtained in 13% yield as transparent pasty matter. MS (API-ES, positive), *m*/*z*: 410 ([M+H]$^+$); **$^1$H NMR** δ: 7.08 (d, *J* = 10.0 Hz, 1H, Ph-*H*), 6.05 (m, 1H, C*H*=CH$_2$), 5.50 (d, *J* = 14.8 Hz, 1H, 1/2 C$H_2$=), 5.39 (d, *J* = 9.6 Hz, 1H, 1/2 C$H_2$=), 5.05 (d, *J* = 6.0 Hz, 2H, O-C$H_2$), 4.10 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{15}H_9Cl_2F_4N_3O_2$ (410.2): C, 43.93; H, 2.21; N, 10.25. Found: C, 44.00; H, 2.07; N, 9.84.

***2-(Allyloxy)-4-(4-bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-benzoxazole (16f).*** The compound was obtained in 16% yield as transparent pasty matter. MS (API-ES, positive), *m*/*z*: 454 ([M+H]$^+$), 476 ([M+Na]$^+$); **$^1$H NMR** δ: 7.08 (d, *J* = 10.0 Hz, 1H, Ph-*H*), 6.06 (m, 1H, C*H*=CH$_2$), 5.50 (d, *J* = 17.2 Hz, 1H, 1/2 C$H_2$=), 5.38 (d, *J* = 10.4 Hz, 1H, 1/2 C$H_2$=), 5.05 (d, *J* = 6.0 Hz, 2H, O-C$H_2$), 4.12 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{15}H_9BrClF_4N_3O_2$ (454.6): C, 39.63; H, 2.00; N, 9.24. Found: C, 39.72; H, 1.93; N, 9.09.

**General procedure for 17a–17c.** ***7-Chloro-5-fluoro-4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)benzoxazole (17a).*** A mixture of **11a** (500 mg, 1.62 mmol), ethylorthoformate (0.4 mL, 2.42 mmol), Celite (160 mg) and toluene (15 mL) was stirred under nitrogen at 110°C for 18 h. Celite was filtered and filtrate was concentrated under vacuum. The crude product was purified by silica gel chromatography with eluent (petroleum ether:ethyl acetate = 6:1). **17a** was obtained in 42% yield as a light yellow powder; m.p. 158.3–160.5°C; MS (API-ES, positive), *m*/*z*: 320 ([M+H]$^+$), 342 ([M+Na]$^+$); **$^1$H NMR** δ: 8.25 (s, 1H, Oxa-*H*), 7.35 (s, 1H, Pyr-*H*), 7.33 (d, *J* = 10.0 Hz, 1H, Ph-*H*), 4.15 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{12}H_6ClF_4N_3O$ (319.6): C, 45.09; H, 1.89; N, 13.15. Found: C, 45.42; H, 2.04; N, 12.75.

***7-Chloro-4-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-5-fluoro-benzoxazole (17b).*** The compound was obtained in 30% yield as a light brown powder; m.p. 110.7–112.1°C; MS (API-ES, positive), *m*/*z*: 354 ([M+H]$^+$); **$^1$H NMR** δ: 8.22 (s, 1H, Oxa-*H*), 7.35 (d, *J* = 9.6 Hz, 1H, Ph-*H*), 4.13 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{12}H_5Cl_2F_4N_3O$ (354.1): C, 40.70; H, 1.42; N, 11.87. Found: C, 40.34; H, 1.67; N, 11.54.

***4-(4-Bromo-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-7-chloro-5-fluoro-benzoxazole (17c).*** The compound was obtained in 23% yield as a light yellow powder; m.p. 92.1–93.3°C; MS (API-ES, positive), *m*/*z*: 398 ([M+H]$^+$); **$^1$H NMR** δ: 8.21 (s, 1H, Oxa-*H*), 7.35 (d, *J* = 9.6 Hz, 1H, Ph-*H*), 4.14 (s, 3H, Pyr-C$H_3$). Anal. Calcd. for $C_{12}H_5BrClF_4N_3O$ (398.5): C, 36.16; H, 1.26; N, 10.54. Found: C, 36.43; H, 1.56; N, 10.45.

**Herbicidal activity test.** The target plants for the test were *Setaria viridis* (Linn.), *Digitaria sanguinalis* (Linn.) Scop. and *Abutilon theophrasti* Medic.A solution of new compounds or check sample (Fomesafen or Fluazolate) in a small amount of acetone was diluted with stewing tap water which containing 0.1% Tween 80. The solution of the compound to be tested was prepared. Weeds (*Setaria viridis* (Linn.), *Digitaria sanguinalis* (Linn.) Scop. and *Abutilon theophrasti* Medic., two or three leaf stage) which growth well and the same leaf stage were selected, and were spray treated with atomizing machine. The amount of spray was 600 L/hm$^2$. After that the weeds

were aeration-drying and then were cultured at room temperature. Weeds treated with water were the blank test. The herbicidal activity of the compounds was determined after 10 days of treatment. Evaluations were based on a score of 0–10 in which 0 = no activity and 10 = total kill.

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## REFERENCES AND NOTES

[1] Yang, K.; Jung, S.; Lee, Y.; Back, K. Pestic Biochem Physiol 2006, 86, 186.

[2] Scalla, R.; Matringe, M. Rev Weed Sci 1994, 6, 103.

[3] Duke, S. O.; Lydon, J.; Becerril, J. M.; Sherman, T. D.; Lehnen, L. P.; Matsumoto, H. Weed Sci 1991, 39, 465.

[4] (a) Baumgartner, L. L. U.S. Pat. 2,726,947 (1955); (b) Baumgartner, L. L. Chem Abstr 1955, 50, 25653.

[5] Gregory, L. D. Quant Struct Act Relat 1998, 17, 419.

[6] Corradl, H. R.; Corrlgall, A. V.; Bolx, E.; Mohan, C. G.; Sturrock, E. D.; Melssner, P. N.; Achary, K. R. J Biol Chem 2006, 281, 38625.

[7] Patzoldt, W. L.; Hager, A. G.; Mccormick, J. S.; Tranel, P. J. Proc Natl Acad Sci USA 2006, 103, 12329.

[8] (a) Blind, A.; Cassal, J. M.; Boesch, R. D.E. Pat. 2, 039, 397 (1971); (b) Blind, A.; Cassal, J. M.; Boesch, R. Chem Abstr 1971, 74, 100064.

[9] (a) Sato, R.; Morita, K. Eur. Pat. 198, 298 (1985); (b) Sato, R.; Morita, K. Chem Abstr 1985, 106, 28841.

[10] Dayan, F. E.; Duke, S. O.; Weete, J. D.; Hancock, H. G. Pestic Sci 1997, 51, 65.

[11] (a) Hamper, B. C.; Mao, M. K.; Phillips, W. G. U.S. Pat. 6,121,458 (2000); (b) Hamper, B. C.; Mao, M. K.; Phillips, W. G. Chem Abstr 2000, 130, 168364.

[12] Huang, M. Z.; Huang, K. L.; Ren, Y. G.; Lei, M. X.; Huang, L.; Hou, Z. K.; Liu, A. P.; Ou, X. M. J Agric Food Chem 2005, 53, 7908.

[13] Lyga, J. W.; Chang, J. H.; Theodoridis, G.; Baum, J. S. Pestic Sci 1999, 55, 281.

[14] Macfas, F. A.; Marín, D.; Oliveros-Bastidas, A.; Castellano, D.; Simonet, A. M.; Molinillo, J. M. G. J Agric Food Chem 2006, 54, 1040.

[15] Vinod Kumar, R. Chem Asian J 2004, 16, 1241.

[16] Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. J Med Chem 2008, 51, 3367.

[17] Cacic, M.; Trkovnik, M.; Cacic, F.; Has-Schon, E. J Heterocycl Chem 2006, 43, 261.

[18] Umut, S. G.; Nesrin, G. K.; Ozgur, G.; Yavuz, K.; Ekrem, K.; Samil, I.; Goknur, A.; Meral, O. Bioorg Med Chem 2007, 15, 5738.

[19] Nicolaides, D. N.; Gautam, D. R.; Litinas, K. E.; Hadjipavlou-Litina, D. J.; Kontogiorgis, C. A. J Heterocycl Chem 2004, 41, 605.

[20] Zhou, Y.; Miao, W.; Cheng, L.; Wang, D.; Bai, Z. Chem J Chin Univ 2003, 24, 1225.

[21] Zhou, Y.; Miao, W.; Cheng, L. Chin Chem Lett 2003, 14, 897.

[22] Meazza, G.; Bettarini, F.; Porta, P. L.; Piccardi, P.; Signorini, E.; Portoso, D.; Fornara, L. Pest Manag Sci 2004, 60, 1178.

[23] (a) Woodard, S. S.; Hamper, B. C.; Moedritzer, K.; Rogers, M. D.; Mischke, D. A.; Dutra, G. A. U.S. Pat. 5,281,571 (1994); (b) Woodard, S. S.; Hamper, B. C.; Moedritzer, K.; Rogers, M. D.; Mischke, D. A.; Dutra, G. A. Chem Abstr 1994, 122, 10029.

[24] (a) Hirai, K.; Yamashita, M. U.S. Pat. 5,053,557 (1991); (b) Hirai, K.; Yamashita, M. Chem Abstr 114, 206768.

# A Green and Efficient Synthesis of 3,3′-Arylidenebis[4-hydroxy-6-methyl-2(1*h*)-3-pyridinone]s in Water under Microwave Irradiation

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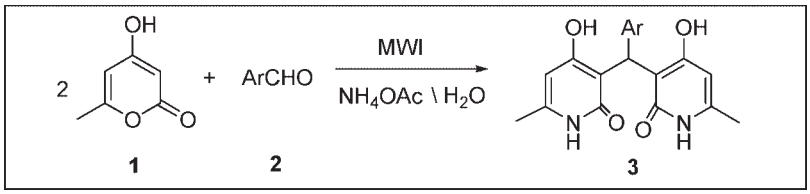


A series of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s were synthesized via three-component reactions of aromatic aldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and ammonium acetate in water under microwave irradiation. This method has the advantages of environmental friendliness, short reaction time, high yields, and easy operation. This efficient synthesis not only offers an economical and green synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted synthesis in water.

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## INTRODUCTION

The pyridinone ring is one of the most well-known systems among the naturally occurring heterocycles. Many members of this class of heterocycles have antibacterial [1], antifungal [2], cardiotonic [3], antineoplastic [4], antiinflammatory and analgesic [5], and other significant bioactivities [6]. Therefore, pyridinone derivatives, especially bispyridinone derivatives, which contain two skeletons of pyridinone in one molecular structure, are of great importance in medicinal and organic chemistry.

However, survey of the literature only reveals two typical methods on synthesizing 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s. One method is the condensation of 4-hydroxy-6-methyl-2-pyridone with aromatic aldehydes catalyzed by triethylamine in ethanol under traditional heating condition [7]. Unfortunately, this method suffers from low yield (14–45%), long reaction time (8–10 h), and use of toxic organic catalyst and solvent.

Another method is the multicomponent reaction of triacetic acid lactone, aromatic aldehydes, and ammonium acetate in ethanol under traditional heating conditions [8]. However, this approach still has disadvantages of lower yield (11–45%), longer reaction time (26 h), and being less environmental-unfriendly because ethanol, a volatile and flammable organic solvent, is used. As a result, developing a green and efficient approach to the synthesis of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s is of great significance.

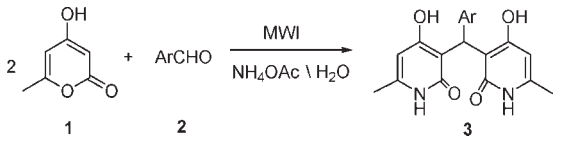
In recent years, microwave-assisted synthesis in water as solvent has become a hotspot of investigation, because it combines the two prominent green chemistry principles of ''safer solvents'' and ''energy efficiency'' [9]. In addition to the general advantages of water as solvent [10], several benefits for the reaction are expected when using water as reaction medium for microwave-superheated protocols [11].

As a continuation of our efforts on synthesizing heterocycles possessing significant bioactivities with green and efficient method [12], we herein report the synthesis of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s through three-component reactions of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1**, aromatic aldehydes **2**, and ammonium acetate in water under microwave irradiation (MWI) (Scheme 1). This efficient synthesis not only offers a green synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted synthesis in water.

## RESULTS AND DISCUSSION

Initially, to demonstrate the superiority of water as solvent, despite its natural property of being harmless to environment, we compared the synthesis of **3c** in water with other organic solvents including glycol, DMF,

**Scheme 1**




glacial acetic acid, and ethanol. The mixture of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** (2 mmol), 4-bromophenyl aldehyde **2c** (1 mmol), ammonium acetate (2 mmol), and corresponding solvent (2 mL) was irradiated under MWI at 100°C and 150 W for a given time, then the crude product was purified by recrystallization from EtOH.

The results (Table 1) reveal that compared with the solvents of glycol, DMF, and EtOH, water can not only improve the yield but also shorten the time of this reaction. Although the yield of the reaction in acetic acid is a little higher than that in water, considering environmental friendliness and avoidance of using toxic organic reagents, water was preferred as solvent for all further microwave-assisted reactions.

Moreover, the same reaction of **1** (2 mmol), **2c** (1 mmol), and ammonium acetate (2 mmol) in water (2 mL) under MWI (150 W) was used to optimize the reaction temperature, and the results are shown in Table 2. It is obvious that 90°C is the most suitable reaction temperature.

Under these optimized reaction conditions, a series of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s **3** were synthesized, and the results are given in Table 3. As shown in Table 3, this protocol can be applied not only to aromatic aldehydes with electron-withdrawing groups but also to those with electron-donating groups under the same conditions. Therefore, the electronic nature of the substrate has no significant effect on this reaction.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s **3** could be explained by a reaction sequence presented in Scheme 2.

First, the condensation of aldehyde **2** and 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** gave intermediate **4**, which was then attacked by **1** to generate another intermediate **5**. Finally, the ammonolysis, intermolecular cyclization and dehydration of **5** gave rise to target product **3**.

**Table 1**

Solvent optimization for the synthesis of **3c**.

| Entry | Solvent | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | glycol | 12 | 76 |
| 2 | water | 8 | 81 |
| 3 | AcOH | 6 | 83 |
| 4 | DMF | 16 | 73 |
| 5 | EtOH | 10 | 78 |

**Table 2**

Temperature optimization for the synthesis of **3c**.

| Entry | T (°C) | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | 60 | 15 | 44 |
| 2 | 70 | 12 | 65 |
| 3 | 80 | 10 | 74 |
| 4 | 90 | 8 | 83 |
| 5 | 100 | 8 | 81 |
| 6 | 110 | 8 | 80 |

All the products were characterized by IR, $^1$H NMR, and elemental analyses.

In conclusion, we have developed a green and efficient approach to the synthesis of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s in water under MWI. This method has the notable advantages over the existing ones owing to its features of environmental friendliness, short reaction time, high yield, low cost, and easy operation. On the other hand, this reaction supplies a good example of efficient microwave-assisted synthesis in water as solvent.

## EXPERIMENTAL

MWI was carried out in a monomodal Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FT-IR-Tensor 27 spectrometer. $^1$H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-$d_6$ as solvent and TMS as internal standard. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

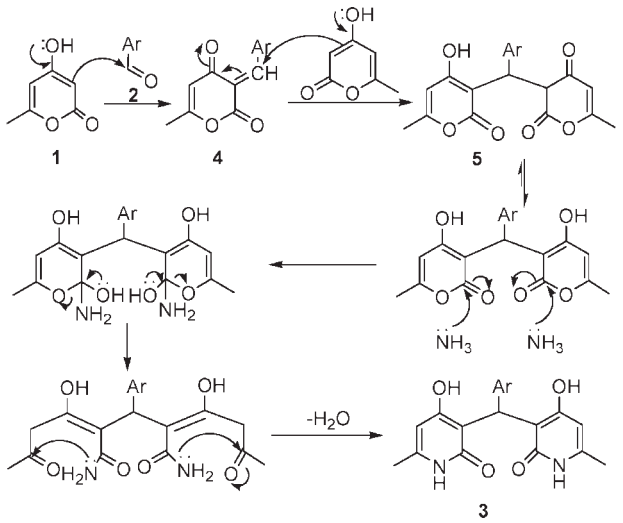
**General procedure for the syntheses of compounds 3 with MWI.** Typically, in a 10-mL Emrys reaction vial, 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** (2 mmol), aldehyde **2** (1 mmol), ammonium acetate (2 mmol), and water (2 mL) were

**Table 3**

Synthesis of **3** under MWI in water.

| Entry | **3** | Ar | Time/ min | Yield / % | Mp (lit.) / °C |
|---|---|---|---|---|---|
| 1 | **3a** | 4-$FC_6H_4$ | 8 | 85 | >300 |
| 2 | **3b** | 4-$ClC_6H_4$ | 10 | 81 | >300 (>300)[7] |
| 3 | **3c** | 4-$BrC_6H_4$ | 8 | 83 | >300 |
| 4 | **3d** | 2,4-$Cl_2C_6H_3$ | 8 | 83 | >300 |
| 5 | **3e** | 3-$NO_2C_6H_4$ | 8 | 82 | >300 (>300)[8] |
| 6 | **3f** | 4-$NO_2C_6H_4$ | 10 | 85 | >300 |
| 7 | **3g** | $C_6H_5$ | 10 | 86 | >300 (>300) [7] |
| 8 | **3h** | 4-$OCH_3C_6H_4$ | 12 | 82 | >300 (>300) [7] |
| 9 | **3i** | 4-$CH_3C_6H_4$ | 10 | 84 | >300 |
| 10 | **3j** | 2-$OCH_3C_6H_4$ | 12 | 81 | >300 |
| 11 | **3k** | Thiophen-2-yl | 15 | 75 | >300 |

**Scheme 2**



mixed and then capped. The mixture was irradiated at 150 W and at 90°C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH.

***3,3′-(4-Fluorobenzylidenebis[4-hydroxy-6-methylpyridin-2(1H)-one] (3a).*** This compound was obtained according to above general procedure; IR (KBr): ν 3433–2611, 1635, 1457, 1389, 1309, 1259, 1222, 1195, 1164, 1005, 932, 883, 848, 781 $cm^{-1}$; $^1H$ NMR: δ 12.28 (s, br, 2H, 2OH), 11.71 (s, 2H, 2NH), 7.05–6.99 (m, 4H, ArH), 5.94(s, 1H, $C^5$-H), 5.88 (s, 1H, $C^{5'}$-H), 5.82 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}FN_2O_4$: C, 64.04; H, 4.81; N, 7.86. Found: C, 64.21; H, 4.83; N, 7.81.

***3,3′-(4-Chlorobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3b).*** This compound was obtained according to above general procedure; IR (KBr): 3600–2600, 1482, 1456, 1382, 1318, 1283, 1249, 1195, 1163, 1007, 883, 821, 753 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$, 25°C): δ 12.20 (s, br, 2H, 2OH), 11.72 (s, 2H, 2NH), 7.28 (d, 2H, $J$ = 8.0 Hz, ArH), 7.01 (d, 2H, $J$ = 8.0 Hz, ArH), 5.91 (s, 2H, $C^5$-H, $C^{5'}$-H), 5.80 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51; Found: C, 61.08; H, 4.62; N, 7.45.

***3,3′-(4-Bromobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3c).*** This compound was obtained according to above general procedure; IR (KBr): ν 3457–2583, 1631, 1486, 1459, 1386, 1314, 1285, 1255, 1191, 1074, 1010, 883, 815, 755 $cm^{-1}$; $^1H$ NMR: δ 12.22 (s, br, 2H, 2OH), 11.74 (s, 2H, 2NH), 7.42 (d, 2H, $J$ = 8.4 Hz, ArH), 6.95 (d, 2H, $J$ = 8.4 Hz, ArH), 5.92 (s, 2H, $C^5$-H, $C^{5'}$-H), 5.87 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$: C, 54.69; H, 4.11; N, 6.71; Found: C, 54.45; H, 4.07; N, 6.75.

***3,3′-(2,4-Dichlorobenzylidene)bis[4-hydroxy-6-methylpyr-idin-2(1H)-one] (3d).*** This compound was obtained according to above general procedure; IR (KBr): ν 3600–2600, 1639, 1462, 1456, 1388, 1325, 1258, 1190, 1127, 1107, 1048, 887, 862, 772 $cm^{-1}$; $^1H$ NMR: δ 11.81 (s, br, 2H, 2OH), 11.44 (s, 2H, 2NH), 7.40 (s, 1H, ArH), 7.33–7.30 (m, 1H, ArH) 7.19 (d, 1H, $J$ = 8.0 Hz, ArH), 6.18 (s, 1H, CH), 5.83 (s, 2H, $C^5$-H, $C^{5'}$-H), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_4$: C, 56.04; H, 3.96; N, 6.88; Found: C, 56.20; H, 3.93; N, 6.81.

***3,3′-(3-Nitrobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3e).*** This compound was obtained according to above general procedure; IR (KBr): ν 3300–2500, 1634, 1526, 1455, 1392, 1351, 1257, 1127, 1108, 1042, 820, 728, 676 $cm^{-1}$; $^1H$ NMR: δ 12.22 (s, br, 2H, 2OH), 11.79 (s, 2H, 2NH), 8.06 (d, 1H, $J$ = 8.4 Hz, ArH), 7.93 (s, 1H, ArH), 7.55 (t, 1H, $J$ = 8.0 Hz, ArH), 7.46 (d, 1H, $J$ = 7.6 Hz, ArH), 6.07 (s, 1H, CH), 5.96 (s, 2H, $C^5$-H, $C^{5'}$-H), 2.19 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96; Found: C, 59.37; H, 4.50; N, 11.00;

***3,3′-(4-Nitrobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3f).*** This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1636, 1518, 1460, 1385, 1347, 1293, 1192, 1008, 883, 921, 8249, 768 $cm^{-1}$; $^1H$ NMR: δ 12.19 (s, br, 2H, 2OH), 11.78 (s, 2H, 2NH), 8.13 (d, 2H, $J$ = 8.4 Hz, ArH), 7.26 (d, 2H, $J$ = 8.4 Hz, ArH), 6.06 (s, 1H, CH), 5.94 (s, 2H, $C^5$-H, $C^{5'}$-H), 2.18 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96; Found: C, 59.41; H, 4.49; N, 11.01.

***3,3′-(Benzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3g).*** This compound was obtained according to above general procedure; IR (KBr): ν3300–2600, 1629, 1494, 1453, 1396, 1363, 1262, 1213, 1181, 1115, 1027, 896, 824, 772 $cm^{-1}$; $^1H$ NMR: δ 12.43 (s, br, 2H, 2OH), 11.69 (s, 2H, 2NH), 6.92–6.78 (m, 5H, ArH), 5.91 (s, 2H, $C^5$-H, $C^{5'}$-H), 5.82 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.30; H, 5.38; N, 8.25.

***3,3′-(4-Methoxylbenzylidene)bis[4-hydroxy-6-methylpyri- din-2(1H)-one] (3h).*** This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1633, 1509, 1459, 1418, 1388, 1302, 1248, 1178, 1035, 850, 832, 774 $cm^{-1}$; $^1H$ NMR: δ 12.41 (s, br, 2H, 2OH), 11.68 (s, 2H, 2NH), 6.91 (d, 2H, $J$ = 8.4 Hz, ArH), 6.79 (d, 2H, $J$ = 8.4 Hz, ArH), 5.90 (s, 2H, $C^5$-H, $C^{5'}$-H), 5.82 (s, 1H, CH), 3.70 (s, 3H, $OCH_3$), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.09; H, 5.45; N, 7.55.

***3,3′-(4-Methylbenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3i).*** This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1634, 1512, 1460, 1387, 1302, 1308, 1127, 1105, 1041, 920, 887, 753 $cm^{-1}$; $^1H$ NMR: δ 12.50 (s, br, 2H, 2OH), 11.67 (s, 2H, 2NH), 7.03 (d, 2H, $J$ = 8.4 Hz, ArH), 6.90 (d, 2H, $J$ = 8.4 Hz, ArH), 5.91 (s, 2H, $C^5$-H, $C^{5'}$-H), 5.83 (s, 1H, CH), 2.25 (s, 3H, $CH_3$), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.23; H, 5.69; N, 7.89.

***3,3′-(2-Methoxylbenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3j).*** This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1632, 1490, 1396, 1356, 1340, 1290, 1243, 1103, 1029, 888, 818, 769 $cm^{-1}$; $^1H$ NMR: δ 12.62 (s, br, 2H, 2OH), 11.47 (s, 2H, 2NH), 7.15–7.08 (m, 2H, ArH), 6.86–6.80 (m, 2H, ArH), 6.02 (s, 1H, CH), 5.84 (s, 2H, $C^5$-H, $C^{5'}$-H), 3.52 (s, 3H, $OCH_3$), 2.13 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.05; H, 5.45; N, 7.66.

***3,3′-(4-Thiophen-2-ylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3k).*** This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1633, 1556, 1537, 1514, 1504, 1486, 1455, 1393, 1360, 1253, 1200, 922, 887, 753 $cm^{-1}$; $^1H$ NMR: δ 12.92 (s, br, 2H, 2OH), 11.66 (s,

2H, 2NH), 7.24 (d, 1H, $J$ = 5.2 Hz, ArH), 6.87–6.84 (m, 1H, ArH), 6.57 (s, 1H, ArH), 6.09 (s, 1H, CH), 5.90 (s, 2H, $C^5$-H, $C^{5'}$-H), 2.16 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.11; H, 4.71; N, 8.09.

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## REFERENCES AND NOTES

[1] Li, Q.; Mitscher, L. A.; Shen, L. L. Med Res Rev 2000, 20, 231.

[2] Cox, R. J.; O'Hagan, D. J. Chem Soc Perkin Trans 1991, 1, 2537.

[3] Deshong, P.; Cipollina, J. A.; Lowmaster, N. K. J Org Chem 1988, 53, 1356.

[4] (a) Nagarajan, M.; Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. J Med Chem 2003, 46, 5712; (b) Hasvold, L. A.; Wang, W.; Gwaltney, S. L.; Rockway, T. W.; Nelson, L. T. J.; Mantei, R. A.; Fakhoury, S. A.; Sullivan, G. M.; Li, Q.; Lin, N. H.; Wang, L.; Zhang, H.; Cohen, J.; Gu, W. Z.; Marsh, K.; Bauch, J.; Rosenberg, S.; Sham, H. L. Bioorg Med Chem Lett 2003, 13, 4001.

[5] Ozturk, G.; Erol, D. D.; Uzbay, T.; Aytemir, M. D.; Il Farmaco 2001, 56, 251.

[6] (a) Li, Q.; Chu, D. T. W.; Claiborne, A.; Cooper, C. S.; Lee, C. M.; Raye, K.; Berst, K. B.; Donner, P.; Wang, W.; Hasvold, L.; Fung, A.; Ma, Z.; Tufano, M.; Flamm, R.; Shen, L. L.; Baranowski, J.; Nilius, A.; Alder, J.; Meulbroek, J.; Marsh, K.; Crowell, D.; Hui, Y.; Seif, L.; Melcher, L. M.; Henry, R.; Spanton, S.; Faghih, R.; Klein, L. L.; Tanaka, S. K.; Plattner, J. J. J Med Chem 1996, 39, 3070; (b) Peterlin-Masic, L.; Kranjc, A.; Marinko, P.; Mlinsek, G.; Solmajer, T.; Stegnar, M.; Kikelj, D. Bioorg Med Chem Lett 2003, 13, 3171; (c) Parlow, J. J.; Kurumbail, R. G.; Stegeman, R. A.; Stevens, A. M.; Stallings, W. C.; South, M. S. J Med Chem 2003, 46, 4696.

[7] Mekheimer, R. A.; Mohamed, N. H.; Sadek, K. U. Bull Chem Soc Jpn 1997, 70, 1625.

[8] Maria, C.; Marcial, M.; Rosrr, P. Tetrahedron 1990, 46, 7885.

[9] Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563.

[10] Andrade, C, K. Z.; Alves, L. M. Curr Org Chem 2005, 9, 195.

[11] Strauss, C. R.; Trainor, R. W. Aust J Chem 1995, 48, 1665.

[12] (a) Tu, S.; Zhang, Y.; Jia, R.; Jiang, B.; Zhang, J.; Ji, S. Tetrahedron Lett 2006, 47, 6521; (b) Shi, F.; Wang, Q.; Tu, S.; Zhou, J.; Jiang, B.; Li, C.; Zhou, D.; Shao, Q.; Cao, L. J. Heterocyclic Chem 2008, 45, 1103; (c) Shi, F.; Zhou, D.; Tu, S.; Shao, Q.; Li, C.; Cao, L. J. Heterocyclic Chem 2008, 45, 1065; (d) Shi, F.; Zhou, D.; Li, C.; Shao, Q.; Cao, L.; Tu, S. J. Heterocyclic Chem 2008, 45, 405.

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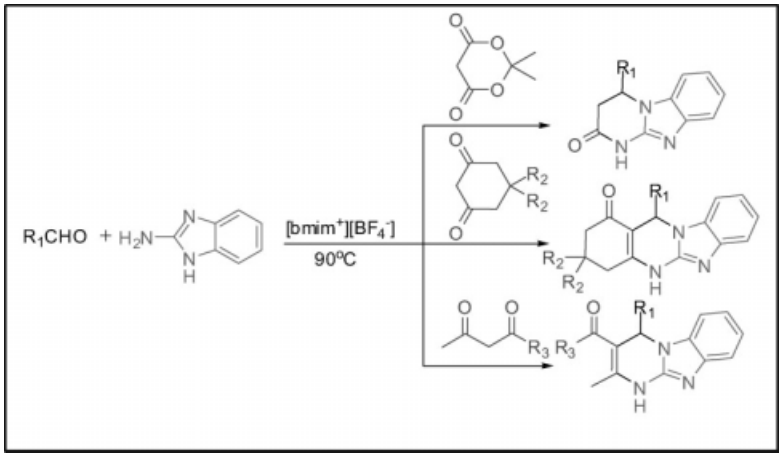


A green and simple synthesis of 4-ayrl-3,4-dihydro-1*H*-pyrimido[1,2-*a*]benzimidazole derivatives was accomplished in excellent yields via the reaction of aryl aldehyde, 1,3-dicarbonyl compounds and 1*H*-benzo[*d*]imidazol-2-amine in ionic liquid of [bmim$^+$][$BF_4^-$]. This protocol has the advantages of easier work-up, mild reaction conditions, high yields, and an environmentally benign procedure compared with the reported methods.

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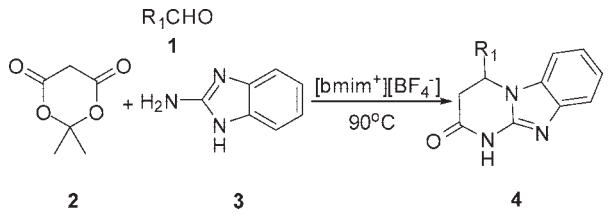
## INTRODUCTION

The small organic molecules, such as, the fused nitrogen-containing heterocycles receive a large amount of attention in the literature due to their exciting biological properties and their roles as pharmacophores of considerable historical importance. For example, the derivatives of pyrimido[1,2-*a*]benzimidazol-2-one can be used as inhibitor of cell proliferation [1], lymphocyte specific kinase [2], DNA-topoisomerase I [3], and protein kinase [4]. Hence, the preparation of this important heterocyclic core unit has gained much importance. However, only one method reported to synthesize these compounds was via the reaction of α, β-unsaturated esters, which could be prepared via the condensation reaction, with 1*H*-benzo [*d*]imidazol-2-amine in the presence of organic solvents or under solvent-free conditions at high temperature [5–9]. Furthermore, most of the synthetic protocols in literature so far have many drawbacks, including prolonged reaction time, drastic reaction conditions, the use of some toxic organic solvents, such as, nitrobenzene, and low yields. Therefore, the development of simple, convenient, and environmentally benign approaches for the synthesis of these compounds is still desirable.

A multicomponent reaction (MCR) can create highly complex molecules from readily available starting materials without the complicated purification operations; thus, MCRs are resource- and time-effective and economically favorable processes in diversity generation [10–13]. Recently, there have been tremendous development in three- and four-component reactions and great efforts continue to be made to develop new MCRs [14–19]. Besides, the ionic liquids have been widely used as environmentally benign reaction media in organic synthesis because of their unique properties of nonvolatility, nonflammability, and recyclability. Many organic reactions, including MCRs, were carried out efficiently in ionic liquids [20–28]. To continue our work on the synthesis of heterocyclic compounds via MCR in ionic liquids [29–31], we report herein the three-component synthesis of 4-aryl-3,4-dihydro-1*H*-pyrimido[1,2-*a*]benzimidazol-2-one in ionic liquid (Scheme 1).

**Scheme 1**




## RESULTS AND DISCUSSION

The effect of solvent on the reaction was initially examined by reacting phenyl aldehyde (1 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (1 mmol), and 1*H*-benzo[*d*]imidazol-2-amine (1 mmol) at room temperature. The results in Table 1 show that only in ionic liquids the expected product **4a** was given with moderate yield (60–75%) by the three-component reaction. Furthermore, the reaction accomplished in [bmim$^+$][BF$_4^-$] exhibited higher yield (75%) than other counterparts. Therefore, we carried out the three-component reaction in [bmim$^+$][BF$_4^-$] to synthesize the desired products.

To find the optimal reaction temperature, the synthesis of (**4a**) was studied at different temperatures. The results are summarized in Table 2. As shown in Table 2, the reaction at 90°C proceeded in highest yield among the six reaction temperatures tested. Therefore, 90°C was chosen for this reaction.

Based on the optimized reaction conditions, a series of 4-aryl-3,4-dihydro-1*H*-pyrimido[1,2-*a*]benzimidazol-2-one were synthesized. The results, summarized in Table 3, show that the three-component reaction in [bmim$^+$][BF$_4^-$] gave the corresponding products in moderate to good yields. This methodology can be applied to aromatic aldehydes either with electron-withdrawing groups (such as, a nitro group, halogen) or electron-donating groups (such as, a methoxy) with excellent yields under the same conditions. Therefore, we conclude that the electronic nature of substituents of the aromatic aldehyde had no significant effect on the reaction. Even the heterocyclic aldehyde could be used in this reaction (**4h**). However, when the aliphatic aldehyde was applied to this reaction, no expected product was obtained.

All of the compounds were characterized by HRMS(ESI), FTIR, and $^1$H NMR. To further elucidate the structure of products, a single crystal of compound **4a** was prepared and its structure was determined by X-ray diffraction (Fig. 1).

The recovery and reuse of solvent and/or catalyst are highly preferable in terms of green synthetic process. Therefore, with the success of the above reactions, we continued our research by studying the reuse of the solvent. It turned out that the recovery and reuse of [bmim$^+$][BF$_4^-$] is not only convenient but also efficient. Thus, at completion monitored by TLC, the reaction mixture was cooled to room temperature and poured into water. The solid product was collected by filtration and recrystallized from ethanol to give the pure product. The filtrate was washed with acetic ester, concentrated under reduced pressure, and dried *in vacuo* at 100°C for several hours to give the reusable solvent. Studies by using phenyl aldehyde, 2,2-dimethyl-1,3-dioxane-4,6-dione and 1*H*-benzo[*d*]imidazol-2-amine as model substrates shows that the recovered solvent could be successively recycled in subsequent reactions without almost

**Table 1**

Solvent effect on the synthesis of **4a**.

| Entry | Solvent[a] | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | [byp$^+$][Br$^-$] | r.t. | 10 | 60 |
| 2 | [byp$^+$][BF$_4^-$] | r.t. | 10 | 62 |
| 3 | [bmim$^+$][Br$^-$] | r.t. | 10 | 70 |
| 4 | [bmim$^+$][BF$_4^-$] | r.t. | 10 | 75 |
| 5 | Ethanol | r.t. | 10 | Trace |
| 6 | $CH_3CN$ | r.t. | 12 | Trace |
| 7 | $CH_3COOH$ | r.t. | 12 | Trace |
| 8 | $CHCl_3$ | r.t. | 12 | Trace |
| 9 | $H_2O$ | r.t. | 15 | Trace |

[a] [byp$^+$][Br$^-$], 1-butylpyridinium bromide; [byp$^+$][BF$_4^-$], 1-butylpyridinium tetrafluoroborate; [bmim$^+$][Br$^-$], 3-butyl-1-methyl-1*H*-imidazol-3-ium bromide; [bmim$^+$] [BF$_4^-$], 3-butyl-1-methyl-1*H*-imidazol-3-ium tetrafluoroborate.

**Table 2**

Temperature optimization for the synthesis of **4a**.

| Entry | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | 20 | 10 | 75 |
| 2 | 40 | 9 | 80 |
| 3 | 60 | 8 | 86 |
| 4 | 80 | 7 | 88 |
| 5 | 90 | 6 | 90 |
| 6 | 100 | 6 | 85 |

**Table 3**

Synthesis of **4** in ionic liquid ([bmim$^+$][BF$_4^-$]).

| Compound no. | $R_1$ | Time (h) | Yield (%) | M.p. (°C) |
|---|---|---|---|---|
| **4a** | $C_6H_5$ | 7 | 90 | 291–293 (ref. 32, 289–290) |
| **4b** | 4-Br$C_6H_4$ | 7 | 85 | 294–296 |
| **4c** | 3,4,5-$(OCH_3)_3C_6H_2$ | 8 | 82 | 273–275 |
| **4d** | 3-$NO_2C_6H_4$ | 8 | 85 | 283–285 |
| **4e** | 2-F$C_6H_4$ | 7 | 88 | 284–285 |
| **4f** | 3,4-$(OCH_2O)C_6H_3$ | 8 | 83 | 236–238 |
| **4g** | 4-$NO_2C_6H_4$ | 8 | 82 | >300 (ref. 6, >300) |
| **4h** | 2-$SC_4H_3$ | 7 | 80 | 285–287 |

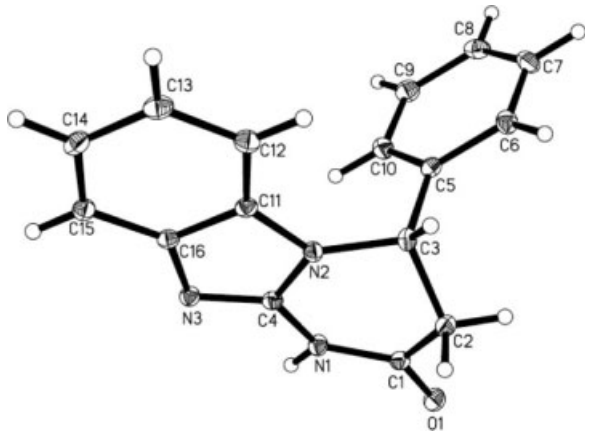



**Figure 1.** The crystal structure of **4a**.

any decrease in its efficiency. The results of the reuse of the ionic liquid are summarized in Table 4. Even in the fourth round, the yield of the product **4a** is fairly high.

A plausible mechanism of the reaction was presented in Scheme 2. Product **4** may be synthesized via sequential Knoevenagel condensation, Michael addition, cyclization, and elimination mechanism (Scheme 2). The condensation between aldehyde and Meldrum's acid gave 5-arylidene substituted Meldrum's acid **5**. Michael addition between **5** and 1*H*-benzo[*d*]imidazol-2-amine **3** then furnished the intermediate **6**, which isomerized to **7**. After that, intramolecular cyclization of **7** gave **8**, which finally afforded **4** by loosing acetone and carbon dioxide.

To test the proposed reaction pathway, compound **5a** was synthesized in [bmim$^+$][BF$_4^-$] and it could react with **3** smoothly and gave product **4a** with yield similar to the three-component reaction in ionic liquid. The fact supported the supposed reaction mechanism.

To extend the scope of this protocol for the synthesis of the derivatives of pyrimido[1,2-*a*]benzimidazole, other cyclic 1,3-dicarbonyl compounds (Scheme 3) and acyclic 1,3-dicarbonyl compounds (Scheme 4) were applied in the three-component synthesis as the surrogates of 2,2-dimethyl-1,3-dioxane-4,6-dione. The results, listed in Tables 5 and 6, show that these three-component reactions in ionic liquid gave the desired products, **10** and **12**, successfully.

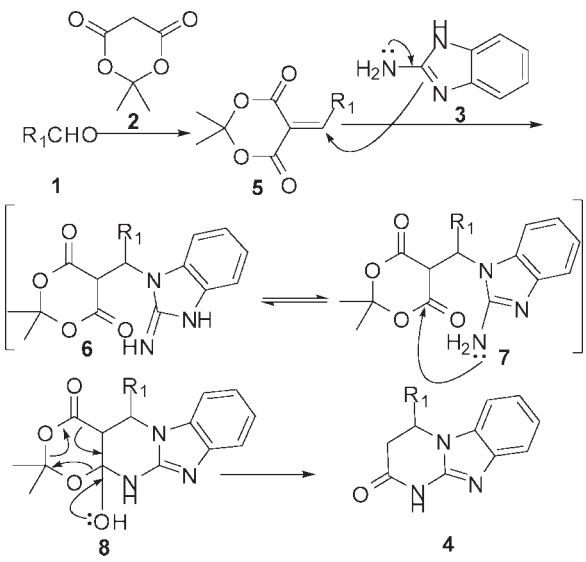
In summary, we have developed an efficient, economical, safe, and environmentally benign procedure for

**Table 4**

Study on the reuse of ionic liquid ([bmim$^+$][BF$_4^-$]).

| Round | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| **4a** Yield (%) | 90 | 88 | 87 | 87 |

**Scheme 2**



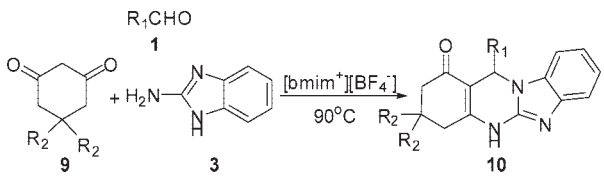

synthesizing 4-aryl-1*H*-pyrimido[1,2-*a*]benzimidazole derivatives in ionic liquid medium [bmim$^+$][BF$_4^-$]. Meanwhile, the ionic liquid was chosen as a kind of green solvent, which could be reused for several rounds without significant loss of activity.

## EXPERIMENTAL

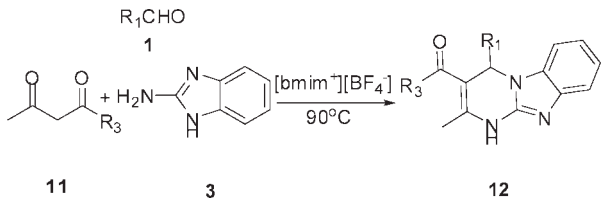
Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. NMR spectra were recorded on a Bruker DPX 400; data for $^1$H are reported as follows: chemical shift (ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad), coupling constant (Hz), and number. Infrared (IR) spectra were recorded on a TENSOR 27 spectrophotometer in KBr pellet and are reported in terms of frequency of absorption (cm$^{-1}$). HRMS (ESI) were determined by using micrOTOF-QIIHRMS/MS instrument (BRUKER). Melting points were determined in open capillaries and are uncorrected. The single crystal diffraction data were gathered on a Rigaku Saturn diffractometer.

**General procedure for the synthesis of 4-Aryl-1*H*-pyrimido[1,2-*a*]benzimidazol derivatives.** Aryl aldehyde **1** (1.0 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione **2** (0.14 g, 1.0 mmol), and 1*H*-benzo[*d*]imidazol-2-amine **3** (0.13 g, 1.0 mmol) were mixed in 3 mL [bmim$^+$][BF$_4^-$]. Then, the mixture was stirred for a certain time (monitored by TLC) at 90°C. The result mixture was cooled to room temperature and poured into 20 mL of water. The solid product was collected by

**Scheme 3**



**Scheme 4**




filtration and recrystallized from ethanol to give the pure compound **4**. The filtrate was washed with acetic ester for several times, concentrated under reduced pressure, and dried *in vacuo* at 100°C for several hours to give the reusable solvent. A similar procedure was used in preparing the following compounds **10** and **12**.

***4-Phenyl-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4a).*** IR (potassium bromide): 3059, 3034, 2912, 1730, 1649, 1590, 1458, 1363, 1323, 1287, 1245, 1168, 926, 890, 766, 743, 700 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δδ11.66 (s, 1H, NH), 7.83 (d, $J$ = 8.0 Hz, 1H, ArH), 7.46–7.40 (m, 2H, ArH), 7.35–7.32 (m, 3H, ArH), 7.08–7.03 (m, 3H, ArH), 5.94 (q, $J$ = 4.0 Hz, 1H, CH), 3.52 (dd, $J_1$ = 8.0 Hz, $J_2$ = 16.0 Hz, 1H, $CH_2$), 2.94 (dd, $J_1$ = 3.2 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 264.1131 $[M+H]^+$, found: 264.1132.

***4-(4-Bromophenyl)-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4b).*** IR (potassium bromide): 3054, 2996, 2929, 2849, 2698, 1694, 1634, 1583, 1505, 1455, 1420, 1359, 1324, 1263, 1239, 1150, 1076, 1010, 974, 894, 843, 817, 759, 741, 677 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.74 (s, 1H, NH), 7.56 (d, $J$ = 7.2 Hz, 2H, ArH), 7.47 (d, $J$ = 8.0 Hz, 1H, ArH), 7.10–7.02 (m, 5H, ArH), 6.00 (dd, $J_1$ = 3.2 Hz, $J_2$ = 7.2 Hz, 1H, CH), 3.54 (dd, $J_1$ = 7.2 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 2.93 (dd, $J_1$ = 3.2 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 342.0237 $[M+H]^+$, found: 342.0252.

***4-(3,4,5-Trimethoxyphenyl)-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4c).*** IR (potassium bromide): 2939, 2846, 2761, 1704, 1633, 1594, 1509, 1460, 1427, 1343, 1331, 1283, 1241, 1129, 1143, 1002, 898, 847, 823, 766, 744, 689 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.76 (s, 1H, NH), 7.45 (d, $J$ = 8.0 Hz, 1H, ArH), 7.20–6.98 (m, 3H, ArH), 6.50–6.46 (m, 2H, ArH), 5.80 (dd, $J_1$ = 4.4 Hz, $J_2$ = 6.8 Hz, 1H, CH), 3.65 (s, 6H, 2 × $OCH_3$), 3.63 (s, 3H, $OCH_3$), 3.40 (dd, $J_1$ = 6.8 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 3.03 (dd, $J_1$ = 4.4 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 354.1448 $[M+H]^+$, found: 354.1439.

***4-(3-Nitrophenyl)-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4d).*** IR (potassium bromide): 3065, 2866, 2729, 1696, 1637, 1586, 1532, 1506, 1458, 1351, 1284, 1246, 1161, 1130, 1085, 921, 873, 813, 731 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.82 (s, 1H, NH), 8.20 (d, $J$ = 8.0 Hz, 1H, ArH), 8.02 (s, 1H, ArH), 7.70–7.66 (m, 1H, ArH), 7.50 (d, $J$ = 4.0 Hz, 2H, ArH), 7.13–7.05 (m, 3H, ArH), 6.17 (dd, $J_1$ = 3.2 Hz, $J_2$ = 7.2 Hz, 1H, CH), 3.57 (dd, $J_1$ = 7.2 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 3.03 (dd, $J_1$ = 3.2 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 309.0983 $[M+H]^+$, found: 309.0985.

***4-(2-Fluorophenyl)-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4e).*** IR (potassium bromide): 3061, 3006, 2923, 2864, 2702, 1687, 1637, 1584, 1486, 1456, 1423, 1377, 1354, 1311, 1286, 1244, 1226, 1160, 1095, 898, 762, 746 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.77 (s, 1H, NH), 7.48 (d, $J$ = 8.0 Hz, 1H, ArH), 7.40–7.30 (m, 2H, ArH), 7.13–7.04 (m, 4H, ArH), 6.68 (t, $J$ = 7.6 Hz, 1H, ArH), 6.17 (dd, $J_1$ = 2.8 Hz, $J_2$ = 7.6 Hz, 1H, CH), 3.60 (dd, $J_1$ = 7.6 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 2.86 (dd, $J_1$ = 2.8 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 282.1037 $[M+H]^+$, found: 282.1034.

***4-Benzo[1,3]dioxol-5-yl-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4f).*** IR (potassium bromide): 3051, 2888, 2725, 1686, 1639, 1585, 1504, 1490, 1456, 1445, 1350, 1241, 1037, 931, 891, 810, 728 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.67 (s, 1H, NH), 7.46 (d, $J$ = 8.0 Hz, 1H, ArH), 7.11–7.09 (m, 1H, ArH), 7.03 (d, $J$ = 8.0 Hz, 2H, ArH), 6.86 (d, $J$ = 8.0 Hz, 1H, ArH), 6.77 (s, 1H, ArH), 6.50 (q, $J$ = 4.0 Hz, 1H, ArH), 6.00 (s, 2H, $OCH_2O$), 5.82 (dd, $J_1$ = 3.6 Hz, $J_2$ = 6.8 Hz, 1H, CH), 3.42 (dd, $J_1$ = 6.8 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 2.94 (dd, $J_1$ = 3.6 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 308.1029 $[M+H]^+$, found: 308.1029.

***4-(4-Nitrophenyl)-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4g).*** IR (potassium bromide): 3050, 2859, 2750, 1702, 1636, 1584, 1524, 1486, 1456, 1412, 1346, 1318, 1286, 1246, 1105, 965, 927, 896, 851, 741, 698 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.82 (s, 1H, NH), 8.22 (d, $J$ = 8.0 Hz, 2H, ArH), 7.50 (d, $J$ = 8.0 Hz, 1H, ArH), 7.33 (d, $J$ = 8.0 Hz, 2H, ArH), 7.14 (d, $J$ = 7.6 Hz, 2H, ArH), 7.05 (d, $J$ = 7.6 Hz, 1H, ArH), 6.17 (dd, $J_1$ = 2.4 Hz, $J_2$ = 7.2 Hz, 1H, CH), 3.60 (dd, $J_1$ = 7.2 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 3.00 (dd, $J_1$ = 2.4 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): $m/z$ cal. for: 309.0982 $[M+H]^+$, found: 309.0985.

***4-Thiophen-2-yl-3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrimidin-2-one (4h).*** IR (potassium bromide): 3098, 2996, 2848, 2696, 1699, 1634, 1602, 1587, 1504, 1456, 1410, 1368, 1343,

**Table 5**

Synthesis of **10** in ionic liquid ([bmim$^+$][$BF_4^-$]).

| Compound no. | $R_1$ | $R_2$ | Time (h) | Yield (%) | M.p. (°C) |
|---|---|---|---|---|---|
| **10a** | $C_6H_5$ | H | 7 | 85 | 291–293 (ref. 33, >300) |
| **10b** | 3-$NO_2C_6H_4$ | H | 6 | 82 | 289–291 (ref. 33, >300) |
| **10c** | 3-$BrC_6H_4$ | H | 7 | 83 | >300 (ref. 33, >300) |
| **10d** | 4-$CH_3C_6H_4$ | H | 7 | 84 | 293–295 (ref. 33, >300) |
| **10e** | $C_6H_5$ | $CH_3$ | 7 | 86 | >300 (ref. 34, 368) |
| **10f** | 3,4-($OCH_2O$)$C_6H_3$ | $CH_3$ | 7 | 85 | 294–296 (ref. 33, >300) |
| **10g** | 3-$BrC_6H_4$ | $CH_3$ | 6 | 84 | 294–296 (ref. 33, >300) |
| **10h** | 4-$OCH_3C_6H_4$ | $CH_3$ | 7 | 83 | >300 (ref. 34, 389) |

**Table 6**

Synthesis of **12** in ionic liquid ([bmim$^+$][$BF_4^-$]).

| Compound no. | $R_1$ | $R_3$ | Time (h) | Yield (%) | M.p. (°C) |
|---|---|---|---|---|---|
| **12a** | $C_6H_5$ | $CH_3$ | 6 | 80 | 294–296 (ref. 35, >300) |
| **12b** | 3-$NO_2C_6H_4$ | $CH_3$ | 5 | 82 | 287–289 (ref. 35, 290–292) |
| **12c** | 4-$OCH_3C_6H_4$ | $CH_3$ | 6 | 83 | 286–288 (ref. 35, 279–282) |
| **12d** | 4-$FC_6H_4$ | $CH_3$ | 7 | 84 | >300 (ref. 35, >300) |
| **12e** | $C_6H_5$ | $OC_2H_5$ | 6 | 83 | 294–296 (ref. 35, 294–297) |
| **12f** | 4-$NO_2C_6H_4$ | $OC_2H_5$ | 6 | 84 | >300 (ref. 35, >300) |
| **12g** | 4-$BrC_6H_4$ | $OC_2H_5$ | 6 | 82 | >300 (ref. 35, >300) |
| **12h** | 4-$FC_6H_4$ | $OC_2H_5$ | 6 | 86 | >300 (ref. 35, >300) |

1295, 1263, 1235, 1154, 1013, 974, 894, 843, 720 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.72 (s, 1H, NH), 7.44 (t, $J$ = 7.6 Hz, 2H, ArH), 7.34–7.36 (m, 1H, thiophene-H), 7.12–7.09 (m, 2H, ArH), 6.99–6.94 (m, 2H, thiophene-H), 6.28 (dd, $J_1$ = 2.0 Hz, $J_2$ = 6.8 Hz, 1H, CH), 3.58 (dd, $J_1$ = 6.8 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$), 3.00 (dd, $J_1$ = 2.0 Hz, $J_2$ = 16.4 Hz, 1H, $CH_2$). HRMS (ESI): *m/z* cal. for: 270.0696 $[M+H]^+$, found: 270.0709.

***5-Phenyl-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10a).*** IR (potassium bromide): 3226, 3029, 2957, 1653, 885, 749 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.10 (s, 1H, NH), 7.38–7.31 (m, 3H, ArH), 7.25–7.22 (m, 3H, ArH), 7.15 (t, $J$ = 7.6 Hz, 1H, ArH), 7.04 (t, $J$ = 7.6 Hz, 1H, ArH), 6.95 (t, $J$ = 7.6 Hz, 1H, ArH), 6.42 (s, 1H, CH), 2.74–2.70 (m, 2H, $CH_2$), 2.32–2.20 (m, 2H, $CH_2$), 2.00–1.86 (m, 2H, $CH_2$). HRMS (ESI): *m/z* cal. for: 316.1444 $[M+H]^+$, found: 316.1459.

***5-(3-Nitrophenyl)-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10b).*** IR (potassium bromide): 3220, 3040, 2950, 1652, 1514, 1020, 744 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.30 (s, 1H, NH), 8.27 (s, 1H, ArH), 8.04 (d, $J$ = 8.4 Hz, 1H, ArH), 7.70 (d, $J$ = 7.6 Hz, 1H, ArH), 7.55 (t, $J$ = 8.0 Hz, 1H, ArH), 7.40 (d, $J$ = 7.6 Hz, 1H, ArH), 7.27 (d, $J$ = 7.6 Hz, 1H, ArH), 7.06 (t, $J$ = 7.2 Hz, 1H, ArH), 6.96 (t, $J$ = 7.6 Hz, 1H, ArH), 6.67 (s, 1H, CH), 2.73–2.70 (m, 2H, $CH_2$), 2.36–2.19 (m, 2H, $CH_2$), 1.99–1.85 (m, 2H, $CH_2$). HRMS (ESI): *m/z* cal. for: 361.1295 $[M+H]^+$, found: 361.1298.

***5-(3-Bromophenyl)-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10c).*** IR (potassium bromide): 3220, 3048, 2891, 1647, 1571, 996, 890 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.16 (s, 1H, NH), 7.55 (s, 1H, ArH), 7.36–7.31 (m, 2H, ArH), 7.24–7.13 (m, 3H, ArH), 7.02 (t, $J$ = 7.6 Hz, 1H, ArH), 6.94 (t, $J$ = 7.6 Hz, 1H, ArH), 6.41 (s, 1H, CH), 2.66–2.63 (m, 2H, $CH_2$), 2.28–2.18 (m, 2H, $CH_2$), 1.95–1.80 (m, 2H, $CH_2$). HRMS (ESI): *m/z* cal. for: 394.0531 $[M+H]^+$, found: 394.0558.

***5-p-Tolyl-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10d).*** IR (potassium bromide): 3224, 3038, 2950, 1645, 1514, 977, 829 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.04 (s, 1H, NH), 7.31 (d, $J$ = 7.6 Hz, 1H, ArH), 7.20–7.14 (m, 3H, ArH), 7.01–6.98 (m, 3H, ArH), 6.90 (t, $J$ = 7.6 Hz, 1H, ArH), 6.33 (s, 1H, CH), 2.65–2.61 (m, 2H, $CH_2$), 2.29–2.19 (m, 2H, $CH_2$), 2.17 (s, 3H, $CH_3$), 1.93–1.80 (m, 2H, $CH_2$). HRMS (ESI): *m/z* cal. for: 330.1601 $[M+H]^+$, found: 330.1637.

***8,8-Dimethyl-5-phenyl-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10e).*** IR (potassium bromide): 3228, 2956, 1658, 1106, 891, 838, 759 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.13 (s, 1H, NH), 7.38–7.33 (m, 3H, ArH), 7.28–7.23 (m, 3H, ArH), 7.18–7.14 (m, 1H, ArH), 7.05 (t, $J$ = 8.0 Hz, 1H, ArH), 6.96 (t, $J$ = 7.6 Hz, 1H, ArH), 6.42 (s, 1H, CH), 2.67–2.50 (m, 2H, $CH_2$), 2.29–2.04 (m, 2H, $CH_2$), 1.06 (s, 3H, $CH_3$), 0.93 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 344.1757 $[M+H]^+$, found: 344.1786.

***5-Benzo[1,3]dioxol-5-yl-8,8-dimethyl-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10f).*** IR (potassium bromide): 3228, 3095, 2966, 1644, 850, 791 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.09 (s, 1H, NH), 7.38–7.31 (m, 2H, ArH), 7.06 (t, $J$ = 7.2 Hz, 1H, ArH), 6.98 (t, $J$ = 7.6 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.82–6.76 (m, 2H, ArH), 6.35 (s, 1H, CH), 5.93 (s, 2H, $OCH_2O$), 2.64–2.53 (m, 2H, $CH_2$), 2.28–2.06 (m, 2H, $CH_2$), 1.06 (s, 3H, $CH_3$), 0.96 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 388.1656 $[M+H]^+$, found: 388.1685.

***5-(3-Bromophenyl)-8,8-dimethyl-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10g).*** IR (potassium bromide): 3222, 3048, 2944, 1650, 887, 743 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.17 (s, 1H, NH), 7.61 (s, 1H, ArH), 7.38 (t, $J$ = 8.0 Hz, 2H, ArH), 7.31–6.98 (m, 3H, ArH), 7.08 (t, $J$ = 7.6 Hz, 1H, ArH), 7.00 (t, $J$ = 7.6 Hz, 1H, ArH), 6.46 (s, 1H, CH), 2.66–2.50 (m, 2H, $CH_2$), 2.29–2.07 (m, 2H, $CH_2$), 1.07 (s, 3H, $CH_3$), 0.94 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 422.0845 $[M+H]^+$, found: 422.0851.

***5-(4-Methoxyphenyl)-8,8-dimethyl-5,8,9,10-tetrahydro-7H-4b,10,11-triaza-benzo[b]fluoren-6-one (10h).*** IR (potassium bromide): 3231, 3099, 2957, 2866, 1645, 838, 737 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.08 (s, 1H, NH), 7.36 (d, $J$ = 7.6 Hz, 1H, ArH), 7.28–7.24 (m, 3H, ArH), 7.04 (t, $J$ = 7.6 Hz, 1H, ArH), 6.96 (t, $J$ = 8.0 Hz, 1H, ArH), 6.76 (d, $J$ = 8.4 Hz, 2H, ArH), 6.36 (s, 1H, CH), 3.66 (s, 3H, $OCH_3$), 2.65–2.51 (m, 2H, $CH_2$), 2.28–2.03 (m, 2H, $CH_2$), 1.06 (s, 3H, $CH_3$), 0.95 (s, 3H, $CH_3$ ). HRMS (ESI): *m/z* cal. for: 374.1863 $[M+H]^+$, found: 374.1853.

***1-(2-Methyl-4-phenyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)-ethanone (12a).*** IR (potassium bromide): 3273, 3103, 3053, 1645, 1536, 1471, 1292, 1158, 806 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.83 (s, 1H, NH), 7.42 (d, $J$ = 8.0 Hz, 3H, ArH), 7.35–7.26 (m, 3H, ArH), 7.20–7.16 (m, 1H, ArH), 7.06–6.95 (m, 2H, ArH), 6.60 (s, 1H, CH), 2.49 (s, 3H, $CH_3$), 2.23 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 304.1444 $[M+H]^+$, found: 304.1471.

***1-[2-Methyl-4-(3-nitrophenyl)-1,4-dihydro-benzo[4,5] imidazo[1,2-a]pyrimidin-3-yl]-ethanone (12b).*** IR (potassium bromide): 3215, 3087, 2881, 1649, 1560, 1458, 1267, 1059, 959, 888, 737, 690 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.01 (s, 1H, NH), 8.28 (s, 1H, ArH), 8.05 (d, $J$ = 8.0 Hz, 1H, ArH), 7.81 (d, $J$ = 8.0 Hz, 1H, ArH), 7.58 (t, $J$ = 7.6 Hz, 1H, ArH), 7.45 (d, $J$ = 8.0 Hz, 1H, ArH), 7.37 (d, $J$ = 8.0 Hz, 1H, ArH), 7.06 (t, $J$ = 7.2 Hz, 1H, ArH), 6.99 (t, $J$ = 7.6 Hz, 1H, ArH), 6.77 (s, 1H, CH), 2.53 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 349.1295 $[M+H]^+$, found: 349.1326.

***1-[4-(4-Methoxyphenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidin-3-yl]-ethanone (12c).*** IR (potassium bromide): 3227, 3099, 3002, 2832, 1654, 1628, 1590, 1514, 1459, 1335, 1228, 958, 807, 744, 659 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.75 (s, 1H, NH), 7.43 (d, $J$ = 8.0 Hz, 2H, ArH), 7.05–6.97 (m, 4H, ArH), 6.83 (d, $J$ = 8.0 Hz, 2H, ArH), 6.57 (s, 1H, CH), 3.67 (s, 3H, $OCH_3$), 2.47 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 334.1550 $[M+H]^+$, found: 334.1565.

***1-[4-(4-Fluorophenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidin-3-yl]-ethanone (12d).*** IR (potassium bromide): 3227, 3100, 3022, 2914, 2840, 1653, 1627, 1565, 1459, 1330, 1229, 1006, 954, 854, 747 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.85 (s, 1H, NH), 7.48–7.42 (m, 3H, ArH), 7.35 (d, $J$ = 8.0 Hz, 1H, ArH), 7.12–6.98 (m, 4H, ArH), 6.62 (s, 1H, CH), 2.49 (s, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 322.1350 $[M+H]^+$, found: 322.1389.

***2-Methyl-4-phenyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (12e).*** IR (potassium bromide): 3234, 3103, 3026, 2928, 2865, 1698, 1615, 1572, 1365, 1255, 1092, 893, 794, 730 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.82 (s, 1H, NH), 7.35 (t, $J$ = 6.8 Hz, 3H, ArH), 7.27 (t, $J$ = 8.0 Hz, 3H, ArH), 7.20–7.16 (m, 1H, ArH), 7.04 (t, $J$ = 8.0 Hz, 1H, ArH), 6.95 (t, $J$ = 7.6 Hz, 1H, ArH), 6.43 (s, 1H, CH), 4.02 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 2.46 (s, 3H, $CH_3$), 1.14 (t, $J$ = 7.2 Hz, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 334.1550 $[M+H]^+$, found: 334.1607.

***2-Methyl-4-(4-nitrophenyl)-1,4-dihydro-benzo[4,5]imidazo [1,2-a]pyrimidine-3-carboxylic acid ethyl ester (12f).*** IR (potassium bromide): 3234, 3105, 2978, 2861, 1697, 1619, 1572, 1518, 1458, 1235, 870, 755, 715, 608 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.99 (s, 1H, NH), 8.15 (d, $J$ = 8.4 Hz, 2H, ArH), 7.66 (d, $J$ = 8.8 Hz, 2H, ArH), 7.37 (d, $J$ = 7.6 Hz, 1H, ArH), 7.28 (d, $J$ = 7.6 Hz, 1H, ArH), 7.06 (t, $J$ = 7.2 Hz, 1H, ArH), 6.96 (t, $J$ = 7.2 Hz, 1H, ArH), 6.62 (s, 1H, CH), 4.03 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 2.48 (s, 3H, $CH_3$), 1.16 (t, $J$ = 7.2 Hz, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 379.1401 $[M+H]^+$, found: 379.1422.

***4-(4-Bromophenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo [1,2-a]pyrimidine-3-carboxylic acid ethyl ester (12g).*** IR (potassium bromide): 3233, 3101, 3023, 2978, 2849, 1698, 1618, 1571, 1487, 1385, 1234, 1010, 893, 801, 730 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.87 (s, 1H, NH), 7.47 (d, $J$ = 8.4 Hz, 2H, ArH), 7.36–7.32 (m, 3H, ArH), 7.26 (d, $J$ = 8.0 Hz, 1H, ArH), 7.06 (t, $J$ = 7.6 Hz, 1H, ArH), 6.96 (t, $J$ = 8.0 Hz, 1H, ArH), 6.45 (s, 1H, CH), 4.02 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 2.46 (s, 3H, $CH_3$), 1.16 (t, $J$ = 7.2 Hz, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 412.0655 $[M+H]^+$, found: 412.0663.

***4-(4-Fluorophenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester (12h).*** IR (potassium bromide): 3235, 3039, 2929, 1697, 1617, 1458, 1303, 1096, 792, 637 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.84 (s, 1H, NH), 7.43–7.40 (m, 2H, ArH), 7.35 (d, $J$ = 8.0 Hz, 1H, ArH), 7.28 (d, $J$ =7.6 Hz, 1H, ArH), 7.12–7.03 (m, 3H, ArH), 6.96 (t, $J$ = 7.6 Hz, 1H, ArH), 6.46 (s, 1H, CH), 4.02 (q, $J$ = 7.2 Hz, 2H, $CH_2$), 2.46 (s, 3H, $CH_3$), 1.15 (t, $J$ = 7.2 Hz, 3H, $CH_3$). HRMS (ESI): *m/z* cal. for: 352.1456 $[M+H]^+$, found: 352.1486.

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## REFERENCES AND NOTES

[1] (a) Whitten, J. P.; Schwaebe, M. WO Pat. 2,008,060,693 (2008); (b) Whitten, J. P.; Schwaebe, M. Chem Abstr 2008, 148, 561911.

[2] Martin, M. W.; Newcomb, J.; Nunes, J. J.; Boucher, C.; Chai, L.; Epstein, L. F.; Faust, T.; Flores, S.; Gallant, P.; Gore, A.; Gu, Y.; Hsieh, F.; Huang, X.; Kim, J. L.; Middleton, S.; Morgenstern, K.; Oliveira-dos-Santos, A.; Patel, V. F.; Powers, D.; Rose, P.; Tudor, Y.; Turci, S. M.; Welcher, A. A.; Zack, D.; Zhao, H. L.; Zhu, L.; Zhu, X. T.; Ghiron, C.; Ermann, M.; Johnston, D.; Saluste, C.-G. P. J Med Chem 2008, 51, 1637.

[3] Zanatta, N.; Amaral, S. S.; Esteves-Souza, A.; Echevarria, A.; Brondani, P. B.; Flores, D. C.; Bonacorso, H. G.; Flores, A. F. C.; Martins, M. A. P. Synthesis 2006, 2305.

[4] (a) Nunes, J. J.; Zhu, X. T.; Ermann, M.; Ghiron, C.; Johnston, D. N.; Saluste, C.-G. P. WO Pat. 2,005,021,551 (2005); (b) Nunes, J. J.; Zhu, X. T.; Ermann, M.; Ghiron, C.; Johnston, D. N.; Saluste, C.-G. P. Chem Abstr 2005, 142, 298123.

[5] Abdel-Hafez, A. A.-M. Arch Pharm Res 2007, 30, 678.

[6] Lipson, V. V.; Orlov, V. D.; Desenko, S. M.; Shishkina, S. V.; Shishkin, O. V.; Shirobokova, M. G. Chem Heterocycl Compd 2001, 36, 1039.

[7] Nawrocka, W.; Zimecki, M. Arch Pharm 1998, 331, 249.

[8] Abdelhamid, A. O.; Riad, B. Y.; Aziz, S. I. Arch Pharm 1987, 320, 642.

[9] Kadyrov, Ch. Sh.; Mukhitdinova, M. Kh.; Shazhenov, A. A. Zh Vses Khim O-va im D I Mendeleeva 1986, 31, 231.

[10] Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005.

[11] Ramon, D. J.; Yus, M. Angew Chem Int Ed Engl 2005, 44, 1602.

[12] Orru, R. V. A. QSAR Comb Sci 2006, 25, 417.

[13] Marek, I. Tetrahedron 2005, 61, 11309.

[14] Bohn Rhoden, C. R.; Westermann, B.; Wessjohann, L. A. Synthesis 2008, 2077.

[15] Groenendaal, B.; Ruijter, E.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. Org Biomol Chem 2008, 6, 3158.

[16] Noel, R.; Fargeau-Bellassoued, M. C.; Vanucci-Bacque, C.; Lhommet, G. Synthesis 2008, 1948.

[17] Alizadeh, A.; Rezvanian, A. Synthesis 2008, 1747.

[18] Shen, L.; Cao, S.; Liu, N.; Wu, J.; Zhu, L.; Qian, X. Synlett 2008, 1153.

[19] Yavari, I.; Sabbaghan, M.; Hossaini, Z. Synlett 2008, 1341.

[20] Welton, T. Chem Rev 1999, 99, 2071.

[21] Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. Chem Rev 2008, 108, 2015.

[22] Hapiot, P.; Lagrost, C. Chem Rev 2008, 108, 2238.

[23] Plaquevent, J.-C.; Levillain, J.; Guillen, F.; Malhiac, C.; Gaumont, A.-C. Chem Rev 2008, 108, 5035.

[24] Karthikeyan, G.; Perumal, P. T. J Heterocycl Chem 2004, 41, 1039.

[25] Le, Z. G.; Chen, Z. C.; Hu, Y.; Zhen, Q. G. J Heterocycl Chem 2005, 42, 735.

[26] Muthukrishnan, M.; More, S. V.; Garud, D. R.; Ramana, C. V.; Joshi, R. R.; Joshi, R. A. J Heterocycl Chem 2006, 43, 767.

[27] Valizadeh, H.; Shockravi, A.; Gholipur, H. J Heterocycl Chem 2007, 44, 867.

[28] Shi, D. Q.; Ni, S. N.; Yang, F.; Ji, S. J. J Heterocycl Chem 2004, 45, 1275.

[29] Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. J Heterocycl Chem 2008, 45, 71.

[30] Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S. J Heterocycl Chem 2008, 45, 653.

[31] Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S.; Ji, S. J. J Heterocycl Chem 2008, 45, 653.

[32] Shazhenov, A. A.; Kadyrov, C. S. Chem Heterocycl Compd 1977, 13, 1114.

[33] Shao, Q. Q.; Tu, S. J.; Li, C. M.; Cao, L. J.; Zhou, D. X.; Wang, Q.; Jiang, B.; Zhang, Y.; Hao, W. J. J Heterocycl Chem 2008, 45, 411.

[34] Insuasty, B.; Salcedo, A.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J.; Salido, S. Hetercycl Commun 2004, 10, 399.

[35] Tu, S. J.; Shao, Q. Q.; Zhou, D. X.; Cao, L. J.; Shi, F.; Li, C. M. J Heterocycl Chem 2007, 44, 1401.

[36] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed using a Rigaku Saturn diffractometer. Crystal data for **4a**: $C_{16}H_{13}N_3O$, crystal dimension 0.18 mm × 0.16 mm × 0.12 mm, Orthorhombic, space group *P*bca, $a = 13.606(3)$, $b = 7.5674(15)$, $c = 24.578(5)$ Å, $V = 2530.6(9)$ Å$^3$, $M_r = 263.29$, $Z = 8$, $D_c = 1.382$ g/cm$^3$, $\lambda = 0.71073$ Å, $\mu$ (Mok$\alpha$) = 0.090 mm$^{-1}$, $F(000) = 1104$, $S = 1.151$, $R_1 = 0.0366$, $wR_2 = 0.0976$.

# Synthesis and Anti-bacterial Activity of New Series of 4-(Substituted biphenyl-4-yl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic Acid Ethyl Ester



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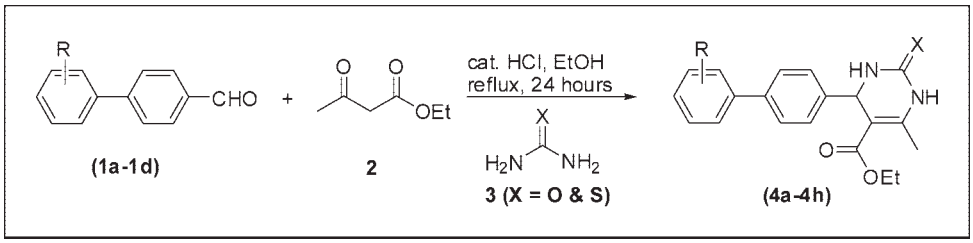


New series of 4-(substituted biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester and 4-(substituted biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester has been synthesized and the structures of the new compounds were established on the basis of $^1$H NMR, Mass (ES/MS), elemental analysis, and melting point. *In-vitro* antibacterial activity (MIC activity) was evaluated and compared with standard drugs ciprofloxacin, sparfloxacin, and trovafloxacin. Most of the compounds in this new series have shown moderate antibacterial activity against both Gram-positive and Gram-negative organisms.

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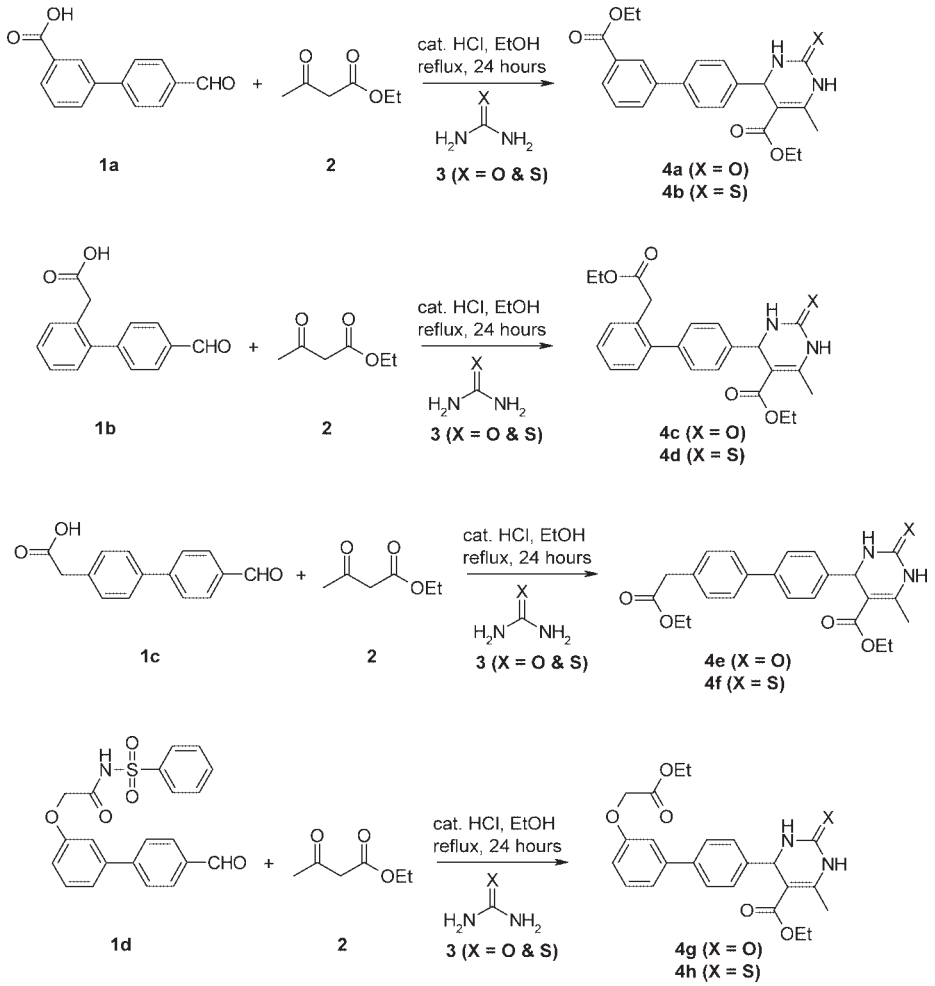
## INTRODUCTION

Numerous antibiotics have been prescribed and found to be effective on various infectious disorders. However, the appearance of multidrug-resistant Gram-positive bacteria, in particular, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE) is causing a serious menace. Moreover, the emergence of vancomycin-resistant MRSA can be anticipated in foreseeable future. For the treatment of these intractable infections, a new anti-infectious agent is needed. The synthetic antibiotics include the sulphonamide drugs, nitrofuran derivative, pyridine- carboxylic acid analogues, fluoroquinolones, and oxazolidinones. The semi-synthetic antibiotics include the penicillins, cephalosporins, tetracyclines, and macrolides. Among them, the sulphonamide drugs, nitrofuran derivatives, penicillins, and tetracyclines are scarcely used in clinical therapy. Quinolone antibiotics are widely prescribed drugs because of their safety, good tolerance, broad antibacterial spectrum, and less resistance [1–4]. Macrolide antibiotics, including Erythromycin and related compounds, continue to be an important therapeutic class against Gram-positive organisms, with second generation macrolides such as Clarithromycin and Azithromycin being widely prescribed due to their efficacy, safety, and lack of serious side effects [5]. Oxazolidinone antibacterial agents [6] are newer class of synthetic antibacterial agents with activity against Gram-positive bacteria. Linezolid [7] is well known as first promising candidate of oxazolidinone and works effectively against numerous serious Gram-positive human pathogens caused by MRSA and VRE. Quinolines and naphthyridines are also emerging as a new class of synthetic antibacterial agents.

- Dihydropyrimidones and their thione analogues have been reported to exhibit wide range of biological activities such as antiviral, antitumor agents, anti-carcinogenic, anti-inflammatory, analgesic, and most important anti-hypertensive activity. Dihydropyrimidinones (DHPMS) have now been recognized as vital drugs in the antihypertensive treatment as well as calcium channel blockers, $\alpha$-1$\alpha$-antagonists, and neuropeptide Y (NPY) antagonists [8]. Some of them are batzeladine alkaloids, which have been found to be potent HIV gp 120-CD4 inhibitors [9]. DHPMS and their sulfur analogues are pharmacologically important because of their antibacterial, antitumor, and anti-inflammatory properties [10]. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the corresponding molecule [11]. Since dihydropyrimidones and thiones have been reported to exhibit wide range of biological activity and so far none of

**Scheme 1**

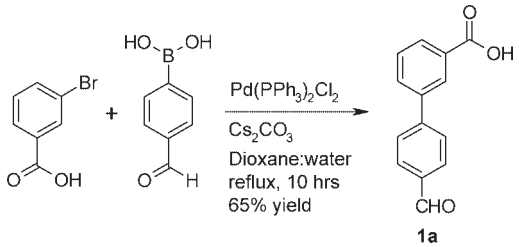



them have been evaluated for anti-bacterial activity, we decided to synthesise new series of dihydropyrimidones and thiones and evaluate them for anti-bacterial activity.

- In 1893, Biginelli [12] reported the first synthesis of DHPMS by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde, and urea. In the following decades, the original cyclocondensation reaction had been extended widely to include variation in all three components, allowing access to a large number of multifunctionalized DHPMS derivatives. However, it suffers from low yields of the product particularly in the case of substituted aromatic and aliphatic aldehydes. Recently, several methods have been reported for preparing dihydropyrimidines using different lewis acid such as $BF_3.OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$ $ZnCl_2$, $ZnBr_2$, $ZrCl_4$, $BiCl_3$, $Bi(OTf)_3$, LiBr, $LiClO_4$, $Mn(OAc)_3$, CAN, $FeCl_3.6H_2O$, $NiCl_2.6H_2O$, *etc*.[13] as well as protic acids such as $H_2SO_4$, HOAc, conc. HCl [14] as promoters.
- Oxazolidinones, a new class of antibacterial agent has many promising candidates with biaryl moiety [15]. The excellent *in vitro* antibacterial activity (MIC activity) has been attributed because of biaryl part and accordingly new series of biaryl dihydropyrimidones and thiones has been synthesized.

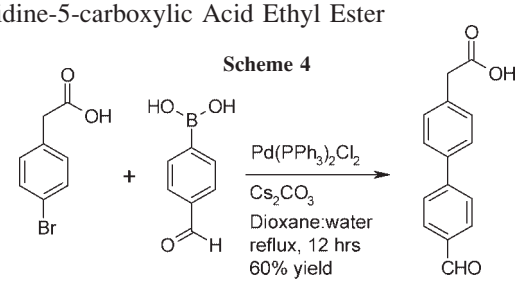
Herein, we describe the synthesis, characterization, and biological evaluation of new series of 4-(substituted biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester and 4-(substituted biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester as potential antibacterials along with their *in vitro* biological activity (MIC activity). The synthesis of [4-(substituted biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester and 4-(substituted biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester is outlined in Scheme 1.

**Scheme 2**




**1a**

**Scheme 4**



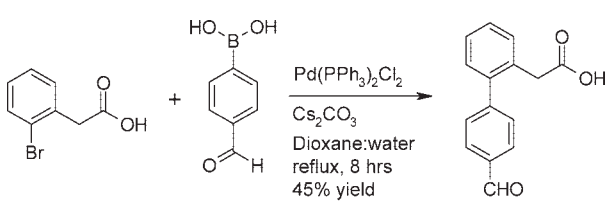

**1c**

The synthesis is achieved in two parts: first part involves the synthesis of differentially substituted biaryl aldehydes and the second part involves Biginelli condensation of these biaryl aldehydes with ethylacetoacetate and urea or thiourea to afford the desired compounds. The biaryl aldehydes **1a** (4′-formyl-biphenyl-3-carboxylic acid), **1b** (4′-formyl-biphenyl-2-yl-acetic acid), and **1c** (4′-formyl-biphenyl-4-yl-acetic acid) have been synthesized by Suzuki coupling of 4-formylphenylboronic acid with respective aryl bromide using bis(triphenylphosphine) palladium(II) chloride as a catalyst and cesium carbonate as a base in dioxane: water as solvent at reflux temperature (Schemes 2–4).

**N-[2-(4′-Formyl-biphenyl-2-yloxy)-acetyl]-benzenesulfonamide (1d).** The synthesis starts with alkylation of 3-bromo phenol (**i**) with chloroacetic acid in water using sodium hydroxide as base to afford (2-bromo-phenoxy)-acetic acid (**ii,** CAS#1798-99-8). Second step involves reaction of compound **ii** (acid chloride) with benzene sulphonamide in DCM using triethylamine as a base to afford *N*-[2-(2-bromo-phenoxy)-acetyl]-benzenesulfonamide (**iii**). Third step involves Suzuki coupling of compound **iii** with 4-formylphenylboronic acid using bis(triphenyl-phosphine)palladium(II) chloride as a catalyst and cesium carbonate as a base in dioxane: water at reflux temperature to afford the desired biaryl aldehyde **1d** (Scheme 5).

Second part of synthesis involves Biginelli condensation of these biaryl aldehydes (**1a, 1b, 1c,** and **1d**) with ethylacetoacetate (**2**) and urea/thiourea (**3**) in ethanol using catalytic HCl to afford the desired dihydropyrimidones and thiones (**4a–4h,** Scheme 1). Since the reaction is carried out with catalytic HCl in ethanol, all the final compounds are isolated as respective ethyl esters (**4a–4h,** Scheme 1). The benzenesulphonamido side chain was incorporated in biaryl aldehyde since sulphonamides have been reported to exhibit good antibacterial activity. However, during the reaction, the benzenesulphonamido portion of biaryl aldehyde was hydrolysed to acid and finally isolated as ethyl ester (**4g, 4h,** Scheme 1). The Biginelli condensation of biaryl aldehyde, ethylacetoacetate, and urea is clean and high yielding (60–70% yield) when compared with thiourea, where the yields are between 45 and 60%.

**Scheme 3**



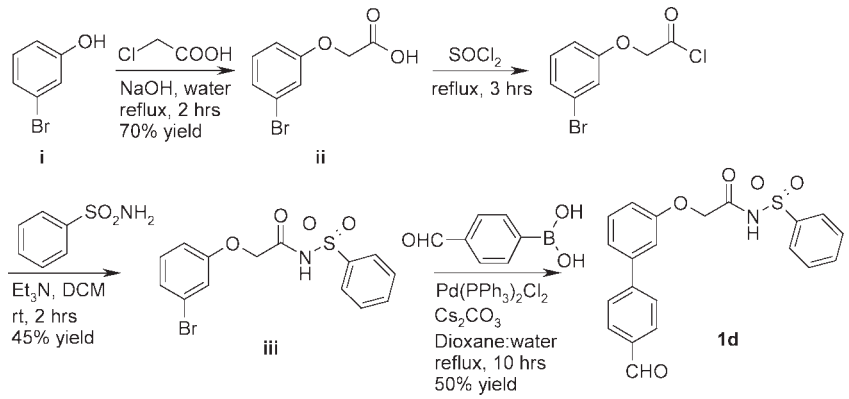

**1b**

The new 4-(substituted-biphenyl-4-yl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl esters prepared above were tested *in vitro versus* a panel of Gram-positive and Gram-negative clinical isolates. Minimum inhibitory concentration (MIC) was determined by standard agar dilution method as per NCCLS guidelines and the values are shown in Table 1. The data of ciprofloxacin, sparfloxacin, and trovafloxacin were used as reference standards.

**Results of biological evaluation.** Most of the compounds in the series have shown moderate antibacterial activity against both Gram-positive and Gram-negative strains, except for *Pseudomonas aeruginosa* and *E. faecium*, where all the tested compounds were inactive (MIC $>$ 32 μg/ml) in comparison with ciprofloxacin, sparfloxacin, and trovafloxacin as reference standards. In all the cases, the thioxo analogues have shown one-fold better activity with respect to their oxo counterparts.

In summary, the synthesis of new 4-(substituted-biphenyl-4-yl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl esters has been described. Most of the compounds in the series have shown moderate antibacterial activity against *S. aureus*, *S. epidermis*, *E. coli*, and *Klebsiella species* as compared to ciprofloxacin, sparfloxacin, and trovafloxacin. Since the preliminary series of novel dihydropyrimidones and thiones have shown moderate antibacterial activity, the possibility remains that more structural variation might change/ improve the activity profile. In connection with this notion, we point out for the first time dihydropyrimidones and their thione analogues as potential antibacterial agents and suggest that the further study is warranted.

**Scheme 5**




## EXPERIMENTAL

Melting points were determined on Quality Precise apparatus and are uncorrected. $^1$H NMR spectra were recorded on Bruker 400-MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Electron spray ionization mass spectra (ES-MS) were recorded on Water-Micromass Quattro-II spectrometer. All the solvents and reagents used were of AR grade and were used without further purification.

**4′-Formyl-biphenyl-3-carboxylic acid (1a).** To a stirred solution of 3-bromobenzoic acid (1 g, 4.98 mmol) in dioxane: water (20 mL, 4:1) was added cesium carbonate (4.85 g, 14.92 mmol) followed by addition of 4-formylphenylboronic acid (0.90 g, 5.96 mmol) and the resulting solution was stirred and degassed under nitrogen for 15 min. Bis(triphenylphosphine) palladium(II) chloride (0.17 g, 0.24 mmol) was added and the reaction mixture was stirred at reflux temperature for 10 h. After completion (monitored by TLC, 1:9 MeOH: CHCl3 as

**Table 1**

Minimum inhibitory concentration (μg/mL) of 4-(substituted-biphenyl-4-yl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester.

| | *P. aeruginosa* ($n$ = 26) | | | *S. aureus* ($n$ = 80) | | | *E. coli* ($n$ = 54) | | | *S. epidermidis* ($n$ = 33) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comp. | MIC 50 | MIC 90 | Range | MIC | MIC | Range | MIC 50 | MIC 90 | Range | MIC50 | MIC 90 | Range |
| **4a** | Inactive (>32) | | | 16 | >32 | 8–32 | 8 | >16 | 4–>32 | 16 | >32 | 8–32 |
| **4b** | Inactive (>32) | | | 8 | >16 | 4–>32 | 8 | >16 | 2–>32 | 8 | >16 | 4–>32 |
| **4c** | Inactive (>32) | | | 16 | >32 | 8–32 | 8 | >16 | 4–>32 | 16 | >32 | 8–32 |
| **4d** | Inactive (>32) | | | 8 | >16 | 4–>32 | 8 | >16 | 2–>32 | 8 | >16 | 4–>32 |
| **4e** | Inactive (>32) | | | 16 | >32 | 8–32 | 8 | >16 | 4–>32 | 16 | >32 | 8–32 |
| **4f** | Inactive (>32) | | | 8 | >16 | 4–>32 | 8 | >16 | 2–>32 | 8 | >16 | 4–>32 |
| **4g** | Inactive (>32) | | | 16 | >32 | 8–32 | 8 | >16 | 4–>32 | 16 | >32 | 8–32 |
| **4h** | Inactive (>32) | | | 8 | >16 | 4–>32 | 8 | >16 | 2–>32 | 8 | >16 | 4–>32 |
| Cipro. | 0.25 | 1 | 0.12–4 | 1 | 4 | 0.5–8 | 0.007 | 0.015 | 0.003–0.03 | 1 | 4 | 0.5–8 |
| Spar. | 1.0 | 2 | 0.25–4 | 1 | 2 | 0.5–4 | 0.007 | 0.03 | 0.003–0.03 | 1 | 2 | 0.5–4 |
| Trova. | 0.25 | 1 | 0.06–4 | 0.5 | 1 | 0.25–4 | 0.002 | 0.015 | 0.003–0.03 | 0.5 | 1 | 0.25–4 |

| | *Klebsiella sp.* ($n$ = 24) | | | *E. faecium* ($n$ = 16) | | | *E. faecalis* ($n$ = 24) | | |
|---|---|---|---|---|---|---|---|---|---|
| | MIC 50 | MIC 90 | Range | MIC 50 | MIC 90 | Range | MIC 50 | MIC 90 | Range |
| **4a** | 8 | >32 | 2–>32 | Inactive (>32) | | | 8 | >32 | 2–>32 |
| **4b** | 8 | >16 | 2–>32 | Inactive (>32) | | | 8 | >16 | 2–>32 |
| **4c** | 8 | >32 | 2–>32 | Inactive (>32) | | | 8 | >32 | 2–>32 |
| **4d** | 8 | >16 | 2–>32 | Inactive (>32) | | | 8 | >16 | 2–>32 |
| **4e** | 8 | >32 | 2–>32 | Inactive (>32) | | | 8 | >32 | 2–>32 |
| **4f** | 8 | >16 | 2–>32 | Inactive (>32) | | | 8 | >16 | 2–>32 |
| **4g** | 8 | >32 | 2–>32 | Inactive (>32) | | | 8 | >32 | 2–>32 |
| **4h** | 8 | >16 | 2–>32 | Inactive (>32) | | | 8 | >16 | 2–>32 |
| Cipro | 0.01 | 0.02 | 0.01–0.5 | >16 | >16 | NA | 2 | 8 | 0.5–16 |
| Spar. | 0.01 | 0.02 | 0.01–0.25 | >16 | >16 | NA | 1 | 4 | 0.5–8 |
| Trova. | 0.025 | 0.1 | 0.06–0.4 | 16 | 16 | NA | 1 | 2 | 0.5–4 |

$n$ = number of strains tested.

mobile phase), solvent was removed under reduced pressure and diluted with water. The aqueous phase was acidified upto pH 4 by dilute HCl and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude compound was purified by column chromatography (60–120 mesh silica gel) eluting with methanol: chloroform (2:98) to afford the title compound **1a** as light yellow solid (0.70 g, 65% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.65 (t, 1H), 7.95–7.97 (d, $J$ = 8.08 Hz, 2H), 8.00–8.03 (m, 4H), 8.26 (s, 1H), 10.07 (s, 1H), 13.20 (s, 1H, COOH); Mass ($m/z$): 228 (M + H, 100%).

**(4′-Formyl-biphenyl-2-yl)-acetic acid (1b).** To a stirred solution of 2-bromophenylacetic acid (1 g, 4.65 mmol) in dioxane: water (20 mL, 4:1) was added cesium carbonate (4.53 g, 13.95 mmol) followed by addition of 4-formylphenylboronic acid (0.84 g, 5.58 mmol) and the resulting solution was stirred and degassed under nitrogen for 15 min. Bis(triphenyl-phosphine)palladium(II) chloride (0.16 g, 0.23 mmol) was added and the reaction mixture was stirred at reflux temperature for 8 h. After completion (monitored by TLC, 1:9 MeOH: CHCl3 as mobile phase), solvent was removed under reduced pressure and diluted with water. The aqueous phase was acidified upto pH 4 by dilute HCl and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude compound was purified by column chromatography (60–120 mesh silica gel) eluting with methanol: chloroform (2:98) to afford the title compound 1b as yellow solid (0.49 g, 45% yield). M.p. 171–173°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.54 (s, 2H), 7.35–7.40 (m, 2H), 7.53 (d, $J$ = 8.16 Hz, 2H), 7.89–7.92 (m, 2H), 7.96–8.02 (m, 2H), 10.07 (s, 1H), 12.31 (bs, 1H, COOH); Mass ($m/z$): 241 (M + H, 100%).

**(4′-Formyl-biphenyl-4-yl)-acetic acid (1c).** To a stirred solution of 4-bromophenylacetic acid (1 g, 4.65 mmol) in dioxane: water (20 mL, 4:1) was added cesium carbonate (4.53 g, 13.95 mmol) followed by addition of 4-formylphenylboronic acid (0.84 g, 5.58 mmol) and the resulting solution was stirred and degassed under nitrogen for 15 min. Bis(triphenyl-phosphine)palladium(II) chloride (0.16 g, 0.23 mmol) was added and the reaction mixture was stirred at reflux temperature for 12 h. After completion (monitored by TLC, 1:9 MeOH: CHCl3 as mobile phase), solvent was removed under reduced pressure and diluted with water. The aqueous phase was acidified upto pH 4 by dilute HCl and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude compound was purified by column chromatography (60–120 mesh silica gel) eluting with methanol: chloroform (2:98) to afford the title compound 1c as yellow solid (0.65 g, 60% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.64 (s, 2H), 7.40 (d, $J$ = 8 Hz, 2H), 7.72 (d, $J$ = 7.96 Hz, 2H), 7.91 (d, $J$ = 8.08 Hz, 2H), 7.99 (d, $J$ = 7.96 Hz, 2H), 10.05 (s, 1H), 12.41 (s, 1H, COOH); Mass ($m/z$): 241 (M + H, 100%).

**(3-Bromo-phenoxy)-acetic acid (ii).** To a stirred solution of 3-bromo phenol (i) (5 g, 28 mmol) in water (50 mL) was added NaOH (1.34 g, 33.6 mmol) followed by addition of chloroacetic acid (2.89 g, 30.8 mmol) and the resulting solution was refluxed for 2 h. After completion, the reaction mixture was acidified upto pH 4 by 6*N* HCl and the resulting mixture was extracted ethyl acetate (3 × 50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to afford the title compound ii as yellow solid (4.67 g, 70% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 4.72 (s, 2H), 6.92–6.95 (m, 1H), 7.12–7.15 (m, 2H), 7.24 (t, $J$ = 7.84, 1.96 Hz, 1H), 13.09 (s, 1H, COOH); Mass ($m/z$): 232 (M + H, 100%).

***N*-[2-(3-Bromo-phenoxy)-acetyl]-benzenesulfonamide (iii).** A stirred solution of compound ii (2.5 g, 10.82 mmol) in $SOCl_2$ (15 mL) was refluxed under nitrogen atmosphere for 3 h. After completion, solvent was removed completely under reduced pressure to afford the acid chloride. To this acid chloride solution dissolved in DCM (25 mL) was added triethylamine (3 mL, 21.64 mmol) followed by addition of benzenesulphonamide (2.03 g, 12.98 mmol) under cooling. After addition, the reaction mixture was stirred at room temperature for additional 2 h. After completion, the reaction mixture was quenched with water (25 mL) and the organic phase was separated, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude compound was purified by column chromatography (60–120 mesh silica gel) eluting with 1:1 ethyl acetate: hexane to afford the title compound iii (1.80 g, 45% yield). M.p. 207–210°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 4.70 (s, 2H), 6.81–6.84 (dd, $J$ = 2.32, 1.84 Hz, 1H), 7.02 (t, $J$ = 2.2, 1.96 Hz, 1H), 7.12 (d, $J$ = 8.08 Hz, 1H), 7.19 (m, 1H), 7.63 (m, 2H), 7.72 (m, 1H), 7.92 (m, 2H), 12.49 (bs, 1H, COOH); Mass ($m/z$): 371 (M + H, 100%).

***N*-[2-(4′-Formyl-biphenyl-3-yloxy)-acetyl]-benzenesulfonamide (1d).** To a stirred solution of *N*-[2-(3-bromo-phenoxy)-acetyl]-benzenesulfonamide (**iii**) (1 g, 2.70 mmol) in dioxane: water (20 mL, 4:1) was added cesium carbonate (2.63 g, 8.10 mmol) followed by addition of 4-formylphenylboronic acid (0.49 g, 3.24 mmol) and the resulting solution was stirred and degassed under nitrogen for 15 min. Bis(triphenylphosphine)palladium(II) chloride (0.094 g, 0.13 mmol) was added and the reaction mixture was stirred at reflux temperature for 10 h. After completion (monitored by TLC, 1:9 MeOH: CHCl3 as mobile phase), solvent was removed under reduced pressure and diluted with water. The aqueous phase was acidified upto pH 4 by dilute HCl and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude compound was purified by column chromatography (60–120 mesh silica gel) eluting with methanol: chloroform (1:99) to afford the title compound **1d** as yellow solid (0.53 g, 50% yield). M.p. 143–145°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 4.77 (s, 2H), 6.88 (d, $J$ = 7.84 Hz, 1H), 7.13 (s, 1H), 7.32–7.39 (m, 2H), 7.55–7.59 (m, 2H), 7.61–7.65 (m, 1H), 7.81 (d, $J$ = 8.08 Hz, 2H), 7.92 (d, $J$ = 7.80 Hz, 2H), 7.99 (d, $J$ = 8.12 Hz, 1H), 10.06 (s, 1H), 12.52 (bs, 1H, COOH); Mass ($m/z$): 396 (M + H, 100%).

**General procedure for synthesis of compounds 4a to 4h.** To a stirred solution of ethyl acetoacetate (**2**) (2 mmol) in ethanol was added biaryl aldehyde (**1a-1d**) (2 mmol), urea/thiourea (**3**) (3 mmol) followed by addition of 0.5 mL of 6*N* HCl. The resulting solution was stirred at reflux for 16 h. After completion, solvent was removed under reduced pressure and the residue obtained was extracted with ethyl acetate. The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude compound was purified by column chromatography (60–120 mesh silica gel) eluting with ethyl acetate: hexane (1:1) to afford the title compounds **4a–4h** as solid.

**4-(3′-Ethoxycarbonyl-biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4a).** Light yellow solid; 65% yield; M.p. 128–130°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.12 (t, $J$ = 7.08, 7.08 Hz, 3H), 1.33 (t, $J$ = 7.12, 7.08 Hz, 3H), 2.26 (s, 3H), 3.98–4.03 (q, $J$ = 7.08, 7.16 Hz, 2H), 4.31–4.37 (q, $J$ = 7.04, 7.16 Hz, 2H), 5.20 (d, $J$ = 2.96 Hz, 1H), 7.35 (d, $J$ = 8.24 Hz, 2H), 7.59–7.63 (m, 2H), 7.66 (d, $J$ = 8.28 Hz, 2H), 7.91–7.95 (m, 2H), 8.15 (bs, 1H, NH), 9.25 (s, 1H, NH); Mass (*m/z*): 409 (M + H, 100%); Anal. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.88; H, 5.97; N, 6.92.

**4-(3′-Ethoxycarbonyl-biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4b).** Yellow solid, 50% yield; M.p. 141–142°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.15 (t, $J$ = 7.12, 7.08 Hz, 3H), 1.33 (t, $J$ = 7.12, 7.04 Hz, 3H), 2.40 (s, 3H), 4.02–4.06 (q, $J$ = 7.12, 7.12 Hz, 2H), 4.31–4.36 (q, $J$ = 7.08, 7.08 Hz, 2H), 5.36 (s, 1H), 7.27 (d, $J$ = 8.16 Hz, 2H), 7.55–7.64 (m, 5H), 7.90–7.94 (m, 2H), 8.14 (s, 1H); Mass (*m/z*): 425 (M + H, 100%); Anal. Calcd. for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60. Found: C, 64.84; H, 5.67; N, 6.66.

**4-(2′-Ethoxycarbonylmethyl-biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4c).** Off-white solid; 60% yield; M.P. 94–96°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.05 (t, $J$ = 6.76, 6.68 Hz, 3H), 1.15 (t, $J$ = 6.48, 5.72 Hz, 3H), 2.26 (s, 3H), 3.58 (s, 2H), 3.90–3.94 (q, $J$ = 6.78, 6.92 Hz, 2H), 3.99–4.03 (q, $J$ = 7.02, 7.02 Hz, 2H), 5.19 (s, 1H), 7.21–7.33 (m, 7H), 7.62 (m, 1H), 7.79 (s, 1H), 9.23 (s, 1H); Mass (*m/z*): 423 (M + H, 100%); Anal. Calcd. for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.57; H, 6.25; N, 6.68.

**4-(2′-Ethoxycarbonylmethyl-biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4d).** Light yellow solid; 50% yield; M.p. 99–101°C, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.04 (t, $J$ = 7.16, 7.08 Hz, 3H), 1.12 (t, $J$ = 7.08, 7.04 Hz, 3H), 2.30 (s, 3H), 3.58 (s, 2H), 3.89–3.95 (q, $J = J$ = 7.00, 7.04 Hz, 2H), 4.02-4.05 (q, $J$ = 7.08, 7.12 Hz, 2H), 5.21 (d, $J$ = 3.60 Hz, 1H), 7.20–7.26 (m, 5H), 7.31–7.34 (m, 3H), 9.71 (s, 1H, NH), 10.39 (s, 1H, NH); Mass (*m/z*): 439 (M + H, 100%); Anal. Calcd. for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39. Found: C, 65.41; H, 5.93; N, 6.35.

**4-(4′-Ethoxycarbonylmethyl-biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4e).** Yellow solid; 65% yield; M.p. 146–148°C, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.12 (t, $J$ = 7.08, 7.08 Hz, 3H), 1.19 (t, $J$ = 7.08, 7.08 Hz, 3H), 2.26 (s, 3H), 3.69 (s, 2H), 3.97–4.03 (q, $J$ = 7.08, 7.04 Hz, 2H), 4.06–4.11 (q, $J$ = 7.16, 7.08 Hz, 2H), 5.17 (d, $J$ = 3.08 Hz, 1H), 7.30–7.34 (m, 4H), 7.60 (m, 4H), 7.78 (s, 1H, NH), 9.24 (s, 1H, NH); Mass (*m/z*): 423 (M + H, 100%); Anal. Calcd. for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 67.95; H, 6.16; N, 6.59.

**4-(4′-Ethoxycarbonylmethyl-biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4f).** Yellow solid; 55% yield; M.p. 134–136°C, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.06-1.20 (m, 6H), 2.28 (s, 3H), 3.67 (s, 2H), 3.99–4.07 (m, 4H), 5.18 (s, 1H), 7.25–7.32 (m, 4H), 7.56–7.62 (m, 4H), 9.68 (s, 1H, NH), 10.36 (s, 1H, NH); Mass (*m/z*): 439 (M + H, 100%); Anal. Calcd. for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39. Found: C, 65.38; H, 6.03; N, 6.44.

**4-(3′-Ethoxycarbonylmethoxy-biphenyl-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4g).** Yellow solid; 50% yield; M.p. 151–152°C, $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.12 (t, $J$ = 7.12, 7.04 Hz, 3H), 1.20 (t, $J$ = 7.20, 7.12 Hz, 3H), 2.26 (s, 3H), 3.97–4.03 (q, $J$ = 6.96, 7.08 Hz, 2H), 4.14–4.20 (q, $J$ = 7.12, 7.12 Hz, 2H), 4.85 (s, 2H), 5.17 (d, $J$ = 2.96 Hz, 1H), 6.89–6.92 (dd, $J$ = 1.96, 1.92 Hz 1H), 7.16 (bs, 1H), 7.23 (d, $J$ = 7.92 Hz, 1H), 7.30 (d, $J$ = 8.20 Hz, 2H), 7.36 (t, $J$ = 7.88, 8.00 Hz, 1H), 7.62 (d, $J$ = 8.24 Hz, 2H), 7.79 (s, 1H, NH), 9.25 (s, 1H, NH); Mass (*m/z*): 439 (M + H, 100%); Anal. Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.02; H, 5.93; N, 6.43.

**4-(3′-Ethoxycarbonylmethoxy-biphenyl-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4h).** Yellow solid; 40% yield; M.p. 163–165°C, $^1$H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, $J$ = 7.12, 7.12 Hz, 3H), 1.29 (t, $J$ = 7.12, 7.12 Hz, 3H), 2.37 (s, 3H), 4.10–4.12 (q, $J$ = 7.08, 7.12 Hz, 2H), 4.25–4.30 (q, $J$ = 7.12, 7.16 Hz, 2H), 4.66 (s, 2H), 5.44 (d, $J$ = 2.40 Hz, 1H), 6.87 (d, $J$ = 8.12 Hz, 1H), 6.99 (d, $J$ = 7.36 Hz, 1H), 7.10 (s, 1H), 7.17 (d, $J$ = 7.92 Hz, 1H), 7.32–7.35 (m, 4H); Mass (*m/z*): 455 (M + H, 100%); Anal. Calcd. for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.11; H, 5.83; N, 6.23.

**MIC determination.** ***Bacterial isolates.*** The strains were collected from major hospitals of India during the period 2003–2006 and were identified by standard laboratory procedures.

MIC was determined by standard agar dilution method as per CLSI (formerly, NCCLS) guidelines (Approved Standard M7-A6, vol. 23, 2003) on Mueller-Hinton agar containing serial two-fold dilutions of the compounds. Strains were grown in Tryptic Soya Broth (TSB, HiMedia, India) for 18–24 h. The overnight grown cultures were diluted appropriately so that the final density is approximately $10^7$ CFU/mL. A portion of this diluted broth was transferred to seed block of a multipoint inoculator (Applied Quality Services, United Kingdom). The inoculating pins were standardized to inoculate 1–2 μL of this broth, so that the final CFU was $1 \times 10^4$–$5 \times 10^4$ CFU/ spot. The inoculated plates were allowed to stand until the moisture in the inoculum spot has been absorbed in the media.

The inoculated plates were inverted and incubated for 18–24 h at 35°C in an ambient air incubator (Newtronic, India). After the completion of incubation period, the plates were read visually.

MIC was defined as the lowest concentration that inhibited the growth of strain completely. Drug free plates were used to ensure the growth of strains. *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains for each run of MIC determination.

## REFERENCES AND NOTES

[1] Appelbaum, P. C.; Hunter, P. A. Int J Antimicrob Agents 2000, 16, 5.

[2] Mizuki, Y.; Fujawara, I.; Yamaguchi, T. J Antimicrob Chemother 1996, 37, 41.

[3] Ball, P. J Antimicrob Chemother 2000, 46, 17.

[4] Snaz-Nebot, V.; Valls, I.; Barbero, D.; Barbosa, J. Acta Chem Scand 1997, 51, 896.

[5] Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. Experimentia 1971, 27, 362.

[6] Gregory, W. A.; Britteli, D. R.; Wang, C.-L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Sler, A. M.; Forbes, M. J Med Chem 1988, 32, 1218.

[7] Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninem, P. R.; Wanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Topps, D. S.; Ford, C. W.; Zurenko, G. E. J Med Chem 1996, 39, 673.

[8] (a) Atwal, S. S.; Mallary, M. F. J Med Chem 1990, 33, 2629; (b) Atwal, K. S.; Moreland, S.; O'Reilly, B. C. J Med Chem 1991, 34, 806.

[9] (a) Patil. A. D.; Westley, J. W.; Potts, B. C. M. J Org Chem 1995, 60, 1182; (b) Snider, B. B.; Freyer, A. J. Tetrahedron Lett 1996, 37, 6977.

[10] (a) Kappe, C. O. Tetraherdron 1993, 49, 6937. (b) Kappe, C. O.; Fabian, W. M. F. Tetrahedron 1997, 53, 2803. (c) Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[11] (a) Snider, B. B.; Shi, Z. J Org Chem 1993, 58, 3828; (b) Overman, L. E.; Robinowitz, M. H.; Renhowe, P. A. J Am Chem Soc 1995, 117, 2657; (c) Rovnyak, G.C.; Kimball, S. D.; Beyer, B.; Cuciotta, G.; Dimacro, J. D.; Gougoutas, J.; Moreland, S. J Med Chem 1995, 38, 119.

[12] Biginelli, P. Gazz Chim Ital 1893, 23, 360.

[13] (a) Hu, E. H.; Sidler, D. R.; Dolling, U. H. J Org Chem 1998, 63, 3454; (b) Lu, B. Y.; Wang, Z.; Yang, B.; Ma, H. Tetrahedron Lett 2000, 41, 9075; (c) Ma, Y.; Qianc, W. L.; Yang, M. J Org Chem 2000, 65, 3864; (d) Ranu, B. C.; Hajra, A.; Jana U.J Org Chem 2000, 65, 6270; (e) Fu, N. Y.; Peppe, C. Tetrahedron 2002, 58, 4801; (f) Reddy, C. V.; Mahesh. M. Reddy, V. V. N. Tetrahedron Lett 2002, 43, 2657; (g) Ramalinga, K.; Kamial, T. N. B. Synlett 2001, 6, 863; (h) Varala, R.; Adapa, S. R. Synlett 2003, 1, 67; (i) Gourhari, M. Tetrahedron Lett 2003, 44, 2757; (j) Yadav, J. S. Synthesis 2001, 9, 1341; (k) Kumar K. A.; Reddy, C. D. Tetrahedron Lett 2001, 42, 7873; (l) Yadav, J. S. J Chem Soc Perkin Trans 2001, 16, 1939; (m) Jun, L.; Yinjuan, B. Synthesis 2002, 4, 466; (n) Salehi, P.; Fard, M. A. B. Tetrahedron Lett 2003, 44, 2889.

[14] (a) Bussolari, J. C.; McDonnell, P. A. J Org Chem 2000, 65, 6777; (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramaling, T. J Chem Res Synop 2000, 7, 354; (c) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Schwartz, J. J Org Chem 1985, 54, 5898.

[15] (a) Barman, T. K.; Panday, M.; Mathur, T.; Bhadauriya, T.; Rao, M.; Khan, S.; Singhal, S.; Bhateja, P.; Sood, R.; Malhotra, S.; Das, B.; Paliwal, J.; Bhatnagar, P. K.; Upadhyay, D. J. Int J Antimicrob Agents 2009, 33, 280; (b) Takashi, K.; Akihiko, K.; Yoshikazu, A.; Tatsuhiro, S.; Hisashi, T.; Taku, S.; Yasumichi, F. J Med Chem 2008, 51, 6558; (c) Laura, L.; Paul, D.; Joe, D.; Francois, F.; Joyee, S. Antimicrob Agents Chemother 2008, 52, 1653.

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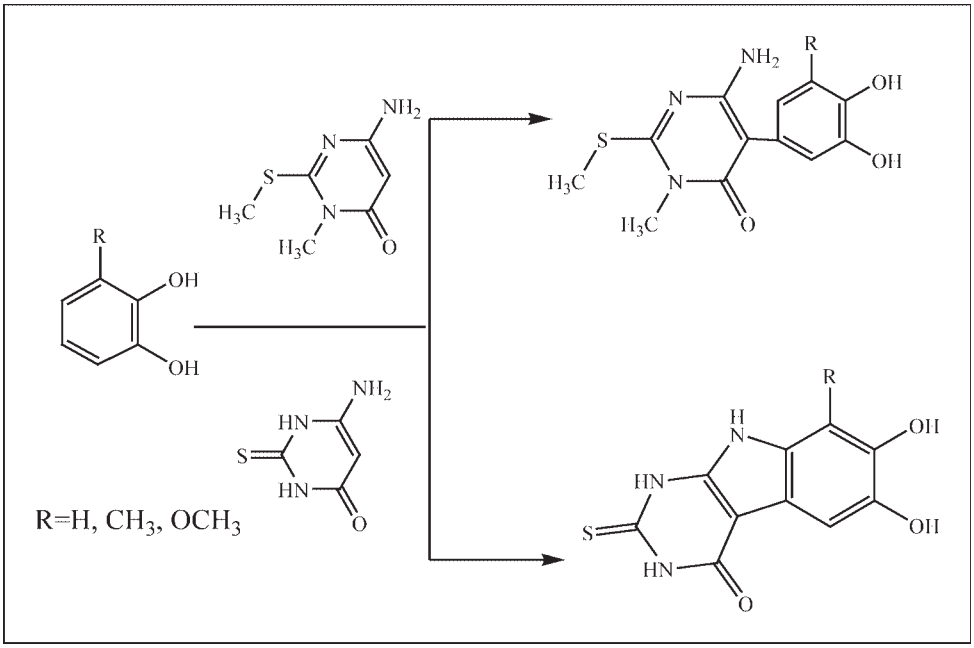


Electrochemical oxidations of catechols have been studied in the presence of 6-amino pyrimidine derivatives as nucleophiles in aqueous solution using cyclic voltammetry. The efficient electro-organic synthesis of products has been successfully performed at carbon rod electrodes in an undivided cell under controlled potential conditions in good yield and purity.

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## INTRODUCTION

Pyrimidine and its derivatives are attracting the attention of an increasing number of synthetic organic chemists because of their broad range of biological activity and medicinal importance [1,2]. Numerous reports delineate the antitumor [3], antiviral [4], antioxidant [5], antifungal [6], and hepatoprotective [7], activities of these compounds. Therefore, large efforts for the preparation of these molecules have been directed toward the synthetic manipulation of uracils [8]. The importance of pyrimidine derivatives prompted us to synthesis a number of these compounds from catechols and thiouracils. We have investigated the electrochemical oxidation of catechols (**1a**–**1c**) in the presence of 6-amino pyrimidine derivatives (**3a**, **3b**) as nucleophiles. This work has led to the development of a facile and environmentally friendly electrochemical method for synthesis of pyrimidine derivatives (**5a**–**5c**) and uracil derivatives (**8d**–**8f**).

## RESULTS AND DISCUSSION

Cyclic voltammetry of 2 m*M* solution of catechol (**1a**) in 0.2*M* sodium acetate solution containing 10% acetonitrile as supporting electrolyte shows an anodic ($A_1$) and a corresponding cathodic peak ($C_1$), which correspond to the transformation of (**1a**) to *o*-quinone (**2a**) and *vice versa* within a quasi-reversible two electrons reaction (Fig. 1, curve a). A peak current ratio ($I_P^{C1}/I_P^{A1}$) of nearly unity can be considered as a criterion for the stability of *o*-quinones (**2a**) produced at the surface of the electrode under the experimental conditions [9,10]. In other words, any hydroxylation [11,12], dimerization

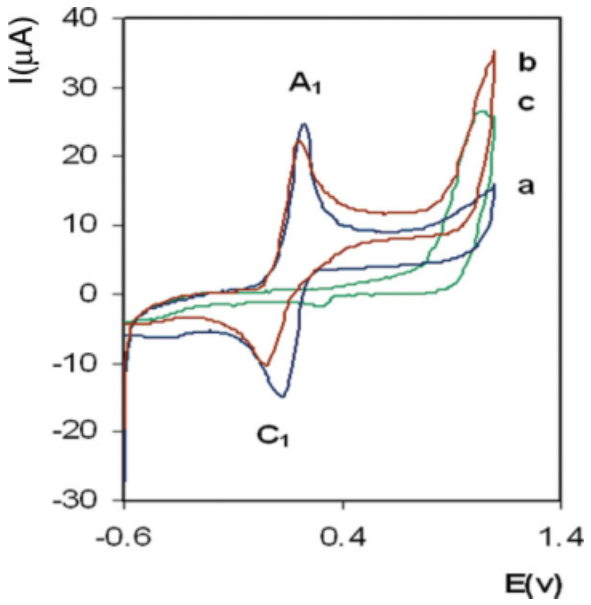



**Figure 1.** Cyclic voltammogram of 2 m*M* catechol (**1a**): (a) in absence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**), (b) in the presence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one, (c) cyclic voltammogram of 2 m*M* 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**) in the absence of catechol, at glassy carbon electrode, in 0.2*M* sodium acetate solution containing 10% acetonitrile. Scan rate: 100 $mVs^{-1}$, $T$ = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

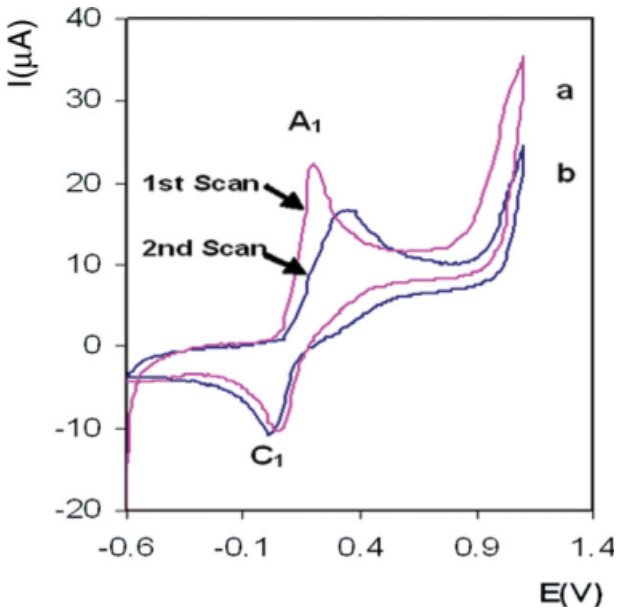



**Figure 2.** Cyclic voltammogram of 2 m*M* catechol: (a) in the presence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (first cycle), (b) in the presence of 2 m*M* 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (second cycle), at glassy carbon electrode, in 0.2*M* sodium acetate solution containing 10% acetonitrile. Scan rate: 100 mV $s^{-1}$, $T$ = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

[13,14], or radical cations formation [15–18] are too slow to be observed on the time scale of cyclic voltammetry.

To get further support on the electrochemical oxidation of catechol (**1a**), it was studied in the presence of **3a** as a nucleophile. Curve b in Figure 1 shows the cyclic voltammogram obtained for a 2.0 m*M* solution of **1a** in the presence of 2.0 m*M* **3a**. The voltammogram exhibits decreasing in cathodic counterpart ($C_1$) of anodic peak ($A_1$). This is due to the reactivity of **1a** with **3a**. The cyclic voltammogram of 2.0 m*M* of **3a** is shown in Figure 1 curve c, for comparison.

The multicyclic voltammogram of **1a** in the presence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**) are shown in Figure 2. In this figure, the second scan exhibits a relatively intense decrease in anodic peak current $A_1$ together with a potential shift in a positive direction. The decrease in $A_1$ peak current and positive shift of this peak are probably due to the formation of a thin film of product at the surface of the electrode inhibiting to a certain extent the performance of electrode process [19,20].

Furthermore, it was observed that the height of the $C_1$ peak increased proportional to augmentation of potential scan rate (Fig. 3, curve a–f). This confirms the reactivity of **2a** toward **3a**. A similar situation was observed when **3a**/**1a** concentration ratio is decreases. Moreover, the current function for $A_1$ peak ($I_P^{A1}/v^{1/2}$) decreases slightly with increasing scan rate (Fig. 3, curve g).

Controlled-potential coulometry was performed in an aqueous solution containing 0.5 mmol of **1a** and 0.5 mmol of **3a** at the potential of $A_1$ peak. At the end of coulometry, it was specified that charge consumption per molecules of **1a** becomes about $2e^-$.

The coulometry and voltammetry results allow us to propose an EC mechanism[16,17] for the electro-oxidation of **1a** in the presence of **3a** (Scheme 1). According to our results, the Michael addition reaction of **3a** to *o*-quinone (**2a**) [eq. (2)] seems to occur much faster than other side reactions, which leads to the product **5a**. The overoxidation of **5a** was circumvented during the preparative reaction because of the almost insolubility of the product in acetate buffer solution medium.

The electro-organic synthesis of **5b** and **5c** has been performed using oxidation of **1b** and **1c** in the presence of **3a** as described for **5a** (Table 1).

The electro-oxidation of catechol (**1a**) in the presence of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one (**3b**) as a nucleophile was studied by cyclic voltammetry and controlled-potential coulometry in 0.2*M* sodium acetate solution containing 10% acetonitrile too. Figure 4, curve b, shows the cyclic voltammogram obtained for a 2.0 m*M*

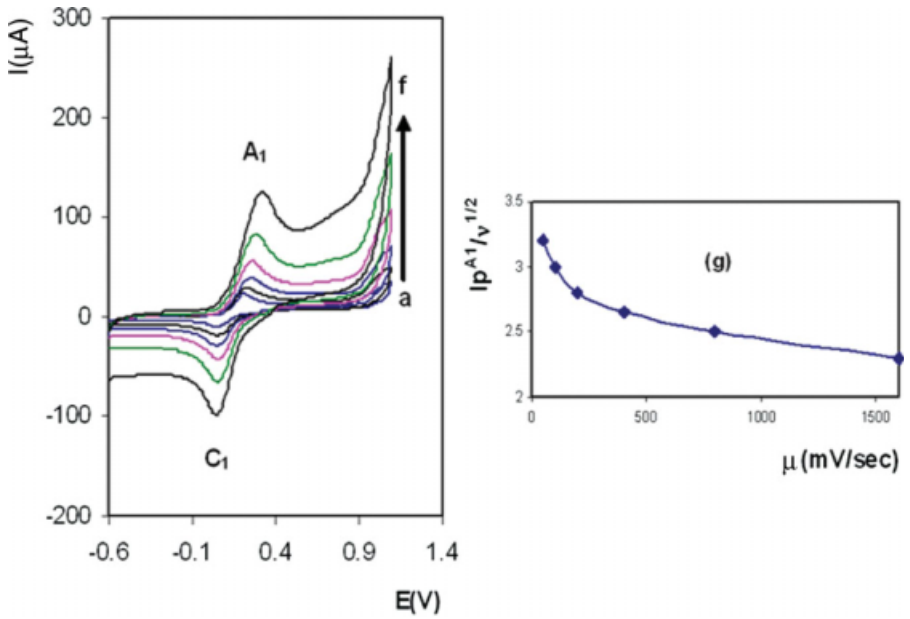
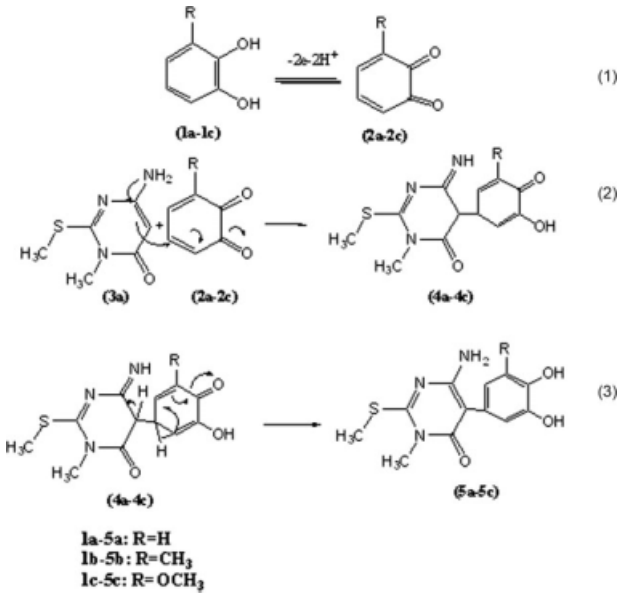



**Figure 3.** Typical cyclic voltammogram of 2 m*M* catechol (**1a**) in the presence of 2 m*M* 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**) in 0.2*M* sodium acetate solution containing 10% acetonitrile at a glassy carbon electrode (1.8-mm diameter) at various scan rate. Scan rate from (a) to (f) are 50, 100, 200, 400, 800, and 1600 mV $s^{-1}$, respectively. (g) Variation of peak current ratio ($I_P^{A1}/v^{1/2}$) *versus* scan rate, $T$ = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

solution of **1a** in the presence of 2.0 m*M* **3b**. The voltammogram clearly exhibits an increase in anodic peak $A_1$ and a decrease in the cathodic peak $C_1$. This is due to the reactivity of **2a** with **3b**. For comparison, the cyclic voltammogram of 2.0 m*M* solutions of catechol (**1a**) and **3b** are shown in Figure 4, curves a and c, respectively.

The possible reason for the observed large increase in the $\mathbf{A_1}$ peak current could be the oxidation of

**Scheme 1**



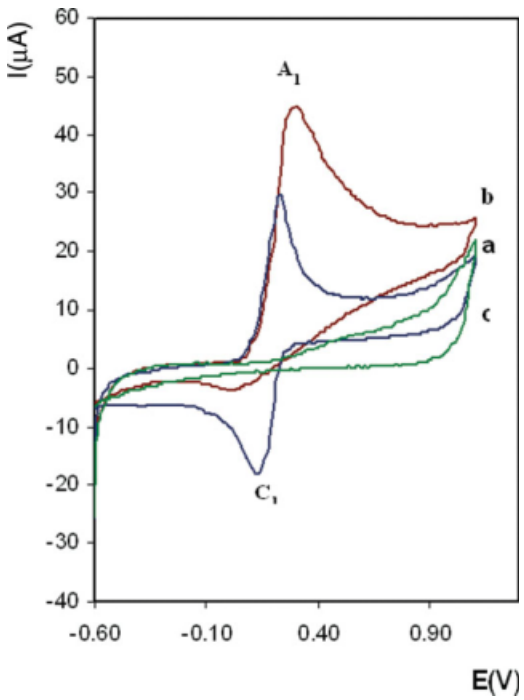
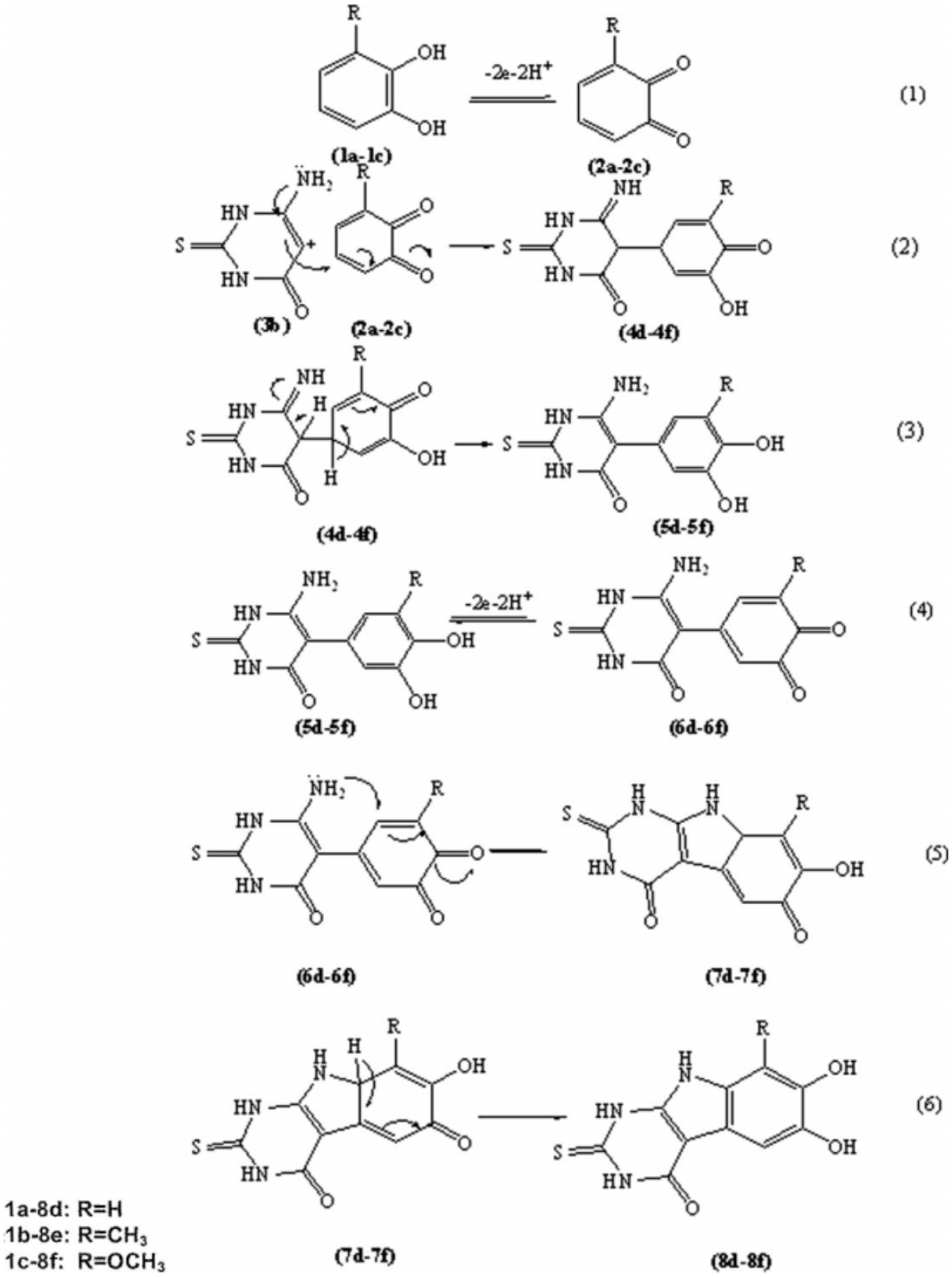




**Figure 4.** Cyclic voltammogram of 2 m*M* catechol (**1a**): (a) in the absence of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one (**3b**), (b) in the presence of **3b**, (c) cyclic voltammogram of 2 m*M* 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1H)-one (**3b**) in the absence of catechol, at glassy carbon electrode, in 0.2*M* sodium acetate solution containing 10% acetonitrile. Scan rate: 100 mV $s^{-1}$, $T$ = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2**




intermediate **5c** at a potential close to that of the starting catechol. This oxidation is due to solubility of the **5c** in the reaction medium. The most important differences between this and previous cases are the large increase in the $A_1$ peak current (Fig. 4, curve b) and the number of transferred electrons during controlled-potential coulometry.

The results demonstrate that contrary to the previous cases, the consumed charge is about $4e^-$ per molecule of catechol (**1a**). This is related to two two-electron transfer processes [eqs. (1) and (4) in Scheme 2]. The coulometry, voltammetry, and NMR results allow us to propose an ECEC mechanism [21–24], indicated in

Scheme 2 for the electro-oxidation of catechol (**1a**) in the presence of **3b**.

## CONCLUSIONS

In conclusion, the results of this work show that catechols (**1a–1c**) are oxidized to their respective *o*-benzoquinone (**2a–2c**). The formed *o*-benzoquinones are attacked by nucleophiles **3a** and **3b** to form final products **5a–5c** and **8d–8f**. We observed an interesting diversity in the electro-oxidation mechanism and products of catechols (**1a–1c**) in the presence of (**3a**, **3b**). In the cases of **1a–1c** in the presence of **3a**, the final products **5a–5c** are pyrimidine derivatives that were obtained after consumption of $2e^-$ per molecule **1a**, **1b**, and **1c**. In the case of **1a–1c** in the presence of **3b**, the final products **8d–8f** are uracil derivatives that were obtained after consumption of $4e^-$ per molecule **1a–1c**, *via* intermolecular and intramolecular Michael addition reactions. The overall mechanism for anodic oxidation of catechols (**1a–1c**) in the presence of **3a** and **3b** are presented in Schemes 1 and 2. These mechanisms show a good diversity in anodic oxidation of **1a–1c** in the presence of **3a** and **3b**.

## EXPERIMENTAL

**Chemical and solutions.** Catechol derivatives were reagent-grade materials, sodium acetate, and other solvents were of proanalysis grade (all from E. Merck). These chemicals were used without further purification. The stock solution of catechols was prepared daily.

**Electrode and electrochemical instrument.** A cyclic voltammetry was performed using a micro-Autolab type III potentiostat/galvanostat and millimole scale electrolysis was performed using a pp-200 Zahrner potentiostat/galvanostat. The working electrode used in voltammetry experiments was a glassy carbon disc (2.7 $mm^2$ area) and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and millimole scale electrolysis was assembly of three carbon rods (27 $cm^2$ area) and large platinum gauze constituted the counter electrode. The working electrode potentials were measured *versus* 3*M* Ag/AgCl reference electrode (carbon rods from Azar electrode and other electrodes from Metrohm).

Bruker IFS-66 FTIR spectrometer, Shimadzu QP 1100-EX mass spectrometer operating at an ionization potential of 70 eV, and Bruker DRX-300 AVANCE NMR spectrometer were used for recording different spectra.

**Electrochemical synthesis of 5a–c and 8d–f.** In a typical procedure, 100 mL of 0.2*M* sodium acetate solution containing 10% acetonitrile was pre-electrolyzed at mentioned potential (Table 1) *versus* 3*M* Ag/AgCl in an undivided cell. Then 2 mmol of catechols (**1a–1c**) and 2 mmol of nucleophiles (**3a**, **3b**) were added to the cell. Initially, the current density was ~2 $mA/cm^2$ and the electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted during the electrolysis and the graphite anode was washed in acetone to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and purified by washing with hot water (Table 1).

**Table 1**

Electro-analytical and preparative data.

| Conversion | Applied potential (V) *vs.* (Ag/AgCl) | Yield (%) | Consumed charge (C) | Time of electrolysis (h) |
|---|---|---|---|---|
| **1a–5a** | 0.3 | 68 | 98.1 | 16.3 |
| **1b–5b** | 0.3 | 72 | 97.8 | 16.2 |
| **1c–5c** | 0.3 | 69 | 98.2 | 16.4 |
| **1a–8d** | 0.25 | 64 | 196.2 | 33.4 |
| **1b–8e** | 0.25 | 67 | 196.8 | 33.1 |
| **1c–8f** | 0.25 | 62 | 196.5 | 33.8 |

**Characteristics of products**

***6-Amino-5-(3,4-dihydroxyphenyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one (5a).*** Mp > 270°C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3438, 3324, 3225, 2931, 1635, 1590, 1537, 1505, 1418, 1359, 1223, 1092, 845. $^1$H NMR (DMSO-$d_6$): δ = 3.30 (s, 3H, $CH_3$), 3.36 (s, 3H, $CH_3$), 5.86 (s, 2H, $NH_2$), 6.31 (d, *J* = 8Hz,1H, Ar—H), 6.45 (s, 1H, Ar—H), 6.59 (d, *J* = 10Hz, 1H, Ar—H), 8.16 (s, 1H, OH), 8.79 (s, 1H, OH) ppm; $^{13}$C NMR (DMSO-$d_6$): δ = 14.6, 29.9, 95.1, 106.1, 111.7, 124.2, 133.3, 146.0, 148.6, 158.0, 159.8, 160.8 ppm; MS, m/z (%): 279 ($M^+$, 100), 230 (10), 171 (40), 126 (30), 110 (50), 83 (46), 63 (50), 47 (90). *Anal*. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04. Found: C, 51.48; H, 4.73; N, 14.98.

***6-Amino-5-(3,4-dihydroxy-5-methylphenyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one (5b).*** Mp > 270°C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3445, 3157, 2930, 1636, 1516, 1411, 1359, 1298, 1204, 1093, 1036, 906, 860. $^1$H NMR (DMSO-$d_6$): δ = 2.09 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 3.16 (s, 3H, $CH_3$), 5.78 (s, 2H, $NH_2$), 6.42 (s, 1H, H-Ar), 6.53 (s, 1H, H-Ar), 8.11 (s, 1H, OH), 9.09 (s, 1H, OH) ppm. $^{13}$C NMR (DMSO-$d_6$): δ = 14.6, 16.5, 29.9, 95.1, 115.7, 123.5, 124.3, 124.5, 142.4, 145.0, 158.0, 159.7, 160.9 ppm; MS (EI, 70 eV): m/z (%) = 293 ($M^+$, 100), 243 (5), 171 (25), 124 (50), 105 (20), 88(50), 57 (55), 41 (50). *Anal*. Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23 H, 5.15; N, 14.31. Found: C, 53.18; H, 5.18; N, 14.31.

***6-Amino-5-(3,4-dihydroxy-5-methoxyphenyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one (5c).*** Mp > 270°C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3456, 1636, 1583, 1523, 1388, 1251, 1041, 998, 844, 800, 578. $^1$H NMR (DMSO-$d_6$): δ = 3.21 (s, 3H, $OCH_3$), 3.49 (s, 3H, $CH_3$), 3.71 (s, 3H, $CH_3$) 5.86 (s, 2H, $NH_2$), 6.33 (s, 1H, H-Ar), 6.62 (s, 1H, H-Ar), 8.35 (s, 1H, OH), 9.85 (s, 1H, OH) ppm.$^{13}$C NMR (DMSO-$d_6$): δ = 19.3, 23.4, 29.9, 90.2, 105.7, 121.4, 125.2, 145.4, 153.2, 157.2, 159.9, 161.0, 163.4 ppm; MS (EI, 70 eV): m/z (%) = 309 ($M^+$, 100), 236 (10), 171 (12), 140 (32), 88(25), 57 (30), 41 (50). *Anal*. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.47 H, 4.89; N, 13.58. Found: C, 50.46; H, 4.89; N, 13.60.

***2,3-Dihydro-6,7-dihydroxy-2-thioxo-1H-pyrimido[4,5-b]indol-4(9H)-one (8d).*** Mp > 270°C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3415, 3343, 3173, 1639, 1566, 1481, 1450, 1366, 1309, 1201, 864.

$^1$H NMR (DMSO-$d_6$): δ = 5.03 (s,1H, NH), 639 (s, 1H, H-Ar), 6.70 (s, 1H, H-Ar), 7.20 (s, 1H, NH), 8.38 (s, 1H, NH), 9.37 (s, 1H, OH), 9.41 (s, 1H, OH) ppm; $^{13}$C NMR (DMSO-$d_6$): δ = 81.1, 106.4, 108.6, 112.3, 129.3, 144.9, 145.1, 161.0, 162.4, 163.0 ppm; MS (EI, 70 eV): m/z (%) = 249 ($M^+$, 80), 221 (25), 210 (25), 182(90), 155(10), 128 (10), 85 (30), 68 (100), 41 (55). *Anal*. Calcd for $C_{10}H_7N_3O_3$ S: C, 48.19; H, 2.83; N, 19.25. Found: C, 48.22; H, 2.85; N, 19.75.

***2,3-Dihydro-6,7-dihydroxy-8-methyl-2-thioxo-1H-pyrimido[4,5-b]indol-4(9H)-one (8e).*** Mp > 270°C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3464, 3367, 2928, 1633, 1505 1452, 1361, 1297, 1228, 1033, 804. $^1$H NMR (DMSO-$d_6$) δ = 2.17 (s, 3H, $CH_3$), 5.01 (s, 1H, NH), 6.94 (s, 1H, H-Ar), 7.28 (s, 1H, NH), 8.22 (s, 1H, NH), 8.86 (s, 1H, OH), 9.97 (s, 1H, OH) ppm; $^{13}$C NMR (DMSO-$d_6$) δ = 14.6, 81.2, 105.7, 113.9, 117.3, 118.0, 128.2, 142.6, 144.9, 161.1, 162.4 ppm; MS (EI, 70 eV): m/z (%) = 263 ($M^+$, 100), 223 (15), 196 (75), 150 (10), 124 (25), 85 (30), 68 (60), 41 (100). *Anal*. Calcd for $C_{11}H_9N_3O_3$ S: C, 50.18; H, 3.44; N, 15.96. Found: C, 50.17; H, 3.45; N, 15.97.

***2,3-Dihydro-6,7-dihydroxy-8-methoxy-2-thioxo-1H-pyrimido[4,5-b]indol-4(9H)-one (8f).*** Mp > 270°C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3435, 3336, 3339, 2924, 1659, 1565, 1463, 1394, 1278, 1020, 768. $^1$H NMR (DMSO-$d_6$) δ = 2.93 (s, 3H, $OCH_3$), 4.91 (s, 1H, NH), 6.11 (s, 1H, H-Ar), 6.68 (s, 1H, NH), 7.88 (s, 1H, NH), 8.35 (s, 1H, OH), 10.31 (s, 1H, OH) ppm; $^{13}$C NMR (DMSO-$d_6$) δ = 59.6, 91.5, 108.2, 121.4, 128.9, 132.2, 150.9, 152.6, 158.5, 166.3, 170.1 ppm; MS (EI, 70 eV): m/z (%) = 279 ($M^+$, 93), 251 (70), 223 (15), 157 (50), 140 (30), 110 (27), 60 (80), 41 (100). *Anal*. Calcd for $C_{11}H_9N_3O_4S$: C, 47.31; H, 3.25; N, 15.05. Found: C, 47.29; H, 3.26; N, 15.06

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## REFERENCES AND NOTES

[1] Yamashita, S. Tetrahedron 1980, 36, 865; (b) Bradshaw, T. K.; Hutchison, D. W. Chem Soc Rev 1977, 6, 43.

[2] (a) Maumato, R.; Farukawa, Y. Chem Pharm Bull 1977, 25, 2974; (b) Cheng, C. C.; Roth, B. Med Chem 1971, 8, 61; (c) Jones, A. S.; Swgers, J. R.; Walker, R. T.; Clercq, E. D. J Med Chem 1988, 31, 268; (d) Griengl, H. H.; Wanck, E.; Schwarz.W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. J Med Chem 1987, 30, 1199; (e) Clercq, E. D.; Benaerts, R. J Biol Chem 1987, 262, 1495.

[3] Sanghhvi, Y. S.; Larson, S. B.; Matsumoto, S. S.; Nord, L. D.; Smeet, D. F.; Willis, R. C.; Avery, T. H.; Robins, R. K.; Revankar, G. R. J Med Chem 1989, 32, 629.

[4] Tenser, R. B.; Gaydos, A.; Hay, K. A. Antimicrob Agents Chemother 2001, 45, 3657.

[5] De la Cruz, J. P., Carrasco, T.; Ortega, G.Sanchez De la Cuesta, F. Lipid 1992, 27, 192.

[6] Mishra, M. N.; Srivastava, M. K.; Khan, M. H. Indian J Chem 2001, 40, 49.

[7] Ram, V. J.; Goel, A.; Sarkhel, S.; Maulik, P. R. Bioorg Med Chem 2002, 10, 1275.

[8] (a) Hirota, K.; Huang, J.; Sajiki, H.; Maki, Y. Heterocycles 1986, 24, 2293; (b) Niess, R.; Robins, R. K. J Heterocycl Chem 1970, 7, 243; (c) Hirota, K.; Kitade, H.; Sajiki, H.; Maki, Y. Synthesis 1984, 7, 589; (d) Gohain, M.; Prajapati, D.; Gogoi, B. J.; Sandhu, J. S. Synlett 2004, 7, 1179; (e) Bernier, J. L.; Lefebvre, A.; Lespognol, C.; Navarro, J.; Perio, A. Eur J Chem Chim Ther 1977, 12, 341; (f) Parajapati, D.; Thakur, A. J Tetrahedron Lett 2005, 46, 1433.

[9] Nematollahi, D.; Tammari, E. J Org Chem 2005, 70, 7769.

[10] Bayandory Moghaddam, A.; Kobarfard, F.; Fakhari, A. R.; Nematollahi, D.; Hosseiny Davarani, S. S. Electrochim Acta 2005, 51, 739.

[11] Papouchado, L.; Petrie, G., Adams, R. N. J Electroanal Chem 1972, 38, 389.

[12] Young, T. E.; Griswold, J. R.; Hulbert, M. H. J Org Chem 1974, 39, 1980.

[13] Rayn, M. D.; Yueh, A.; Wen-Yu, C. Electrochem Soc 1980, 27, 1489.

[14] Nematollahi, D.; Rafiee, M.; Samadi-Maybodi, A. Electrochim Acta 2004, 49, 2495.

[15] Sioda, R. E. J Phys Chem 1968, 72, 2322.

[16] Sioda, R. E.; Frankowska, B. J Electroanal Chem 2004, 568, 365.

[17] Sioda, R. E.; Frankowska, B. Tetrahedron Lett 2005, 46, 2747.

[18] Sioda, R. E.; Frankowska, B. J Electroanal Chem 2008, 612, 147.

[19] Nematollahi, D.; Habibi, D.; Rahmati, M. J Org Chem 2004, 6, 2637.

[20] Nematollahi, D.; Rafiee, M. Electroanal Chem 2004, 566, 31.

[21] Bard, A. J. Electrochemical Methods, 2nd ed.; Wiley: New York, 2001; p 495.

[22] Shamsipur, M.; Hosseiny Davarani, S. S.; Nasiri Aghadam, M.; Nematollahi, D. Electrochim Acta 2006, 51, 3327.

[23] Hosseiny Davarani, S. S.; Nematallahi, D.; Shamsipur, M.; Mashkuri Najafi, N.; Masumi, L.; Ramyar, S. J Org Chem 2006, 71, 2139.

[24] Nematollahi, D.; Rafiee, M. Green Chem 2005, 7, 638.

# Clean Synthesis of Spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles and Spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles by One-Pot, Three-Component Reactions

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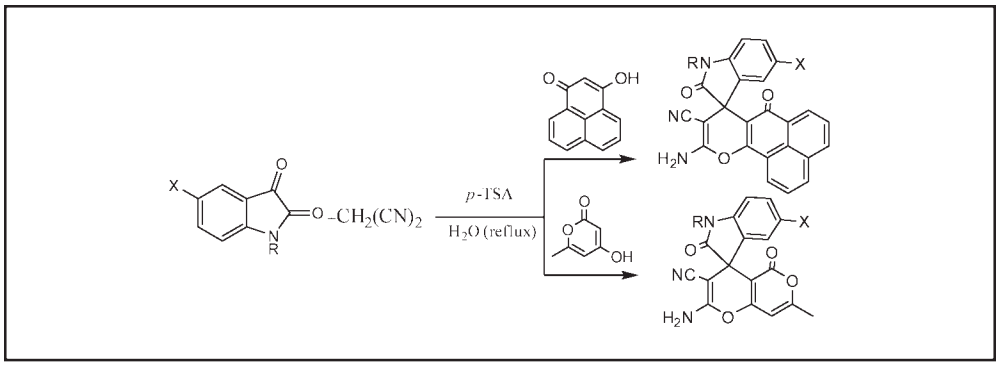


An environmentally benign three-component reaction in aqueous media has been reported for the synthesis of spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles and spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles.

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## INTRODUCTION

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity [1]. One of the best methods to fulfill these goals is the development and use of multicomponent reactions (MCRs), which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner [2]. MCRs are economically and environmentally very advantageous because multistep syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step.

Indole and indoline fragments are important moieties of a large number of a variety of natural products and medicinal agents [3], and some of indolines, spiro-annulated with heterocycles in the third position, have shown high biological activity [4–6]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [7–9]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [10].

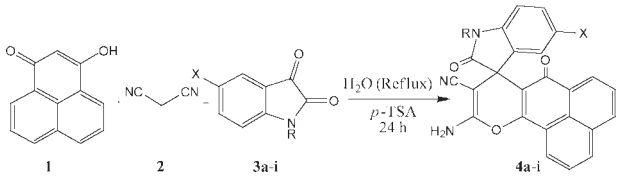
Chromene derivatives are an important group of compounds, widely exist in plants, including edible vegetables and fruits [11]. Synthetic analogues were developed over the years, some of them displaying remarkable effects as pharmaceuticals [12–14], including antifungal [15] and antimicrobial activity [16]. Similarly, substituted 2-amino-pyrans take a significant place among the six-membered oxygen-containing heterocycles. Some of them possess anticancer and antimicrobial activity [17]. Serotonin receptor modulators (pteropodine and its stereoisomers), natural alkaloids, containing both spiroindole and pyran cycles, were isolated from stem bark of *Uncaria tomentosa* [7]. Several spiroheterocycles, containing both indole and pyran heterocycles possess anticonvulsant and analgetic [18], herbicidal [19], and antibacterial activities [20].

As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds [21], we performed the preparation of some new spirooxindole containing chromene or pyran ring fragments via a three-component condensation reaction using water as the reaction medium. Organic transformations in water without using toxic organic solvents are one of the current focuses today, especially in our environmentally conscious society [22].

## RESULTS AND DISCUSSION

The one-pot, three-component condensation reaction of 3-hydroxy-1*H*-phenalen-1-one 1, malononitrile 2, and

**Scheme 1**




isatins 3a–i in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst proceeded rapidly in refluxing water and were complete after 24 h to afford 10′-amino-1,2-dihydro-2,7′-dioxospiro[3*H*-indole-3,8′(7*H*,8*H*)-phenaleno[1,2-*b*]pyran]-9′-carbonitrile derivatives 4a–i in good yields (Scheme 1). $^{1}$H and $^{13}$C NMR spectra of the crude products clearly indicated the formation of fused indoline phenalenopyran 4.

The optimized results are summarized in Table 1. The results were excellent in terms of yields and product purity using isatin derivatives in the presence of *p*-TSA, whereas without it the yields of products were low (<30%) even after 48 h. To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles **4**. However, when this reaction was carried out with ethyl cyanoacetate, the TLC and $^{1}$H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the expected product was obtained in only trace amount.

A possible mechanism for the formation of **4** is proposed in Scheme 2. It is reasonable to assume that **4** results from initial formation of intermediate isatylidene malononitriles **5** by standard Knoevenagel condensation of the malonitrile **2** and isatin **3**. Then, the subsequent Michael-type addition of the 3-hydroxy-1*H*-phenalen-1-one (**1**) to the intermediate **5**, followed by cyclization and tautomerization affords the corresponding products **4** (Scheme 2).

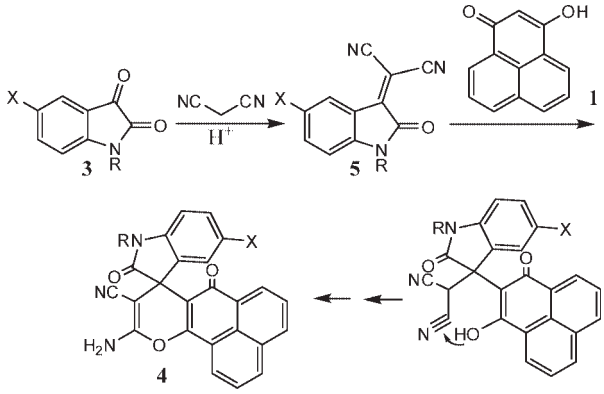
The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4** are stable solids whose structures are fully supported by IR, $^{1}$H and $^{13}$C NMR spectroscopy, mass spectrometry, and elemental analysis.

**Table 1**

Synthesis of Spiro[indole-3,8′-phenalenopyran]-9′-carbonitriles **4**.

| Products **4** | R | X | Yield (%) |
|---|---|---|---|
| **a** | H | H | 93 |
| **b** | Me | H | 75 |
| **c** | Et | H | 83 |
| **d** | H | $NO_2$ | 90 |
| **e** | Me | $NO_2$ | 73 |
| **f** | Et | $NO_2$ | 88 |
| **g** | H | Br | 94 |
| **h** | Me | Br | 91 |
| **i** | Et | Br | 89 |

**Scheme 2**




As expected, when the 3-hydroxy-1*H*-phenalen-1-one **1** was replaced by 4-hydroxy-6-methyl-2*H*-pyran-2-one **6**, another series of spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles **7** were obtained under the same reaction conditions (Scheme 3).

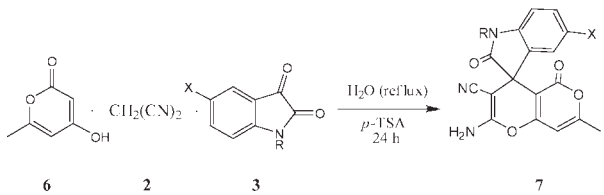
Finally, when we extended this reaction to 1*H*-inden-1,2,3-trion (**8**), product of 2′-amino-1,3-dihydro-7′-methyl-1,3,5′-trioxospiro[2*H*-indene-2,4′(4*H*,5*H*)-pyrano[4,3-*b*]pyran]-3′-carbonitrile **9** was generated in 65% yield after 24 h (Scheme 4).

In conclusion, we have developed an efficient, clean, one-pot and three-component synthesis of new spiro[indole-3,8′-phenaleno[1,2-*b*]pyran]-9′-carbonitriles, spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitriles and spiro[2*H*-indene-2,4′(4*H*,5*H*)-pyrano[4,3-*b*]pyran]-3′-carbonitrile in aqueous media. Prominent among the advantages of this new method are operational simplicity, good yields, and easy work-up procedures used.

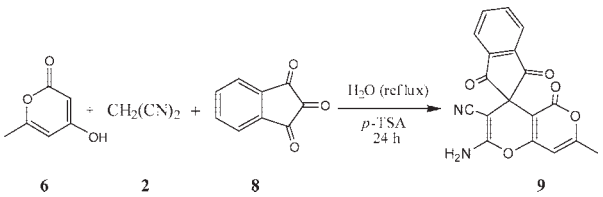
## EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. $^{1}$H and $^{13}$C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 MHz and 75.47 MHz, respectively. IR spectra were

**Scheme 3**



**Scheme 4**




6 2 8 9

recorded using an FTIR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

**Typical procedure for the preparation of spirooxindoles 4a–i, 7a–c, and 9.** A mixture of malononitrile (1 mmol), isatins (1 mmol), 3-hydroxy-1*H*-phenalen-1-one or 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), *p*-TSA (0.1 g) was refluxed in water (5 mL) for 24 h (TLC). After completion of reaction, the reaction mixture was filtered and the precipitate washed with ethanol to afford the pure product.

***10′-Amino-1,2-dihydro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4a).*** Yellow powder (93%); mp >300°C dec. IR (potassium bromide): 3403, 3015, 2200, 1730, 1669 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 6.87–8.41 (m, 12H, H—Ar and $NH_2$), 10.63 (s, 1H, NH). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 48.2, 57.7, 109.8, 113.4, 117.8, 121.0, 122.2, 123.9, 125.4, 127.3, 127.7, 127.9, 128.8, 130.4, 131.9, 134.1, 134.9, 136.1, 142.7, 155.3, 156.2, 178.5, 181.0. MS (70 eV, electron impact) *m/z*: 391 ($M^+$). Anal. Calcd for $C_{24}H_{13}N_3O_3$: C, 73.65; H, 3.35; N, 10.74%. Found: C, 73.60; H, 3.39; N, 10.80%.

***10′-Amino-1,2-dihydro-1-methyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4b).*** Yellow powder (75%); mp >300°C dec. IR (potassium bromide): 3347, 3111, 2200, 1724, 1663 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 3.25 (s, 3H, $NCH_3$), 6.95–8.48 (m, 12H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 31.7, 52.7, 62.2, 113.5, 118.1, 122.4, 125.8, 127.8, 128.4, 130.2, 132.1, 132.7, 133.8, 135.3, 136.7, 138.8, 139.0, 141.1, 149.0, 160.2, 164.1, 181.8, 185.8. MS (70 eV, electron impact) *m/z*: 405 ($M^+$). Anal. Calcd for $C_{25}H_{15}N_3O_3$: C, 74.07; H, 3.73; N, 10.36%. Found: C, 74.01; H, 3.67; N, 10.28%.

***10′-Amino-1,2-dihydro-1-ethyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4c).*** Yellow powder (83%); mp >300°C dec. IR (potassium bromide): 3312, 2993, 2192, 17.9, 1664 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 1.24 (bs, 3H, $CH_3$), 4.05 (bs, 2H, $NCH_2$), 6.93–8.42 (m, 12H, H—Ar and $NH_2$). MS (70 eV, electron impact) *m/z*: 419 ($M^+$). Anal. Calcd for $C_{26}H_{17}N_3O_3$: C, 74.45; H, 4.09; N, 10.02%. Found: C, 74.40; H, 4.05; N, 10.09%.

Due to very low solubility of the product **4c**, we cannot report the $^{13}C$ NMR data for this product.

***10′-Amino-1,2-dihydro-5-nitro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4d).*** Yellow powder (90%); mp >300°C dec. IR (potassium bromide): 3328, 3018, 2197, 1714, 1666 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 7.11–8.46 (m, 11H, H—Ar and $NH_2$), 11.41 (s, 1H, NH). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 48.4, 56.2, 109.9, 112.2, 117.6, 120.0, 121.1, 125.5, 126.3, 127.2, 127.3, 127.9, 128.1, 130.6, 131.9, 134.3, 135.9, 136.4, 143.0, 149.3, 156.1, 159.6, 179.2, 181.2. MS (70 eV, electron impact) *m/z*: 436 ($M^+$). Anal. Calcd for $C_{24}H_{12}N_4O_5$: C, 66.06; H, 2.77; N, 12.84%. Found: C, 66.12; H, 2.82; N, 12.75%.

***10′-Amino-1,2-dihydro-1-methyl-5-nitro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4e).*** Yellow powder (97%); mp >300°C dec. IR (potassium bromide): 3311, 3198, 2197, 1730, 1666 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 3.36 (s, 3H, $NCH_3$), 7.36–8.48 (m, 11H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 27.4, 47.9, 55.8, 109.0, 112.1, 117.5, 119.7, 121.1, 125.5, 126.4, 127.1, 127.3, 127.9, 128.2, 130.7, 131.9, 134.5, 135.1, 136.5, 153.5, 150.1, 156.2, 159.7, 177.9, 181.2. MS (70 eV, electron impact) *m/z*: 450 ($M^+$). Anal. Calcd for $C_{25}H_{14}N_4O_5$: C, 66.67; H, 3.13; N, 12.44%. Found: C, 66.61; H, 3.17; N, 12.49%.

***10′-Amino-1,2-dihydro-1-ethyl-5-nitro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4f).*** Yellow powder (88%); mp >300°C dec. IR (potassium bromide): 3435, 3322, 2207, 1719, 1667 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 1.30 (t, 3H, $^3J_{HH}$ = 6.9 Hz, $CH_3$), 3.87–4.01 (m, 2H, $NCH_2$), 7.39–8.45 (m, 11H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 12.7, 47.8, 56.0, 109.0, 112.0, 117.4, 119.8, 121.0, 125.5, 126.4, 127.0, 127.1, 127.2, 127.8, 128.1, 130.6, 131.9, 134.4, 135.3, 136.4, 143.3, 149.2, 156.2, 159.6, 177.4, 181.2. MS (70 eV, electron impact) *m/z*: 464 ($M^+$). Anal. Calcd for $C_{26}H_{16}N_4O_5$: C, 67.24; H, 3.47; N, 12.06%. Found: C, 67.30; H, 3.42; N, 12.13%.

***10′-Amino-5-bromo-1,2-dihydro-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4g).*** Yellow powder (94%); mp 310°C dec. IR (potassium bromide): 3322, 3198, 2199, 1724, 1665 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 6.86–8.40 (m, 11H, H—Ar and $NH_2$), 10.77 (s, 1H, NH). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 48.5, 57.0, 111.6, 112.7, 113.9, 117.8, 121.1, 125.4, 126.9, 127.2, 127.8, 130.4, 131.5, 131.8, 134.1, 136.1, 137.3, 142.1, 155.7, 159.3, 178.2, 181.1. MS (70 eV, electron impact) *m/z*: 471 ($M^+$ +2), 469 ($M^+$). Anal. Calcd for $C_{24}H_{12}BrN_3O_3$: C, 61.30; H, 2.57; N, 8.94%. Found: C, 61.25; H, 2.52; N, 8.87%.

***10′-Amino-5-bromo-1,2-dihydro-1-methyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4h).*** Yellow powder (91%); mp >300°C dec. IR (potassium bromide): 3378, 3306, 3142, 2207, 1716, 1676 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 3.35 (s, 3H, $NCH_3$), 7.11–8.46 (m, 11H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 27.1, 48.0, 56.6, 110.7, 112.6, 114.8, 117.7, 121.1, 125.5, 126.7, 127.2, 127.3, 127.9, 128.0, 130.6, 131.7, 131.9, 134.3, 136.3, 136.4, 143.6, 155.8, 159.4, 176.8, 181.1. MS (70 eV, electron impact) *m/z*: 485 ($M^+$ +2), 483 ($M^+$). Anal. Calcd for $C_{25}H_{14}BrN_3O_3$: C, 62.00; H, 2.91; N, 8.68%. Found: C, 61.96; H, 2.96; N, 8.60%.

***10′-Amino-5-bromo-1,2-dihydro-1-ethyl-2,7′-dioxospiro[3H-indole-3,8′(7H,8H)-phenaleno[1,2-b]pyran]-9′-carbonitrile (4i).*** Yellow powder (89%); mp >300°C dec. IR (potassium bromide): 3265, 2962, 2192, 1698, 1665 $cm^{-1}$.1H NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 1.25 (t, 3H, $^3J_{HH}$ = 6.9 Hz, $CH_3$), 3.74–3.90 (m, 2H, $NCH_2$), 7.10–8.47 (m, 11H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 110.0, 111.6, 112.0, 120.1, 120.8. 121.1, 121.8, 122.4, 126.0, 127.1, 127.6, 127.8, 129.5, 131.5, 133.1, 134.6, 138.7, 139.8, 140.7, 146.8, 149.7, 153.4. MS (70 eV, electron impact) *m/z*: 499 ($M^+$ +2), 497 ($M^+$). Anal. Calcd for $C_{26}H_{16}BrN_3O_3$: C, 62.67; H, 3.24; N, 8.43%. Found: C, 62.61; H, 3.20; N, 8.50%.

***2′-Amino-1,2-dihydro-7′-methyl-2,5′-dioxospiro[3H-indoline-3,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (7a).*** Brown powder (54%); mp 265°C dec. IR (potassium bromide): 3337,

3187, 2192, 1735, 1691 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 2.24 (s, 3H, $CH_3$), 6.36 (s, 1H, CH), 6.80–7.21 (m, 4H, H—Ar), 7.46 (s, 2H, $NH_2$), 10.59 (s, 1H, NH). MS (70 eV, electron impact) *m/z*: 321 ($M^+$). Anal. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.49; H, 3.40; N, 13.01.

Due to very low solubility of the product **7a**, we cannot report the $^{13}C$ NMR data for this product.

***2′-Amino-1,2-dihydro-7′-methyl-5-nitro-2,5′-dioxospiro[3H-indoline-3,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (7b).*** Brown powder (62%); mp >300°C dec. IR (potassium bromide): 3358, 3167, 2192, 1726, 1698 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 2.25 (s, 3H, $CH_3$), 6.40 (s, 1H, CH), 7.04–8.21 (m, 5H, H—Ar and $NH_2$), 11.36 (s, 1H, NH). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 19.7, 47.6, 55.8, 97.7, 98.7, 110.1, 117.4, 120.6, 126.7, 134.5, 143.1, 149.1, 159.4, 160.7, 160.8, 164.6, 178.5. MS (70 eV, electron impact) *m/z*: 366 ($M^+$). Anal. Calcd for $C_{17}H_{10}N_4O_6$: C, 55.74; H, 2.75; N, 15.30. Found: C, 55.79; H, 2.79; N, 15.36.

***2′-Amino-1,2-dihydro-1,7′-dimethyl-5-nitro-2,5′-dioxospiro[3H-indoline-3,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (7c).*** Brown powder (57%); mp 269°C dec. IR (potassium bromide): 3414, 3168, 2187, 1714, 1690 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 2.25 (s, 3H, $CH_3$), 3.26 (s, 3H, $NCH_3$), 6.41 (s, 1H, CH), 7.30–8.31 (m, 5H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 19.8, 27.4, 47.1, 55.4, 97.6, 98.7, 109.2, 117.3, 120.2, 126.8, 133.7, 143.7, 150.0, 159.6, 160.7, 164.7, 177.1. MS (70 eV, electron impact) *m/z*: 380 ($M^+$). Anal. Calcd for $C_{18}H_{12}N_4O_6$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.79; H, 3.24; N, 14.79.

***2′-Amino-1,3-dihydro-7′-methyl-1,3,5′-trioxospiro[2H-indene-2,4′(4H,5H)-pyrano[4,3-b]pyran]-3′-carbonitrile (9).*** Green powder (65%); mp 275°C. IR (potassium bromide): 3281, 2926, 2197, 1732, 1675, 1642 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide-$d_6$): $\delta_H$ 2.27 (s, 1H, $CH_3$), 6.46 (s, 1H, CH), 7.90–8.08 (m, 6H, H—Ar and $NH_2$). $^{13}C$ NMR (dimethyl sulfoxide-$d_6$): $\delta_C$ 19.9, 52.1, 53.1, 97.1, 98.5, 117.0, 123.9, 137.7, 140.9, 160.2, 161.6, 161.8, 165.6, 199.7. MS (70 eV, electron impact) *m/z*: 334 ($M^+$). Anal. Calcd for $C_{18}H_{10}N_2O_5$: C, 64.67; H, 3.02; N, 8.38. Found: C, 64.61; H, 3.07; N, 8.44.

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## REFERENCES AND NOTES

[1] Trost, B. M. Science 1991, 254, 1471.

[2] (a) Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471; (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmidt, P. Chem—Eur J 2000, 6, 3321.

[3] Sundberg, R. J. The Chemistry of Indoles;Academic Press: New York, NY, 1996.

[4] Joshi, K. C.; Chand, P. Pharmazie 1982, 37.

[5] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[6] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. Bioorg Med Chem 2004, 12, 2483.

[7] Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39.

[8] Ma, J.; Hecht, S. M. Chem Commun 2004, 1190.

[9] Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. Farmaco 2002, 57, 715.

[10] (a) Zhu, S.-L.; Ji, S.-J.; Zhang, Y. Tetrahedron 2007, 63, 9365; (b) Kumar, R. S.; Perumal, S. Terahedron Lett 2007, 48, 7164; (c) Redkin, R. Gr.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. Tetrahedron 2007, 63, 11444; (d) Shanthi, G.; Subbulakshmi, G.; Perumal, P. T.;Tetrahedron 2007, 63, 2057.

[11] Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. Curr Med Chem 2006, 13, 199.

[12] Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. Med Res Rev 2003, 23, 322.

[13] Abd El-Aziz, A. S.; El-Agrody, A. M.; Bedair, A. H.; Corkery, T. C.; Ata, A. Heterocycles 2004, 63, 1793.

[14] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[15] Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. Tetrahedron Lett 2006, 47, 3067.

[16] (a) Kitamura, R. O. S.; Romoff, P.; Young, M. C. M.; Kato, M. J.; Lago, J. H. G. Phytochemistry 2006, 67, 2398; (b) Kraus, G. A.; Kim, I. J Org Chem 2003, 68, 4517.

[17] (a) Al-Haiza, M. A.; Mostafa, M. S.; El-Kady, M. Y. Molecules 2003, 8, 275; (b) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zho, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. J Med Chem 2004, 47, 6299.

[18] Joshi, K. C.; Jain, R.; Sharma, K. J Indian Chem Soc 1988, 65, 202.

[19] Joshi, K. C.; Jain, R.; Arora, S. J Indian Chem Soc 1988, 65, 277.

[20] Higashiyama, K.; Otomasu, H. Chem Pharm Bull 1980, 28, 648.

[21] (a) Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. Tetrahedron Lett 2007, 48, 8790; (b) Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 2375; (c) Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. J Heterocycl Chem 2007, 44, 1009; (d) Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. Heterocycles 2008, 75, 87; (e) Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2007, 63, 1770; (f) Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543; (g) Ghahremanzadeh, R.; Shakibaei, G. I.; Bazgir, A. Synlett 2008, 1129.

[22] (a) Herrerias, C. I.; Yao, X.; Li, Z.; Li, C. Chem Rev 2007, 107, 2546; (b) Li, C. J.; Chan, T. H. Comprehensive Organic Reactions in Aqueous Media, 2nd ed.; Wiley: New York, 2007.

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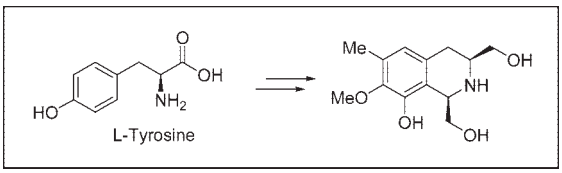


Using L-tyrosine as a chiral starting material, we developed an efficient synthetic route to (–)-MY 336a. A key step in the sequence is a highly regio- and diastereoselective intermolecular Pictet-Spengler cyclization reaction between amino alcohol and benzyloxyacetaldehyde.

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## INTRODUCTION

MY 336a was isolated in 1986 from the culture broth of *Streptomyces gabonae* KY2234 (ATCC 15282) and was characterized as a β-adrenergic receptor antagonist with high affinities toward $\beta_1$- and $\beta_2$-adrenergic receptors [1] (Fig. 1). Although the relative stereochemistry of MY 336a was determined by an X-ray study of its tetra-acetyl derivative, there has been no report on the elucidation of its absolute stereochemistry so far [2]. Kaufman reported the total synthesis of the racemic MY 336a and its epimer, which used Jackson's isoquinoline synthesis as the key reaction [3]. To date, there has been no report on the total synthesis of its optically pure isomer except an attempt to an enantioselective synthesis of MY336a [4].

In the course of our study of the total synthesis of (–)-Renieramycin G and (–)-Lemonomycin, we take (–)-MY 336a as a key precursor for the construction of the AB ring system of (–)-Renieramycin G and (–)-Lemonomycin. Our group had previously reported the construction of the AB ring system of ecteinascidin-saframycin alkaloids by the Pictect-Spengler cyclization between the L-DOPA derivatives and benzyloxyacetaldehyde in which the 1,3-*cis*-diastereoisomer was the main product [5]. Herein, we report an efficient total synthesis of (–)-MY 336a on the basis of this methodology.

## RESULTS AND DISCUSSION

Various methods to synthesize the highly functionalized L-tyrosine derivatives have been reported [6], and we followed an existing procedure under modified conditions to prepare compound **7** (Scheme 1) [7]. Compound **4** was conveniently prepared from L-tyrosine in four steps [7a]: Reduction of compound **4** by catalytic hydrogenation to give compound **5**; Formylation of **5** with $MeOCHCl_2$ in $CH_2Cl_2$ at room temperature in the presence of $TiCl_4$ to afford aldehyde **6**; Baeyer-Villiger oxidation of **6** using MCPBA in chloroform at room temperature and the subsequent hydrolysis of the resulting formate to give phenol **7**. Next, compound **7** was reduced to the corresponding alcohol **8** by $LiBH_4$ in 91% yield. The *N*-acetyl group was removed with 6*N* aq HCl in $CH_3OH$ to give the amino alcohol **9** in 87% yield. The highly regio- and diastereoselective Pictet-Spengler cyclization reaction between amino alcohol **9** and benzyloxyacetaldehyde at 0°C provided the 1,3-*cis*-tetrahydroisoquinoline **10** in 64% yield and **11** in 20% yield, respectively [8]. Initially, we removed the *N*-acetyl group of compoud **7** to get a phenylalanine methyl ester. However, the Pictet-Spengler cyclization reaction between phenylalanine methyl ester and benzyloxyacetaldehyde to construct the tetrahydrosioquinoline fragment met with low yield and poor diastereoselectivity and was ultimately abandoned [5,8a]. Finally, the *O*-benzyl group of tetrahydroisoquinoline **10** was removed by catalytic hydrogenation to give the expected product (–)-MY 336a in 86% yield.

The stereochemistry of compound **1** was verified on the basis of its NOE spectroscopy. Obvious NOE enhancement was observed between 1-H and 3-H; thus a *cis*-1,3-diaxial relationship was confirmed. The ortho-relationship between 5-H and 6-Me was confirmed by the observed NOE enhancement between them.

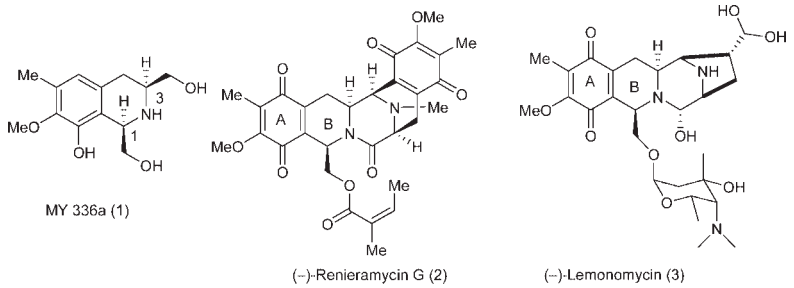



**Figure 1.** Structures of (–)-MY 336a and related tetrahydroisoquinoline alkaloids.

In summary, we have developed a new efficient route to synthesize (–)-MY 336a using L-tyrosine as a chiral starting material, which can be used to elucidate the absolute stereochemistry of natural MY 336a. Further study on the synthesis of Renieramycin G and Lemonomycin based on the methodology is ongoing in our laboratory.

## EXPERIMENTAL

**General.** $^1$H NMR spectra were recorded at 600 MHz or 300 MHz spectrometer at 24 °C in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. $^{13}$C NMR spectra were recorded at 150 or 75 MHz spectrometer at 24°C in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS were carried out by Agilent LC/MSD TOF. Optical rotations were measured on a PerkinElmer Polarimeter 341LC using 10 cm cells and the sodium D line (589 nm) at 20°C and concentration indicated. All reagents were obtained from commercial suppliers unless otherwise stated.

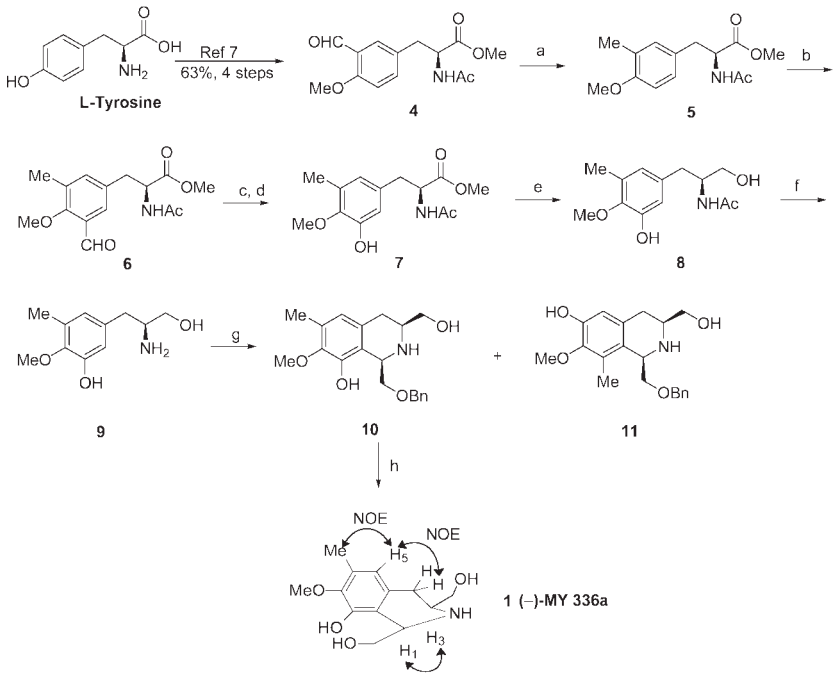
**(*S*)-Methyl-2-acetamido-3-(4-methoxy-3-methylphenyl)propanoate (5).** To a solution of compound **4** (48 g, 0. 17 mol) in MeOH (750 mL) at room temperature was added 1*N* aq. HCl (40 mL) and 10% Pd-C (moist, 30 g), and the mixture was hydrogenated in a Parr apparatus (50 psi $H_2$) for 4 h. The reaction mixture was filtered through celite, washed with MeOH, and concentrated under vacuum. The residue was dissolved in EtOAc (500 mL) and was then washed with saturated aq. $NaHCO_3$. The phases were separated, and the aqueous phase was extracted with EtOAc (200 mL 2×). The combined organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$) to afford compound **5** (38 g, 83%) as a clear oil. $[\alpha]_D^{20}$: +103.6 (c 1.0, $CHCl_3$). HRMS calcd. for $C_{14}H_{20}NO_4(M+H^+)$ 266.1392, found 266.1390. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.89 (m, 2 H), 6.74 (d, $J$ = 8.1 Hz, 1 H), 6.00 (d, $J$ = 7.5 Hz, 1 H), 4.85 (m, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.08 (m, 2 H), 2.17 (s, 3 H), 1.98 (s, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.5, 156.8, 131.4, 127.3, 127.1, 126.6, 109.8, 55.1, 53.2, 52.1, 36.8, 23.0, 16.1.

**(*S*)-Methyl-2-acetamido-3-(3-formyl-4-methoxy-5-methylphenyl)propanoate(6).** Titanium chloride (58 mL, 0.42 mol, 3 equiv) in $CH_2Cl_2$ (150 mL ) was added dropwise over 1 h to a solution of compound **5** (37 g, 0.14 mol) and α,α-dichloromethyl methyl ether (16 mL, 0.18 mol, 1.3 equiv) in $CH_2Cl_2$ (250 ml) with stirring under 0°C. The cooling bath was removed, and the mixture was stirred for a further 3 h, and then poured into ice-water (400 mL). The phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (200 mL 2×). The combined organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated by rotary evaporation. The residue was purified by column chromatography (25% *n*-hexane in EtOAc) to provide compound **6** (37.7 g, 92%) as a white solid. $[\alpha]_D^{20}$: +102.5 (c 1.0, $CHCl_3$). HRMS calcd. for $C_{15}H_{20}NO_5(M+H^+)$ 294.1341, found 294.1339. $^1$H NMR (300 MHz, $CDCl_3$): δ 10.33 (s, 1 H), 7.41 (d, $J$ = 2.1 Hz, 1 H), 7.22 (d, $J$ = 2.1 Hz, 1 H), 6.09 (d, $J$ = 7.5 Hz, 1 H), 4.88 (m, 1 H), 3.88 (s, 3 H), 3.75 (s, 3 H), 3.17 (dd, $J$ = 13.8, 5.4 Hz, 1 H), 3.06 (dd, $J$ = 13.8, 6.0 Hz, 1 H), 2.31 (s, 3 H), 1.99 (s, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 190.0, 171.8, 169.4, 160.8, 138.3, 132.5, 132.1, 128.9, 126.6, 63.1, 53.0, 52.4, 37.0, 23.0, 15.5.

**(*S*)-methyl-2-acetamido-3-(3-hydroxy-4-me-thoxy-5-methylphenyl)propanoate (7).** To an ice cold solution of compound **6** (15.0 g, 51.2 mmol) in $CHCl_3$ (300 mL) was added MCPBA (26.5 g, 153.6 mmol). The mixture was stirred vigorously at room temperature for 6 h and then washed sequentially with 10% $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, brine, and dried over $Na_2SO_4$. The solution was concentrated, and the residue was dissolved in MeOH (150 mL). Then concentrated HCl (12 N, 1.28 mL, 15.3 mmol, 0.3 equiv) was added at 0°C. The solution was then stirred for 10 h at room temperature and then concentrated by rotary evaporation. The residue was purified by column chromatography (2% $CH_3OH$ in $CHCl_3$) to provide compound **7** (13.2 g, 91%) as a yellow oil. $[\alpha]_D^{20}$: +91.5 (c 0.5, $CHCl_3$). HRMS calcd. for $C_{14}H_{20}NO_5(M+H^+)$ 282.1345, found 282.1341.$^1$H NMR (300 MHz, $CDCl_3$): δ 6.54 (d, $J$ = 1.5 Hz, 1 H), 6.42 (d, $J$ = 1.2 Hz, 1 H), 6.14 (d, $J$ = 7.5 Hz, 1 H), 4.83 (dd, $J$ = 12.9, 5.7 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 2.97 (m, 2 H), 2.24 (s, 3 H), 2.00 (s, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.1, 170.0, 148.9, 144.5, 131.9, 130.9, 122.9, 114.2, 60.3, 53.1, 52.2, 37.1, 22.9, 15.7.

**(*S*)-5-(2-Amino-3-hydroxypropyl)-2-meth-oxy-3-methylphenol (9).** To a solution of compound **7** (5.0 g, 13.9 mmol) in THF (25 mL) was added $LiBH_4$ (0.39 g, 18.1 mmol, 1.3 equiv) in portions at 0°C. Then, the mixture was stirred for 18 h at room temperature and quenched slowly with saturated aqueous $NH_4Cl$ (60 mL) and extracted with EtOAc (80 mL 3×). The organic layer was washed with brine (100 mL), dried over $Na_2SO_4$, and concentrated by rotary evaporation. The residue was purified by column chromatography (EtOAc) to provide **8** (4.2 g, 91%) as a white solid.

**Scheme 1.** Reagents and conditions: (a) $H_2$ (50 psi), 10% Pd-C, 1*N* aq. HCl, $CH_3OH$, 4 h, 83%; (b) $MeOCHCl_2$, $TiCl_4$, $CH_2Cl_2$, r.t., 4 h, 92%; (c) MCPBA, $CHCl_3$, r.t., 6 h; (d) 12*N* HCl, $CH_3OH$, 10 h, 91% for two steps; (e) $LiBH_4$, THF, r.t., 24 h, 91%; (f) 6*N* aq. HCl, $CH_3OH$, reflux, 10 h, 87% ; (g) $BnOCH_2CHO$, 4 Å molecular sieves, $CH_2Cl_2/CF_3CH_2OH$=7:1, 0°C, 8 h, compound **10** in 64% yield, compound **11** in 20% yield; (h) $H_2$(50 psi), $Pd(OH)_2$, $CH_3OH$, 12 h, 86%.




To a solution of **8** (3.4 g, 10.2 mmol) in $CH_3OH$ (60 mL) was added 6 *N* aq. HCl (11 mL), and then, the mixture was refluxed in an oil bath (80°C) for 6 h. The reaction solution was removed by rotary evaporation, and the residue was dissolved in $CH_3OH$. The solution was basified with $NEt_3$ and purified directly by column chromatography ($SiO_2$ treated with $NEt_3$, 5% $CH_3OH$ in $CHCl_3$; then 10% $CH_3OH$ in $CHCl_3$) to provide **9** (2.6 g, 87%) as a white solid. $[\alpha]_D^{20}$: −7.4 (c 0.5, $CH_3OH$). HRMS calcd. for $C_{11}H_{18}NO_3(M+H^+)$ 212.1281, found 212.1313. $^1$H NMR (300 MHz, $CD_3COD$): δ 6.78 (d, *J* = 2.1 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 3.90 (s, 3 H), 3.85 (dd, *J* = 11.7 Hz, 3.9 Hz, 1H), 3.67 (dd, *J* = 11.7 Hz, 6.6Hz, 1H), 3.52 (m, 1H), 2.92 (m, 2 H), 2.40 (s, 3 H). $^{13}$C NMR (75MHz, $CD_3COD$): δ 151.4, 146.5, 133.1, 133.0, 123.4, 116.0, 61.9, 60.4, 55.8, 36.3, 15.9.

**(1R,3*S*)-1-(Benzyloxymethyl)-3-(hydroxyl-methyl)-7-methoxy-6-methyl-1,2,3,4-tetra-hydroisoquinolin-8-ol (10) and (1R,3S)1-(benzyloxymethyl)-3-(hydroxyl-methyl)-7-methoxy-8-methyl-1,2,3,4-tetra-hydroisoquinolin-6-ol (11).** To a solution of **9** (0.60 g, 2.84 mmol), acetic acid (0.43 g, 0.42 mL, 7.5 mmol, 2.5 equiv) and the 4 Å molecular sieves (0.5 g) in dichloromethane and 2,2,2-trifluoroethanol (7:1, v/v, 12 mL), a solution of benzyloxyacetaldehyde (0.47 g, 3.1 mmol, 1.1 equiv) in dichloromethane was added slowly *via* syringe over 1 h at 0°C. After being stirred at 0°C for 8 h, the reaction mixture was diluted with dichloromethane and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (2% MeOH in chloroform) to afford **10** (0.63 g, 64%) and **11** (0.19 g, 20%) as white solid. Compound 10: $[\alpha]_D^{20}$: −115.2 (c 0.5, $CH_3OH$). HRMS calcd. for $C_{20}H_{26}NO_4(M+H^+)$ 344.1856, found 344.1885. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.65 (s, 1 H), 7.32 (m, 5 H ), 6.37 (s, 1 H), 4.71(t, *J* = 5.1 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.31 (brd, *J* = 6.0 Hz, 1 H), 4.13 (dd, *J* = 8.7, 2.7 Hz,1 H), 3.59 (s, 3 H), 3.46 (m, 1 H), 3.43 (d, *J* = 8.7 Hz, 1 H ), 3.34 (m, 1 H), 3.33 (s, 1H), 2.68(m, 1 H), 2.42 (dd, *J* = 14.7, 2.4 Hz, 1 H), 2.28(dd, *J* = 14.7, 10.8 Hz, 1 H), 2.14(s, 3 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 146.7, 143.8, 138.7, 132.6, 128.1, 128.0, 127.3, 127.2, 120.9, 73.8, 72.0, 65.2, 59.9, 53.9, 53.0, 33.0, 15.3. Compound **11**: $^1$H NMR (300 MHz, DMSO-*d*6): δ 8.94 (s, 1 H), 7.35 (m, 5 H ), 6.40 (s, 1 H), 4.77(t, *J* = 2.4 Hz, 1 H), 4.59 (d, *J* = 12.3 Hz, 1 H), 4.53 (d, *J* = 12.3 Hz, 1 H), 4.09 (dd, *J* = 9.9, 2.7 Hz, 1 H), 3.60 (s, 3 H), 3.50 (d, *J* = 9.9, 5.4 Hz, 1 H), 3.47(d, *J* = 12.9 Hz, 1 H), 3.28(dd, *J* = 8.4, 2.7 Hz, 1 H), 3.22(m, 1 H), 3.10 (m, 1 H), 2.74(s, 1 H), 2.44 (dd, *J* = 15.9, 3.9 Hz, 1 H), 2.17(dd, *J* = 15.9, 10.8 Hz, 1 H), 2.03(s, 3 H). $^{13}$C NMR (75 MHz, DMSO-*d*6): δ 148.1, 143.9, 138.6, 130.4, 128.2, 127.8, 127.5, 127.3, 125.8, 124.4, 114.2, 71.9, 68.8, 65.7, 59.3, 53.0, 47.5, 31.3, 11.2.

**(–)-MY 336a (1).** To a solution of compound **10** (230 mg, 0.67 mmol ) in MeOH (4 mL) at room temperature was added $Pd(OH)_2$ (moist, Pd content 20%, 50 mg), and the mixture was hydrogenated in a Parr apparatus (50 psi $H_2$) for 10 h. The reaction mixture was filtered through celite, washed with MeOH, and concentrated under vacuum. The pale yellow residue was purified by column chromatograph ($SiO_2$ treated with triethylamine, 5% MeOH in $CHCl_3$) to afford compound **1** (147 mg, 86%) as a yellow solid. $[\alpha]_D^{20}$: −97.3 (c 0.5, $CH_3OH$). HRMS calcd. for $C_{13}H_{20}NO_4(M+H^+)$ 254.1387, found 254.1421 $^1$H NMR (600 MHz, DMSO- $d_6$): δ 8.65 (s, 1 H), 6.34 (s, 1 H), 4.66 (s, 1 H), 4.10 (t, *J* = 4.2 Hz, 1 H), 3.90 (dd, *J* = 10.2, 4.2 Hz, 1 H, 1-$CH_2OH$,), 3.59(s, 3 H, 7-OMe), 3.43 (dd, *J* = 10.8, 4.8

Hz, 1H, 3-$CH_2OH$), 3.36 (dd, $J = 10.2$, 6.6 Hz, 1H, 1-$CH_2OH$), 3.32 (dd, $J = 10.8$, 6.6 Hz, 1 H, 3-$CH_2OH$), 2.68 (m, 1 H, 3-H), 2.41 (dd, $J = 15.0$, 2.4 Hz, 1 H, 4-$H_{eq}$), 2.24 (dd, $J = 14.4$, 11.4 Hz, 1 H, 4-$H_{ax}$), 2.11(s, 3 H, 6-Me). $^{13}C$ NMR (75MHz, DMSO-$d_6$): δ 146.8, 143.9, 132.4, 127.8, 121.9, 120.9, 65.3, 64.8, 59.7, 54.9, 53.9, 33.0, 15.3.

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## REFERENCES AND NOTES

[1] Kase, H.; Fujita, H.; Nakamura, J.; Hashizumi, K.; Goto, J.; Kubo, K.; Shito, K. J Antibiot 1986, 39, 354.

[2] Hirayama, N.; Iida, T.; Shirahata, K. Acta Crystaallogr Sect C 1990, 46, 86.

[3] (a) Kaufman, T. S. J Chem Soc Perkin Trans 1 1993, 4, 403; (b) Kaufman, T. S. J Chem Soc Perkin Trans 1 1996, 20, 2497.

[4] Kaufman, T. S. Tetrahedron Lett 1996, 37, 5329.

[5] (a) Wang, Y.; Liu, Z. Z.; Chen, S. Z.; Liang, X. T. Chin Chem Lett 2004, 15, 505; (b) Tang, Y. F.; Liu, Z. Z.; Chen, S. Z. Tetrahedron Lett 2003, 44, 7091; (c) Liu, Z. Z.; Wang, Y.; Tang, Y. F.; Chen, S. Z.; Chen, X. G.; Li, H. Y. Bioorg Med Chem Lett 2006, 16, 1282.

[6] (a) Schmidt, E. W.; Nelson, J. T.; Fillmore, J. P. Tetrahedron Lett 2004, 45, 3921; (b) Jin, W.; Williams, R. M. Tetrahedron Lett 2003, 44, 4635; (c) Paolis, M. D.; Chen, X. C.; Zhu, J. P. Synlett 2004, 4, 729.

[7] (a) Arnold, Z. S. Polish J Chem 1985, 59, 837; (b) Jow, C. K. Ph.D. Dissertation, W. M. Rice University, Texas, 1995.

[8] (a) Kwon, S.; Myers, A. G. J Am Chem Soc 2005, 127, 16796; (b) Chen, J.; Chen, X.; Zhu, J. J Am Chem Soc 2006, 128, 87.

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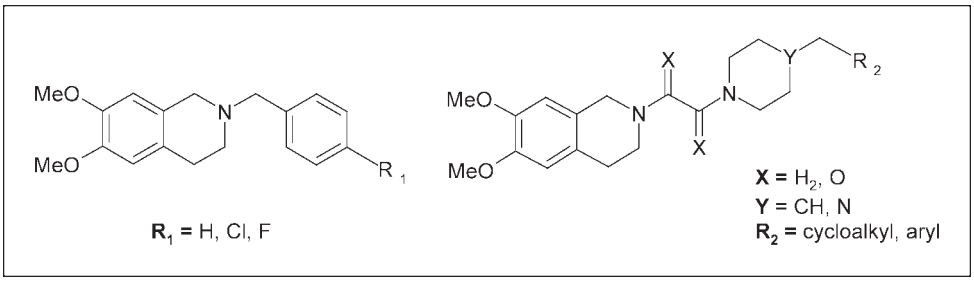


*N*-substituted donepezil-related isoquinolines have been prepared as potential acetylcholinesterase inhibitors (AChEIs). Microwave assisted procedures and solution-phase parallel synthesis were chosen to optimize the synthetic approach and improve the yields. All synthesized compounds were tested for their AChE inhibitory activity by colorimetric Ellman method and some of them (**10**, **13**, and **28**) displayed low inhibitory effects at μ*M* concentrations.

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## INTRODUCTION

Alzheimer's disease (AD), the most common cause of senile dementia, is a neurodegenerative disorder characterized by loss of cognitive ability and severe behavioral abnormalities, which become increasingly serious with disease progression [1].

AD is mainly characterized by a pronounced degeneration of the cholinergic system and by the alteration of other neurotransmitter systems such as the glutamatergic system. Cholinergic abnormalities are associated with (a) the accumulation of protein deposits as β-amyloid peptide (Aβ), the main component of the senile plaques and derived from amyloid precursor protein (APP); (b) the abnormal phosphorylation of τ protein resulting in the formation of neurofibrillary tangles (NFT).

As the cause of the disease has yet to be identified, despite the numerous drugs have been studied as potential anti-AD agents, its treatment has been confined to limiting the progression of the disease. Until now, drug development has focused on (i) symptomatic treatments for restoring deficient neurotransmitters and (ii) etiologically based treatments for slowing or halting the rate of progression [2,3].

Current strategies in the search for new therapeutic approaches are based on different morphological and biochemical characteristics of AD and focus on the following directions: (i) agents compensating the cholinergic system hypofunction; (ii) agents interfering with the metabolism of Aβ; (iii) agents affecting the process of τ protein iperphosphorylation and formation of NFT; (iv) agents protecting neurons from toxic metabolites formed in neurodegenerative processes; and (v) agents activating other neurotransmitter systems to indirectly compensate the cholinergic function deficit.

Currently, only a few therapeutic drugs are available for the treatment of AD; their pharmacological effect is the enhancement of the central cholinergic function, by increasing brain acetylcholine (ACh) level [2,4–6].

Cholinergic therapy for Alzheimer's disease is mainly concentrated on the inhibition of acetylcholinesterase (AChE, EC 3.1.1.7), the main enzyme involved in the breakdown of acetylcholine in the normal brain [7,8]. Tacrine (**1**, Cognex®), donepezil (**2**, Aricept®), rivastigmine (**3**, Exelon®), and galantamine (**4**, Reminyl®) (Fig. 1) are the most widely used acetylcholinesterase inhibitors (AChEIs) [9]. The main effect of AChEIs on neurotransmission is thought to be associated with the increase of both the duration of action and the concentration of the neurotransmitter in the synaptic cleft, resulting in an improvement of the activation of the cholinergic receptors [10].

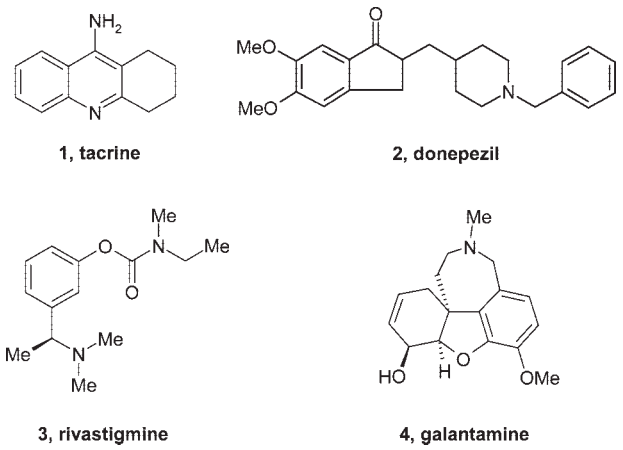



**Figure 1.** AChE inhibitors used for the treatment of AD.

Recently, it has been pointed out that AChE exerts secondary noncholinergic functions and it is also responsible for the pro-aggregating activity toward Aβ, thus suggesting that AChE plays a key role in the development of the senile plaques. In particular, the peripheral anionic binding site (PAS) of AChE is responsible for the AChE–Aβ interaction promoting amyloid fibril formation [11,12]. For these reasons AChEIs able to interact with both catalytic and peripheral binding sites (i.e., dual binding site inhibitors) represent a new therapeutic approach to counteract hypofunction of the cholinergic system and to avoid Aβ aggregation [13]. On the basis of this evidence several classes of dual binding site AChE inhibitors have been developed. Recently, different classes of such compounds have been designed from donepezil (**2**) [14–18]. As demonstrated by the crystal structure of their complex with *Torpedo californica* AChE (*Tc*AChE), **2** is able to occupy the entire length of the enzyme active-site gorge forming various interactions with specific residues, such as aromatic residues, stacking interactions between the benzyl and indanone moieties and the indole ring of Trp84 and Trp279 at the catalytic and peripheral sites, respectively, and the cation–π interaction between the piperidine nitrogen and the phenyl ring of Phe330 residue.

However, now it also seems that the role of butyrylcholinesterase (BChE, EC 3.1.1.8) in hydrolysing acetylcholine may be relevant in brain degenerative conditions. In fact, as Alzheimer disease progresses, AChE activity decreases in some brain regions, while BChE activity increases. This is probably related to a relative increase in the numbers of BChE-positive neurons, likely as compensation for AChE decrease. For these reasons, one of the most innovative approaches is the development of cholinesterase inhibitors (ChEIs), able to inhibit AChE and BChE [6].

We herein report the design, the synthesis and the cholinesterase (AChE and BChE) inhibitory activity of a new series of *N*-substituted 6,7-dimethoxyisoquinoline derivatives (**5–30**, Fig. 2) containing in their structures some moieties considered able to inhibit enzyme activity. The 6,7-dimethoxyisoquinoline nucleus and the benzyl substituent were chosen considering the donepezil chemical structure; furthermore, the linker was modified with the aim of evaluating the effect on the inhibitory potency of the distance between (i) the two aromatic rings that could be involved in stacking interactions with the indole ring of Trp84 and Trp279; (ii) the aromatic ring and the positive ionisable nitrogen atom of benzyl-piperidine or -piperazine moiety. Moreover, we inserted into the linker the carbonyl group that characterizes a useful interaction point for the donepezil-like derivatives.

All synthesized compounds were tested for their ability to inhibit AChE and some compounds were also evaluated against BChE.

## RESULTS AND DISCUSSION

As shown in Scheme 1, the synthesis of designed compounds was performed starting from the commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**31**) that was functionalized to give the different *N*-substituted derivatives **5–29**.

Compounds **5–7** were easily prepared by reaction of derivative **31** with a suitable arylbromide under basic conditions. The reaction of isoquinoline **31** and ethyl oxalylchloride in the presence of triethylamine gave ethyl ester intermediate which was converted into derivative **32** by hydrolysis under basic conditions and then treatment with 6*N* HCl. Thus, 1-(4-benzylpiperidin-1-yl)-2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl) ethane-1,2-dione (**8**) was easily achieved by HBTU-mediated coupling of intermediate **32** with benzylpiperidine.

Also compounds **9–29** were prepared in two steps. In the first step, **31** was combined with 2-chloroacetyl chloride to give the key intermediate **33**, which in the second step was reacted with benzylpiperidine or 4-arylmethylpiperazine derivatives to provide compounds **9–29**. These reactions were carried out following a solution phase parallel

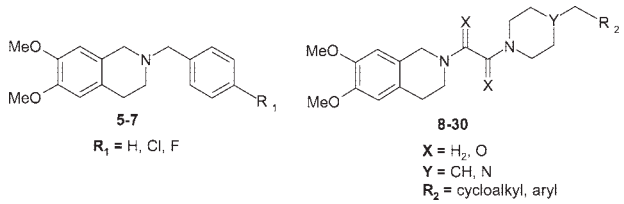
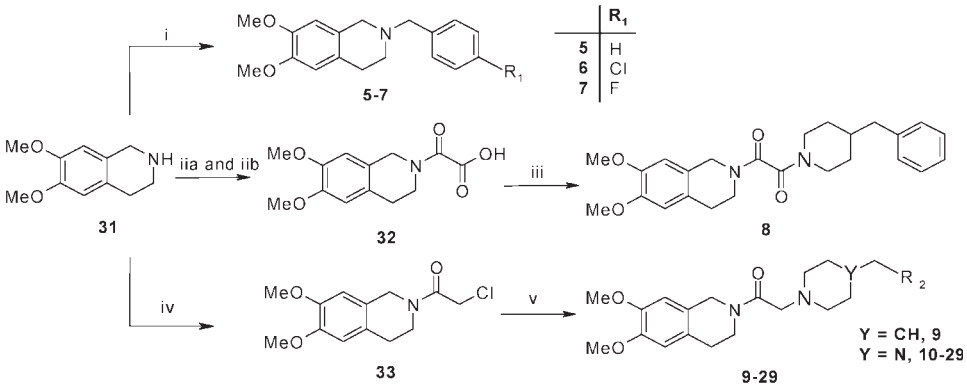



**Figure 2.** Designed molecules.

**Scheme 1**




| Cpd | $R_2$ |
|---|---|
| 9 | $C_6H_5$ |
| 10 | $C_6H_5$ |
| 11 | 4-$BrC_6H_4$ |
| 12 | 4-$ClC_6H_4$ |
| 13 | 2-$FC_6H_4$ |
| 14 | 3-$FC_6H_4$ |
| 15 | 4-$FC_6H_4$ |
| 16 | 3-$MeC_6H_4$ |
| 17 | 4-$MeC_6H_4$ |
| 18 | 4-$OMeC_6H_4$ |
| 19 | 3-$CF_3C_6H_4$ |

| Cpd | $R_2$ |
|---|---|
| 20 | 4-$CF_3C_6H_4$ |
| 21 | 4-$(Me_3C)C_6H_4$ |
| 22 | 3,4-$Cl_2C_6H_3$ |
| 23 | 2-Cl,6-$FC_6H_3$ |
| 24 | 2,4-$F_2C_6H_3$ |
| 25 | 2,4,6-$Me_3C_6H_2$ |
| 26 | $CH_2C_6H_5$ |
| 27 | CH–CH-$C_6H_5$ |
| 28 | cyclohexyl |
| 29 |  |
| | |

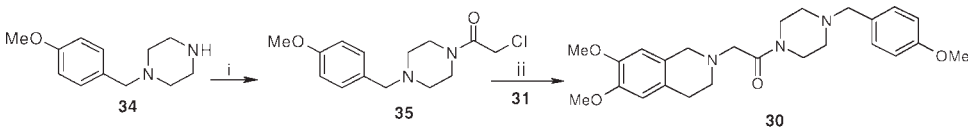
**Reagents and conditions:** i) $R_1C_6H_4CH_2Br$, TEA, DCM r.t., 24 h or NaH, DMF, r.t., 3 h; iia) ClCOCOOEt, TEA, DCM, 25°C, 5 min., 280 Watt; iib) KOH, EtOH/$H_2O$, HCl 6N; iii) HBTU, TEA, benzylpiperidine, DMF, 40 min, 25°C, 250 Watt; iv) $ClCOCH_2Cl$, TEA, DCM, 0°C, 1h; v) cycloalkylamine, TEA, DCM, Δ, 24h.

synthetic (SPPS) approach, using a Buchi Syncore reactor, which allowed us to prepare a small library of analogs.

As shown in Scheme 2, the synthesis of 2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-1-[4-(4-methoxybenzyl)piperazin-1-yl]ethanone (**30**) was realized by using an alternative procedure. Compound **35** was prepared by the same method employed for compound **33** but starting from the 4-(4-methoxyphenyl)methyl-piperazine **34**. Then, the reactive intermediate **35** was combined with **31** to give **30** under basic conditions.

To evaluate the inhibitory activity, all compounds were prepared as hydrochloride derivatives (except compound **8**) and tested on human recombinant AChE according to Ellman [19], using tacrine (**1**) as reference compound. Unfortunately, only derivatives **10**, **13**, and **28** showed inhibitory effects at μ*M* concentrations. The $IC_{50}$ values were 176 μ*M* (**10**), 102 μ*M* (**13**), and 148 μ*M* (**28**), respectively. These results showed that our compounds exhibited lower potency than **1** ($IC_{50}$ = 424 n*M*) and **2** ($IC_{50}$ = 23.1 n*M*) [20].

**Scheme 2**




**Reagents and conditions:** i) $ClCOCH_2Cl$, TEA, DCM, rt, 1h; ii) NaH, dry DMF, $N_2$, r.t., 20h.

Moreover, to explore the dual inhibitor effects of the most active compounds (**10**, **13**, and **28**), we performed the assay against the BChE enzyme at different concentrations (25–800 μ*M*). The results obtained suggest that these compounds did not significantly inhibit BChE; only compound **13** showed 82% of inhibitory activity at the highest tested dose (800 μ*M*).

In conclusion, microwave-assisted procedures and solution-phase parallel synthesis were set up to prepare new isoquinoline derivatives (**5–30**) as potential donepezil-like AChE inhibitors. These approaches allowed us to successfully obtain a small library of compounds that were tested as cholinesterase inhibitors. Some of the synthesized compounds showed inhibitory activity at μ*M* concentrations. However, these results are not useful to make structure-activity relationships for this new series of isoquinolines.

## EXPERIMENTAL

**Chemistry.** All microwave-assisted reactions were carried out in a CEM Focused Microwave Synthesis System, Model Discover working at the potency necessary for refluxing under atmospheric conditions (i.e., 250–300 W). Melting points were determined on a BUCHI Melting Point B-545 apparatus and are uncorrected. Elemental analyses were carried out by University of Messina (C, H, N) using a Carlo Erba Model 1106 Elemental Analyzer and by Redox S.n.c. (Monza, Italy) (C, H, N, Cl). The obtained results are within ± 0.4% of the theoretical values. Merck silica gel 60 $F_{254}$ plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (230–400 mesh) and Flash Chromatography (FC) on a Biotage SP4 EXP. $^1$H NMR spectra were recorded in deuterochloroform ($CDCl_3$) with TMS as internal standard or hexa-deutero-dimethylsulfoxide (DMSO-$d_6$) on a Varian Gemini-300 spectrometer. Chemical shifts were expressed in δ (ppm) and coupling constants (*J*) in Hz.

**General procedure for the synthesis of 2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline derivatives (5–7).** 1, 2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (229.70 mg, 1 mmol) was dissolved in water (10 mL) and alkalinized with a saturated aqueous solution of NaOH until pH = 10–11. The resulting mixture was extracted with ethyl acetate, dried over sodium sulfate ($Na_2SO_4$) and concentrated in vacuo to give the corresponding free-base **31**. Then 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**31**) (193.25 mg, 1 mmol) was dissolved in dichloromethane (DCM) (10 mL) and triethylamine (TEA) (102.20 mg, 1 mmol) was added. The mixture was treated with the suitable benzyl bromide (1 mmol) and stirred for 24 h at room temperature. The reaction was quenched with water (10 mL), extracted with ethyl acetate (3 × 10 mL) and dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the residue was powdered by treatment with diethyl ether and crystallized from ethanol to give derivatives **5–7**. Compounds **5–7** were also obtained in higher yields using a catalytic amount of sodium hydride (NaH) in dimethylformamide (DMF) (2 mL). In this case, the reaction mixture was stirred at room temperature for 3 h and then a saturated aqueous $NaHCO_3$ solution was added. After the extraction with ethyl acetate (3 × 10 mL) the organic phase was reduced under vacuo, the residue powdered by treatment with diethyl ether and crystallized from ethanol to give the desired derivatives **5–7**.

**2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (5).** Mp 85–87°C, yield 77%; $^1$H NMR (δ in $CDCl_3$) : 2.72–2.83 (m, 4H, $CH_2$), 3.55 (s, 2H, $CH_2$), 3.68 (s, 2H, $CH_2$), 3.81 (s, 3H, $CH_3O$), 3.84 (s, 3H, $CH_3O$), 6.48 (s, 1H, ArH), 6.60 (s, 1H, ArH), 7.28–7.41 (m, 5H, ArH). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.42; H, 7.50; N, 4.79. Found: C, 76.30; H, 7.47; N, 4.94.

**2-(4-Chlorobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (6).** Mp 95–97°C, yield 52%; $^1$H NMR (δ in $CDCl_3$) : 2.70–2.84 (m, 4H, $CH_2$), 3.53 (s, 2H, $CH_2$), 3.64 (s, 2H, $CH_2$), 3.81 (s, 3H, $CH_3O$), 3.84 (s, 3H, $CH_3O$), 6.48 (s, 1H, ArH), 6.60 (s, 1H, ArH), 7.30 (d, 2H, $J$ = 8.8, ArH), 7.34 (d, 2H, $J$ = 8.8, ArH). Anal. Calcd for $C_{18}H_{20}ClNO_2$: C, 68.23; H, 6.20; N, 4.32. Found: C, 68.03; H, 6.34; N, 4.41.

**2-(4-Fluorobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (7).** Mp 96–98°C, yield 43%; $^1$H NMR (δ in $CDCl_3$) : 2.77–2.87 (m, 4H, $CH_2$), 3.58 (s, 2H, $CH_2$), 3.69 (s, 2H, $CH_2$), 3.86 (s, 3H, $CH_3O$), 3.89 (s, 3H, $CH_3O$), 6.53 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.07–7.41 (m, 4H, ArH). Anal. Calcd for $C_{18}H_{20}FNO_2$: C, 71.87; H, 6.60; N, 4.51. Found: C, 71.74; H, 6.69; N, 4.65.

**Synthesis of 1-(4-benzylpiperidin-1-yl)-2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethane-1,2-dione (8).** A mixture of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**31**) (193.25 mg, 1 mmol) in DCM (3 mL), ethyl oxalylchloride (166.50 mg, 1.22 mmol) and TEA (173.70 mg, 1.72 mmol) was placed in a cylindrical quartz tube (Ø 2 cm), then stirred and irradiated in a microwave oven (280 Watt, 5 min, 25°C). The resulting mixture was diluted with DCM (15 mL), washed with a saturated $NaHCO_3$ aqueous solution (2 × 10 mL) and with water (2 × 10 mL) and then extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and evaporated under reduced pressure to give the ester intermediate as a yellow oil which was dissolved in 50% EtOH/water (5 mL), basified with KOH and stirred at room temperature for 5 min. Successively the mixture was acidified by the addition of HCl (6.0*N*) and the resulting solution was extracted with chloroform (3 × 10 mL), dried over $Na_2SO_4$ and the solvent removed under reduced pressure to afford the corresponding

acid **32**. To a solution in DMF (5 mL) of crude material obtained in previous step (265 mg, 1 mmol) and O-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluoro-phosphate (HBTU) (379 mg, 1 mmol) 4-benzylpiperidine (352 mg, 2 mmol) was added; the reaction mixture was placed in a cylindrical quartz tube (Ø 2 cm), stirred and irradiated in a microwave oven for two subsequent periods in the same conditions (250 Watt, 20 min, 25°C). The cooled organic layer was diluted with water (10 mL), extracted with ethyl acetate (3 × 10 mL) and dried over $Na_2SO_4$. The solvent was removed until dryness under reduced pressure and the resultant crude purified by silica gel column chromatography (chloroform/methanol; 99:1) to give compound **8** as a white solid.

**1-(4-Benzylpiperidin-1-yl)-2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethane-1,2-dione (8).** Mp 115–117°C, yield 66%. $^1$H NMR (δ, ppm, in $CDCl_3$): 1.24–1.43 (m, 4H, $CH_2$), 1.62–1.74 (m, 3H, CH and $CH_2$), 2.53–3.04 (m, 6H, $CH_2$), 3.62–3.66 (m, 2H, $CH_2$), 3.86 (s, 6H, $CH_3O$), 4.69 (s, 2H, $CH_2$), 6.55 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.08–7.29 (m, 5H, ArH). Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.15; H, 7.04; N, 6.46. Found: C, 71.07; H, 7.16; N, 6.63.

**Synthesis of 2-(4-benzylpiperidin-1-yl)-2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-yl)ethanone (9).** 1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline (**31**) (193.25 mg, 1 mmol) was dissolved in DCM (10 mL) and TEA (102.20 mg, 1 mmol) was added. After the addition dropwise at 0°C of 2-chloroacetyl chloride (56 mg, 0.5 mmol), the reaction mixture was stirred at rt for 1 h. The solution was washed with water (3 × 10 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was powdered by treatment with diethyl ether to provide intermediate **33**. To a solution of 2-chloro-1-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethanone (**33**) (270 mg, 1 mmol) in DCM (10 mL), 4-benzylpiperidine (175.28 mg, 1 mmol) and TEA (102.20 mg, 1 mmol) were added. The mixture was heated under reflux, stirred for 24 h, cooled to r.t., washed with water (3 × 10 mL) and dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the residue was powdered by treatment with diethyl ether and crystallized from ethanol to give compound **9**.

**2-Chloro-1-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl) ethanone (33).** Mp 198–200°C, yield 75%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.68–2.78 (m, 2H, $CH_2$), 3.62–3.66 (m, 2H, $CH_2$), 3.70 (s, 6H, $CH_3O$), 4.44 (s, 2H, $CH_2$), 4.51 (s, 2H, $CH_2$), 6.74 (s, 1H, ArH), 6.79 (s, 1H, ArH). Anal. Calcd for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; N, 5.19. Found: C, 57.97; H, 5.76; N, 5.23.

**2-(4-Benzylpiperidin-1-yl)-2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-yl)ethanone (9).** Mp110–111°C, yield 45%. $^1$H NMR (δ, ppm, in $CDCl_3$): 1.25–1.32 (m, 4H, $CH_2$), 1.65–1.98 (m, 1H, CH), 2.01 (t, 4H, $J$ = 10.4, $CH_2N$), 2.53 (d, 2H, $J$ = 7.1, $CH_2$), 2.76–2.83 (m, 2H, $CH_2$), 3.21 (s, 2H, $CH_2N$), 3.77–3.81 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64 (s, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.12–7.25 (m, 5H, ArH). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.44; H, 7.75; N, 6.91. Found: C, 73.50; H, 7.90; N, 6.86.

**General procedure for the synthesis of 2-(4-arylpiperazin-1-yl)-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl] ethanone derivatives (10-27).** To a solution of the intermediate **33** (270 mg, 1 mmol) in DCM (10 mL) suitable arylpiperazine (1 mmol) and TEA (101 mg, 1 mmol) were added in the Buchi Syncore reactor. The mixture was heated under reflux and stirred for 24 h, cooled to room temperature, washed with water (10 mL × 3) and dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the residue was powdered by treatment with diethyl ether and crystallized from ethanol or, in some cases, purified by flash chromatography (FC) eluting with chloroform/ethyl acetate (90:10) as eluent to give the pure derivatives (**10**–**27**).

In order to prepare compound **10** the 4-benzylpiperazine was prepared by the following procedure: mono Boc-protected piperazine (1 mmol) was dissolved in DMF (10 mL) and treated with benzylbromide (171.04 mg, 1 mmol). The mixture was cooled at 0°C and NaH (24 mg, 1 mmol) was cautiously added. The reaction was stirred in ice-bath for 1 hour and then washed with a solution of water/diethyl ether (1:2) (3 × 8 mL). The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was powdered by treatment with diethyl ether to provide 4-benzyl-piperazine-1-carboxylic acid tert-butyl ester intermediate which was used for the next step without further purification. Deprotection was achieved by dissolving Boc-intermediate in trifluoroacetic acid. The mixture was stirred at 0°C for 30 min and then concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ aqueous solution until pH = 9 and extracted with chloroform (3 × 10 mL). The combined organic phases were dried over $Na_2SO_4$, evaporated under reduced pressure and the residue powdered by treatment with diethyl ether to give the desired 4-benzylpiperazine.

**2-(4-Benzylpiperazin-1-yl)-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (10).** Mp 102°C dec, yield 70%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.49–2.54 (m, 8H, $CH_2$), 2.82–2.86 (m, 2H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.48–3.51 (m, 2H, $CH_2$), 3.76–3.81 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.86 (s, 3H, $CH_3O$), 4.64–4.68 (m, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.24–7.32 (m, 5H, ArH). Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.53; H, 7.43; N, 10.45.

**2-[4-(4-Bromobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (11).** Mp 137–139°C, yield 51%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.42–2.49 (m, 8H, $CH_2$), 2.64–2.76 (m, 2H, $CH_2$), 3.20 (s, 2H, $CH_2$), 3.31–3.62 (m, 4H, $CH_2$), 3.69 (s, 3H, $CH_3O$) 3.70 (s, 3H, $CH_3O$), 4.48–4.61 (m, 2H, $CH_2$), 6.71 (s, 1H, ArH), 6.75 (s, 1H, ArH), 7.20–7.53 (m, 4H, ArH). Anal. Calcd for $C_{24}H_{30}BrN_3O_3$: C, 59.02; H, 6.19; N, 8.60. Found: C, 59.17; H, 6.22; N, 8.43.

**2-[4-(4-Chlorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (12).** Mp 109–111°C, yield 64%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.46–2.54 (m, 8H, $CH_2$), 2.74–2.86 (m, 2H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.46 (s, 2H, $CH_2$), 3.75–3.82 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64–4.68 (m, 2H, $CH_2$), 6.58 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.26–7.28 (m, 4H, ArH). Anal. Calcd for $C_{24}H_{30}ClN_3O_3$: C, 64.93; H, 6.81; N, 9.46. Found: C, 65.09; H, 6.96; N, 9.23.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(2-fluorobenzyl)piperazin-1-yl]ethanone (13).** Mp 81–83°C, yield 70%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.52–2.74 (m, 8H, $CH_2$), 2.76–2.85 (m, 2H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.60 (s, 2H, $CH_2$), 3.75–3.81 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64–4.67 (m, 2H, $CH_2$), 6.58 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.00–7.38 (m, 4H, ArH). Anal. Calcd for $C_{24}H_{30}FN_3O_3$: C, 67.43; H, 7.07; N, 9.83. Found: C, 67.71; H, 7.18; N, 9.29.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(3-fluorobenzyl)piperazin-1-yl]ethanone (14).** Mp 88–90°C, yield 63%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.49–2.55 (m, 8H, $CH_2$), 2.76–2.86 (m, 2H, $CH_2$), 3.27 (s, 2H, $CH_2$), 3.47–3.49 (m, 2H, $CH_2$), 3.76–3.82 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.65–4.68 (m, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.94–7.25 (m, 4H, ArH). Anal. Calcd for $C_{24}H_{30}FN_3O_3$: C, 67.43; H, 7.07; N, 9.83. Found: C, 67.68; H, 7.11; N, 9.53.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-fluorobenzyl)piperazin-1-yl]ethanone (15).** Mp 95–96°C, yield 72%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.34–2.47 (m, 8H, $CH_2$), 2.64–2.76 (m, 2H, $CH_2$), 3.19 (s, 2H, $CH_2$), 3.37–3.41 (m, 2H, $CH_2$), 3.58–3.62 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3O$), 3.70 (s, 3H, $CH_3O$), 4.48–4.61 (m, 2H, $CH_2$), 6.72 (s, 1H, ArH), 6.75 (s, 1H, ArH), 7.09–7.32 (m, 4H, ArH). Anal. Calcd for $C_{24}H_{30}FN_3O_3$: C, 67.43; H, 7.07; N, 9.83. Found: C, 67.52; H, 7.02; N, 9.77.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(3-methylbenzylpiperazin-1-yl]ethanone (16).** Mp 139–141°C, yield 55%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.34 (s, 3H, $CH_3$), 2.50–2.55 (m, 8H, $CH_2$), 2.76–2.84 (m, 2H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.45 (s, 2H, $CH_2$), 3.76–3.82 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64–4.67 (m, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.05–7.20 (m, 4H, ArH). Anal. Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 70.63; H, 7.71; N, 10.12.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-methylbenzyl)piperazin-1-yl]ethanone (17).** Mp 94°C dec, yield 69%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.34 (s, 3H, $CH_3$), 2.46–2.54 (m, 8H, $CH_2$), 2.74–2.86 (m, 2H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.46 (s, 2H, $CH_2$), 3.75–3.82 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64 (s, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.13–7.23 (m, 4H, ArH). Anal. Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 70.73; H, 7.69; N, 9.75.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-methoxybenzyl)piperazin-1-yl]-ethanone (18).** Mp 94°C dec, yield 69%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.46–2.53 (m, 8H, $CH_2$), 2.76–2.83 (m, 2H, $CH_2$), 3.25 (s, 2H, $CH_2$), 3.44 (s, 2H, $CH_2$), 3.71 (s, 3H, $CH_3O$), 3.75–3.85 (m, 5H, $CH_2$ and $CH_3O$) 3.86 (s, 3H, $CH_3O$), 4.64–4.68 (m, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.83–7.23 (m, 4H, ArH). Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.54; H, 7.43; N, 9.48.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(3-trifluoromethylbenzyl)piperazin-1-yl]ethanone (19).** Mp 101–103°C, yield 77%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.41–2.48 (m, 8H, $CH_2$), 2.62–2.78 (m, 2H, $CH_2$), 3.20 (s, 2H, $CH_2$), 3.50–3.53 (m, 2H, $CH_2$), 3.57–3.62 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3O$), 3.70 (s, 3H, $CH_3O$), 4.48–4.62 (m, 2H, $CH_2$), 6.71 (s, 1H, ArH), 6.75 (s, 1H, ArH), 7.57–7.61 (m, 4H, ArH). Anal. Calcd for $C_{25}H_{30}F_3N_3O_3$: C, 62.88; H, 6.33; N, 8.80. Found: C, 62.71; H, 6.46; N, 8.94.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethanone (20).** Mp 102–104°C, yield 75%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.41–2.48 (m, 8H, $CH_2$) 2.64–2.78 (m, 2H, $CH_2$), 3.19 (s, 2H, $CH_2$), 3.49–3.53 (m, 2H, $CH_2$), 3.60–3.67 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3O$), 3.71 (s, 3H, $CH_3O$), 4.48–4.62 (m, 2H, $CH_2$), 6.71 (s, 1H, ArH), 6.75 (s, 1H, ArH), 7.48–7.68 (m, 4H, ArH). Anal. Calcd for $C_{25}H_{30}F_3N_3O_3$: C, 62.88; H, 6.33; N, 8.80. Found: C, 62.96; H, 6.52; N, 8.67.

**2-[4-(4-*t*-Butylbenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (21).** Mp 97–99°C, yield 80%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 1.29 (s, 9H, $CH_3$), 2.41–2.47 (m, 8H, $CH_2$), 2.70–2.81 (m, 2H, $CH_2$), 3.15 (s, 2H, $CH_2$), 3.36–3.57 (m, 4H, $CH_2$), 3.70 (s, 6H, $CH_3O$), 4.50–4.55 (m, 2H, $CH_2$), 6.77–6.82 (m, 2H, ArH), 7.46–7.53 (m, 4H, ArH). Anal. Calcd for $C_{28}H_{39}N_3O_3$: C, 72.23; H, 8.44; N, 9.02. Found: C, 72.47; H, 8.62; N, 9.14.

**2-[4-(3,4-Dichlorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (22).** Mp 78–80°C, yield 34%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.41–2.55 (m, 8H, $CH_2$), 2.76–2.84 (m, 2H, $CH_2$), 3.27 (s, 2H, $CH_2$), 3.44 (s, 2H, $CH_2$), 3.75–3.82 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64–4.67 (m, 2H, $CH_2$), 6.62 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.14–7.42 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{29}Cl_2N_3O_3$: C, 60,25; H, 6.11; N, 8.78. Found: C, 60.32; H, 6.06; N, 8.90.

**2-[4-(2-Chloro-6-fluorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (23).** Mp 78–80°C, yield 71%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.53–2.57 (m, 8H, $CH_2$), 2.74-2.86 (m, 2H, $CH_2$), 3.23 (s, 2H, $CH_2$), 3.69 (s, 2H, $CH_2$), 3.70-3.81 (m, 2H, $CH_2$), 3.85 (s, 3H, $OCH_3$), 3.87 (s, 3H, $CH_3O$), 4.64-4.67 (m, 2H, $CH_2$), 6.61 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.95-7.20 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{29}ClFN_3O_3$: C, 62.40; H, 6.33; N, 9.10. Found: C, 62.72; H, 6.48; N, 9.21.

**2-[4-(2,4-Difluorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (24).** Mp 100–102°C, yield 66%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.40–2.48 (m, 8H, $CH_2$), 2.64–2.76 (m, 2H, $CH_2$), 3.19 (s, 2H, $CH_2$), 3.45–3.48 (m, 2H, $CH_2$), 3.58–3.62 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3O$), 3.70 (s, 3H, $CH_3O$), 4.48–4.61 (m, 2H, $CH_2$), 6.72 (s, 1H, ArH), 6.75 (s, 1H, ArH), 7.14–7.22 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{29}F_2N_3O_3$: C, 64.70; H, 6.56; N, 9.43. Found: C, 67.59; H, 6.77; N, 9.31.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(2,4,6-trimethylbenzyl)piperazin-1-yl]ethanone (25).** Mp 99–101°C, yield 78%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.17 (s, 3H, $CH_3$), 2.26 (s, 6H, $CH_3$), 2.34–2.44 (m, 8H, $CH_2$), 2.64–2.78 (m, 2H, $CH_2$), 3.16 (s, 2H, $CH_2$), 3.36 (s, 2H, $CH_2$), 3.60–3.65 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3O$), 3.70 (s, 3H, $CH_3O$), 4.62 (s, 2H, $CH_2$), 6.71–6.77 (m, 4H, ArH). Anal. Calcd for $C_{27}H_{37}N_3O_3$: C, 71.81; H, 8.26; N, 9.30. Found: C, 72.01; H, 8.33; N, 9.16.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-(4-phenethylpiperazin-1-yl]ethanone (26).** Mp 88–90°C, yield 88%. $^1$H NMR (δ, ppm, in $CDCl_3$): 2.59–2.84 (m, 14H, $CH_2$), 3.28 (s, 2H, $CH_2$), 3.78–3.87 (m, 8H, $CH_2$ and $CH_3O$), 4.65–4.69 (m, 2H, $CH_2$), 6.58–6.62 (m, 2H, ArH), 7.26–7.28 (m, 5H, ArH). Anal. Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 70.95; H, 7.67; N, 9.81.

**2-(4-*trans*-Cinnamylpiperazin-1-yl)-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (27).** Mp 147–149°C, yield 73%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.41–2.48 (m, 8H, $CH_2$), 2.64–2.76 (m, 2H, $CH_2$), 3.01–3.07 (m, 2H, $CH_2$), 3.19 (s, 2H, $CH_2$), 3.35–3.60 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3O$), 3.70 (s, 3H, $CH_3O$), 4.48–4.62 (m, 2H, $CH_2$), 6.23–6.53 (m, 2H, CH=CH), 6.71 (s, 1H, ArH), 6.75 (s, 1H, ArH), 7.18–7.42 (m, 5H, ArH). Anal. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.70; H, 7.64; N, 9.65. Found: C, 71.83; H, 7.45; N, 9.53.

**Synthesis of 2-[4-(cyclohexylmethyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone (28).** Derivative **28** was obtained with the same procedure of compounds **10–27** by treatment of intermediate **33** (270 mg, 1 mmol) with 1-(cyclohexylmethyl)piperazine (183 mg, 1 mmol). Mp102–104°C, yield 80%. $^1$H NMR (δ, ppm, in $CDCl_3$): 0.83–1.76 (m, 11H, $CH_2$ and CH), 2.07–2.12 (m, 2H, $CH_2$), 2.40–2.52 (m, 8H, $CH_2$), 2.75–2.86 (m, 2H, $CH_2$), 3.25 (s, 2H, $CH_2$), 3.77–3.82 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 4.64–4.70 (m, 2H, $CH_2$), 6.59–6.63 (m, 2H, ArH). Anal. Calcd for $C_{24}H_{37}N_3O_3$: C, 69.36; H, 8.97; N, 10.11. Found: C, 69.77; H, 9.05; N, 10.23.

**Synthesis of 1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-((1,3-dioxolan-2-yl)methyl)piperazin-1-yl] ethanone (29).** Derivative **29** was obtained with the same procedure of compounds **10–27** by treatment of intermediate **33** (270 mg, 1 mmol) with 1-[(1,3-dioxolan-2-yl)methyl]piperazine (172 mg, 1 mmol). Mp 113–115°C, yield 89%. $^1$H nmr (δ, ppm, in $CDCl_3$): 2.58–2.60 (m, 12H, $CH_2$), 2.75–2.86 (m, 2H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.76–3.80 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 3.87 (s, 3H, $CH_3O$), 3.88–3.99 (m, 2H, $CH_2$), 4.65–4.69 (m, 2H, $CH_2$), 4.99–5.00 (m, 1H, CH), 6.58–6.63 (m, 2H, ArH). Anal. Calcd for $C_{21}H_{31}N_3O_5$: C, 62.20; H, 7.71; N, 10.36. Found: C, 62.41; H, 7.59; N, 10.14.

**Synthesis of 2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-1-[4-(4-methoxybenzyl)piperazin-1-yl]ethanone (30).** 1-(4-Methoxybenzyl)piperazine (**34**) (206 mg, 1 mmol) was dissolved in DCM (10ml) and TEA (101 mg, 1 mmol) was added. 2-Chloroacetyl chloride (113 mg, 1 mmol) was added dropwise at 0°C and the solution stirred at room temperature for 1 h. The reaction mixture was washed with water (3 × 10 mL), dried over $Na_2SO_4$ and concentrated to give intermediate **35** as an oily residue, which was used in the next step without further purification. To a suspension of **35** (369 mg, 1 mmol) and NaH (120 mg, 5 mmol) in dry DMF (2 mL) **31** was added and the reaction was stirred at r.t. under $N_2$ atmosphere for 20 h. Then it was quenched with a saturated $NaHCO_3$ aqueous solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with water, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was crystallized upon trituration with diethyl ether and ethyl acetate and the solid was recrystallized from ethanol to provide compound **30**. Mp 132–133°C, yield 46%. $^1$H NMR (δ, ppm, in DMSO-$d_6$): 2.25–2.29 (m, 4H, $CH_2$), 2.62–2.67 (m, 4H, $CH_2$), 3.26 (s, 2H, $CH_2$), 3.37 (s, 2H, $CH_2$), 3.43–3.52 (m, 4H, $CH_2$), 3.48 (s, 2H, $CH_2$), 3.67 (s, 3H, $CH_3O$), 3.69 (s, 3H, $CH_3O$), 3.71 (s, 3H, $CH_3O$), 6.59–7.18 (m, 6H, ArH). Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.51; H, 7.72; N, 9.39.

For the biological evaluation, the hydrochloride salts of compounds **5–7** and **9–30** were prepared as follows: the free bases were dissolved in DCM and HCl (g) was bubbled over a period of 1 h. The solvent was removed under reduced pressure to give the corresponding hydrochloride derivatives which were crystallized by diethyl ether. The obtained compounds were characterized by elemental analysis and the melting points are reported later.

**2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (5·HCl).** Mp 243–245°C. Anal. Calcd for $C_{18}H_{21}NO_2$·HCl: C, 67.60; H, 6.93; N, 4.38; Cl 11.08. Found: C, 67.72; H, 6.69; N, 4.52; Cl 11.23.

**2-(4-Chlorobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (6·HCl).** Mp 247–249°C. Anal. Calcd for $C_{18}H_{20}ClNO_2$·HCl: C, 61.03; H, 5.97; N, 3.95; Cl 20.01. Found: C, 61.22; H, 6.08; N, 4.11; Cl 19.89.

**2-(4-Fluorobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (7·HCl).** Mp 220–222°C. Anal. Calcd for $C_{18}H_{20}FNO_2$·HCl: C, 64.00; H, 6.27; N, 4.15; Cl 10.49. Found: C, 64.13; H, 6.14; N, 4.04; Cl 10.61.

**2-(4-Benzylpiperidin-1-yl)-2-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-yl)ethanone hydrochloride (9·HCl).** Mp 213–215°C. Anal. Calcd for $C_{25}H_{32}N_2O_3$·HCl: C, 67.48; H, 7.47; N, 6.30; Cl 7.97. Found: C, 67.29; H, 7.28; N, 6.54; Cl 8.10.

**2-(4-Benzylpiperazin-1-yl)-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (10·2HCl).** Mp 234–236°C. Anal. Calcd for $C_{24}H_{31}N_3O_3$·2HCl·0.5$H_2O$: C, 58.66; H, 6.97; N, 8.55; Cl 14.43. Found: C, 58.76; H, 7.13; N, 8.36; Cl 14.66.

**2-[4-(4-Bromobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (11·2HCl).** Mp 235–237°C. Anal. Calcd for $C_{24}H_{30}BrN_3O_3$·2HCl·0.5$H_2O$: C, 50.54; H, 5.83; N, 7.37; Cl 12.43. Found: C, 50.61; H, 5.62; N, 7.43 Cl 12.22.

**2-[4-(4-Chlorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (12·2HCl).** Mp 249–251°C. Anal. Calcd for $C_{24}H_{30}ClN_3O_3$·2HCl·0.5$H_2O$: C, 54.81; H, 6.32; N, 7.99; Cl 20.22. Found: C, 54.69; H, 6.54; N, 8.12 Cl 20.01.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(2-fluorobenzyl)piperazin-1-yl]ethanone dihydrochloride (13·2HCl).** Mp 226–228°C. Anal. Calcd for $C_{24}H_{30}FN_3O_3$·2HCl·0.5$H_2O$: C, 56.58; H, 6.53; N, 8.25; Cl 13.92. Found: C, 56.72; H, 6.31; N, 8.51 Cl 13.68.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(3-fluorobenzyl)piperazin-1-yl]ethanone dihydrochloride (14·2HCl).** Mp 223–225°C. Anal. Calcd for $C_{24}H_{30}FN_3O_3$·2HCl·0.5$H_2O$: C, 56.58; H, 6.53; N, 8.25; Cl 13.92. Found: C, 56.27; H, 6.41; N, 8.52 Cl 13.73.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-fluorobenzyl)piperazin-1-yl]ethanone dihydrochloride (15·2HCl).** Mp 230–232°C. Anal. Calcd for $C_{24}H_{30}FN_3O_3$·2HCl·0.5$H_2O$: C, 56.58; H, 6.53; N, 8.25; Cl 13.92. Found: C, 56.48; H, 6.72; N, 8.56 Cl 13.81.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(3-methylbenzylpiperazin-1-yl]ethanone dihydrochloride (16·2HCl).** Mp 139–141°C. Anal. Calcd for $C_{25}H_{33}N_3O_3$·2HCl· 0.5$H_2O$: C, 59.40; H, 7.18; N, 8.31; Cl 14.03. Found: C, 59.53; H, 7.06; N, 8.52 Cl 14.28.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-methylbenzyl)piperazin-1-yl]ethanone dihydrochloride (17·2HCl).** Mp 94°C dec. Anal. Calcd for $C_{25}H_{33}N_3O_3$·2HCl·0.5$H_2O$: C, 59.40; H, 7.18; N, 8.31; Cl 14.03. Found: C, 59.33; H, 6.98; N, 8.57 Cl 14.32.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-methoxybenzyl)piperazin-1-yl]-ethanone dihydrochloride (18·2HCl).** Mp 134–136°C. Anal. Calcd for $C_{25}H_{33}N_3O_4$·2HCl·0.5$H_2O$: C, 57.58; H, 6.96; N, 8.06; Cl 13.60. Found: C, 57.72; H, 7.08; N, 8.24 Cl 13.41.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(3-trifluoromethylbenzyl)piperazin-1-yl]ethanone dihydrochloride (19·2HCl).** Mp 230–232°C. Anal. Calcd for $C_{25}H_{30}F_3N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 53.67; H, 5.95; N, 7.51; Cl 12.67. Found: C, 53.84; H, 6.09; N, 7.38 Cl 12.52.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethanone dihydrochloride (20·2HCl).** Mp 222–224°C. Anal. Calcd for $C_{25}H_{30}F_3N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 53.67; H, 5.95; N, 7.51; Cl 12.67. Found: C, 53.82; H, 6.13; N, 7.72 Cl 12.49.

**2-[4-(4-*t*-Butylbenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (21·2HCl).** Mp 230–232°C. Anal. Calcd for $C_{28}H_{39}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 61.42; H, 7.73; N, 7.67; Cl 12.95. Found: C, 61.58; H, 7.52; N, 7.81; Cl 13.08.

**2-[4-(3,4-Dichlorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (22·2HCl).** Mp 239–241°C. Anal. Calcd for $C_{24}H_{29}Cl_2N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 51.44; H, 5.76; N, 7.50; Cl 25.31. Found: C, 51.23; H, 5.42; N, 7.78; Cl 25.57.

**2-[4-(2-Chloro-6-fluorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (23·2HCl).** Mp 237–239°C. Anal. Calcd for $C_{24}H_{29}ClFN_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 53.00; H, 5.93; N, 7.73; Cl 19.55. Found: C, 52.88; H, 5.87; N, 7.89; Cl 19.36.

**2-[4-(2,4-Difluorobenzyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (24·2HCl).** Mp 223–225°C. Anal. Calcd for $C_{24}H_{29}F_2N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 54.65; H, 6.12; N, 7.97; Cl 13.44. Found: C, 54.73; H, 6.27; N, 8.11; Cl 13.32.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-(2,4,6-trimethylbenzyl)piperazin-1-yl]ethanone dihydrochloride (25·2HCl).** Mp 232–234°C. Anal. Calcd for $C_{27}H_{37}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 60.78; H, 7.56; N, 7.88; Cl 13.29. Found: C, 60.65; H, 7.43; N, 8.01; Cl 13.37.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-(4-phenethylpiperazin-1-yl]ethanone dihydrochloride (26·2HCl).** Mp 246–248°C. Anal. Calcd for $C_{25}H_{33}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 59.40; H, 7.18; N, 8.31; Cl 14.03. Found: C, 59.57; H, 7.24; N, 8.17; Cl 14.12.

**2-(4-*trans*-Cinnamylpiperazin-1-yl)-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (27·2HCl).** Mp 249–251°C. Anal. Calcd for $C_{25}H_{31}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 59.64; H, 6.81; N, 8.35; Cl 14.08. Found: C, 59.72; H, 6.93; N, 8.22; Cl 14.16.

**2-[4-Cyclohexylmethyl)piperazin-1-yl]-1-[3,4-dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]ethanone dihydrochloride (28·2HCl).** Mp 232–234°C. Anal. Calcd for $C_{24}H_{37}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 57.94; H, 8.10; N, 8.45; Cl 14.25. Found: C, 58.03; H, 8.24; N, 8.70; Cl 14.12.

**1-[3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl]-2-[4-((1,3-dioxolan-2-yl)methyl)piperazin-1-yl]ethanone dihydrochloride (29·2HCl).** Mp 239–241°C. Anal. Calcd for $C_{21}H_{31}N_3O_5 \cdot 2HCl \cdot 0.5H_2O$: C, 51.75; H, 7.03; N, 8.62; Cl 14.55. Found: C, 51.53; H, 7.22; N, 8.54; Cl 14.23.

**2-(3,4-Dihydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-1-[4-(4-methoxybenzyl)piperazin-1-yl]ethanone dihydrochloride (30·2HCl).** Mp 249–251°C. Anal. Calcd for $C_{25}H_{33}N_3O_4 \cdot 2HCl \cdot 0.5H_2O$: C, 57.58; H, 6.96; N, 8.06; Cl 13.60. Found: C, 57.71; H, 7.13; N, 7.95; Cl 13.81.

## INHIBITION OF AChE AND BChE

The cholinesterase assays were performed using colorimetric method reported by Ellman [19]. The assay solution consisted of a 0.1*M* phosphate buffer pH 8.0, with the addition of 0.01*M* 5,5′-dithio-bis(2-nitrobenzoic acid), 0.044 Unit/mL human recombinant AChE or BChE derived from human serum and 0.037*M* of substrate (acetylthiocholine iodide or butyrylthiocholine iodide, respectively). All the reagents were purchased from Sigma Chemical Company. AChE and BChE were dissolved in 0.1*M* phosphate buffer pH 8.0 containing Triton X-100 0.1%. The enzymes were diluted before use in order to reach an activity ranging between 0.250 and 0.100 AU $min^{-1}$ in the final assay conditions. Stock solutions of the tested compounds were prepared in water. Different concentrations of each test compound (analyzed in triplicate) were used to obtain inhibition of ACh- and BChE activity ranging between 20 and 80%. Following a 20 min pre-incubation at 37°C with inhibitor and enzyme, the reaction was started by the addition of substrate. Initial rates were determined at 37°C by measuring the absorbance at 412 nm every 1 min during 5 min with a Beckman DU 800 spectrophotometer. The reaction rates were compared and the percent inhibition due to the presence of test compounds was calculated. Blanks containing all components except enzyme were run in order to account for nonenzymatic reactions. Tacrine (0.5 μ*M*), a reversible, non selective inhibitor of AChE and an ever stronger inhibitor of BChE was used to test assay efficiency (–65% and –93%, respectively). The percent inhibition of the enzyme activity due to the presence of increasing test compound concentration was calculated by the following expression: $100 - (v_i/v_0 \times 100)$, where $v_i$ is the initial rate calculated in the presence of inhibitor and $v_0$ is the enzyme activity. The concentration producing 50% inhibition ($IC_{50}$) was calculated using a computer programme (SAS/STAT) of the method of Litchfield and Wilcoxon.

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### REFERENCES AND NOTES

[1] Akhondzadeh, S.; Noroozian, M. IDrugs 2002, 5, 1062.

[2] Lleo, A.; Greenberg, S. M.; Growdon, J. H. Annu Rev Med 2006, 57, 513.

[3] Reichman, W. E. Ann Gen Hosp Psychiatry 2003, 2, 1.

[4] Sugimoto, H. Chem Biol Interact 2008, 175, 204.

[5] Munoz-Torrero, D. Curr Med Chem 2008, 15, 2433.

[6] Musial, A.; Bajda, M.; Malawska, B. Curr Med Chem 2007, 14, 2654.

[7] Krall, W. J.; Sramek, J. J.; Cutler, N. R. Ann Pharmacother 1999, 33, 441.

[8] Recanatini, M.; Valenti, P. Curr Pharm Des 2004, 10, 3157.

[9] Bianchetti, A.; Ranieri, P.; Margiotta, A.; Trabucchi, M. Aging Clin Exp Res 2006, 18, 158.

[10] Small, D. H. Expert Opin Emerg Drugs 2005, 10, 817.

[11] Racchi, M.; Mazzucchelli, M.; Lenzken, S. C.; Porrello, E.; Lanni, C.; Govoni, S. Chem Biol Interact 2005, 157–158, 335.

[12] Inestrosa, N. C.; Alvarez, A.; Perez, C. A.; Moreno, R. D.; Vicente, M.; Linker, C.; Casanueva, O. I.; Soto, C.; Garrido, J. Neuron 1996, 16, 881.

[13] Kapkova, P.; Alptuzun, V.; Frey, P.; Erciyas, E.; Holzgrabe, U. Bioorg Med Chem 2006, 14, 472.

[14] Alonso, D.; Dorronsoro, I.; Rubio, L.; Munoz, P.; Garcia-Palomero, E.; Del Monte, M.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J.; Castro, A.; Medina, M.; Martinez, A. Bioorg Med Chem 2005, 13, 6588.

[15] Sugimoto, H.; Yamanishi, Y.; Iimura, Y.; Kawakami, Y. Curr Med Chem 2000, 7, 303.

[16] Munoz-Ruiz, P.; Rubio, L.; Garcia-Palomero, E.; Dorronsoro, I.; del Monte-Millan, M.; Valenzuela, R.; Usan, P.; de Austria, C.; Bartolini, M.; Andrisano, V.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J.; Medina, M.; Martinez, A. J Med Chem 2005, 48, 7223.

[17] Shao, D.; Zou, C.; Luo, C.; Tang, X.; Li, Y. Bioorg Med Chem Lett 2004, 14, 4639.

[18] Camps, P.; Formosa, X.; Galdeano, C.; Gomez, T.; Munoz-Torrero, D.; Scarpellini, M.; Viayna, E.; Badia, A.; Clos, M. V.; Camins, A.; Pallas, M.; Bartolini, M.; Mancini, F.; Andrisano, V.; Estelrich, J.; Lizondo, M.; Bidon-Chanal, A.; Luque, F. J Med Chem 2008, 51, 3588.

[19] Ellman, G. L.; Courtney, K. D.; Andres, V., Jr.; Feather-Stone, R. M. Biochem Pharmacol 1961, 7, 88.

[20] Bartolini, M.; Bertucci, C.; Cavrini, V.; Andrisano, V. Biochem Pharmacol 2003, 65, 407.

# Synthesis of 4*H*-Benzopyrans Catalyzed by Acyclic Acidic Ionic Liquids in Aqueous Media



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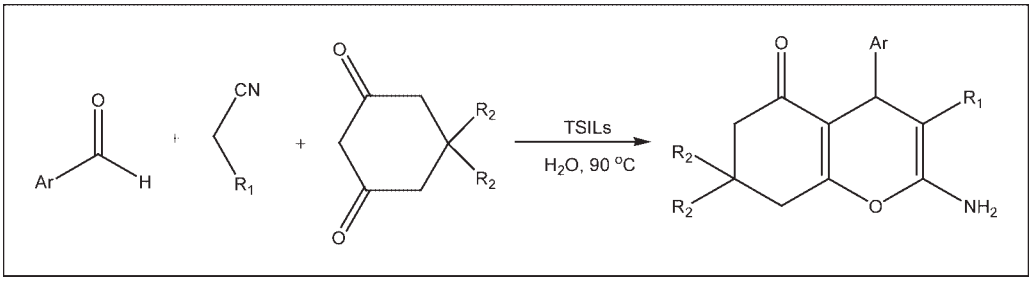


Some halogen-free acyclic task-specific ionic liquids (TSILs) were synthesized as novel and recyclable catalysts for the synthesis of 5-oxo-5,6,7,8-tetrahydro-4H-benzo[b]pyrans by one-pot three-component condensation of aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and dimedone (or 1,3-cyclohexanedione) in water. The condensation accomplished successfully with good yields ranged from 86 to 94%. After the reaction, the products could simply be separated from the catalyst/water, and the catalyst could be reused at least 10 times without noticeably decreasing the catalytic activity.

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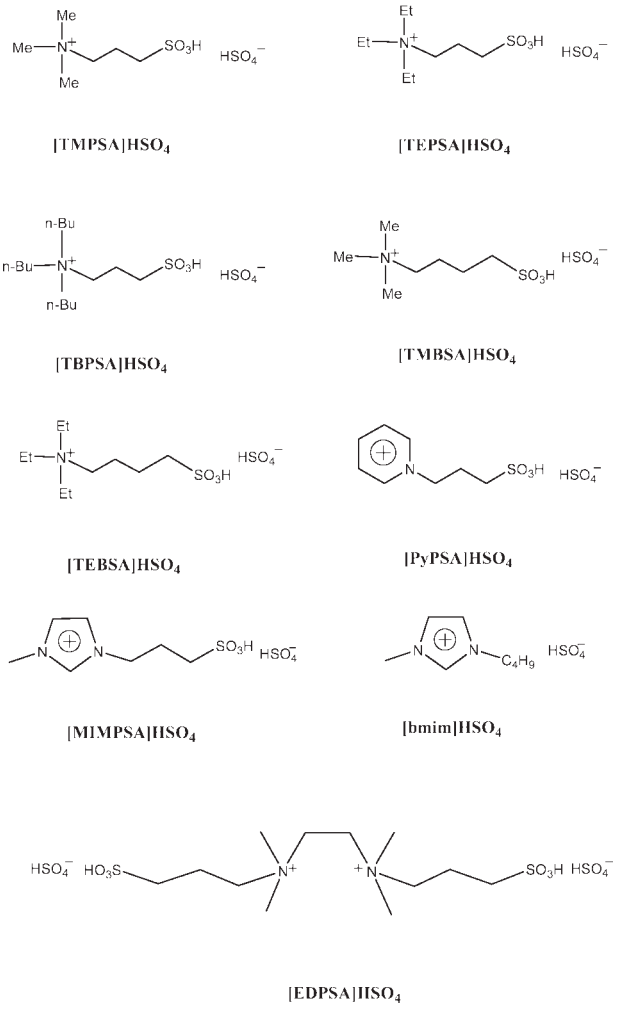
## INTRODUCTION

4*H*-Benzopyrans have attracted considerable attention because of their useful biological and pharmacological properties [1]. The synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans usually involves a condensation of appropriate active methylene carbonyl compounds, aromatic aldehydes, and malononitrile (or cyanoacetates) catalyzed mainly by organic and mineral acids in organic solvents, which often suffer from the drawbacks of low yield, high reaction temperature, toxicity and difficulty in product separation. Recently, many synthetic methods for preparing these compounds have been reported by the condensation of aromatic aldehydes and active methylene carbonyl compounds in the presence of phase transfer catalyst [2], rare earth perfluorooctanoates [3], KF-Alumina [4], sodium selenate [5], and proline [6] as catalysts, as well as with the assistance of microwave [7] or ultrasound irradiation [8]. However, the search for the new readily available and green catalysts is still being actively pursued these years.

Ionic liquids have attracted wide interest as environmental benign catalysts or excellent alternatives to organic solvents these years because of their favorable properties such as negligible volatility, high thermal stability [9]. Brønsted acidic or basic task-specific ionic liquids (TSILs) are designed to replace traditional acids or bases in organic synthetic procedure. In view of both the advantages and disadvantages of homogeneous and heterogeneous catalytic reactions, the use of TSILs as reaction medium/catalytic system may offer a convenient solution to both the solvent emission and catalytic recycling problem. Some researchers have already used ionic liquids as solvents/catalysts in condensation reactions [10–12]. Recently, Luo and coworkers [13] reported a new temperature-dependent biphasic system comprising PEG-1000-based acidic ionic liquid/toluene, and it is used in preparation of benzopyrans. Chen *et al*. [14] used *N*,*N*-dimethylamino-functionalized basic ionic liquid to catalyze one-pot multicomponent reaction for the synthesis of benzopyrans. In fact, the use of Brønsted-acidic or basic TSILs as catalysts is an area of ongoing activity; however, the development and exploration of TSILs are currently in the preliminary stage. On the other hand, reactions in aqueous media may offer many advantages such as simple operation and high efficiency in many organic reactions. Thus, it is necessary to carry out this condensation using TSILs as catalysts in aqueous media.

In our previous work, some novel and cheap $SO_3H$-functional halogen-free acidic ionic liquids that bear an

**Scheme 1**




alkane sulfonic acid group in an acyclic trialkylammonium cation have been synthesized to catalyze some organic reactions [15]. In continuation of our work in studying acid-catalyzed reactions in ionic liquids, we report here the synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b] pyrans by condensation of aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and dimedone (or 1,3-cyclohexanedione) in water catalyzed by acidic ionic liquids.

## RESULTS AND DISCUSSION

The preparation of $SO_3H$-functionalized halogen-free acidic ionic liquids (Scheme 1) was made up of two-step atom economic reaction. The chemical yields for both the zwitterions formation and acidification steps were essentially quantitative since neither reaction produced byproducts. The preparation of [bmim]$HSO_4$ was accomplished by anion metathesis with $NaHSO_4$ in good yield of 96%.

The fresh new TSILs with $HSO_4^-$ anion are somewhat viscous colorless or pale brown liquids at room temperature. All produced TSILs are entirely miscible with water and soluble or partly soluble in organic solvents.

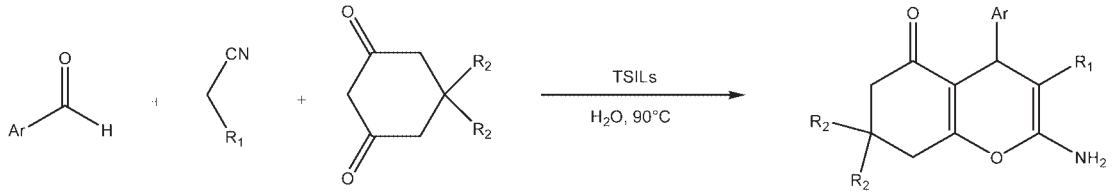
To optimize the reaction conditions (Scheme 2), for the beginning of this study, benzaldehyde, malononitrile, and dimedone were used as the model reactants at 90°C in TSILs/water for a length of time to compare the catalytic performance of the TSILs in aqueous medium. As shown in Table 1, no desirable product could be detected when a mixture of model reactants was heated at 90°C for 8 h in the absence of ionic liquid (Table 1, entry 1), which indicated that the catalysts should be absolutely necessary for this condensation. All the nine TSILs proved to be very active, leading to 82–90% yield of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans in the presence of 10% TSILs (entries 5, 10–17). In addition, ionic liquids containing the longer length of alkyl chain are relatively efficient; however, the better immiscibility of the resulted product with the shorter length of alkyl chain ionic liquids should facilitate the separation in work-up procedure. Hence, [TEBSA]$HSO_4$ should be the best catalyst for this condensation among these ionic liquids and the optimized reaction conditions went to entry 5 in Table 1.

Condensation reaction in [TEBSA]$HSO_4$/$H_2O$ gave a yield of 89%, which was nearly the same as that in organic solvents. The chemical industry is under considerable pressure to replace many of the volatile organic compounds (VOCs) that are currently used as solvents in organic synthesis. As a clean and cheap solvent, it is of great importance to carry out this reaction in water for the environmental and economic reasons.

While optimizing the reaction condition, the recycling performance of [TEBSA]$HSO_4$ was investigated using the above-mentioned model reaction. After the separation of the products **4**, the catalyst-containing filtrate was reused in the next run without further purification. The data listed in Table 2 showed that the [TEBSA]$HSO_4$ could be reused at least 10 times without obviously decreasing of the catalytic activity. Compared with the traditional solvents and catalysts, the easy and efficient recycling performance is also an attractive property of the ionic liquids for the environmental protection and economic reasons.

Then, the condensation reaction of various aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and dimedone (or 1,3-cyclohexanedione) in the presence of [TEBSA]·$HSO_4$ as an environmentally benign ionic liquid was explored under the optimized reaction conditions described earlier, and the results are presented in Table 3. It can easily be seen that in all cases the reactions gave the products in good yields ranged from 86 to 94%. Aromatic aldehydes carrying either electron-donation or electron-withdrawing substituents afforded good yields of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b] pyrans in high purity. However, the product obtained is

**Scheme 2**




racemic, which indicated that the reaction was accomplished with no regioselectivity in this procedure.

In conclusion, some acyclic TSILs such as [TEBSA]·$HSO_4$, [TBPSA]·$HSO_4$, [EDPSA]·$HSO_4$, and so on were synthesized in an atom-economic procedure. These ionic liquids were found to be efficient catalysts for the synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b] pyrans in aqueous media, offering the practical convenience in the product separation from the ionic liquid/water system. The merit of this methodology is that it is simple, mild, and efficient, and the raw materials are cheaper than TSILs with imidazole or triphenylphosphine as the cation. Therefore, we believe that the work reported here would have potential application in green chemistry.

## EXPERIMENTAL

Melting points were determined on X-6 microscope melting apparatus. The IR spectra were run on a Nicolete spectrometer and expressed in $cm^{-1}$ (KBr). $^1H$ NMR spectra were recorded on Bruker DRX300 (300 MHz) and $^{13}C$ NMR spectra on Bruker DRX300 (75.5 MHz) spectrometer. Elemental analyses were recorded on Perkin–Elmer C spectrometer. Mass spectra were obtained with automated FININIGAN Trace Ultra-Trace DSQ GC/MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

**Synthesis of halogen-free $SO_3$-functional acidic ionic liquids (TSILs).** All acyclic $SO_3H$-functionalized halogen-free acidic ionic liquids, such as [TEBSA]$HSO_4$, [TBPSA]$HSO_4$, were synthesized according to our previous methods [15d], and the pyridine, imidazole-based acidic ionic liquids for comparison were synthesized according to reported methods [15c]. Their structures were analyzed by $^1H$ NMR, $^{13}C$ NMR, and MS spectral data. The selected spectral data for acidic halogen-free TSILs.

***N,N,N-Triethyl-N-butanesulfonic acid ammonium hydrogen sulfate ([TEBSA]$HSO_4$).*** $^1H$ NMR (300 MHz, $D_2O$): δ 3.15 (q, $J$ = 7.2 Hz, 6H, N—$CH_2$—$CH_3$), 3.07 (t, $J$ = 8.4 Hz, 2H, N—$CH_2$—C—C—C—$SO_3$), 2.82 (t, $J$ = 7.2 Hz, 2H, N—C—C—C—$CH_2$—$SO_3$), 1.63–1.70 (m, 4H, N—C—$C_2H_4$—C—$SO_3$), 1.09–1.13 (m, 9H, N—$CH_2$—$CH_3$). $^{13}C$ NMR (75.5 MHz, $D_2O$): δ 56.21, 52.85, 50.32, 21.50, 20.20, 6.90. MS (*m*/*z*): 335.35 ($M^+$), 208.36 (100).

***N,N,N-Tributyl-N-propanesulfonic acid ammonium hydrogen sulfate ([TBPSA]$HSO_4$).*** $^1H$ NMR (500 MHz, $D_2O$): δ 3.28 (t, 2H, $J$ = 4.0 Hz, N—$CH_2$—C—C—$SO_3$), 3.13 (t, 6H, $J$

**Table 1**

Synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans catalyzed by acidic ionic liquids.[a]

| Entry | Catalyst | TSILs (mol%)[b] | $T$ (°C) | Time (h) | Yields (%)[c] |
|---|---|---|---|---|---|
| 1 | – | – | 100 | 8.0 | – |
| 2 | [TEBSA]·$HSO_4$ | 4 | 90 | 6.0 | 87 |
| 3 | [TEBSA]·$HSO_4$ | 6 | 90 | 4.5 | 89 |
| 4 | [TEBSA]·$HSO_4$ | 8 | 90 | 1.5 | 89 |
| 5 | [TEBSA]·$HSO_4$ | 10 | 90 | 1.0 | 89 |
| 6 | [TEBSA]·$HSO_4$ | 12 | 90 | 1.0 | 90 |
| 7 | [TEBSA]·$HSO_4$ | 15 | 90 | 1.0 | 91 |
| 8 | [TEBSA]·$HSO_4$ | 10 | 70 | 3.5 | 86 |
| 9 | [TEBSA]·$HSO_4$ | 10 | 80 | 2.0 | 90 |
| 10 | [TMBSA]·$HSO_4$ | 10 | 90 | 1.0 | 84 |
| 11 | [TMPSA]·$HSO_4$ | 10 | 90 | 1.0 | 82 |
| 12 | [TEPSA]·$HSO_4$ | 10 | 90 | 1.0 | 84 |
| 13 | [TBPSA]·$HSO_4$ | 10 | 90 | 1.0 | 90 |
| 14 | [PyPSA]·$HSO_4$ | 10 | 90 | 1.0 | 83 |
| 15 | [MIMPSA]·$HSO_4$ | 10 | 90 | 1.0 | 85 |
| 16 | [bmim]·$HSO_4$ | 10 | 90 | 1.5 | 82 |
| 17 | [EDPSA]·$HSO_4$ | 10 | 90 | 1.0 | 86 |

[a] Acidic ionic liquids are 5 mmol benzaldehyde, 5 mmol malononitrile, 5 mmol dimedone, and water is used as a solvent.
[b] Molar ration of TSILs to benzaldehyde.
[c] Isolated yields.

**Table 2**

Reusing of the ionic liquid [TEBSA]·$HSO_4$.[a]

| Entry | Run | Isolated yield (%) |
|---|---|---|
| 1 | Fresh | 89 |
| 2 | 1 | 90 |
| 3 | 2 | 90 |
| 4 | 3 | 88 |
| 5 | 4 | 89 |
| 6 | 5 | 90 |
| 7 | 6 | 89 |
| 8 | 7 | 88 |
| 9 | 8 | 88 |
| 10 | 9 | 86 |
| 11 | 10 | 87 |

[a] Acidic ionic liquids are 5 mmol benzaldehyde, 5 mmol malononitrile, 5 mmol dimedone, 0.5 mmol catalyst, 90°C, 1.0 h.

= 8.5 Hz, N—$CH_2$—C—C—$CH_3$), 2.85 (t, 2H, $J$ = 7.0 Hz, N—C—C —$CH_2$—$SO_3$), 2.00–2.06 (m, 2H, N—C—$CH_2$—C —$SO_3$), 1.53–1.59 (m, 6H, N—C—$CH_2$—C—$CH_3$), 1.22–1.30 (m, 6H, N—C—C—$CH_2$—$CH_3$), 0.84 (t, 9H, $J$ = 7.5 Hz, N—C—C—C—$CH_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 58.49, 50.66, 48.42, 23.93, 20.36, 19.16, 14.46. MS (*m*/*z*): 405.29 ($M^+$), 406.28, 404.28 (100).

***N*-Propanesulfonic acid pyridinium hydrogen sulfate ([PyPSA]$HSO_4$).** $^1$H NMR (300 MHz, $D_2O$): δ 8.62 (d, $J$ = 6.0 Hz, 2H, H-2, H-6), 8.30 (t, $J$ = 7.8 Hz, 1H, H-4), 7.84 (t, $J$ = 6.9 Hz, 2H, H-3, H-5), 4.51 (t, $J$ = 7.5 Hz, 2H, N—$CH_2$ —C—C—$SO_3$), 2.73 (t, $J$ = 7.2 Hz, 2H, N—C—C—C —$CH_2$—$SO_3$), 2.18–2.23 (m, 2H, N—C—$CH_2$—C—$SO_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 146.35, 144.70, 128.82, 60.28, 47.48, 26.47.

***1*-Methyl-3-propanesulfonic acid imidazolium hydrogen sulfate ([MIMPSA]$HSO_4$).** $^1$H NMR (300 MHz, $D_2O$): δ 8.47 (s, 1H, CH), 7.24 (d, $J$ = 1.5 Hz, 1H, CH), 7.17 (d, $J$ = 1.5 Hz, 1H, CH), 4.08 (t, $J$ = 6.9 Hz, 2H, N—$CH_2$—C—C—$SO_3$), 3.62 (s, 3H, N—$CH_3$), 2.64 (t, 2H, $J$ = 7.5 Hz, 2H, N—C—C —$CH_2$—$SO_3$), 2.01–2.06 (m, 2H, N—C—$CH_2$—C—$SO_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 136.53, 124.32, 122.57, 48.13, 47.66, 36.46, 25.48. MS (*m*/*z*): 302.0 ($M^+$), 300.93 (100).

***1*-Butyl-3-methylimidazolium hydrogen sulfate ([bmim]$HSO_4$).** $^1$H NMR (300 MHz, $D_2O$): δ 8.62 (s, 1H, H-2), 7.33v7.38 (m, 2H, H-4, H-5), 4.09 (t, 2H, $J$ = 7.1 Hz), 3.79 (s, 3H), 1.68–1.78 (m, 2H), 1.16–1.24 (m, 2H), 0.79 (t, 3H, J =7.4 Hz). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 136.35, 124.07, 122.80, 49.85, 36.33, 31.80, 19.31, 13.25. *m*/*z*: 236 ($M^+$), 139 (100, $M^+$-$HSO_4$).

***N*,*N*,*N*′,*N*′-Tetramethyl-*N*,*N*′-dipropanesulfonic acid ethylenediammonium hydrogen sulfate ([EDPSA]·$HSO_4$).** $^1$H NMR (300 MHz, $D_2O$): δ 3.60 (s, 4H, —$CH_2$—), 3.24 (t, 4H, $J$ = 8.4 Hz, —$CH_2$—), 2.89 (s, 12H, $CH_3$), 2.64 (t, 4H, $J$ = 6.9 Hz, —$CH_2$—), 1.85–1.95 (q, 4H, $J$ = 7.65 Hz, —$CH_2$—). Anal. Calcd. For C12H32N2O14S4: C, 25.89; H, 5.79; N, 5.03; Found: C, 25.65; H, 5.80; N, 4.81. *m*/*z*: 556.88 ($M^+$), 361.07 ($M^+$-2$H_2SO_4$,100).

**General procedure for the synthesis of 5-oxo-5,6,7,8-tetrahydro-4H-benzo[b]pyrans.** To a round-bottomed flask charged with aromatic aldehyde (5 mmol) **1**, malononitrile or ethyl cyanoacetate (5 mmol) **2**, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) or 1,3-cyclohexanedione (5 mmol) **3** in 5 mL of water was added acidic ionic liquid (0.5 mmol) under stirring. The mixture was then stirred for a certain time at 90°C. On completion (monitored by TLC), the precipitated crude product was collected by filtration and recrystallized form ethanol (95%) to afford pure 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans **4**. The filtrated containing ionic liquid

**Table 3**

Synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans catalyzed by [TEBSA]·$HSO_4$.[a]

| Entry | Ar | $R_1$ | $R_2$ | Time (h) | Mp (°C) [Lit.] | Yields (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | CN | $CH_3$ | 1.0 | 226-228 [13] | 89 |
| 2 | *p*-$CH_3OC_6H_4$ | CN | $CH_3$ | 1.0 | 197-199 [13] | 93 |
| 3 | *o*-$CH_3C_6H_4$ | CN | $CH_3$ | 1.0 | 212-214 [13] | 86 |
| 4 | *m*-$HOC_6H_4$ | CN | $CH_3$ | 1.0 | 230-232 [13] | 92 |
| 5 | *p*-$FC_6H_4$ | CN | $CH_3$ | 1.5 | 191-193 [2b] | 87 |
| 6 | *o*-$ClC_6H_4$ | CN | $CH_3$ | 1.0 | 214-215 [13] | 91 |
| 7 | *m*-$ClC_6H_4$ | CN | $CH_3$ | 1.0 | 230-232 [13] | 91 |
| 8 | *p*-$ClC_6H_4$ | CN | $CH_3$ | 1.0 | 209-211 [13] | 91 |
| 9 | *p*-$BrC_6H_4$ | CN | $CH_3$ | 1.0 | 205-207 [13] | 94 |
| 10 | *m*-$NO_2C_6H_4$ | CN | $CH_3$ | 1.0 | 208-210 [13] | 92 |
| 11 | *p*-$NO_2C_6H_4$ | CN | $CH_3$ | 1.0 | 179-180 [13] | 93 |
| 12 | 2,4-$Cl_2C_6H_3$ | CN | $CH_3$ | 1.0 | 189-191 [13] | 87 |
| 13 | *p*-$CH_3OC_6H_4$ | CN | H | 1.0 | 190-192 [2b] | 92 |
| 14 | *o*-$ClC_6H_4$ | CN | H | 1.0 | 210-212 [2b] | 86 |
| 15 | *p*-$ClC_6H_4$ | CN | H | 1.0 | 225-227 [6b] | 93 |
| 16 | *m*-$NO_2C_6H_4$ | CN | H | 1.0 | 198-200 [2b] | 92 |
| 17 | 2,4-$Cl_2C_6H_3$ | CN | H | 1.5 | 220-222 [2b] | 87 |
| 18 | *p*-$ClC_6H_4$ | $CO_2Et$ | $CH_3$ | 1.5 | 155-157 [13] | 88 |
| 19 | *m*-$NO_2C_6H_4$ | $CO_2Et$ | $CH_3$ | 1.5 | 185-187 [13] | 89 |

[a] Acidic ionic liquids are 5 mmol benzaldehyde, 5 mmol malononitrile (or ethyl cyanoacetate), 5 mmol dimedone (or 1,3-cyclohexanedione), 0.5 mmol catalyst, 90°C.
[b] Isolated yields.

could be reused directly in the next run without further purification. The products were identified by IR, $^1$H NMR, and physical data (Mp) with those reported in the literatures.

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## REFERENCES AND NOTES

[1] Green, G. R.; Evans, J. M.; Vong, A. K. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1995; Vol. 5, p 469.

[2] (a) Rong, L. C.; Li, X. Y.; Shi, D. Q.; Zhuang, Q. Y. Synth Commun 2006, 36, 2363; (b) Balalaie, S.; Sheikh-Ahmadi, M.; Bararjanian, M. Catal Commun 2007, 8, 1724.

[3] Wang, L.-M.; Shao, J.-H.; Tian, H.; Wang, Y.-H.; Liu, B. J Fluorine Chem 2006, 127, 97.

[4] Wang, X. S.; Shi, D. Q.; Tu, S. J.; Yao, C. S. Synth Commun 2003, 33, 119.

[5] Hekmatshoar, R.; Majedi, S.; Bakhtiari, K. Catal Commun 2008, 9, 307.

[6] (a) Balalaie, S.; Bararjanian, M.; Amani A. M.; Movassagh, B. Synlett 2006, 263; (b) Guo, S. B.; Wang, S. X.; Li, J. T. Synth Commun 2007, 37, 2111.

[7] (a) Saini, A.; Kumar, S.; Sandhu, J. S. Synlett 2006, 1928. (b) Devi, I.; Bhuyan, P. J. Tetrahedron Lett 2004, 45, 8625.

[8] Tu, S. J.; Jiang, H.; Zhuang, Q. Y., Miao, C. B.; Shi, D. Q.; Wang, X. S.; Gao, Y. Chin J Org Chem 2003, 23, 488.

[9] (a) Wasserscheid, P.; Keim, W. Angew Chem Int Ed 2000, 39, 3772; (b) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. Chem Rev 2002, 102, 3667; (c) Sheldon, R. Chem Commun 2001, 23, 2399; (d) Poliakof, M.; Fitzpartrick, J. M. Science 2002, 297, 807; (e) Blanchard, L. A.; Hancu, K. R.; Beckman, E. J.; Brennecke, J. F. Nature 1999, 399, 28; (f) Rogers, R. D.; Seddon, K. R. Science 2003, 302, 792; (g) Greaves, T. L.; Drummond, C. J. Chem Rev 2008, 108, 206; (h) Lee, S.-G. Chem Commun 2006, 10, 1049.

[10] Fan, X.; Hu, X.; Zhang, X.; Wang, J. Can J Chem 2005, 83, 16.

[11] Valizadeh, H.; Amiri, M.; Gholipur, H. J Heterocyclic Chem 2009, 46, 108.

[12] (a) Zhang, Z. H.; Liu, Y. H. Catal Common 2008, 9, 1715; (b) Zhang, Z. H.; Tao, X. Y. Aust J Chem 2008, 61, 77.

[13] Zhi, H.; Lv, C.; Zhang, Q.; Luo, J. Chem Commun 2009, 2878.

[14] Chen, L.; Li, Y.-Q.; Huang, X.-J.; Zheng, W.-J. Heteroatom Chem 2009, 20, 91.

[15] (a) Fang, D.; Zhou, X.-L.; Ye, Z.-W.; Liu, Z.-L. Ind Eng Chem Res 2006, 45, 7982; (b) Fang, D.; Luo, J.; Zhou, X.-L.; Liu, Z.-L. J Mol Catal A Chem 2007, 274, 208; (c) Fang, D.; Liu, Z.-L.; Zhou, X.-L. Chin Appl Chem 2007, 24, 85; (d) Fang, D.; Cheng, J.; Gong, K.; Shi, Q.-R.; Liu, Z.-L. Catal Lett 2008, 121, 255.

# Efficient Synthesis of Benzothieno[3,2-*d*]-imidazo[1,2-*a*] pyrimidine-2,5-(1*H*, 3*H*)-diones *via* a Tandem aza-Wittig/ Heterocumulene-Mediated Annulation

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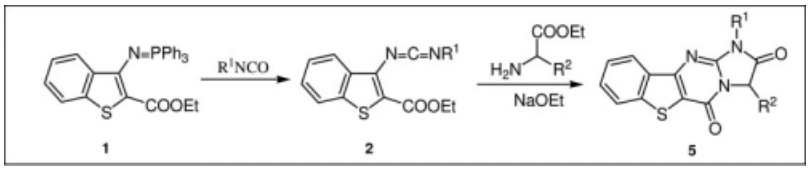


Carbodiimide **2**, obtained from aza-Wittig reaction of iminophosphorane **1** with aromaic isocyanate, reacted with α-amino ester in the presence of catalytic amount of sodium ethoxide to give selectively new tetracyclic benzothieno[3,2-d]-imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones **5** in good yields. X-Ray structure analysis of **5b** verified the proposed structure and the reaction selectivity.

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## INTRODUCTION

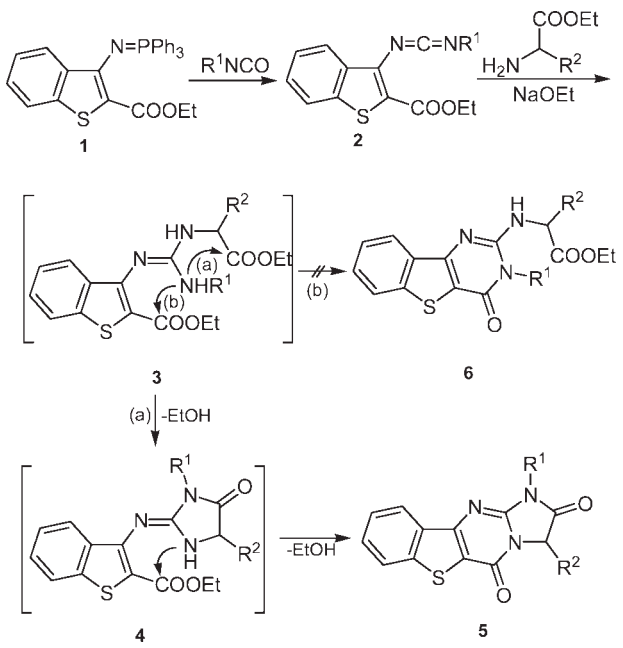
Thienopyrimidines are of great importance because of their significant antifungal and antibacterial activities, as well as their good anticonvulsant and angiotensin or $H_1$ receptor antagonistic activities [1,2]. Although some derivatives of benzothienopyrimidines have shown good antithrombotic, cardiotonic, and α adrenergic antagonistical activities [3,4], there are few reports on synthesis of benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones, which are of considerable interest as potential biological active compounds or pharmaceuticals. On the other hand, heterocycles containing imidazolones nucleus also exhibit various biological activities. Several of them have shown good antibacterial, antifungal activities or being used as leukotriene $B_4$ receptor antagonist and potassium channel openers [5,6]. The introduction of an imidazolone ring to the benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one system is expected to influence the biological activities significantly. However, this tetracyclic system has been much less investigated and there is no report on synthesis of benzothieno[3,2-d]-imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones, probably due to the fact that the tetracyclic system is not easily accessible by routine synthetic methods.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds [7–23]. Annelation of ring systems with N-heterocycles by means of an aza-Wittig reaction has been widely utilized because of the availability of functionalized iminophosphoranes. Recently, we have been interested in the synthesis of pyrimidinones and imidazolones *via* aza-Wittig reaction, with the aim of evaluating their fungicidal activities [24–32]. We also reported an efficient synthesis of benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones *via* aza-Wittig reaction of β ethoxycarbonyl iminophosphorane **1** with isocyanate and subsequent reaction with various nucleophiles under mild conditions [29]. However, the reaction of α-amino ester with β ethoxycarbonyl carbodiimde was not investigated. Here, we wish to report further a selective synthesis of the previously unreported benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones *via* a tandem aza-Wittig/heterocumulene-mediated annulation.

## RESULTS AND DISCUSSION

Iminophosphorane **1** reacted with isocyanates to give carbodiimides **2**, which were allowed to react with α-amino ester at room temperature in the presence of catalytic amount of sodium ethoxide to give benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones **5** selectively (Scheme 1). A variety of α-amino ester and isocyanate could be used for this synthetic strategy and the products **5** were obtained in good yields (Table 1). Presumably, the reaction of carbodiimides **2** with α-amino ester should afford primarily guanidine intermediates of type **3**. From these intermediates **3**, the formation of two cyclized products imidazolone **4** (*via* path a), benzothieno[3,2-d]pyrimidin-4(3*H*)-one **6** (*via* path b) could in principle take place. The formation of **5** might probably due to a tandem cyclization of **3** to

**Scheme 1**




imidazolone intermediate **4** and further base catalytic cyclization between the imidazolone ring's NH and ethoxylate. An imidazolone intermediate **4d** had been successfully isolated before the reaction mixture was treated with sodium ethoxide. Further treatment of **4d** with sodium ethoxide also gave the cyclized product **5d**. The result illustrated that the imidazolone **4** is more easily produced from intermediate **3** than benzothieno[3,2-d]pyrimidin-4(3*H*)-one **6**, and the cyclization of **4** to product **5** should be carried out in strong basic condition.

When chiral α-amino ester was used, recemization of the product **5** took place completely under the reaction condition. This is probably due to the easy recemization of C-3 of the benzothieno[3,2-d]imidazo[1,2-a] pyrimidine-2,5-(1*H*, 3*H*)-dione ring under the strong basic condition.

The structure of benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones **5** was confirmed by their spectrum data. For example, the $^1$H NMR spectrum of **5b** shows two singlets at 4.98 ppm as quarterlets and 1.95 ppm as doublet due to the CH and $CH_3$, respectively. The signals attributable to the Ar—Hs are found at 8.12 ppm–7.44 ppm as mutiplets. The IR spectra of **5b** revealed two C=O absorption bands at 1761 and 1683 $cm^{-1}$ due to the imidazolone and pyrimidinone carbonyl group, respectively. The MS spectrum of **5b** shows strong molecular ion peak at m/z 347 with 100% abundance. Furthermore, a single crystal of **5b** was obtained from a $CH_2Cl_2$ solution of **5b**. X-ray structure analysis verified again the proposed structure (Fig. 1). The pyrimidine ring has a flattened-boat conformation and a pseudo-mirror plane running through the bridgehead N atom and the opposite C atom. The dihedral angles between the planar fused benzene (*A*), thienyl (*B*), imidazole (*D*), and substituent phenyl (*E*) rings are

**Table 1**

Physical and analytical data of compounds **5**.

| Comp. | $R^1$ | $R^2$ | Time (hours) | Mp (°C) | Yield %[a] | Molecular formula | Analysis % calcd./found | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| **5a** | Ph | sec-Bu | 4 | 246–247 | 81 | $C_{22}H_{19}N_3O_2S$ | 67.84 | 4.92 | 10.79 |
| | | | | | | | 67.97 | 5.04 | 10.69 |
| **5b** | Ph | Me | 2 | 268–269 | 87 | $C_{19}H_{13}N_3O_2S$ | 65.69 | 3.77 | 12.10 |
| | | | | | | | 65.73 | 3.89 | 12.01 |
| **5c** | Ph | i-Pr | 5 | 263–265 | 88 | $C_{21}H_{17}N_3O_2S$ | 67.18 | 4.56 | 11.19 |
| | | | | | | | 67.46 | 4.75 | 11.03 |
| **5d** | Ph | $PhCH_2$ | 3 | 225–227 | 89 | $C_{25}H_{17}N_3O_2S$ | 70.90 | 4.05 | 9.92 |
| | | | | | | | 70.99 | 4.15 | 9.88 |
| **5e** | 4-$ClC_6H_4$ | $PhCH_2$ | 4 | 223–224 | 83 | $C_{25}H_{16}ClN_3O_2S$ | 65.57 | 3.52 | 9.18 |
| | | | | | | | 65.70 | 3.66 | 9.01 |
| **5f** | 4-$ClC_6H_4$ | i-Pr | 3 | 219–220 | 87 | $C_{21}H_{16}ClN_3O_2S$ | 61.53 | 3.93 | 10.25 |
| | | | | | | | 61.70 | 4.08 | 9.79 |
| **5g** | i-Pr | Me | 2 | 189–190 | 76 | $C_{16}H_{15}N_3O_2S$ | 61.32 | 4.82 | 13.41 |
| | | | | | | | 61.44 | 4.97 | 13.33 |
| **5h** | i-Pr | $PhCH_2$ | 3 | 189–191 | 84 | $C_{22}H_{19}N_3O_2S$ | 67.84 | 4.92 | 10.79 |
| | | | | | | | 67.95 | 5.01 | 10.69 |
| **5i** | Bu | $PhCH_2$ | 3 | 202–203 | 76 | $C_{23}H_{21}N_3O_2S$ | 68.46 | 5.25 | 10.41 |
| | | | | | | | 68.52 | 5.34 | 10.29 |
| **5j** | Bu | Me | 3 | 175–176 | 80 | $C_{17}H_{17}N_3O_2S$ | 62.36 | 5.23 | 12.83 |
| | | | | | | | 62.50 | 5.37 | 12.74 |

[a] Yields based on iminophosphorane **1**.

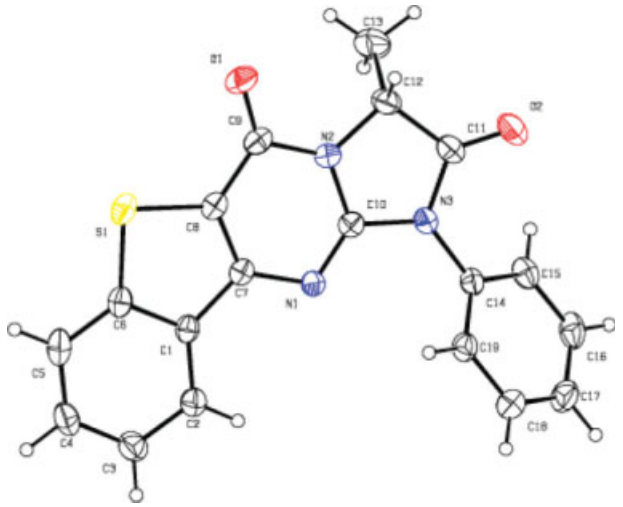



**Figure 1.** ORTEP diagram of the crystal structure of tricyclic compound **5b** (Drawn at the 50% thermal ellipsoids). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

*A*/*B* = 1.63 (3)°, *A*/*D* = 5.80 (2)°, *B*/*D* = 5.49 (3)°, and *D*/*E* = 39.73 (3)°.

In summary, we have developed an efficient synthesis of benzothieno [3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones *via* a cascade aza-Wittig/heterocumulene-mediated annulation. This method utilizes easily accessible starting material and allows mild reaction conditions, straightforward product isolation and good yields.

## EXPERIMENTAL

Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 400 (400 Hz) spectrometer and chemical shifts (δ) were given in ppm using $(CH_3)_4Si$ as an internal reference (δ = 0). IR was recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in $cm^{-1}$. Elementary analyses were taken on a Vario EL III elementary analysis instrument. The X-ray diffraction data were collected on a Bruker SMART AXS CCD diffractometer.

**General procedure for the preparation of benzothieno [3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones (5).** To a solution of iminophosphorane **1** (0.96 g, 2 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (2 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 6–8 h at 0–5°C, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **2**, which was directly used without further purification. A mixture of α-amino acid ester hydrochloride (2 mmol) and triethylamine (0.61 g, 4 mmol) in acetonitrile (10 mL) was stirred for 10 min and filtered. Then, the filtrate was added to the solution of carbodiimide **2** prepared above in dry methylene dichloride (10 mL) at room temperature. After stirring for 0.5 h, the solution was concentrated and anhydrous EtOH (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 4–6 h at room temperature The solution was concentrated under reduced pressure and the residual was recrystallized from methylene dichloride/petroleum ether to give benzothieno [3,2-d]-imidazo[1,2-a]pyrimidine-2,5-(1*H*, 3*H*)-diones **5**.

***3-(Sec-butyl)-1-phenylbenzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5a).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 7.6 Hz, 1H, Ar—H), 7.89 (d, *J* = 8.4 Hz, 1H, Ar—H), 7.61–7.43 (m, 7H, Ar—H), 5.02 (d, *J* = 3.6 Hz, 1H, NCH), 3.01–2.96 (m, 1H, CH), 1.93–1.71 (m, 2H, $CH_2$), 1.11 (t, *J* = 7.2 Hz, 3H, $CH_3$), 0.92 (d, *J* = 6.8 Hz, 3H, $CH_3$). IR (KBr): 1756 (C=O), 1686 (C=O), 1599, 1500, 1366, 750 $cm^{-1}$. MS: *m*/*z* (%) 389 (55, $M^+$), 313 (43), 201 (24), 146 (100), 77 (75).

***3-Methyl-1-phenylbenzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5b).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.88 (d, *J* = 8.4 Hz, 1H, Ar—H), 7.63–7.44 (m, 7H, Ar—H), 4.98 (q, *J* = 7.2 Hz, 1H, NCH), 1.95 (d, *J* = 6.4 Hz, 3H, $CH_3$). IR (KBr): 1761 (C=O), 1683 (C=O), 1603, 1498, 1396, 752 $cm^{-1}$. MS: *m*/*z* (%) 347 (36, $M^+$), 271 (46), 201 (33), 146 (100), 77 (65).

***1-Phenyl-3-(i-propyl)benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5c).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.89 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.61–7.43 (m, 7H, Ar—H), 4.93 (d, *J* = 2.8 Hz, 1H, NCH), 3.28–3.16 (m, 1H, CH), 1.38 (d, *J* = 6.8 Hz, 3H, $CH_3$), 0.97 (d, *J* = 7.2 Hz, 3H, $CH_3$). IR (KBr): 1756 (C=O), 1687 (C=O), 1603, 1501, 1364, 751 $cm^{-1}$. MS: *m*/*z* (%) 375 (48, $M^+$), 299 (26), 201 (41), 146 (100), 77 (73).

***3-Benzyl-1-phenylbenzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5d).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J* = 7.6 Hz, 1H, Ar—H), 7.89 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.56–7.08 (m, 12H, Ar—H), 5.26 (dd, $J_1$ = 4.8 Hz, $J_2$ = 2.8 Hz, 1H, NCH), 4.11 (dd, $J_1$ = 14.0 Hz, $J_2$ = 4.8 Hz, 1H, $CH_2$), 3.53 (dd, $J_1$ = 14.0 Hz, $J_2$ = 2.8 Hz, 1H, $CH_2$). IR (KBr): 1761 (C=O), 1684 (C=O), 1584, 1497, 1357, 749 $cm^{-1}$. MS: *m*/*z* (%) 423 (59, $M^+$), 347 (39), 201 (37), 146 (100), 91 (57), 77 (54).

***3-Benzyl-1-(4-chlorophenyl)benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5e).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.01 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.90 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.58–7.04 (m, 11H, Ar—H), 5.26 (dd, $J_1$ = 2.8 Hz, $J_2$ = 4.8 Hz, 1H, NCH), 4.11 (dd, $J_1$ = 14.0 Hz, $J_2$ = 4.8 Hz, 1H, $CH_2$), 3.51 (dd, $J_1$ = 14.0 Hz, $J_2$ = 2.8 Hz, 1H, $CH_2$). IR (KBr): 1751 (C=O), 1697 (C=O), 1602, 1501, 1360, 749 $cm^{-1}$. MS: *m*/*z* (%) 457 (47, $M^+$), 347 (45), 200 (30), 146 (100), 91 (57), 77 (60).

***3-Benzyl-1-(4-chlorophenyl)benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5f).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.90 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.59–7.45 (m, 6H, Ar—H), 4.92 (d, *J* = 2.4 Hz, 1H, NCH), 3.23–3.18 (m, 1H, CH), 1.37 (d, *J* = 7.2 Hz, 3H, $CH_3$), 0.95 (d, *J* = 6.8 Hz, 3H, $CH_3$). IR (KBr): 1752 (C=O), 1698 (C=O), 1592, 1503, 1387, 748 $cm^{-1}$. MS: *m*/*z* (%) 409 (44, $M^+$), 299 (33), 200 (22), 146 (100), 77 (77).

***3-Methyl-1-(iso-propyl)benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5g).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.26 (d, *J* = 7.6 Hz, 1H, Ar—H), 7.90

(d, $J$ = 8.0 Hz, 1H, Ar—H), 7.58–7.50 (m, 2H, Ar—H), 4.82–4.74 (m, 2H, 2CH), 1.82 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 1.64 (d, $J$ = 6.4 Hz, 6H, $2CH_3$), 1.62 (d, $J$ = 6.0 Hz, 3H, $CH_3$). IR (KBr): 1742 (C=O), 1685 (C=O), 1594, 1505, 1336, 748 $cm^{-1}$. MS: *m/z* (%) 313 (66, $M^+$), 271 (42), 201 (29), 146 (100), 77 (67).

***3-Benzyl-1-(iso-propyl)benzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5h).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (d, $J$ = 8.0 Hz, 1H, Ar—H), 7.91 (d, $J$ = 8.4 Hz, 1H, Ar—H), 7.59–7.01 (m, 7H, Ar—H), 5.01 (t, $J$ = 2.8 Hz, 1H, NCH), 4.54–4.50 (m, 1H, NCH), 4.02 (dd, $J_1$ = 14.0 Hz, $J_2$ = 3.6 Hz, 1H, $CH^aPh$), 3.42 (dd, $J_1$ = 13.6 Hz, $J_2$ = 2.8 Hz, 1H, $CH^bPh$), 1.32 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 1.25 (d, $J$ = 7.2 Hz, 3H, $CH_3$). IR (KBr): 1750 (C=O), 1683 (C=O), 1592, 1503, 1387, 748 $cm^{-1}$. MS: *m/z* (%) 389 (58, $M^+$), 347 (31), 201 (18), 146 (76), 91 (67), 77 (100).

***3-Benzyl-1-butylbenzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5i).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.17 (d, $J$ = 8.0 Hz, 1H, Ar—H), 7.91 (d, $J$ = 8.0 Hz, 1H, Ar—H), 7.59–7.03 (m, 7H, Ar—H), 5.05 (dd, $J_1$ = 2.8 Hz, $J_2$ = 4.8 Hz, 1H, NCH), 4.04 (dd, $J_1$ = 14.0 Hz, $J_2$ = 4.8 Hz, 1H, $CH^aPh$), 3.68–3.61 (m, 2H, $NCH_2$), 3.44 (dd, $J_1$ = 14.0 Hz, $J_2$ = 2.8 Hz, 1H, $CH^bPh$), 1.41–1.37 (m, 2H, $CH_2$), 1.10–1.02 (m, 2H, $CH_2$), 0.86 (t, $J$ = 7.2 Hz, 3H, $CH_3$). IR (KBr): 1754 (C=O), 1673 (C=O), 1605, 1505, 1364, 750 $cm^{-1}$. MS: *m/z* (%) 403 (55, $M^+$), 347 (44), 201 (34), 146 (75), 91 (66), 77 (100).

***1-Butyl-3-methylbenzothieno[3,2-d]imidazo[1,2-a]pyrimidine-2,5-(1H, 3H)-dione (5j).*** White solid. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.28 (d, $J$ = 7.6 Hz, 1H, Ar—H), 7.90 (d, $J$ = 8.4 Hz, 1H, Ar—H), 7.59–7.52 (m, 2H, Ar—H), 4.81 (q, $J$ = 6.8 Hz, 1H, NCH), 3.93–3.89 (m, 2H, $NCH_2$), 1.85–1.79 (m, 5H, $CH_2$ and $CH_3$), 1.47–1.41 (m, 2H, $CH_2$), 1.01 (t, $J$ = 7.2 Hz, 3H, $CH_3$). IR (KBr): 1747 (C=O), 1680 (C=O), 1605, 1504, 1353, 751 $cm^{-1}$. MS: *m/z* (%) 327 (65, $M^+$), 271 (39), 201 (26), 146 (100), 77 (48).

**Isolation of the intermediate 4d.** A mixture of ethyl 2-amino-3-phenylpropanoate hydrochloride (0.46 g, 2 mmol) and triethylamine (0.61 g, 4 mmol) in acetonitrile (10 mL) was stirred for 10 min and filtered. Then, the filtrate was added to the solution of carbodiimide 2 prepared above in dry methylene dichloride (10 mL) at room temperature. After stirring for 2 h, the solution was concentrated under reduced pressure and the residual was recrystallized from methylene dichloride/petroleum ether to give imidazolone 4d. White solid; mp: 191–193°C. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73–7.13 (m, 14H, Ar—H), 4.87 (s, 1H, NH), 4.42–4.32 (m, 3H, $OCH_2$ and CH), 3.25 (dd, $J_1$ = 3.6 Hz, $J_2$ = 14.0 Hz, 1H, $PhCH^a$), 3.06 (dd, $J_1$ = 8.0 Hz, $J_2$ = 14.0 Hz, 1H, $PhCH^b$), 1.39 (t, $J$ = 7.2 Hz, 3H, $CH_3$). IR (KBr): 3324 (NH), 1762 (C=O), 1691 (C=O), 1596, 1503, 1428, 1239 $cm^{-1}$. MS: m/z (%) 469 (100, $M^+$), 333 (27), 277 (28), 146 (50), 91 (34). Anal. Calcd for $C_{27}H_{23}N_3O_3S$: C, 69.06; H, 4.94; N, 8.95. Found: C, 69.24; H, 4.87; N, 8.73.

**Crystallographic data of 5b.** Crystallographic data for the structures of 5b reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-647685. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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## REFERENCES AND NOTES

[1] Chambhare, R. V.; Khadse, B. G.; Bobde, A. S.; Bahekar, R. H. Eur J Med Chem 2003, 38, 89.

[2] Shishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. Eur J Med Chem 2000, 35, 351.

[3] Nomoto, Y.; Takai, H.; Ohno, T.; Kubo, K. Chem Pharm Bull 1991, 39, 352.

[4] Ehrlich, P. P.; Ralston, J. W.; Daanen, J. F.; Meyer, M. D. PCT Int Appl WO 9,957,122 (1999); Ehrlich, P. P.; Ralston, J. W.; Daanen, J. F.; Meyer, M. D. Chem Abstr 1999, 131, 337029w.

[5] O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. J Am Chem Soc 2007, 129, 4762.

[6] Gadwood, R. C.; Kamdar, B. V.; Dubray, L. A. C.; Wolfe, M. L.; Smith, M. P.; Watt, W.; Mizsak, S. A.; Groppi, V. E. J Med Chem 1993, 36, 1480.

[7] Barluenga, J.; Palacios, F. Org Prep Proced Int 1991, 23, 1.

[8] Eguchi, S.; Matsushita, Y.; Yamashita, K. Org Prep Proced Int 1992, 24, 209.

[9] Molina, P.; Vilaplana, M. J. Synthesis 1994, 1197.

[10] Wamhoff, H.; Richard, G.; Stoelben, S. Adv Heterocycl Chem 1995, 64, 159.

[11] Fresneda, P. M.; Molina, P. Synlett 2004, 1.

[12] Eguchi, S. ARKIVOC 2005, ii, 98.

[13] Eguchi, S. Top Heterocycl Chem 2006, 6, 113.

[14] Lertpibulpanya, D.; Marsden, S. P.; Rodriguez-Garcia, I.; Kilner, C. A. Angew Chem Int Ed 2006, 45, 5000.

[15] Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; Santos, J. M. Tetrahedron 2007, 63, 523.

[16] Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. Org Lett 2008, 10, 2589.

[17] Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. Synthesis 2006, 1953.

[18] Chan, J.; Faul, M. Tetrahedron Lett 2006, 47, 3361.

[19] Blanco, G.; Quintela, J. M.; Peinador, C. Tetrahedron 2008, 64, 1333.

[20] Blanco, G.; Fernandez-Mato, A.; Quintela, J. M.; Peinador, C. Tetrahedron 2008, 64, 11136.

[21] Bobeck, D. R.; France, S.; Leverett, C. A.; Sanchez-Cantalejo, F.; Padawa, A. Tetrahedron Lett 2009, 50, 3145.

[22] Hao, J.; Xia, Y.; Wang, L.; Ruhlmann, L.; Zhu, Y.; Li, Q.; Yin, P.; Wei, Y.; Guo, H. Angew Chem Int Ed 2008, 47, 2626.

[23] Li, Q.; Wei, Y.; Hao, J.; Zhu, Y.; Wang, L. J Am Chem Soc 2007, 129, 5810.

[24] Zhao, J. F.; Xie, C.; Xu, S. Z.; Ding, M. W.; Xiao, W. J. Org Biomol Chem 2006, 4, 130.

[25] Huang, N. Y.; Liang, Y. J.; Ding, M. W.; Fu, L. W.; He, H. W. Bioorg Med Chem Lett 2009, 19, 831.

[26] Xie, C.; Huang, N. Y.; Ding, M. W. ARKIVOC 2009, (x), 220.

[27] Liu, M. G.; Hu, Y. G.; Ding, M. W. Tetrahedron 2008, 64, 9052.

[28] Zeng, G. P.; Hu, Y. G.; Ding, M. W. J Heterocycl Chem 2008, 45, 1809.

[29] Xu, S. Z.; Hu, Y. G.; Ding, M. W. Synthesis 2006, 4180.

[30] Ding, M.-W.; Chen, Y.-F.; Huang, N.-Yu. Eur J Org Chem 2004, 3872.

[31] Yuan, J.-Z.; Fu, B.-Q.; Ding, M.-W.; Yang, G.-F. Eur J Org Chem 2006, 4170.

[32] Zhao, J.-F.; Xie, C.; Xu, S.-X.; Ding, M.-W.; Xiao, W.-J. Org Biomol Chem 2006, 4, 130.

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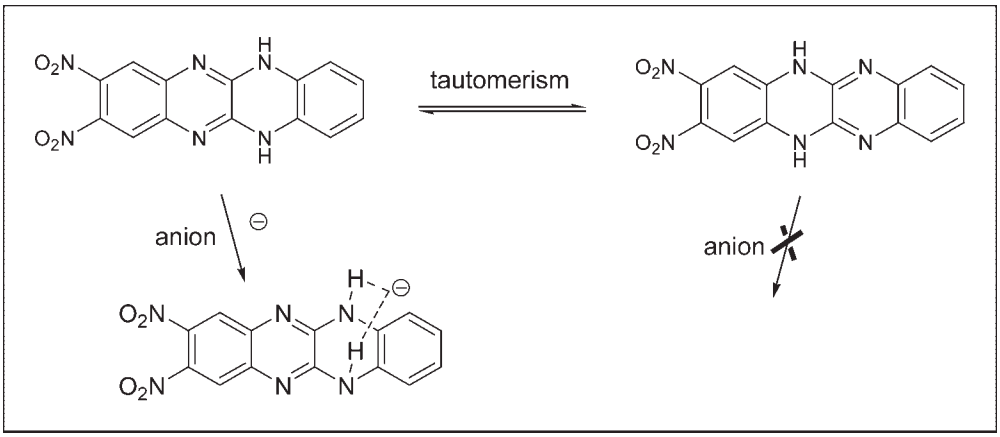


*O*-phenylene-diamine derivative containing colorimetric dinitroquinoxaline has been synthesized. Its UV-vis spectroscopy and $^1$H NMR investigation reveal that the receptor shows the strong binding ability for $AcO^-$, $F^-$, and $H_2PO_4^-$, moderate binding abilities for $OH^-$ and almost no binding abilities for $Cl^-$, $Br^-$, and $I^-$. The interaction of the receptor with studied anions achieving the recognition of anions is proposed to come from the N—H. . .F and potential C—H. . .F hydrogen bonding in its neutral form. The results indicate that it is well suitable for the anion complexation, which is presumably contributed to its ring topology possessing a rigidity conjugation system. Moreover, the molecular orbital level of this receptor and its tautomer were further determined by means of theoretical investigations.

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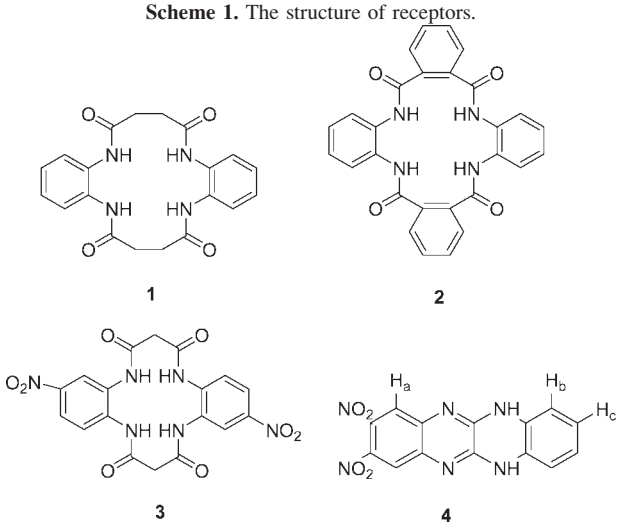
## INTRODUCTION

Host-guest systems for recognition of anionic guest species play an important role in the development of supramolecular chemistry [1]. The molecular recognition of anionic guests by synthetic hosts is an area of ever increasing research activity [2]. Study of anion receptors has special potential applications in the synthesis of anion sensors [3], membrane transmit carriers [4], and mimic enzyme catalysts, etc. [5,6]. Particularly there is a current interest in the synthesis of colorimetric neutral chemosensors for detection of anions. Synthetic nitrogen-based receptors designed for the selective binding of anions are usually either the positively charged ammonium salts, i.e., protonated polyamines and/or quaternary ammonium salts, or some of the neutral species, such as, amides, sulfonamides, pyrroles, ureas, and thioureas [7–9]. For example, in 1968, Park and Simmons [10] synthesized a series of dicyclopolyamines compounds and the results indicated that it is the protonated polyamines that interacted with anions. Lehn and coworkers [11–16] reported that during the interaction of polyamines with anions, the polyamines were in the form of protonated polyamines too. However, the neutral amine receptors which can interact with various anions have not yet been reported, and even more for achieving the possibility of the naked-eye detection about the bonding of anions. In the previous work, we studied the recognition property of 16-membered or 14-membered amide macrocycle (Scheme 1, **1**–**3**) with various anions [17,18]. In this article, we synthesized and studied the anion binding abilities of six-membered cycle, a neutral diamine receptor containing dinitroquinoxaline (Scheme 1, **4**) in order to find the difference of anion binding ability between macro and microcycle. The anion recognition properties of receptor **4** with different anions ($F^-$, $Cl^-$, $Br^-$, $I^-$, $AcO^-$, $H_2PO_4^-$, and $OH^-$) has been studied by UV-vis and $^1$H NMR experiment and the results indicate that the receptor shows higher binding abilities for $AcO^-$, $F^-$, and $H_2PO_4^-$ and the interaction of receptor **4** with various anions is in the form of a neutral diamine. This work is one of the progressive steps in pushing the development of an anion recognition method based upon the neutral amine recognition sites.

**Scheme 1.** The structure of receptors.




## RESULTS AND DISCUSSION

The interaction of receptor **4** with anions was investigated through the spectrophotometric titration by the addition of a standard dimethyl sulfoxide (DMSO) solution of the tetrabutyl ammonium salt (TBA) of the investigated anion to a DMSO solution of **4**.

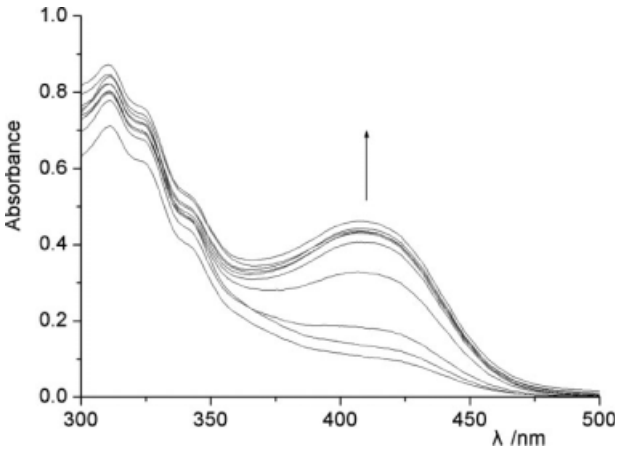



**Figure 1.** UV-vis spectrum of receptor **4** changes upon the addition of fluoride anion; [**4**] = $4.0 \times 10^{-5}$ mol/L, [$F^-$] = 0–$160 \times 10^{-5}$ mol/L. Arrows indicate the direction of increasing anion concentration.

Figure 1 shows the changes in the absorption spectrum of receptor **4** observed upon the addition of fluoride anion. In the absence of anion, the spectrum of receptor **4** is characterized by the presence of one peak at 315 nm. The addition of fluoride anion results in the development of a new band at 409 nm, changing the

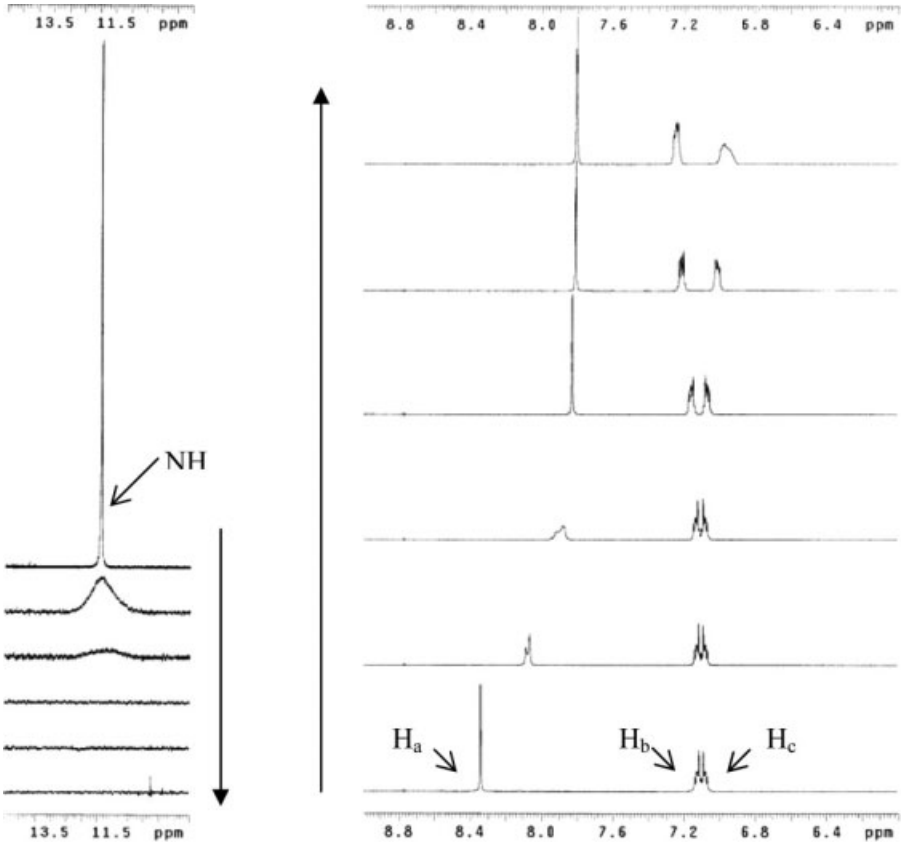



**Figure 2.** Plots of $^1$H NMR spectra of receptor **4** in DMSO-$d_6$ upon the addition of various quantities of $Bu_4NF$. The arrows' direction represent the additions of $Bu_4NF$ are 0, 0.5, 1, 2, 5, 10 equiv., respectively.

**Table 1**

Affinity constants of receptor **4** with various anions.

| Anion | $K_s$ ($M^{-1}$) |
|---|---|
| $AcO^-$ | $(3.20 \pm 0.35) \times 10^4$ |
| $F^-$ | $(1.32 \pm 0.33) \times 10^4$ |
| $H_2PO_4^-$ | $(1.12 \pm 0.12) \times 10^4$ |
| $OH^-$ | $(2.99 \pm 0.41) \times 10^3$ |

color of the solution from colorless to pale-yellow. The addition of $AcO^-$, $H_2PO_4^-$, and $OH^-$, respectively, induces a similar color change. On the other hand, exposure to $Cl^-$, $Br^-$ or $I^-$, i.e., species that do not bind to receptor **4** appreciably, do not lead to any noticeable change in the solution color. This phenomenon makes this system an effective anion sensor under these solution conditions.

Very recently, a number of fluorogenic and/or chromogenic anion sensors comprising recognition moieties, such as, urea, thiourea, or amide have been reported to undergo an anion-induced deprotonation [19–21]. According to these reports, there appears one new triplet resonance at 16.1 ppm, the characteristic resonance of bifluoride (F—H—F) and the chemical shifts of noninteracted sites' proton signals occur up-field. To look into the anion binding properties of receptor for fluoride on anion recognition, $^1H$ NMR titration experiments in DMSO-$d_6$ were performed (Fig. 2). From Figure 2, different patterns are observed in the titration ranges of 0–1 and 1–2 equiv. ranges. The NH signal (11.9 ppm) becomes broadened and the chemical shift of the phenyl signal $H_a$ upfield after the addition of 1 quantities of TBAF. During this process, the chemical shifts of $H_b$ and $H_c$ do not change. After the addition of 2 equiv of TBAF, the NH signal completely disappears and the shift of $H_a$ is stopped, only peak-shape change occur (from broad to sharp). The state of affairs can be accounted by hypothesizing that the first added fluoride anion establishes H-bonding interaction with the NH of receptor **4**. Due to the strong electron-withdrawing effect of $NO_2$, the shielding effect induced by H-bonding is more sensitive to $H_a$ than $H_b$ and $H_c$. Therefore, the signal of $H_a$ upfield and the signal of $H_b$, $H_c$ almost occurs no changes. On addition of 2 equiv. fluoride anion, detailed analysis reveals the significant upfield shifts of $H_c$, except $H_b$, which exhibits a downfield shift from 7.1 to 7.3 ppm, indicating the formation of potential C—H. . .F H-bonding during the titration [22].

Job plots for receptor **4** at 298 K with anions as guest in DMSO solution show the maxima at a mole fraction of 0.5, which signifies that the host binds the anionic guest in a 1:1 ratio. Affinity constants of receptor **4** for anionic species are calculated according to the eq. (1), 1:1 host-guest complexation [23–25].

$$X = X_0 + 0.5\Delta\varepsilon\{c_H + c_G + 1/K_s - [(c_H + c_G + 1/K_s)^2 - 4c_H c_G]^{1/2}\} \quad (1)$$

where $c_G$ and $c_H$ are the concentration of guest and host, respectively. $X$ is the intensity of absorbance at certain concentration of host and guest. $X_0$ is the intensity of absorbance of host when the anion is not added. $K_s$ is the affinity constant of host-guest complexation. $\Delta\varepsilon$ is the change in molar extinction coefficient.

Affinity constants of receptor **4** for anionic species are summarized in Table 1. The affinity constants of receptor with $Cl^-$, $Br^-$, and $I^-$ cannot be determined because the anions almost have no binding abilities with receptor. From Table 1, the anion affinity of receptor **4** is decreased in the order of $AcO^- > F^- > H_2PO_4^- > OH^- >> Cl^-$, $Br^-$, and $I^-$. Among the anions investigated, the highest affinity is observed with acetate. The reason may be that only the acetate matches perfectly with receptor **4** geometrically and thus has the highest affinity with receptor **4**.

As is well-known, neutral amines almost have no binding ability with anions. However, receptor **4** we synthesized has high affinity with some anions. We speculate that the electron density of diamine moieties is decreased due to the very strong electron-withdrawing effect of $NO_2$. Theoretical investigation on molecular orbital level using density functional theory at B3LYP/3-21G level with Gaussion03 program [26] can prove this (Fig. 3). In receptor **4**, the charges of the nitrogen atoms interacted with anion (N11, N12) are −0.569624 and −0.569623, respectively. The charges of N11 and N12 interacted with anions in non-containing $NO_2$

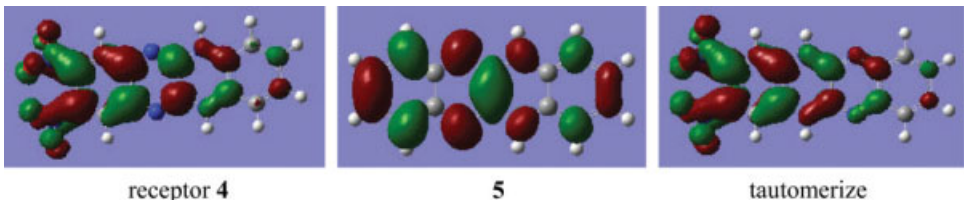



**Figure 3.** Molecular orbital level of receptor **4**, its tautomer and compound **5**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

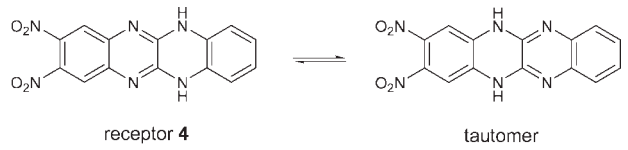



**Figure 4.** The structure of receptor **4** and tautomer.

compound (**5**) are both −0.581427. The stronger the binding ability, the smaller the charge of N11 and N12. Thus, the ability of forming the hydrogen bond between diamine and anion is appeared in receptor **4**. In addition, receptor **4** exists as tautomer (Fig. 4). Whether does receptor **4** or its tautomer interact with various anions? The molecular orbital level of its tautomer was optimized (Fig. 3). The charges of N11 and N12 in tautomer are both −0.655013. Therefore, receptor **4** may interact with anions rather than its tautomer.

These results enable us to assume that the binding of anion with diamine moieties will induce a spectral change in the complex (Fig. 5). From Figure 5, the difference in spacer units are responsible for the anion selectivity. Fluoride anion, a spherical ion, interacts with diamines through the H-bonding. Both of the two oxygen atoms of acetate anion, forming a ''Y'' configuration, probably interact with diamines through two H-bonding. The affinity constant of acetate anion is higher than that of fluoride anion due to the ''Y'' configuration, acetate anion, is better matched with receptor than spherical configuration, fluoride anion in space. Therefore, the affinity constant is related on the matched degree between receptor and anion. Here, it should be pointed out that the proposed binding mode in Figure 5 as drown is planar structure and does not present its geometry. According to optimized results, the geometry of receptor **4** is planar. It may change under the inducement of anions, especially the NH ring may distort [27].

However, the selectivity between $AcO^-$ and $F^-$ is unfortunately not large enough for any practical application purpose. The selectivity is probably also influenced by the size complementarity between anions and cavity.

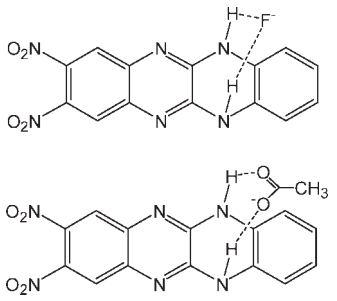
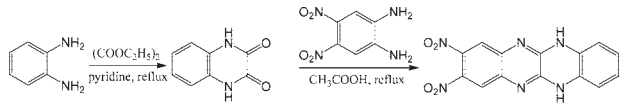


**Figure 5.** A proposed hydrogen bond configuration formed between receptor **4** and anions.

**Scheme 2.** The synthesis route of **4**.




In previous papers, 16-membered and 14-membered amide macrocycle (receptor **1**-**3**) show high selectivity for certain anion. So, we may be further modify the receptor by tuning the size of the ring in receptor **4** (for example, altered to a 16-membered or a 18-membered ring, etc.) in order to find a receptor containing amine recognition site that fits well for $AcO^-$, $F^-$, or other anions geometrically.

## CONCLUSION

In summary, we have synthesized a neutral cyclic diamine containing phenyl ring and colorimetric dinitroquinoxaline. The UV-vis titration and $^1$H NMR experiments indicate that receptor **4** shows the strong affinity for $AcO^-$, $F^-$, and $H_2PO_4^-$, moderate affinities for $OH^-$, and almost no affinities for $Cl^-$, $Br^-$, and $I^-$. Moreover, the interaction of the synthetic receptor with $F^-$, $AcO^-$, $H_2PO_4^-$, and $OH^-$ results in a visible change of color, and the receptor can thus be used as a colorimetric sensor. Receptor **4** interacts with various anions in the form of a neutral diamine, not protonated polyamines. In addition, we found that the selectivity of six-membered amine cycle (**4**) is not better than that of 16- or 14-membered amide cycle (**1**–**3**). In addition, theoretical investigations show that receptor **4** may interact with anions rather than its tautomer.

This work is one of the progressive steps in pushing the development of an anion recognition method based upon the neutral amine recognition site. Further studies on this line are in progress.

## EXPERIMENTAL

Most of the starting materials were obtained commercially and all reagents and solvents used were of analytical grade. All anions, in the form of TBAs, were purchased from Sigma-Aldrich Chemical Co., stored in a desiccator under vacuum containing self-indicating silica, and used without any further purification. DMSO was distilled *in vacuo* after dried with $CaH_2$. Tetra-*n*-butylammonium salts (such as $(n\text{-}C_4H_9)_4NF$, $(n\text{-}C_4H_9)_4NCl$, $(n\text{-}C_4H_9)_4NBr$, $(n\text{-}C_4H_9)_4NI$, $(n\text{-}C_4H_9)_4NAcO$, $(n\text{-}C_4H_9)_4NH_2PO_4$, and $(n\text{-}C_4H_9)_4NOH$) were dried for 24 h in vacuum with $P_2O_5$ at 333 K before use. C, H, and N elemental analyses were made on Vanio-EL. $^1$H NMR spectra were recorded on a Varian UNITY Plus-400 MHz Spectrometer. FAB-MS was made on VG ZAB-HS. UV-vis spectroscopy titrations were made on Shimadzu UV2450 spectrophotometer.

*N*,*N*′-(*o*-phenylene)-6,7-dinitro-2,3-diamino-quinoxaline (**4**) was synthesized according to the route shown in Scheme 2.

**1,4-Quinoxaline-2,3-dione [28].** *o*-diaminebenzene (10.8 g, 0.1 mol), diethyl oxalate (13.5 mL, 0.1 mol), and pyridine (200 mL) were added in 250 mL three-neck. The mixture refluxed with $N_2$ for 72 h. After cooled, the mixture was filtrated and we obtained colorless solid. The solid was washed with ethanol, ether, and dried in vacuum. Yield 61.3%. $^1$H NMR (400 MHz DMSO-$d_6$) δ 11.9 (s, 2H), 7.1 (m, 4H). Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28; Found: C, 59.73; H 3.58; N, 17.67. FAB-MS (*m*/*z*): 163 $(M + H)^+$.

***N*,*N*′-(*o*-Phenylene)-6,7-dinitro-2,3-diamino-quinoxaline (4).** 1,4-quinoxaline-2,3-dione (2.5 mmol, 0.81 g), 4,5-dinitro-*o*-diaminebenzene (2.5 mmol, 0.49 g), and acetic acid (100 mL) were refluxed for 12 h. After cooled, the mixture was filtrated and we obtained brown solid. The solid was washed with water, ethanol, and recrystallized, respectively, from acetic acid and dried in vacuum. Yield 84.8%. $^1$H NMR (400 MHz DMSO-$d_6$) δ 11.9 (s, 2H), 8.3 (s, 2H), 7.1 (m, 4H). Anal. Calcd. for $C_{28}H_{16}N_{12}O_8 \cdot 2CH_3COOH$: C, 50.01; H, 3.15; N, 21.87; Found: C, 49.73; H, 3.58; N, 21.77.

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## REFERENCES AND NOTES

[1] (a) Steed, J. W.; Atwood, J. L. Supramolecular Chemistry: A Concise Introduction; Wiley: Chichester, 2000; (b) Lehn, J. M. Supramolecular Chemistry: Conceptors and Perspective; VCH: Weinheim, 1995; (c) Vogtle, F. Supramolekulare Chemie; Teubner: Stuttgart, 1991.

[2] Yuan, Y.; Gao, G.; Jiang, Z. L.; You, J. S.; Zhou, Z. Y.; Yuan, D. Q.; Xie, R. G. Tetrahedron 2002, 58, 8993.

[3] Buhlmann, P.; Pretsch, E.; Bakker, E. Chem Rev 1998, 98, 1593.

[4] Kral, V.; Sessier, J. L. Tetrahedron 1995, 51, 539.

[5] Kavauierators, K.; Carbtree, R. H. Chem Commun 1999, 20, 2109.

[6] Hubner, G.; Glaser, M.; Seel, J. C. Angew Chem Int Ed Engl 1999, 38, 383.

[7] Bianchi, A.; Bowman-James, K.; Garcia-Espana, E., Eds. Supramolecular Chemistry of Anions; Wiley-VCH: New York, 1997.

[8] Schneider, H. J.; Yatsimirsky, A. Principles and Methods in Supramolecular Chemistry; Wiley: New York, 2000.

[9] Jose, D. A.; Kumar, D. K.; Ganguly, B.; Das, A. Org Lett 2004, 6, 3445.

[10] Park, C. H.; Simmons, H. E. J Am Chem Soc 1968, 90, 2431.

[11] Graf, E.; Lehn, J. M. J Am Chem Soc 1976, 98, 6403.

[12] Lehn, J. M.; Sonveaux, E.; Willard, A. K. J Am Chem Soc 1978, 100, 4914.

[13] Dietrich, B.; Guihem, J. M.; Pascard, C.; Sonveaux, E. Helv Chim Acta 1984, 67, 91.

[14] Hosseini, M. W.; Lehn, J. M. J Am Chem Soc 1982, 104, 3525.

[15] Hosseini, M. W.; Lehn, J. M. Helv Chim Acta 1986, 69, 587.

[16] Aguilar, J. A.; Garcia-Espana, E.; Guerrero, J. A.; Luis, S. V.; Linarese, J. M.; Miravet, J. F.; Ramirez, J. A.; Soriano, C. J Chem Soc Chem Commun 1995, 2237.

[17] Shang, X.-F.; Cai, Z.-S.; Lin, H.-K.; Lin, H. J Heterocycl Chem 2008, 45, 1329.

[18] Shang, X.-F.; Xu, X.-F.; Lin, H.; Shao, J.; Lin, H.-K. J Mol Recognit 2007, 20, 39.

[19] Wu, C. Y.; Chen, M. S.; Lin, C. A.; Lin, C.; Sun, S. S. Chem Eur J 2006, 12, 2263.

[20] Zhang, B. G.; Xu, J.; Zhao, Y. G.; Duan, C. Y.; Cao, X.; Meng, Q. J. Dalton Trans 2006, 1271.

[21] Esteban-Gomez, D.; Fabbrizzi, L.; Licchellic, M. J Org Chem 2005, 70, 5717.

[22] Lin, Z. H.; Zhao, Y. G.; Duan, C. Y.; Zhang, B. G.; Bai, Z. P. Dalton Trans 2006, 3678.

[23] Gans, P.; Sabatini, A. Talanta 1996, 43, 1793.

[24] Liu, Y.; Han, B. H.; Zhang, H. Y. Curr Org Chem 2004, 8, 35.

[25] Bourson, J.; Pouget, J.; Valeur, B. J Phys Chem 1997, 17, 4552.

[26] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E., et al. Gaussian 03, Revision A. 1; Gaussian, Inc.: Pittsburgh PA, 2003.

[27] Shang, X.-F.; Xu, X.-F.; Lin, H.; Shao, J.; Lin, H.-K. J Inclusion Phenom Macrocyclic Chem 2007, 58, 275.

[28] Lu, W. B. Guangzhou Chem 2002, 27, 26.

# Synthesis and Antifungal Activity of Novel 2-Benzimidazolylimino-5-arylidene-4-thiazolidinones



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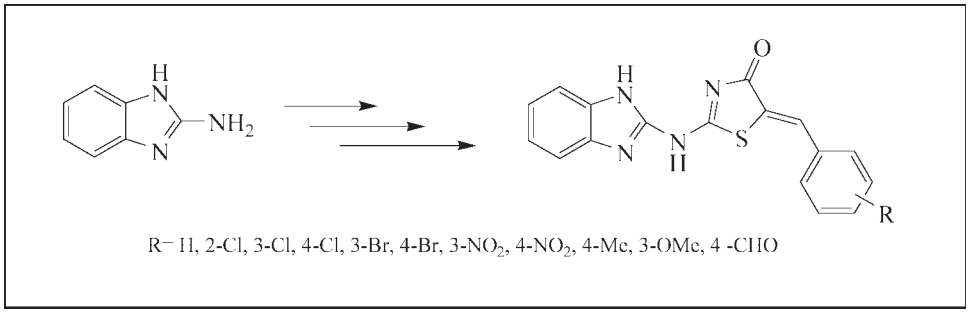


A series of 5-arylidene derivatives **3a-k**, as potential antifungal agents, were synthesized in good to high yields by the reaction of 2-benzimidazolylimino-4-thiazolidinone and corresponding aromatic aldehyde in a buffered medium. These compounds were evaluated for their antifungal activities against four agricultural fungi, *Botrytis elliptica*, *Fusarium graminearum, Phytophthora nicotianae*, and *Rhizoctonia solani*. Thereby, it was found that the compound **1** exhibits an antifungal effect against *P. nicotianae* and *B. elliptica*, comparable with carbendazim as a standard antifungal. Our results may provide some guidance for development of some novel benzimidazole-based antifungal lead structures.

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## INTRODUCTION

Thiazolidin-4-ones constitute an important class of heterocyclic compounds because of their broad range of biological activities [1–5]. It is also well known that thiazolidin-4-ones have antifungal activity [6–9] and are used as a new class of potent anti-HIV-1 agents with marked reverse transcriptase (RT) inhibitory effects [10,11].

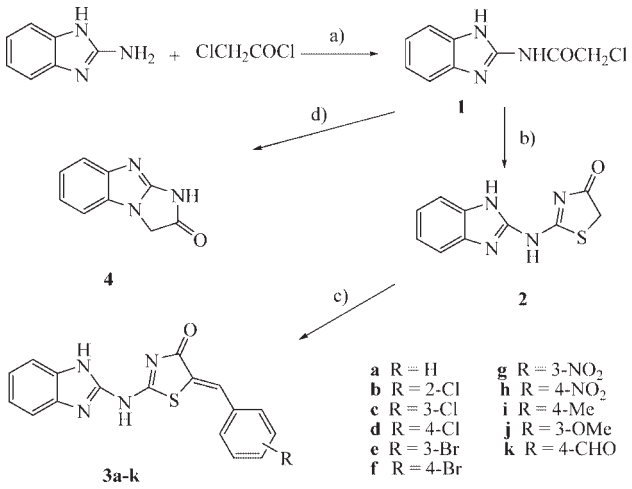
Benzimidazole derivatives are also of wide interest because of their diverse biological activities, such as anticancer, antiproliferative, antiviral, and platelet-anti-aggregating agents [12–16]. Benzimidazoles containing a subunit group, especially a methyl carbamate group on position C(2) (Carbendazim), are found as potential antifungal agent for plants [17]. Because of the aforementioned findings and also because of the incessant interest in the chemistry and antimicrobial activity of benzimidazoles, substantial attention should be paid to the synthesis of novel benzimidazole derivatives especially benzimidazolyl substituted 2-iminiothiazolidin-4-ones. In view of these reports, we extended our research for the synthesis of a novel class of benzimidazole substituted 2-iminiothiazolidin-4-ones resulting from the reaction of 2-(1H-benzimidazol-2-ylamino)-1,3-thiazol-4(5H)-one **2** with various aromatic aldehydes. The antifungal activity of these compounds was investigated against some agricultural fungi.

## RESULTS AND DISCUSSION

Compound **1**, N-(1*H*-benzimidazol-2-yl)-2-chloroactamide, was synthesized from 2-amino benzimidazole using a variation of the reported procedure [9]. The compound **1** on heterocyclization in the presence of ammonium thiocyanate in refluxing ethanol (96%) efficiently produced compound **2** without any further purification [5]. Compounds **3a–k** were obtained by refluxing **2** with corresponding aromatic aldehydes in buffered glacial acetic acid (Scheme 1). Compound **3k** was selectively obtained by the reaction of **2** with an aromatic dialdehyde. The presence of an aldehyde group in the phenyl ring of the product was evidently confirmed by $^1$H NMR, Ms, and infrared (IR) data. Finally, compound **4** was synthesized by refluxing **1** in the presence of $K_2CO_3$ in acetone. All new compounds were characterized using spectroscopy data (IR, $^1$H, and $^{13}$C NMR).

Compounds **2** and **3a–k** exist as lactam forms on the basis of the mechanism suggested by Vicini *et al.* [18]. This mechanism is more reasonable than that one led to

**Scheme 1.** Conditions: (a) Acetone, 2 h, reflux. (b) $NH_4SCN$, 96% EtOH, 8 h, reflux. (c) AcOH, AcONa, 3–10 h, reflux. (d) Acetone, $K_2CO_3$, 4 h, reflux.




the formation of an imine structure **5** as shown in Scheme 2 [9]. In $^1$H NMR spectra of compounds **2** and **3a–k**, the resonance of two NH protons at 12.13 and 12.37–12.85 ppm are in support of the lactam form, because an imine proton appears at much higher field (about 9.70) [19,20]. The $^1$H NMR and IR spectroscopy data (the absence signal of an OH group) is in agreement with a γ-lactam, confirm the $\mathbf{2}_a$ and $\mathbf{2}_b$ tautomeric forms in the solid and liquid states (Scheme 2).

Compounds (**1, 2, 3a–k, 4**) were tested for fungicidal activity against four agricultural fungi. The results (Table 1) show that the compounds **1** and **2** have higher antifungal activity than others and are comparable with carbendazim. The more interesting result could be observed in the treatment of compound **1**, which could completely inhibit the growth of *Phytophthora nicotianae* and *Botrytis elliptica* isolates. Compounds **3b** and **3f** also completely inhibit the growth of *B. elliptica*. Although, all of the compounds have the inhibiting effect against *B. elliptical*, no *Rhizoctonia solani* have. The other results are briefly mentioned in Table 1. It may also be noticed that introduction of benzylidene group at C-5 decreased the fungicidal activity.

**Table 1**

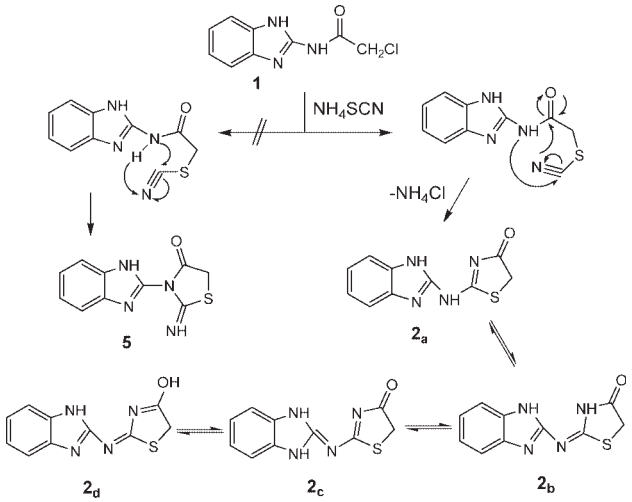
Antifungal activity studies by the agar growth medium poison technique.[a]

| Compound | *Phytophthora nicotianae* | *Botrytis elliptica* | *Rhizoctonia solani* | *Fusarium graminearum* |
|---|---|---|---|---|
| **1** | 100 | 100 | 0 | 40 |
| **2** | 58 | 50 | 0 | 0 |
| **3a** | 0 | 28 | 0 | 0 |
| **3b** | 0 | 100 | 0 | 0 |
| **3c** | 0 | 33 | 0 | 20 |
| **3d** | 15 | 50 | 0 | 0 |
| **3e** | 0 | 33 | 0 | 0 |
| **3f** | 5 | 100 | 0 | 30 |
| **3g** | 25 | 50 | 0 | 0 |
| **3h** | 0 | 33 | 0 | 0 |
| **3i** | 0 | 57 | 0 | 0 |
| **3j** | 0 | 57 | 0 | 6 |
| **3k** | 15 | 50 | 0 | 10 |
| **4** | 30 | 64 | 0 | 0 |
| **MBC**[b] | 0 | 100 | 100 | 100 |

[a] The results are reported as a percentage (%) inhibition of the fungi growth, and the concentration of the tested compounds was 50 ppm.
[b] Carbendazim as a reference.

In conclusion, we have described the synthesis of 2-benzimidazolylimino-5-arylidene-4-thiazolidinones, **3a–k** by the reaction of 2-benzimidazolylimino-4-thiazolidinone, **2** and corresponding aromatic aldehydes in a buffered medium with good to high yields. We also evaluated their antifungal activities against four agricultural fungi.

**Scheme 2**




## EXPERIMENTAL

All used chemicals were prepared from Merck or Fluka Company. Melting points were determined using an electro thermal digital apparatus and are uncorrected. IR spectra were performed on a Galaxy series FT IR 5000 spectrometer using KBr discs. NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referenced to the internal standards tetramethylsilane. Elemental analyses were performed on a Vario EL III elemental analyzer. Reactions were monitored by thin layer chromatography (TLC).

**Synthesis of N-(1H-benzimidazol-2-yl)-2-chloroactamide (1).** A solution of 2-amino benzimidazole (4.0 g, 0.03 mole) in dry acetone (40 mL) was cooled to 0–5°C. A solution of chloroacetyl chloride (4.78 mL, 0.06 mole) in dry acetone (15 mL) was slowly added to it with vigorous stirring. The reaction mixture was refluxed for 2 h, and the solvent was removed under reduced pressure. The residue was washed with sodium bicarbonate (5%) and subsequently with water. The crude product was air dried and crystallized from ethanol to give the colorless crystals **1**, 4.1 g (65%), mp 219–222°C; $R_f$ (ethyl

acetate/hexane 3:1) 0.65; IR (KBr): 3333 (NH), 3055 (CH), 2966 (CH$_2$), 1685 (C=O), 1633, 1583 (C=N), 1456 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 4.37 (s, 2H, CH$_2$), 7.09–7.13 (m, 2H, H-Ar), 7.43–7.46 (q, 2H, H-Ar), 12.08 (s, 2H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 43.9 (CH$_2$), 114.3, 121.9, 135.7, 147.4 (C=N), 167.7 (C=O). Anal. Calcd. for $C_9H_8ClN_3O$: C, 51.56; H, 3.85; N, 20.04. Found: C, 51.45; H, 3.82; N, 20.14.

**Synthesis of 2-(1H-benzimidazol-2-ylamino)-1,3-thiazol-4(5H)-one (2).** A solution of compound **1** (3.0 g, 0.01 mole) and ammonium thiocyanate (1.96 g, 0.02 mole) in 50 mL of ethanol (96%) was refluxed for 8 h and allowed to stand for 2 h. The precipitate was filtered, washed with aqueous ethanol, and recrystallized from dioxane/water to give light yellow crystals **2** to yield 2.7 g (81%), mp 284°C; $R_f$ (ethylacetate/hexane 3:1) 0.5; IR (KBr): 3138 (NH), 3065 (CH-Ar), 2926 (CH), 1697 (C=O), 1620, 1581 (C=N), 1352 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 3.96 (s, 2H, CH$_2$), 7.12–7.49 (m, 4H, H-Ar), 12.13 (br., 2H, NH); the NH protons disappeared on D$_2$O addition; $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 35.2 (CH$_2$), 112.7, 121.8, 142.6, 152.2 (C=N), 164.6 (C=N), 174.7 (C=O). Anal. Calcd. for $C_{10}H_8N_4OS$: C, 51.71; H, 3.47; N, 24.12; S, 13.81. Found: C, 51.58; H, 3.51; N, 24.22; S, 13.80.

**General procedure for the synthesis of compounds (3).** A well-stirred solution of compound **2** (0.2 g, 0.86 mmole) in 4–6 mL of acetic acid was buffered with sodium acetate (0.2 g, 2.58 mmole) and added the appropriate arylaldehyde (1.7 mmole). The solution was refluxed for desired time. The completion of the reaction was monitored by TLC (toluene/dioxane/acetic acid 18:2:1). The reaction mixture was then cooled to room temperature to produce the precipitate. The precipitate was filtered, abundantly washed with water, and then recrystallized from dioxane or dioxane/water to give the pure crystals (**3a**–**k**).

***2-(1H-Benzimidazol-2-ylamino)-5-benzylidene-1,3-thiazol-4(5H)-one (3a).*** This compound was obtained by refluxing for 7 h to yield 0.26 g (96%), mp 326–327°C; IR (KBr): 3138 (NH), 3067 (CH-Ar), 1697 (C=O), 1618, 1581 (C=N), 1454, 1352, 1253 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.14–7.71 (m, 10H, H-Ar and C=CH-Ph), 12.38 (s, 1H, NH), 12.75 (s, 1H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 121.8, 124.1, 129.1, 129.6, 129.9, 130.5, 133.8, 134.1, 150.3 (C=N), 179.3 (C=N), 181.2 (C=O). Anal. Calcd. for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49; S, 10.01. Found: C, 64.01; H, 3.81; N, 17.39; S, 10.00.

***2-(1H-Benzimidazol-2-ylamino)-5-(2-chlorobenzylidene)-1,3-thiazol-4(5H)-one (3b).*** This compound was obtained by refluxing for 6 h to yield 0.16 g (52%), mp 304°C; IR (KBr): 3151 (NH), 3063 (CH-Ar), 1695 (C=O), 1622, 1589 (C=N), 1471, 1352, 1255 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.15–7.68 (m, 8H, H-Ar), 7.87 (s, 1H, C=CH-Ar), 12.42 (s, 1H, NH), 12.92 (br., s, 1H, NH); $^{13}$C-NMR (DMSO-d$_6$ (CD$_3$)$_2$SO, 75 MHz): 112.9, 123.8, 124.2, 128.4, 129.0, 129.7, 130.6, 131.1, 131.9, 132.9, 134.6, 150.1 (C=N), 179.3 (C=N), 180.7 (C=O). Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.12; N, 15.79; S, 9.04. Found: C, 57.79; H, 3.16; N, 15.88; S, 9.13.

***2-(1H-Benzimidazol-2-ylamino)-5-(3-chlorobenzylidene)-1,3-thiazol-4(5H)-one (3c).*** This compound was obtained by refluxing for 4 h to yield 0.26 g (85%), mp 320–322°C; IR (KBr): 3138 (NH), 3063 (CH-Ar), 1695 (C=O), 1618, 1581 (C=N), 1469, 1350, 1251 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.15–7.63 (m, 9H, H-Ar and C=CH-Ar), 12.40–12.85 (br., s, 2H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 122.3, 124.1, 127.3, 127.9, 129.2, 129.7, 131.3, 132.8, 134.2, 137.2, 150.3 (C=N), 179.2 (C=N), 180.9 (C=O). Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.12; N, 15.79; S, 9.04. Found: C, 57.33; H, 3.17; N, 15.58; S, 9.14.

***2-(1H-Benzimidazol-2-ylamino)-5-(4-chlorobenzylidene)-1,3-thiazol-4(5H)-one (3d).*** This compound was obtained by refluxing for 8 h to yield 0.16 g (52%), mp 337°C; IR (KBr): 3421, 3308 (NH), 3053 (CH-Ar), 1676 (C=O), 1618, 1574 (C=N), 1473, 1350, 1259 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.15–7.69 (m, 9H, H-Ar. and C=CH-Ph), 12.39 (s, 1H, NH), 12.75 (br., s, 1H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 124.1, 127.6, 129.6, 129.7, 131.5, 132.1, 133.8, 134.1, 150.3 (C=N), 179.3 (C=N), 181.1 (C=O). Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.12; N, 15.79; S, 9.04. Found: C, 57.43; H, 3.07; N, 15.78; S, 9.09.

***2-(1H-Benzimidazol-2-ylamino)-5-(3-bromobenzylidene)-1,3-thiazol-4(5H)-one (3e).*** This compound was obtained by refluxing for 5 h to yield 0.26 g (75%), mp 306–307°C; IR (KBr): 3192 (NH), 3068 (CH-Ar), 1699 (C=O), 1622, 1585 (C=N), 1481, 1251 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.16–7.88 (m, 9H, H-Ar. and C=CH-Ar), 12.79 (br., s, 2H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.8, 122.8, 124.1, 127.2, 128.3, 129.7, 131.6, 132.1, 136.5, 137.4, 150.2, 153.1 (C=N), 179.2 (C=N), 180.8 (C=O). Anal. Calcd. for $C_{17}H_{11}BrN_4OS$: C, 51.14; H, 2.78; N, 14.03; S, 8.03. Found: C, 51.34; H, 2.76; N, 14.12; S, 7.99.

***2-(1H-Benzimidazol-2-ylamino)-5-(4-bromobenzylidene)-1,3-thiazol-4(5H)-one (3f).*** This compound was obtained by refluxing for 10 h to yield 0.28 g (85%), mp 325–327°C; IR (KBr): 3217, 3136 (NH), 3026 (CH-Ar), 1691 (C=O), 1633, 1609 (C=N), 1487, 1350, 1257 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.02–7.95 (m, 9H, H-Ar and C=CH-Ar), 12.40 (s, 1H, NH), 12.78 (br., s, 1H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 123.0, 124.1, 127.7, 129.7, 131.7, 132.3, 132.5, 134.2, 150.3 (C=N), 179.3 (C=N), 181.0 (C=O). Anal. Calcd. for $C_{17}H_{11}BrN_4OS$: C, 51.14; H, 2.78; N, 14.03; S, 8.03. Found: C, 50.91; H, 2.75; N, 14.02; S, 8.05.

***2-(1H-Benzimidazol-2-ylamino)-5-(3-nitrobenzylidene)-1,3-thiazol-4(5H)-one (3g).*** This compound was obtained by refluxing for 3 h to yield 0.28 g (90%), mp 333°C; IR (KBr): 3138 (NH), 3068 (CH-Ar), 1716 (C=O), 1655, 1620 (C=N), 1531, 1352 (NO2), 1464, 1265 (C=C) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.17–8.55 (m, 9H, H-Ar and C=CH-Ar), 12.43 (s, 1H, NH), 12.85 (br., s, 1H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 123.8, 124.2, 126.4, 129.7, 131.0, 134.0, 135.7, 136.7, 148.6, 150.1, 172.5 (C=N), 178.9 (C=N), 180.8 (C=O). Anal. Calcd. for $C_{17}H_{11}N_5O_3S$: C, 55.88; H, 3.03; N, 19.17; S, 8.78. Found: C, 55.80; H, 3.05; N, 19.19; S, 8.75.

***2-(1H-Benzimidazol-2-ylamino)-5-(4-nitrobenzylidene)-1,3-thiazol-4(5H)-one (3h).*** This compound was obtained by refluxing for 10 h to yield 0.30 g (96%), mp 353°C; IR (KBr): 3148 (NH), 3076 (CH-Ar), 1705 (C=O), 1631, 1599 (C=N), 1512, 1342 (NO$_2$) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.16–8.32 (m, 9H, H-Ar and C=CH-Ar), 12.42 (s, 1H, NH), 12.92 (s, 1H, NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 124.1, 124.5, 126.2, 129.6, 130.6, 135.6, 141.4, 146.9, 150.1

(C=N), 178.9 (C=N), 180.7 (C=O). Anal. Calcd. for $C_{17}H_{11}N_5O_3S$: C, 55.88; H, 3.03; N, 19.17; S, 8.78. Found: C, 56.07; H, 3.02; N, 19.20; S, 8.80.

***2-(1H-Benzimidazol-2-ylamino)-5-(4-methylbenzylidene)-1, 3-thiazol-4(5H)-one (3i).*** This compound was obtained by refluxing for 9 h to yield 0.15 g (52%), mp 331°C; IR (KBr): 3217, 3144 (NH), 3043 (CH-Ar), 2943 (Me), 1685 (C=O), 1620, 1533 (C=N), 1444, 1273 (C=C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 2.35 (s, 1H, $CH_3$), 7.15–7.67 (m, 9H, H-Ar and C=CH-Ar), 12.37 (s, 1H, NH), 12.70 (br., s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 21.5 ($CH_3$), 112.8, 118.5, 121.8, 124.1, 150.4, 129.8, 130.6, 131.8, 139.7, 157.4 (C=N), 179.5 (C=N), 181.2 (C=O). Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.93; H, 4.23; N, 16.78; S, 9.56.

***2-(1H-Benzimidazol-2-ylamino)-5-(3-methoxybenzylidene)-1,3-thiazol-4(5H)-one (3j).*** This compound was obtained by refluxing for 5 h to yield 0.24 g (80%), mp 271–272°C; IR (KBr): 3200, 3148 (NH), 3045 (CH-Ar), 2960 (Me), 1695 (C=O), 1640, 1620 (C=N), 1533, 1448, 1352 (C=C) $cm^{-1}$; 1273, 1228 (OMe); $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 3.81 (s, 3H, OMe), 6.98–7.68 (m, 9H, H-Ar and C=CH-Ar), 12.39 (s, 1H, NH), 12.74 (br., s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 55.6 (OMe), 112.8, 115.4, 116.2, 122.3, 124.1, 129.7, 129.0, 129.7, 130.8, 131.3, 150.3, 160.0 (C=N), 179.5 (C=N), 181.1 (C=O). Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99; S, 9.15. Found: C, 62.02; H, 4.00; N, 15.87; S, 9.10.

***4-{[2-(1H-Benzimidazol-2-ylamino)-4-oxo-1,3-thiazol-5(4H)-ylidene]methyl} benzaldehyde (3k).*** This compound was obtained by refluxing for 3 h to yield 0.27 g (90%). mp 339–341°C; IR (KBr): 3452, 3221 (NH), 3065 (CH-Ar), 2785, 2885 (CH, aldehyde), 1691 (C=O), 1622, 1589 (C=N), 1481, 1350, 1261 (C=C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 7.17–8.02 (m, 9H, H-Ar and C=CH-Ar), 10.03 (s, 1H, CHO), 12.85–12.94 (br., s, 2H, NH); MS (*m/z*, %): 348 ($M^+$, 100), 159 (92), 133 (15), 105 (12), 89 (24). Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08; S, 9.20. Found: C, 62.37; H, 3.45; N, 16.17; S, 9.17.

**Synthesis of 1H-imidazo[1,2-a]benzimidazol-2(3H)-one (4).** To a well-stirred solution of compound **1** (0.4 g, 2 mmole) in dry acetone (30 mL), $K_2CO_3$ (0.32 g, 2 mmole) was added. The reaction mixture was refluxed for 4 h. The result solid was filtered, and water (5 mL) was added to the filtration to give compound **4,** which then filtered and washed with water and air dried to yield 0.16 g (50 %); mp 216–219°C; IR (KBr): 3358 (NH), 3051 (CH-Ar), 2991, 2930 ($CH_2$), 1666 (C=O), 1585, 1527 (C=N), 1448, 1336 (C=C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 4.90 (s, 2H, $CH_2$), 7.10–7.42 (m, 4H, H-Ar), 12.51 (br. s, 1H, NH); The NH proton disappeared on $D_2O$ addition; $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 47.6 ($CH_2$), 110.6, 112.3, 121.8, 123.1, 129.4, 130.4, 147.6, 175.2 (C=O). Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.22; H, 4.08; N, 24.32.

**Antifungal assays.** Fungicidal activity of compounds (**1**, **2**, **3a–k**, and **4**) were tested against four phytopathogenic fungal isolates, including *B. elliptica*, *Fusarium graminearum*, *P. nicotianae*, and *R. solani,* provided by Department of Plant diseases of Iranian Plant Protection Research Institute *in vitro*. Two negative controls: one with DMSO, the solvent of all tested compounds (no antifungal activity has been noted) and the other as untreated potato dextrose agar petri dishes used using the agar growth medium poison technique [8]. The medium was potato dextrose agar, and the concentration of the tested compounds was 50 ppm. After 5 days incubation at 25°C, the growth diameter of treatments was measured, and the percentage inhibition of growth for each compound was determined based on the negative control growth of each fungal species under the same incubation conditions. Carbendazim as a reference was included to compare with compounds (**1**, **2**, **3a–k**, and **4**). All tests were performed in triplicate and the average results, as a percentage (%) inhibition of growth, are shown in Table 1.

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## REFERENCES AND NOTES

[1] Gaikwad, N. J.; Tirpude, R. N. Indian Drugs 1994, 31, 593.

[2] Diurno, M. V.; Mazzoni, O.; Piscopo, E.; Calignano, A.; Giordano, F.; Bolognese, A. J Med Chem 1992, 35, 2910.

[3] Kouznetsov, V.; Rodríguez, W.; Stashenko, E.; Ochoa, C.; Vega, C.; Rolón, M.; Pereira, D. M.; Escario, J. A.; Barrio, A. G. J Heterocycl Chem 2004, 41, 995.

[4] Ramla, M. M.; Omar, A. M.; Tokudo, H.; El-Diwoni, I. H. Bioorg Med Chem 2007, 15, 6489.

[5] Vicini, P.; Geronikaki, A.; Incerti, M.; Zani, F.; Dearden, J.; Hewitt, M. Bioorg Med Chem 2008, 16, 3714.

[6] Lakhan, R.; Singh, O. P. J Ind Chem Soc 1984, 61, 784.

[7] Bhargava, P. N.; Prakash, S.; Lakhan, R. Ind J Chem 1981, 20B, 927.

[8] Lokhan, R. Agric Biol Chem 1982, 46, 557.

[9] Hui-ling, L.; Zongcheng, L.; Thorleif, A. Molecules 2000, 5, 1055.

[10] Barreca, M. L.; Balzarini, J.; chimirri, A.; De-clercq, E.; De-luca, L.; Holtje, H. D.; Holtje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappala, M. J Med Chem 2002, 45, 5410.

[11] Rao, A.; Balzarini, J.; Carbone, A.; chimirri, A.; De-clercq, E.; Monforte, A. M.; Monforte, P.; Ponnecouque, C.; Zappala, M. Il Farmaco 2004, 59, 33.

[12] (a) Desai, G. K.; Desai, R. K. J Saudi Chem Soc 2006, 9, 631; (b) Desai, G. K.; Desai, R. K. J Sulfur Chem 2006, 27, 315; (c) Desai, G. K.; Desai, R. K. Bioorg Med Chem 2006, 14, 8271.

[13] Andrzejewska, M.; Mulia, L. Y.; Rivera, R. C.; Tapia, A.; Vilpo, L.; Kazimierezuk, Z. Eur J Med Chem 2002, 37, 973.

[14] Ottana, R.; Carotti, S.; Maccari, R.; Landini, I.; Chiricosta, G.; Cacigli, B.; Vigorita, G. M.; Mini, E. Bioorg Med Chem Lett 2005, 15, 3930.

[15] Tonelli, M.; Paglietti, G.; Boido, V.; Marongiu, F.; Marongiu, E.; Colla, P. L.; Loddo, R. Chem Biodiv 2008, 5, 2386.

[16] Vazzana, I.; Terranova, E.; Tasso, B.; Tonelli, M.; Piana, A.; Gastaldi, S.; Sparatore, F. Chem Biodiv 2008, 5, 714.

[17] Clemons, G. P.; Sisler, H. D. Pestic Biochem Physiol 1971, 1, 32.

[18] Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. Bioorg Med Chem 2006, 14, 3859.

[19] Ottana, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Paola, R. D.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. Bioorg Med Chem 2005, 13, 4243.

[20] Bacchi, A.; Careelli, M.; Pelizzi, G.; Vicini, P. Arch Pharm 1995, 328, 217.

# Piperidine Mediated Synthesis of *N*-Heterocyclic Chalcones and Their Antibacterial Activity



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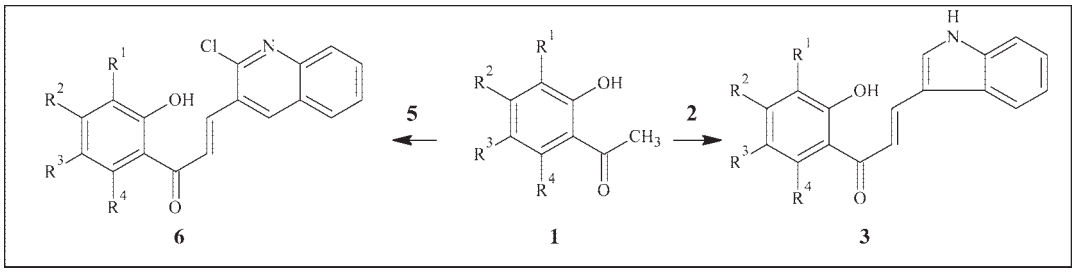


The chalcones 1-(2′-hydroxy-aryl)-3-(1-indol-3-yl)-prop-2-en-1-one **(3)** and 1-(2′-hydroxy-aryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one **(6)** were synthesised by piperidine mediated condensation of an ethanolic solution of an *o*-hydroxyacetophenone **(1)** with corresponding heteroaryl-3-carboxaldehyde. The structures have been established on the basis of elemental (C, H, N) analysis, UV, IR, $^1$H NMR spectral data. The compounds **3** and **6** were screened for antimicrobial activities against a variety of bacterial agents.

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## INTRODUCTION

Chalcones are well known naturally occurring pigments which serve as valuable intermediate in organic synthesis of flavonoid compounds [1]. It has found significant role in pharmaceutical effects [2] including antioncogenic, antiinflammatory, antiulcerative, analgesic, antiviral, antimalarial and antibacterial activities. Chloroquinoline [3] and indole [4] compounds are known to exhibit variety of antimicrobial activity. Also, it has been reported that chalcone having quinoline moiety is an intermediate for the synthesis of chloroquinoline cyanopyridines and cyanopyrans derivatives [5].

In the Claisen-Schemidt condensation of Chalcone synthesis, 2′-hydroxy functional group may cyclise to the corresponding flavanones under higher concentration of alkali. Also, side reactions such as multiple condensations, polymerizations, and rearrangements are common. These undesirable side reaction decreases the yields of the target adduct and render their purification difficult [6]. So, it was planned to use a weaker base like piperidine instead of using strong base to enhance the better yields.

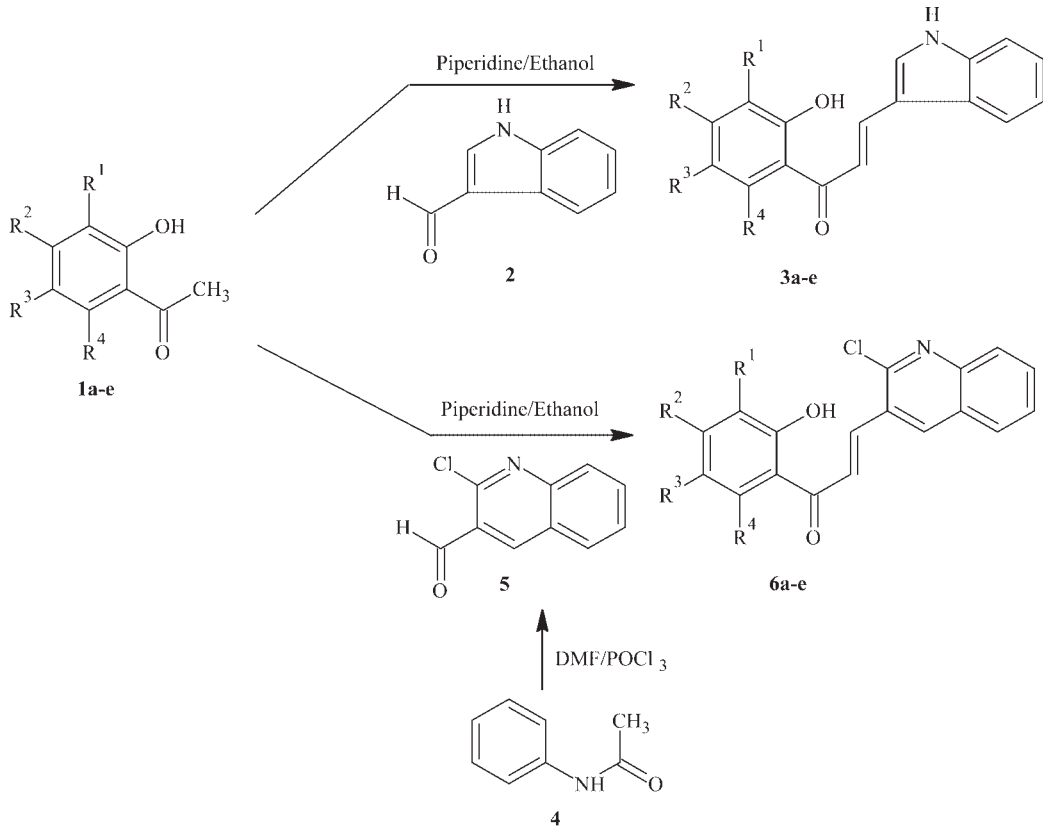
In present communication, we report piperidine mediated synthesis of N-heterocyclic chalcones **3** and **6** from indole-3-carboxaldehyde and 2-chloroquinoline-3-carboxaldehyde respectively. The structures of the compound **3** and **6** have been established on the basis of elemental (C, H, N) analysis, UV, IR, $^1$H NMR spectral data and they were screened for antibacterial activities.

## RESULTS AND DISCUSSION

The syntheses of 1-(2′-hydroxy-aryl)-3-(1-indol-3-yl)-prop-2-en-1-one **(3)** and 1-(2′-hydroxyaryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one **(6)** was carried out by condensation of an ethanolic solution of an *o*-hydroxyacetophenone **(1)** in the presence of piperidine with indole-3-carboxaldehyde **(2)** and with 2-chloroquinolin-3-carboxaldehyde **(5)** as shown in Scheme 1.

The compounds **3** and **6** gave violet colouration with alcoholic $FeCl_3$ test indicating the presence of chelated hydroxyl group in it. Also, gave positive test for presence of elements such as N and Cl in corresponding chalcone by sodium fusion extraction test. When using $AlCl_3$-HCl as shift reagents, bathochromic shift about 40 nm at band-I was observed in UV spectral studies of products **3** and **6** due to presence of chelated hydroxyl group. IR spectra of compounds **3** revealed the presence of —NH absorption bands in the region of 3228–3098 cm$^{-1}$, in addition to two characteristic signals about 1630 cm$^{-1}$ for the unsaturated keto group and 3043–3444 cm$^{-1}$ for hydroxyl groups. Similarly, IR spectrum of compounds **6** showed absorption at 3436–3431 cm$^{-1}$, 1654–1621 cm$^{-1}$, 1446–1432 cm$^{-1}$ and 744–756 cm$^{-1}$ for presence of —OH, —C=O, —C=N—, —Cl groups, respectively. The $^1$H NMR spectra gave two doublet centred about δ 7.6 and δ 8.2 with coupling constant about $J = 15$ Hz were assigned to the trans olefinic proton at $C_\alpha$ and $C_\beta$ position. The entire $^1$H NMR spectral data were given in the experimental part and the values were in accordance with the title compounds **3** and **6**.

**Scheme 1**




**Antibacterial activities.** The antibacterial activity of the compounds **3** and **6** have been evaluated using filter paper disc diffusion method [7] at a concentration of 100 μg/disc against human pathogenic bacteria such as *Staphylococcus aureus* ($G^+$), *Shigella dysenteriae* ($G^-$) and *Salmonella typhi* ($G^-$). Kanamycin (30 μg/disc) was used as standard for comparing the activity. Each sample was used in triplicates for the determination of antibacterial activity. The diameter of observed inhibition zone of **3** and **6** were measured (in mm) and they are given in Table 1.

By visualizing the antibacterial data, it could be observed that most of the compound shows significant activity. The compound **3e**, **6a**, **6e** showed excellent activity for all the three test microorganisms. However, compounds **3d, 6c** are inactive against *S. aureus* and compounds **3d, 6b** are inactive for *S. dysenteriae*. Similarly compounds **3b, 6d** are inactive against *S. typhi*. The preliminary result confirms the importance of chloroquinone nucleus and indole nucleus with respect to antibacterial activity.

## EXPERIMENTAL

Melting point determinations were made in open capillaries and were uncorrected. TLC was carried out using Merck brand Silica Gel-G and spotting was done using iodine or UV light. UV spectra were taken in Perkin-Elmer 402 UV-Vis spectrophotometer. IR spectra were recorded in Perkin-Elmer 577 IR spectrophotometer. $^1$H NMR spectra were conducted on Bruker (300 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The chemical shifts are reported in ppm scale. The compound **(2)** was obtained from SISCO research laboratories and used as such. The compound **(5)** was prepared adopting the published procedure with the same melting point at 150°C [8].

**General procedure for synthesis of 1-(2′-hydroxy-aryl)-3-(1-indol-3-yl)-prop-2-en-1-one (3).** To a mixture of *o*-hydroxyacetophenone (0.01 mol) and indole-3-carboxaldehyde (0.01 mol) in ethanol (50 mL), piperidine (1 mL) was added and refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcone **3**.

***Synthesis of 1-(2′-hydroxy-4′-methoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3a).*** Yellow solid (0.75 g, 25.6%); mp. 196°C; $\lambda_{max}$ ($CHCl_3$, nm): 274, 396; ir (KBr, $cm^{-1}$): 3374($\nu_{OH}$), 3225($\nu_{>NH}$), 1625($\nu_{C=O}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 13.90 (s, 1H, 2′-OH), 6.54 (d, 1H, 3′-H), 3.87 (s, 3H, 4′-$OCH_3$), 6.44 (d, 1H, 5′-H), 7.96 (d, 1H, 6′-H), 7.81 (d, 1H, $C_\alpha$H, $J$ = 15.3 Hz), 8.18 (d, 1H, $C_\beta$H, $J$ = 15.3 Hz), 8.61 (s, 1H, > NH), 7.66 (d, 1H, 2-H), 8.04 (d, 1H, 4-H), 7.33 (m, 2H, 5- and 6-H), 7.46 (m, 1H, 7-H); *Anal*. Calcd for

**Table 1**

Antibacterial activity of compound **3** and **6**.

| R | Compound | Diameter of zone inhibition (mm) | | |
|---|---|---|---|---|
| | | *S. aureus* | *S. dysenteriae* | *S. typhi* |
| | **3a** | 18 ± 0.7 | 19 ± 1.1 | 21 ± 0.6 |
| | **3b** | 12 ± 0.9 | 18 ± 0.8 | – |
| | **3c** | 10 ± 0.7 | 16 ± 0.9 | 15 ± 0.7 |
| **a:** $R^2 = OCH_3$; $R^1$, $R^3$, $R^4 = H$ | **3d** | – | – | 12 ± 1.1 |
| **b:** $R^3 = OCH_3$; $R^1$, $R^2$, $R^4 = H$ | **3e** | 28 ± 1.2 | 27 ± 1.1 | 24 ± 2.1 |
| **c:** $R^1$, $R^2 = OCH_3$; $R^3$, $R^4 = H$ | **6a** | 26 ± 2.3 | 26 ± 1.2 | 22 ± 0.5 |
| **d:** $R^1$, $R^2$, $R^4 = OCH_3$; $R^3 = H$ | **6b** | 23 ± 1.8 | – | 14 ± 0.7 |
| **e:** $R^2$, $R^4 = OCH_3$; $R^1$, $R^3 = H$ | **6c** | – | 13 ± 0.5 | 11 ± 0.7 |
| | **6d** | 20 ± 1.3 | 22 ± 0.9 | – |
| | **6e** | 22 ± 0.9 | 24 ± 0.5 | 22 ± 0.8 |
| | Kanamycin | 29 ± 2.1 | 31 ± 1.8 | 28 ± 1.6 |

$C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.52; H, 5.14; N, 4.71.

***Synthesis of 1-(2′-hydroxy-5′-methoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3b).*** Yellow solid (0.9 g, 30.7%); mp. 120°C; $\lambda_{max}$ ($CHCl_3$, nm): 258, 344; ir (KBr, $cm^{-1}$): 3444($\nu_{OH}$), 3166($\nu_{>NH}$), 1633($\nu_{C=O}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 12.80 (s, 1H, 2′-OH), 6.97 (d, 1H, 3′-H), 7.11 (d, 1H, 4′-H), 3.87 (s, 3H, 5′-$OCH_3$), 7.97 (s, 1H, 6′-H), 7.85 (d, 1H, $C_\alpha$H, $J$ = 15.3 Hz), 8.22 (d, 1H, $C_\beta$H, $J$ = 15.3 Hz), 8.61 (s, 1H, > NH), 7.54 (d, 1H, 2-H), 8.04 (d, 1H, 4-H), 7.34 (m, 2H, 5- and 6-H), 7.46 (m, 1H, 7-H); *Anal*. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.73; H, 5.16; N, 4.72.

***Synthesis of 1-(2′-hydroxy-3′,4′-dimethoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3c).*** Yellow solid (1.32 g, 40.8%); mp. 124°C; $\lambda_{max}$ ($CHCl_3$, nm): 268, 345; ir (KBr, $cm^{-1}$): 3438($\nu_{OH}$), 3228($\nu_{>NH}$), 1627($\nu_{C=O}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 13.6 (s, 1H, 2′-OH), 3.94 (s, 3H, 3′-$OCH_3$), 3.96 (s, 3H, 4′-$OCH_3$), 6.57 (d, 1H, 5′-H), 7.98 (d, H, 6′-H), 7.82 (d, 1H, $C_\alpha$H, $J$ = 15.3 Hz), 8.15 (d, 1H, $C_\beta$H, $J$ = 15.3 Hz), 8.70 (s, 1H, > NH), 7.61 (s, 1H, 2-H), 8.04 (d, 1H, 4-H), 8.34 (m, 2H, 5- and 6-H), 7.49 (d, 1H, 7 H); Anal. Calcd for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.36; H, 5.28; N, 4.35.

***Synthesis of 1-(2-hydroxy-3′,4′,6′-trimethoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3d).*** Yellow solid (0.84 g, 23.8%); mp. 202°C; $\lambda_{max}$ ($CHCl_3$, nm): 296, 402; ir (KBr, $cm^{-1}$): 3143($\nu_{OH}$), 3098($\nu_{>NH}$), 1637($\nu_{C=O}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 12.2 (s, 1H, 2′-OH), 3.8 (s, 9H, 3′-, 4′- and 6′-$OCH_3$), 7.19 (s, 1H, 5′-H), 7.89 (d, 1H, $C_\alpha$H, $J$ = 15.3 Hz), 8.19 (d, 1H, $C_\beta$H, $J$ = 15.3 Hz), 9.9 (s, 1H, > NH), 7.61 (s, 1H, 2-H), 7.99 (s, 1H, 4-H), 7.29 (m, 2H, 5- and 6-H), 7.47 (d, 1H, 7-H); *Anal*. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.91; H, 5.41; N, 3.89.

***Synthesis of 1-(2-hydroxy-4′,6′-dimethoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3e).*** Yellow solid (1.46 g, 45.2%); mp. 198°C; $\lambda_{max}$ ($CHCl_3$, nm): 281, 396; ir (KBr, $cm^{-1}$): 3410($\nu_{OH}$), 3230($\nu_{>NH}$), 1610($\nu_{C=O}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 14.05 (s, 1H, 2′-OH), 6.01 (d, 1H, 3′-H), 3.82 (s, 3H, 4′-$OCH_3$), 6.13 (s, 1H, 5′-H), 3.88 (s, 3H, 6′-$OCH_3$), 7.74 (d, 1H, $C_\alpha$H, $J$ = 15.3 Hz), 8.15 (d, 1H, $C_\beta$H, $J$ = 15.3 Hz), 8.99 (s, 1H, > NH), 7.48 (d, 1H, 2-H), 8.12 (m, 1H, 4-H), 7.33 (m, 2H, 5- and 6-H), 7.40 (d, 1H, 7-H); Anal. Calcd for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.41; H, 5.29; N, 4.29.

**General procedure for synthesis of 1-(2′-hydroxy-aryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6).** To a mixture of *o*-hydroxyacetophenone (0.01 mol) and 2-chloroquinoline-3-carboxaldehyde (0.01 mol) in ethanol (50 mL), piperidine (1 mL) was added and refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcone **6**.

***Synthesis of 1-(2′-hydroxy-4′-methoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6a).*** Yellow solid (1.32 g, 38.9%); mp. 226°C; $\lambda_{max}$ ($CHCl_3$, nm): 269, 361; ir (KBr, $cm^{-1}$): 3432($\nu_{OH}$), 1633($\nu_{C=O}$), 1432($\nu_{-C=N-}$), 748($\nu_{Cl}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 13.10 (s, 1H, 2′-OH), 6.48 (s, 1H, 3′-H), 3.75 (s, 3H, 4′-$OCH_3$), 6.42 (d, 1H, 5′-H), 7.92 (d, 1H, 6′-H), 7.56 (d, 1H, CαH, $J$ = 15.2 Hz), 7.83 (d, 1H, $C_\beta$H, $J$ = 15.2 Hz), 8.06 (s, 1H, 4-H), 7.72 (d, 1H, 5-H), 7.48 (m, 2H, 6- and 7-H), 7.61 (m, 1H, 8-H); Anal. Calcd for $C_{19}H_{14}ClNO_3$ (339.77): C, 67.16; H, 4.15; N, 4.12. Found: C, 67.27; H, 4.12; N, 4.17.

***Synthesis of 1-(2′-hydroxy-5′-methoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6b).*** Yellow solid (0.83 g, 24.5%); mp. 216°C; $\lambda_{max}$ ($CHCl_3$, nm): 258, 331; ir (KBr, $cm^{-1}$): 3434($\nu_{OH}$), 1654($\nu_{C=O}$), 1434($\nu_{-C=N-}$), 750($\nu_{Cl}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 12.80 (s, 1H, 2′-OH), 6.97 (d, 1H, 3′-H), 7.18 (d, 1H, 4′-H), 3.76 (s, 3H, 5′-$OCH_3$), 7.98 (s, 1H, 6′-H), 7.66 (d, 1H, $C_\alpha$H, $J$ = 15.1 Hz), 8.11 (d, 1H, $C_\beta$H, $J$ = 15.1 Hz), 8.06 (s, 1H, 4-H), 7.74 (d, 1H, 5-H), 7.58 (m, 2H, 6- and 7-H), 7.90 (m, 1H, 8-H); Anal. Calcd for $C_{19}H_{14}ClNO_3$ (339.77): C, 67.16; H, 4.15; N, 4.12. Found: C, 66.99; H, 4.16; N, 4.11.

***Synthesis of 1-(2′-hydroxy-3′,4′-dimethoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6c).*** Yellow solid (1.48 g, 40%); mp. 216°C; $\lambda_{max}$ ($CHCl_3$, nm): 267, 349; ir (KBr, $cm^{-1}$): 3434($\nu_{OH}$), 1654($\nu_{C=O}$), 1446($\nu_{-C=N-}$), 750($\nu_{Cl}$); $^1$H NMR (300 MHz, $CDCl_3$): δ 13.6 (s, 1H, 2′-OH), 3.86 (s, 3H, 3′-$OCH_3$), 3.82 (s, 3H, 4′-$OCH_3$), 6.61 (d, 1H, 5′-H), 7.52 (d, 1H, 6′-H), 7.88 (d, 1H, $C_\alpha$H, $J$ = 15.2 Hz), 8.18 (d, 1H, $C_\beta$H, $J$ = 15.2 Hz), 8.10 (s, 1H, 4-H), 7.68 (d, 1H, 5-H), 7.62 (m, 2H, 6- and 7-H), 7.94 (d, 1H, 8-H); Anal. Calcd for

$C_{20}H_{16}ClNO_4$ (369.79): C, 64.96; H, 4.36; N, 3.79. Found: C, 64.79; H, 4.35; N, 3.75.

***Synthesis of 1-(2-hydroxy-3′,4′,6′-trimethoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6d).*** Yellow solid (0.86 g, 21.5%); mp. 216°C; $\lambda_{max}$ ($CHCl_3$, nm): 265, 383; ir (KBr, $cm^{-1}$): 3432($\nu_{OH}$), 1633($\nu_{C=O}$), 1432($\nu_{-C=N-}$), 746($\nu_{Cl}$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 12.2 (s, 1H, 2′-OH), 3.86 (s, 9H, 3′-, 4′- and 6′-$OCH_3$), 7.12 (s, 1H, 5′-H), 7.69 (d, 1H, $C_\alpha H$, $J$ = 15.3 Hz), 8.18 (d, 1H, $C_\beta H$, $J$ = 15.3 Hz), 8.09 (s, 1H, 4-H), 7.32 (d, 1H, 5-H), 7.44 (m, 2H, 6- and 7-H), 7.92 (d, 1H, 8-H); *Anal*. Calcd for $C_{21}H_{18}ClNO_5$ (399.82): C, 63.08; H, 4.54; N, 3.50. Found: C, 62.88; H, 4.56; N, 3.51.

***Synthesis of 1-(2-hydroxy-4′,6′-dimethoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6e).*** Yellow solid (1.36 g, 36.8%); mp. 216°C; $\lambda_{max}$ ($CHCl_3$, nm): 270, 345; ir (KBr, $cm^{-1}$): 3431($\nu_{OH}$), 1621($\nu_{C=O}$), 1436($\nu_{-C=N-}$), 756($\nu_{Cl}$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 14.05 (s, 1H, 2′-OH), 6.54 (s, 1H, 3′-H), 3.76 (s, 3H, 4′-$OCH_3$), 6.18 (d, 1H, 5′-H), 3.82 (s, 3H, 6′-$OCH_3$), 7.72 (d, 1H, $C_\alpha H$, $J$ = 15.2 Hz), 8.21 (d, 1H, $C_\beta H$, $J$ = 15.2 Hz), 8.09 (s, 1H, 4-H), 7.58 (d, 1H, 5-H), 7.42 (m, 2H, 6- and 7-H), 7.86 (m, 1H, 8-H); Anal. Calcd for $C_{20}H_{16}ClNO_4$ (369.79): C, 64.96; H, 4.36; N, 3.79. Found: C, 64.76; H, 4.34; N, 3.75.

**Antibacterial activities.** The antibacterial activity of the compounds **3** and **6** have been evaluated using filter paper disc diffusion method [7] at a concentration of 100 μg/disc against human pathogenic bacteria such as *Staphylococcus aureus* ($G^+$), *Shigella dysenteriae* ($G^-$), and *Salmonella typhi* ($G^-$). Kanamycin (30 μg/disc) was used as standard for comparing the activity. Each sample was prepared with dimethyl sulfoxide (DMSO) to the concentration of 100 μg/mL. Dried and sterilized filter paper discs (6 mm in diameter) were impregnated with test solution using micropipette and the residual solvents were completely evaporated. Discs containing the test materials were placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard disc of kanamycin (30 μg/disc) and blank discs were used as positive and negative control, respectively. These plates were then kept at low temperature (4°C) for 24 h to allow maximum diffusion of test materials and kanamycin. The plates were then incubated at 37°C for 18 h to allow maximum growth of the organisms. Then, the antimicrobial activity of the test agents was determined by measuring the diameter of zone of inhibition expressed in mm. The experiment was carried out in triplicate.

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## REFERENCES AND NOTES

[1] Dhar, D. N. The Chemistry of Chalcone and Related Compounds; Wiley: New York, 1981; pp 33–146.

[2] (a) Aichaoui, H.; Guenadil, F.; Kapanda, C. N.; Lambert, D. M.; McCurdy, C. R.; Poupaert, J. H. Med Chem Res 2009, 18, 467; (b) Yarishkin, O. V.; Ryu, H. W.; Park, J.; Yang, M. S.; Hong, S.; Park, K. H. Bioorg Med Chem Lett 2008, 18, 137.

[3] (a) Vlahov, R.; Parushev, St.; Vlahov, J.; Nickel, P.; Snatzke, G. Pure Appl Chem 1990, 62, 1303; (b) Rajkumar, U. P.; Rajkumar, V. H.; Prakash, V. M.; Murlidhar, S. S. ARKIVOC 2006, 6, 196; (c) Amit, N.; Rahul, J. Indian J Chem 2008, 47B, 117; (d) Nandakumar, R.; Suresh, T.; Mohan, P. S. Acta Pharm 2003, 53, 1.

[4] (a) Olgena, S.; Altanlarb, N.; Karatayli, E.; Bozdayi, M. Z Naturforsch 2008, 63c, 189; (b) Heda, L. C.; Sharma, R.; Pareek, C.; Chaudhari, P. B. Eur J Chem 2009, 6, 770; (c) Husain, K.; Abid, M.; Azam, A. Eur J Med Chem 2007, 42, 1300.

[5] Patel, J. R.; Dobaria, A. V.; Kansagra, B. P.; Parikh, A. R. Indian J Heterocycl Chem 2003, 12, 237.

[6] (a) Devitt, P. F.; Timoney, A.; Vickars, M. A. J Org Chem 1961, 26, 4941; (b) Trivedi, J. C.; Bariwal, J. B.; Upadhyay, K. D.; Naliapara, Y. T.; Joshi, S. K.; Pannecouque, C. C.; De Clercq, E.; Shah, A. K. Tetrahedron Lett 2007, 48, 8472.

[7] (a) Rollas, S.; Kalyoncuoglu, N.; Sür-Altiner, D.; Yegenoglu, Y. Pharmazie 1993, 48, 308; (b) Ramazanzadeh, R.; Nasiri, F. J Appl Sci 2009, 9, 2198.

[8] (a) Pavia, M. R.; Taylor, C. P.; Hershenson, F. M.; Lobbestael, S. J. J Med Chem 1987, 30, 1210; (b) Meth-Cohn, O.; Narine, B.; Tarnowski, B. J Chem Soc Perkin Trans I 1981, 1520.

# Regioselective Synthesis of Pyrimido[5,4-c][2,1]benzothiazines by Reactions of β-Chloroaldehydes with N-C-N Binucleophiles



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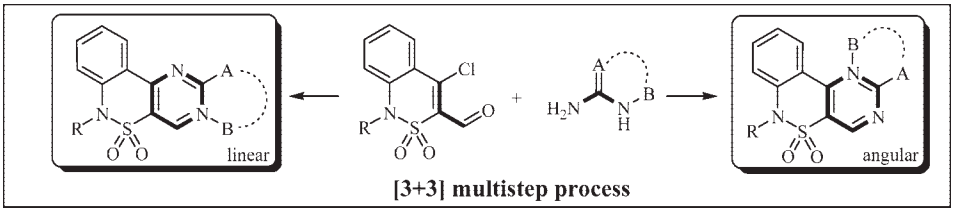


The method of pyrimidine ring fusion at the [*c*] side of benzothiazines based on the reaction of their chloroaldehyde derivatives with amidines is described. Formation of the structural isomers of reaction products was investigated, and regioselectivity of heterocyclization reactions was shown. A number of novel pyrimidobenzothiazines were synthesized.

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## INTRODUCTION

Among benzothiazine derivatives, there are a number of compounds known to show biological activity [1]. In particular, heterocyclic ring fusion on a side [*c*] of benzothiazine leads to the condensed systems some representatives of which are known as drugs. Thus, 5-methyl-3-(2-pyridyl)-2H,5H-1,3-oxazino[5,6c][1,2]benzo thiazin-2, 4-(3H)-dione-6,6-dioxide **1** [2] is a well-known anti-inflammatory agent (trade name ''Droxicam''), and (4-methoxy-3,5-dimethyl-phenyl)-(9-methyl-9H-10-thia-2,4,9-triaza-phenantren-3-yl)-amine **2** is a protein tyrosine kinase inhibitor [3] (Fig. 1). However, condensed benzothiazines currently used in medicine have a number of adverse effects [4].

## RESULTS AND DISCUSSION

In our previous paper [5], we have reported the synthesis of some novel benzo[*e*][2,1]thiazine derivatives—chloroaldehydes **3a–e** (Fig. 2), and their chemistry was shown to be quite diverse. Compounds **3** contain labile chlorine atom at C-4 and carbonyl group at C-3 position of the ring. We assumed that the studies of chloroaldehyde fragment reactivity could provide a way to obtain new condensed benzothiazines devoid of side effects or less toxic.

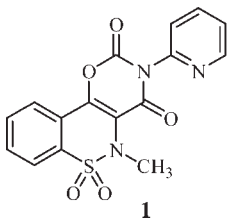
In this article, we describe the method of pyrimidine ring fusion at the [*c*] side of benzothiazines. The route developed by our group involves the interaction of chloroaldehydes **3a–e** with bis-nucleophilic agents **4a–i** containing N-C-N fragment (Table 1). When amidines **4a–c** are used as nucleophiles, the formation of pyrimidobenzothiazines as only products is expected. In case of asymmetric bis-nucleophiles **4d–i**, structural isomers of the reaction product can be formed. Depending on which electrophilic center is attacked by nucleophile at the first stage of heterocyclization process, linear- or angular-type fused compound is obtained.

Pyrazoles **4d–f** and benzoimidazole **4h** both contain two N-nucleophilic centers, thus in reactions with chloroaldehydes **3** two different isomeric pyrazolobenzothiazine products are possible (Scheme 1). Triazole **4g** and quinazalone **4i** contain three N-nucleophilic centers each, which causes four possible isomeric products in reaction with **3** (Scheme 2). One of current research goals was to establish exactly which isomer is formed in every case.

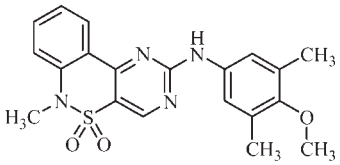
The interaction of chloroaldehydes **3a,b** with amidines **4a–c** (Scheme 3) led to pyrimidobenzothiazines **5a–f**. Reactions proceeded under mild conditions, and no first-stage intermediates were observed in the reaction mixtures.

The next step of this work was to investigate the reactions of compounds **3** with aminopyrazoles **4d–f**. The heating of **3** with **4d–f** resulted in crystalline products **6** (Scheme 4). We have expected the formation of angular products, and $^1$H NMR spectra of compounds **6a–l** did not contradict angular structures, as H-1 phenylene proton doublet was observed to undergo low-field shift. However, X-ray analysis proved the structure of compounds **6a–l** to be linear (Fig. 3). It seems that the signal of phenylene proton in compound **6** can shift to 8.5 ppm due to the effect of nitrogen atom of pyrimidine ring.

We have not found in the literature any example of the reaction of β-halogenvinylcarbonyl compounds with

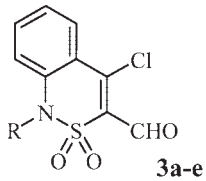


1



2

**Figure 1.** Examples of biologically active condensed benzothiazines.



**3a-e**

| Label | R |
|---|---|
| **3a** | -$CH_3$ |
| **3b** | -$C_2H_5$ |
| **3c** | -*n*-$C_3H_7$ |
| **3d** | -*n*-$C_4H_9$ |
| **3e** | -$CH_2Ph$ |

**Figure 2.** 4-Chloro-benzo[c][1,2]thiazine-3-carbaldehydes **3a–e**.

amidine nucleophiles proceeding *via* nucleophilic substitution of halogen atom at the first stage of the reaction followed by nucleophilic addition to carbonyl group resulting in the products of linear type. All reactions of analogous nature described until now proceed by Schiff base formation at first stage, then displacement of chlorine. What we observe is opposite to that route. Aldehyde group in compounds **3** is more sterically available than C-4 carbon atom; therefore, its reactions have to proceed under kinetic control, whereas the substitution of chlorine is rather thermodynamically controlled process. We assume the nucleophilic substitution of chlorine atom to be the ''push–pull'' process, with addition of exocyclic amino function of **4d–f** to C-4 carbon followed by halogen cleavage with C3–C4 double bond restoration.

The interaction of **3b,c** with 2-aminobenzoimidazole **4h** proceeds in a similar way (Scheme 5). Upon mild heating (30–35°C) of the reaction solution in DMF, the mixture of the Schiff base **8a,b** and the heterocyclization product **9a,b** is formed in the equimolar ratio ($^1$H NMR data). Subsequent temperature increase (50–70°C) acts in favor of the cyclic derivative **9a,b** (1:2 ratio). Heating the mixture to 100°C results in the formation of **9a,b** only. The interaction between the protons with chemical shifts 7.51 and 8.45 ppm (Scheme 5) observed during 1D-NOESY experiment proved angular structure of products **9**. Analysis of 3D molecular models led to the conclusion that compounds **9** most probably adopt helical-type structure.

When 3-aminotriazole **4g** was used as a nucleophile, the reaction with **3a–c** proceeded in more common manner: the initial condensation of exocyclic amino function with carbonyl group is followed by the displacement of chlorine atom (Scheme 6). Depending on which nitrogen atom (N-2 or N-4) attacks the C-4 position at the second stage of the heterocyclization, formation of structural isomers of the reaction products **7** can occur. 1D-NOESY experiment revealed strong interaction between the protons with chemical shifts 8.82 and 9.58 ppm (Scheme 6) that proved N-4 (but not N-2) nitrogen atom of 3-aminotriazole to participate in the ring formation.

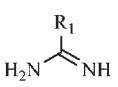
The reactions of chloroaldehydes **3** with 2-aminoquinazolin-4-one **4i** give angular compounds **10a–c** (Scheme 7).

To determine the structure of the product isolated from the reaction mixture, $^1$H and $^{13}$C NMR spectroscopy was used. The investigation of 3D models of the product showed that in the structure **10** the doublet of H-1 proton should be shifted to low field due to the neighboring carbonyl oxygen effect.

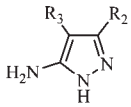
In experimental NMR spectrum, we observe a pronounced shift of the doublet that due to homonuclear (COSY) and heteronuclear ($^1$H-$^{13}$C HMBC, HMQC) correlation experiments originated from the H-5 proton of starting benzothiazine **3**. Thus, the reaction proceeds regioselectively; the ''amide'' nitrogen of the starting quinazoline **4i** participates in cyclization.

**Table 1**

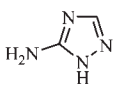
Structures of bis-nucleophilic reagents.



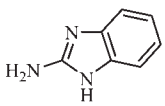
| Label | $R_1$ |
|---|---|
| **4a** | -*i*-$C_3H_7$ |
| **4b** | -Ph |
| **4c** | -Thienyl |



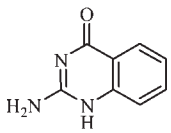
| Label | $R_2$, $R_3$ |
|---|---|
| **4d** | -$CH_3$, -H |
| **4e** | -$CH_3$, -*m*-Cl-Ph |
| **4f** | -H, $CO_2Et$ |



**4g**

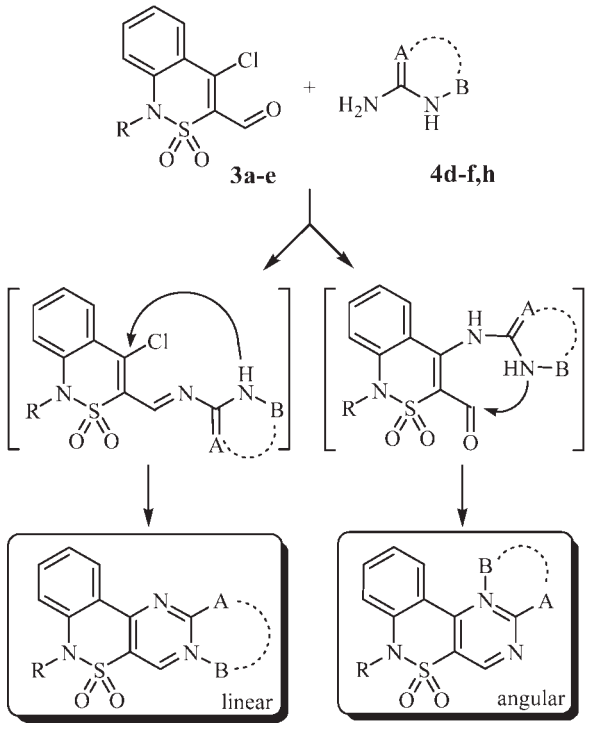


**4h**



**4i**

**Scheme 1**




Structures of all aforementioned compounds were established on the basis of their $^1$H NMR, $^{13}$C NMR, Mass spectrometry data, and elemental microanalyses.

In summary, we disclose the synthesis of novel benzo [*e*][2,1]thiazine derivatives, in particular substituted pyrimidobenzothiazines and pyrazolo-, imidazo-, triazolopyrimidobenzothiazines. These compounds were obtained in high yields (∼70–80%) *via* convenient protocols involving heterocyclization reactions of chloroaldehydes **3a–e** with N-C-N bisnucleophiles **4a–i**.

## EXPERIMENTAL

The NMR spectra were measured on a Varian 400 spectrometer at 25°C using DMSO-$d_6$. All chemical shifts are reported in ppm relative to TMS.

Starting materials used were obtained from Makrochim and used without further purification. Dry solvents were prepared according to the standard methods.

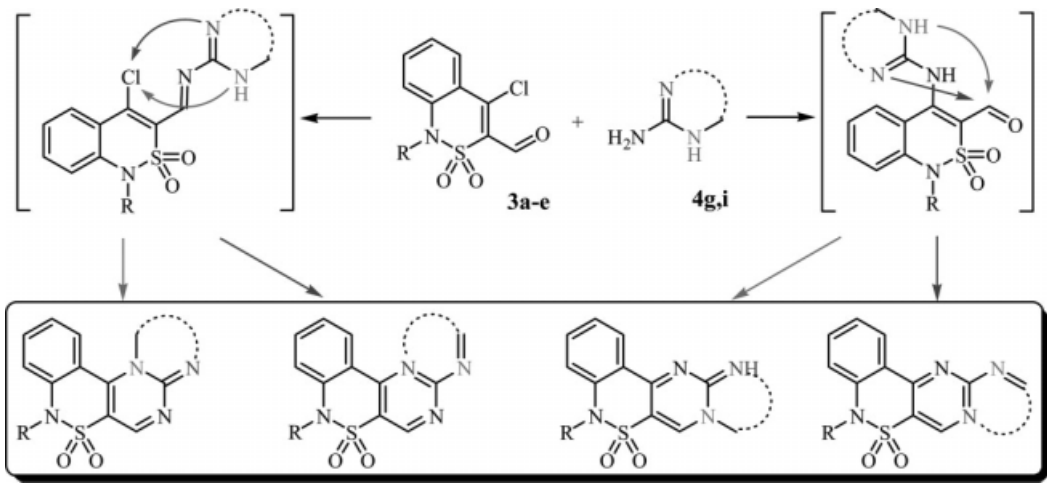
**6-Alkyl-6H-pyrimido[5,4-c][2,1]benzothiazine-5,5-dioxides (5a–f); general procedure.** The mixture of β-chloroaldehyde **3** (1 mmol) with the corresponding amidine **4a–c** (1.2 mmol) was dissolved in 2 mL of dry DMF. Triethylamine (2 mL) was added and the reaction mixture was heated for 6 h at 80°C. The mixture was cooled to room temperature, quenched with water (20 mL), solid product was filtered off, and then washed with ethanol. The pure product was obtained by crystallization from DMF (64–86%).

***Product 5a (77%, R Me, R$_1$ i-Pr).*** m.p.: 103–104°C; $^1$H NMR (400 MHz, DMSO): δ = 1.42 (d, *J* = 7.8 Hz, 6H), 3.48 (quin. *J* = 7.7 Hz, 1H), 3.58 (s, 3H), 7.48(t, *J* = 7.8, 1H), 7.63(d, *J* = 7.8 Hz, 1H), 7.75(t, *J* = 7.8 Hz, 1H), 8.68(d, *J* = 7.75 Hz, 1H), 9.11 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 14.55 (×2), 43.78, 49.13, 122.63, 125.36, 128.65, 129.47, 135.34, 141.17, 143.19, 153.17, 156.22, 164.62; MS (CI): 290(M+H)$^+$; Anal. calcd. C, 58.11; H, 5.23; N, 14.52; found C, 58.14; H, 5.25; N, 14.54.

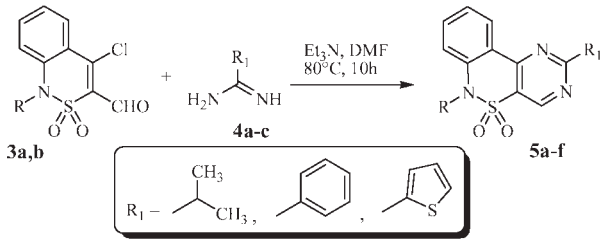
***Product 5b (79%, R Me, R$_1$ Ph).*** m.p.: 202–203°C; $^1$H NMR (400 MHz, DMSO): δ = 3.59 (s, 3H) 7.45–7.63 (m, 5H), 7.82 (t, *J* = 7.8 Hz, 1H), 8.57(d, *J* = 8 Hz, 2H), 8.83 (d, *J* = 7.8 Hz, 1H) 9.30 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 38.22, 120.51, 123.34, 126.72, 126.97, 127.62, 129.38, 129.68, 133.29, 135.07, 136.54, 140.07, 141.04, 142.57, 152.88, 156.23, 166.91; MS (CI): 324(M+H)$^+$; Anal. calcd. C, 63.14; H, 4.05; N, 12.99; found C, 63.17; H, 4.07; N, 13.02.

***Product 5c (64%, R Me, R$_1$ Thienyl).*** m.p.: 194–195°C; $^1$H NMR (400 MHz, DMSO): δ = 3.59 (s, 3H) 7.26 (t, *J* = 8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.74–7.81 (m, 2H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.69 (d, *J* = 7.8 Hz, 1H), 9.15 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 37.74, 120.44, 123.75, 125.37, 126.74, 128.68, 129.15, 129.94, 133.45, 135.89, 136.35, 141.94, 152.56, 156.84, 164.89; MS

**Scheme 2**

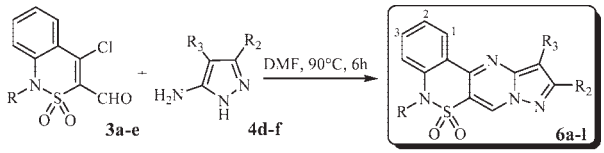


**Scheme 3**




Synthesis of pyrimido-annelated benzothiazines **5**

**Scheme 4**




Condensation with aminopyrazoles **4d-f**

(CI): 330(M+H)$^+$; Anal. calcd. C, 54.69; H, 3.37; N, 12.76; found C, 54.72; H, 3.40 N, 12.77.

***Product 5d (82%, R Et, $R_1$ i-Pr).*** m.p.: 114–115°C; $^1$H NMR (400 MHz, DMSO): δ = 1.22 (t, *J* = 8 Hz, 3H), 1.42 (d, *J* = 7.8 Hz, 6H), 3.48 (quin. *J* = 7.8 Hz, 1H), 4.08 (q, *J* = 8 Hz, 2H), 7.46(t, *J* = 7.8, 1H), 7.60(d, *J* = 7.8 Hz, 1H), 7.78(t, *J* = 7.8 Hz, 1H), 8.63(d, *J* = 7.8 Hz, 1H), 9.16 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 14.64 (×2), 44.25, 49.02, 121.60, 123.37, 125.76, 127.65, 129.78, 132.15, 135.33, 141.09, 142.18, 152.77, 156.20, 162.82; MS (CI): 304(M+H)$^+$; Anal. calcd. C, 59.38; H, 5.65; N, 13.85; found C, 59.40; H, 5.66; N, 13.85.

***Product 5e (86%, R Et, $R_1$ Ph).*** m.p.: 214–215°C; $^1$H NMR (400 MHz, DMSO): δ = 1.23 (t, *J* = 7.6 Hz, 3H), 4.08 (q, *J* = 7.6 Hz, 2H), 7.49–7.67 (m, 5H), 7.80 (t, *J* = 7.8 Hz, 1H), 8.61(d, *J* = 8 Hz, 2H), 8.80 (d, *J* = 7.8 Hz, 1H) 9.32 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 14.71, 44.22, 121.52, 123.64, 125.76, 126.59, 127.82, 129.35, 129.62, 132.89, 135.27, 136.59, 141.02, 152.60, 156.12, 165.93; MS (CI): 338(M+H)$^+$; Anal. calcd. C, 64.08; H, 4.48; N, 12.45; found C, 64.09; H, 4.47; N, 12.47.

***Product 5f (71%, R Et, $R_1$ Thienyl).*** m.p.: 205–206°C; $^1$H NMR (400 MHz, DMSO): δ = 1.21 (t, *J* = 8 Hz, 3H), 4.07 (q, *J* = 8 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.75–7.82 (m, 2H), 8.17 (d, *J* = 8 Hz, 1H), 8.67 (d, *J* = 7.8 Hz, 1H), 9.18 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 14.73, 22.05, 43.96, 121.43, 123.50, 125.68, 126.37, 135.16, 140.88, 152. 07, 155.60, 178.09; MS (CI): 344(M+H)$^+$; Anal. calcd. C, 55.96; H, 3.82; N, 12.24; found C, 55.96; H, 3.83; N, 12.27.

**5-Alkyl-5*H*-pyrazolo[1′,5′:1,2]pyrimido[5,4-*c*][2,1]benzo thiazin-6,6-dioxides (6a–l); general procedure.** The mixture of β-chloroaldehyde **3** (1 mmol) with the corresponding aminopyrazole **4d–f** (1.2 mmol) was dissolved in 2 mL of dry DMF. The reaction mixture was heated for 10 h at 90°C. The mixture was cooled to room temperature; solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (59–86%).

***Product 6a (68%, R Me, $R_2$ Me, $R_3$ H).*** m.p.: 178–179°C; $^1$H NMR (400 MHz, DMSO): δ = 3.35 (s, 3H), 3.37 (s, 3H), 6.81 (s, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 8.47 (d, *J* = 8 Hz, 1H), 9.86 (s, 1H); MS (CI): 301(M+H)$^+$; Anal. calcd. C, 55.99; H, 4.03; N, 18.65; found C, 56.02; H, 4.03; N, 18.68.

***Product 6b (70%, R Et, $R_2$ Me, $R_3$ H).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, DMSO): δ = 1.03 (t, *J* = 6.8 Hz, 3H), 3.35 (s, 3H), 3.91 (q, *J* = 6.8 Hz, 2H), 6.80 (s, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 9.83 (s, 1H); MS (CI): 315 (M+H)$^+$; Anal. calcd. C, 57.31; H, 4.49; N, 17.82; found C, 57.32; H, 4.51; N, 17.81.

***Product 6c (86%, R Pr, $R_2$ Me, $R_3$ H).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, DMSO): δ = 0.80 (t, *J* = 6.8 Hz,3H), 1.54 (m, 2H), 2.50 (s, 3H), 3.83 (t, *J* = 6.8 Hz,2H), 6.67 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 9.61 (s, 1H); MS (CI): 329(M+H)$^+$; Anal. calcd. C, 58.52; H, 4.91; N, 17.06; found C, 58.53; H, 4.93; N, 17.07.

***Product 6d (75%, R Bu, $R_2$ Me, $R_3$ H).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, DMSO): δ = 0.83 (t, *J* = 6.8 Hz,3H), 1.22 (m, 2H), 1.50 (m, 2H), 2.54 (s, 3H), 3.86 (t, *J* = 6.8 Hz, 2H), 6.67 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 9.61 (s, 1H); MS (CI): 343(M+H)$^+$; Anal. calcd. C, 59.63; H, 5.30; N, 16.36; found C, 59.64; H, 5.33; N, 16.36.

***Product 6e (78%, R Bn, $R_2$ Me, $R_3$ H).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, DMSO): δ = 2.55 (s, 3H), 5.08 (s, 2H), 6.65 (s, 1H), 7.12–7.15 (m, 5H), 7.41–7.45 (m, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 9.63 (s, 1H); MS (CI): 377(M+H)$^+$; Anal. calcd. C, 63.81; H, 4.28; N, 14.88; found C, 63.83; H, 4.29; N, 14.90.

***Product 6f (63%, R Me, $R_2$ Me, $R_3$ m-Cl-Ph).*** m.p.: 219–220°C; $^1$H NMR (400 MHz, DMSO): δ = 2.68 (s, 3H), 3.41 (s, 3H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.44–7.52 (m, 3H), 7.68–7.74 (m, 2H), 7.83 (s, 1H), 8.48 (d, *J* = 8 Hz, 1H), 9.75 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 13.99, 15.16, 19.84, 30.18, 49.53, 108.72, 119.39, 123.53, 125.62, 126.74, 127.44, 127.72, 128.62, 131.18, 133.18, 140.62, 145.83, 147.95, 156.77; MS (CI): 411(M+H)$^+$; Anal. calcd. C, 58.46; H, 3.68; N, 13.64; found C, 58.48; H, 3.70; N, 13.65.

***Product 6g (59%, R Et, $R_2$ Me, $R_3$ m-Cl-Ph).*** m.p.: 232–233°C; $^1$H NMR (400 MHz, DMSO): δ = 1.28 (t, *J* = 6.7 Hz, 3H), 2.62 (s, 3H), 3.93 (q, *J* = 6.7 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.42–7.53 (m, 3H), 7.68–7.75 (m, 2H), 7.82 (s, 1H),

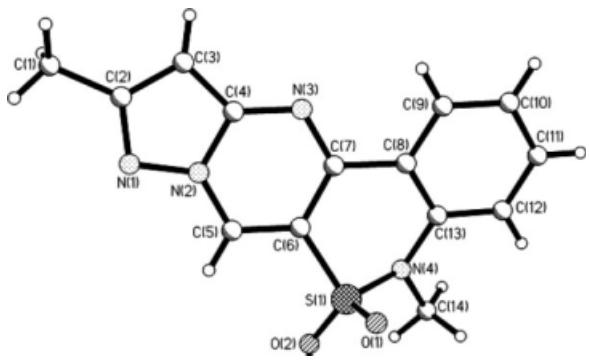
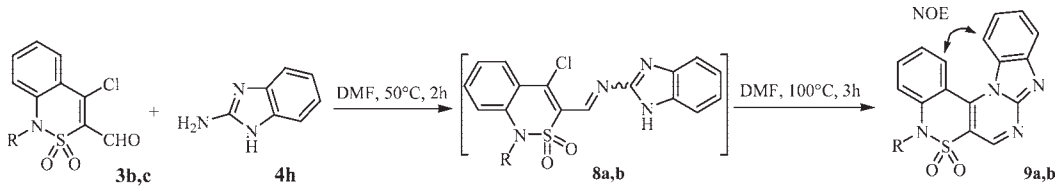



**Figure 3.** X-ray structure of compound **6a**.

**Scheme 5**




Two stage reaction with 2-aminobenzoimidazole **4h**

8.51 (d, $J$ = 7.8 Hz, 1H), 9.73 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 15.04, 30.24, 53.22, 118.86, 123.72, 126.07, 126.88, 127.36, 128.49, 129.67, 132.96, 133.86, 136.63, 140.36, 147.37, 149.14, 159.63; MS (CI): 425(M+H)$^+$; Anal. calcd. C, 59.36; H, 4.03; N, 13.19; found C, 59.36; H, 4.05; N, 13.23.

***Product 6h (67%, R Pr, $R_2$ Me, $R_3$ m-Cl-Ph).*** m.p.: >250°C; $^1$H NMR (400 MHz, DMSO): δ = 0.86 (t, $J$ = 6.8 Hz, 3H), 1.65 (m, $J$ = 6.8 Hz, 2H), 2.72 (s, 3H), 4.03 (t, $J$ = 6.8 Hz, 2H), 7.35 (d, $J$ = 7.8 Hz, 1H), 7.49 (t, $J$ = 7.8 Hz, 1H), 7.59 (t, $J$ = 7.8 Hz, 1H), 7.66 (d, $J$ = 8 Hz, 1H), 7.74 (d, $J$ = 7.8 Hz, 1H), 7.77 (s, 1H), 7.86 (t, $J$ = 7.8 Hz, 1H), 8.92 (s, 1H), 9.74 (d, $J$ = 8 Hz, 1H); MS (CI): 439.5(M+H)$^+$; Anal. calcd. C, 60.20; H, 4.36; N, 12.76; found C, 60.23; H, 4.39; N, 12.77.

***Product 6i (61%, R Bu, $R_2$ Me, $R_3$ m-Cl-Ph).*** m.p.: >250°C; $^1$H NMR (400 MHz, DMSO): δ = 0.84 (t, $J$ = 6.8 Hz, 3H), 1.23 (m, 2H), 1.50 (m, 2H), 2.68 (t, $J$ = 7.8 Hz, 2H), 3.89 (s, 3H), 7.35–7.85 (m, 7H), 8.48 (d, $J$ = 7.8 Hz, 1H), 9.71 (s, 1H); MS (CI): 453.5(M+H)$^+$; Anal. calcd. C, 60.99; H, 4.67; N, 12.37; found C, 61.04; H, 4.69; N, 12.36.

***Product 6j (60%, R Bn, $R_2$ Me, $R_3$ m-Cl-Ph).*** m.p.: >250°C; $^1$H NMR (400 MHz, DMSO): δ = 2.69 (s, 3H), 5.09 (s, 2H), 7.16 (s, 5H), 7.34 (d, $J$ = 7.8 Hz, 1H), 7.41–7.46 (m, 2H), 7.50 (t, $J$ = 7.8 Hz, 1H), 7.59 (t, $J$ = 8 Hz, 1H), 7.72 (d, $J$ = 7.8 Hz, 1H), 7.82 (s, 1H), 8.42 (d, $J$ = 8 Hz, 1H), 9.72 (s, 1H); MS (CI): 487.5(M+H)$^+$; *Anal.*calcd. C, 64.13; H, 3.93; N, 11.51; found C, 64.15; H, 3.97; N, 11.54.

***Product 6k (79%, R Me, $R_2$ H, $R_3$ $CO_2$Et).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, DMSO): δ = 1.23 (t, $J$ = 6.8 Hz, 3H), 3.46 (s, 3H), 3.89 (q, $J$ = 6.7 Hz, 2H), 7.37 (t, $J$ = 7.8 Hz, 1H), 7.56 (d, $J$ = 7.8 Hz, 1H), 7.74 (t, $J$ = 7.8 Hz, 1H), 7.86 (s, 1H), 8.49 (d, $J$ = 7.8 Hz, 1H), 9.75 (s, 1H); $^{13}$C NMR (100 MHz, DMSO): δ = 15.03, 34.80, 61.02, 117.69, 122.04, 124.47, 126.27, 133.34, 134.08, 141.87, 147.31, 149.32, 159.68; MS (CI): 359(M+H)$^+$; Anal. calcd. C, 53.62; H, 3.94; N, 15.63; found C, 53.64; H, 3.94; N, 15.62.

***Product 6l (82%, R Et, $R_2$ H, $R_3$ $CO_2$Et).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, DMSO): δ = 1.27 (t, $J$ = 6.8 Hz, 3H), 1.46 (t, $J$ = 6.8 Hz, 3H), 3.67 (q, $J$ = 6.8 Hz,2H), 3.89 (q, $J$ = 6.8 Hz, 2H), 7.35 (t, $J$ = 7.8 Hz, 1H), 7.86 (d, $J$ = 7.8 Hz, 1H), 7.77 (t, $J$ = 7.8 Hz, 1H), 7.89 (s, 1H), 8.43 (d, $J$ = 7.8 Hz, 1H), 9.78 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 14.28, 15.02, 34.78, 60.44, 108.55, 118.29, 122.04, 124.36, 127.15, 128.55, 131.16, 133.69, 134.27, 141.98, 145.86, 147.87, 156.98; MS (CI): 373(M+H)$^+$; Anal. calcd. C, 54.83; H, 4.33; N, 15.04; found C, 54.85; H, 4.36; N, 15.05.

**7-Alkyl-7*H*-[1,2,4]triazolo[3′,4′:2,3]pyrimido[5,4-*c*][2,1] benzothiazine-6,6-dioxides (7a–c); general procedure.** The mixture of the β-chloroaldehyde **3** (1 mmol) with the aminotriazole **4g** (0.1 g, 1.2 mmol) was dissolved in 2 mL of dry DMF. The reaction mixture was heated for 2.5 h at 80°C. The mixture was cooled to room temperature; solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (52–57%).

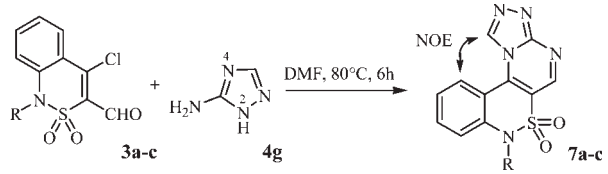
***Product 7a (54%, R Me).*** $^1$H NMR (400 MHz, DMSO): δ = 3.51 (s, 3H), 7.62 (t, $J$ = 7.8 Hz, 1H), 7.73 (d, $J$ = 7.8 Hz, 1H), 7.90 (t, $J$ = 7.8 Hz, 1H), 8.60 (d, $J$ = 7.8 Hz, 1H), 9.06 (s, 1H), 10.04 (s, 1H); MS (CI): 288(M+H)$^+$; Anal. calcd. C, 50.17; H, 3.16; N, 24.38; found C, 50.19; H, 3.16; N, 24.39.

***Product 7b (52%, R Et).*** $^1$H NMR (400 MHz, DMSO): δ = 1.28 (t, $J$ = 6.8 Hz, 3H), 4.09 (q, $J$ = 6.8 Hz, 2H), 7.61 (t, $J$ = 7.8 Hz, 1H), 7.79 (d, $J$ = 7.8 Hz, 1H), 7.88 (t, $J$ = 8 Hz, 1H), 8.60 (d, $J$ = 8 Hz, 1H), 9.04 (s, 1H), 10.02 (s, 1H); MS (CI): 302(M+H)$^+$; Anal. calcd. C, 51.82; H, 3.68; N, 23.24; found C, 51.82; H, 3.67; N, 23.27.

***Product 7c (57%, R Pr).*** $^1$H NMR (400 MHz, DMSO): δ = 0.86 (t, $J$ = 6.8 Hz, 3H), 1.67 (m, 2H), 4.04 (t, $J$ = 6.8 Hz, 2H), 7.60 (t, $J$ = 7.8 Hz, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.89 (t, $J$ = 7.8 Hz, 1H), 8.89 (d, $J$ = 7.8 Hz, 1H), 9.07 (s, 1H), 10.04 (s, 1H); MS (CI): 317(M+H)$^+$; Anal. calcd. C, 53.32; H, 4.16; N, 22.21; found C, 53.33; H, 4.13; N, 22.22.

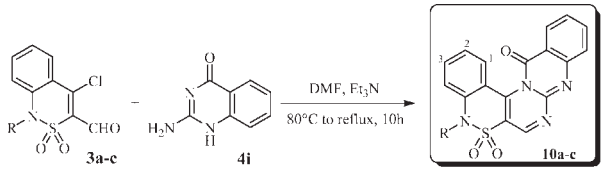
**5-Alkyl-5*H*-benzimidazo[2′,1′:2,3]pyrimido[5,4-*c*][2,1] benzothiazin-6,6-dioxides (9a,b); general procedure.** The mixture of the chloroaldehyde **3** (1 mmol) with the aminobenzoimidazole **4h** (0.16 g, 1.2 mmol) was dissolved in 3 mL of dry DMF. The reaction mixture was heated for 2 h at 50°C, 2 h at 70°C, and 1 h at 100°C. The mixture was cooled to room

**Scheme 6**




Condensation with aminotriazole **4g**, 1D-NOESY correlation is shown

**Scheme 7**




Reaction with 2-aminoquinazoline-4-one **4i**

temperature; solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (61–63%).

***Product 9a (61%, R Et).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, TFA): δ = 1.49 (t, *J* = 6.8 Hz, 3H), 4.29 (q, *J* = 6.8 Hz, 2H), 7.70–7.75 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 8.02 (t, *J* = 7.8 Hz, 1H), 8.12 (m, 2H), 8.24 (d, *J* = 8 Hz, 1H), 8.53 (d, *J* = 8 Hz, 1H), 9.57 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 14.63, 49.34, 115.62, 117.19, 120.01, 121.16, 122.76, 123.67, 125.28, 128.48, 128.79, 135.64, 139.95, 143.84, 145.89, 148.43, 151.79; MS (CI): 351(M+H)$^+$; Anal. calcd. C, 61.70; H, 4.03; N, 15.99; found C, 61.72; H, 4.04; N, 15.99.

***Product 9b (63%, R Pr).*** m.p.: >250°C (decomp.); $^1$H NMR (400 MHz, TFA): δ = 0.98 (t, *J* = 6.8 Hz, 3H), 1.90 (m, 2H), 4.16 (q, *J* = 6.8 Hz, 2H), 7.71–7.77 (m, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.10 (t, *J* = 7.8 Hz, 1H), 8.15 (m, 2H), 8.27 (d, *J* = 8 Hz, 1H), 8.50 (d, *J* = 7.8 Hz, 1H), 9.58 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ = 11.62, 21.93, 49.74, 116.63, 118.18, 120.21, 121.15, 122.34, 123.92, 125.20, 128.50, 128.76, 135.61, 139.89, 143.87, 145.88, 148.20, 151.78; MS (CI): 365(M+H)$^+$; Anal. calcd. C, 62.62; H, 4.43; N, 15.37; found C, 62.65; H, 4.45; N, 15.39.

**5-Alkyl-14-oxo-5,14-dihydroquinazolino[2′,3′:2,3]pyrimido[5,4-*c*][2,1]benzothiazin-6,6-dioxides (10a–c); general procedure.** The mixture of 2-amino-quinazolin-4-one **4i** (0.21 g, 1.3 mmol) and a catalytic amount of triethylamine in 2 mL of dry DMF was heated to 100°C. To the resulting solution chloroaldehyde **3** (1 mmol) was added in portions at 80°C. The reaction mixture was heated for 10 h at reflux and then cooled to room temperature. Solid product was filtered off and washed with ethanol. The pure product was obtained by crystallization from DMF (56–59%).

***Product 10a (58%, R Me).*** m.p.: 206–207°C; $^1$H NMR (400 MHz, TFA): δ = 3.98 (s, 3H), 7.12 (m, 2H), 7.78 (m, 2H), 7.89 (t, *J* = 8 Hz, 1H), 8.08 (t, *J* = 8 Hz, 1H), 8.46 (d, *J* = 8 Hz, 1H), 8.65 (t, *J* = 7.8 Hz, 1H), 9.35 (s, 1H)

$^{13}$C NMR (100 MHz, TFA): δ = 50.01, 108.65, 118.86, 119.47, 123.58, 125.89, 126.87, 127.35, 129.08, 130.43, 131.24, 133.41, 135.64, 140.46, 145.79, 147.97, 156.92, 159.61; MS (CI): 365(M+H)$^+$; Anal. calcd. C, 59.33; H, 3.32; N, 15.38; found C, 59.35; H, 3.36; N, 15.41.

***Product 10b (59%, R Et).*** m.p.: 234°C; $^1$H NMR (400 MHz, TFA): δ = 1.37 (t, *J* = 6.8 Hz, 3H), 4.24 (q, *J* = 6.8 Hz, 2H), 7.63 (m, 2H), 7.78 (m, 2H), 7.87 (t, *J* = 7.8 Hz, 1H), 8.11 (t, *J* = 7.8 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.67 (t, *J* = 7.8 Hz, 1H), 9.38 (s, 1H). $^{13}$C NMR (100 MHz, TFA): δ = 15.09, 54.02, 118.67, 124.01, 126.12, 126.87, 127.43, 128.66, 129.54, 133.04, 135.61, 137.76, 140.72, 142.85, 144.50, 146.08, 147.76, 149.34, 159.76; MS (CI): 379(M+H)$^+$; Anal. calcd. C, 60.31; H, 3.73; N, 14.81; found C, 60.34; H, 3.75; N, 14.81.

***Product 10c (56%, R Pr).*** m.p.: >250°C (decomp); $^1$H NMR (400 MHz, TFA): δ = 0.91 (t, *J* = 6.8 Hz, 3H), 1.77 (m, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 7.13 (m, 2H), 7.77 (m, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 8.10 (t, *J* = 7.8 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.66 (t, *J* = 7.8 Hz, 1H), 9.37 (s, 1H). $^{13}$C NMR (100 MHz, TFA): δ = 15.04, 38.44, 53.22, 118.86, 123.69, 126.06, 126.85, 127.37, 128.49, 132.94, 135.63, 137.76, 140.37, 142.58, 144.51, 146.03, 147.36, 149.14, 150.05, 159.62; MS (CI): 393(M+H)$^+$; Anal. calcd. C, 61.21; H, 4.11; N, 14.28; found C, 61.22; H, 4.14; N, 14.31.

## REFERENCES AND NOTES

[1] Catsoulacos, P.; Camoutsis, C. J Heterocycl Chem 1979, 16, 1503.

[2] Olkkola, K. T.; Brunetto, A. V.; Mattila, M. J. Clin Pharmacokinet 1994, 26, 107.

[3] Davis, J. M.; Davis, P. D.; Moffat, D. C.; Batchelor, M. J. WO 9,828,281, (1998).

[4] Rossi, S. Australian Medicines Handbook 2006; Adelaide: Australian Medicines Handbook, 2006. ISBN 0-9757919-2-3.

[5] Popov, K. S.; Volovnenko, T. A.; Volovenko, Yu. M. J Heterocycl Chem 2007, 44, 1413.

# Unusual Anisotropic Effects from 1,3-Dipolar Cycloadducts of 4-Azidomethyl Coumarins



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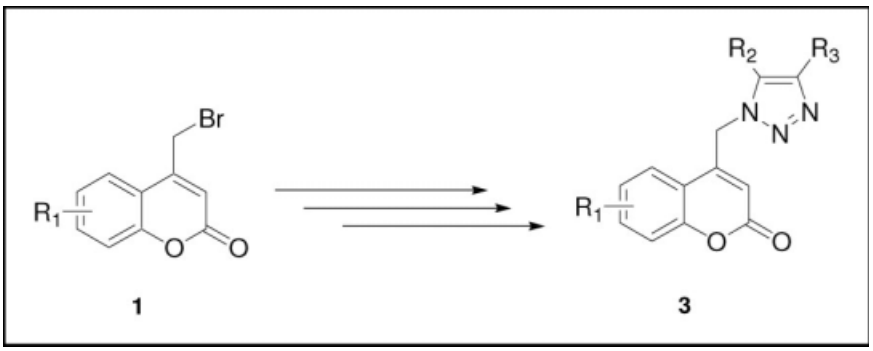


4-Bromomethylcoumarins (**1**) reacted with sodium azide in aqueous acetone to give 4-azidomethylcoumarins (**2**), which underwent 1,3-dipolar cycloaddition with acetylenic dipolarophiles to give triazoles (**3**). These triazoles (**3**) have been found to exhibit interesting variations in the chemical shifts of $C_3$—H and $C_4$-methylene protons. Protonation studies indicate that the shielding effect of the $C_3$—H of coumarin is due to π-electrons of the triazole ring, further supported by diffraction and computational studies.

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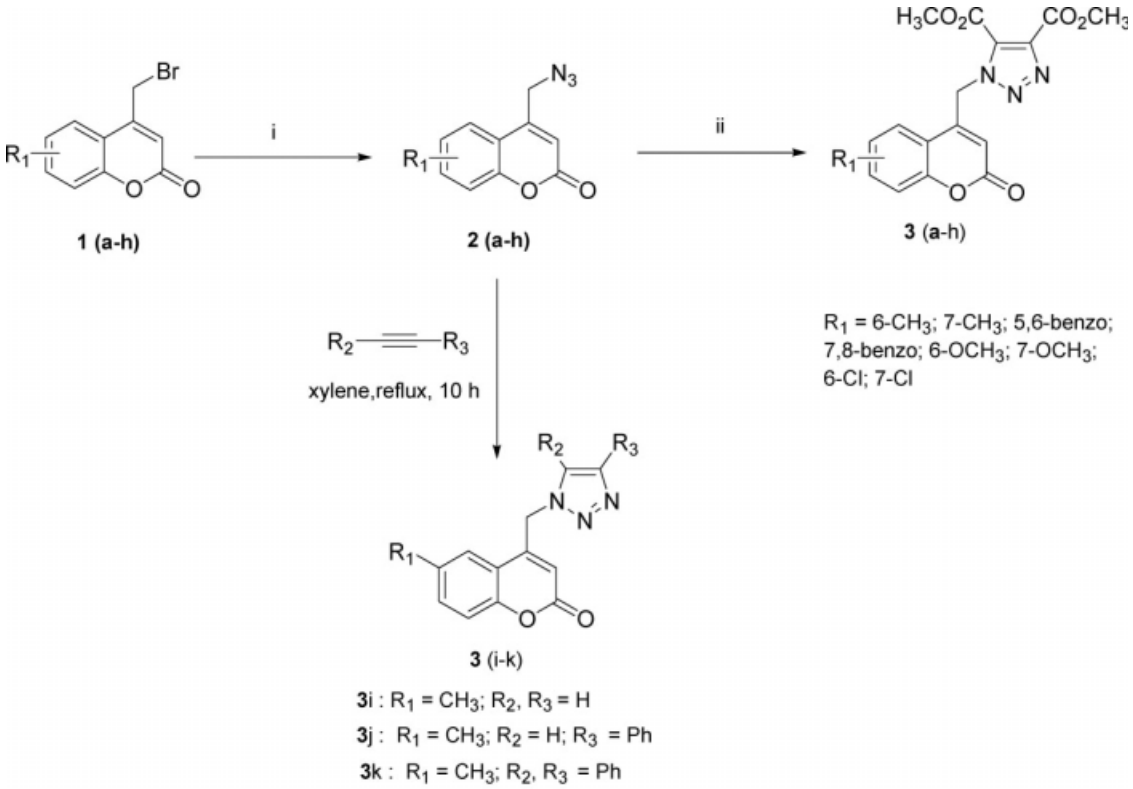
## INTRODUCTION

Organic azides are an important class of 1,3-dipoles, which have been recently recognized as crucial functional groups in click chemistry [1]. The exergonic reaction of azides with acetylenic dipolarophiles has resulted in one of the best synthetic routes to 1,2,3-triazoles [2]. This single-step transformation has been investigated for its regioselectivity in aqueous systems [3], in ionic liquids [4], in copper (I) catalysis [5], and by the solid-phase approach [6]. In view of the wide range of biological activities of 1,2,3-triazoles [7,8] and in continuation of our study on biologically active and fluorescent 4-substituted coumarins [9,10], it was thought of substantial intellectual appeal to link the 1,2,3-triazole moiety at the allylic position with respect to the biogenetically important $C_3$—$C_4$ double bond of coumarin. There are very few reports on pyranone-substituted 1,3 dipoles except for the reactions of coumarin 4-nitrile oxides [11].

## RESULTS AND DISCUSSION

The required dipolar azide intermediates (**2**) were synthesized by the reaction of sodium azide with various 4-bromomethylcoumarins (**1**) [12] in aqueous acetone at room temperature and were quite stable even above 100°C. The first acetylenic dipolarophile used in this investigation was dimethylacetylenedicarboxylate (DMAD), giving rise to triazolomethylcoumarins (**3**) in refluxing xylene (Scheme 1). In the $^1$H NMR spectrum of the azide, (**2a**, $R_1$ = 6-$CH_3$) as expected, the $C_4$—$CH_2$ protons linked to the azido group were observed at 4.57 ppm and the $C_3$—H of coumarin, appeared as a singlet at 6.52 ppm. The $^1$H NMR of DMAD adduct **3a** showed two interesting features such as (i) $C_4$—$CH_2$ protons showed a downfield shift and were observed at 6.05 ppm when compared with 4.56 ppm observed in the case of 4-anilinomethylcoumarins or 5.20 ppm observed in the case of 4-phenoxymethylcoumarins. (ii) The $C_3$—H of coumarin in the DMAD

**Scheme 1.** Synthesis of triazolomethylcoumarins from click chemistry.




adduct experienced an upfield shift and was observed as a singlet at 5.60 ppm, as against 6.60–6.70 ppm in the case of both 4-anilinomethyl or 4-phenoxymethyl coumarins [13,14]. To the best of our knowledge, there is only one report in the literature on this type of shielding effect of coumarin $C_3$—H in 7-methoxy-4-platinomethylcoumarin complex coordinated with 1,10-phenanthroline [15]. This rare type of shielding effect of coumarin $C_3$—H and simultaneous pronounced deshielding of the $C_4$-methylene protons were due to the triazole on the $C_4$—$CH_2$ group, which has been consistently observed in all the cycloaddition adducts of the azides and DMAD (Table 1). It is interesting to note that benzylic azides have also been reported to undergo similar dipolar cycloaddition reaction [16], but no effects on the chemical shifts of the *ortho* protons have been observed. The chemical shift for the methylene protons in *p*-hydroxybenzyl azide and DMAD adduct is around 5.60 ppm, whereas the aromatic *ortho* protons were found to resonate at 7.11 ppm [17].

**Table 1**

Chemical shift values of $C_4$—$CH_2$ and $C_3$—H in azides (**2**) and cycloadducts (**3**) ($CDCl_3$).

| | | $C_4$—$CH_2$ | | $C_3$—H | |
|---|---|---|---|---|---|
| Entry | R | Azide (**2**) | DMAD adduct (**3**) | Azide (**2**) | DMAD adduct (**3**) |
| **a** | 6-$CH_3$ | 4.57 | 6.05 | 6.52 | 5.60 |
| **b** | 7-$CH_3$ | 4.56 | 6.03 | 6.47 | 5.67 |
| **c** | 5,6-benzo | 4.96 | 6.54 | 6.71 | 5.46 |
| **d** | 7,8-benzo | 4.63 | 6.10 | 6.57 | 5.78 |
| **e** | 6-$OCH_3$ | 4.57 | 6.01 | 6.53 | 5.80 |
| **f** | 7-$OCH_3$ | 4.61 | 6.08 | 6.53 | 5.89 |
| **g** | 6-Cl | 4.55 | 6.01 | 6.58 | 5.77 |
| **h** | 7-Cl | 4.54 | 6.06 | 6.56 | 5.81 |

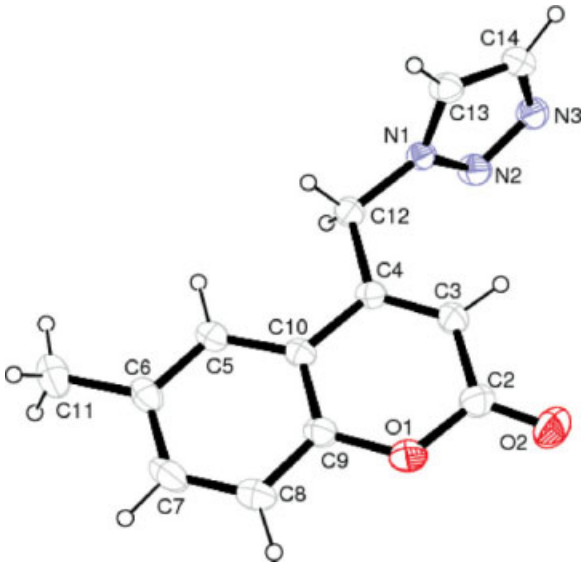



**Figure 1.** ORTEP diagram of triazole adduct **3i**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Effect of substituents.** The possible role played by the two ester groups in this observation was verified by using other dipolarophiles such as acetylene, phenylacetylene, and diphenylacetylene in this reaction with azide **2a** (Fig. 1). This led to the formation of adducts **3i**, **3j**, and **3k**, respectively (Scheme 1). In all these cases, similar trend has been observed. Hence, the origin of this effect lies in the triazole ring rather than the substituents.

**Temperature effect.** To understand the nature of this phenomenon, we recorded the temperature-dependent NMR for one of the DMAD adducts (**3a)** at various temperatures. Up to a temperature of 393 K, there was a regular decrease in the chemical shift values of $C_4$-methylene protons from 6.1790 to 6.1090 δ ppm. The $C_3$—H protons showed a slight increase from 5.638 to 5.790 ppm (Table 2). This behavior indicated the absence of any intramolecular hydrogen bonding between $C_3$—H and triazole nitrogen *via* a six-membered ring.

**Table 2**

Temperature dependence of chemical shifts of C4—$CH_2$ and C3—H of (**3a**) in DMSO-$d_6$.

| | Chemical shifts (δ ppm) | |
|---|---|---|
| Temperature (K) | $C_4$—$CH_2$ | $C_3$—H |
| 303.1 | 6.1790 | 5.638 |
| 313.1 | 6.1710 | 5.654 |
| 323.1 | 6.1645 | 5.670 |
| 333.1 | 6.1565 | 5.689 |
| 343.1 | 6.1475 | 5.706 |
| 353.1 | 6.1405 | 5.725 |
| 373.1 | 6.1245 | 5.758 |
| 393.1 | 6.1090 | 5.790 |

**Protonation behavior.** Qualitative protonation studies were performed by adding two drops of trifluoroacetic acid ($CF_3CO_2H$) in $CDCl_3$, which resulted in significant changes in the chemical shifts of $C_3$—H and $C_4$—$CH_2$ protons. In the case of **3a,** the $C_3$—H proton was further shifted downfield to 6.01 ppm from 5.60 ppm and $C_4$—$CH_2$ protons were also deshielded to 6.30 ppm from 6.05 ppm. This trend was observed for all the substituted cycloadducts (**3**) (Table 3). In the case of acetylene adduct **3i**, the trend was also similar, whereas the $C_4$—$CH_2$ protons showed downfield shift from 5.77 to 6.16 ppm and the $C_3$—H from 5.94 to 6.41 ppm. Probable structures of the protonated species **5** and **6** (Scheme 2) indicate that $N_1$ of the triazole ring can be quaternized and inductively withdraw the electron density at $C_4$—$CH_2$, which would cause deshielding effect.

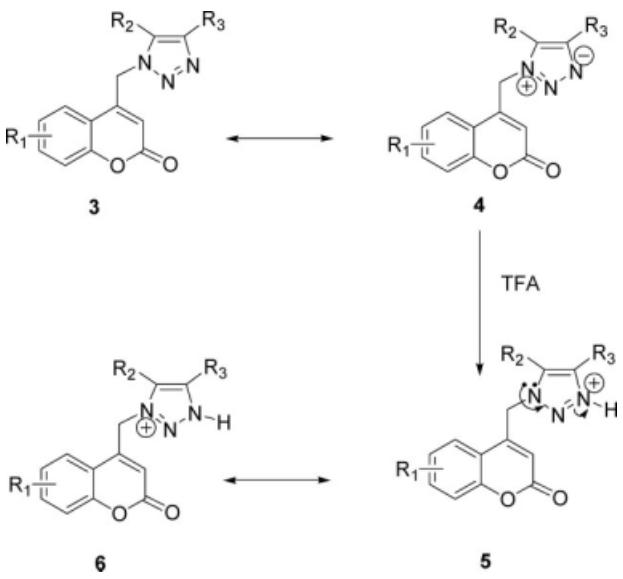
However, the simultaneous deshielding effect of $C_3$—H under this condition strongly supports an argument that the $C_3$—H proton falls in the shielding zone of the triazole moiety, which is perturbed due to protonation. Further, the higher deshielding of the methylene protons was observed, which can also be explained in

**Table 3**

Chemical shifts of C4—$CH_2$ and C3—H upon protonation ($CDCl_3$ + TFA) in DMAD adducts (**3a–3h**).

| | | $C_4$—$CH_2$ | | $C_3$—H | |
|---|---|---|---|---|---|
| Compound | R | $CDCl_3$ | $CDCl_3$ + TFA | $CDCl_3$ | $CDCl_3$ + TFA |
| **3a** | 6-$CH_3$ | 6.05 | 6.30 | 5.60 | 6.01 |
| **3b** | 7-$CH_3$ | 6.03 | 6.21 | 5.67 | 5.94 |
| **3c** | 5,6-benzo | 6.54 | 6.73 | 5.46 | 5.87 |
| **3d** | 7,8-benzo | 6.10 | 6.33 | 5.78 | 6.06 |
| **3e** | 6-$OCH_3$ | 6.01 | 6.21 | 5.85 | 6.09 |
| **3f** | 7-$OCH_3$ | 6.08 | 6.29 | 5.89 | 6.02 |
| **3g** | 6-Cl | 5.94 | 6.19 | 5.77 | 6.16 |
| **3h** | 7-Cl | 6.06 | 6.17 | 5.81 | 6.00 |

**Scheme 2.** Schematic representation of protonation behavior.




terms of enhanced contribution of the dipolar form **4** to the ground-state resonance of compound **3**.

**Diffraction studies.** We have performed a single crystal analysis of the acetylene adduct **3i**. The ORTEP diagram (Fig. 1) clearly shows that the planar triazole ring is oriented at an angle of 78.88° with respect to the coumarin ring. This supports our argument that the shielding of the $C_3$—H is due to the triazole ring and not because of any substituents.

**Computational support.** We have also performed the geometry optimization of the triazoles **3a** and **3k** molecules, which are shown in the Figure 2 using the Gaussian 03 program [18]. The minimization was performed according to the density functional theory at the B3LYP method with standard Gaussian split-valence 6-31G (d,p) basis set. The two structures clearly revealed the relative orientations of the triazole ring with respect to the $C_3$ proton of the coumarin (Fig. 2). The anisotropic effect observed on the $C_3$—H of coumarin is due to the angularly oriented triazole ring, the π-electron cloud of which will have a shielding effect.

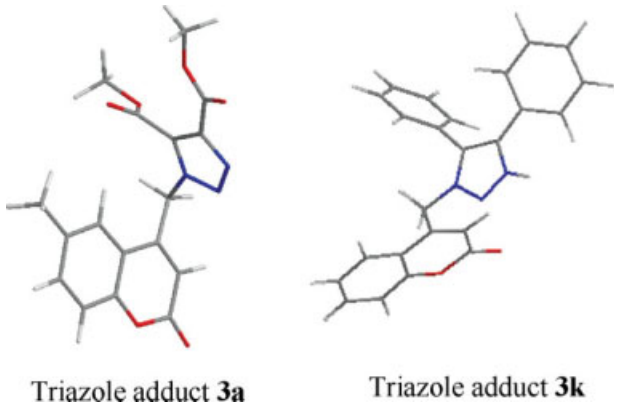



**Figure 2.** Optimized geometries of compounds **3a** and **3k**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

## CONCLUSIONS

The unusual anisotropic effects observed in the 4-triazolomethyl coumarins synthesized from 4-azidomethyl-coumarins **2** and a variety of acetylenic dipolarophiles are due to the angularly oriented triazole, which has been shown by NMR, X-ray diffraction, and computational studies.

**Table 4**

Synthesis of 4-azidomethyl-chromen-2-ones **(2a–2h)**and 1-(2-oxo-*2H*-chromen-4-ylmethyl)-*1H*-[1,2,3]triazoles **(3a–3k).**

| Entry | Product | $R_1$ | $R_2$ | $R_3$ | Melting point (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **2a** | 6-$CH_3$ | – | – | 110 | 63 |
| 2 | **2b** | 7-$CH_3$ | – | – | 104 | 60 |
| 3 | **2c** | 5,6-Benzo | – | – | 146 | 65 |
| 4 | **2d** | 7,8-Benzo | – | – | 131 | 64 |
| 5 | **2e** | 6-$OCH_3$ | – | – | 106 | 62 |
| 6 | **2f** | 7-$OCH_3$ | – | – | 92 | 59 |
| 7 | **2g** | 6-Cl | – | – | 118 | 66 |
| 8 | **2h** | 7-Cl | – | – | 102 | 65 |
| 9 | **3a** | 6-$CH_3$ | $COOCH_3$ | $COOCH_3$ | 192 | 76 |
| 10 | **3b** | 7-$CH_3$ | $COOCH_3$ | $COOCH_3$ | 151 | 75 |
| 11 | **3c** | 5,6-Benzo | $COOCH_3$ | $COOCH_3$ | 180 | 78 |
| 12 | **3d** | 7,8-Benzo | $COOCH_3$ | $COOCH_3$ | 226 | 79 |
| 13 | **3e** | 6-$OCH_3$ | $COOCH_3$ | $COOCH_3$ | 194 | 70 |
| 14 | **3f** | 7-$OCH_3$ | $COOCH_3$ | $COOCH_3$ | 182 | 69 |
| 15 | **3g** | 6-Cl | $COOCH_3$ | $COOCH_3$ | 209 | 72 |
| 16 | **3h** | 7-Cl | $COOCH_3$ | $COOCH_3$ | 194 | 70 |
| 17 | **3i** | 6-$CH_3$ | H | H | 199 | 69 |
| 18 | **3j** | 6-$CH_3$ | H | Ph | 168 | 71 |
| 19 | **3k** | 6-$CH_3$ | Ph | Ph | 170 | 67 |

## EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. The elemental analysis was performed using Heraus CHN rapid analyzer. Analytical TLC was performed on Merck precoated 60 $F_{254}$ silica gel plates. IR spectra (KBr disc) were recorded on a Nicolet-5700 FTIR spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker 300 MHz spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. The chemical shifts are expressed in δ ppm scale down field from tetramethylsilane and proton signals are indicated as s = singlet, d = doublet, t = triplet and m = multiplet. EI 70 EV and AUTOSPEC electron impact mass spectrometer was used to record mass spectra.

**Preparation of substituted 4-bromomethylcoumarins (1a–1h).** The required substituted 4-bromomethylcoumarins **1** [14] have been synthesized by the Pechmann cyclization of various phenols with 4-bromoethylacetoacetate.

**General procedure for the preparation of 4-azidomethylchromen-2-ones (2a–2h).** 4-Bromo-methylcoumarin **1** (0.01 mol) was taken in acetone (20 mL) in a round bottom flask. To this, sodium azide (0.012 mol) in 3 mL of water was added dropwise with stirring. The stirring was continued for 10 h (reaction was monitored by TLC). Then, the reaction mixture was poured to ice cold water. The separated solid was filtered and recrystallized using suitable solvent (Table 4).

***4-Azidomethyl-6-methyl-chromen-2-one (2a).*** Colorless solid (ethanol), mp. 110°C, yield 63%; IR (KBr, ν in $cm^{-1}$): 1722 (lactone C=O), 2109 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, C6—$CH_3$), 4.57 (s, 2H, CH2—$N_3$), 6.52 (s, 1H, C3—H), 7.30 (s, 1H, C5—H), 7.32 (d, 1H, C7—H, $J$ = 7.9 Hz), 7.40 (d, 1H, C8—H, $J$ = 8.3 Hz); LCMS *m/z*: 216 [M + 1]. Anal. Calcd. for $C_{11}H_9N_3O_2$; C, 61.39; H, 4.22; N, 19.53; Found: C, 61.36; H, 4.10; N, 19.51.

***4-Azidomethyl-7-methyl-chromen-2-one (2b).*** Colorless solid (petroleum ether + benzene), mp. 104°C, yield 60%; IR (KBr, ν in $cm^{-1}$): 1732 (lactone C=O), 2098 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, C7—$CH_3$), 4.56 (s, 2H, CH2—$N_3$), 6.47 (s, 1H, C3—H), 7.27 (s, 1H, C8—H), 7.13 (d, 1H, C6—H, $J$ = 8.0 Hz), 7.41 (d, 1H, C5—H, $J$ = 8.0 Hz); LCMS *m/z*: 216 [M + 1]. Anal. Calcd. for $C_{11}H_9N_3O_2$; C, 61.39; H, 4.22; N, 19.53; Found: C, 61.32; H, 4.08; N, 19.47.

***1-Azidomethyl-benzo[f]chromen-3-one (2c).*** Colorless solid (ethanol), mp. 146°C, yield 65%; IR (KBr, ν in $cm^{-1}$): 1727 (lactone C=O), 2099 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.96 (s, 2H, CH2—$N_3$), 6.71 (s, 1H, C3—H), 7.50 (d, 1H, Ar—H, $J$ = 8.8 Hz), 7.58 (t, 1H, Ar—H, $J$ = 6.6 Hz), 7.69 (t, 1H, Ar—H, $J$ = 6.6 Hz), 7.94 (d, 1H, C7—H, $J$ = 8.1 Hz), 8.02 (d, 1H, Ar—H, $J$ = 8.9 Hz), 8.25 (d, 1H, C8—H, $J$ = 8.0 Hz). Anal. Calcd. for $C_{14}H_9N_3O_2$; C, 66.93; H, 3.61; N, 16.73; Found: C, 66.90; H, 3.54; N, 16.70.

***4-Azidomethyl-benzo[h]chromen-2-one (2d).*** Colorless solid (ethanol), mp. 131°C, yield 64%; IR (KBr, ν in $cm^{-1}$): 1716 (lactone C=O), 2115 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.63 (s, 2H, CH2—$N_3$), 6.57 (s, 1H, C3—H), 7.26–8.54 (m, 6H, Ar—H). Anal. Calcd. for $C_{14}H_9N_3O_2$; C, 66.93; H, 3.61; N, 16.73; Found: C, 66.87; H, 3.53; N, 16.66.

***4-Azidomethyl-6-methoxy-chromen-2-one (2e).*** Colorless solid (petroleum ether), mp. 106°C, yield 62%; IR (KBr, ν in $cm^{-1}$): 1710 (lactone C=O), 2115 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, C6—$OCH_3$), 4.57 (s, 2H, CH2—$N_3$), 6.53 (s, 1H, C3—H), 6.96 (d, 1H, C7—H, $J$ = 8.1 Hz), 7.26 (d, 1H, C8—H, $J$ = 8.1 Hz), 7.40 (s, 1H, C5—H). Anal. Calcd. for $C_{11}H_9N_3O_3$; C, 57.14; H, 3.92; N, 18.17; Found: C, 57.11; H, 3.83; N, 18.06.

***4-Azidomethyl-7-methoxy-chromen-2-one (2f).*** Colorless solid (petroleum ether), mp. 92°C, yield 59%; IR (KBr, ν in $cm^{-1}$): 1712 (lactone C=O), 2116 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H, C7—$OCH_3$), 4.61 (s, 2H, CH2—$N_3$), 6.53 (s, 1H, C3—H), 6.55–7.44 (m, 3H, Ar—H). Anal. Calcd. for $C_{11}H_9N_3O_3$; C, 57.14; H, 3.92; N, 18.17; Found: C, 57.09; H, 3.86; N, 18.02.

***4-Azidomethyl-6-chloro-chromen-2-one (2g).*** Colorless solid (petroleum ether), mp. 118°C, yield 66%; IR (KBr, ν in $cm^{-1}$): 1720 (lactone C=O), 2121 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.55 (s, 2H, CH2—$N_3$), 6.58 (s, 1H, C3—H), 7.32 (d, 1H, C7—H, $J$ = 8.2 Hz), 7.54 (d, 1H, C8—H, $J$ = 8.2 Hz), 7.70 (s, 1H, C5—H); LCMS *m/z*: 237 [M + 2]. Anal. Calcd. for $C_{10}H_6ClN_3O_2$; C, 50.97; H, 2.57; N, 15.05; Found: C, 50.82; H, 2.54; N, 15.01.

***4-Azidomethyl-7-chloro-chromen-2-one (2h).*** Colorless solid (petroleum ether), mp. 102°C, yield 65%; IR (KBr, ν in $cm^{-1}$): 1710 (lactone C=O), 2120 ($N_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.54 (s, 2H, CH2—$N_3$), 6.56 (s, 1H, C3—H), 7.21 (d, 1H, C6—H, $J$ = 8.1 Hz), 7.41 (s, 1H, C8—H), 7.71 (d, 1H, C5—H, $J$ = 7.9 Hz). Anal. Calcd. for $C_{10}H_6ClN_3O_2$; C, 50.97; H, 2.57; N, 15.05; Found: C, 50.91; H, 2.52; N, 15.00.

**General procedure for the preparation of 1-(2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3a–3h).** Mixture of 4-azidomethylcoumarin **2** (0.01 mol) and DMAD (0.01 mol) was taken in a dry xylene (5 mL) in a round bottom flask. The mixture was refluxed in an oil bath at 130°C under dry conditions for 8 h (reaction was monitored by TLC) and then cooled. The separated solid was collected by filtration and recrystallized using suitable solvent.

**1-(6-Methyl-2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3a).** Colorless solid (ethanol), mp. 192°C, yield 76%; IR (KBr, ν in $cm^{-1}$): 1722 (lactone C=O), 1722 (ester C=O); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H, C6—$CH_3$), 3.95 (s, 3H, —$COOCH_3$), 4.02 (s, 3H, —$COOCH_3$), 5.60 (s, 1H, C3—H), 6.05 (s, 2H, C4—$CH_2$), 7.36 (d, 1H, C7—H, $J$ = 8.4 Hz), 7.51 (d, 1H, C8—H, $J$ = 8.4 Hz), 7.67 (s, 1H, C5—H); $^{13}C$ NMR (75 MHz, $CDCl_3$): 22, 50, 53, 54, 114, 117, 118, 124, 130, 134, 135, 141, 148, 152, 158, 161, 162; LCMS *m/z*: 358 [M + 1]. Anal. Calcd. for $C_{17}H_{15}N_3O_6$; C, 57.14; H, 4.23; N, 11.76; Found: C, 57.18; H, 4.17; N, 11.69.

**1-(7-Methyl-2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3b).** Colorless solid (benzene), mp. 151°C, yield 75%; IR (KBr, ν in $cm^{-1}$): 1722 (lactone C=O), 1754 (ester C=O); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H, C7—$CH_3$), 3.94 (s, 3H, —$COOCH_3$), 4.01 (s, 3H, —$COOCH_3$), 5.67 (s, 1H, C3—H), 6.03 (s, 2H, C4—$CH_2$), 7.17 (d, 1H, C6—H, $J$ = 7.2 Hz), 7.37 (s, 1H, C8—H), 7.57 (d, 1H, C5—H, $J$ = 7.1 Hz); LCMS *m/z*: 358 [M + 1]. Anal. Calcd. for $C_{17}H_{15}N_3O_6$; C, 57.14; H, 4.23; N, 11.76; Found: C, 57.19; H, 4.16; N, 11.72.

**1-(3-Oxo-3*H*-benzo[f]chromen-1-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3c).** Colorless solid (ethanol), mp. 180°C, yield 78%; IR (KBr, ν in $cm^{-1}$): 1731 (lactone C=O), 1731 (ester C=O); $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, —$COOCH_3$), 4.03 (s, 3H, —$COOCH_3$),

5.46 (s, 1H, C3—H), 6.54 (s, 2H, C4—$CH_2$), 7.52 (d, 1H, $J$ = 8.9 Hz), 7.62 (t, 1H, $J$ = 7.3 Hz), 7.72 (t, 1H, $J$ = 7.5 Hz), 8.00 (d, 1H, C7—H, $J$ = 8.0 Hz), 8.07 (d, 1H, $J$ = 8.9 Hz), 8.19 (d, 1H, C8—H, $J$ = 8.0 Hz). Anal. Calcd. for $C_{20}H_{15}N_3O_6$; C, 61.07; H, 3.84; N, 10.68; Found: C, 61.01; H, 3.79; N, 10.60.

**1-(2-Oxo-2*H*-benzo[*h*]chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3d).** Colorless solid (ethanol + dioxane), mp. 226°C, yield 79%; IR (KBr, ν in $cm^{-1}$): 1711 (lactone C=O), 1738 (ester C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H, —$COOCH_3$), 4.01 (s, 3H, —$COOCH_3$), 5.78 (s, 1H, C3—H), 6.10 (s, 2H, C4—$CH_2$), 7.20–8.54 (m, 6H, Ar—H). Anal. Calcd. for $C_{20}H_{15}N_3O_6$; C, 61.07; H, 3.84; N, 10.68; Found: C, 61.04; H, 3.80; N, 10.63.

**1-(6-Methoxy-2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3e).** Colorless solid (ethanol + dioxane), mp. 194°C, yield 70%; IR (KBr, ν in $cm^{-1}$): 1720 (lactone C=O), 1744 (ester C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, C6—$OCH_3$), 3.93 (s, 3H, —$COOCH_3$), 4.00 (s, 3H, —$COOCH_3$), 5.85 (s, 1H, C3—H), 6.01 (s, 2H, C4—$CH_2$), 7.16–7.34 (m, 3H, Ar—H). Anal. Calcd. for $C_{17}H_{15}N_3O_7$; C, 54.69; H, 4.05; N, 11.26; Found: C, 54.62; H, 4.17; N, 11.25.

**1-(7-Methoxy-2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3f).** Colorless solid (ethanol + dioxane), mp. 182°C, yield 69%; IR (KBr, ν in $cm^{-1}$): 1722 (lactone C=O), 1742 (ester C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, C7—$OCH_3$), 3.96 (s, 3H, —$COOCH_3$), 4.01 (s, 3H, —$COOCH_3$), 5.89 (s, 1H, C3—H), 6.08 (s, 2H, C4—$CH_2$), 7.21–7.92 (m, 3H, Ar—H). Anal. Calcd. for $C_{17}H_{15}N_3O_7$; C, 54.69; H, 4.05; N, 11.26; Found: C, 54.60; H, 4.13; N, 11.21.

**1-(6-Chloro-2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3g).** Colorless solid (ethanol), mp. 209°C, yield 72%; IR (KBr, ν in $cm^{-1}$): 1726 (lactone C=O), 1726 (ester C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H, —$COOCH_3$), 4.02 (s, 3H, —$COOCH_3$), 5.77 (s, 1H, C3—H), 6.01 (s, 2H, C4—$CH_2$), 7.35 (d, 1H, C7—H, $J$ = 8.8 Hz), 7.57 (d, 1H, C8—H, $J$ = 8.7 Hz), 7.70 (s, 1H, C5—H); LCMS *m/z*: 379 [M + 2]. Anal. Calcd. for $C_{16}H_{12}ClN_3O_6$; C, 50.87; H, 3.20; N, 11.12; Found: C, 50.79; H, 3.15; N, 11.05.

**1-(7-Chloro-2-oxo-2*H*-chromen-4-ylmethyl)-1*H*-[1,2,3]triazole-4,5-dicaboxylic acid dimethyl ester (3h).** Colorless solid (ethanol), mp. 194°C, yield 70%; IR (KBr, ν in $cm^{-1}$): 1721 (lactone C=O), 1754 (ester C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, —$COOCH_3$), 4.04 (s, 3H, —$COOCH_3$), 5.81 (s, 1H, C3—H), 6.06 (s, 2H, C4—$CH_2$), 7.72–7.64 (m, 3H, Ar—H). Anal. Calcd. for $C_{16}H_{12}ClN_3O_6$; C, 50.87; H, 3.20; N, 11.12; Found: C, 50.75; H, 3.12; N, 11.09.

***Preparation of 6-methyl-4-[1,2,3]triazol-1ylmethyl-chromen-2-one (3i).*** To the 4-azido-methylcoumarin **2a** (0.01 mol) in a dry xylene (15 mL), dry acetylene gas was passed for 30 min and then the flask was sealed and heated in an oil bath at 130°C for 10 h (reaction was monitored by TLC). The flask was cooled, and the separated solid was filtered and recrystallized from alcohol. Colorless solid (ethanol), mp. 199°C, yield 69%; IR (KBr, ν in $cm^{-1}$): 1720 (lactone C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, C6—$CH_3$), 5.77 (s, 2H, C4—$CH_2$), 5.94 (s, 1H, C3—H), 7.28 (d, 1H, C7—H, $J$ = 8.7 Hz), 7.36 (s, 1H, C5—H), 7.40 (d, 1H, C8—H, $J$ = 8.6 Hz), 7.66 (d, 1H, triazole), 7.82 (d, 1H, triazole); LCMS *m/z*: 242 [M + 1]. Anal. Calcd. for $C_{13}H_{11}N_3O_2$; C, 64.72; H, 4.60; N, 17.42; Found: C, 64.68; H, 4.58; N, 17.40.

***Preparation of 6-methyl-4-(4-phenyl-[1,2,3]triazol-1-ylmethyl)-chromen-2-one (3j).*** Mixture of 4-azidomethylcoumarin **2a** (0.01 mol) and phenyl acetylene (0.01 mol) was taken in a dry xylene (5 mL) in a dry round bottom flask. The mixture was refluxed in an oil bath at 130°C under dry conditions for 10 h (reaction was monitored by TLC) and cooled. The separated solid was filtered and recrystallized from alcohol.Colorless solid (ethanol), mp. 168°C, yield 71%; IR (KBr, ν in $cm^{-1}$): 1738 (lactone C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, C6—$CH_3$), 5.77 (s, 2H, C4—$CH_2$), 6.10 (s, 1H, C3—H), 7.28–7.84 (m, 9H, Ar—H); LCMS *m/z*: 318 [M + 1]. Anal. Calcd. for $C_{19}H_{15}N_3O_2$; C, 71.91; H, 4.76; N, 13.24; Found: C, 71.80; H, 4.72; N, 13.18.

***Preparation of 4-(4,5-diphenyl-[1,2,3]triazol-1-ylmethyl)-6-methyl-chromen-2-one (3k).*** Mixture of 4-azidomethylcoumarin **2a** (0.01 mol) and diphenylacetylene (0.01 mol) was taken in a dry xylene (5 mL) in a dry round bottom flask. The mixture was refluxed in an oil bath at 130°C under dry conditions for 10 h (reaction was monitored by TLC) and cooled. The separated solid was filtered and recrystallized from alcohol.

Colorless solid (ethanol), mp. 170°C, yield 67%; IR (KBr, ν in $cm^{-1}$): 1732 (lactone C=O); $^1$H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, C6—$CH_3$), 5.58 (s, 2H, C4—$CH_2$), 5.70 (s, 1H, C3—H), 7.24–7.58 (m, 13H, Ar—H); LCMS *m/z*: 394 [M + 1]. Anal. Calcd. for $C_{25}H_{19}N_3O_2$; C, 76.32; H, 4.87; N, 10.68; Found: C, 76.26; H, 4.84; N, 10.65.

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## REFERENCES AND NOTES

[1] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew Chem Int Ed 2001, 40, 2004.

[2] Huisgen, R. Pure Appl Chem 1989, 61, 613.

[3] Wang, Z. Y.; Li, Q. H. Chem Commun 2003, 2450.

[4] Seregin, I. V.; Batog, L. V.; Makhova, N. N. Mendeleev Commun 2002, 12, 83.

[5] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew Chem Int Ed 2002, 114, 2708.

[6] Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-kauhaluoma, J. J Comb Chem 2003, 5, 826.

[7] Biagi, G.; Calderone, V.; Giorgi, I.; Livi, O.; Scartoni, V.; Baragatti, B.; Martinotti, E. Eur J Med Chem 2000, 5, 715.

[8] Kelley, J. L.; Kolbe, C. S.; Davis, R. G.; Mclean, E. W.; Soroko, F. E.; Cooper, B. R. J Med Chem 1995, 38, 4131.

[9] Ghate, M. D.; Kulkarni, M. V.; Shobha, R.; Kattimani, S. Y. Eur J Med Chem 2003, 38, 297.

[10] Melavanki, R. M.; Kusanur, R. A.; Kulkarni, M. V.; Kadadevarmath, J. S. J Lumin 2008, 128, 573.

[11] Nicolaides, D. N.; Fylaktakdiou, K. C.; Litinas, K. E.; Papageorgiou, G. K.; Hadjipavlou-Litina, D. J. J Heterocycl Chem 1998, 35, 619.

[12] Dey, B. B.; Shankarnarayan, Y. J Indian Chem Soc 1934, 11, 687.
[13] Kulkarni, M. V.; Pujar, B. G.; Patil, V. D. Arch Pharm (Weinheim) 1982, 316, 15.
[14] Kulkarni, M. V.; Patil, V. D. Arch Pharm (Weinheim) 1981, 314, 708.
[15] Aye, K. T.; Puddephatt, R. Inorg Chim Acta 1995, 235, 711.
[16] Abu-Orabi, S. T. Molecules 2002, 7, 302.
[17] Ziegler, T. Chem Rev 1991, 91, 651.
[18] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; et al. Gaussian 03 Revision B 04; Gaussian: Pittsburgh, 2003.

# *N*-Butyllithium-Mediated Reactions of 1-(2-Azidoarylmethyl)-1*H*-benzotriazoles with Alkyl Halides



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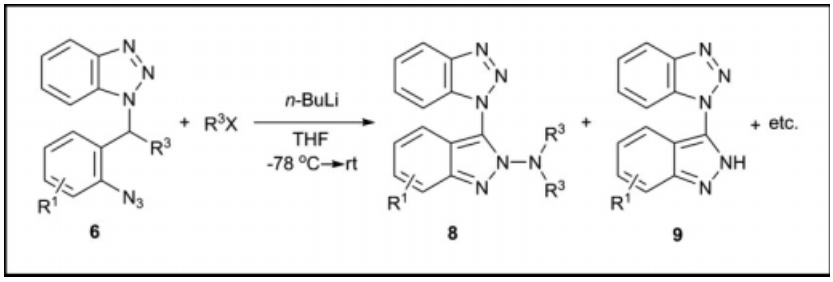



Treatment of 1-(2-azidoarylmethyl)-1*H*-benzotriazoles (**6**) with *n*-BuLi (2.5 equiv.) in THF at −78°C, followed by an addition of alkyl halides such as allyl, benzyl, and ethyl bromides with stirring for 2 h at room temperature afforded 2-(dialkylamino)-3-(benzotriazol-1-yl)-2*H*-indazoles (**8**), 3-(benzotriazol-1-yl)-2*H*-indazoles (**9**), 2-[(benzotriazol-1-yl)methyl]arylamine (**10**), and 2-[(benzotriazol-1-yl)(alkyl) methyl]arylamine (**11**).

*J. Heterocyclic Chem.*, **47**, 98 (2010).

## INTRODUCTION

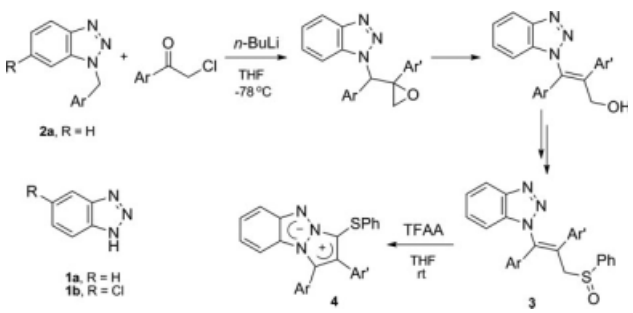
Benzotriazole has received a great amount of attention over the last three decades owing to the potential utility as a synthetic auxiliary for the synthesis of a diverse class of organic compounds [1]. Recently, we reported the reactions of 3-(benzotriazol-1-yl)-2,3-disubstituted propenyl phenyl sulfoxides **3** [2], prepared from 1-(arylmethyl)-1*H*-benzotriazoles **2a** and 1-aryl-2-chloroethanone in five steps, with trifluoroacetic anhydride (TFAA) yielding triazapentalenes **4** *via* a Pummerer-type intramolecular nucleophilic attack of N-2 of the benzotriazole moiety [2a] (Scheme 1).

In connection with the exploration of the synthetic utility of **1**, the introduction of an alkyl group at the benzylic position of 1-(2-azidoarylmethyl)-1*H*-benzotriazoles **6** ($R^2$ = 2-$N_3$) was attempted simply because the azido group may be utilized as a precursor for generation of nitrene [3]. Nitrene is known as a useful reactive species for the synthesis of nitrogen-containing heterocyclic compounds *via* insertion or addition reactions. One can envisage the reaction of a benzylic carbanion, generated from compounds **6** by a strong base, with alkyl halides. However, a problem to be encountered with this methodology is to overcome the possible reaction of the azido group with the strong base. A search through the literature showed that simple alkyl azides reacted with both Grignard reagents in diethyl ether at 0°C or alkyllithiums in *n*-pentane to give alkyltriazenes [4]. The latter reactions in ether did not occur. The reaction leading to triazenes was sensitive to the solvents. Furthermore, to the best of our knowledge, there has been no report on the reactions of aryl azides with both Grignard reagents and alkyllithiums. Compounds **6** are insoluble in *n*-pentane at room temperature. Consequently, it was necessary to obtain information on the reactivity of aryl azides including **6** toward various bases. The results obtained from our examination are described herein.

## RESULTS AND DISCUSSION

2-Azidobenzyl bromides **5** ($R^2$ = 2-$N_3$, X = Br), precursors of 1-(2-azidoarylmethyl)-1*H*-benzotriazoles **6a-b**, **6d-e**, and **6g**, were prepared by diazotization of *o*-toluidine derivatives, followed by bromination of the methyl group using NBS in the presence of benzoyl peroxide [5b]. On the other hand, 2-azidobenzyl chloride **5** ($R^2$ = 2-$N_3$, X = Cl), precursors of compounds **6c** and **6f**, were prepared by diazotization of 2-aminobenzyl alcohols, followed by chlorination using $SOCl_2$ in $CH_2Cl_2$. Treatment of **5** with benzotriazoles **1a-b** in the presence of NaOEt in absolute ethanol [6] gave a mixture of **6** and 2-(2-azidoarylmethyl)-2*H*-benzotriazoles **7** which were separated by chromatography (Scheme 2).

**Scheme 1**




Yields of compounds **6** and **7** are summarized in Table 1.

Treatment of **6a** with *n*-BuLi (1.1 equiv.) in THF at −78°C, followed by addition of allyl bromide (1.1 equiv.) with stirring for 1 h did not reveal any new spots except for those of the starting materials on TLC. However, after being stirred at room temperature for 2 h, TLC of the reaction mixture showed four spots including that corresponding to **6a** ($R_f$ = 0.71, EtOAc:*n*-hexane = 1:4). Chromatography of the reaction mixture (silica gel, 70–230 mesh) gave two 2*H*-indazole derivatives **8a** (R = $R^1$ = H) (25%), **9a** (R = $R^1$ = H) (21%), 2-[(benzotriazol-1-yl)methyl]phenylamine (**10a**) (R = $R^1$ = H) (25%) and 2-[1-(benzotriazol-1-yl)-3-butenyl]phenylamine (**11a**) (R = $R^1$ = H) (0%) together with unreacted **6a** (24%) containing a minute amount of 1-[(2-azidophenyl)(allyl)methyl]-1*H*-benzotriazole (**12a**) (Scheme 3). The yield of each product was variable depending on the concentrations of *n*-BuLi and allyl bromide. The results are summarized in Table 2.

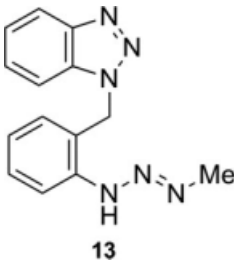
Table 2 shows that compounds **9a** and **10a** were formed without allyl bromide and a considerable amount of **6a** (40%) remained unreacted when 1.0 molar equiv. of *n*-BuLi was employed (entry 1). The result is inconsistent with the formation of dialkyltriazenes from analogous reactions involving simple alkyl azides and alkyllithiums in *n*-pentane [4a]. However, the reaction of **6a** with MeMgBr in THF for 1 h at 0°C, and subsequently at room temperature for 2 h, gave methyltriazene **13** (91%) as expected. The $^1$H NMR (300 MHz, $CDCl_3$) spectrum showed a singlet at 3.24 ppm, corresponding to the structure of **13**.

**Table 1**

Yields of compounds **6** and **7**.

| Compd | R | $R^1$ | $R^2$ | X | Compd | Yield[a] (%) **6** | **7** |
|---|---|---|---|---|---|---|---|
| **1a** | H | H | 2-$N_3$ | Br | **a** | 50 | 19 |
| **1a** | H | 5-MeO | 2-$N_3$ | Br | **b** | 44 | 19 |
| **1a** | H | 3-Me | 2-$N_3$ | Cl | **c** | 55 | 16 |
| **1a** | H | 5-Br | 2-$N_3$ | Br | **d** | 47 | 22 |
| **1a** | H | 4-Cl | 2-$N_3$ | Br | **e** | 51 | 26 |
| **1a** | H | 5-Cl | 2-$N_3$ | Cl | **f** | 48 | 23 |
| **1a** | H | 5-$NO_2$ | 2-$N_3$ | Br | **g** | 42 | 18 |
| **1a** | H | H | 4-$N_3$ | Br | **h** | 47 | 20 |
| **1b** | Cl | H | 2-$N_3$ | Br | **i** | 44[b] | 19 |

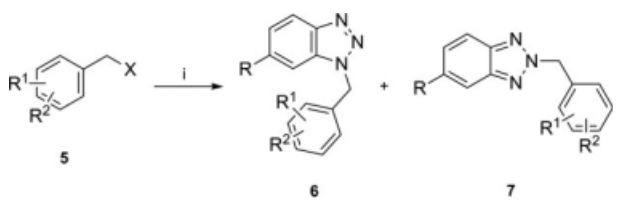
[a] Isolated yields.
[b] Total yield of 1-(2-azidobenzyl)-5-chloro-1*H*-benzotriazole (**6i′**) and 1-(2-azidobenzyl)-6-chloro-1*H*-benzotriazole (**6i**).




**13**

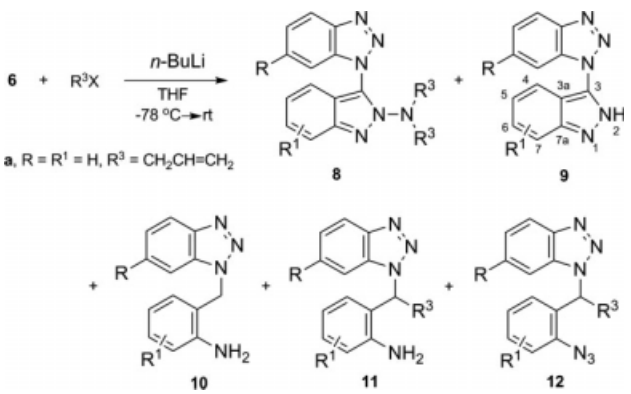
On addition of allyl bromide (1.1 equiv.), compound **8a** was obtained in 20% yield at the expense of **6a** and **10a** (entry 2). The amounts of recovered **6a** as well as **8a** were decreased somewhat by two-fold increase of the concentration of *n*-BuLi only (entry 3). When the concentrations of *n*-BuLi and allyl bromide were increased two-fold, respectively (entry 4), the yield of **8a** increased to 38% at the expense of **9a** and **6a**. However, further increase in the concentration of *n*-BuLi (4.0 equiv.) while maintaining the same concentration of

**Scheme 2.** Reagents and conditions: For X = Br, (i) **1a** (or **1b**), NaOEt, absolute EtOH, rt, 12 h; For X = Cl, (i) **1a**, NaOEt, absolute EtOH, reflux, 5 h.




**5** **6** **7**

**Scheme 3**




**8** **9** **10** **11** **12**

**Table 2**

Yields of compounds **8a**-**11a** at the different concentrations of *n*-BuLi and allyl bromide when [**6a**] = 1.40 mmol.

| Entry | *n*-BuLi (equiv.) | Allyl bromide (equiv.) | Yield[a] (%) | | | | |
|---|---|---|---|---|---|---|---|
| | | | **8a** | **9a** | **10a** | **11a** | Unreacted (**6a**) |
| 1 | 1.0 | 0 | 0 | 24 | 37 | 0 | 40 |
| 2 | 1.1 | 1.1 | 20 | 21 | 25 | 0 | 24[b] |
| 3 | 2.0 | 1.1 | 15 | 17 | 28 | 0 | 18[b] |
| 4 | 2.5 | 2.2 | 38 | 15 | 5 | 18 | 13[b] |
| 5 | 4.0 | 2.2 | 39 | 13 | 0 | 25 | 5[b] |

[a] Isolated yields.
[b] Yields on the basis of the $^1$H NMR intensities of a mixture of **6a** and **12a**.

allyl bromide (2.2 equiv.), did not affect the yields of **8a** and **9a** but only reduced the amount of unreacted **6a** by 5% (entry 5). Finally, the amount of unreacted **6a** decreased with increase in the concentration of *n*-BuLi and yet the yield of **8a** did not exceed 39%. In addition, the yields of **9a** were not much affected by altering the concentrations of either *n*-BuLi or allyl bromide.

Since the yields of compound **11a** increased with the concentrations of *n*-BuLi and allyl bromide (entries 4 and 5) and the sum of the yields of **10a** and **11a** appeared nearly constant, **10a**, prepared independently from **6a** and $NaBH_4$ [7], was treated with allyl bromide (2.5 and 3.0 equiv.) in the presence of *n*-BuLi (2.5 and 3.0 equiv.) in THF for 1 h at 0°C, and subsequently at room temperature for 2 h to observe if compound **11a** is formed *via* compound **10a**. From the reactions were obtained **11a** (0 and 3%), allyl[2-{(benzotriazol-1-yl)methyl}phenyl]amine (**14**) (38 and 16%), diallyl[2-{(benzotriazol-1-yl)methyl}phenyl]amine (**15**) (33 and 41%), and allyl[2-{1-(benzotriazol-1-yl)-3-butenyl}phenyl]-amine (**16**) (5 and 17%), respectively (Scheme 4). Compounds **14**–**16** were not detected in the reaction of **6a** under similar conditions but compound **11a** was observed (Scheme 4).

The result indicates that a small portion of compound **11a** may be formed *via* **10a**. For optimization of the reaction conditions, the reactions of **6a** (1.25 mmol) with allyl bromide were carried out in the presence of various bases under the same foregoing conditions. The results are summarized in Table 3.

Table 3 showed that not only a considerable amount of **6a** was used up to give unidentifiable mixtures but also a large quantity of unreacted **6a** was recovered. Consequently, *n*-BuLi was employed as a base for reactions of other compounds **6**. Yields of **8**–**11** and unreacted **6** are summarized in Table 4.

The structure of **8** was determined on the basis of the X-ray crystal structure of **8g** (Fig. 1).

The structures of **9** were determined on the basis of spectroscopic and analytical data. In particular, the HMBC spectrum of **9a** shows that the N2-H proton correlates with C3a and C7a carbon atoms, which clearly indicates that the compound is 2*H*-indazole derivative [8] rather than 1*H*-indazole derivative.

To obtain mechanistic information, **6h** was subjected to the same foregoing conditions (Scheme 5). From the reaction were obtained allylated compound **19** (4%) and amino compound **20** (45%) together with unreacted **6h** (28%). The result indicated that reduction of the azido group yielding amino group occurs readily compared with allylation at the benzylic position.

Although there exist plentiful examples of the direct conversion of an azido group to an amino group [9], *n*-BuLi-mediated the same type of conversion has seldom appeared in the literature [10]. We have found that treatment of simple aryl azides with *n*-BuLi (2.0 equiv.) under the same foregoing conditions gave arylamine as

**Scheme 4**

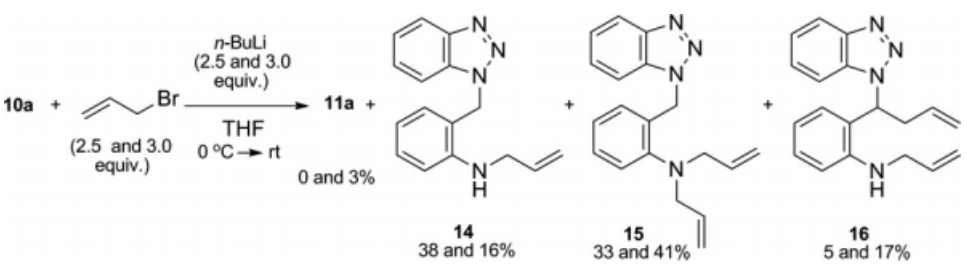


**Table 3**

Yields of compounds **8a**, **9a**, **10a**, and unreacted **6a**.

| Base (equiv.) | Condition[a] | Yield[b] (%) 8a | 9a | 10a | 6a |
|---|---|---|---|---|---|
| *tert*-BuLi (1.5) | [c] | | | [g] | |
| NaH (1.5) | [d] | 0 | 0 | trace | 82 |
| $NaNH_2$ (1.5) | [c] | 0 | 0 | 0 | 75 |
| *n*-BuLi (1.5) | [c,e] | 15 | 12 | 25 | 21 |
| $KN(SiMe_3)_2$ (1.5) | [c] | 5 | 0 | 0 | 81 |
| LDA (1.5) | [c,f] | 6 | 8 | 15 | 41 |
| LDA (1.2) | [c] | 9 | 15 | 13 | 33 |

[a] Allyl bromide (1.5 equiv.) was used.
[b] Isolated yields.
[c] −78°C (1 h) → rt (2 h), THF.
[d] rt (5 h), THF.
[e] *n*-BuLi, followed by *tert*-BuOK (1.0 equiv.) was added.
[f] LDA, followed by TMEDA (1.0 equiv.) was added.
[g] Unidentifiable complex mixture.

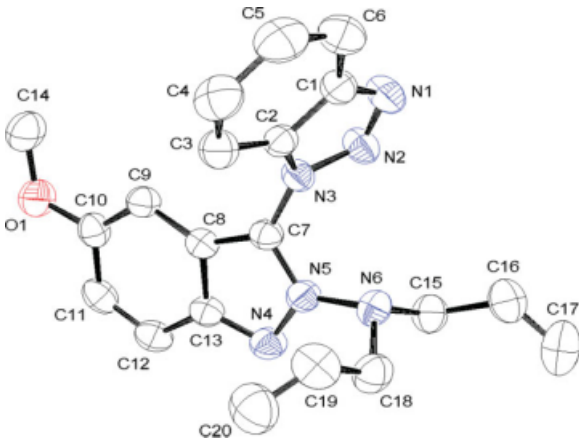



**Figure 1.** ORTEP drawing of **8g**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

major compounds (Scheme 6). Product yields are summarized in Table 5.

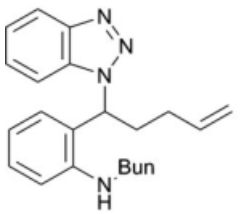
The formation of **19** coupled with **12c** as minor product indicates that alkylation at the benzylic position occurs under the conditions where the azido group is intact. Of course, compounds analogous to **8** and **9** cannot be formed from the reaction of **6h**. Interestingly, the reaction of **6a** with a mixture of an equal

**Table 4**

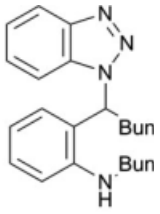
Yields of compounds **8a**, **9a**, **10a**, and unreacted **6a**.

| Reactant | | Product, Yield[a] (%) | | | | | |
|---|---|---|---|---|---|---|---|
| Compd (R) | $R^3$ | Compd | **8** ($R^1$) | **9** ($R^1$) | **10** ($R^1$) | **11** ($R^1$) | **6** ($R^1$) |
| **6a** (H) | $CH_2CH{=}CH_2$ | **a** | 38 (H) | 14 (H) | 2 (H) | 19 (H) | 3 (H) |
| **6a** (H) | Et | **b** | 25 (H) | 13 (H) | 21 (H) | 0 (H) | trace (H) |
| **6a** (H) | $CH_2CH_2CH{=}CH_2$ | **c** | 0 (0)[b] (H) | 16 (21)[b] (H) | 20 (14)[b] (H) | 4 (0)[b,c] | 0 (4)[b] (H) |
| **6a** (H) | Bn | **d** | 31 (H) | 16 (H) | 5 (H) | 6 (H) | 4 (H) |
| **6a** (H) | *n*-Bu | **e** | 0 (H) | 18 (H) | 0 (H) | 13[d] (H) | 0 (H) |
| **6a** (H) | *tert*-Bu | **f** | 0 (H) | 21 (H) | 14 (H) | 0 (H) | 31 (H) |
| **6b** (H) | $CH_2CH{=}CH_2$ | **g** | 24 (5-MeO) | 19 (5-MeO) | 8 (4-MeO) | 3[e] (4-MeO) | 3 (5-MeO) |
| **6c** (H) | $CH_2CH{=}CH_2$ | **h** | 34 (7-Me) | 13 (7-Me) | 10 (6-Me) | 5[e] (6-Me) | trace (3-Me) |
| **6d** (H) | $CH_2CH{=}CH_2$ | **i** | 26 (5-Br) | 14 (5-Br) | 7 (4-Br) | 4[e] (4-Br) | 2 (5-Br) |
| **6e** (H) | $CH_2CH{=}CH_2$ | **j** | 26 (6-Cl) | 16 (6-Cl) | 5 (5-Cl) | 6[e] (5-Cl) | 2 (4-Cl) |
| **6f** (H) | $CH_2CH{=}CH_2$ | **k** | 28 (5-Cl) | 17 (5-Cl) | 2 (4-Cl) | 8[e] (4-Cl) | 4 (5-Cl) |
| **6g** (H) | $CH_2CH{=}CH_2$ | | | | [f] | | |
| **6i** (Cl) | $CH_2CH{=}CH_2$ | **l** | 30 (H) | 12 (H) | 6 (H) | 0 (H) | 2 (H) |

[a] Isolated yields.
[b] All data were obtained when alkyl bromides (X = Br) were used. Number in the parenthesis represents yields when iodide was used.
[c] When $CH_2{=}CHCH_2CH_2Br$ was used, compounds **12c** (R = $R^1$ = H, $R^3$ = $CH_2CH_2CH{=}CH_2$) and **17** were additionally isolated in 18 and 3% yields, respectively, whereas only **12c** was additionally isolated in 13% yield when $CH_2{=}CHCH_2CH_2I$ was used.
[d] When *n*-BuBr was used, compound **18** was additionally isolated in 11% yield.
[e] Yields calculated on the basis of the intensities of the $^1H$ NMR spectra of a mixture of **10** and **11**.
[f] Unidentifiable complex mixtures were obtained when $R^1$ = 5-$NO_2$.

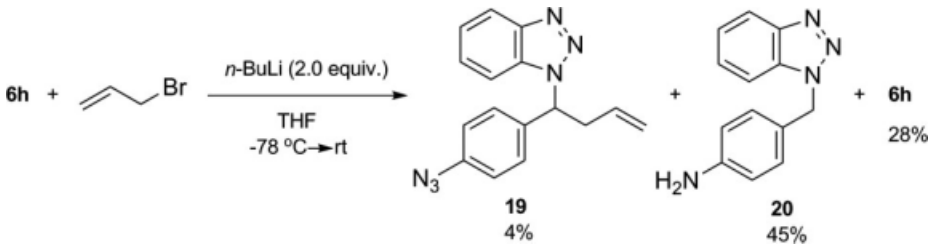



**17**




**18**

**Scheme 5**



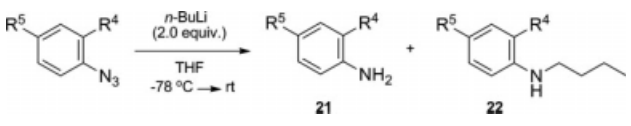

molar amount of allyl bromide (1.2 equiv.) and benzyl bromide (1.2 equiv.) under the same foregoing conditions showed four spots on TLC (silica gel, EtOAc:*n*-hexane = 1:4), corresponding to **8d** ($R_f = 0.79$), a mixture of **8a** and **23** ($R_f = 0.70$), **9a** ($R_f = 0.42$), and **10a** ($R_f = 0.27$) along with a weak spot having a long tail (Scheme 7).

An attempt at separation of the mixture of **8a** and **23** was unsuccessful. However, FAB MS shows mass number (*m*/*z*) 331 ($M^+ + 1$) and 381 ($M^+ + 1$), corresponding to the molecular weight of **8a** and **23** plus one, respectively. The formation of **23** suggests that the $R^3$ of compounds **8** is introduced in a stepwise manner.

The formation of compound **8a** may be initiated by deprotonation of benzylic hydrogen to give a carbanion **24**, followed by an intramolecular nucleophilic attack of the carbanion on the tetravalent nitrogen atom of an azido group, leading to a five-membered intermediate **25** with a negative charge on each nitrogen atom (Scheme 8).

Monoalkylation of **25** gives 1,3-dipolar intermediate **26a**, which is stabilized by a resonance form **26b**. Subsequent allylation, followed by deprotonation would give **8a**. In the meantime, a nucleophilic attack of *n*-butyl carbanion on an azido group gives 1-*n*-butyl-3-phenyltriazene **27a** [4], which may be stabilized by a resonance form **27b**. Intramolecular proton transfer of **27a** would generate a carbanion **28**. Protonation of **28**, followed by decomposition would give **10a** or **17** [11]. Alternatively, compounds **10a** and **17** can be formed from intermediate **27** *via* the same protonation and decomposition processes. In contrast, intramolecular nucleophilic attack of the benzylic carbanion **29**, a tautomer of **28**, on the trivalent nitrogen concomitant with displacing the *n*-butylamide ion would lead to **30**, a tautomer of **9a** and **31**. However, we obtained **9a** as a single compound. It has been reported that 1*H*-indazoles are thermodynamically more stable than 2*H*-indazoles [12] and that the equilibrium position between tautomers is dependent on the solvent polarity. However, molecular mechanics calculations show that **8g** ($E = 35.75$ kcal/mol) is more stable than its 1*H*-isomer ($E = 38.54$ kcal/mol) by 2.79 kcal/mol [13]. Similarly, 2*H*-indazole **9a** ($E = 29.75$ kcal/mol) is more stable than its 1*H*-indazole isomer ($E = 33.70$ kcal/mol) by 3.95 kcal/mol. This tendency is consistent with the experimental results. Further study is necessary to delineate why 2*H*-**8** and 2*H*-**9** are more stable than 1*H*-**8** and 1*H*-**9**, respectively. A nucleophilic attack of the carbanion **24** on allyl bromide would give **12a**, analogous to **19**. A similar reaction of **12a** as shown in the formation of **10a** from **27a** would give **11a**.

**Scheme 6**




## CONCLUSION

In summary, when 1-(2-azidoarylmethyl)-1*H*-benzotriazoles (**6**) was treated with *n*-BuLi in THF at −78°C, followed by an addition of alkyl halides, *i.e.*, allyl, benzyl, ethyl bromides, TLC did not exhibit any new spots. On the other hand, four new spots corresponding to 2*H*-indazole derivatives **8** and **9**, which to the best of our knowledge had not been previously reported in the reactions of azido compounds, together with some weak spots, were observed at room temperature. Compounds **8** are envisaged to be formed by a nucleophilic attack of benzylic carbanion on the azido group, followed by displacement of halides twice in stepwise manner by the $S_N2$ mechanism. Compounds **9** would be formed by a nucleophilic attack of benzylic carbanion on triazenes. The formation of compounds **10** and **11** may be

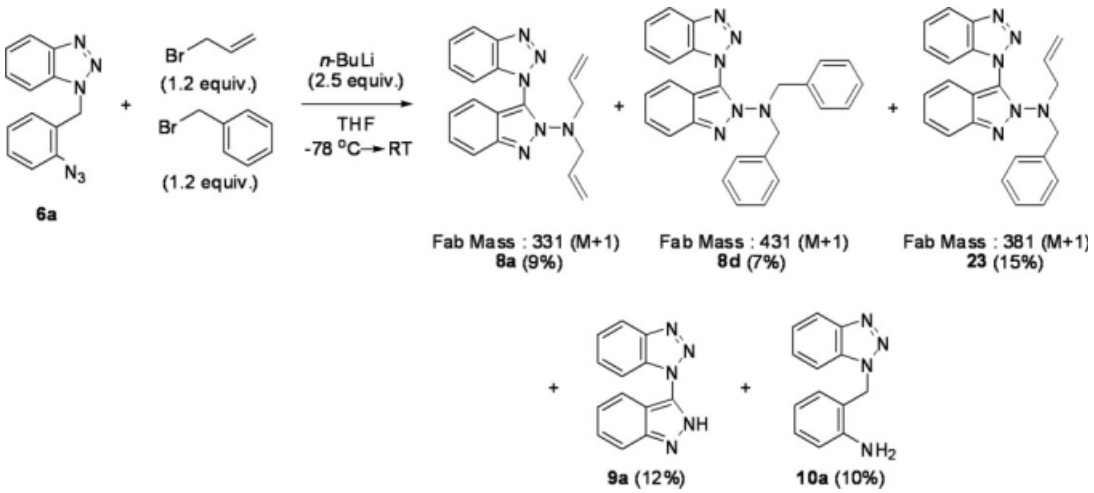
**Table 5**

Yields of compounds **21** and **22**.

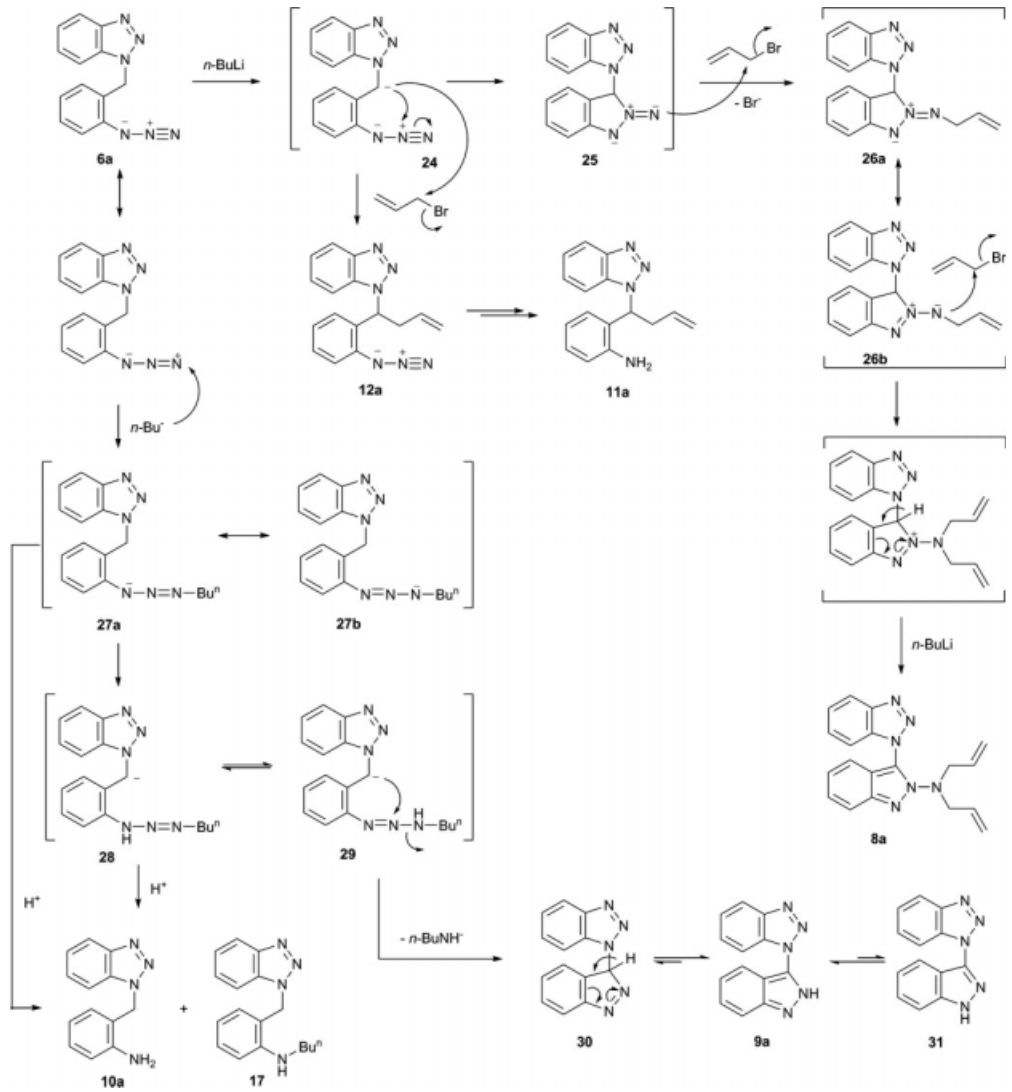
| Compd | $R^4$ | $R^5$ | Yield[a] (%) **21** | Yield[a] (%) **22** |
|---|---|---|---|---|
| **a** | H | Me | 69 | 8 |
| **b** | Me | H | 76 | 6 |
| **c** | Et | H | 69 | 8 |
| **d** | Bz | H | 72 | 7 |

[a] Isolated yields.

**Scheme 7.** Reaction of **6a** with the mixture of an equal molar amount of allyl bromide and benzyl bromide.




**Scheme 8.** Proposed mechanism of formation to the compounds **8**, **9**, **10**, **11**, and **17**.



explained in terms of decomposition of triazene, which has been reported in the literature [5].

## EXPERIMENTAL

The $^1$H NMR spectra was recorded at 300 MHz, unless otherwise stated in $CDCl_3$ solution containing tetramethylsilane as internal standard: *J* values are given in hertz (Hz). The $^{13}$C NMR spectra were recorded at 75 MHz, unless otherwise stated in $CDCl_3$ solution. IR spectra were recorded in KBr or thin-film samples on KBr plates. Mass spectra were obtained by electron impact at 70 eV. Elemental analyses were determined by the National Center for Inter-University Research Facilities, Seoul National University. Column chromatography was performed using silica gel (Merck, 70-230 mesh ASTM). Mps were determined on a Fisher–Johns melting-point apparatus and are uncorrected.

**General procedure for the synthesis of 2-azidoarylmethyl halides 5**

***2-Azidoarylmethyl bromides 5a-b, 5d-e, and 5g-h.*** To a stirred solution of arylamine (32.80 mmol) in concentrated $H_2SO_4$ (6 mL) was added $NaNO_2$ (39.36 mmol) at 0°C. The mixture was stirred for 30 min, followed by addition of $NaN_3$ (55.76 mmol), which was additionally stirred for 24 h. Work-up according to the literature procedure [5a] gave substituted 2-azidotoluenes. A mixture of 2-azidotoluene, *N*-bromosuccinimide (NBS) (1.05 equiv.) and benzoyl peroxide (0.05 equiv.) in benzene (60 mL) was heated at reflux for 24 h [5b]. Usual work-up of the reaction mixture gave **5a-b** (73, 87%), **5d-e** (79, 64%), and **5g** (89%), respectively. Similarly, 4-azidobenzyl bromide (**5h**) was prepared from 4-azidotoluene in 90% yield.

***2-Azidoarylmethyl chlorides 5c and 5f.*** To a stirred solution of substituted 2-aminoarylmethyl alcohols (32.80 mmol) in concentrated $H_2SO_4$ (6 mL) was added $NaNO_2$ (39.36 mmol) at 0°C for 30 min, followed by addition of $NaN_3$ (55.76 mmol). The mixture was additionally stirred for 24 h, followed by usual work-up gave substituted 2-azidoarylmethyl alcohol. Treatment of 2-azidoarylmethyl alcohols with thionyl chloride [5c] (1.2 equiv.) at 0°C for 3 h gave **5c** (63%) and **5f** (62%).

**General procedure for the synthesis of 1-(2-azidoarylmethyl)-1*H*-benzotriazoles 6 and 2-(2-azidoarylmethyl)-2*H*-benzotriazoles 7.** To a stirred solution of sodium (5.65–8.82 mmol) in absolute ethanol (20 mL) was added a solution of benzotriazole (**1a**) (5.38–8.40 mmol) in absolute ethanol (30 mL). The mixture was stirred for 20 min, followed by addition of **5** (5.65–8.82 mmol), which was heated for 3.5 h at reflux. Work-up according to the literature procedure [6] gave compounds **6** and **7**. Yields are listed in Table 1.

***1-(2-Azidophenylmethyl)-1H-benzotriazole 6a.*** Mp 97–99°C (from EtOAc–*n*-hexane) (Found: C, 62.3; H, 3.95; N, 33.7. Calc. for $C_{13}H_{10}N_6$: C, 62.4; H, 4.0; N, 33.6%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3040, 2944, 2112, 1572, 1480, 1441, 1302, 1278, 1216, 1152, 1073, 752, 739, and 523; $^1$H NMR δ 5.83 (2H, s, $CH_2$), 7.05–7.16 (2H, m, ArH), 7.22 (1H, d, *J* 8.0, ArH), 7.34–7.41 (2H, m, ArH), 7.46 (1H, dd, *J* 8.3 and 1.0, ArH), 7.53 (1H, d, *J* 7.2, ArH) and 8.08 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 47.4, 110.2, 118.7, 120.4, 124.3, 125.6, 126.3, 126.4, 127.8, 130.3, 133.3, 138.3, and 146.5.

***2-(2-Azidophenylmethyl)-2H-benzotriazole 7a.*** Mp 114–116°C (from EtOAc–*n*-hexane) (Found: C, 62.35; H, 3.9; N, 33.7. Calc. for $C_{13}H_{10}N_6$: C, 62.4; H, 4.0; N, 33.6%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2936, 2104, 1577, 1489, 1444, 1283, 1158, 1084, 851, 745, and 530; $^1$H NMR δ 5.86 (2H, s, $CH_2$), 7.05 (1H, t, *J* 7.5, ArH), 7.12 (1H, d, *J* 7.5, ArH), 7.21 (1H, d, *J* 7.6, ArH), 7.28 (1H, d, *J* 7.7, ArH), 7.33 (2H, dd, *J* 6.6 and 3.1, ArH), and 7.86 (2H, dd, *J* 6.6 and 3.1, ArH); $^{13}$C NMR δ 55.6, 118.6, 118.7, 125.4, 126.2, 126.8, 130.4, 130.9, 138.7, and 144.7.

***1-[(2-Azido-5-methoxy)phenylmethyl]-1H-benzotriazole 6b.*** Mp 89–91°C (from EtOAc–*n*-hexane) (Found: C, 56.1; H, 4.3; N, 30.1. Calc. for $C_{14}H_{12}N_6O$: C, 56.0; H, 4.3; N, 30.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2930, 2824, 2108, 1603, 1494, 1446, 1424, 1281, 1236, 1155, 1078, 1032, 811, 744, and 521; $^1$H NMR δ 3.67 (3H, s, $OCH_3$), 5.77 (2H, s, $CH_2$), 6.67 (1H, d, *J* 2.8, 1H, ArH), 6.88 (1H, dd, *J* 8.8 and 2.8, ArH), 7.12 (1H, d, *J* 8.8, ArH), 7.36 (1H, t, *J* 7.1, ArH), 7.45 (1H, t, *J* 6.8, ArH), 7.55 (1H, d, *J* 8.3, ArH), and 8.06 (1H, *J* 8.3 Hz, ArH); $^{13}$C NMR δ 47.3, 56.0, 110.3, 115.4, 116.0, 119.8, 120.4, 124.4, 127.4, 127.9, 130.4, 133.2, 146.5, and 157.4.

***2-[(2-Azido-5-methoxy)phenylmethyl]-2H-benzotriazole 7b.*** Mp 102–104°C (from EtOAc–*n*-hexane) (Found: C, 56.2; H, 4.3; N, 29.9. Calc. for $C_{14}H_{12}N_6O$: C, 56.0; H, 4.3; N, 30.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2936, 2824, 2112, 1603, 1556, 1489, 1454, 1424, 1281, 1236, 1161, 1030, 841, 746, 624, and 521; $^1$H NMR δ 3.71 (3H, s, $OCH_3$), 5.85 (2H, s, $CH_2$), 6.79 (1H, d, *J* 2.9, ArH), 6.90 (1H, dd, *J* 8.8 and 2.9, ArH), 7.11 (1H, d, *J* 8.8, ArH), 7.37 (2H, dd, *J* 6.6 and 3.1, ArH), and 7.88 (2H, dd, *J* 6.6 and 3.1, ArH); $^{13}$C NMR δ 55.6, 56.0, 115.9, 116.2, 118.6, 119.8, 126.9, 127.1, 131.0, 144.9, and 157.3.

***1-[(2-Azido-3-methyl)phenylmethyl]-1H-benzotriazole 6c.*** Mp 54–56°C (from EtOAc–*n*-hexane) (Found: C, 63.55; H, 4.5; N, 31.9. Calc. for $C_{14}H_{12}N_6$: C, 63.6; H, 4.6; N, 31.8%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2936, 2104, 1606, 1585, 1454, 1427, 1340, 1286, 1220, 1153, 1084, 774, 740, and 520; $^1$H NMR δ 2.42 (3H, s, $CH_3$), 5.86 (2H, s, $CH_2$), 6.91 (1H, d, *J* 7.1, ArH), 6.99 (1H, t, *J* 7.6, ArH), 7.10 (1H, d, *J* 7.4, ArH), 7.32 (1H, dt, *J* 1.3 and 6.7, ArH), 7.37–7.49 (2H, m, ArH), and 8.04 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 18.3, 48.6, 110.1, 120.3, 124.3, 126.7, 127.7, 127.8, 128.8, 132.3, 133.3, 133.5, 136.5, and 146.5.

***2-[(2-Azido-3-methyl)phenylmethyl]-2H-benzotriazole 7c.*** Viscous liquid (Found: C, 63.5; H, 4.5; N, 31.95. Calc. for $C_{14}H_{12}N_6$: C, 63.6; H, 4.6; N, 31.8%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3040, 2948, 2110, 1607, 1585, 1454, 1420, 1342, 1286, 1221, 1150, 1084, 845, 746, and 521; $^1$H NMR δ 2.48 (3H, s, $CH_3$), 5.99 (2H, s, $CH_2$), 7.06–7.11 (2H, m, ArH), 7.15–7.19 (1H, m, ArH), 7.38 (2H, dd, *J* 6.6 and 3.1, ArH), and 7.89 (2H, dd, *J* 6.6 and 3.1, ArH); $^{13}$C NMR δ 18.5, 56.9, 118.6, 126.7, 126.8, 128.5, 128.8, 132.5, 133.6, 137.2, and 145.0.

***1-[(2-Azido-5-bromo)phenylmethyl]-1H-benzotriazole 6d.*** Mp 84–86°C (from EtOAc–*n*-hexane) (Found: C, 47.3; H, 2.8; N, 25.45. Calc. for $C_{13}H_9BrN_6$: C, 47.4; H, 2.8; N, 25.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2948, 2110, 1574, 1482, 1441, 1302, 1288, 1217, 1154, 1073, 752, 740, and 521; $^1$H NMR δ 5.77 (2H, s, $CH_2$), 7.09 (1H. d, *J* 8.5, ArH), 7.27 (1H, d, $J = 2.1$, ArH), 7.37–7.43 (1H, m, ArH), 7.46–7.56 (3H, m, ArH), and 8.10 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 46.8, 109.9, 118.5, 120.3, 120.6, 124.5, 128.1, 133.2, 133.3, 137.5, and 146.5.

***2-[(2-Azido-5-bromo)phenylmethyl]-2H-benzotriazole 7d.*** Mp 94–96°C (from EtOAc–*n*-hexane) (Found: C, 47.25; H, 2.9; N, 25.5. Calc. for $C_{13}H_9BrN_6$: C, 47.4; H, 2.8; N, 25.5%); $\nu_{max}$

(KBr)/cm$^{-1}$ 3056, 2942, 2110, 1575, 1480, 1444, 1302, 1289, 1218, 1156, 1074, 754, 739, and 521; $^1$H NMR δ 5.85 (2H, s, $CH_2$), 7.09 (1H. d, *J* 8.6, ArH), 7.38 (1H, d, *J* = 2.2, ArH), 7.42 (2H, dd, 6.6 and 3.1, ArH), 7.50 (1H, dd, 8.5 and 2.2, ArH), and 7.90 (2H, dd, 6.6 and 3.1, ArH); $^{13}$C NMR δ 55.1, 118.3, 118.6, 120.3, 127.1, 127.9, 133.5, 133.7, 138.0, and 145.0.

***1-[(2-Azido-4-chloro)phenylmethyl]-1H-benzotriazole 6e.*** Mp 72–74°C (from EtOAc–*n*-hexane) (Found: C, 54.9; H, 3.1; N, 29.4. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2952, 2112, 1572, 1480, 1444, 1302, 1278, 1210, 1160, 1074, 756, and 516; $^1$H NMR δ 5.77 (2H, s, $CH_2$), 7.06 (2H, s, ArH), 7.20 (1H, s, ArH), 7.37–7.42 (1H, m, ArH), 7.45–7.54 (2H, m, ArH), and 8.08 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 46.8, 110.0, 118.9, 120.5, 124.5, 124.8, 125.9, 128.0, 131.4, 133.2, 135.9, 139.6, and 146.5.

***2-[(2-Azido-4-chloro)phenylmethyl]-2H-benzotriazole 7e.*** Mp 80–82°C (from EtOAc–*n*-hexane) (Found: C, 54.8; H, 3.15; N, 29.3. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2947, 2112, 1575, 1489, 1441, 1302, 1268, 1211, 1160, 1084, 756, 642, and 516; $^1$H NMR δ 5.85 (2H, s, $CH_2$), 7.10 (1H, dd, *J* 8.2 and 1.9, ArH), 7.20 (1H, d, *J* 1.9, ArH), 7.21 (1H, d, *J* 8.2, ArH), 7.41 (2H, dd, *J* 6.6 and 3.1, ArH), and 7.88 (2H, dd, *J* 6.6 and 3.1, ArH); $^{13}$C NMR δ 55.1, 118.5, 119.0, 124.6, 125.8, 127.0, 123.1, 136.2, 140.1, and 145.0.

***1-[(2-Azido-5-chloro)phenylmethyl]-1H-benzotriazole 6f.*** Mp 97–99°C (from EtOAc–*n*-hexane) (Found: C, 54.7; H, 3.2; N, 29.6. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3052, 2952, 2829, 2110, 1576, 1442, 1306, 1281, 1224, 1156, 1077, 904, 742, and 520; $^1$H NMR δ 5.77 (2H, s, $CH_2$), 7.11 (1H, s, ArH), 7.15 (1H, dd, *J* 8.6 and 2.7, ArH), 7.32–7.43 (2H, m, ArH), 7.47–7.54 (2H, m, ArH), and 8.09 (1H, d, *J* 7.7, ArH); $^{13}$C NMR δ 46.9, 109.9, 119.9, 120.6, 124.5, 128.0, 128.1, 130.2, 130.4, 131.1, 133.2, 136.9, and 146.5.

***2-[(2-Azido-5-chloro)phenylmethyl]-2H-benzotriazole 7f.*** Mp 113–115°C (from EtOAc–*n*-hexane) (Found: C, 54.8; H, 3.1; N, 29.65. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3054, 2952, 2828, 2112, 1580, 1444, 1307, 1281, 1224, 1156, 1078, 905, 746, and 516; $^1$H NMR δ 5.82 (2H, s, $CH_2$), 7.06 (1H, d, *J* 8.6, ArH), 7.19 (1H, d, *J* 2.4, ArH), 7.28 (1H, dd, *J* 8.6 and 2.4, ArH), 7.36 (2H, dd, *J* 6.6 and 3.1, ArH), and 7.87 (2H, dd, *J* 6.6 and 3.1, ArH); $^{13}$C NMR δ 55.1, 118.6, 119.9, 127.0, 127.7, 130.4, 130.7, 130.8, 137.3, and 145.0.

***1-[(2-Azido-5-nitro)phenylmethyl]-1H-benzotriazole 6g.*** Mp 144–146°C (from EtOAc–*n*-hexane) (Found: C, 52.9; H, 3.1; N, 10.7. Calc. for $C_{13}H_9N_7O_2$: C, 52.85; H, 3.1; N, 10.8%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3064, 3024, 2112, 1603, 1574, 1504, 1476, 1331, 1281, 1214, 1148, 1081, 824, 768, 736, and 526; $^1$H NMR δ 5.84 (2H, s, $CH_2$), 7.34 (1H, d, *J* 8.8, ArH), 7.37–7.43 (1H, m, ArH), 7.48–7.56 (2H, m, ArH), 8.03 (1H, d, *J* 2.5, ArH), 8.09 (1H, d, *J* 8.3, ArH), and 8.24 (1H, dd, *J* 8.8 and 2.6, ArH); $^{13}$C NMR δ 46.9, 109.6, 119.2, 120.7, 124.7, 125.8, 126.0, 127.5, 128.3, 133.2, 145.0, 145.1, and 146.4.

***2-[(2-Azido-5-nitro)phenylmethyl]-2H-benzotriazole 7g.*** Mp 171–173°C (from EtOAc–*n*-hexane) (Found: C, 53.0; H, 3.2; N, 10.7. Calc. for $C_{13}H_9N_7O_2$: C, 52.85; H, 3.1; N, 10.8%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3058, 3026, 2112, 1605, 1578, 1506, 1476, 1334, 1280, 1148, 1080, 824, 768, 624, and 526; $^1$H NMR δ 5.94 (2H, s, $CH_2$), 7.34 (1H, d, *J* 8.8, ArH), 7.42 (2H, dd, *J* 6.6 and 3.1, ArH), 7.88 (2H, dd, 6.6 and 3.1, ArH), 8.17 (1H, d, *J* 2.5, ArH), and 8.28 (1H, dd, *J* 8.8 and 2.5, ArH); $^{13}$C NMR δ 55.0, 118.6, 119.2, 125.9, 126.7, 127.1, 127.2, 144.9, 145.1, and 145.4.

***1-(4-Azidophenylmethyl)-1H-benzotriazole 6h.*** Mp 90–92°C (from EtOAc–*n*-hexane) (Found: C, 62.5; H, 4.0; N, 33.7. Calc. for $C_{13}H_{10}N_6$: C, 62.4; H, 4.0; N, 33.6%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2944, 2112, 1600, 1571, 1494, 1438, 1297, 1214, 1147, 1081, 822, 776, 758, 740, and 524; $^1$H NMR δ 5.83 (2H, s, $CH_2$), 7.00 (2H, d, *J* 8.5, ArH), 7.29 (2H, d, *J* 8.5, ArH), 7.33–7.46 (3H, m, ArH), and 8.08 (1H, d, *J* 9.0, ArH); $^{13}$C NMR δ 52.0, 109.9, 120.0, 120.6, 124.4, 127.9, 129.6, 131.8, 133.1, 140.8, and 146.8.

***2-(4-Azidophenylmethyl)-2H-benzotriazole 7h.*** Mp 108–110°C (from EtOAc–*n*-hexane) (Found: C, 62.45; H, 3.9; N, 33.7. Calc. for $C_{13}H_{10}N_6$: C, 62.4; H, 4.0; N, 33.6%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2924, 2110, 1601, 1573, 1495, 1438, 1280, 1210, 1147, 1081, 822, 774, 740, and 518; $^1$H NMR δ 5.87 (2H, s, $CH_2$), 7.01 (2H, d, *J* 8.4, ArH), 7.30 (2H, d, *J* 8.4, ArH), 7.38 (2H, dd, *J* 6.6 and 3.1, ArH), and 7.89 (2H, dd, *J* 6.6 and 3.1, ArH); $^{13}$C NMR δ 58.4, 111.4, 120.2, 124.5, 126.6, 130.3, 138.7, and 146.1.

**Reaction of 5-chlorobenzotriazole (1b) with 2-azidobenzyl bromide (5a).** In accordance with the aforementioned general procedure, **5a** (1770 mg, 8.34 mmol) was added to a mixture of **1b** (1220 mg, 7.94 mmol) and Na (183 mg, 8.34 mmol) in absolute ethanol (50 mL). The mixture was stirred for 12 h at room temperature. After removal of the solvent *in vacuo*, the residue was chromatographed on a silica gel (3.0 × 15 cm$^2$) using a mixture of EtOAc and *n*-hexane (1:5) to give 2-(2-azidophenylmethyl)-2*H*-(5-chlorobenzotriazole) (**7i**) (407 mg, 18%), a mixture of 1-(2-azidophenylmethyl)-6-chloro-1*H*-benzotriazole (**6i**) and 1-(2-azidophenylmethyl)-5-chloro-1*H*-benzotriazole (**6i′**) (995 mg, 44%) and unreacted **1b**. The mixture of **6i** and **6i′** (1:1 based on the $^1$H NMR signal of $CH_2$) was separated by the repeated recrystallization using a mixture of EtOAc and *n*-hexane (1:15) to give **6i** and **6i′** as solids.

***6i.*** Mp 77–79°C (from EtOAc–*n*-hexane) (Found: C, 54.7; H, 3.1; N, 29.5. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2952, 2848, 2112, 1575, 1481, 1440, 1302, 1278, 1206, 1155, 1074, 740, and 518; $^1$H NMR δ 5.78 (2H, s, $CH_2$), 7.07–7.17 (2H, m, ArH), 7.27 (1H, d, *J* 8.0, ArH), 7.33 (1H, dd, *J* 8.7 and 1.5, ArH), 7.40 (1H, td, *J* 7.5 and 2.0, ArH), 7.53 (1H, d, *J* 1.7, ArH), and 7.99 (1H, d, *J* 8.8, ArH); $^{13}$C NMR δ 47.6, 110.1, 118.8, 121.4, 125.6, 125.7, 125.8, 130.4, 130.6, 133.9, 134.3, 138.4, and 145.1.

***6i′.*** Mp 116–118°C (from EtOAc–*n*-hexane) (Found: C, 54.9; H, 3.0; N, 29.4. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3048, 2954, 2110, 1572, 1488, 1444, 1302, 1278, 1201, 1160, 1074, 756, 642, and 516; $^1$H NMR δ 5.80 (2H, s, $CH_2$), 7.10–7.18 (2H, m, ArH), 7.22 (1H, d, *J* 7.9, ArH), 7.39 (1H, d, *J* 1.4, ArH), 7.42 (1H, d, *J* 1.7, ArH), 7.46 (1H, s, ArH), and 8.04 (1H, d, *J* 1.7, ArH); $^{13}$C NMR δ 47.7, 111.3, 118.8, 119.7, 125.7, 128.8, 130.3, 130.4, 130.5, 130.6, 131.9, 138.4, and 147.1.

***7i.*** Mp 102–104°C (from EtOAc–*n*-hexane) (Found: C, 54.9; H, 3.1; N, 29.3. Calc. for $C_{13}H_9ClN_6$: C, 54.8; H, 3.2; N, 29.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3050, 2952, 2112, 1574, 1480, 1441, 1308, 1280, 1200, 1157, 1065, 756, 648, and 520; $^1$H NMR δ 5.88 (2H, s, $CH_2$), 7.14 (1H, td, *J* 7.7 and 1.5, ArH), 7.34 (1H,

dd, *J* 9.1 and 1.9, ArH), 7.42 (1H, td, *J* 8.0 and 1.5, ArH), 7.82 (1H, d, *J* 1.9, ArH), and 7.88 (1H, d, *J* 1.6, ArH); $^{13}$C NMR δ 55.9, 117.6, 118.8, 119.8, 125.5, 125.7, 128.4, 130.7, 131.0, 132.7, 138.9, 143.4, and 145.2.

**General procedure for the reactions of 6 with alkyl halides in the presence of *n*-BuLi.** To a solution of **6** (1.80 mmol) in THF (40 mL) at –78°C were added *n*-BuLi (2.5*M* in *n*-hexane, 4.50 mmol) and alkyl halide (4.50 mmol), which was stirred for 1 h. The mixture was additionally stirred for 2 h at room temperature, quenched by addition of water (30 mL) and extracted with $CH_2Cl_2$ (20 mL × 3). The combined extract was dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue, which was chromatographed on a silica gel (2.5 × 13 cm$^2$) using a mixture of EtOAc and *n*-hexane (1:6) to give 2-(*N*,*N*-dialkylamino)-3-(benzotriazol-1-yl)-2*H*-indazoles **8**, 3-(benzotriazol-1-yl)-2*H*-indazole **9**, 2-[(benzotriazol-1-yl)methyl]arylamines **10**, 2-[(benzotriazol-1-yl)(alkyl)methyl]arylamines **11**, and unreacted **6**.

**Reaction of 6a with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6a** (350 mg, 1.40 mmol), allyl bromide (423 mg, 3.50 mmol), and *n*-BuLi (3.50 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-diallylamino)-3-(benzotriazol-1-yl)-2*H*-indazole (**8a**) (176 mg, 38%), 3-(benzotriazol-1-yl)-2*H*-indazole (**9a**) (46 mg, 14%), 2-[(benzotriazol-1-yl)methyl]phenylamine (**10a**) (6 mg, 2%), 2-[1-(benzotriazol-1-yl)-3-butenyl]-phenylamine (**11a**) (70 mg, 19%), and unreacted **6a** (11 mg, 3%).

***8a.*** Mp 89–91°C (from *n*-hexane) (Found: C, 68.95; H, 5.5; N, 25.4. Calc. for $C_{19}H_{18}N_6$: C, 69.1; H, 5.5; N, 25.4%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2912, 2848, 1630, 1601, 1555, 1523, 1440, 1398, 1371, 1280, 1227, 1200, 1166, 1033, 990, 924, 836, 740, and 516; $^1$H NMR δ 3.86 (4H, d, *J* 6.6, $CH_2$), 4.96 (2H, *J* 17.4, $=CH_2$), 5.01 (2H, d, *J* 24.7, $=CH_2$), 5.49–5.65 (2H, m, =CH), 7.08–7.16 (1H, m, ArH), 7.23–7.31 (2H, m, ArH), 7.33–7.41 (1H, m, ArH), 7.43–7.57 (2H, m, ArH), 7.79 (1H, d, *J* 8.9, ArH), and 8.20 (1H, d, *J* 7.9, ArH); $^{13}$C NMR δ 60.8, 110.4, 115.7, 118.7, 118.8, 120.5, 120.7, 124.3, 125.0, 127.4, 129.1, 132.8, 135.1, 145.4, and 145.7.

***9a.*** Mp 219–220°C ($CH_2Cl_2$–*n*-hexane) (Found: C, 66.3; H, 3.8; N, 29.8. Calc. for $C_{13}H_9N_5$: C, 66.4; H, 3.9; N, 29.8%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3136, 3040, 2928, 2880, 1609, 1523, 1488, 1436, 1385, 1342, 1273, 1244, 1166, 1094, 1003, 984, 918, 892, and 737; $^1$H NMR δ (DMSO) 7.34 (1H, t, *J* 7.8, ArH), 7.52–7.62 (2H, m, ArH), 7.66–7.79 (2H, m, ArH), 8.25 (2H, d, *J* 8.3, ArH), 8.37 (1H, d, *J* 8.4, ArH), and 13.6 (1H, s, NH); $^{13}$C NMR δ (DMSO) 111.8, 113.7, 115.0, 120.5, 121.8, 122.9, 126.2, 128.8, 130.0, 132.1, 140.3, 142.1, and 145.9.

***10a.*** Mp 111–113°C (from EtOAc–*n*-hexane) (Found: C, 69.5; H, 5.3; N, 25.05. Calc. for $C_{13}H_{12}N_4$: C, 69.6; H, 5.4; N, 25.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3352, 3232, 3056, 2912, 1627, 1601, 1577, 1488, 1446, 1299, 1262, 1219, 1152, 1006, 740, and 521; $^1$H NMR δ 4.32 (2H, s, $NH_2$), 5.74 (2H, s, $CH_2$), 6.67 (1H, d, *J* 7.9, ArH), 6.77 (1H, t, *J* 7.5, ArH), 7.14 (1H, t, *J* 7.8, ArH), 7.29–7.36 (2H, m, ArH), 7.42 (1H, t, *J* 6.8, ArH), 7.53 (1H, d, *J* 8.3, ArH), and 8.04 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 50.6, 110.4, 117.2, 118.7, 118.9, 120.4, 124.5, 126.3, 128.0, 130.7, 131.1, 133.1, and 146.5.

***11a.*** Viscous liquid (Found: C, 72.6; H, 6.0; N, 21.35. Calc. for $C_{16}H_{16}N_4$: C, 72.7; H, 6.1; N, 21.2%); $\nu_{max}$ (film)/cm$^{-1}$ 3432, 3344, 3224, 3056, 2920, 1624, 1486, 1446, 1304, 1265, 1228, 1153, 996, 918, 740, and 520; $^1$H NMR δ 3.24–3.31 (1H, m, $CH_2$), 3.40–3.51 (1H, m, $CH_2$), 4.02 (2H, s, $NH_2$), 5.02 (1H, d, *J* 14.3, $=CH_2$), 5.07 (1H, d, *J* 20.6, $=CH_2$), 5.68–5.82 (1H, m, =CH), 6.09 (1H, dd, *J* 9.2 and 6.5, CH), 6.65 (1H, d, *J* 8.0, ArH), 6.84 (1H, t, *J* = 7.6, ArH), 7.14 (1H, dt, *J* 1.4 and 7.7, ArH), 7.28–7.39 (2H, m, ArH), 7.41–7.48 (2H, m, ArH), and 8.05 (1H, d, *J* = 7.4, ArH); $^{13}$C NMR δ 36.5, 60.8, 110.8, 117.6, 118.8, 119.2, 120.5, 124.4, 127.7, 128.0, 130.1, 132.6, 133.6, 145.8, and 147.0.

**Reaction of 6a with ethyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6a** (500 mg, 2.00 mmol), ethyl bromide (545 mg, 5.00 mmol), and *n*-BuLi (5.00 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-diethylamino)-3-(benzotriazol-1-yl)-2*H*-indazole (**8b**) (153 mg, 25%), **9a** (66 mg, 13%), and **10a** (94 mg, 21%).

***8b.*** Viscous liquid (Found: C, 66.7; H, 6.1; N, 27.25. Calc. for $C_{17}H_{18}N_6$: C, 66.65; H, 5.9; N, 27.4%); $\nu_{max}$ (film)/cm$^{-1}$ 3048, 2960, 2856, 1606, 1526, 1444, 1371, 1275, 1206, 1081, 1038, 1000, 966, 938, and 739; $^1$H NMR δ 0.83 (6H, t, *J* 7.1, $CH_3$), 3.27 (4H, d, *J* 6.2, $CH_2$), 7.15–7.21 (1H, m, ArH), 7.30 (2H, d, *J* 8.5, ArH), 7.42–7.56 (3H, m, ArH), 7.83 (1H, d, *J* 8.9, ArH), and 8.23 (1H, d, *J* 7.8, ArH); $^{13}$C NMR δ (DMSO) 12.6, 52.7, 110.1, 115.9, 118.6, 118,8, 120.8, 124.3, 124.9, 127.5, 129.2, 135.3, 145.6, and 145.7.

**Reaction of 6a with 4-bromo-1-butene.** In accordance with the aforementioned general procedure, a mixture of **6a** (400 mg, 1.60 mmol), 4-bromo-1-butene (540 mg, 4.00 mmol), and *n*-BuLi (4.00 mmol) was stirred for 1 h at −78°C and 2 h at room temperature. Chromatography of the reaction mixture gave **9a** (31 mg, 16%), **10a** (72 mg, 20%), 2-[1-(benzotriazol-1-yl)-4-pentenyl]phenylamine (**11c**) (18 mg, 4%), 1-[1-(2-azidophenyl)-4-pentenyl]-1*H*-benzotriazole (**12c**) (88 mg, 18%), [2-{1-(benzotriazol-1-yl)-4-pentenyl}phenyl]butylamine (**17**) (14 mg, 3%).

***11c.*** Viscous liquid (Found: C, 73.6; H, 6.4; N, 19.9. Calc. for $C_{17}H_{18}N_4$: C, 73.35; H, 6.5; N, 20.1%); $\nu_{max}$ (film)/cm$^{-1}$ 3434, 3226, 3048, 2924, 1604, 1487, 1441, 1308, 1272, 1220, 1154, 996, 740, and 520; $^1$H NMR δ 1.97–2.21 (2H, m, $CHCH_2CH_2$), 1.38–1.50 (1H, m, $CHCH_2CH_2$), 2.89–3.01 (1H, m, $CHCH_2CH_2$), 4.95 (1H, d, *J* 17.1, $=CH_2$), 5.03 (1H, d, *J* 10.1, $=CH_2$), 5.76–5.89 (1H, m, =CH), 6.20 (1H, dd, *J* 9.4 and 5.7, CH), 7.10 (1H, dt, *J* 1.0 and 7.3, ArH), 7.18 (1H, dd, *J* 8.0 and 1.0, ArH), 7.25–7.38 (2H, m, ArH), 7.42–7.51 (2H, m, ArH), 7.57 (1H, d, *J* 8.3, ArH), and 8.07 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 30.9, 34.3, 56.1, 110.2, 116.5, 118.4, 120.3, 124.4, 125.9, 127.6, 128.6, 129.9, 131.1, 133.7, 137.1, 137.4, and 146.2.

***12c.*** Viscous liquid (Found: C, 67.2; H, 5.2; N, 27.4. Calc. for $C_{17}H_{16}N_6$: C, 67.1; H, 5.3; N, 27.6%); $\nu_{max}$ (film)/cm$^{-1}$ 3056, 2928, 2848, 2112, 1675, 1632, 1601, 1483, 1443, 1264, 1211, 1153, 1070, 993, 910, 743, 696, and 523; $^1$H NMR δ 2.03–2.15 (2H, m, $CHCH_2CH_2$), 2.50–2.62 (1H, m, $CHCH_2CH_2$), 2.88–3.01 (1H, m, $CHCH_2CH_2$), 4.98 (1H, d, *J* 17.0, $=CH_2$), 5.04 (1H, d, *J* 10.2, $=CH_2$), 5.75–5.91 (2H, m, =CH and CH), 7.25–7.40 (7H, m, ArH), and 8.07 (1H, d, *J* 8.0, ArH); $^{13}$C NMR δ 30.9, 34.3, 63.0, 110.2, 116.7, 120.4, 124.3, 127.3, 127.6, 128.7, 129.3, 133.3, 137.2, 139.6, and 146.6.

***17.*** Viscous liquid (Found: C, 75.5; H, 7.65; N, 16.8. Calc. for $C_{21}H_{26}N_4$: C, 75.4; H, 7.8; N, 16.75%); $\nu_{max}$ (film)/cm$^{-1}$ 3264, 3056, 2936, 2856, 1630, 1603, 1475, 1440, 1392, 1198,

993, 910, 740, and 518; $^1$H NMR δ 1.03 (3H, t, *J* 7.3, $CH_3$), 1.45–1.57 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.69–1.72 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.01–2.14 (2H, m, $CHCH_2CH_2$), 2.48–2.59 (1H, m, $CHCH_2CH_2$), 2.91–3.06 (1H, m, $CHCH_2CH_2$), 3.76 (2H, t, *J* 7.1, $NCH_2$), 4.93 (1H, d, *J* 17.7, $=CH_2$), 4.98 (1H, d, *J* 10.5, $=CH_2$), 5.73–5.90 (2H, m, =CH and CH), 6.82 (1H, t, *J* = 7.2, NH), 7.13 (1H, t, *J* 6.9, ArH), 7.23 (1H, t, *J* 7.4, ArH), 7.29–7.51 (5H, m, ArH), and 8.06 (1H, d, *J* 7.7, ArH); $^{13}$C NMR δ 14.3, 20.9, 31.1, 33.0, 34.5, 44.6, 56.3, 110.6, 116.1, 120.1, 124.3, 127.0, 127.2, 127.3, 128.0, 129.0, 129.4, 133.8, 137.7, and 146.3.

**Reaction of 6a with 4-iodo-1-butene.** In accordance with the aforementioned general procedure, a mixture of **6a** (350 mg, 1.40 mmol), 4-iodo-1-butene (644 mg, 3.50 mmol), and *n*-BuLi (3.50 mmol) was stirred for 1 h at −78°C and 2 h at room temperature. Chromatography of the reaction mixture gave **9a** (68 mg, 21%), **10a** (44 mg, 14%), **12c** (55 mg, 13%), and unreacted **6a** (14 mg, 4%).

**Reaction of 6a with benzyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6a** (320 mg, 1.28 mmol), benzyl bromide (547 mg, 3.20 mmol), and *n*-BuLi (3.20 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-dibenzylamino)-3-(benzotriazol-1-yl)-2*H*-indazole (**8d**) (171 mg, 31%), **9a** (48 mg, 16%), **10a** (14 mg, 5%), 2-[{1-(benzotriazol-1-yl)-2-phenyl}ethyl]phenylamine (**11d**) (24 mg, 6%), and unreacted **6a** (13 mg, 4%).

***8d.*** Mp 115–117°C (from EtOAc–*n*-hexane) (Found: C, 75.25; H, 5.0; N, 19.6. Calc. for $C_{27}H_{22}N_6$: C, 75.3; H, 5.15; N, 19.5%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3040, 2912, 2848, 1628, 1595, 1555, 1524, 1486, 1446, 1396, 1372, 1278, 1227, 1198, 1166, 1030, 904, 739, 694, and 520; $^1$H NMR δ 4.49 (4H, s, $CH_2$), 6.52 (1H, d, *J* 8.3, ArH), 6.99–7.21 (11H, m, ArH), 7.29–7.36 (2H, m, ArH), 7.41–7.47 (2H, m, ArH), 7.89 (1H, d, *J* 8.9, ArH), 8.22 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 61.5, 110.4, 114.9, 118.7, 118.8, 120.3, 124.1, 124.8, 127.5, 128.2, 128.7, 129.6, 134.5, 136.2, 145.4, and 145.5.

***11d.*** Viscous liquid (mixed with **10a**); $^1$H NMR δ 4.28 (2H, s, $NH_2$), 4.50 (2H, d, *J* 5.0, $CH_2$), 6.18 (1H, dd, *J* 8.2 and 4.9, CH), 6.53 (1H, d, *J* 8.3, ArH), 7.09–7.46 (10H, m, ArH), 8.06 (1H, d, *J* 8.3, ArH), and 8.43 (1H, d, *J* 8.3, ArH).

**Reaction of 6a with *n*-butyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6a** (350 mg, 1.40 mmol), *n*-butyl bromide (480 mg, 3.50 mmol), and *n*-BuLi (3.50 mmol) was stirred. Chromatography of the reaction mixture gave **9a** (59 mg, 18%), 2-[1-(benzotriazol-1-yl)pentyl]phenylamine (**11e**) (51 mg, 13%), [2-{1-(benzotriazol-1-yl)pentyl}phenyl]butylamine (**18**) (50 mg, 11%).

***11e.*** Viscous liquid (Found: C, 72.6; H, 7.3; N, 19.9. Calc. for $C_{17}H_{20}N_4$: C, 72.8; H, 7.2; N, 20.0%); $\nu_{max}$ (film)/cm$^{-1}$ 3048, 2928, 2856, 1600, 1577, 1483, 1448, 1368, 1264, 1214, 1155, 774, 739, 694, and 518; $^1$H NMR δ 0.89 (3H, t, *J* 7.2, $CH_3$), 1.24–1.37 (4H, m, $CH_2CH_2CH_2CH_3$), 2.45–2.56 (1H, m, $CHCH_2$), 2.74–2.87 (1H, m, $CHCH_2$), 4.05 (2H, s, $NH_2$), 5.80 (1H, dd, *J* 9.0 and 6.5, CH), 7.29–7.40 (7H, m, ArH), and 8.07 (d, *J* 8.0, ArH); $^{13}$C NMR δ 14.3, 22.7, 29.2, 34.9, 64.2, 110.3, 120.4, 124.3, 126.3, 127.3, 127.5, 128.6, 128.8, 129.3, 133.2, 139.8, and 146.6.

***18.*** Viscous liquid (Found: C, 67.2; H, 5.2; N, 27.4. Calc. for $C_{21}H_{28}N_4$: C, 67.1; H, 5.3; N, 27.6%); $\nu_{max}$ (film)/cm$^{-1}$ 3385, 3056, 2928, 2850, 1601, 1578, 1473, 1446, 1392, 1193, 1153, 1086, 774, 740, and 521; $^1$H NMR δ 0.88 (3H, t, *J* 6.8, $CHCH_2CH_2CH_2CH_3$), 1.02 (3H, t, *J* 7.3, $NCH_2CH_2CH_2CH_3$), 1.27–1.44 (4H, m, $CHCH_2CH_2CH_2CH_3$), 1.45–1.56 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.69–180 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.40–2.51 (1H, m, $CHCH_2CH_2CH_2CH_3$), 2.77–2.90 (1H, m, $CHCH_2CH_2CH_2CH_3$), 3.76 (2H, dt, *J* 3.4 and 7.0, $NCH_2$), 6.72 (1H, t, *J* 6.9, NH), 7.12 (1H, dt, *J* 1.1 and 7.4, ArH), 7.24 (1H, dt, *J* 1.4 and 7.9, ArH), 7.31–7.49 (5H, m, ArH), and 8.05 (1H, d, *J* 7.3, ArH); $^{13}$C NMR δ 14.2, 14.3, 20.7, 22.7, 29.2, 32.1, 35.1, 44.0, 57.3, 110.5, 117.2, 120.1, 124.1, 127.0, 127.1, 127.3, 128.9, 133.8, and 146.3.

**Reaction of 6a with *tert*-butyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6a** (350 mg, 1.40 mmol), *tert*-butyl bromide (480 mg, 3.50 mmol), and *n*-BuLi (3.50 mmol) was stirred. Chromatography of the reaction mixture gave **9a** (69 mg, 21%), **10a** (60 mg, 14%), and unreacted **6a** (109 mg, 31%).

**Reaction of 6b with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6b** (400 mg, 1.43 mmol), allyl bromide (432 mg, 3.58 mmol), and *n*-BuLi (3.58 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-dibenzylamino)-3-(benzotriazol-1-yl)-5-methoxy-2*H*-indazole (**8g**) (124 mg, 24%), 3-(benzotriazol-1-yl)-5-methoxy-2*H*-indazole (**9g**) (72 mg, 19%), [2-(benzotriazol-1-yl)methyl-4-methoxy]phenylamine (**10g**) (29 mg. 8%), [2-{1-(benzotriazol-1-yl)-3-butenyl}-4-methoxy]phenylamine (**11g**) (13 mg, 3%), and unreacted **6b** (12 mg, 3%).

***8g.*** Mp 151–153°C (from EtOAc–*n*-hexane) (Found: C, 66.7; H, 5.5; N, 23.3. Calc. for $C_{20}H_{20}N_6O$: C, 66.65; H, 5.6; N, 23.3%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3064, 2936, 2848, 1638, 1600, 1558, 1499, 1446, 1278, 1212, 1036, 926, 809, 742, and 521; $^1$H NMR δ 3.69 (3H, s, $OCH_3$), 3.83 (4H, d, *J* 7.6, $CH_2$), 4.99 (2H, d, *J* 10.1, $=CH_2$), 5.04 (2H, d, *J* 17.2, $=CH_2$), 5.47–5.62 (2H, m, =CH), 6.43 (1H, d, *J* 2.2, ArH), 7.09 (1H, dd, *J* 9.4, 2.4, ArH), 7.32 (1H, d, *J* 6.7, ArH), 7.46–7.59 (2H, m, ArH), 7.69 (1H, d, *J* 9.4, ArH), and 8.23 (1H, d, *J* 8.1, ArH); $^{13}$C NMR δ 55.8, 60.8, 110.5, 116.0, 120.3, 120.4, 120.8, 122.7, 124.9, 126.3, 128.9, 132.9, 135.2, 141.9, and 145.7.

***Crystal data for 8g.*** $C_{20}H_{20}N_6O$, *M* = 360.42, triclinic, *a* = 8.009(3), *b* = 8.019(2), *c* = 14.760(8) Å, α = 81.91(5), β = 82.16(4), γ = 96.01(3)°, *U* = 928.5(7) Å$^3$, *T* = 293(2) K, space group *P*-1, *Z* = 2, μ(Mo-K$_\alpha$) = 0.085 mm$^{-1}$, λ = 0.71070 Å, 3266 reflections measured, 3265 unique ($R_{int}$ = 0.0029) which were used in all calculations. The final $wR(F^2)$ was 0.1110. CCDC 212914.

***9g.*** Mp 234–236°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 63.4; H, 4.0; N, 26.3. Calc. for $C_{14}H_{11}N_5O$: C, 63.4; H, 4.2; N, 26.4%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3130, 3048, 2928, 1632, 1609, 1525, 1478, 1431, 1386, 1344, 1273, 1167, 1094, 984, 918, 892, and 740; $^1$H NMR δ (DMSO) 3.85 (3H, s, $OCH_3$), 7.19 (1H, dd, *J* 9.1 and 2.2, ArH), 7.54–7.63 (3H, m, ArH), 7.73 (1H, t, *J* 7.3, ArH), 8.24 (1H, d, *J* 8.3, ArH), 8.32 (1H, d, *J* 8.3, ArH), and 13.5 (1H, s, NH); $^{13}$C NMR δ (DMSO) 56.3, 100.0, 113.0, 113.7, 115.2, 120.4, 121.2, 126.1, 129.9, 132.1, 138.0, 139.7, 145.8, and 155.9.

***10g.*** Viscous liquid (mixed with **11g**); $^1$H NMR δ 3.65 (3H, s, $OCH_3$), 4.29 (2H, s, $NH_2$), 5.78 (2H, s, $CH_2$), 6.65 (1H, d, *J* 2.9, ArH), 6.84 (1H, d, *J* 8.9, ArH), 7.31–7.58 (4H, m, ArH), and 8.08 (1H, d, *J* 8.3, ArH).

***11g.*** Viscous liquid (mixed with **10g**); $^1$H NMR δ 3.20–3.29 (1H, m, $CH_2$), 3.36–3.48 (1H, m, $CH_2$), 3.62 (3H, s, $OCH_3$), 4.10 (2H, s, $NH_2$), 5.04 (1H, d, *J* 11.7, $=CH_2$), 5.11 (1H, d, *J* 19.1, $=CH_2$), 5.61–5.77 (1H, m, =CH), 6.10 (1H, dd, *J* 9.3

and 6.1, CH), 6.58 (1H, d, *J* 8.8, ArH), 7.10–7.59 (m, 5H, ArH), and 8.11 (1H, d, *J* 8.2, ArH).

**Reaction of 1-[(2-azido-3-methyl)phenylmethyl]benzotriazole (6c) with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6c** (350 mg, 1.32 mmol), allyl bromide (399 mg, 3.30 mmol), and *n*-BuLi (3.30 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-dibenzylamino)-3-(benzotriazol-1-yl)-7-methyl-2*H*-indazole (**8h**) (168 mg, 34%), 3-(benzotriazol-1-yl)-7-methyl-2*H*-indazole (**9h**) (43 mg, 13%), [2-(benzotriazol-1-yl)methyl-6-methyl]phenylamine (**10h**) (32 mg, 10%), [2-{1-(benzotriazol-1-yl)-3-butenyl}-6-methyl]phenylamine (**11h**) (18 mg, 5%).

***8h.*** Mp 123–125°C (from EtOAc–*n*-hexane) (Found: C, 69.6; H, 5.9; N, 24.5. Calc. for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.4%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2904, 2840, 1627, 1604, 1547, 1505, 1443, 1371, 1280, 1233, 1168, 1038, 990, 924, 864, 747, and 521; $^1$H NMR δ 2.71 (3H, s, $CH_3$), 3.89 (4H, d, *J* 6.6, $CH_2$), 4.97 (2H, d, *J* 10.1, $=CH_2$), 5.05 (2H, d, *J* 17.1, $=CH_2$), 5.52–5.66 (2H, m, =CH), 7.01–7.17 (3H, m, ArH), 7.31 (1H, d, *J* 7.8, ArH), 7.47–7.58 (2H, m, ArH), and 8.22 (1H, d, *J* 7.9, ArH); $^{13}$C NMR δ 17.2, 60.7, 110.5, 115.6, 116.0, 120.2, 120.7, 124.5, 124.9, 126.2, 128.9, 129.0, 133.1, 135.2, 145.6, and 145.7.

***9h.*** Mp 210–212°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 67.6; H, 4.6; N, 28.0. Calc. for $C_{14}H_{11}N_5$: C, 67.5; H, 4.45; N, 28.1%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3144, 3056, 2928, 1606, 1516, 1440, 1344, 1270, 1246, 1176, 1153, 1097, 1035, 852, 779, 737, and 521; $^1$H NMR δ (DMSO) 2.61 (3H, s, $CH_3$), 7.23 (1H, t, *J* 7.9, ArH), 7.32 (1H, d, *J* 6.8, ArH), 7.58 (1H, t, *J* 7.9, ArH), 7.76 (1H, t, *J* 7.8, ArH), 8.05 (1H, d, *J* 8.1, ArH), 8.25 (1H, d, *J* 8.3, ArH), 8.35 (1H, d, *J* 8.3, ArH), and 13.7 (1H, s, NH); $^{13}$C NMR δ (DMSO) 17.4, 113.7, 114.9, 119.1, 120.5, 121.7, 123.2, 126.1, 128.4, 130.0, 132.1, 140.5, 142.2, and 145.9.

***10h.*** Viscous liquid (mixed with **11h**); $^1$H NMR δ 2.14 (3H, s, $CH_3$), 4.28 (2H, s, $NH_2$), 5.79 (2H, s, $CH_2$), 6.73 (1H, t, *J* 7.5, ArH), 7.08 (1H, d, *J* 7.2, ArH), 7.24–7.61 (4H, m, ArH), and 8.06 (1H, d, *J* 8.3, ArH).

***11h.*** Viscous liquid (mixed with **10h**); $^1$H NMR δ 2.19 (3H, s, $CH_3$), 4.06 (2H, s, $NH_2$), 3.21–3.30 (1H, m, $CH_2$), 3.39–3.50 (1H, m, $CH_2$), 5.04 (1H, d, *J* 11.3, $=CH_2$), 5.11 (1H, d, *J* 18.7, $=CH_2$), 5.65–5.79 (1H, m, =CH), 6.10 (1H, dd, *J* 9.2 and 6.5, CH), 6.72 (1H, t, *J* 7.5, ArH), 7.07 (1H, d, *J* 7.6, ArH), 7.18–7.54 (4H, m, ArH), and 8.05 (1H, d, *J* 8.3, ArH).

**Reaction of 1-[(2-azido-5-bromo)phenylmethyl]benzotriazole (6d) with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6d** (300 mg, 0.91 mmol), allyl bromide (276 mg, 2.28 mmol), and *n*-BuLi (2.28 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-dibenzylamino)-3-(benzotriazol-1-yl)-5-bromo- 2*H*-indazole (**8i**) (97 mg, 26%), 3-(benzotriazol-1-yl)-5-bromo-2*H*- indazole (**9i**) (40 mg, 14%), [2-(benzotriazol-1-yl) methyl-4-bromo]phenylamine (**10i**) (19 mg, 7%), [2-{1-(benzotriazol-1-yl)-3-butenyl}-4-bromo]phenylamine (**11i**) (12 mg, 4%), and unreacted **6d** (6 mg, 2%).

***8i.*** Viscous liquid (Found: C, 55.6; H, 4.35, N, 20.0. Calc. for $C_{19}H_{17}BrN_6$: C, 55.8; H, 4.2; N, 20.5%); $\nu_{max}$ (film)/cm$^{-1}$ 3064, 2936, 2856, 1632, 1603, 1582, 1558, 1516, 1444, 1384, 1278, 1196, 1092, 990, 924, 739, and 518; $^1$H NMR δ 3.85 (4H, d, *J* 6.8, $CH_2$), 4.99 (2H, d, *J* 10.8, $=CH_2$), 5.04 (2H, d, *J* 17.7, $=CH_2$), 5.50–5.65 (2H, m, =CH), 7.27–7.35 (2H, m, ArH), 7.48 (1H, s, ArH), 7.52 (1H, d, *J* 7.7, ArH), 7.57 (1H, d, *J* = 8.8, ArH), and 8.23 (1H, d, *J* 8.1, ArH); $^{13}$C NMR δ 60.8, 110.2, 116.8, 118.0, 120.6, 120.7, 120.8, 120.9, 124.6, 129.3, 131.3, 132.6, 135.0, 143.7, and 145.7.

***9i.*** Mp 260–262°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 49.6; H, 2.6; N, 22.35. Calc. for $C_{13}H_8BrN_5$: C, 49.7; H, 2.6; N, 22.3%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3140, 3056, 2930, 2889, 1612, 1541, 146, 1381, 1339, 1241, 1165, 1089, 984, 918, 892, 737, and 642; $^1$H NMR δ (DMSO) 7.59 (1H, t, *J* 7.4, ArH), 7.66–7.72 (2H, m, ArH), 7.77 (1H, t, *J* 7.3, ArH), 8.26 (1H, d, *J* 8.3, ArH), 8.36 (1H, d, *J* 8.3, ArH), 8.42 (1H, s, ArH), and 13.8 (1H, s, NH); $^{13}$C NMR δ (DMSO) 113.7, 114.0, 115.0, 116.3, 120.6, 124.0, 126.3, 130.2, 131.6, 131.9, 140.8, and 145.9.

***10i.*** Viscous liquid (mixed with **11i**); $^1$H NMR δ 4.32 (2H, br, $NH_2$), 5.77 (2H, s, $CH_2$), 7.10–7.62 (6H, m, ArH), and 8.11 (1H, d, *J* 8.3, ArH).

***11i.*** Viscous liquid (mixed with **10i**); $^1$H NMR δ 3.21–3.30 (1H, m, $CH_2$), 3.35–3.49 (1H, m, $CH_2$), 4.25 (2H, br, $NH_2$), 5.01 (1H, d, *J* 10.8, $=CH_2$), 5.07 (1H, d, *J* 18.2, $=CH_2$), 5.65–5.81 (1H, m, =CH), 6.60 (1H, dd, *J* 9.1 and 6.0, CH), 7.10–7.62 (6H, m, ArH), and 8.17 (1H, d, *J* 8.2, ArH).

**Reaction of 1-[(2-azido-4-chloro)phenylmethyl]benzotriazole (6e) with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6e** (480 mg, 1.69 mmol), allyl bromide (512 mg, 4.23 mmol), and *n*-BuLi (4.23 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-dibenzylamino)-3-(benzotriazol-1-yl)-6-chloro-2*H*-indazole (**8j**) (160 mg, 26%), 3-(benzotriazol-1-yl)-6-chloro-2*H*-indazole (**9j**) (73 mg, 16%), [2-(benzotriazol-1-yl)methyl-5-chloro]phenylamine (**10j**) (22 mg, 5%), [2-{1-(benzotriazol-1-yl)-3-butenyl}-5-chloro]phenylamine (**11j**) (30 mg, 6%), and unreacted **6e** (10 mg, 2%).

***8j.*** Mp 80–82°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 62.5; H, 4.6; N, 23.2. Calc. for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.7; N, 23.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3064, 2908, 2848, 1630, 1608, 1518, 1473, 1443, 1374, 1280, 1195, 1163, 1043, 992, 928, 851, 744, and 520; $^1$H NMR δ 3.85 (4H, d, *J* 6.7, $CH_2$), 4.98 (2H, d, *J* 10.1, $=CH_2$), 5.04 (2H, d, *J* 17.1, $=CH_2$), 5.48–5.62 (2H, m, =CH), 7.12 (1H, dd, *J* 8.9, 1.7, ArH), 7.22–7.31 (2H, m, ArH), 7.48–7.60 (2H, m, ArH), 7.80 (1H, d, *J* 1.3, ArH), and 8.23 (1H, d, *J* 8.1, ArH); $^{13}$C NMR δ 60.8, 110.3, 114.0, 117.8, 120.1, 120.7, 120.9, 125.1, 125.8, 125.9, 129.3, 132.6, 133.6, 135.0, 145.4, and 145.7.

***9j.*** Mp 172–174°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 57.8; H, 3.1; N, 26.1. Calc. for $C_{13}H_8ClN_5$: C, 57.9; H, 3.0; N, 26.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3156, 3052, 2908, 2850, 1639, 1608, 1523, 1478, 1436, 1375, 1278, 1244, 1196, 1049, 984, 918, 852, 738, and 516; $^1$H NMR δ (DMSO) 7.35 (1H, d, *J* = 8.7, ArH), 7.59 (1H, t, *J* 7.8, ArH), 7.75 (1H, d, *J* 7.6, ArH), 7.79 (1H, s, ArH), 8.25 (1H, d, *J* 5.9, ArH), 8.28 (1H, d, *J* 6.3, ArH), 8.36 (1H, d, *J* 8.4, ArH), and 13.7 (1H, s, NH); $^{13}$C NMR δ (DMSO) 111.3, 113.7, 120.5, 123.6, 123.7, 126.2, 126.3, 130.2, 131.9, 133.8, 142.3, and 145.9

***10j.*** Viscous liquid (mixed with **11j**); $^1$H NMR δ 4.27 (2H, s, $NH_2$), 5.77 (2H, s, $CH_2$), 7.06 (1H, d, *J* 8.5, ArH), 7.21–7.42 (4H, m, ArH), 7.48 (1H, s, ArH), and 8.06 (1H, d, *J* 7.9, ArH).

***11j.*** Viscous liquid (mixed with **10j**); $^1$H NMR δ 3.19–3.30 (1H, m, $CH_2$), 3.35–3.49 (1H, m, $CH_2$), 4.17 (2H, s, $NH_2$), 5.01 (1H, d, *J* 10.7, $=CH_2$), 5.06 (1H, d, *J* 18.9, $=CH_2$), 5.63–5.80 (1H, m, =CH), 6.02 (1H, dd, *J* 9.1 and 6.6, CH), 6.64 (1H, d, *J* 2.0, ArH), 6.78 (1H, dd, *J* 8.3 and 2.0, ArH), 7.31–7.43 (4H, m, ArH), and 8.04 (1H, d, *J* 7.7, ArH).

**Reaction of 1-[(2-azido-5-chloro)phenylmethyl]benzotriazole (6f) with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6f** (350 mg, 1.23 mmol), allyl bromide (377 mg, 3.08 mmol), and *n*-BuLi (3.08 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-dibenzylamino)-3-(benzotriazol-1-yl)-5-chloro-2*H*-indazole (**8k**) (126 mg, 28%), 3-(benzotriazol-1-yl)-5-chloro-2*H*-indazole (**9k**) (56 mg, 17%), [2-(benzotriazol-1-yl)methyl-4-chloro]phenylamine (**10k**) (6 mg, 2%), [2-{1-(benzotriazol-1-yl)-3-butenyl}-4-chloro]phenylamine (**11k**) (29 mg, 8%), and unreacted **6f** (14 mg, 4%).

***8k.*** Mp 102–104°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 62.6; H, 4.8; N, 22.9. Calc. for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.7; N, 23.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3053, 2910, 2848, 1627, 1600, 1520, 1445, 1380, 1284, 1159, 1045, 996, 924, 849, 742, and 521; $^1$H NMR δ 3.85 (4H, d, *J* 6.7, $CH_2$), 4.99 (2H, d, *J* = 12.7, =$CH_2$), 5.04 (2H, d, *J* 18.0, =$CH_2$), 5.48–5.63 (2H, m, =CH), 7.27–7.36 (3H, m, ArH), 7.46–7.61 (2H, m, ArH), 7.75 (1H, d, *J* 9.1, ArH), and 8.23 (1H, d, *J* 8.1, ArH); $^{13}$C NMR δ 110.2, 116.1, 117.4, 120.5, 120.7, 120.9, 125.1, 129.0, 129.3, 130.2, 132.6, 135.2, 143.7, and 145.7.

***9k.*** Mp 198–200°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 57.8; H, 2.9; N, 26.0. Calc. for $C_{13}H_8ClN_5$: C, 57.9; H, 3.0; N, 26.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3144, 3054, 2918, 2838, 1630, 1609, 1523, 1450, 1385, 1340, 1278, 1167, 1039, 994, 928, 837, 737, and 516; $^1$H NMR δ (DMSO) 7.55 (1H, t, *J* 2.6, ArH), 7.58 (1H, d, *J* 2.2, ArH), 7.75 (2H, d, *J* 9.1, ArH), 8.25 (1H, d, *J* 5.7, ArH), 8.26 (1H, d, *J* 4.3, ArH), 8.36 (1H, d, *J* 8.3, ArH), and 13.8 (1H, s, NH); $^{13}$C NMR δ (DMSO) 111.7, 113.5, 121.0, 123.7, 123.8, 126.5, 126.6, 130.1, 132.0, 133.9, 142.5, and 145.9.

***10k.*** Viscous liquid (mixed with **11k**); $^1$H NMR δ 4.35 (2H, s, $NH_2$), 5.70 (2H, s, $CH_2$), 6.61 (1H, d, *J* 8.5, ArH), 7.11 (1H, d, *J* 8.4, ArH), 7.28–7.54 (4H, m, ArH), and 8.12 (1H, d, *J* 8.1, ArH).

***11k.*** Viscous liquid (mixed with **10k**); $^1$H NMR δ 3.21–3.29 (1H, m, $CH_2$), 3.39–3.50 (1H, m, $CH_2$), 4.05 (2H, s, $NH_2$), 5.02 (1H, d, *J* 11.6, =$CH_2$), 5.08 (1H, d, *J* 17.1, =$CH_2$), 5.66–5.81 (1H, m, =CH), 6.01 (1H, dd, *J* 9.2 and 6.1, CH), 6.58 (1H, d, *J* 8.6, ArH), 7.09 (1H, d, *J* 8.5, ArH), 7.31–7.59 (4H, m, ArH), and 8.06 (1H, d, *J* 8.2, ArH).

**Reaction of 1-[(2-azido-5-nitro)phenylmethyl]benzotriazole (6g) with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6g** (300 mg, 1.02 mmol), allyl bromide (308 mg, 2.55 mmol), and *n*-BuLi (2.55 mmol) was stirred to give very complex mixtures, which were unidentifiable.

**Reaction of 1-(4-azidophenylmethyl)benzotriazole (6h) with allyl bromide.** In accordance with the aforementioned general procedure, **6h** (500 mg, 2.00 mmol) was treated with *n*-BuLi (4.00 mmol), followed by addition of allyl bromide (484 mg, 4.00 mmol). Chromatography of the reaction mixture gave 1-[{(4-azidophenyl)(allyl)}methyl]-1*H*-benzotriazole (**19**) (23 mg, 4%), 4-[(benzotriazol-1-yl)methyl]phenylamine (**20**) (202 mg, 45%), and unreacted **6h** (140 mg, 28%).

***19.*** Viscous liquid (Found: C, 66.4; H, 4.8; N, 29.0. Calc. for $C_{16}H_{14}N_4$: C, 66.2; H, 4.9; N, 28.95%); $\nu_{max}$ (film)/cm$^{-1}$ 3056, 2920, 2848, 2112, 1683, 1595, 1500, 1443, 1276, 1224, 1155, 1064, 992, 916, 824, 744, and 529; $^1$H NMR δ 3.17–3.28 (1H, m, $CH_2$), 3.46–3.58 (1H, m, $CH_2$), 5.04 (1H, d, *J* 10.2, =$CH_2$), 5.13 (d, *J* 18.4, =$CH_2$), 5.65–5.77 (1H, m, =CH), 5.83 (1H, dd, *J* 8.8, 6.7, CH), 7.00 (2H, d, *J* 8.6, ArH), 7.34–7.50 (5H, m, ArH), and 8.07 (1H, d, *J* 7.8, ArH).

***20.*** Mp 128–130°C (from EtOAc–*n*-hexane) (Found: C, 69.7; H, 5.3; N, 25.1. Calc. for $C_{13}H_{12}N_4$: C, 69.6; H, 5.4; N, 25.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3448, 3336, 3040, 2920, 1611, 1507, 1436, 1283, 1216, 1176, 1126, 1076, 830, 776, 736, and 518; $^1$H NMR δ 3.76 (2H, s, $NH_2$), 5.73 (2H, s, $CH_2$), 6.61 (2H, d, *J* 8.4, ArH), 7.13 (2H, d, *J* 10.1, ArH), 7.33–7.42 (3H, m, ArH), and 8.04 (1H, d, *J* 8.1, ArH); $^{13}$C NMR δ 52.6, 110.4, 115.6, 120.3, 124.2, 124.6, 127.6, 129.5, 133.4, 146.7, and 147.2.

**Reaction of 1-(2-azidophenylmethyl)-6-chloro-1*H*-benzotriazole (6i) with allyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6i** (199 mg, 0.70 mmol), allyl bromide (212 mg, 1.75 mmol), and *n*-BuLi (1.75 mmol) was stirred. Chromatography of the reaction mixture gave 2-(*N*,*N*-diallylamino)-3-(6-chlorobenzotriazol-1-yl)-2*H*-indazole (**8l**) (77 mg, 30%), 3-(6-chlorobenzotriazol-1-yl)-2*H*-indazole (**9l**) (23 mg, 12%), 2-[(6-chlorobenzotriazol-1-yl)methyl]-phenylamine (**10l**) (11 mg, 6%), and unreacted **6i** (4 mg, 2%).

***8l.*** Viscous liquid (Found: C, 62.6; H, 4.6; N, 23.15. Calc. for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.7; N, 23.0%); $\nu_{max}$ (film)/cm$^{-1}$ 3056, 2906, 2865, 1631, 1608, 1518, 1473, 1444, 1374, 1280, 1166, 1043, 992, 928, 851, 744, and 522; $^1$H NMR δ 3.87 (4H, d, *J* 6.3, $CH_2$), 5.01 (2H, d, *J* 9.0, =$CH_2$), 5.06 (2H, d, *J* 15.9, =$CH_2$), 5.49–5.64 (2H, m, =CH), 7.22 (1H, d, *J* 6.7, ArH), 7.29–7.34 (2H, m, ArH), 7.42–7.49 (2H, m, ArH), 7.82 (1H, d, *J* 8.9, ArH), and 8.15 (1H, d, *J* 8.8, ArH); $^{13}$C NMR δ 60.9, 110.5, 115.7, 118.5, 118.9, 120.8, 121.7, 124.6, 126.2, 127.6, 132.7, 135.7, 144.3 and 145.4.

***9l.*** Mp 215–217°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 57.95; H, 3.1; N, 26.0. Calc. for $C_{13}H_8ClN_5$: C, 57.9; H, 3.0; N, 26.0%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3124, 3058, 2920, 2846, 1627, 1600, 1523, 1456, 1385, 1340, 1278, 1175, 1039, 994, 928, 837, 737, 694, and 516; $^1$H NMR δ (DMSO) 7.35 (1H, dd, *J* 7.7 and 6.6, ArH), 7.56 (1H, dt, *J* 1.0 and 6.9, ArH), 7.61 (1H, dd, *J* 8.9 and 1.9, ArH), 7.70 (1H, d, *J* 8.5, ArH), 8.24 (1H, d, *J* 8.3, ArH), 8.29 (1H, d, *J* 8.8, ArH), 8.39 (1H, d, *J* 1.7, ArH), and 13.6 (s, 1H, NH); $^{13}$C NMR δ (DMSO) 111.8, 113.3, 114.8, 121.7, 122.1, 123.1, 126.9, 128.9, 132.6, 134.9, 140.0, 142.1, and 144.6.

***10l.*** Mp 87–89°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 60.5; H, 4.1; N, 21.6. Calc. for $C_{13}H_{11}ClN_4$: C, 60.35; H, 4.3; N, 21.7%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3348, 3231, 3042, 2950, 2856, 1601, 1580, 1441, 1281, 1154, 1072, 906, 742, and 521; $^1$H NMR δ 4.29 (2H, s, $NH_2$), 5.77 (2H, s, $CH_2$), 7.10–7.19 (2H, m, ArH), 7.28 (1H, d, *J* 8.0, ArH), 7.31 (1H, d, *J* 8.7, ArH), 7.42–7.52 (2H, m, ArH), and 8.17 (1H, d, *J* 8.8, ArH); $^{13}$C NMR δ 50.6, 110.1, 118.8, 121.4, 125.6, 125.7, 125.8, 130.4, 130.6, 133.9, 134.3, 138.4, and 145.1.

**Reaction of 6a with a mixture of allyl bromide and benzyl bromide.** In accordance with the aforementioned general procedure, a mixture of **6a** (330 mg, 1.32 mmol), allyl bromide (191 mg, 1.58 mmol), benzyl bromide (270 mg, 1.58 mmol), and *n*-BuLi (3.30 mmol) in THF was stirred for 1 h at −78°C to room temperature for 2 h. TLC (silica gel, EtOAc: *n*-hexane = 1:4) showed four major spots ($R_f$ = 0.79, 0.70, 0.42, and 0.27). The mixture was chromatographed on a silica gel (2.5 × 13 cm$^2$). Elution with EtOAc and *n*-hexane (1:6) gave **8a** (40 mg, 7%), a mixture of compounds (114 mg), **9a** (37 mg, 12 %), and **10a** (29 mg, 10%). Separation of the mixture has been unsuccessful. However, the $^1$H NMR spectrum of the mixture indicated that the mixture consisted of **8a** (39 mg, 9%) and 2-(*N*-allyl-*N*-benzylamino)-3-(benzotriazol-1-yl)-2*H*-indazole (**23**) (75 mg, 15%). FAB MS showed mass

number (*m*/*z*) 331 and 381, which corresponding to the molecular weights of **8a** plus 1 and **23** plus 1, respectively.

***23.*** Viscous liquid (mixed with **8a**); $\nu_{max}$ (KBr)/cm$^{-1}$ 3056, 2924, 2840, 1628, 1600, 1554, 1523, 1444, 1370, 1226, 1160, 990, 942, 830, 740, and 520; $^1$H NMR δ 3.97 (1H, d, *J* 4.6, C*H*$_2$CH=CH$_2$), 4.09 (2H, s, C*H*$_2$Ph), 5.06 (1H, d, *J* 16.9, =CH$_2$), 5.14 (1H, d, *J* 17.2, =CH$_2$), 5.71–5.87 (1H, m, =CH), 6.77–6.97 (4H, m, ArH), 7.01–7.25 (3H, m, ArH), 7.30–7.51 (4H, m, ArH), 7.85 (1H, d, *J* 8.7, ArH), and 8.21 (1H, d, *J* 8.3, ArH); $^{13}$C NMR δ 61.1, 61.6, 110.4, 118.7, 120.5, 124.2, 124.8, 127.5, 128.1, 128.6, 128.7, 128.9, 129.5, 129.6, 132.8, 134.7, 135.9, 145.4, and 145.5.

**Reaction of 6a with allyl bromide in the presence of various bases.** In accordance with the aforementioned general procedure, **6a** (200 mg, 1.25 mmol) was treated with bases such as *tert*-BuLi (1.88 mmol), $NaNH_2$ (1.88 mmol), $KN(SiMe_3)_2$ (1.88 mmol), LDA (1.88 mmol) followed by TMEDA (145 mg, 1.25 mmol), and *n*-BuLi (1.88 mmol) followed by *tert*-BuOK (140mg, 1.25 mmol) in THF (25 mL) for 1 h at −78°C and then 2 h at room temperature. The only exception was the reaction with NaH (1.88 mmol) for 5 h at room temperature. The reaction was quenched by addition of water (30 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL × 3). The combined extract was dried over $MgSO_4$. Chromatography (2.5 × 10 cm$^2$, EtOAc:*n*-hexane = 1:5) of the residue gave unreacted **6a** and **8a**-**10a**, depending on the bases. The results are summarized in Table 3.

**General procedure for the reactions of simple aryl azides with *n*-BuLi.** To a stirred solution of aryl azides (4.88 mmol) in THF (25 mL) for 1 h at −78°C was added *n*-BuLi (9.76 mmol). The mixture was stirred for 2 h at room temperature and worked up as usual. Chromatography of the residue using a mixture of EtOAc and *n*-hexane (1:10) gave alkyl aryl amines **22**, aryl amines **22**, and unreacted aryl azides.

**Reaction with *p*-azidotoluene.** In accordance with the aforementioned general procedure, *p*-azidotoluene (540 mg, 4.06 mmol) was treated with *n*-BuLi (8.12 mmol) to give *p*-toluidine (**21a**) (300 mg, 69%), *N*-butyl-*p*-toluidine [14] (**22a**) (53 mg, 8%) and unreacted *o*-azidotoluene (5 mg, 1%).

**Reaction with *o*-azidotoluene.** In accordance with the aforementioned general procedure, *o*-azidotoluene (650 mg, 4.88 mmol) was treated with *n*-BuLi (9.76 mmol) to give *o*-toluidine (**21b**) (397 mg, 76%), *N*-butyl-*o*-toluidine [14] (**22b**) (48 mg, 6%) and unreacted *o*-azidotoluene (13 mg, 2%).

**Reaction with *o*-azidoethylbenzene.** In accordance with the aforementioned general procedure, *o*-azidoethylbenzene (520 mg, 3.53 mmol) was treated with *n*-BuLi (7.06 mmol) to give *o*-ethylamine (**21c**) (295 mg, 69%) and *N*-butyl-2-ethylphenyl amine [15] (**22c**) (50 mg, 8%).

**Reaction with 2-azidodiphenylmethane.** In accordance with the aforementioned general procedure, 2-azidodiphenylmethane (500 mg, 2.39 mmol) was treated with *n*-BuLi (4.78 mmol) to give *o*-(*n*-butylamino)diphenylmethane [16] (**22d**) (40 mg, 7%) and 2-benzylaniline [17] (**21d**) (315 mg, 72%).

**Reaction of 6a with methylmagnesium bromide.** To a solution of methylmagnesium bromide (250 mg, 2.10 mmol) in THF (15 mL) at 0°C was added **6a** (350 mg, 1.40 mmol). The mixture was stirred for 1 h at 0°C and then at room temperature for 2 h. The mixture was worked up as usual and chromatographed on a silica gel (2.5 × 5 cm$^2$) using a mixture of EtOAc and *n*-hexane (1:1) to give 2-[(benzotriazol-1-yl)methyl]phenyl methyltriazene (**13**) (338 mg, 91%). Mp 133–135°C (from $CH_2Cl_2$–*n*-hexane) (Found: C, 63.0; H, 5.3; N, 31.65. Calc. for $C_{14}H_{14}N_6$: C, 63.1; H, 5.3; N, 31.6%); $\nu_{max}$ (KBr)/cm$^{-1}$ 3263, 3066, 3003, 2954, 1431, 1371, 1220, 1077, 943, 746, 718, and 531; $^1$H NMR δ 3.24 (3H, s, $CH_3$), 6.16 (2H, s, $CH_2$), 7.07–7.07 (2H, m, ArH), 7.25–7.38 (3H, m, ArH), 7.42–7.51 (2H, m, ArH), 8.05 (1H, d, *J* 7.1, ArH), and 8.36 (1H, s, NH); $^{13}$C NMR δ 48.4, 110.7, 120.2, 124.2, 126.7, 127.5, 129.4, 129.6, 133.4, and 146.6.

**Preparation of 1-(2-aminophenylmethyl)benzotriazole 10a.** In accordance with the literature procedure [7], a solution of 1-(2-azidophenylmethyl)benzotriazole (**6a**) (250 mg, 1.00 mmol) in a mixture of THF (30 mL) and MeOH (0.3 mL) was treated with $NaBH_4$ (12 mg, 0.30 mmol). The mixture was heated at reflux for 2 h. Work-up gave **10a** (202 mg, 90%).

**Reaction of 10a with allyl bromide in the presence of *n*-BuLi.** To a stirred solution of **10a** (202 mg, 0.90 mmol) in THF (25 mL) at −78°C was added *n*-BuLi (2.25 mmol) and allyl bromide (272 mg, 2.25 mmol). After being stirred for 2 h at room temperature, the mixture was worked up as usual. Chromatography (2.5 × 13 cm$^2$) using a mixture of EtOAc and *n*-hexane (1:4) as an eluent gave allyl[2-{1-(benzotriazol-1-yl)-3-butenyl}-phenyl]amine (**16**) (14 mg, 5%), diallyl[2-{(benzotriazol-1-yl)methyl}phenyl]amine (**15**) (89 mg, 33%), allyl[2-{(benzotriazol-1-yl)methyl}phenyl]amine (**14**) (90 mg, 38%).

***14.*** Viscous liquid (Found: C, 72.65; H, 5.9; N, 21.4. Calc. for $C_{16}H_{16}N_4$: C, 72.7; H, 6.1; N, 21.2%); $\nu_{max}$ (film)/cm$^{-1}$ 3260, 3054, 2928, 2865, 1603, 1480, 1446, 1316, 1228, 1156, 994, 742, and 526; $^1$H NMR δ 3.78 (2H, s, $NCH_2$), 4.95 (1H, s, NH), 5.14 (1H, d, *J* 11.8, =CH$_2$), 5.19 (1H, d, *J* 17.6, =CH$_2$), 5.78 (2H, s, $CH_2$), 5.83–5.98 (1H, m, =CH), 6.65 (1H, d, *J* 8.2, ArH), 6.76 (1H, t, *J* 7.4, ArH), 7.25 (1H, t, *J* 7.6, ArH), 7.32–7.46 (3H, m, ArH), 7.54 (1H, d, *J* 7.4, ArH), and 8.05 (1H, d, *J* 7.6, ArH); $^{13}$C NMR δ 46.4, 51.1, 110.5, 112.2, 116.6, 117.1, 118.6, 120.5, 124.4, 127.9, 130.8, 131.2, 133.2, 135.0, 146.7, and 147.4.

***15.*** Viscous liquid (Found: C, 75.2; H, 6.5; N, 18.25. Calc. for $C_{19}H_{20}N_4$: C, 75.0; H, 6.6; N, 18.4%); $\nu_{max}$ (film)/cm$^{-1}$ 3056, 3001, 2948, 2920, 1608, 1511, 1490, 1442, 1248, 1110, 996, 910, 740, 694, and 516; $^1$H NMR δ 3.65 (4H, d, *J* 6.3, $NCH_2$), 5.17 (2H, d, *J* 11.5, =CH$_2$), 5.23 (2H, d, *J* 17.2, =CH$_2$), 5.83–5.92 (2H, m, CH), 6.02 (2H, s, $CH_2$), 6.87 (1H, d, *J* 8.2, ArH), 7.01 (1H, t, *J* 7.4, ArH), 7.22–7.43 (6H, m, ArH), and 8.08 (1H, d, *J* 8.2, ArH).

***16.*** Viscous liquid (Found: C, 74.9; H, 6.5; N, 18.6. Calc. for $C_{19}H_{20}N_4$: C, 75.0; H, 6.6; N, 18.4%); $\nu_{max}$ (film)/cm$^{-1}$ 3271, 3048, 2920, 1624, 1489, 1445, 1300, 1256, 1221, 1154, 996, 740, and 521; $^1$H NMR δ 3.25–3.34 (1H, m, CHC*H*$_2$CH=CH$_2$), 3.45–3.56 (1H, m, CHC*H*$_2$CH=CH$_2$), 3.69 (2H, s, NHC*H*$_2$CH=CH$_2$), 4.54 (1H, s, NH), 4.98–5.14 (4H, m, CHCH$_2$CH=C*H*$_2$ and NHCH$_2$CH=C*H*$_2$), 5.68–5.89 (2H, m, CHCH$_2$C*H*=CH$_2$ and NHCH$_2$C*H*=CH$_2$), 6.14 (1H, dd, *J* 9.4 and 6.2, CH), 6.63 (1H, d, *J* 8.2, ArH), 6.82 (1H, t, *J* 7.5, ArH), 7.23 (1H, t, *J* 8.4, ArH), 7.28–7.36 (2H, m, ArH), 7.42–7.46 (1H, m, ArH), 7.52 (1H, d, *J* 7.7, ArH), and 8.04 (1H, d, *J* 7.2, ArH); $^{13}$C NMR δ 36.5, 46.4, 60.8, 110.9, 112.5, 116.5, 117.3, 119.1, 120.5, 121.1, 124.4, 127.7, 127.9, 130.3, 132.5, 133.7, 134.9, 146.8, and 147.1.

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## REFERENCES AND NOTES

[1] (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. Chem Rev 1998, 98, 409; (b) Katritzky, A. R.; Henderson, S. A.; Yang, B. J. Heterocycl Chem 1998, 35, 1123; (c) Katirtzky, A. R. J. Heterocycl Chem 1999, 36, 1501; (d) Katritzky, A. R.; Rogovoy, B. V. Chem Eur J 2003, 9, 4586; (e) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Idzik, K. R.; El-Gendy, B. E.-D. M.; Soloducho, J. Tetrahedron 2007, 63, 6477.

[2] (a) Kim, T.; Kim, K.; Park, Y. Eur J Org Chem 2002, 493; (b) Kim, T.; Kim, K. Tetrahedron Lett 2002, 43, 3021.

[3] (a) Dyall, L. K. In the Chemistry of Functional Group, Supplement D, Part 1, Patai, S.; Rapport, Z., Eds.; Wiley: New York, 1983, pp 287–320; (b) Duerr, H.; Kober, H. Top Curr Chem 1976, 66, 89; (c) Abbe, L. Chem Rev 1969, 69, 345; (d) Badiei, Y. M.; Krishnaswamy, A.; Melzer, M. M.; Warren, T. H. J Am Chem Soc 2006, 128, 15056.

[4] (a) Sieh, D. H.; Wilbur, D. J.; Michejda, C. J. J Am Chem Soc 1980, 102, 3883; (b) Di Nunno, L.; Scilimati, A. Tetrahedron 1986, 42, 3913; (c) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. J Org Chem 2005, 70, 3046.

[5] (a) Smith, P. A. S.; Brown, B. B. J Am Chem Soc 1951, 73, 2438; (b) Mornet, R.; Leonard, N. J.; Theiler, J. B.; Doree, M. J Chem Soc Perkin Trans 1, 1984, 879. (c) Alajarin, M.; Lopez-Lazaro, A.; Vidal, A.; Berna, J. Chem Eur J 1998, 4, 2558.

[6] Kang, Y. H.; Kim, K. J Heterocycl Chem 1997, 34, 1741.

[7] Soai, K.; Yokoyama, S.; Ookawa, A. Synthesis 1987, 48.

[8] For synthesis of 2H-indazoles, refer to (a) Song, J. J.; Yee, N. K. Org Lett 2000, 2, 519, and references therein; (b) Taher, A.; Ladwa, S.; Rajan, S.; Weaver, G. W. Tetrahedron Lett 2000, 41, 9893; (c) Kuvshinov, A. M.; Gulevskaya, V. I.; Rozkov, V. V.; Shevelev, S. A. Synthesis 2000, 1474; (d) Langa, F.; de la Cruz, P.; Delgado, J. L.; Haley, M. M.; Shirtcliff, L.; Alkorta, I.; Elguero, J. J Mol Struct 2004, 699, 17; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. Tetrahedron Lett 2005, 46, 5387; (f) Rosati, O.; Curini, M.; Marcotullio, M. C.; Macchiarulo, A.; Perfumi, M.; Mattioli, L.; Rismondo, F.; Cravotto, G. Bioorg Med Chem 2007, 15, 3463.

[9] (a) Bosch, I.; Costa, A. M.; Martin, M.; Urpi, F.; Vilarrasa, J. Org Lett 2000, 2, 397; (b) Hossain, M. T.; Timberlake, J. W. J Org Chem 2001, 66, 4409; (c) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. J Am Chem Soc 2002, 124, 10773; (d) Kamal, A.; Laxman, E.; Arifuddin, M. Tetrahedron Lett 2000, 41, 7743; (e) Kamal, A.; Reddy, P. S. S. M.; Reddy, D. R. Tetrahedron Lett 2002, 43, 6629; (f) Kamal, A.; Ramana, K. V.; Ankati, H. B.; Ramana, A. V. Tetrahedron Lett 2002, 43, 6861; (g) Salunkhe, A. M.; Ramachandran, P. V.; Brown, H. C. Tetrahedron 2002, 58, 10059; (h) Sureshan, K. M.; Ikeda, K.; Asano, N.; Watanabe, Y. Tetrahedron Lett 2004, 45, 8367; (i) Kudaj, A.; Olma, A. Tetrahedron Lett 2007, 48, 6794.

[10] Bartra, M.; Urpi, F.; Vilarrasa, J. Tetrahedron Lett 1987, 28, 5941.

[11] Kawanisi, M.; Otani, I.; Nozaki, H. Tetrahedron Lett 1968, 9, 5575.

[12] (a) Catalan, J.; del Valle, J. C.; Claramunt, R. M.; Boyer, G.; Laynez, J.; Gomez, J.; Jimenez, P.; Tomas, F.; Elquero, J. J Phys Chem 1994, 98, 10606; (b) Ballesteros, P.; Elguero, J.; Claramunt, R. M.; Faure, R.; Foces-Foces, C.; Cano, F. H.; Rousseau, A. J Chem Soc Perkin Trans 2, 1986, 1677.

[13] Software is HyperChem version 5.01.

[14] Hamann, B. C.; Hartwig, J. F. J Am Chem Soc 1998, 120, 7369.

[15] Meng, Y.; Zhao, M.; Zhang, D. Shenyang Huagong Xueyuan Xuebao 1997, 11, 11.

[16] Yudin, L. G.; Rumyantsev, A. N.; Sagitullin, R. S.; Kost, A. N. Chem Heterocycl Compd 1983, 19, 57.

[17] Jones, G.; Long, B. D.; Thorne, M. P. J Chem Soc Perkin Trans 2 1992, 903.

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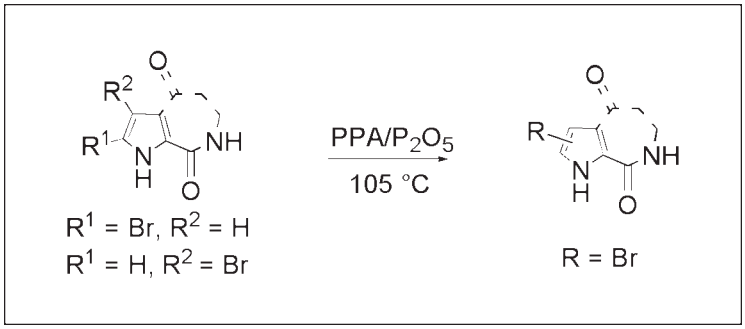


A study on the acid catalyzed halogen dance (ACHD) on deactivated bromopyrroles is reported. A different behavior is observed when considering singly deactivated pyrrole alkylcarboxamides, or doubly deactivated pyrroleketo-lactams (aldisines). Although less electron deficient pyrrole alkylcarboxamides suffer from ACHD, the double deactivation on keto-lactams disfavors pyrrole ring protonation thus preventing halogen scrambling. The mechanism involved in the rearrangement is hypothesized.

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## INTRODUCTION

The first example of the well-known Halogen Dance (HD, also named halogen scrambling, halogen migration, halogen isomerization, halogen shift) reaction dates back to 1951, when Vaitiekunas isolated tetrabromothiophene instead of 2-ethynylthiophene by treating 2-bromothiophene with sodium acetylide in liquid ammonia [1]. The reaction was induced by the presence of the base and since then it has been largely investigated. Currently, the base catalyzed halogen dance (BCHD) is considered a useful tool for the introduction of halogen on aromatic and heteroaromatic substrates in positions that could be hardly reached with other methods. A recently published review thoroughly describes BCHD with elucidations of the mechanism and description of the factors that influence the reaction [2]. Among all the heteroaromatic substrates, no examples on pyrrole have been reported.

What is known in the literature referring to pyrroles solely deals with the effect of acids on substituents in the 2 position of the ring. In this context, acyl [3] and sulfinyl [4] moieties as well as halogens (bromine and chlorine) [5] have been considered. Rearrangement of 2-acylpyrroles aimed at the synthesis of 3-acyl isomers has been studied in the presence of strong acids (PPA, TFA). A [1,2]-acyl shift was hypothesized to rationalize the formation of the products [3(b)], as it was previously postulated for the isomerization of 2-acetylindoles [6]. Rearrangement as side-reaction, on the contrary, was observed in the sulfinylation of pyrroles with sulfinylchlorides: 2-sulfinylpyrroles were contaminated by 3-sulfinyl isomers, likely coming from an acid-catalyzed migration of the substituent in 2-position due to HCl released during the reaction [4]. Moreover, PPA-mediated cyclization of 3-(2-pyrrolyl)propionic acids afforded the expected products along with undesired regioisomers arising from both alkyl and acyl migration [3(a)]. Complex reaction mixtures were also obtained when pyrrole was treated with molecular bromine: beside the expected 2-bromopyrrole, products deriving from both isomerization and disproportionation of the brominated substrate were detected [5(a)]. The mechanism of bromine isomerization and disproportionation of *N*-benzyl-2-bromopyrrole in the presence of TFA has been recently investigated by Park *et al*., who suggested a 1,3-bromine shift to explain rearrangement on the corresponding *N*-benzyl-2-bromo-5-deuterio pyrrole [5(c)].

Thus, if on one hand halogen dance may be useful for the insertion of groups in specific positions of aromatic and heteroaromatic substrates, on the other hand it could represent a parasitic reaction when the shift of the halogen is unwanted. This is the case, for instance, of 2-bromoaldisine **1** (common name of 2-Bromo-6,7-

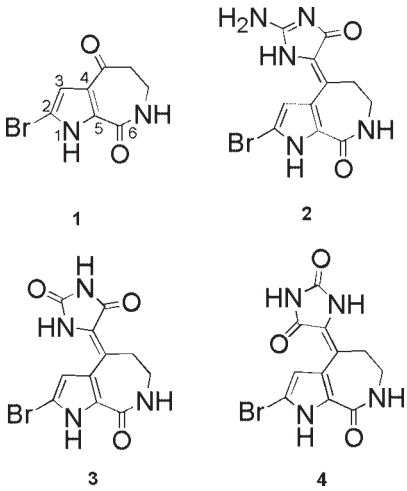


**Figure 1.** Bromopyrrole alkaloids derived from 2-bromoaldisine **1**.

dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione), envisaged as the key-intermediate for the synthesis of some bromopyrrole alkaloids, such as (*Z*)-hymenialdisine **2** [7], (*Z*)-axinohydantoin **3,** and (*E*)-axinohydantoin **4** [8] (Fig. 1).

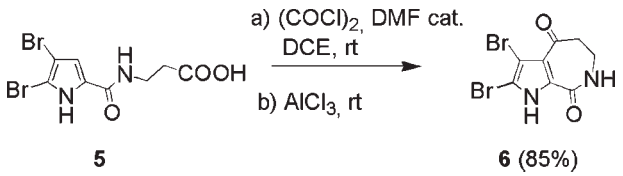
The synthesis of **1** was reported for the first time by Annoura by means of a $PPA/P_2O_5$-mediated cyclization of the corresponding 2-bromopyrrole propionic acid [7(a)]. The reaction suffered from bromine scrambling, delivering a 1:1 mixture of hardly separable bromoaldisine regioisomers. Interestingly, this was the first example of acid catalyzed halogen dance (ACHD) on deactivated pyrroles.

This side-reaction was later efficiently avoided by exploiting a Friedel-Craft-type cyclization on the acyl chloride intermediate in the presence of $AlCl_3$, affording **1** as the sole product in 69% optimized yield [8]. The same synthetic protocol allowed the preparation of 2,3-dibromoaldisine **6** [9] from the corresponding dibromoacid **5** [10] in 85% yield without any bromine rearrangement, differently from what previously reported in the presence of $PPA/P_2O_5$ [10] (Scheme 1).

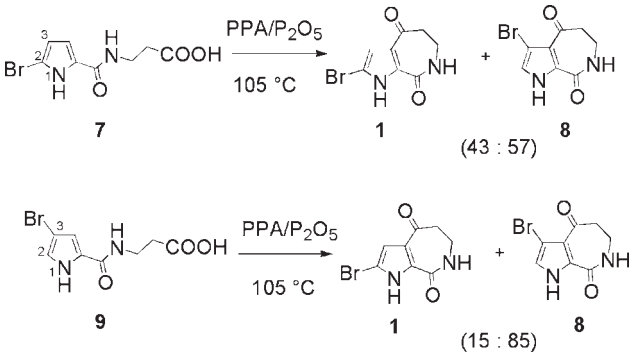
## RESULTS AND DISCUSSION

The different reaction outcomes that a protic acid ($PPA/P_2O_5$) *versus* a Lewis acid ($AlCl_3$) displayed while performing the synthesis of bromoaldisines **1** and **6**, prompted us to study in more detail the ACHD on variously deactivated bromopyrroles in a strong acidic environment.

**Scheme 1.** Lewis acid-mediated synthesis of **6.**



**Scheme 2.** ACHD on bromopyrrolecarboxamides **7** and **9.**



To this purpose we decided, at first, to confirm the observations previously published for the synthesis of 2-bromo (**1**) and 3-bromoaldisine (**8**), by using the same reaction conditions (reagents, temperature, and reaction time) in the cyclization of **7** and **9** [11] (Scheme 2). As described, treatment of **7** with $PPA/P_2O_5$ at 105°C for 1 h produced a mixture of **1** and **8** in a 43:57 ratio (measured by $^1H$ NMR). On the contrary, in our hands regioisomer **9** [12] gave rise to a 15:85 mixture of **1** and **8** under the same conditions, in contrast with the literature (1:1 ratio as for **7**) [7(a)].

In these examples, $PPA/P_2O_5$ mediates both cyclization and scrambling of bromine atom. With the aim of trying to understand whether halogen dance (HD) took place before or after cyclization, the same acidic treatment was performed directly on brominated aldisines **1** and **8**. 2-Bromoaldisine **1** was synthesized as already described [8], while 3-bromoaldisine **8** was successfully isolated from the enriched mixture (15:85) deriving from **9** (see Scheme 2) by means of preparative HPLC. The two substrates have then been subjected to $PPA/P_2O_5$ treatment. The results highlighted minor differences, namely 2-bromoaldisine **1** was not prone at all to

**Scheme 3.** ACHD on aldisines **1** and **8.**

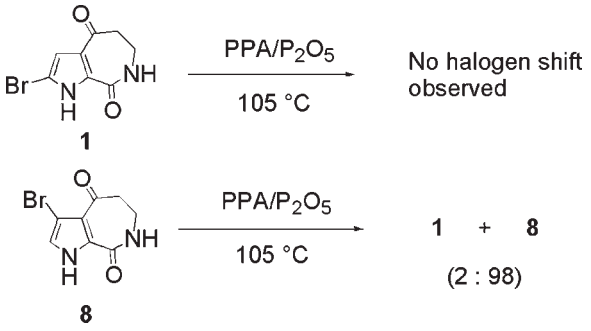


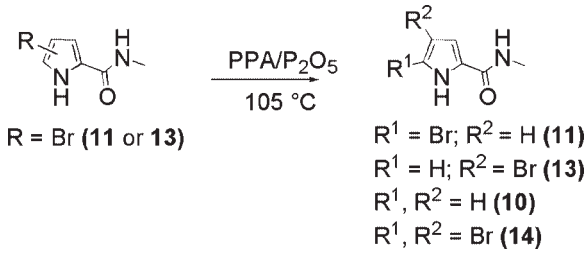
**Table 1**

Results of ACHD on **1**, **8**, **7**, and **9** (105°C, 1 h).

| Entry | Substrate | **1** (%)[a] | **8** (%)[a] |
|---|---|---|---|
| 1 | **1** | 100 | – |
| 2 | **8** | 2 | 98 |
| 3 | **7** | 43 | 57 |
| 4 | **9** | 15 | 85 |

[a] Measured by integrating pyrrole CH signal in $^1$H NMR spectrum.

**Scheme 5.** ACHD on **11** and **13.**




rearrangement, while 3-bromoaldisine **8** produced a small percentage (2%) of 2-bromoisomer **1** (Scheme 3). This means that these keto-lactams hardly undergo halogen scrambling and HD occurs before cyclization.

The observations of ACHD on these substrates are summarized in Table 1.

Intrigued by these outcomes, we decided to evaluate the effect of PPA/$P_2O_5$ on bromopyrroles that: (a) were singly deactivated, like pyrrole alkylcarboxamides **7** and **9**, and (b) could not undergo cyclization, differently from **7** and **9**. Bromopyrrole methylcarboxamides **11** and **13** [11] have been chosen as the suitable substrates to the purpose, having the same EWG as **7** and **9**. Their synthesis is reported in Scheme 4: treatment of 2-trichloroacetylpyrrole with methylamine and subsequent bromination of **10** with NBS in THF/MeOH (2:1) afforded **11** (60% yield over two steps). The direct bromination of the same starting material with $Br_2$ in $CHCl_3$ and subsequent reaction of intermediate **12** with methylamine yielded **13** [13] (70% yield over two steps).

Both bromopyrroles **11** and **13** underwent rearrangement in different ratios, along with disproportionation that generated des-bromo derivative **10** and 4,5-di-bromomethylamide **14** (Scheme 5, Table 2).

As previously mentioned, the amount of the products has been determined by integrating isolated pyrrole CH signals in the $^1$H NMR spectra of the reaction mixtures [Fig. 2(a,b)].

These results allowed us to make some considerations about the kinetics/thermodynamics of the ACHD on deactivated pyrroles compared to cyclization and to hypothesize a possible mechanism. First, it is evident that pyrrole alkylcarboxamides (*i.e.*, **7**, **9**, **11**, and **13**) are more prone to halogen rearrangement (Table 1, Entries 3 and 4; Table 2) than aldisines (Table 1, Entries 1 and 2). Second, scrambling of the halogen is faster when involving a shift from 2- to 3-position at the pyrrole ring (Table 1, Entry 3; Table 2, Entry 1) than vice versa (Table 1, Entry 4; Table 2, Entry 2). The ratio of 2-bromo and 3-bromoaldisine generated from **7** and the distribution of 2- and 3-regioisomers deriving from **11** (Table 1, Entry 3; Table 2, Entry 1) are the same. This means that the two mixtures reach the equilibrium during the reaction (thermodynamic conditions). Moreover, considering that aldisines are insensitive to ACHD, it is fair to assert that, for **7**, $V_{2S} > V_{2C}$, where $V_{2S}$ represents the velocity of scrambling, and $V_{2C}$ the velocity of cyclization (Scheme 6).

On the contrary, the same treatment on **9** and **13** did not spring out analogous results. The ratios of the two aldisines (products of **9**) and of 2- and 3-regioisomers arising from **13** measured in the experiments are different, meaning that these reaction mixtures are under kinetic conditions. It is possible to postulate that, for **9**, $V_{3C} \geq V_{3S}$, meaning that the velocity of cyclization and of scrambling are competitive (see Table 1, Entry 4). Furthermore, rearrangement from 2-position of **7** and **11** is faster than from carbon 3 of **9** and **13**, that explains the higher velocity with which **11** and **7** reach the equilibrium ($V_{2S} > V_{3S}$, see Table 1, Entries 3 and 4, and Table 2). Finally, disproportionation on **7** and **9** and on aldisines **1** and **6** has never been observed, while for **11** and **13** only to a less extent, meaning that this side-reaction is the slowest ($V_D << V_S$ and $V_C$, being $V_D$ = velocity of disproportionation).

**Scheme 4.** Synthesis of pyrrolecarboxamides **11** and **13.**

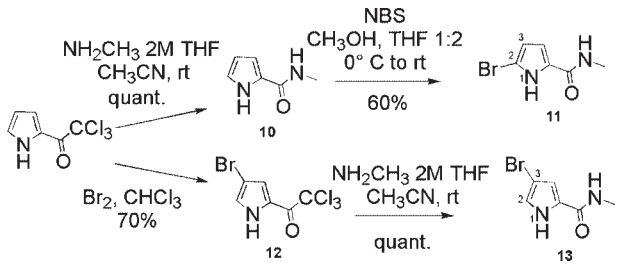



**Table 2**

Results of ACHD on **11** and **13** (105°C, 1 h).

| Entry | Substrate | **11** (%)[a] | **13** (%)[a] | **10** (%)[a] | **14** (%)[a] |
|---|---|---|---|---|---|
| 1 | **11** | 32 (46)[b] | 38 (54)[b] | 15 | 15 |
| 2 | **13** | 25 (34)[b] | 49 (66)[b] | 13 | 13 |

[a] Measured by integrating isolated pyrrole CH signals in $^1$H NMR spectrum.
[b] In brackets the relative percentage of **11** and **13** is reported.

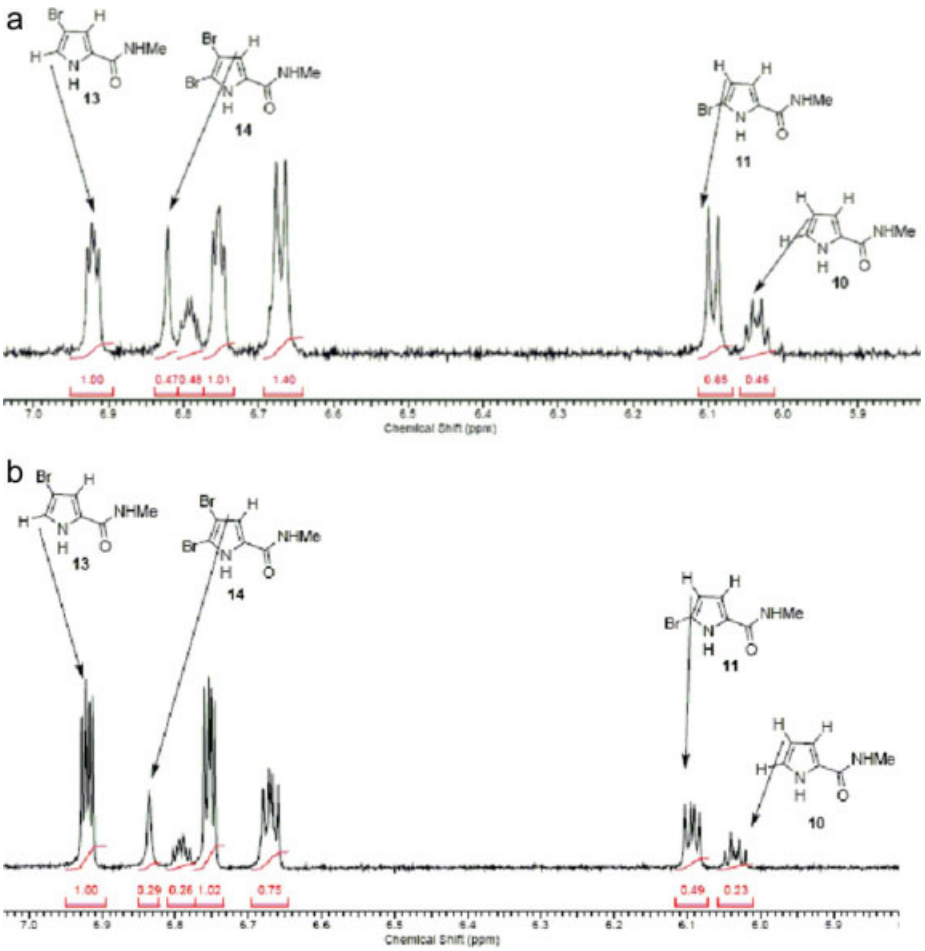


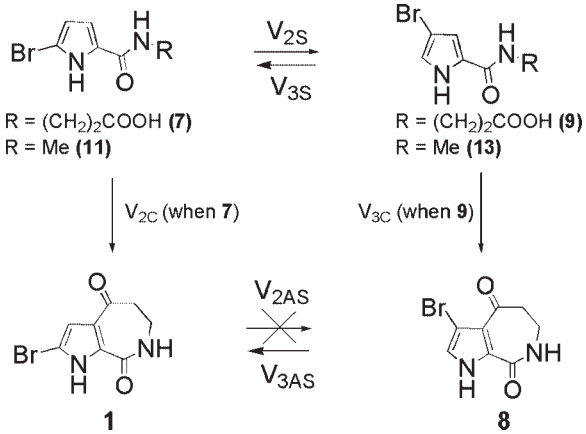

**Figure 2.** $^{1}$H NMR analysis of ACHD on **11** (**2a**: top) and **13** (**2b**: bottom). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

A rearrangement mechanism was postulated to explain ACHD (Scheme 7). In strong acid media, **7** and **11** are subjected to protonation at the 2-position of the pyrrole affording **7a** and **11a**, respectively, which undergo a 1,2-bromine shift toward **9a** and **13a**, passing through transient cyclic bromonium intermediate **15**. The same mechanism can be invoked for **9** and **13**, that are protonated at 3-position generating **9a** and **13a**, respectively. A cyclic bromonium intermediate has been hypothesized instead of free $Br^{+}$ cation because statistically this would have generated a higher amount of dibrominated pyrrole from **11** and **13** (see Table 2) and the presence of dibromo/desbromo aldisines from **7** and **9** (see Table 1).

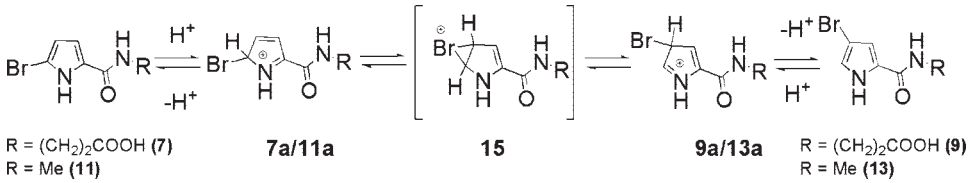
## EXPERIMENTAL

**General.** Melting points were determined in open glass capillaries with a Buchi 535 melting point apparatus, and are uncorrected. NMR spectra (1D $^{1}$H and 2D H-C hetero correlated) were recorded at 25°C in DMSO-$d_6$ on a Varian Inova 500 spectrometer equipped with a 5 mm $^{1}$H{$^{13}$C,$^{15}$N} z-axis-PFG indirect detection cold probe or at 28°C on a Varian Mercury 300 spectrometer equipped with a 5 mm switchable probe $^{15}$N-$^{31}$P{$^{1}$H,$^{19}$F}. Residual solvent signal was used as

**Scheme 6.** Velocity of cyclization *versus* scrambling.



**Scheme 7.** ACHD mechanism hypothesized.




reference; chemical shifts and coupling constants are reported, respectively, in δ (ppm) and Hz. ESI(+) high-resolution mass spectra (HRMS) were obtained on a Waters Q-Tof Ultima directly connected with micro HPLC 1100 Agilent [14].

## CONCLUSION

In conclusion, a study on the ACHD on deactivated bromopyrroles has been reported and an hypothetical mechanism has been suggested. A different behavior was observed when considering singly deactivated pyrrole alkylcarboxamides, or doubly deactivated pyrrole-keto-lactams (aldisines). While less electron deficient pyrrole alkylcarboxamides suffered from ACHD, the double deactivation on keto-lactams disfavored protonation thus preventing halogen scrambling. Moreover, in the carboxamides series, scrambling was faster when bromine atom was in the 2-position rather than on 3-carbon. In addition, during the conversion of pyrrole alkylcarboxamides **7** and **9** into aldisines, cyclization occurred, respectively, after scrambling and at a competitive velocity.

## EXPERIMENTAL

**General procedure for ACHD.** $P_2O_5$ (2 eq) and PPA (28 eq) were mechanically stirred and heated at 120°C for 50 min, to obtain a clear solution. The substrate was then added and the mixture was heated at 105°C for 1 h. The mixture was poured into ice water and stirred for 1 h. The solid was filtered off, washed with water, and dried. A second aliquot of reaction mixture was recovered from the aqueous phase as follow: the water solution was cooled, neutralized with concentrated sodium hydroxide, and extracted with $CH_2Cl_2$. The organic phase was dried over anhydrous $Na_2SO_4$, concentrated, and combined with the solid.

**2,3-Dibromo-6,7-dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione (6).** To a suspension of **5** (414 mg, 1.21 mmol) in dry $CH_2Cl_2$ (15 mL) oxalyl chloride (0.21 mL, 2.43 mmol) and $DMF_{cat}$ (0.015 mL) were added. The mixture was stirred under nitrogen until completion of gas evolution. The solvent was removed under reduced pressure and the crude was dissolved in 1,2-dichloroethane (40 mL). 4-Å molecular sieves and aluminium trichloride (0.65 g, 4.87 mmol) were subsequently added. The red solution was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the residue was dissolved in water, made alkaline by addition of 2*N* sodium hydroxide and then acidified to pH 2 with conc. HCl. The precipitate was filtered, washed with water, and dried under vacuum. **6** was isolated as white solid (334 mg, 85%). mp: 270–272°C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.76 (m, 2 H) 3.34 (m, 2 H) 8.47 (br. s., 1 H) 13.46 (br. s., 1 H). $^{13}$C NMR (125.7 and 75.4 MHz, DMSO-$d_6$) δ 36.0, 44.3, 99.0, 110.3, 120.5, 130.6, 161.5, 192.6. HRMS calcd for $C_8H_7Br_2N_2O_2$ [M+H$^+$] 320.8869 found 320.8853.

**3-Bromo-6,7-dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione (8).** The general procedure for ACHD was performed on **9** (170 mg, 0.65 mmol). One hundred thirty milligram of crude were purified by prep-HPLC (eluant 0,05% $NH_3$ in $H_2O$/Acetonitrile 95:5 as a mobile phase A and Acetonitrile as mobile phase B), affording **8** (102 mg, 64%) as a white solid. The separation was achieved using a rapid gradient increasing 0–25% B in 15 min followed by a hold at 100% B for 2 min at a flow rate of 20 mL/min. mp: 248–250°C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.76 (m, 2 H, $CH_2CO$) 3.35 (m, 2 H, C*H*$_2$NH) 7.20 (s, 1 H, C*H*NH) 8.45 (t, $J$ = 5.12 Hz, 1 H, N*H*CH$_2$) 12.52 (br. s., 1 H, NH). $^{13}$C NMR (125.7 MHz, DMSO-$d_6$) δ 35.6, 44.6, 96.7, 118.9, 124.0, 128.8, 161.5, 193.8, HRMS calcd for $C_8H_8BrN_2O_2$ [M+H$^+$] 242.9764 found 242.9759.

**1H-Pyrrole-2-carboxylic acid methyl amide (10).** To a solution of 2-trichloroacetylpyrrole (2.12 g, 9.98 mmol) in 40 mL of dry $CH_3CN$, a 2*M* solution of $MeNH_2$ in THF was added (12.5 mL, 25 mmol). The mixture was stirred under nitrogen, at room temperature for 48 h, until HPLC revealed the disappearance of the starting material. The solvent was removed under reduced pressure to give **10** as white solid. mp: 151–152°C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.72–2.74 (d, 3 H, $J$ = 5 Hz, $CH_3$) 6.06 (dt, $J$ = 3.63, 2.40 Hz, 1 H, CHC*H*CH) 6.70 (ddd, $J$ = 3.69, 2.41, 1.46 Hz, 1 H, CHC*H*C) 6.82 (td, $J$ = 2.69, 1.46 Hz, 1 H, CHC*H*N) 7.89 (br. s., 1 H, N*H*CH$_3$) 11.37 (br. s., 1 H, NH).

**5-Bromo-1H-pyrrole-2-carboxylic acid methylamide (11).** To a stirred solution of **10** (500 mg, 4.03 mmol) in dry MeOH (84 mL) and dry THF (168 mL) at 0°C, *N*-bromosuccinimide (NBS) (323 mg, 1.81 mmol) was added. The cold bath was removed and the reaction mixture was allowed to warm to room temperature under stirring. After 3 h, a HPLC control revealed a 50% conversion of **10–11**. The mixture was recooled to 0°C and more NBS (323 mg, 1.81 mmol) was added. The ice bath was removed and the reactants were stirred for further 2 h at room temperature. The solvent was then removed under vacuum and the residue was purified by flash chromatography (eluant $Et_2O$/Hexane 2:1) to give **11** in mixture with **14** as side product. **11** was isolated as white solid by reverse-phase chromatography (eluant 0.1% trifluoroacetic

acid in $H_2O$/acetonitrile 95/5 as mobile phase A and Acetonitrile as mobile phase B) (490 mg, 60%). mp: 173–175°C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.71 (d, $J$ = 4.64 Hz, 3 H, $CH_3$) 6.11 (dd, $J$ = 3.72, 2.38 Hz, 1 H, CHC*H*CBr) 6.69 (dd, $J$ = 3.78, 2.69 Hz, 1 H, CHC*H*C) 7.93 (q, $J$ = 3.99 Hz, 1 H, N*H*$CH_3$) 12.15 (br. s., 1 H, NH). $^{13}$C NMR (125.7 MHz, DMSO-$d_6$) δ 25.0, 102.1, 110.5, 111.2, 128.8, 160.5. HRMS calcd for $C_6H_8BrN_2O$ [M+H$^+$] 202.9815 found 202.9821.

**4-Bromo-2-(trichloroacetyl)pyrrole (12).** 2-(Trichloroacetyl)pyrrole (10 g, 0.05 mol) in $CHCl_3$ (50 mL) was treated with $Br_2$ (9.5 g, 0.06 mol) in $CHCl_3$ (3 mL) at 5°C. The ice bath was removed and the reactants were stirred for 1 h at room temperature. The mixture was diluted with $CH_2Cl_2$ and washed with $H_2O$, $NaHCO_3$, and brine. The organic layer was dried (over $Na_2SO_4$) and concentrated under vacuum. The crude was then crystallized from hexane-$CH_2Cl_2$ affording **12** (11.3 g, 70%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 7.34 (dd, $J$ = 2.68, 1.46 Hz, 1 H, CC*H*C) 7.56 (dd, $J$ = 3.29, 1.46 Hz, 1 H, C*H*N) 12.85 (br. s., 1 H).

**4-Bromo-1H-pyrrole-2-carboxylic acid methylamide (13).** Compound **12** (575 mg, 1.98 mmol) was treated with a 2*M* solution of $MeNH_2$ in THF (2.45 mL, 4.95 mmol) delivering **13** (400 mg, quantitative) as white solid after removal of the solvent. mp: 178–180°C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 2.70 (d, $J$ = 4.69 Hz, 3 H, $CH_3$) 6.75 (dd, $J$ = 2.64, 1.47 Hz, 1 H, CHCBr) 6.92 (dd, $J$ = 2.93, 1.47 Hz, 1 H, CHN) 8.01 (q, 1 H, N*H*$CH_3$) 11.75 (br. s., 1 H, NH).

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## REFERENCES AND NOTES

[1] Vaitiekunas, A.; Nord, F. F. Nature 1951, 168, 875.

[2] Schnürch, M.; Spina, M.; Farooq Khan, A.; Mihovilovic, M. D.; Stanetty, P. Chem Soc Rev 2007, 36, 1046.

[3] (a) Palmer, M. H.; Leitch, D. S. Tetrahedron 1978, 34, 1015; (b) Carson, J. R.; Davis, N. M. J Org Chem 1981, 46, 839.

[4] Carmona, O.; Greenhouse, R.; Landeros, R.; Muchowski, J. M. J Org Chem 1980, 45, 5336.

[5] (a) Gilow, H. M.; Burton, D. E. J Org Chem 1981, 46, 2221; (b) De Rosa, M. J Org Chem 1982, 47, 1008; (c) Park, S.-H.; Ha, H.-J.; Lim, C.; Lim, D.-K.; Lee, K.-H.; Park, Y.-T. Bull Korean Chem Soc 2005, 26, 1190.

[6] Chastrette, F. Bull Chem Soc Fr 1970, 3, 1151.

[7] (a) Annoura, H.; Tatsuoka, T. Tetrahedron Lett 1995, 36, 413; (b) Papeo, G.; Posteri, H.; Borghi, D.; Varasi, M. Org Lett 2005, 7, 5641.

[8] Tutino, F.; Posteri, H.; Borghi, D.; Quartieri, F.; Mongelli, N.; Papeo, G. Tetrahedron 2009, 65, 2372.

[9] For the isolation of **6** and **8** from marine sponges see: Hassan, W.; Elkhayat, E. S.; Edrada, R. A.; Ebel, R.; Proksch, P. Nat Prod Comm 2007, 11, 1149.

[10] For the synthesis of **5** see: Wan, Y.; Hur, W.; Cho, C. Y.; Liu, Y.; Adrian, F. J.; Lozach, O.; Bach, S.; Mayer, T.; Fabbro, D.; Meijer, L.; Gray, N. S. Chem Biol 2004, 2, 247.

[11] For better clarity, numbering system of pyrrolecarboxamides **7**, **9**, **11**, and **13** was considered the same as for aldisines.

[12] Zeng, X.-C.; Xu, S.-H.; Liu, P.-R.; Gu, J. Acta Crystallographica 2005, E61, o1076.

[13] Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinehart, K. L. J Org Chem 1991, 56, 2965.

[14] Colombo, M.; Riccardi Sirtori, F.; Rizzo, V. Rapid Commun Mass Spectrom 2004, 18, 511.

# Investigation of Interaction of Benzoquinones and Naphthoquinones with Substituted Hydrazides

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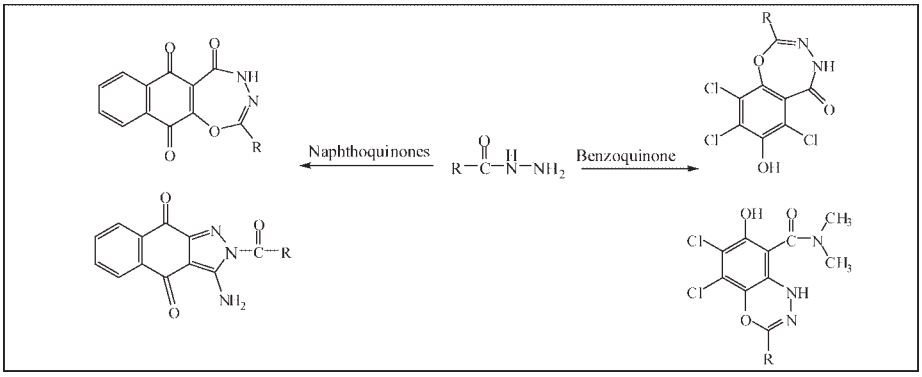


Nucleophilic attack by substituted hydrazides on C-2, C-3 of 2,3,5,6-tetrachloro-1,4-benzoquinone and 2,3-dichloro-1,4-naphthoquinone initiates the formation of benzo[e][1,3,4]oxadiazine and benzo- as well as naphthoxadiazepine derivatives. On the other hand, substituted hydrazides attack 1,4-naphthoquinone-2,3-dicarbonitrile to form benzo[f]indazole-4,9-dione derivatives. A rationale for the conversions observed is presented.

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## INTRODUCTION

2,3,5,6-Tetrachloro-1,4-benzoquinone (**2**) and 2,3-dichloro-1,4-naphthoquinone (**3**) undergo nucleophilic substitution of one or two chlorine atoms by primary amines [1,2], amino acids [3,4], and aziridines [5]. Up to four nitrogen residues are introduced into **2** and **3** in their reaction with pyrazole [6], imidazole [7,8], and 1,2,4-triazole [7,9]. Amides and thioamides were added to **3** to produce two related heterocyclic diones series in excellent yields [10–14]. The reaction of **2** and **3** with $N^1$, $N^2$-diarylamidines to give benzimidazole and indole derivatives has been reported [15,16]. Heterocyclization of substituted thiosemicarbazides and dithiobiureas during the reaction with benzoquinones and naphthoquinones, different successful approach for the synthesis of oxathiadiazole [17], thiadiazine [17,18], imidazoxadiazole [19], imidazothiadiazole [20], and indazole [21] derivatives. A large variety of quinones, including many fused heterocyclic rings, have been used as synthetic intermediates in medicinal [22–25] and dye chemistry [26–29].

## RESULTS AND DISCUSSION

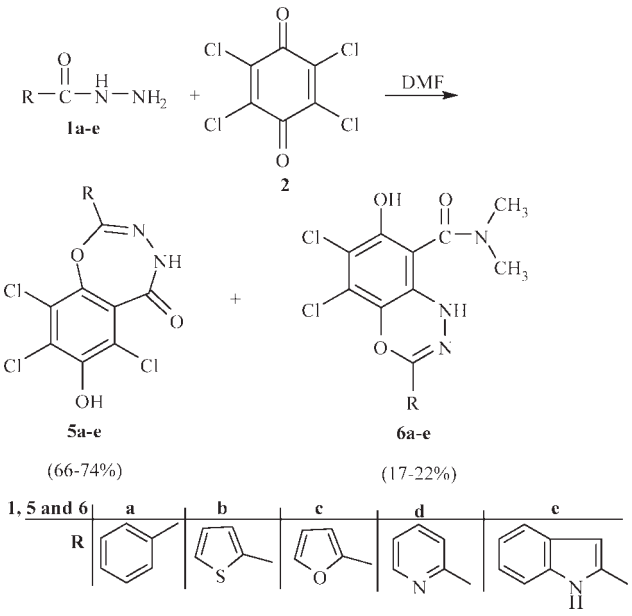
We report herein the results of our recent investigation on the reactions of substituted hydrazides **1a-e** with 2,3,5,6-tetrachloro-1,4-benzoquinone (**2**), 2,3-dichloro-1,4-naphthoquinone (**3**) and 1,4-naphthoquinone-2,3-dicarbonitrile (**4**).

Equimolar solutions of **1a-e** and **2** in DMF upon standing for 48 hours at room temperature formed the derivatives of benzoxadiazepine **5a-e** as major product (66–74%) and benzoxadiazine **6a-e** as minor product (17–22%) (Scheme 1).

The structural assignment of 6,8,9-trichloro-7-hydroxy-2-(substituted)benzo[*f*][1,3,4]oxadiazepine-5(*H*)-one **5a-e** are based on the following spectral data: The IR spectrum showed a broad bands at $\nu_{max}$ 3455–3480 and 3280–3335 because of OH and NH, sharp band at 1700–1710 for carbonyl group and 1620–1630 $cm^{-1}$ for C=N.

The $^1H$ NMR displayed two broad singlets, one at $\delta$ = 7.79–7.86 ppm and the other at $\delta$ = 9.57–9.62 ppm because of oxadiazepine-NH and phenolic-OH, respectively. The $^{13}C$ NMR spectrum showed a signal at $\delta$ = 152.46–152.75 ppm for aromatic quaternary carbon atom bearing a hydroxyl group [30], the presence of one carbonyl group at $\delta$ = 169.73–169.84 ppm and oxadiazepinone-C-2 at $\delta$ = 156.66–156.86 ppm. In the $^{13}C$ NMR the absence of characteristic resonance signals of the carbonyl carbon atoms of chloranil **2** around 182–184 [31] ppm support the structure **5a-e**. The formation of **5b** was further confirmed by mass spectrometry.

**Scheme 1**



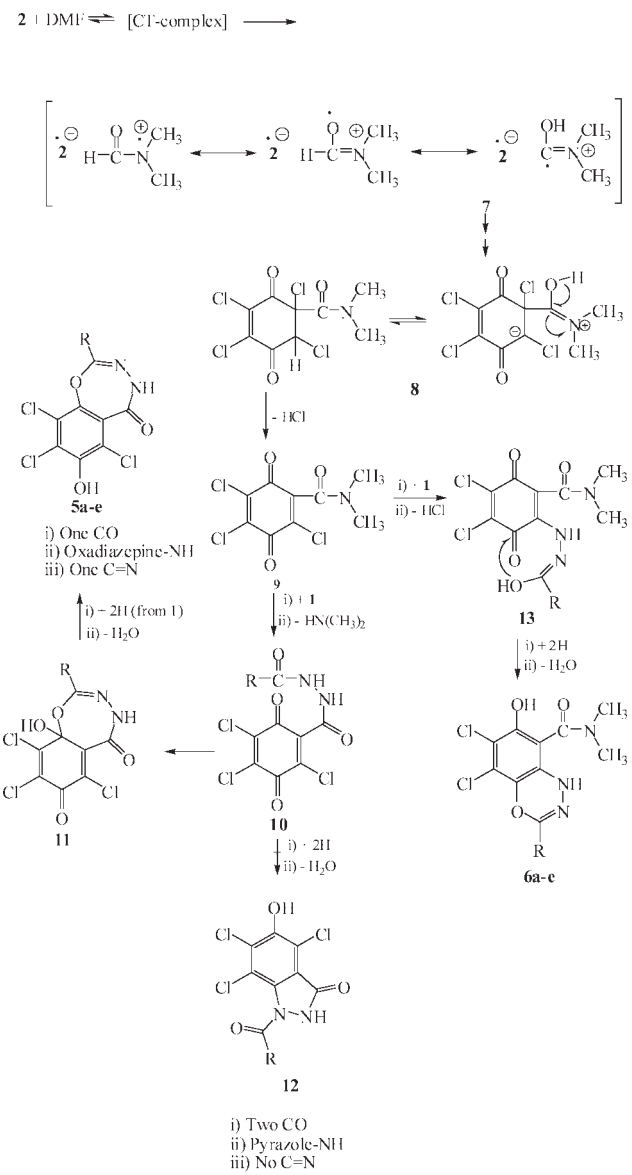

Besides the molecular ion at 362/368, the characteristic fragment ion patterns of trichloro compounds were observed. The EI mass spectrum of **5b** is characterized by loss of 111 a.m.u (most likely thiophene carbonyl group) followed by loss of 28 a.m.u (dinitrogen or carbonyl group). The *a priori* possible isomeric structure **12a-e** (Scheme 2) was ruled out on the basis of IR and $^{13}C$ NMR spectral data.

The structural assignment of **6a-e** was supported by the following spectral data: In its $^{13}C$ NMR spectrum, the characteristic absorption signal of two carbonyl carbon atoms of chloranil are replaced by signals at $\delta$ = 140.87–141.12 and $\delta$=152.46–153.04 ppm, which are characteristic of aromatic quaternary carbon bearing oxygen [30]. In addition Ph—C—Cl appears at 121.94–122.32 and 123.14–123.46 [31] ppm. The carbonyl group attached to $N(CH_3)_2$ resonates at $\delta$ = 171.23–171.42 [31] ppm. The IR spectrum of **6a-e** showed bands at 3470–3490 and 3290–3315 due to OH and NH, and strong absorption at 1680–1690 due to carbonyl group. The $^1H$ NMR spectrum of **6a-e** showed signals at 3.36–344, 7.69–7.81, and 9.61–9.74 due to $N(CH_3)_2$, oxadiazine–NH and hydroxyl group, respectively. It is worthy to note that the mass spectra of compounds **6a-e** show the loss of O=C—$N(CH_3)_2$, $N_2$ or CO, as well as RCO from the molecular ions.

Scheme 2 summarizes the reactions responsible for the formation of compounds **5** and **6**. It shows the interaction of **1a-e** with chloranil (**2**) in DMF as a solvent proceeded in an interesting manner because of the participation of DMF in the course of the reaction, as reported in our earlier publications on the reactions of hydrazino-1,2,4-triazinoindole [32], amino- and diamino-1,2,4-triazole derivatives [9] and 3,5-diaminopyrazoles [6] with chloronated benzoquinones and naphthoquinones.

Unstable charge-transfer complexes may be formed during the reaction between chlorinated quinone and DMF, followed by the formation of anionic cationic radicals **7**. Recombination of the radicals afforded the adduct **8**, which gradually split off a molecule of hydrogen chloride to form **9**. The latter interacted with the hydrazide **1** with elimination a molecule of dimethylamine and another of water in presence of hydrogen protons (possibly from **1**) to afford benzoxadiazepine derivatives **5a-e**. On the other hand compound **9** reacted with **1** to give **6a-e** as illustrated in Scheme 2.

**Scheme 2**



2,3-Dichloro-1,4-naphthoquinone **3** was chosen to compare its reactivity toward the hydrazides **1a-e** with chloranil (**2**).

It has been described in the literature that **3** resembles **2** in most of its substitution reactions, especially with compounds containing nucleophilic nitrogen (amines, amino acids, pyrazoles, imidazoles, etc) [1–7,9]. From this point of view one might expect that **1a-e** should react with **2** similarly like **3**. Earlier, it had been reported that **1a** reacted with **3**, ultimately giving 2,3-di(benzoyl-hydrazinyl)naphthalene-1,4-dione (**14**) (Scheme 3). We report here the results of recent investigations on the reaction of **1a-e** with **3**.

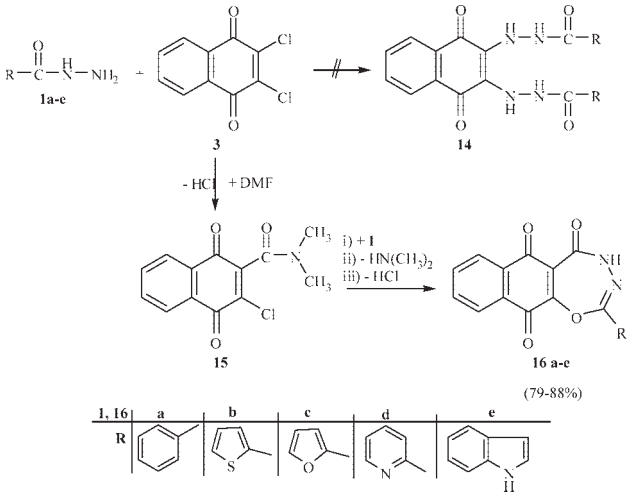
Mixing equimolar amounts of **1a-e** and **3** in DMF for 72 hours led to the formation of 2-substituted naphtho[2,3-*f*][1,3,4]oxadiazepine-5,6,11-(4*H*)-triones **16a-e** (Scheme 3). The IR spectra of **16a-e** (in KBr) showed NH absorption at 3230–3245 $cm^{-1}$, carbonyl groups at 1705–1725 and 1680–1690, as well as bands characteristic of C—O—C and C=N at 1090 and 1620–1630, respectively. The $^1H$ NMR spectra of **16a-e** clearly show one broad signal at 7.78–7.84 ppm due to oxadiazepine-NH.

Signals around 169.58–169–84 (C-5), 187.39–187.78 (C–6) [31] and 187.33–187.80 (C-11) [31] and 156.78–156.86 (C-2), in $^{13}C$ NMR spectra lend further support to the structure assigned to **16a-e**. The EI-mass spectra need a brief comment for **16a-e**, m/z = 213 represent the derivative of benzindazolyl fragment formed by release of corresponding RCO from the molecular ion, which undergo loss of 28 a.m.u (dinitrogen or CO group).

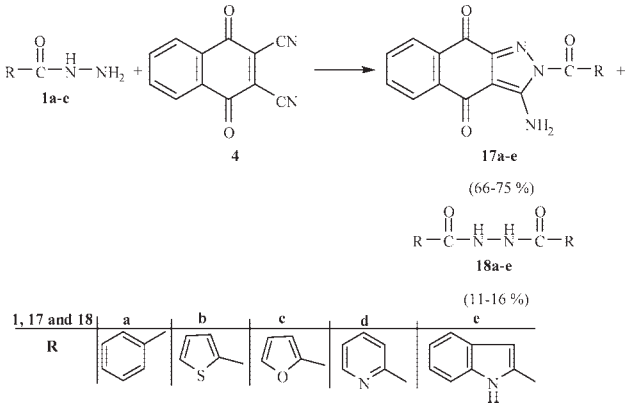
The present investigation also dealt with the study of the chemical behavior of hydrazides **1a-e** toward 1,4-naphthoquinone-2,3-dicarbonitrile (**4**). Substituted benzo[*f*]indazolediones **17a-e** and diacylhydrazines **18a-e** were obtained from the reaction of **1a-e** with (**4**) (Scheme 4).

Compounds **17a-e** exhibited IR absorptions at 3330–3345 ($NH_2$), 1685–1690 and 1660–1665 (CO). The $^1H$ NMR spectra of **17a-e** clearly showed one broad signal at 6.67–6.73 ppm because of $NH_2$, besides the aromatic protons. Signals at 153.29–153.48 (C-3), 100.89–101.46 (C-3a), 139.81–140.11 (C9a), 188.54–188.74 (C-4), 187.75–187.89 (C-9), 165.46–165.73 (CO), 137.86 (indole-C-2) and 99.74 (indole-C-5) in the $^{13}C$ NMR spectra of **17a-e** lend further supported the structure assigned to **17a-e**. The structure of **17e** was evidently confirmed by mass spectrometrically, besides the molecular ion at m/z = 356 (39%), the characteristic fragment ion pattern of indole-2-carbonyl at 144 (86), $C_6H_4CO^+$ group at 104 (77), benzoyl cation at 91 (89) and 77 (100) as a base peak. A possible reaction process is depicted in Scheme 5.

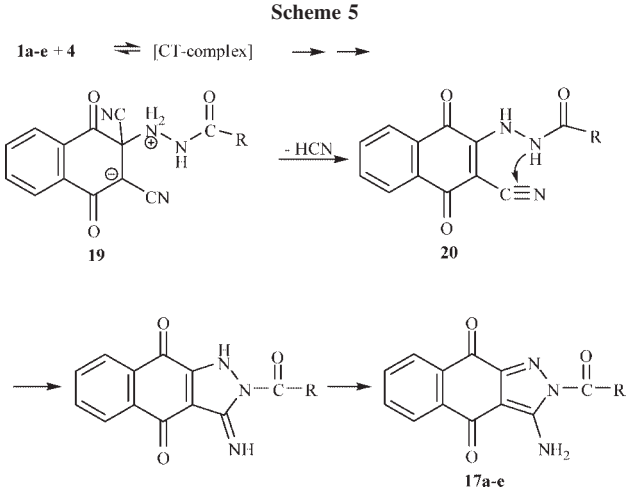
**Scheme 3**




**Scheme 4**




**Scheme 5**



## CONCLUSIONS

In a fairly complex and multistep process, benzo[e][1,3,4]oxadiazine, benzo[f]indazole-4,9-dione and benzoxadiazepine as well as naphthoxadiazepine derivatives are formed from **1a-e** and (**2-4**) during the nucleophilic attack by substituted hydrazides on C-2, C-3 of 2,3,5,6-tetrachloro-1,4-benzoquinone and 2,3-dichloro-1,4-naphthoquinone. On the other hand, 1,4-naphthoquinone-2,3-dicarbonitrile (**4**) may act as either as a mediator or as a building block in heterocyclization of substituted hydrazides. The results reported here supplement the rich of substituted hydrazides **1a-e**.

## EXPERIMENTAL

Mp's were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded with a Shimadzu 408 instrument using potassium bromide pellets. The $^1$H NMR (400.13 MHz) and $^{13}$C NMR (100.6 MHz) spectra were measured in DMSO-$d_6$ using a Bruker AM400 with TMS as an internal standard. Chemical shifts are expressed as δ [ppm], s = singlet, m = multiplet and b = broad. Assignments of carbon resonances have been supported by DEPT experiments. Mass spectra have been obtained with Varian MAT CH-7 instrument using electron impact ionization (70 eV). Elemental analyses have been determined by the Microanalytical Center, Cairo University, Egypt. For preparative layer chromatography (plc) 1.0 mm thick air-dried layers of slurry applied silica gel, Merck $Pf_{254}$ on 48 cm wide and 20 cm high glass plates were used, zones were detected by their color and indicator fluorescence quenching upon exposure to 254 nm light and extracted with acetone.

**Starting materials.** Substituted hydrazides **1a-e** were prepared according to published procedures, as were 2-thiophene carbohydrazide (**1b**), mp 135–137°C (ref. [33] 134–136°C); furan-2-carbohydrazide (**1c**), mp 77–79 (ref. [34] 78°C); 2-pyridine carbohydrazide (**1d**), mp 136–138°C (ref. [35] 137°C); indole-2-carbohydrazide (**1e**), mp 243–245°C (ref. [36,37] 246°C) and phenyl carbohydrazide (**1a**) (Aldrich), 2,3,5,6-tetrachloro-1,4-benzoquinone (**2**) (Aldrich) and 2,3-dichloro-1,4-naphthoquinone (**3**) (Aldrich) were used as received. 1,4-Naphthoquinone-2,3-dicarbonitrile (**4**) was prepared from 2,3-dichloro-1,4-naphthoquinone (**3**) according to Budni et al [38].

**Reaction of substituted hydrazides 1a-e with (2).** To a solution of **2** (246 mg, 1 mmol) in dry DMF (15 mL) a solution of **1a-e** (1.0 mmol each) in 5 mL of DMF was added dropwise over 5 min. at room temperature with stirring and admission of air. The stirring was continued for 48 h with admission of air to complete the reaction. The reaction mixture was concentrated to drynes. The residue was taken up several times with cold ethanol (10 mL) and slurry was concentrated again to remove any residual DMF. The residue was dissolved in acetone (5 mL). This solution in each case was applied to 5 plc-plates and developed with toluene/ethyl acetate (5:1) for the run with **1a**, toluene/ethyl acetate (4:1) for the runs with **1b-d** and toluene/ethyl acetate (3:1) for the run with **1e** to give numerous colored zones. The two intense of which were removed and extracted. The fastest migrating one contained substituted benzo[1,3,4]oxadiazepine **5a-e**, the slowest migrating zone contained substituted benzo-[1,3,4]oxadiazinecarboxamide **6a-e**. Extraction of zones with acetone and recrystallized.

**6,8,9-Trichloro-7-hydroxy-2-phenylbenzo[*f*][1,3,4]-oxadiazepin-5-(4*H*)-one (5a).** Compound **5a** was obtained as reddish brown crystals (0.264 g, 74%), mp 216–217°C (acetonitrile), IR: 3460 (OH), 3310 (NH), 1705 (CO), 1625 (C=N), 1596 (Ar—C=C), 1085 (C—O—C). $^1$H NMR: δ 7.18–7.53 (m, 5H, Ar—H), 7.84 (br, 1H, oxadiazepine—NH), 9.56 (br, 1H, OH); $^{13}$C NMR: δ 120.71 (C-5a), 122.53, 123.74, 124.17 (C-6, 8 and 9), 126.51, 128.26, 130.14 (Ar—CH), 134.72 (Ar—C), 147.38 (C-9a), 152.56 (C-7), 156.86 (C-2), 169.84 (CO); ms m/z: 356/362 ($M^+$, 42), 322 (26), 286 (34), 250 (21), 194 (26), 158 (11), 105 (67), 77 (100), 65 (49); Anal. Calcd. for $C_{14}H_7Cl_3N_2O_3$ (357.58): C, 47.02; H, 1.97; Cl, 29.74; N, 7.83. Found: C, 46.81; H, 2.11; Cl, 29.51; N, 7.64.

**6,8,9-Trichloro-7-hydroxy-2-(thiophen-2-yl)benzo[*f*][1,3,4]-oxadiazepin-5-(4*H*)-one (5b).** Compound **5b** was obtained as reddish brown crystals (0.258g, 71%), mp 257–259°C (acetonitrile). IR: 3470 (OH), 3295 (NH), 1700 (CO), 1630 (C=N), 1585 (Ar—C=C), 1090 (C—O—C). $^1$H NMR: δ 7.05–7.38 (m, 3H, thiophene-H), 7.79 (br, 1H, oxadiazepine-NH), 9.62 (br, 1H, OH); $^{13}$C NMR: δ 120.59 (C-5a), 122.42, 123.55, 123.96 (C-6, 8 and 9), 126.27, 127.69, 127.94 (thiophene-CH), 130.16 (thiophene-C), 148.06 (C-9a), 152.61 (C-7), 156.79 (C-2), 169.76 (CO); ms m/z: 362/368 ($M^+$, 34), 328 (18), 292 (27), 218 (41), 111 (100), 107 (53), 82 (46); Anal. Calcd. for $C_{12}H_5Cl_3N_2O_3S$ (363.60): C, 39.64; H, 1.39; Cl, 29.25; N, 7.70. Found C, 39.41; H, 1.51; Cl, 29.47; N, 7.54.

**6,8,9-Trichloro-7-hydroxy-2-(furan-2-yl)benzo[*f*][1,3,4]-oxadiazepin-5-(4*H*)-one (5c).** Compound **5c** was obtained as reddish brown crystals (0.229 g, 66%), mp 207–208°C (acetonitrile). IR: 3455 (OH), 3335 (NH), 1710 (CO), 1625 (C=N), 1085 (C—O—C); $^1$H NMR: δ 7.11–7.46 (m, 3H, furan-H), 7.82 (br, 1H, oxadiazepine-NH), 9.57 (br, 1H, OH); $^{13}$C NMR: δ 120.71 (C-5a), 122.19, 123.64, 123.92 (C-6, 8 and 9), 125.98, 126.11 (furan-CH), 141.57, 142.11 (furan-C-2, C-5), 147.96 (C-9a), 152.75 (C-7), 156.68 (C-2), 169.81 (CO); ms m/z: 346/352 ($M^+$, 38), 312 (25), 276 (16), 220 (31), 184 (27), 95 (100), 67 (71); Anal. Calcd. For $C_{12}H_5Cl_3N_2O_4$ (347.54): C, 41.47; H, 1.45; Cl, 30.60; N, 8.06. Found C, 41.66; H, 1.56; Cl, 30.38; N, 7.87.

**6,8,9-Trichloro-7-hydroxy-2-(pyridin-2-yl)benzo[*f*][1,3,4]-oxadiazepin-5-(4*H*)-one (5d).** Compound **5d** was obtained as reddish brown crystals (0.247g, 69%), mp 226–228°C (ethanol). IR: 3480 (OH), 3315 (NH), 1705 (CO), 1620 (C=N), 1590 (Ar—C=C), 1080 (C—O—C); $^1$H NMR: δ 7.48–8.41 (m, 5H, pyridine-H and oxadiazepine-NH), 9.57 (br, 1H, OH); $^{13}$C NMR: δ 121.07 (C-5a), 122.31, 123.62, 123.89 (C-6, 8 and 9), 127.89, 128.75, 130.14 (pyridine-CH), 146.35, 147.11 (pyridine C-2, C-6), 148.22 (C-9a), 152.57 (C-7), 156.85 (C-2), 169.73 (CO); ms m/z: 357/363 ($M^+$, 21), 323 (18), 287 (34), 195 (47), 106 (83), 78 (100); Anal. Calcd. for $C_{13}H_6Cl_3N_3O_3$ (358.56): C, 43.55; H, 1.69; Cl, 29.66; N, 11.72. Found C, 43.33; H, 1.78; Cl, 29.43; N, 11.87.

**2-(1*H*-Indole-2-yl)-6,8,9-trichloro-7-hydroxy-benzo[*f*][1,3,4]-oxadiazepin-5-(4*H*)-one (5e).** Compound **5e** was obtained as reddish brown crystals (0.265g, 67%), mp 271–273°C (methanol). IR: 3475–3280 (OH, NH's), 1710 (CO), 1630 (C=N), 1595 (Ar—C=C), 1090 (C—O—C); $^1$H NMR: δ 6.64 (s, 1H,

indole-CH), 7.12–7.68 (m, 4H, Ar—H), 7.86 (br, 1H, oxadiazepine-NH), 9.58 (br, 1H, OH), 11.62 (br, 1H, indole-NH); $^{13}$C NMR: δ 99.71(indole-CH), 121.98 (C-5a), 121.87, 123.35, 123.92 (C-6, 8 and 9), 127.14, 127.96 (Ar—CH), 130.55 (indole-C3a), 134.66, 137.12 (indole C-2 and C-7a), 152.46 (C-7), 156.81 (C-2), 169.80 (CO); MS m/z: 395/361 ($M^+$, 29), 331 (26), 295 (38), 242 (21), 186 (12), 144 (62), 116 (76), 92 (100), 77 (83), 65 (41); Anal. Calcd. for $C_{16}H_8Cl_3N_3O_3$ (396.61): C, 48.45; H, 2.03; Cl, 26.82; N, 10.59. Found C, 48.64; H, 1.91; Cl, 27.03; N, 10.77.

**5,6-Dichloro-7-hydroxy-*N,N′*-dimethyl-3-phenyl-1*H*-benzo[*e*][1,3,4]oxadiazine-8-carboxamide (6a).** Compound **6a** was obtained as deep red brown crystals (0.062g, 17%), mp 248–250°C (acetonitrile). IR: 3485 (OH), 3290 (NH), 1690 (CO), 1625 (C=N), 1585 (Ar—C=C), 1080 (C—O—C); $^1$H NMR: δ 3.44 (s, 6H, $N(CH_3)_2$), 7.24–7.79 (m, 6H, Ar—H and oxadiazine-NH), 9.67 (br, 1H, OH); $^{13}$C: δ 36.29 ($CH_3$), 106.83 (C-8), 122.27, 123.14 (C-5 and C-6), 127.21, 128.54, 130.16 (Ar-CH), 134.27 (Ar-C), 138.44 (C-8a), 141.11 (C-4a), 152.51 (C-7), 156.76 (C-3), 171.41 (CO); MS m/z: 365/369 ($M^+$, 41), 329 (18), 257 (44), 193 (29), 105 (81), 77 (100), 65 (74); Anal. Calcd. for $C_{16}H_{13}Cl_2N_3O_3$ (366.20): C, 52.48; H, 3.58; Cl, 19.36; N, 11.47. Found C, 52.66; H, 3.45; Cl, 19.59; N, 11.65.

**5,6-Dichloro-7-hydroxy-*N,N′*-dimethyl-3-(thio-phen-2-yl-1*H*-benzo[*e*][1,3,4]oxadiazine-8-carbox-amide (6b).** Compound **6b** was obtained as reddish brown crystals (0.067g, 18%), mp 276–278°C (ethanol). IR: 3470 (OH), 3310 (NH), 1685 (CO), 1630 (C=N), 1590 (Ar—C=C), 1085 (C—O—C); $^1$H NMR: δ 3.36 (s, 6H, $N(CH_3)_2$), 7.11–7.39 (m, 3H, thiophene-H), 7.71 (br, 1H, oxadiazine-NH), 9.70 (br, 1H, OH); $^{13}$C: δ 36.41 ($CH_3$), 107.12 (C-8), 121.94, 123.32 (C-5 and C-6), 126.22, 127.56, 127.84 (thiophene-CH), 130.12 (thiophene-C), 138.51 (C-8a), 140.97 (C-4a), 152.46 (C-7), 156.81 (C-3), 171.23 (CO); ms m/z: 371/375 ($M^+$, 26), 336 (29), 300 (12), 264 (21), 153 (8), 111 (100), 83 (76); Anal. Calcd. for $C_{14}H_{11}Cl_2N_3O_3S$ (372.23): C, 45.17; H, 2.98; Cl, 19.05; N, 11.29; S, 8.61. Found C, 44.94; H, 3.10; Cl, 18.88; N, 11.41; S, 8.83.

**5,6-Dichloro-7-hydroxy-*N,N′*-dimethyl-3-(thio-phen-2-yl-1*H*-benzo[*e*][1,3,4]oxadiazine-8-carbox-amide (6c).** Compound **6c** was obtained as brown crystals (0.078g, 22%), mp 235–237°C (ethanol). IR: 3480 (OH), 3300 (NH), 1680 (CO), 1625 (C=N), 1590 (Ar—C=C), 1085 (C—O—C); $^1$Hnmr: δ 3.40 (s, 6H, $N(CH_3)_2$), 6.95–7.35 (m, 3H, furan-H), 7.69 (br, 1H, oxadiazine-NH), 9.67 (br, 1H, OH); $^{13}$C: δ 36.38 ($CH_3$), 106.91 (C-8), 122.18, 123.27 (C-5 and C-6), 125.96, 126.47 (furan-CH), 138.36 (C-8a), 141.12 (C-4a), 142.76, 143.63 (furan-C-2 and C-5), 152.64 (C-7), 156.77 (C-3), 171.34 (CO); MS m/z: 355/359 ($M^+$, 27), 320 (42), 284 (18), 212 (37), 117 (52), 95 (100), 67 (68); Anal. Calcd. for $C_{14}H_{11}Cl_2N_3O_4$ (356.16): C, 47.21; H, 3.11; Cl, 19.91; N, 11.80. Found C, 47.44; H, 2.98; Cl, 20.08; N, 12.02.

**5,6-Dichloro-7-hydroxy-*N,N′*-dimethyl-3-(pyridin-2-yl-1*H*-benzo[*e*][1,3,4]oxadiazine-8-carboxamide (6d).** Compound **6d** was obtained as brown crystals (0.062g, 17%), mp 261–263°C (acetonitrile). IR: 3490 (OH), 3315 (NH), 1690 (CO), 1630 (C=N), 1585 (Ar—C=C), 1080 (C—O—C); $^1$H: δ 3.38 (s, 6H, $N(CH_3)_2$), 7.36—8.48 (m, 5H, pyridine-H and oxadiazine-NH), 9.74 (br, 1H, OH); $^{13}$C: δ 36.44 ($CH_3$), 107.09 (C-8), 122.28, 123.46 (C-5 and C-6), 127.16, 128.91, 130.28 (pyridine-CH), 138.42 (C-8a), 140.87 (C-4a), 146.42, 147.83 (pyridine-C-2 and C-6), 152.71 (C-7), 156.84 (C-3), 171.42 (CO); MS m/z: 366/370 ($M^+$, 35), 332 (19), 296 (27), 224 (41), 196 (23), 106 (74), 78 (100); Anal. Calcd. for $C_{15}H_{12}Cl_2N_4O_3$ (367.19): C, 49.07; H, 3.29; Cl, 19.31; N, 15.26. Found C, 48.84; H, 3.41; Cl, 19.07; N, 15.43.

**5,6-Dichloro-7-hydroxy-*N,N′*-dimethyl-3-(pyridin-2-yl-1*H*-benzo[*e*][1,3,4]oxadiazine-8-carboxamide (6e).** Compound **6e** was obtained as brown crystals (0.073g, 18%), mp 301–303°C (methanol). IR: 3485 (OH), 3340-3295 (NH's), 1690 (CO), 1630 (C=N), 1600 (Ar-C=C), 1085 (C—O—C); $^1$H NMR: δ 3.41 (s, 6H, $N(CH_3)_2$), 6.64 (s, 1H, indole-CH), 7.26–7.81 (m, 5H, Ar—H and oxadiazine-NH), 9.62 (br, 1H, OH), 11.71 (br, 1H, indole-NH); $^{13}$C NMR: δ 36.45 ($CH_3$), 98.95 (indole-CH), 106.88 (C-8), 122.32, 123.41 (C-5 and C-6), 126.37, 127.74 (Ar-CH), 130.71 (indole-C-3a), 135.07, 137.36 (indole-C-2 and C-7a), 138.53 (C-8a), 141.07 (C-4a), 153.04 (C-7), 156.91 (C-3), 171.26 (CO); MS m/z: 404/408 ($M^+$, 25), 370 (32), 334 (12), 262 (46), 234 (19), 144 (56), 91 (76), 77 (100), 65 (85); Anal. Calcd. for $C_{18}H_{14}Cl_2N_4O_3$ (405.23): C, 53.35; H, 3.48; Cl, 17.50; N, 13.83. Found C, 53.17; H, 3.61; Cl, 17.72; N, 14.05.

**Reaction of substituted hydrazides 1a-e with (3).** A solution of **1a-e** (1.0 mmol) in 15 mL of dry DMF was added dropwise with stirring to a solution of **3** (1.0 mmol) in 10 mL of dry DMF. The reaction mixture was stirring for 72 h, during which time it turned from faint orange into deep red. The precipitate of substituted naphtho[2,3-*f*][1,3,4]oxadiazepine-5,6,11-(4*H*)-trione **16** was filtered and washed several times with cold ethanol, and crystallized from suitable solvent.

**2-Phenylnaphtho[2,3-*f*][1,3,4]oxadiazepine-5,6,11-(4*H*)-trione (16a).** Compound **16a** was obtained as reddish brown crystals (0.280g, 88%), mp 289–291°C (acetonitrile). IR: 3230 (NH), 1710, 1685 (CO), 1620 (C=N), 1585 (Ar—C=C), 1090 (C—O—C); $^1$H NMR: δ 7.14–7.76 (m, 5H, Ar—H), 7.84 (br, 1H, oxadiazepine-NH), 8.04–8.21 (m, 4H, Ar—H); $^{13}$C NMR: δ 126.49, 128.84, 129.12, 134.61, 136.66 (Ar—CH), 131.45, 132.45, 132.17, 141.36 (Ar—C), 156.86 (C-2), 169.64 (oxadiazepine-CO), 187.44, 187.78 (C-6 and C-11); ms m/z: 318 ($M^+$, 46), 213 (26), 185 (61), 105 (81), 104 (76), 77 (100), 65 (67); Anal. Calcd. for $C_{18}H_{10}N_2O_4$ (318.28): C, 67.92; H, 3.17; N, 8.80. Found C, 68.14; H, 3.06; N, 9.04.

**2-(Thiophen-2-yl)naphtho[2,3-*f*][1,3,4]oxadiaz-epine-5,6,11-(4*H*)-trione (16b).** Compound **16b** was obtained as brown crystals (0.272 g, 84%), mp 307–309°C (ethanol). IR: 3245 (NH), 1715, 1680 (CO), 1625 (C=N), 1585 (Ar-C=C), 1080 (C-O-C); $^1$H NMR: δ 7.08–7.46 (m, 3H, thiophene-H), 7.80 (br, 1H, oxadiazepine-NH), 8.05–8.19 (m, 4H, Ar—H); $^{13}$C NMR: δ 126.23, 127.76, 128.33, (thiophene-CH), 129.36, 136.94 (Ar-CH), 131.64, 131.16, 141.19 (Ar—C), 156.80 (C-2), 169.58 (oxadiazepine-CO), 187.39, 187.68 (C-6 and C-11); ms m/z: 324 ($M^+$, 23), 213 (34), 185 (48), 111 (100), 104 (56), 77 (86), 65 (61); Anal. Calcd. for $C_{16}H_8N_2O_4S$ (324.31): C, 59.26; H, 2.49; N, 8.64; S, 9.89. Found C, 59.09; H, 2.61; N, 8.43; S, 10.04.

**2-(Furan-2-yl)naphtho[2,3-*f*][1,3,4]oxadiazepine-5,6,11-(4*H*)-trione (16c).** Compound **16c** was obtained as brown crystals (0.253 g, 82%), mp 274–276°C (ethanol). IR: 3235 (NH), 1710, 1690 (CO), 1620 (C=N), 1590 (Ar—C=C), 1085 (C—O—C); $^1$H: δ 6.97–7.38 (m, 3H, furan-H), 7.78 (br, 1H, oxadiazepine-NH), 8.00–8.22 (m, 4H, Ar—H); $^{13}$C NMR: δ

126.08, 126.26 (furan-CH), 129.54, 136.89 (Ar—CH), 131.55, 131.96, 140.87 (Ar—C), 141.62, 142.26 (furan-C-2 and C-5), 156.85 (C-2), 169.84 (oxadiazepine-CO), 187.46, 187.72 (C-6 and C-11); ms m/z: 308 ($M^+$, 32), 213 (28), 185 (57), 157 (21), 104 (71), 95 (63), 77 (100), 65 (84); Anal. Calcd. for $C_{16}H_8N_2O_5$ (308.25): C, 62.34; H, 2.62; N, 9.09. Found C, 62.51; H, 2.77; N, 8.83.

**2-(Pyridin-2-yl)naphtho[2,3-*f*][1,3,4]oxadiazepine-5,6,11-(4*H*)-trione (16d).** Compound **16d** was obtained as brown crystals (0.255 g, 80%), mp 297-299°C (acetonitrile). IR: 3245 (NH), 1705, 1690 (CO), 1625 (C=N), 1585 (Ar—C=C), 1090 (C—O—C); $^1$H NMR: δ 7.36–8.49 (m, 9H, Ar—H, pyridine-H and oxadiazepine-NH); $^{13}$C NMR: δ 126.54, 128.73 (pyridine-CH), 129.49, 130.37, 136.94 (Ar-CH and pyridine-CH), 131.57 (Ar-C), 146.39, 147.81 (pyridine-C-2 and C-6), 156.82 (C-2), 169.64 (oxadiazepine-CO), 187.51, 187.80 (C-6 and C-11); ms m/z: 319 ($M^+$, 28), 213 (41), 185 (64), 157 (22), 106 (88), 104 (73), 77 (100), 65 (56); Anal. Calcd. for $C_{17}H_9N_3O_4$ (319.27): C, 63.95; H, 2.84; N, 13.16. Found C, 64.16; H, 2.71; N, 12.98.

**2-(1*H*-Indol-2-yl)naphtho[2,3-*f*][1,3,4]oxadiaz-epine-5,6,11-(4*H*)-trione (16e).** Compound **16e** was obtained as reddish brown crystals (0.282 g, 79%), mp 331–333°C (methanol). IR: 3330-3240 (NH's), 1710, 1685 (CO), 1630 (C=N), 1600 (Ar—C=C), 1085 (C—O—C); $^1$H NMR: δ 6.61 (s, 1H, indole-CH), 7.16–7.64 (m, 4H, Ar—H), 7.82 (br, 1H, oxadiazepine-NH), 8.05–8.27 (m, 4H, Ar—H), 11.71 (br, 1H, indole-NH); $^{13}$C NMR: δ 99.63 (indole-CH), 127.26, 129.41, 136.22, 137.38 (Ar—CH), 130.26, 131.66, 134.27, 139.26 (Ar—C and indole-C-2), 156.78 (C-2), 169.75 (oxadiazepine-CO), 187.48, 187.73 (C-6 and C-11); ms m/z: 357 ($M^+$, 34), 213 (26), 185 (54), 144 (62), 104 (57), 91 (74), 77 (100), 65 (63); Anal. Calcd. for $C_{20}H_{11}N_3O_4$ (357.32): C, 67.23; H, 3.10; N, 11.76. Found C, 67.06; H, 2.97; N, 11.89.

**Reactions of substituted hydrazides 1a-e with (4).** A solution of **1a-e** (1.0 mmol) in 15 mL of dry DMF was added dropwise with stirring to a solution of 1,4-naphthoquinone-2,3-dicarbonitrile (**4**) (208 mg, 1.0 mmol) in 10 mL of dry DMF. The reaction colour changed gradually from green to purple and latter turns into brown colour. The stirring was continued for 72 h with admission of air to complete the reaction. The reaction mixture was concentrated and the residue was then separated by plc using toluene/ethyl acetate (5:1) for the runs with (**1a-d**) and toluene/ethyl acetate (3:1) for the run with (**1e**) to give numerous zones, two intense of which were removed and extracted. The fastest migrating one which quenched all indicator fluorescence upon exposure to 254nm UV-light contained diacylhydrazines **18a-e**. The slowest migrating zone (which is always characterized by deep yellow colour) contained substituted benzo[*f*]- indazolediones **17a-e**.

**3-Amino-2-benzoyl-2*H*-benzo[*f*]indazole-4,9-dione (17a).** Compound **17a** was obtained as deep yellow crystals (0.222 g, 70 %), mp 271–273°C (ethanol). IR: 3345 ($NH_2$), 1685, 1660 (CO), 1620 (C=N), 1585 (Ar-C=C); $^1$H NMR: δ 6.71 (br, 2H, $NH_2$), 7.28–7.77 (m, 5H, Ar—H), 8.06–8.22 (m, 4H, Ar—H); $^{13}$C NMR: δ 101.16 (C-3a), 126.52, 128.32, 129.26, 133.12, 136.51 (Ar—CH), 130.76, 131.44 (Ar-C), 139.86 (C-9a), 153.46 (C-3), 165.55 (CO), 187.82 (C-9), 188.68 (C-4); ms m/z: 317 ($M^+$, 52), 212 (41), 184 (26), 105 (100), 104 (76), 77 (81), 65 (72); Anal. Calcd. for $C_{18}H_{11}N_3O_3$ (317.30): C, 68.14; H, 3.49; N, 13.24. Found C, 67.88; H, 3.61; N, 13.40.

**3-Amino-2-(thiophen-2-carbonyl)-2*H*-benzo[*f*]-indazole-4,9-dione (17b).** Compound **17b** was obtained as yellow crystals (0.242 g, 75%), mp 295–297°C (acetonitrile). IR: 3335 ($NH_2$), 1690, 1660 (CO), 1625 (C=N), 1590 (Ar-C=C); $^1$H NMR: δ 6.67 (br, 2H, $NH_2$), 7.14–7.52 (m, 3H, thiophene-H), 8.05–8.19 (m, 4H, Ar—H); $^{13}$C NMR: δ 100.89 (C-3a), 126.72, 129.33, 129.78, 130.12, 136.44 (Ar—CH and thiophene-CH), 131.58, 132.29 (Ar—C and thiophene-C), 140.08 (C-9a), 153.36 (C-3), 165.46 (CO), 187.76 (C-9), 188.54 (C-4); ms m/z: 323 ($M^+$, 41), 212 (56), 184 (44), 111 (100), 104 (62), 77 (83), 65 (74); Anal. Calcd. for $C_{16}H_9N_3O_3S$ (323.33): C, 59.44; H, 2.81; N, 13.00; S, 9.92. Found C, 59.26; H, 2.94; N, 12.82; S, 10. 13.

**3-Amino-2-(furan-2-carbonyl)-2*H*-benzo[*f*]-indazole-4,9-dione (17c).** Compound **17c** was obtained as yellow crystals (0.209 g, 68%), mp 259–261°C (ethanol). IR: 3330 ($NH_2$), 1685, 1665 (CO), 1620 (C=N), 1590 (Ar—C=C), 1080 (C-O-C); $^1$H NMR: δ 6.69 (br, 2H, $NH_2$), 7.08–7.46 (m, 3H, furan-H), 8.08-8.24 (m, 4H, Ar—H); $^{13}$C NMR: δ 101.14 (C-3a), 126.13, 126.76, 129.41, 136.28 (Ar—CH and furan-CH), 131.64 (Ar—C), 139.90 (C-9a), 147.42, 148.51 (furan-C-2 and C-5), 153.29 (C-3), 165.65 (CO), 187.89 (C-9), 188.74 (C-4). ms m/z: 307 ($M^+$, 59), 212 (38), 184 (61), 104 (72), 95 (86), 77 (100), 65 (76); Anal. Calcd. for $C_{16}H_9N_3O_4$ (307.26): C, 62.54; H, 2.95; N, 13.68. Found C, 62.37; H, 3.10; N, 13.87.

**3-Amino-2-picolinoyl-2*H*-benzo[*f*]indazole-4,9-dione (17d).** Compound **17d** was obtained as yellow crystals (0.229 g, 72%), mp 276-278°C (acetonitrile). IR: 3335 ($NH_2$), 1685, 1660 (CO), 1620 (C=N), 1585 (Ar—C=C). $^1$H NMR: δ 6.68 (br, 2H, $NH_2$), 7.56–8.48 (m, 8H, Ar—H and pyridine-H). $^{13}$C NMR: δ 100.96 (C-3a), 126.43, 128.51, 129.55, 130.12, 136.34 (Ar—CH and pyridine-CH), 131.59 (Ar—C), 139.81 (C-9a), 147.86, 148.62 (pyridine-C-2, C-6), 153.37 (C-3), 165.55 (CO), 187.75 (C-9), 188.64 (C-4). ms m/z: 318 ($M^+$, 62), 212 (53), 184 (67), 106 (100), 104 (76), 77 (83), 65 (64). $C_{17}H_{10}N_4O_3$ (318.29): C, 64.15; H, 3.17; N, 17.60. Found C, 63.96; H, 3.28; N, 17.76.

**3-Amino-2-(1*H*-indole-2-carbonyl)-2*H*-benzo[*f*]-indazole-4,9-dione (17e).** Compound **17e** was obtained as yellowish brown crystals (0.235 g, 66%), mp 324–326°C (acetonitrile). IR: 3340, 3270 ($NH_2$, NH), 1690, 1665 (CO), 1625 (C=N), 1590 (Ar-C=C); $^1$H NMR: δ 6.59 (s, 1H, indole-CH), 6.73 (br, 2H, $NH_2$), 7.28–7.83 (m, 4H, Ar—H), 8.05–8.26 (m, 4H, Ar—H), 11.69 (br, 1H, indole-NH); $^{13}$C NMR: δ 99.74 (indole-C-3), 101.46 (C-3a), 126.46, 127.29, 129.41, 130.29, 136.36 (Ar—CH), 130.52, 131.64 (Ar—C), 137.86 (indole-C-2), 138.68 (indole-C-7a), 140.11 (C-9a), 153.48 (C-3), 165.73 (CO), 187.75 (C-9), 188.65 (C-4); ms m/z: 356 ($M^+$, 39), 212 (26), 184 (55), 144 (86), 104 (77), 91 (89), 77 (100), 65 (62); Anal. Calcd. for $C_{20}H_{12}N_4O_3$ (356.33): C, 67.41; H, 3.39; N, 15.72. Found C, 67.22; H, 3.27; N, 15.89.

***N*′-Benzoylbenzohydrazide (18a).** Yield (0.038g, 16%), mp 239–241°C (ref. [39,40] 237–238°C). $^1$H NMR: δ 7.26–7.40 (m, 3H, Ar—H), 7.44–7.64 (m, 4H, Ar—H), 7.78–7.83 (m, 3H, Ar—H), 10.68 (br, 2H, NH).

***N*′-(Thiophene-2-carbonyl)thiophen-2-hydrazide (18b).** Yield (0.035g, 14%), mp 276–278°C (ref. [41,42] 274–277°C). $^1$H NMR: δ 7.19–7.58 (m, 6H, thiophene-H), 10.62 (br, 2H, NH).

***N′*-(Furan-2-carbonyl)furan-2-hydrazide (18c).** Yield (0.026g, 12%), mp 240–242°C (ref. [44] 238–239°C). $^1$H NMR: δ 7.05–7.52 (m, 6H, furan-H), 10.66 (br, 2H, NH).

***N′*-Picolinoylpicolinohydrazide (18d).** Yield (0.036mg, 15%), mp 224–226°C (ref. [44] 224–225°C). $^1$H NMR: δ 7.52–8.37 (m, 8H, pyridine-H), 10.65 (br, 2H, NH).

***N′*-(1*H*-Indole-2-carbonyl)-1*H*-indole-2-hydrazide (18e).** Yield (0.035g, 11%), mp 355–357°C (ref. [44] 356.5–357.5°C). $^1$H NMR: δ 6.62 (s, 2H, indole-CH), 7.30–7.84 (m, 8H, Ar—H), 10.66 (br, 2H, NH), 11.67 (br, 2H, indole-NH).

## REFERENCES AND NOTES


[1] Nagomi, T.; Yoshihara, K.; Nagakura, S. Bull Chem Soc Jpn 1972, 45, 122.

[2] Agarawai, N. L.; Mital, R. I. Philppine J Chem Sci 1976, 125.

[3] Kulevsky, R.; Foster. N.; Wanigaskera, D. S. J Chem Soc Perkin Trans I 1974, 1318.

[4] Belitskaya, L.; Kolesnikov, V. T. Zh Org Khim 1984, 20, 1753.

[5] Khan, A. H.; Driscoll, J. S. J Med Chem 1976, 19, 313.

[6] Hassan, A. A.; Mohamed, N. K.; Aly, A. A.; Mourad, A. E. Bull Soc Chim Belg 1996, 105, 159.

[7] Gauss, W.; Heitzer, H.; Petersen, S. Liebigs Ann Chem 1977, 764, 131.

[8] Hassan, A. A. Pharmazie 1994, 49, 239.

[9] Hassan, A. A.; Mohamed, N. K.; Aly, A. A.; Mourad, A. E. Pharmazie 1997, 52, 23.

[10] Katritzky, A. R.; Fan, W. Q. J Heterocycl Chem 1988, 25, 90.

[11] Matsuoka, M.; Iwamato, A.; Furukawa, N.; Kitao, T. J Heterocycl Chem 1992, 29, 434.

[12] Matsuoka, M.; Iwamato, A. J Heterocycl Chem 1993, 30, 173.

[13] Katritzky, A. R.; Fan, W. Q. J Heterocycl Chem 1993, 30, 1679.

[14] Knieb, T.; Mayer, K. Phosphorus, Sulfur and Silicon 1994, 97, 223.

[15] Nour El-Din, A. M.; Mourad, A. E.; Hassan, A. A.; Gomaa, M. A. Bull Chem Soc Jpn 1991, 64, 1966.

[16] Döpp, D.; Gomaa, M. A.; Henkel, G.; Nour El-Din, A. M. J Heterocyclic Chem 1995, 32, 603.

[17] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M. J Sulfur Chem 2007, 28, 211.

[18] Hassan, A. A.; Mourad, A. E.; El-Shaieb, K. M.; Abou-Zied, A. H. J. Heterocyclic Chem. 2006, 43, 471.

[19] Hassan, A. A.; Mourad, A. E.; Abou-Zied, A. H. Arkivoc 2007, i, 222.

[20] Hassan, A. A.; Aly, A. A.; El-Sheref, E. M. Arkivoc 2007, xiv, 229.

[21] Hassan, A. A.; Refaey, S. M.; Shehatta, H. S. Arkivoc 2007, xv, 265.

[22] Lee, H.–J.; Park, S.–Y.; Kim, J. S.; Song, H. M.; Suh, M.–E.; Lee, C.–O. Bioorg Med Chem 2003, II, 4791.

[23] Gomez-Monterrey, I.; Campiglia, P.; Grieco, P.; Diurno, M. V.; Bolognese, A.; Lacolla, P.; Novellino, E. Bioorg Med Chem 2003, II, 3769.

[24] Lee, H.–J.; Suh, M. E.; Lee, C. O. Bioorg Med Chem 2003, II, 1511.

[25] Vanelle, P.; Donini, S.; Maldonado, J.; Crozet, M. P.; Delmas, F.; Gasquet, M.; Timan-David, P. Eur J Med 1997, 32, 523.

[26] Ballesteros, P.; Claramunt, R. M.; Escolastico, C.; Santa Maria, M. D. J. Elguerc, J Org Chem 1992, 57, 1873.

[27] Fabris, F.; De Lucchi, O.; Valle, G.; Cossu, S. Heterocycles 1995, 41, 665.

[28] Henrion, J. C.; Jacquet, B.; Hocquaux, M.; Barre, G.; Lion, C. Bull Chim Belg 1994, 103, 31 and 163.

[29] Patai, S.; Rappopert, Z. In the chemistry of quinonoid compounds; Wiley: New York, 1988; Vol. 2, Part 1.

[30] Kalinowski, H. O.; Bergen, S.; Broun, S. $^{13}$C-NMR Spectroscopy; Georg Thieme Verlag: Struttgart 1984.

[31] Pertsch, E.; Seibl, J.; Simon, W.; Clerc, T. Tables of spectral data fir structure determination of organic compounds, 2nd ed.; Springer-Verlag: Berlin, Heidelberg, 1989.

[32] Hassan, A. A.; Mohamed, N. K.; Ali, B. A.; Mourad, A. E. Tetrahedron 1994, 50, 9997.

[33] Curtius, T.; Thyssen, J. J. prakt Chem 1902, 7, 65.

[34] Cook, M. J.; Bes, E. J. Tetrahedron 1968, 24, 450.

[35] Iqbal, R.; Malik, F. J Chem Soc Pak 1984, 6, 43.

[36] Põnez, S.; Lasheras, B.; Oset, C.; Monge, A.; J Heterocyclic Chem 1997, 34, 1527.

[37] Cruces, M. A.; Elorriage, C.; Fernande-Alvarez, E. Biochem Pharmacol 1990, 40, 535.

[38] Budni, M. L.; Jayadevappa, E. S. Spectrochim Acta 1988, 44A, 607.

[39] Singh, S. P.; Batra, H.; Sharma, P. K. J Chem Res (S) 1997, 468.

[40] Kepe, V.; Požgan, F.; Golobic, A.; Polane, S.; Kocevar, M. J Chem Soc Perkin Trans I 1998, 1813.

[41] Kossmehl, G.; Manecke, G. Makromol Chem 1969, 123, 233, C. A. 1969, 71, 3748b.

[42] Zhao, H.; Burke, T. R., Jr. Tetrahedron 1997, 53, 4219.

[43] Petersen, S.; Gauss, W.; Urbschat, E. Angew Chem Ed 1955, 67, 217.

[44] Marco, J. I. J Heterocyclic Chem 1998, 35, 475.

# One Pot Synthesis of [1,3]-Oxazine and [1,3]-Thiazine Derivatives Under Thermal and Microwave Conditions



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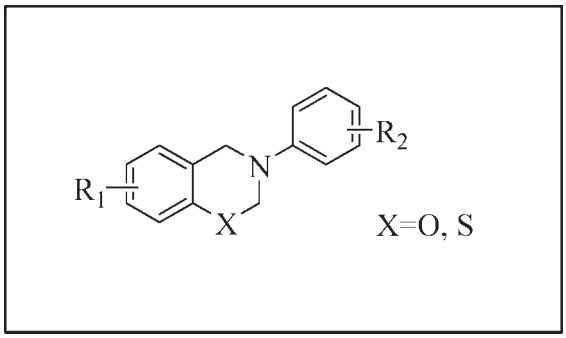


A simple and efficient synthesis of substituted benzo [1,3] oxazine and benzo [1,3] thiazine derivatives under conventional heating, as well as microwave irradiation is reported. The compounds were obtained by the reaction of electron rich phenols, formaldehyde, and aromatic amines in methanol. Reactions which take 12–16 hr under conventional heating were successfully completed within a few minutes under microwave irradiation (solventless) with moderate to excellent yields.

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## INTRODUCTION

Development of novel synthetic methods for the construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. The importance of [1,3]-oxazines and [1,3]-thiazines in biological systems has attracted great interest because of their medicinal and pharmacological characteristics [1]. Many compounds containing [1,3]-oxazine moiety have found wide biological activities such as being anticancer [2], analgesic [3], antifungal [3], antitubercular [4], antihypertensive [5], antithromobotic [6], antiulcer [7], anticonvulsant, and antibacterial [8]. Moreover, certain kinds of [1,3]-oxazines are of interest as photochromic compounds [9].

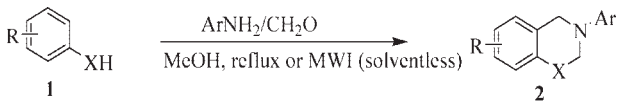
It is well known that the presence of a thiol function in many enzymes ('–SH enzymes') is essential for their enzyme activity. Likewise, incorporation of a thiol function in heterocycles, nucleosides or nucleotides has led to a number of analogues possessing interesting biological and therapeutic properties [10–17]. The [1,3]-thiazine nucleus is the active core of cephalosporins, which are among the most widely used β-lactam antibiotics. Owing to their chemical and biological interest, synthesis of various unsubstituted and substituted 1,3-oxazine and 1,3-thiazine derivatives is reported as they appear to be attractive scaffolds for exploiting chemical diversity. Previously, napth-1, 3-oxazine derivatives have been reported using 2-napthol and various substituted aryl and heteroaryl aldehydes in the presence of dry methanolic ammonia [18–20]. In view of the importance of substituted [1,3]-oxazines and [1,3]-thiazines, we have initiated a programme for the development of simpler and more convenient methods for preparing heterocyclic systems with high efficacy.

## RESULTS AND DISCUSSION

Our present study mainly focuses on the synthesis of various substituted [1,3]-oxazines and [1,3]-thiazines (Scheme 1) and their relative comparison with microwave assisted synthesis. $^{1}H$ and $^{13}C$ NMR spectra show that the products were obtained in good purity. The substituents on benzyl ring did not have significant influence on the reaction time and yields. All reactions which take many hours under conventional heating were completed in 3–8 min under microwave irradiation with enhanced yields. The results are presented in Table 1.

For these one-pot reactions of phenol, formaldehyde, and aromatic amines, it is noteworthy that simultaneous mixing resulted in poor yields [21]; however good

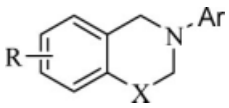
**Scheme 1**



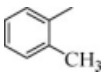
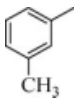
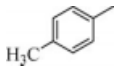
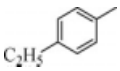
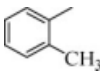
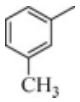
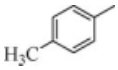
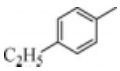
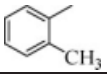

yields were obtained by the pretreatment of formaldehyde with the aromatic amines to form Schiff bases, which upon treatment with phenol yielded the required 1,3-oxazines. Also it has been found that this reaction worked well with formaldehyde but failed with other aldehydes. Here we presume that steric hindrance stops

**Table 1**

Comparison between microwave irradiation (MWI) and conventional heating in the synthesis of compounds 2 (**a**–**y**).

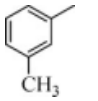
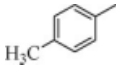
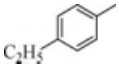
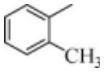
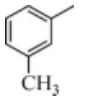
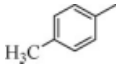
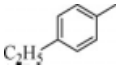
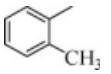
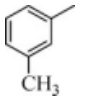
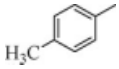
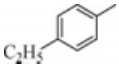



**2 (a-y)**

| | | | | | Thermal | | MWI | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Products | R | Ar | X | Mp (°C) | Time (hr) | Yield (%) | Press. (bar) | Power (watt) | Time (sec) | Yield (%) |
| **2a** | H |  | O | 48 | 14 | 62 | 5 | 80 | 180 | 71 |
| **2b** | H |  | O | 52 | 14 | 66 | 5 | 80 | 200 | 72 |
| **2c** | H |  | O | 55 | 16 | 57 | 6 | 85 | 180 | 68 |
| **2d** | H |  | O | 66 | 15 | 63 | 6 | 90 | 180 | 70 |
| **2e** | H |  | O | 69 | 15 | 59 | 8 | 80 | 210 | 68 |
| **2f** | 2-$CH_3$ |  | O | 42 | 15 | 62 | 6 | 90 | 180 | 70 |
| **2g** | 2-$CH_3$ |  | O | 54 | 16 | 64 | 5 | 100 | 180 | 73 |
| **2h** | 2-$CH_3$ |  | O | 57 | 16 | 63 | 7 | 90 | 225 | 70 |
| **2i** | 2-$CH_3$ |  | O | 68 | 15 | 65 | 7 | 110 | 185 | 71 |
| **2j** | 2-$CH_3$ |  | O | 67 | 14 | 66 | 8 | 110 | 180 | 72 |
| **2k** | 3-$CH_3$ |  | O | 54 | 15 | 65 | 6 | 90 | 220 | 73 |
| **2l** | 3-$CH_3$ |  | O | 63 | 16 | 60 | 7 | 90 | 200 | 68 |

(*Continued*)

**Table 1**
(*Continued*)

| | | | | | Thermal | | MWI | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Products | R | Ar | X | Mp (°C) | Time (hr) | Yield (%) | Press. (bar) | Power (watt) | Time (sec) | Yield (%) |
| **2m** | 3-$CH_3$ |  | O | 75 | 15 | 66 | 7 | 120 | 180 | 72 |
| **2n** | 3-$CH_3$ |  | O | 78 | 16 | 65 | 8 | 120 | 185 | 71 |
| **2o** | 3-$CH_3$ |  | O | 72 | 15 | 62 | 9 | 90 | 250 | 69 |
| **2p** | 4-$CH_3$ |  | O | 40 | 16 | 62 | 7 | 90 | 190 | 70 |
| **2q** | 4-$CH_3$ |  | O | 62 | 15 | 63 | 6 | 80 | 195 | 71 |
| **2r** | 4-$CH_3$ |  | O | 68 | 16 | 64 | 7 | 90 | 190 | 72 |
| **2s** | 4-$CH_3$ |  | O | 65 | 16 | 64 | 8 | 100 | 200 | 72 |
| **2t** | 4-$CH_3$ |  | O | 66 | 16 | 60 | 10 | 120 | 210 | 68 |
| **2u** | H |  | S | 38 | 15 | 58 | 8 | 100 | 180 | 67 |
| **2v** | H |  | S | 43 | 16 | 59 | 8 | 110 | 200 | 68 |
| **2w** | H |  | S | 45 | 16 | 61 | 9 | 100 | 210 | 68 |
| **2x** | H |  | S | 56 | 16 | 63 | 9 | 110 | 215 | 71 |
| **2y** | H |  | S | 58 | 16 | 58 | 10 | 120 | 240 | 67 |

the reaction at the open-chain Schiff bases without proceeding further to the cyclocondensation products. Reactions with other aromatic aldehydes gave same results [18,22]. Mcdonagh and Smith [23] reported the ring-chain tautomerism of the condensation products of o-hydroxybenzylamine with a number of aldehydes where aliphatic aldehydes tend to give predominantly or exclusively 1, 3-oxazines whereas aromatic aldehydes tend to give predominantly open chain structures (Schiff bases). Hence, it suggests that the Schiff bases formed are quite stable and do not react further even with increasing reaction time as well as temperature. In course of our study, it has been found that electron donating substituents on the alcohol, as well as the aromatic primary amines favour the reactions to give the desired products. All the observations in both conventional as well as microwave synthesis are similar except in the reaction time and yield. This clearly indicates the advantages of microwave chemistry which is fast developing as a convenient and ecofriendly mode of synthesis.

In summary, the aforementioned protocol reports the conventional and microwave synthesis of 1, 3-oxazines, as well as a few numbers of 1, 3-thiazines from simple and easily available starting materials in which microwave synthesis is preferred as an alternative mode of reactions. This microwave induced procedure offers several advantages including operational simplicity, high yields, simple work up and reactions are completed within short time.

## EXPERIMENTAL SECTION

Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in $cm^{-1}$. $^1H$ and $^{13}C$ NMR (400 MHz) spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All compounds give satisfactory elemental analyses within ± 0.4% of the theoretical values. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 254 0.2 mm thickness) and developed in an iodine chamber or under UVGL-15 mineral light 254 lamp. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

**General procedure for conventional synthesis.** To a well stirred solution of the amine (1 mmol) in 5 mL of methanol, formaldehyde (2 mmol) was added dropwise upon which a thick white precipitate was formed. After stirring at room temperature for about 15–20 min, phenol (1 mmol) dissolved in methanol was added dropwise. The reaction mixture was then refluxed at 70°C for 14–16 hr. After the reaction was completed (monitored by TLC), the solvent was evaporated under reduced pressure and the resultant mixture was purified by column chromatography to afford the pure compound.

**General procedure for microwave assisted synthesis.** A mixture of the amine (1 mmol), formaldehyde (2 mmol) and phenol (1 mmol) was irradiated in a microwave digester at 5–10 bar, 80–120 W, 180–250 seconds without the use of solvent. After the reaction was completed (monitored by TLC) the resultant mixture was purified by column chromatography to afford the pure compound.

The physical and spectral data of the products are as follows:

**3,4-Dihydro-3-phenyl-2*H*-benzo[e][1,3]oxazine (2a).** mp 48°C, IR (KBr): 3036 (Ar—C—H), 1597 (C=C), 1227 (Ar—C—O), 1087 (—$CH_2$—O), 1370 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 4.61 (s, 2H, $CH_2$), 5.34 (s, 2H, $CH_2$), 6.77–7.02 (m, 9H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 49.9, 79.0, 115.4, 116.1, 117.9, 120.3, 125.4, 127.4, 128.8, 128.9, 128.9, 129.4, 147.9, 153.9. MS: m/z =211 ($M^+$). *Anal. Calcd*. For $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.63; H, 6.18; N, 6.67%.

**3,4-Dihydro-3-o-tolyl-2*H*-benzo[e][1,3]oxazine (2b).** mp 52°C, IR (KBr): 3037 (Ar—C—H), 1596 (C=C), 1227 (Ar—C—O), 1084 (—$CH_2$—O), 1372 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.24 (s, 3H, $CH_3$), 4.55 (s, 2H, $CH_2$), 5.33 (s, 2H, $CH_2$), 6.65–7.11 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 18.7, 58.3, 79.6, 115.1, 115.9, 118.5, 121.3, 122.7, 127.4, 127.9, 128.6, 129.8, 130.6, 148.0, 157.6. MS: m/z =225 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 79.99; H, 6.75; N, 6.18%.

**3,4-Dihydro-3-m-tolyl-2*H*-benzo[e][1,3]oxazine (2c).** mp 55°C, IR (KBr): 3035 (Ar—C—H), 1597 (C=C), 1226 (Ar—C—O), 1079 (—$CH_2$—O), 1373 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 3H, $CH_3$), 4.60 (s, 2H, $CH_2$), 5.41 (s, 2H, $CH_2$), 6.39–7.02 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 18.4, 55.1, 78.9, 110.7, 115.2, 115.8, 118.4, 120.7, 123.0, 127.8, 129.8, 130.2, 138.8, 147.9, 157.4. MS: m/z =225 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 79.98; H, 6.74; N, 6.19%.

**3,4-Dihydro-3-p-tolyl-2*H*-benzo[e][1,3]oxazine (2d).** mp 66°C, IR (KBr): 3037 (Ar—C—H), 1597 (C=C), 1228 (Ar—C—O), 1088 (—$CH_2$—O), 1371 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.35 (s, 3H, $CH_3$), 4.55 (s, 2H, $CH_2$), 5.40 (s, 2H, $CH_2$), 6.47–7.10 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 23.2, 55.7, 79.2, 113.7, 114.6, 114.8, 120.4, 123.7, 126.0, 128.4, 129.6, 130.7, 132.8, 145.9, 155.4. MS: m/z =225 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 80.01; H, 6.67; N, 6.26%.

**3-(4-ethylphenyl)-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (2e).** mp 69°C, IR (KBr): 3036 (Ar—C—H), 1596 (C=C), 1225 (Ar—C—O), 1087 (—$CH_2$—O), 1368 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.26 (s, 3H, $CH_3$), 2.63 (q, 2H, $CH_2$), 4.60 (s, 2H, $CH_2$), 5.42 (s, 2H, $CH_2$), 6.54–7.02 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 16.1, 35.2, 54.3, 88.9, 113.8, 114.2, 114.6, 120.5, 123.3, 127.1, 127.9, 128.7, 129.2, 129.7, 147.4, 156.8. MS: m/z =239 ($M^+$). *Anal. Calcd*. For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.34; H, 7.14; N, 5.88%.

**3,4-Dihydro-8-methyl-3-phenyl-2*H*-benzo[e][1,3]oxazine (2f).** mp 42°C, IR (KBr): 3024 (Ar—C—H), 1609 (C=C), 1223 (Ar—C—O), 1085 (—$CH_2$—O), 1336 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.33 (s, 3H, $CH_3$), 4.58 (s, 2H, $CH_2$), 5.34 (s, 2H, $CH_2$), 6.56–7.13 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 15.3, 56.3, 79.9, 114.2, 114.6, 118.5, 121.3, 122.1, 124.9, 126.7, 128.2, 129.1, 129.7, 148.4, 157.6. MS: m/z =225 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 80.00; H, 6.68; N, 6.24%.

**3,4-Dihydro-8-methyl-3-o-tolyl-2*H*-benzo[e][1,3]oxazine (2g).** mp 54°C, IR (KBr): 3025 (Ar—C—H), 1583 (C=C), 1227 (Ar—C—O), 1085 (—$CH_2$—O), 1367 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 6H, $CH_3$), 4.62 (s, 2H, $CH_2$), 5.35 (s, 2H, $CH_2$), 6.47–7.02 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 15.3, 16.4, 58.3, 79.7, 114.7, 118.5, 120.5, 124.5, 126.3, 126.5, 127.4, 128.9, 126.7, 128.2, 146.6, 156.6. MS: m/z =239 ($M^+$). *Anal. Calcd*. For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.33; H, 7.13; N, 5.81%.

**3,4-Dihydro-8-methyl-3-m-tolyl-2*H*-benzo[e][1,3]oxazine (2h).** mp 57°C, IR (KBr): 3027 (Ar—C—H), 1590 (C=C), 1223 (Ar—C—O), 1087 (—$CH_2$—O), 1375 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.36 (s, 6H, $CH_3$), 4.62 (s, 2H, $CH_2$), 5.41 (s, 2H, $CH_2$), 6.39–7.11 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 15.7, 23.7, 58.3, 79.3, 111.4, 114.4, 118.7, 120.2, 121.4, 123.5, 126.6, 128.3, 129.4, 138.9, 148.6, 156.8. MS: m/

z = 239 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.34; H, 7.12; N, 5.82%.

**3,4-Dihydro-8-methyl-3-p-tolyl-2*H*-benzo[e][1,3]oxazine (2i).** mp 68°C, IR (KBr): 3027 (Ar—C—H), 1581 (C=C), 1220 (Ar—C—O), 1085 (—$CH_2$—O), 1360 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.32 (s, 6H, $CH_3$), 4.58 (s, 2H, $CH_2$), 5.40 (s, 2H, $CH_2$), 6.47–7.10 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 14.7, 25.7, 58.2, 78.9, 115.4, 115.4, 120.6, 122.4, 124.5, 126.7, 127.7, 128.6, 129.4, 130.8, 147.6, 155.8. MS: m/z = 239 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.34; H, 7.13; N, 5.87%.

**3-(4-ethylphenyl-3,4-dihydro-8-methyl-2*H*-benzo[e][1,3] oxazine (2j).** mp 67°C, IR (KBr): 3024 (Ar—C—H), 1582 (C=C), 1266 (Ar—C—O), 1087 (—$CH_2$—O), 1362 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.26 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.60 (q, 2H, $CH_2$), 4.60 (s, 2H, $CH_2$), 5.37 (s, 2H, $CH_2$), 6.74–7.18 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 14.1, 15.2, 33.7, 56.9, 78.6, 114.5, 114.6, 120.5, 123.3, 126.1, 127.9, 129.7, 129.7, 130.1, 132.9, 147.4, 157.8. MS: m/z =253 ($M^+$). *Anal. Calcd.* For $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53%. Found: C, 80.64; H, 7.57; N, 5.51%.

**3,4-Dihydro-7-methyl-3-phenyl-2*H*-benzo[e][1,3]oxazine (2k).** mp 54°C, IR (KBr): 3027 (Ar—C—H), 1601 (C=C), 1227 (Ar—C—O), 1084 (—$CH_2$—O), 1327 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.64 (s, 3H, $CH_3$), 4.59 (s, 2H, $CH_2$), 5.34 (s, 2H, $CH_2$), 6.62–7.09 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 21.1, 50.2, 79.4, 114.6, 117.2, 117.7, 118.1, 118.2, 121.3, 126.0, 129.2, 129.2, 137.8, 148.4, 154.1. MS: m/z =225 ($M^+$). *Anal. Calcd.* For $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 79.99; H, 6.75; N, 6.18%.

**3,4-Dihydro-7-methyl-3-o-tolyl-2*H*-benzo[e][1,3]oxazine (2l).** mp 63°C, IR (KBr): 3026 (Ar—C—H), 1589 (C=C), 1223 (Ar—C—O), 1087 (—$CH_2$—O), 1351 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 6H, $CH_3$), 4.35 (s, 2H, $CH_2$), 5.32 (s, 2H, $CH_2$), 6.77–7.01 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 15.6, 25.1, 56.2, 79.4, 112.6, 114.2, 117.7, 119.1, 126.2, 127.3, 128.5, 129.2, 136.2, 137.8, 148.4, 154.1. MS: m/z =239 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.33; H, 7.13; N, 5.82%.

**3,4-Dihydro-7-methyl-3-m-tolyl-2*H*-benzo[e][1,3]oxazine (2m).** mp 75°C, IR (KBr): 3023 (Ar—C—H), 1576 (C=C), 1225 (Ar—C—O), 1084 (—$CH_2$—O), 1327 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 6H, $CH_3$), 4.45 (s, 2H, $CH_2$), 5.33 (s, 2H, $CH_2$), 6.65–7.00 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 24.6, 25.1, 56.2, 79.2, 111.6, 112.2, 114.7, 119.1, 119.2, 121.3, 128.5, 129.2, 136.9, 139.8, 148.5, 156.1. MS: m/z =239 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.34; H, 7.14; N, 5.81%.

**3,4-Dihydro-7-methyl-3-p-tolyl-2*H*-benzo[e][1,3]oxazine (2n).** mp 78°C, IR (KBr): 3036 (Ar—C—H), 1597 (C=C), 1229 (Ar—C—O), 1082 (—$CH_2$—O), 1370 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 6H, $CH_3$), 4.52 (s, 2H, $CH_2$), 5.34 (s, 2H, $CH_2$), 6.67–7.10 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 24.6, 24.1, 56.2, 79.2, 112.2, 113.6, 114.7, 119.3, 121.2, 127.3, 128.5, 129.2, 130.2, 137.8, 146.4, 157.2. MS: m/z =239 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.32; H, 7.15; N, 5.81%.

**3-(4-ethylphenyl)-3,4-dihydro-7-methyl-2*H*-benzo[e][1,3] oxazine (2o).** mp 72°C, IR (KBr): 3041 (Ar—C—H), 1604 (C=C), 1231 (Ar—C—O), 1085 (—$CH_2$—O), 1365 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.25 (s, 3H, $CH_3$), 2.60 (q, 2H, $CH_2$), 4.62 (s, 2H, $CH_2$), 5.38 (s, 2H, $CH_2$), 6.54–7.02 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 14.1, 25.2, 32.6, 53.3, 78.9, 113.8, 114.2, 114.7, 120.5, 121.3, 127.1, 128.5, 128.7, 129.1, 137.7, 147.4, 156.8. MS: m/z =253 ($M^+$). *Anal. Calcd.* For $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53%. Found: C, 80.64; H, 7.52; N, 5.55%.

**3,4-Dihydro-6-methyl-3-phenyl-2*H*-benzo[e][1,3]oxazine (2p).** mp 40°C, IR (KBr): 3110 (Ar—C—H), 1585 (C=C), 1230 (Ar—C—O), 1085 (—$CH_2$—O), 1366 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 3H, $CH_3$), 4.59 (s, 2H, $CH_2$), 5.34 (s, 2H, $CH_2$), 6.62–7.11 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 24.1, 53.2, 79.7, 114.6, 114.2, 115.7, 118.1, 122.2, 128.3, 129.0, 129.2, 129.8, 130.2, 148.5, 154.2. MS: m/z =225 ($M^+$). *Anal. Calcd.* For $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 79.99; H, 6.75; N, 6.18%.

**3,4-Dihydro-6-methyl-3-o-tolyl-2*H*-benzo[e][1,3]oxazine (2q).** mp 62°C, IR (KBr): 3037 (Ar—C—H), 1598 (C=C), 1228 (Ar—C—O), 1087 (—$CH_2$—O), 1370 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 6H, $CH_3$), 4.41 (s, 2H, $CH_2$), 5.32 (s, 2H, $CH_2$), 6.71–7.10 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 15.6, 24.1, 56.2, 79.2, 114.7, 114.9, 118.7, 122.4, 126.6, 127.3, 128.0, 129.2, 130.9, 130.8, 146.5, 155.1. *Anal.* MS: m/z =239 ($M^+$). *Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.34; H, 7.13; N, 5.81%.

**3,4-Dihydro-6-methyl-3-m-tolyl-2*H*-benzo[e][1,3]oxazine (2r).** mp 68°C, IR (KBr): 3041 (Ar—C—H), 1600 (C=C), 1237 (Ar—C—O), 1081 (—$CH_2$—O), 1372 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.34 (s, 6H, $CH_3$), 4.51 (s, 2H, $CH_2$), 5.33 (s, 2H, $CH_2$), 6.68–7.10 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 24.1, 24.1, 56.2, 79.6, 111.7, 114.7, 114.9, 118.4, 122.6, 128.5, 129.5, 130.3, 130.8, 139.0, 148.4, 155.1. MS: m/z =239 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.33; H, 7.14; N, 5.82%.

**3,4-Dihydro-6-methyl-3-p-tolyl-2*H*-benzo[e][1,3]oxazine (2s).** mp 65°C, IR (KBr): 3126 (Ar—C—H), 1580 (C=C), 1227 (Ar—C—O), 1087 (—$CH_2$—O), 1380 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.23 (s, 6H, $CH_3$), 4.55 (s, 2H, $CH_2$), 5.29 (s, 2H, $CH_2$), 6.61–7.02 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 20.5, 21.1, 50.7, 116.8, 117.3, 117.7, 118.6, 119.0, 121.4, 126.5, 127.0, 128.4, 129.7, 129.9, 146.8, 152.8. MS: m/z =238 ($M^+$). *Anal. Calcd.* For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%. Found: C, 80.34; H, 7.14; N, 5.81%.

**3-(4-ethylphenyl)-3,4-dihydro-6-methyl-2*H*-benzo[e][1,3] oxazine (2t).** mp 66°C, IR (KBr): 3036 (Ar—C—H), 1599 (C=C), 1227 (Ar—C—O), 1082 (—$CH_2$—O), 1373 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.25 (s, 3H, $CH_3$), 2.60 (q, 2H, $CH_2$), 4.62 (s, 2H, $CH_2$), 5.32 (s, 2H, $CH_2$), 6.54–7.01 (m, 7H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 14.8, 25.2, 32.5, 53.7, 78.0, 113.9, 114.2, 114.6, 122.5, 128.3, 128.6, 128.8, 129.7, 130.2, 130.7, 147.4, 156.8. MS: m/z =253 ($M^+$). *Anal. Calcd.* For $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53%. Found: C, 80.64; H, 7.52; N, 5.55%.

**3,4-Dihydro-3-phenyl-2*H*-benzo[e][1,3]thiazine (2u).** mp 38°C, IR (KBr): 3036 (Ar—C—H), 1596 (C=C), 756 (C-S), 1367 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 4.63 (s, 2H, $CH_2$), 4.88 (s, 2H, $CH_2$), 6.81–7.03 (m, 9H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 49.5, 61.7, 115.8, 116.1, 117.7, 120.3, 125.4, 127.4, 128.8, 128.9, 128.9, 129.4, 147.9, 153.9. MS: m/z =227 ($M^+$). *Anal. Calcd.* For $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16%. Found: C, 74.01; H, 5.72; N, 6.18%.

**3,4-Dihydro-3-o-tolyl-2*H*-benzo[e][1,3]thiazine (2v).** mp 43°C, IR (KBr): 3035 (Ar—C—H), 1597 (C=C), 745 (C—S), 1391 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.36 (s, 3H,

$CH_3$), 4.50 (s, 2H, $CH_2$), 4.81 (s, 2H, $CH_2$), 6.67–7.06 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 14.9, 56.3, 62.7, 114.90 118.1, 125.0, 126.6, 126.9, 127.0, 127.8, 128.9, 130.1, 130.2, 147.3, 148.3. MS: m/z =241 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80%. Found: C, 74.68; H, 6.24; N, 5.78%.

**3,4-Dihydro-3-m-tolyl-2*H*-benzo[e][1,3]thiazine (2w).** mp 45°C, IR (KBr): 3041 (Ar—C—H), 1596 (C=C), 756 (C—S), 1365 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.32 (s, 3H, $CH_3$), 4.57 (s, 2H, $CH_2$), 4.81 (s, 2H, $CH_2$), 6.49–7.06 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 24.9, 57.3, 63.0, 111.9, 114.1, 118.0, 125.6, 126.9, 127.0, 128.1, 129.6, 130.1, 131.2, 139.3, 148.3. MS: m/z =241 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80%. Found: C, 74.68; H, 6.23; N, 5.76%.

**3,4-Dihydro-3-p-tolyl-2*H*-benzo[e][1,3]thiazine (2x).** mp 56°C, IR (KBr): 3037 (Ar—C—H), 1597 (C=C), 750 (C—S), 1385 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.38 (s, 3H, $CH_3$), 4.59 (s, 2H, $CH_2$), 4.86 (s, 2H, $CH_2$), 6.81–7.03 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 22.1, 56.3, 67.7, 116.9, 120.1, 121.6, 124.9, 125.0, 126.8, 127.6, 128.6, 129.1, 132.2, 147.3, 150.3. MS: m/z =241 ($M^+$). *Anal. Calcd*. For $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80%. Found: C, 74.69; H, 6.23; N, 5.77%.

**3-(4-ethylphenyl)-3,4-dihydro-2*H*-benzo[e][1,3]thiazine (2y).** mp 58°C, IR (KBr): 3035 (Ar—C—H), 1597 (C=C), 748 (C—S), 1367 (Ar—C—N) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.26 (t, 3H, $CH_3$), 2.56 (q, 2H, $CH_2$), 4.59 (s, 2H, $CH_2$), 4.82 (s, 2H, $CH_2$), 6.51–7.03 (m, 8H, ArH). $^{13}C$ NMR ($CDCl_3$): δ 14.6, 32.1, 57.3, 66.7, 114.9, 115.1, 125.6, 126.9, 127.0, 128.2, 128.6, 128.9, 129.2, 130.3, 131.3, 146.7. MS: m/z =255 ($M^+$). *Anal. Calcd*. For $C_{16}H_{17}NS$: C, 75.25; H, 6.71; N, 5.48%. Found: C, 75.29; H, 6.68; N, 5.49%.

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## REFERENCES AND NOTES

[1] Turgut, Z.; Pelit, E.; Koyeu, A. Molecules 2007, 12, 345.

[2] Poel, H. V.; Guilaumet, G.; Viaud-Massuard, M. Tetrahedron Lett 2002, 43, 1205.

[3] Kurtz, T. Tetrahedron 2005, 61, 3091.

[4] Adib, M.; Sheibani, E.; Mostofi, M.; Ghanbary, K.; Bijanzadeh, H. R. Tetrahedron 2006, 62, 3435.

[5] Kajino, N.; Shibouta, Y.; Nishikawa, K.; Meguro, K. Chem Pharm Bull 1991, 11, 2896.

[6] Buckman, B. O.; Mohan, R.; Koovakkat, S. Bioorg Med Chem Lett 1998, 8, 2235.

[7] Katsura, Y.; Nishino, S.; Takasugi, H. Chem Pharm Bull 1991, 11, 2937.

[8] (a) Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Zhang, Z. Bioorg Med Chem Lett 2003, 13, 1313; (b) Fringuelli, R.; Pietrella, D.; Schiaffella, F.; Guarraci, A.; Perito, S.; Bistoni, F.; Vecchiarelli, A. Bioorg Med Chem 2002, 10, 1681; (c) Macchiarulo, A.; Costantino, G.; Fringuelli, D.; Vecchiarelli, A.; Schiaffella, F.; Fringuelli, R. Bioorg Med Chem 2002, 10, 3415; (d) Nair, M. G.; Salter, O. C.; Kisliuk, R. L.; Gaumont, Y. J Med Chem 1983, 26, 1164; (e) Turgut, Z.; Pelit, E.; Koyeii, A. Molecules 2007, 12, 345.

[9] Kerdesky, F. A. Tetrahedron Lett 2005, 46, 1711.

[10] Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. Eur J Med Chem 2002, 37, 511.

[11] Martin, G.; Lahti, R. A.; Rudzik, A. D.; Duchamp, D. J.; Chidester, C.; Scahill, T. J Med Chem, 1978, 21, 542.

[12] Thomas, G.; Mehta, D. V.; Tahilramani, R.; Joy, D.; Talwalker, P. K. J Med Chem 1971, 14, 335.

[13] Holla, B. S.; Poojary, K. N.; Kalluraya, B.; Gowda, P. V. Il Farmaco 1996, 51, 793.

[14] Wnuk, S. F. Tetrahedron 1993, 49, 9877.

[15] Yuzhakov, A. A.; Chidgeavadze Z. G.; Beabealashvilli, R. S. FEBS 1992, 306, 185.

[16] Yuzhakov, A. A.; Chidgeavadze, Z. G.; Beabealashvilli, R. S.; Kraevskii, A. A.; Galegov, G. A.; Korneeva, M. N.; Nosik, D.N.; Kilesso, T. Y. Bioorg Khim 1991, 17, 504.

[17] Le Hir de Fallois, L.; Decout, J. L.; Fontecave, M. J Chem Soc Perkin Trans 1, 1997, 17, 2587.

[18] Smith, H. E.; Cooper, N. E. J Org Chem 1970, 35, 2212.

[19] Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. Tetrahedron 2003, 59, 2877.

[20] Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. Eur J Org Chem 2004, 2231.

[21] Omura, Y.; Taruno, Y.; Irisa, Y.; Morimoto, M.; Saimoto, H.; Shigemasa, Y. Tetrahedron Lett 2001, 42, 7273.

[22] Salamone, J. C. Polym Mater Encycl 1996, 1, 489.

[23] Mcdonagh, A. F.; Smith, H. E. J Org Chem 1968, 33, 1, 1.

# An Efficient Synthesis of Pyrido[2,3-*d*]pyrimidine Derivatives in Ionic Liquid



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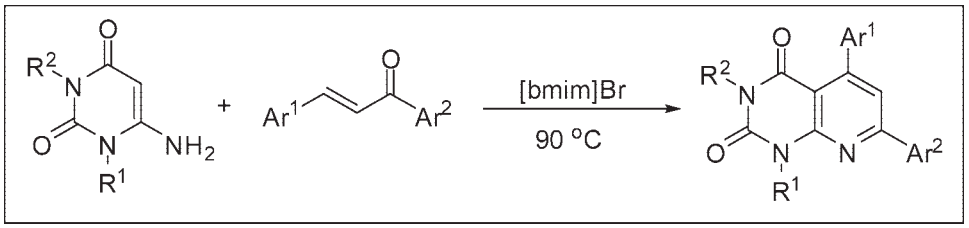


A series of 5,7-diarylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones was synthesized *via* the reaction of 6-aminopyrimidine-2,4-dione and α,β-unsaturated ketones in ionic liquid without using any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure over traditional methods.

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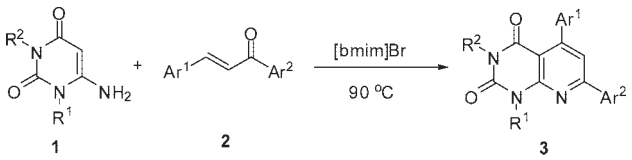
## INTRODUCTION

The importance of uracil and its annulated derivatives is well recognized by synthetic [1] as well as biological [2] chemists. With the development of clinically useful anticancer and antiviral drugs [3], there has recently been remarkable interest in the synthetic manipulations of uracils [4]. Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, which include antitumor [5], antibacterial [6], anti-inflammatory [7], antifungal [8], and antileishmaniasis [9] properties, and also act as cyclin-dependent kinase 4 inhibitors [10]. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. Broom *et al*. [11] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracile in protic solvent but obtained uncyclized condensed acetylenic adduct when the reaction was carried in DMF [12]. Wawzonek reported the synthesis of pyrido[2,3-*d*]pyrimidine-2,4-diones by the acid- and base-catalyzed condensation of 6-amino-1,3-dimethyluracil with α,β-unsaturated carbonyl compounds [13]. Bhuyan *et al*. [14] reported the synthesis of pyrido[2,3-*d*]pyrimidines from the reaction of arylidenemalononitrile with 6-aminouracil in refluxing 1-propanol, but in this reaction, benzylmalononitrile was obtained as by-product and the amount of arylidenemalononitrile needed was in excess. Quiroga *et al* [15] reported the synthesis of prrido[2,3-*d*]pyrimidines by the reaction of 6-amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone and α,β-unsaturated ketones in boiling DMF. Recently, Bagley *et al*. [16] reported a new method for the synthesis of pyrido[2,3-*d*]pyrimidines by the reaction of 2,6-diaminopyrimidin-4-one and butynones in a range of different solvents at room temperature or 60°C. Quiroga *et al*. [17] reported the synthesis of pyrido[2,3-d]pyrimidines *via* a selective cyclocondensation reaction between 6-aminopyrimidines and the Mannich bases, propiophenone hydrochlorides. Devi *et al*. [18] reported a novel three-component one-pot synthesis of pyrido[2,3-*d*]pyrimidines using microwave heating. These methods usually require harsh conditions, using organic solvents, long reaction times and complex synthetic pathways.

The ionic liquids have been the subject of considerable current interest as environmentally benign reaction media in organic synthesis because of their unique properties of nonvolatility, nonflammability, and recyclability, among others [19]. Numerous chemical reaction, such as polymerization [20], hydrogenation [21], regioselective alkylation [22], Friedel-Crafts reactions [23], dimerization of alkenes [24], Diels-Alder reactions [25], Michael reactions [26], Cross-coupling reactions [27], and some enzymic reactions [28] can be carried out in ionic liquid. As part of our current studies on the development of new routes to heterocyclic systems [29], we herein describe a facile synthesis of pyrido[2,3-

**Scheme 1**




1 2 3

*d*]pyrimidine derivatives by the reaction of 6-aminopyrimidine-2,4-dione and α,β-unsaturated ketones in ionic liquid without using any catalyst (Scheme 1).

## RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optimal solvent, the reaction of 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1a** and 1-(4-chlorophenyl)-3-(4-methylphenyl)prop-2-en-1-one **2a** was examined using ionic liquid such as [bmim]Br, [bmim]$BF_4$, [bmim]$PF_6$, acetone, acetonitrile, ethanol, chloroform, and DMF as solvent, respectively, at different temperature for the synthesis of **3a**. The results are summarized in Table 1.

It can be seen from Table 1 that the reactions using ionic liquids (Table 1, entries 6–8) as the solvents resulted in higher yields and shorter reaction times than those using organic solvents (Table 1, entries 1–5). On the basis of the obtained results, [bmim]Br was found to be superior in terms of cheap and yield. To optimize the reaction temperature, the reactions were carried out at different temperature ranging from room temperature to 90°C. We found that the yield of the product **3a** was improved and the reaction time was shortened, as the temperature was increased to 90°C (Table 1, entries 8–12). Therefore, the most suitable reaction temperature is to 90°C. Under these optimized reaction conditions, a series of pyrido[2,3-*d*]pyrimidine derivatives **3** were synthesized. The results are summarized in Table 2.

As shown in Table 2, this protocol can be applied not only to the aromatic rings of α,β-unsaturated ketones with electron-withdrawing groups (such as halide and nitro groups), but also to α,β-unsaturated ketones with electron-donating groups (such as alkyl and alkoxyl groups). Therefore, we concluded that the electronic nature of the substituents of aromatic rings of α,β-unsaturated ketones has no significant effect on this reaction.

In this study, all the products **3** were characterized by mp, IR, and $^1$H NMR spectral data as well as HRMS analysis.

Although the detailed mechanism of above reaction remains not to be fully clarified, the formation of compounds **3** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded *via* a reaction sequence of Michael addition, cyclization, dehydration and aromatization. First, the Michael addition reaction of 6-aminopyrimidine- 2,4-dione **1** to α,β-unsaturated ketones **2** give the intermediate product **4**, which on intermolecular cyclization and dehydration gave rise to **5**. In the last step, the intermediate product **5** aromatized to product **3**.

In conclusion, we have developed an efficient synthesis of 5,7-diarylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones *via* the reaction of 6-aminopyrimidine-2,4-dione and α,β-unsaturated ketones in ionic liquid without any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure over traditional methods.

## EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points were uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in $cm^{-1}$. $^1$H NMR was determined on Varian-400 MHz spectrometer in DMSO-$d_6$ or $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using TOF-MS instrument.

**General procedure for the synthesis of pyrido[2,3-*d*]pyrimidines derivatives 3.** A dry 50 mL flask was charged with 6-aminopyrimidine-2,4-dione 1 (1 mmol), α,β-unsaturated ketones 2 (1 mmol), and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 90°C for 5–7.5 h to complete the reaction (monitored by TLC), then 50 mL $H_2O$ was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give 3.

***7-(4-Chlorophenyl)-1,3-dimethyl-5-p-tolylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3a).*** Mp: 238–239°C; IR (potassium bromide): 3074, 2950, 1707, 1665, 1594, 1576, 1545, 1515, 1420, 1403, 1362, 1281, 1257, 1091, 1003, 834, 821, 784, 750

**Table 1**

Solvent and reaction temperature optimization for the synthesis of **3a**[a].

| Entry | Solvent | Reaction temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | acetone | reflux | 15 | 43 |
| 2 | acetonitrile | reflux | 10 | 58 |
| 3 | ethanol | reflux | 8.5 | 72 |
| 4 | chloroform | reflux | 13 | 52 |
| 5 | DMF | 100 | 7 | 88 |
| 6 | [bmim]Br | 90 | 5 | 96 |
| 7 | [bmim]$BF_4$ | 90 | 6 | 90 |
| 8 | [bmim]$PF_6$ | 90 | 6.5 | 88 |
| 9 | [bmim]Br | r.t. | 18 | 47 |
| 10 | [bmim]Br | 40 | 16 | 62 |
| 11 | [bmim]Br | 60 | 10 | 73 |
| 12 | [bmim]Br | 80 | 6.5 | 81 |

[a] 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1 mmol), 1-(4-chlorophenyl)-3-(4-methylphenyl)prop-2-en-1-one (1 mmol), and 2 mL solvent.

**Table 2**

Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **3** in ionic liquid.

| Entry | $R^1$ | $R^2$ | $Ar^1$ | $Ar^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| **3a** | $CH_3$ | $CH_3$ | 4-$CH_3C_6H_4$ | 4-$ClC_6H_4$ | 5 | 96 |
| **3b** | $CH_3$ | $CH_3$ | 3,4-$Cl_2C_6H_3$ | 4-$MeOC_6H_4$ | 6 | 92 |
| **3c** | $CH_3$ | $CH_3$ | 4-$NO_2C_6H_4$ | 4-$MeOC_6H_4$ | 6 | 92 |
| **3d** | $CH_3$ | $CH_3$ | 4-$BrC_6H_4$ | 4-$ClC_6H_4$ | 6.5 | 90 |
| **3e** | $CH_3$ | $CH_3$ | 3,4-$Cl_2C_6H_3$ | 4-$ClC_6H_4$ | 7.5 | 93 |
| **3f** | $CH_3$ | $CH_3$ | 4-$MeC_6H_4$ | 4-$MeOC_6H_4$ | 5 | 88 |
| **3g** | $CH_3$ | $CH_3$ | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 6 | 87 |
| **3h** | $CH_3$ | $CH_3$ | 4-$MeC_6H_4$ | 4-$MeC_6H_4$ | 5 | 90 |
| **3i** | $CH_3$ | H | 3,4-$OCH_2OC_6H_3$ | 4-$MeOC_6H_4$ | 5 | 90 |
| **3j** | $CH_3$ | H | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 5 | 96 |
| **3k** | H | H | 3,4-$OCH_2OC_6H_3$ | 4-$MeOC_6H_4$ | 5 | 92 |
| **3l** | H | H | 4-$ClC_6H_4$ | 4-$BrC_6H_4$ | 6 | 98 |
| **3m** | H | H | 4-$MeC_6H_4$ | Naphthalene-2-yl | 7 | 98 |

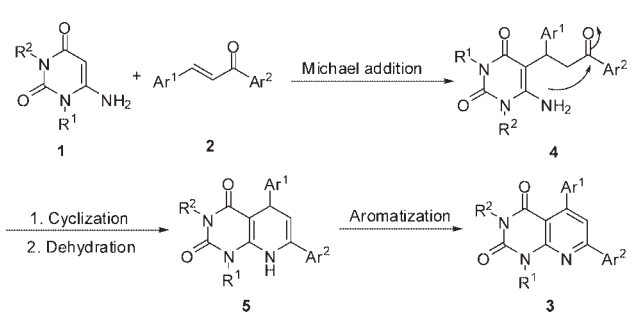
$cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.38 (s, 3H, $CH_3$), 3.18 (s, 3H, $CH_3$), 3.68 (s, 3H, $CH_3$), 7.21–7.29 (m, 4H, ArH), 7.55–7.61 (m, 3H, ArH), 8.27 (d, $J$ = 8.4 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 391.1089($M^+$); Calcd for $C_{22}H_{18}^{35}ClN_3O_2$: M 391.1088].

***5-(3,4-Dichlorophenyl)-7-(4-methoxyphenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3b).*** Mp: 295–296°C; IR (potassium bromide): 1706, 1670, 1578, 1543, 1472, 1422, 1367, 1253, 1221, 1178, 1132, 1027, 832, 753 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.20 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 7.09 (d, $J$ = 8.8 Hz,2H, ArH), 7.38 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H, ArH), 7.66 (s, 1H, ArH), 7.69 (d, $J$ = 8.4 Hz, 2H, ArH), 8.28 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 441.0646 ($M^+$); Calcd for $C_{22}H_{17}^{35}Cl_2N_3O_3$: M 441.0647].

***7-(4-Methoxyphenyl)-1,3-dimethyl-5-(4-nitrophenyl) pyrido[2,3-d]pyrimidine-2,4-(1H,3H)-dione (3c).*** Mp: >300°C; IR (potassium bromide): 1705, 1665, 1587, 1548, 1510, 1418, 1368, 1268, 1245, 1178, 1130, 838, 752 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.19 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 7.09 (d, $J$ = 8.8 Hz, 2H, ArH), 7.65–7.68 (m, 3H, ArH), 7.66 (s, 1H, ArH), 8.27–8.30 (m, 4H, ArH). HRMS [Found: *m*/*z*: 418.1276 ($M^+$); Calcd for $C_{22}H_{18}N_4O_5$: M 418.1277].

***5-(4-Bromophenyl)-7-(4-chlorophenyl)-1,3-dimethyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)- dione (3d).*** Mp: 264–266°C; IR (potassium bromide): 1707, 1668, 1593, 1576, 1547, 1490, 1420, 1363, 1282, 1258, 1178, 1003, 832, 804, 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.38 (s, 3H, $CH_3$), 3.87 (s, 3H, $CH_3$), 7.22 (d, $J$ = 8.8 Hz, 2H, ArH), 7.39 (s, 1H, ArH), 7.48 (d, $J$ = 8.8 Hz, 2H, ArH), 7.59 (d, $J$ = 8.4 Hz, 2H, ArH), 8.07 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 455.0039 ($M^+$); Calcd for $C_{21}H_{15}^{79}Br^{35}ClN_3O_2$: M 455.0036].

**Scheme 2**




***5-(3,4-Dichlorophenyl)-7-(4-chlorophenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3e).*** Mp: 254–256°C; IR (potassium bromide): 1710, 1672, 1575, 1548, 1475, 1421, 1365, 1218, 1089, 1008, 841, 753 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.20 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 7.39 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H, ArH), 7.61 (d, $J$ = 8.8 Hz,2H, ArH), 7.69–7.71 (m, 2H, ArH), 7.76 (s, 1H, ArH), 8.23 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 445.0152 ($M^+$); Calcd for $C_{21}H_{14}^{35}Cl_3N_3O_2$: M 445.0152].

***7-(4-Methoxyphenyl)-1,3-dimethyl-5-p-tolylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3f).*** Mp: 259–260°C; IR (potassium bromide): 1700, 1655, 1604, 1554, 1519, 1423, 1367, 1246, 1225, 1176, 1036, 834, 818, 751 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.38 (s, 3H, $CH_3$), 3.18 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 7.04–7.09 (m, 2H, ArH), 7.20–7.30 (m, 4H, ArH), 7.53 (s, 1H, ArH), 8.20–8.27 (m, 2H, ArH). HRMS [Found: *m*/*z*: 387.1583 ($M^+$); Calcd for $C_{23}H_{21}N_3O_3$: M 387.1583].

***5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3g).*** Mp: 279–280°C; IR (potassium bromide): 1702, 1657, 1607, 1579, 1557, 1519, 1423, 1366, 1249, 1226, 1174, 1087, 1029, 833, 751 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.19 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 7.08 (d, $J$ = 8.0 Hz, 2H, ArH), 7.41 (dd, $J_1$ = 2.0 Hz, $J_2$ = 7.6 Hz, 2H, ArH), 7.48 (dd, $J_1$ = 2.0 Hz, $J_2$ = 7.6 Hz, 2H, ArH), 7.59 (s, 1H, ArH), 8.26 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 407.1037 ($M^+$); Calcd for $C_{22}H_{18}^{35}ClN_3O_3$: M 407.1037].

***1,3-Dimethyl-5,7-di(p-tolyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3h).*** Mp: 217–219°C; IR (potassium bromide): 1704, 1661, 1590, 1546, 1515, 1418, 1363, 1260, 1220, 819, 755 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.43 (s, 6H, 2 × $CH_3$), 3.39 (s, 3H, $CH_3$), 3.88 (s, 3H, $CH_3$), 7.27–7.32 (m, 6H, ArH), 7.44 (s, 1H, ArH), 8.03 (d, $J$ = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 371.1634 ($M^+$); Calcd for $C_{23}H_{21}N_3O_2$: M 371.1634].

***5-(3,4-Methylenedioxyphenyl)-7-(4-methoxyphenyl)-1-methylpyrido[2,3-d]pyrimidine-2,4 (1H, 3H)-dione (3i).*** Mp: 308–309°C; IR (potassium bromide): 3299, 1707, 1687, 1577, 1550, 1502, 1484, 1441, 1376, 1255, 1229, 1180, 1106, 1028,

931, 842, 765 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.68 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 6.08 (s, 2H, $OCH_2O$), 6.91 (d, $J$ = 8.0 Hz, 1H, ArH), 6.96 (d, $J$ = 8.0 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 7.08 (d, $J$ = 8.0 Hz, 2H, ArH), 7.52 (s, 1H, ArH), 8.24 (d, $J$ = 8.0 Hz, 2H, ArH), 11.39 (s, 1H, NH). HRMS [Found: $m/z$: 403.1166 ($M^+$); Calcd for $C_{22}H_{17}N_3O_5$: M 403.1168].

***5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-1-methyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3j).*** Mp: >300°C; IR (potassium bromide): 3172, 1707, 1692, 1579, 1543, 1485, 1448, 1386, 1363, 1262, 1242, 1179, 1032, 981, 833 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.65 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 7.06–7.10 (m, 2H, ArH), 7.41–7.50 (m, 4H, ArH), 7.56 (s, 1H, ArH), 8.23–8.28 (m, 2H, ArH), 11.44 (s, 1H, NH). HRMS [Found: $m/z$: 393.0881 ($M^+$); Calcd for $C_{21}H_{16}^{35}ClN_3O_3$: M 393.0880].

***5-(3,4-Methylenedioxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3k).*** Mp: 317–318°C; IR (potassium bromide): 3294, 1723, 1705, 1593, 1578, 1549, 1441, 1406, 1362, 1253, 1183, 1094, 1037, 932, 871, 827, 804 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.83 (s, 3H, $OCH_3$), 6.07 (s, 2H, $OCH_2O$), 6.91–6.96 (m, 2H, ArH), 7.01 (s, 1H, ArH), 7.06 (d, $J$ = 8.4 Hz, 2H, ArH), 7.44 (s, 1H, ArH), 8.17 (d, $J$ = 8.4 Hz, 2H, ArH), 11.13 (s, 1H, NH), 11.59 (s, 1H, NH). HRMS [Found: $m/z$: 389.1024 ($M^+$); Calcd for $C_{21}H_{15}N_3O_5$: M 389.1012].

***7-(4-Bromophenyl)-5-(4-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3l).*** Mp: >300°C; IR (potassium bromide): 3180, 1714, 1590, 1575, 1553, 1484, 1403, 1361, 1260, 1008, 828, 766 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 7.46–7.48 (m, 4H, ArH), 7.59 (s, 1H, ArH), 7.75 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.4Hz,2H, ArH), 8.17 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.8 Hz, 2H, ArH), 11.28 (s, 1H, NH), 11.77 (s, 1H, NH). HRMS [Found: $m/z$: 426.9724 ($M^+$); Calcd for $C_{19}H_{11}^{79}Br^{35}ClN_3O_2$: M 426.9723].

***7-(Naphthalen-2-yl)-5-p-tolylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3m).*** Mp: 302–304°C; IR(potassium bromide): 3412, 3170, 3056, 1721, 1692, 1594, 1553, 1506, 1409, 1389, 1262, 1197, 860, 747 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.40 (s, 3H, $CH_3$), 7.25 (d, $J$ = 7.6 Hz, 2H, ArH), 7.38 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.0 Hz, 2H, ArH), 7.59–7.63 (m, 2H, ArH), 7.70 (d, $J$ = 1.6 Hz, 1H, ArH), 7.99 (d, $J$ = 8.0 Hz, 1H, ArH), 8.04–8.09 (m, 2H, ArH), 836 (d, $J$ = 8.8 Hz, 1H, ArH), 8.83 (s, 1H, ArH), 11.22 (s, 1H, NH), 11.74 (s, 1H, NH). HRMS [Found: $m/z$: 379.1345 ($M^+$); Calcd for $C_{24}H_{17}N_3O_2$: M 379.1321].

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## REFERENCES AND NOTES

[1] (a) Bradshaw, T. K.; Hutchison, D. W. Chem Soc Rev 1977, 6, 43; (b) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. Tetrahedron 1980, 36, 865; (c) Prajapati, D.; Bhuyan, P. J.; Sandhu, J. S. J Chem Soc Perkin Trans I 1988, 607; (d) Bhuyan, P. J.; Borah, H. N.; Sandhu, J. S. J Chem Soc Perkin Trans I 1999, 3083.

[2] (a) Marumoto, R.; Furukawa, Y. Chem Pharm Bull 1997, 25, 2974; (b) Griengl, R.; Wack, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. J Med Chem 1987, 30, 1199; (c) Clercq, E. D.; Bernaerts, R. J Biol Chem 1987, 262, 14905; (d) Jones, A. S.; Sayers, J. R.; Walker, R. T.; Clercq, E. D. J Med Chem 1988, 31, 268; (e) Mitsuya, H.; Yarchoan, R.; Broder, S. Science 1990, 249, 1533; (f) Pontikis, R.; Monneret, C. Tetrahedron Lett 1994, 35, 4351.

[3] (a) Heidelberger, C.; Arafield, F. J Cancer Res 1963, 23, 1226; (b) Baba, M.; Pauwels, R.; Herdwig, P.; Clercq, E. D.; Desmyster, J.; Vandepulfe, M. Biochem Biophys Res Commun 1987, 142, 128; (c) Clercq, E. D. J Med Chem 1986, 29, 1561; (d) Clercq, E. D. Anticancer Res 1986, 6, 549; (e) Jones, A. S.; Verhalst, G.; Walker, R. T. Tetrahedron Lett 1979, 20, 4415.

[4] (a) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. J Org Chem 1981, 46, 846; (b) Su, T. L.; Huang, J. T.; Burchanal, J. H.; Watanabe, K. A.; Fox, J. J. J Med Chem 1986, 29, 709; (c) Prajapati, D.; Sandhu, J. S. Synthesis 1988, 342.

[5] (a) Broom, A. D.; Shim, J. L.; Anderson, G. L. J Org Chem 1976, 41, 1095; (b) Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. J Med Chem 1980, 23, 327.

[6] (a) Matsumoto, J.; Minami, S. J Med Chem 1975, 18, 74; (b) Suzuki, N. Chem Pharm Bull 1980, 28, 761; (c) Oakes, V.; Rydon, H. N. J Chem Soc 1956, 4433; (d) Degraw, J. I.; Kisliuk, R. L.; Gaumont, Y.; Baugh, C. M. J Med Chem 1974, 17, 470; (e) Zakharov, A. V.; Gavrilov, M. Y.; Novoselova, G. N.; Vakhrin, M. I.; Konshin, M. E. Khim Farm Zh 1996, 30, 39.

[7] Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. Khim Farm Zh 1991, 25, 26.

[8] Heckler, R. E.; Jourdan, G. P.; Eur. Pat. Appl. EP 414386 A1 27, 1991; Chem Abstr 1991, 115, 71630.

[9] Agarwal, A.; Ashutosh, R.; Goyal, N.; Chauhan, P. M. S.; Gupta, S. Bioorg Med Chem 2005, 13, 6678.

[10] Vander Wel, S. N.; Harvey, P. J.; McNamara, D. J.; Repine, J. T.; Keller, P. R.; Quin, J., III; Booth, R. J.; Elliott, W. L.; Dobrusin, E. M.; Fry, D. W.; Toogood, P. L. J Med Chem 2005, 48, 2371.

[11] Broom, A. D.; Shim, J. L.; Anderson, C. L. J Org Chem 1976, 41, 1095.

[12] Shim, J. L.; Neiss, R.; Broom, A. D. J Org Chem 1972, 37, 578.

[13] Wawzonek, S. J Org Chem 1976, 41, 3149.

[14] Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. J Org Chem 1990, 55, 568.

[15] Quiroga, J.; Insuasty, B.; Sanchez, A.; Nogueras, M.; Meier, H. J Heterocycl Chem 1992, 29, 1045.

[16] Bagley, M. C.; Hughes, D. D.; Lloyd, R.; Powers, V. E. C. Tetrahedron Lett 2001, 42, 6585.

[17] Quiroga, J.; Insuasty, H.; Insuasty, B.; Abonía, R.; cobo, J.; Sánchez, A.; Nogueras, M. Tetrahedron 2002, 58, 4873.

[18] Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. Tetrahedron Lett 2003, 44, 8307.

[19] (a) Welton, T. Chem Rev 1999, 99, 2071; (b) Wasserscheid, P.; Keim, W. Angew Chem Int Ed 2000, 39, 3773; (c) Sheldon, R. Chem Commun 2001, 2399; (d) Wilkes, J. S. Green Chem 2002, 4, 73; (e) Yao, Q. Org Lett 2002, 4, 2197; (f) Zerth, H. M.; Leonard, N. M.; Mohan, R. S. Org Lett 2003, 5, 55; (g) Su, C.; Chen, Z. C.; Zheng, Q. G. Synthesis 2003, 555; (h) Rajagopal, R.; Jarikote, D. V.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V. Tetrahedron Lett 2003, 44, 1815; (i) Kumar, A.; Pawar, S. S. J Org Chem 2004, 69, 1419.

[20] Abdul-Sada, A. A. K.; Ambler, P. W.; Hodgson, P. K. G.; Seddon, K. R.; Stewark, N. J. World Pat. WO9521871, 1995.

[21] (a) Chauvin, Y.; Mussman, L.; Olivier, H. Angew Chem Int Ed Engl 1995, 38, 3097; (b) Fisher, T.; Sethi, A.; Wellton, T.; Woolf, J. Tetrahedron Lett 1999, 40, 293; (c) Asams, C. J.; Earle, M. J.; Seddon, K. R. Chem Commun 1999, 25; (d) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. Chem Commun 1999, 1043; (e) Monteiro, A. L.; Zimn, F. K.; de Souza, R. F.; Dupont, J. Tetrahedron:

Asymmetry 1997, 8, 177; (f) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. Polyhedron 1996, 15, 1217.

[22] (a) Badri, M.; Brunet, J. J.; Perron, R. Tetrahedron Lett 1992, 33, 4435; (b) Earle, M. J.; McCormac, P. B.; Seddon, K. R. Chem Commun 1998, 2245.

[23] (a) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. J Org Chem 1986, 54, 480; (b) Luer, G. D.; Bartalk, D. E. J Org Chem 1982, 47, 1238; (c) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. Chem Commun 1998, 2097.

[24] Ellis, B.; Keim, W.; Wasserscheid, P. Chem Commun 1999, 337.

[25] Earle, M. J.; McCormac, P. B.; Seddon, K. R. Green Chem 1999, 1, 23.

[26] Corey, E. J.; Zhang, F. Y. Org Lett 2000, 2, 1097.

[27] (a) Kaufmann, D. E.; Nouroozian, M.; Henze, H. Synlett 1996, 1091; (b) Bohm, V. P. W.; Herrmann, W. A. Chem Eur J 2000, 6, 1017; (c) Carmichael, A. J.; Earle, M. J.; Holberey, J. D.; McCormac, P. B.; Seddon, K. R. Org Lett 1999, 1, 997; (d) Zim, D.; de Souza, R. F.; Dupont, J.; Monteiro, A. L. Tetrahedron Lett. 1998, 39, 7071; (e) Song, L. E.; Roh, E. J Chem Commun 2000, 837.

[28] Schoefer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. Chem Commun 2001, 425.

[29] (a) Shi, D. Q.; Dou, G. L.; Li, Z. Y.; Ni, S. N.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Tetrahedron 2007, 63, 9764; (b) Shi, C. L.; Shi, D. Q.; Kim, S. H.; Huang, Z. B.; Ji, S. J.; Ji, M. Tetrahedron 2008, 64, 2425; (c) Shi, D. Q.; Dou, G. L.; Shi, C. L.; Li, Z. Y.; Ji, S. J. Synthesis 2007, 3117; (d) Shi, D. Q.; Dou, G. L.; Ni, S. N.; Shi, J. W.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Synlett 2007, 2509; (e) Shi, D. Q.; Niu, L. H.; Shi, J. W.; Wang, X. S.; Ji, S. J. J Heterocycl Chem 2007, 44, 1083; (f) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S. J Heterocycl Chem 2008, 45, 653; (g) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S.; Ji, S. J. J Heterocycl Chem 2008, 45, 693; (h) Shi, D. Q.; Yang, F.; Ni, S. N. J Heterocycl Chem 2009, 46, 469; (i) Dou, G. L.; Wang, M. M.; Huang, Z. B.; Shi, D. Q. J Heterocycl Chem 2009, 46, 645; (j) Shi, D. Q.; Niu, L. H.; Yao, H.; Jiang, H. J Heterocycl Chem 2009, 46, 237.

# The Development of an Ecofriendly Procedure for Alkaline Metal (II) Sulfate Promoted Synthesis of *N*,*N*′-Dimethyl Substituted (Unsubstituted)-4-Aryl-3,4-Dihydropyrimidones (Thiones) and Corresponding Bis-Analogues in Aqueous Medium: Evaluation by Green Chemistry Metrics

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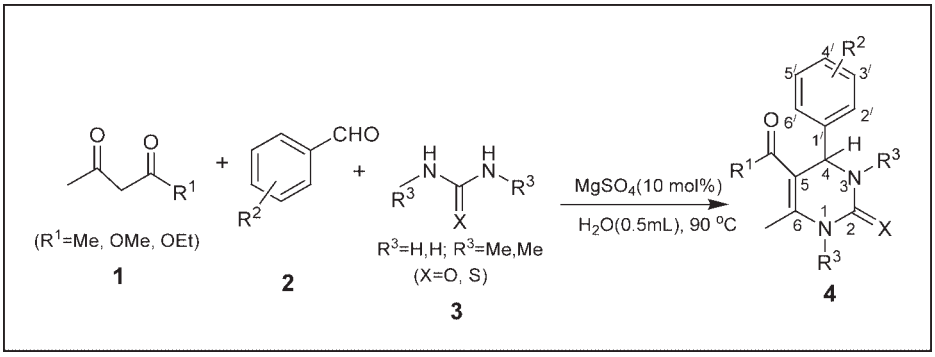


Different alkaline metal (II) sulfates were used as catalysts for the *N*,*N*′-dimethyl substituted as well as unsubstituted 4-aryl-3,4-dihydropyrimidones (thiones) and their corresponding bis-analogues in aqueous medium. Among the various salts, $MgSO_4 \cdot 7H_2O$ (Epsom salt) proved to be the best catalyst giving the desired products in good to excellent yields. This catalyst enables the construction of a series of compound libraries particularly for *N*,*N*′-dimethyl substituted DHPM's whose synthesis is very rare in the literature. The reaction on a wide variety substrates was evaluated by the application of green chemistry metrics and a very good correlation was obtained.

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## INTRODUCTION

The actual driving force for the development of new catalysts for the structural motif-*N*,*N*′-disubstituted(unsubstituted)-4-aryl-3,4-dihydropyrimidones being a heterocyclic moiety of remarkable pharmacological importance [1] is to prepare compound libraries for screening in drug discoveries. The appropriately functionalized dihydropyrimidones (DHPMs) are very prominent as mitotic kinesin inhibitors, $\alpha_1$-adrenergic antagonists and potent hypertensive agents [1]. The importance of the *N*,*N*′-disubstituted DHPMs lies in the fact that *N*,*N*′-disubstitution promotes lipophilicity and advances chemozymatic synthesis of enantiopure DHPMs in organic solvents [2]. When three component coupling (3CC) involving an aldehyde, alkyl acetoacetate, and *N*,*N*′-dimethylurea is performed, the synthesis of the desired dihydropyrimidones often fail or produces the desired products in very low yields due to the formation of multiple side products. Solvent-free conditions also fail to produce them [3]. Till date, the synthesis of *N*,*N*′-disubstituted DHPMs remains a great challenge for organic chemists.

Green Chemistry is a rapidly developing new field that provides a proactive avenue for the sustainable development of future science and technology [4]. Nowadays many reactions are being carried out in water for environmental protection. From this view point, it is desirable, instead of organic solvents, to use water as a reaction medium as, water is safe, easy handling, abundant and an environmentally benign solvent. Therefore, we aimed at the synthesis of the *N*,*N*′-disubstituted and *N*,*N*′-unsubstituted DHPMs in aqueous medium.

## RESULTS AND DISCUSSION

Dihydropyrimidones (DHPMs) possess immense biological activity [5] and therefore the synthesis of this nucleus has received much attention. It must be mentioned that the synthesis of the *N*,*N*′-dimethyl substituted DHPMs is rather difficult and there are only few references in the literature. The simple DHPMs, first synthesized by Biginelli [6], have already been prepared by a number of methods. In spite of this, very few reports of the synthesis of this ring system exist in water [7–9]. Thus, exploration for catalysts leading to the synthesis of this extremely important ring system in aqueous medium is still needed. In continuation of our sincere

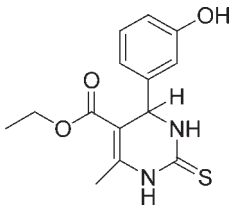


**Figure 1.** Monastrol.

efforts in carrying out reactions in aqueous medium [10–12], we envisaged the construction of a wide variety of *N*,*N*′-unsubstituted and dimethyl substituted dihydropyrimidones and also bis-dihydropyrimidones in water with variations in all the three components. This catalyst has been efficiently utilized for the synthesis of the mitotic kinesin EG 5 inhibitor Monastrol [13] (Fig. 1) in excellent yield.

For the initial exploration, the condensation of ethylacetoacetate, 4-chlorobenzaldehyde and urea with $MgSO_4$ (10 mol %) was studied in different solvents to optimize the reaction condition and to establish the feasibility of our catalyst (Table 1).

From Table 1, we find that the synthesis of the dihydropyrimidone produced from 4-chlorobenzaldehyde, EAA and urea proceeds best in water at 90°C in water (entry 12). Almost no reaction took place in aqueous medium at lower temperatures (entries 9–11). Use of higher temperature did not increase the yield further (entry 13). The yields were much lower when carried out in organic solvents (entries 1–8). Therefore, water has a definite role for the green reaction medium as it has an unique property of inducing hydrophobic interactions between the substrate and the catalyst.

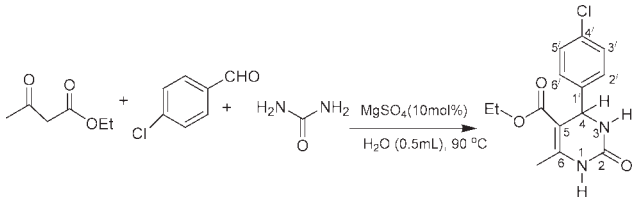
Our next task was the choice of the catalyst for the model reaction with EAA, urea, and 4-chlorobenzaldehyde with 0.5 mL of water at 90°C and the results are summarized in Table 2.

We tried Group IIA metal sulfates as the catalyst for the dihydropyrimidone formation in water at 90°C. It was observed that $MgSO_4 \cdot 7H_2O$ (Epsom salt) produced the desired product in maximum yield. It was also observed that the solubility of the Group IIA metal sulfate decreases down the group in accordance with Fajan's rules, which states that solubility decreases with increasing cationic radius. Therefore, the yield with Epsom salt was maximum probably due to an optimum correlation between its solubility and ionic character. The partial covalent character of $Mg^{+2}$ ion helps to form strong metal-oxygen bonds (similarly as in ref. [5]) thereby increasing the electrophilicity of the carbonyl carbons of the β-keto esters or β-diketones.

Once the optimum reaction conditions were finalized, the catalyst was effectively utilized for the synthesis of a wide variety of *N*,*N*′-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones and thiones (Scheme 1, $R^3 = H$) and the results are summarized in Table 3.

**Table 1**

Optimization of the reaction conditions of synthesis of dihydropyrimidone from 4-chlorobenzaldehyde, ethylacetoacetate, and urea with $MgSO_4$ (10 mol %).




| Entry | Solvent (0.5 mL) | Temperature (°C) | Reaction time (h) | Yield[a] (%) (isolated) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 45 | 5 | 35 |
| 2 | THF | 65 | 4 | 30 |
| 3 | MeOH | 70 | 4 | 35 |
| 4 | EtOH | 80 | 5 | 30 |
| 5 | DMF | 80 | 6 | 40 |
| 6 | DMF | 100 | 4 | 45 |
| 7 | DMSO | 80 | 6 | 40 |
| 8 | DMSO | 100 | 5 | 42 |
| 9 | $H_2O$ | 40 | 4 | 00 |
| 10 | $H_2O$ | 60 | 5 | 03 |
| 11 | $H_2O$ | 70 | 6 | 05 |
| 12 | $H_2O$ | 90 | 4 | 90 |
| 13 | $H_2O$ | 100 | 5 | 90 |
| 14 | $H_2O$ | 90 | 8 | 90 |

[a] Yields calculated with respect to starting aldehyde.

**Table 2**

Choice of catalyst for the reaction of EAA, urea, and 4-chlorobenzaldehyde with 0.5 mL water at 90°C.

| Entry | Catalyst (10 mol%) (with water of hydration) | Time (h) | Yield % (isolated w. r. t. starting aldehyde) |
|---|---|---|---|
| 1 | – | 10 | 5 |
| 2 | $MgSO_4$ | 4 | 90 |
| 3 | $CaSO_4$ | 6 | 60 |
| 4 | $SrSO_4$ | 7 | 47 |
| 5 | $BaSO_4$ | 10 | 20 |

Our next target was the application of our catalyst for the synthesis of the dimethyl substituted DHPM's and hence to synthesize ''drug-like'' molecules. This is because the synthesis of these *N*,*N*′-dimethyl DHPMs are rather difficult and thus references for their synthesis are very rare. To establish the scope and utility of our catalyst, a number of reactions (Table 4) were conducted and the products isolated. It was noted that on scaling up the reaction, the amount of $MgSO_4$ need not be increased proportionately. After lyophilization of the water extract obtained from the filtration of the product, the recovered catalyst could be reused to a maximum of three successive preparations of the DHPMs with almost the same yield of the reaction. The water extract responded to positive tests for both $Mg^{+2}$ and $SO_4^{2-}$ ions indicating that the catalyst remains intact after the reaction. The role of the catalyst is therefore to increase the electrophilicity of the aldehyde carbonyl which is very obvious as with other metal salts and also to coordinate with the carbonyl oxygen of the β-keto ester and the β-diketone.

On analysis of Tables 3 and 4, we find that our catalyst produced the *N*,*N*′-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields and the *N*,*N*′-dimethyl DHPMs in good yields. The reaction also accommodated a wide variety of substrates in the aldehyde part, both electron-donating and electron-withdrawing acting equally well. Ethylacetoacetate, methylacetoacetate, and acetylacetone were varied as the β-keto esters or the β-diketone. Again, urea and thiourea were equally effective in carrying out the reaction. Table 3, entry 4 depicts the synthesis of Monastrol (Fig. 1). In all the cases, the pure product was isolated by simple filtration. Recrystallization from aqueous ethanol produced the pure 3, 4-dihydropyrimidin-2(1*H*)-ones. Thus, the products were obtained in pure form without any column chromatography or any cumbersome work-up techniques. In all the cases, 100% conversion was observed as no starting materials were present in thin layer chromatography (TLC) or in $^1$H NMR (crude) after the reaction. With aliphatic aldehydes, only 10% conversion (by TLC) was observed and the final products cannot be isolated from the reaction mixture. The reaction was also 100% selective as a single product was obtained for all cases for aromatic aldehydes. This is possibly due to the higher stability of the acyl imines (with increasing conjugation) for aromatic aldehydes than with aliphatic ones. This methodology in aqueous medium is obviously a green one as no toxic chemicals or reagents were used and no side products were obtained.

Encouraged by the aforementioned results, we turned our attention toward the utilization of our catalyst toward the construction of the bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones). We found that the reactions proceeded smoothly in aqueous medium with $MgSO_4$ (10 mol %) to produce the *N*,*N*′-unsubstituted bis-compounds in excellent yields (Scheme 2, Table 5). The reaction generated two new chiral centers at $C_4$ and $C_4'$-positions, the relative stereochemistry of which could be either RR or RS. X-ray crystallography of these compounds was not possible due to their amorphous nature. With dimethyl urea and thiourea, the formation of these bis-compounds did not go to completion. These bis-compounds are otherwise quite difficult to achieve and therefore the application of our catalyst provides an easy access to the construction of these compounds.

The mechanism of the dihydropyrimidone formation is similar as proposed by Folkers and Johnson [15]. The

**Scheme 1.** Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones) with $MgSO_4$ (10 mol %) in water at 90°C.

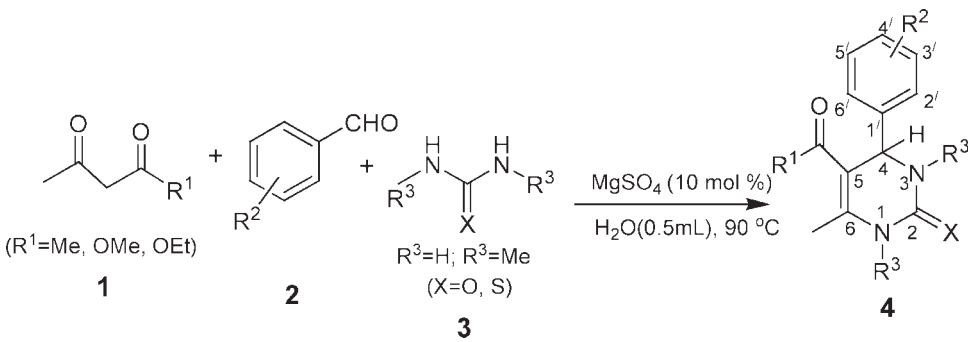


**Table 3**

Synthesis of *N*,*N*′-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) ($R^3$ = H) with $MgSO_4$ (10 mol %) in water at 90°C.

| Entry | $R^1$ | $R^2$ | X | Time (h) | Yield (%) (isolated) | References |
|---|---|---|---|---|---|---|
| 1 | OEt | 4-Cl | O | 8 | 90 | [10] |
| 2 | OMe | 4-OMe | O | 9 | 88 | [10] |
| 3 | OMe | 4-OH-3-OMe | S | 6 | 85 | [10] |
| 4 | OEt | 3-OH | S | 7 | 82 | [13] |
| 5 | OMe | 3-$NO_2$ | O | 10 | 80 | [10] |
| 6 | Me | 2,5-$(OMe)_2$ | O | 5 | 88 | – |
| 7 | OMe | 2,5-$(OMe)_2$ | O | 5 | 87 | – |
| 8 | OMe | 4-CN | O | 6 | 83 | – |
| 9 | OEt | 4-$NO_2$ | O | 10 | 85 | [13] |
| 10 | Me | H | S | 7 | 82 | [13] |
| 11 | Me | 4-CN | S | 8 | 80 | – |
| 12 | OEt | 2-furanyl | O | 4 | 78 | [13] |
| 13 | OMe | 4-CN | S | 8 | 82 | – |
| 14 | OEt | 4-OH | S | 9 | 78 | [13] |
| 15 | OEt | 4-CN | S | 10 | 81 | – |
| 16 | Me | 2-Cl | S | 8 | 79 | [13] |
| 17 | OMe | 3-OH | S | 7 | 75 | – |
| 18 | Me | 2-$NO_2$ | S | 9 | 80 | – |
| 19 | Me | 3-$NO_2$ | S | 9 | 82 | – |
| 20 | Me | 4-OH-3-OMe | S | 8 | 78 | – |
| 21 | OEt | H | O | 9 | 75 | [13] |
| 22 | OEt | H | S | 9 | 78 | [13] |
| 23 | OMe | 4-OH-3-OMe | O | 7 | 79 | [13] |
| 24 | Me | 4-OMe | O | 5 | 82 | [13] |
| 25 | OEt | 4-OMe | S | 5 | 84 | [13] |
| 26 | Me | 3-$NO_2$ | O | 10 | 86 | [13] |
| 27 | OEt | 4-$NMe_2$ | O | 4 | 85 | [13] |
| 28 | OMe | 4-$NMe_2$ | O | 4 | 77 | [13] |
| 29 | Me | 4-$NO_2$ | O | 10 | 73 | [13] |
| 30 | OEt | 3-OH | O | 6 | 76 | [13] |
| 31 | Me | 4-Cl | O | 7 | 77 | [13] |
| 32 | Me | H | O | 8 | 76 | [13] |
| 33 | OMe | H | S | 8 | 85 | [13] |
| 34 | OEt | 4-OMe | O | 6 | 84 | [13] |
| 35 | Me | 4-OH | O | 7 | 83 | [13] |
| 36 | OMe | 4-OH | O | 8 | 82 | [13] |
| 37 | OMe | 4-$NO_2$ | O | 8 | 79 | [13] |

initial formation of the acylimine intermediate takes place which reacts subsequently with the β-diketone or β-ketoester effectively. The partial covalent character of $Mg^{+2}$ helps in forming a strong metal oxygen bond which helps in increasing the electrophilicity of the β-diketone or β-ketoester in the same manner as mentioned in ref. [5]. Finally, a favorable cyclization and dehydration path follows to produce the dihydropyrimidone system.

In a nutshell, our methodology has the following distinct advantages over the earlier reported procedures [6.9]: (a) the reactions are investigated in water and hence avoids the hassles of organic solvents, (b) the catalyst is rather simple and cheap, (c) anhydrous reaction conditions need not be maintained, (d) additional proton sources are not required, (e) the products are obtained by simple filtration without the need for column chromatography, (f) this methodology is particularly useful for the synthesis of the dimethyl dihydropyrimidones and bis-dihydropyrimidones which are otherwise quite rare in the literature, and (g) it is a totally green methodology.

**Green metric calculations.** The green metrics were calculated using the procedures reported in the literature.[4] Their definitions are given as follows:

*Mass Intensity (MI)* = Total mass used in a process or process step (g)/mass of product (g)

*Reaction mass efficiency (RME)* = (Σ mass of products/Σ mass of reactants) × 100

*Carbon efficiency (CE)* = [(No. of moles of product × No. of carbons in product)/Σ (No. of moles of reactant × No. of carbons in reactant)] × 100

*Atom economy (AE)* = [molecular weight of product/Σ molecular weight of reactant] ×100

**Table 4**

Synthesis of *N*,*N*′-dimethyl-4-aryl-dihydropyrimidones (thiones) ($R^3$ = Me) with $MgSO_4$ (10 mol %) in water at 90°C.

| Entry | $R^1$ | $R^2$ | X | Time (h) | Yield[a] | References |
|---|---|---|---|---|---|---|
| 1 | OMe | 4′-OMe | O | 10 | 60 | – |
| 2 | OEt | 4′-OH | O | 8 | 62 | – |
| 3 | OMe | 4′-Cl | O | 8 | 60 | – |
| 4 | OEt | 3′,4′-$(OMe)_2$ | O | 9 | 61 | – |
| 5 | OMe | 2′-$NO_2$ | O | 9 | 65 | – |
| 6 | OMe | 2′,5′-$(OMe)_2$ | O | 9 | 62 | – |
| 7 | OEt | 2′,5′-$(OMe)_2$ | O | 10 | 61 | – |
| 8 | Me | 2′-Cl | O | 6 | 60 | – |
| 9 | Me | 4′-$NO_2$ | O | 7 | 62 | – |
| 10 | Me | 4′-Br | O | 9 | 65 | – |
| 11 | OMe | 4′-Br | O | 10 | 64 | – |
| 12 | OMe | 2′-Cl | O | 7 | 61 | – |
| 13 | Me | 4′-Br | S | 12 | 44 | – |
| 14 | Me | 2′-Cl | S | 10 | 58 | – |
| 15 | OEt | 4′-Cl | O | 7 | 60 | – |
| 16 | Me | 3′-$NO_2$ | O | 7 | 65 | – |
| 17 | OEt | 2′-$NO_2$ | O | 8 | 60 | [2] |
| 18 | OEt | 3′-$NO_2$ | O | 9 | 61 | [2] |
| 19 | OEt | 4′-$NO_2$ | O | 9 | 64 | [2] |
| 20 | OEt | 4′-OMe | O | 9 | 60 | [2] |

[a] Isolated.

Mass intensity (MI), reaction mass efficiency (RME), carbon efficiency (CE), and atom economy (AE) have been considered as a measure of environmental sustainability in minimizing the amount of theoretical waste. MI considers the yield stoichiometry, the solvent and the RME is the natural measure of greenness that takes into account the yield, excess or catalytic amount of reactants used but it does not account for any solvent use. CE is the percentage of carbon gain or loss, that is, whether all the carbon atoms of the reactant are present in the product. It is a very important parameter in our reaction as our reaction involves carbon atoms. Finally, the AE is a theoretical calculation of the chemical and environmental efficiency of the reaction which allows

**Scheme 2.** Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) at 90°C in aqueous medium with $MgSO_4$ (10 mol %).

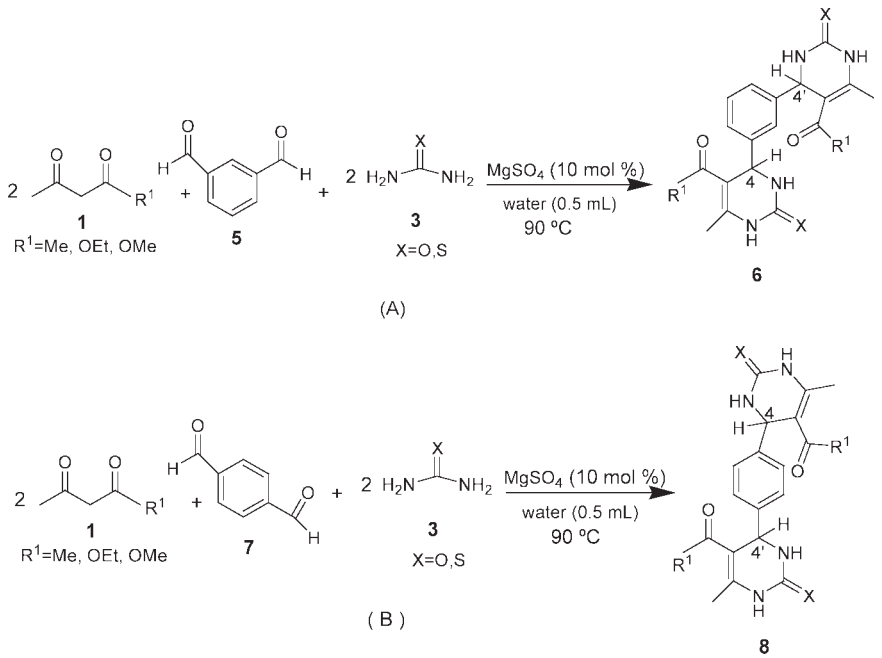


**Table 5**

Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) at 90°C in aqueous medium with $MgSO_4$ (10 mol %).

| Entry | $R^1$ | Starting dialdehyde | X | Time (h) | Yield (%) (isolated) | References |
|---|---|---|---|---|---|---|
| 1 | OMe | **5** | O | 10 | 85 | – |
| 2 | OEt | **5** | O | 11 | 82 | – |
| 3 | OMe | **5** | S | 15 | 75 | – |
| 4 | Me | **5** | O | 10 | 80 | [14] |
| 5 | OMe | **7** | O | 12 | 84 | [14] |
| 6 | OEt | **7** | O | 11 | 82 | [14] |
| 7 | OMe | **7** | S | 10 | 76 | [14] |
| 8 | OEt | **7** | S | 11 | 74 | [14] |

for the effect on stoichiometric equation, not considering any solvent, excess of reagents and formation of intermediate or any other side product, etc. So from this aforementioned point, the ideal situation is MI $\approx$ 1, % RME $\approx$ 100, % CE $\approx$ 100, % AE $\approx$ 100.

We have shown the green metrics calculations for some selected compounds using urea, thiourea, or dimethyl urea (Table 6). The results reveal that our reactions have excellent MI values for almost all the compounds (Table 6). MI values of the reactions are very much dependent on solvent. Use of lesser amount of solvent in the reaction will lead to the ideal situation. We use only 0.5 mL of water in our reactions which is the optimum value. Use of lower amount of solvent (water) in the reaction will lead to increase in MI, but lower yield, as the catalyst will not react in lesser amount of solvent used. Thus, the MI values obtained were highly acceptable. Our reactions have excellent CE (for reactions with urea and thiourea) and quite good CE (for reactions with dimethyl counterparts), which in these cases is equal to the yield because all the carbon atoms of the reactant are present in the

**Table 6**

Green metrics calculations of a wide variety of compounds taken from Tables 3–5.

| Entry | Substrates used | % Yield | FW (product) | Yield (g) | MI | % RME | % CE | % AE |
|---|---|---|---|---|---|---|---|---|
| 1 | Table 3, entry 6 | 88 | 290.317 | 0.255 | 3.32 | 73.70 | 88 | 88.96 |
| 2 | Table 3, entry 7 | 87 | 306.316 | 0.266 | 3.43 | 64.56 | 87 | 89.47 |
| 3 | Table 3, entry 8 | 83 | 271.275 | 0.225 | 3.90 | 59.68 | 83 | 88.28 |
| 4 | Table 3, entry 11 | 80 | 271.342 | 0.217 | 3.81 | 66.36 | 80 | 88.28 |
| 5 | Table 3, entry 13 | 82 | 287.341 | 0.235 | 3.80 | 59.80 | 82 | 88.86 |
| 6 | Table 3, entry 15 | 81 | 301.368 | 0.244 | 3.72 | 59.95 | 81 | 89.32 |
| 7 | Table 3, entry 17 | 75 | 278.291 | 0.208 | 4.25 | 54.16 | 75 | 88.84 |
| 8 | Table 3, entry 18 | 80 | 291.329 | 0.233 | 3.64 | 67.15 | 80 | 88.99 |
| 9 | Table 3, entry 19 | 82 | 291.329 | 0.238 | 3.56 | 68.59 | 82 | 88.99 |
| 10 | Table 3, entry 20 | 78 | 292.356 | 0.228 | 3.72 | 65.52 | 78 | 89.03 |
| 11 | Table 4, entry 1 | 60 | 304.344 | 0.182 | 5.00 | 44.39 | 60 | 89.41 |
| 12 | Table 4, entry 2 | 62 | 304.344 | 0.188 | 4.80 | 45.85 | 62 | 89.42 |
| 13 | Table 4, entry 3 | 60 | 308.763 | 0.185 | 4.94 | 44.69 | 60 | 89.55 |
| 14 | Table 4, entry 4 | 61 | 348.390 | 0.212 | 4.50 | 46.70 | 61 | 90.06 |
| 15 | Table 4, entry 5 | 65 | 319.320 | 0.207 | 4.47 | 48.70 | 65 | 89.86 |
| 16 | Table 4, entry 6 | 62 | 334.370 | 0.207 | 4.54 | 47.70 | 62 | 90.27 |
| 17 | Table 4, entry 7 | 61 | 348.396 | 0.212 | 4.50 | 46.70 | 61 | 90.63 |
| 18 | Table 4, entry 8 | 60 | 292.764 | 0.175 | 4.85 | 50.29 | 60 | 89.04 |
| 19 | Table 4, entry 9 | 62 | 303.316 | 0.188 | 4.75 | 52.37 | 62 | 89.38 |
| 20 | Table 4, entry 10 | 65 | 337.215 | 0.219 | 4.08 | 55.73 | 65 | 90.35 |
| 21 | Table 3, entry 11 | 64 | 353.210 | 0.226 | 4.24 | 49.24 | 64 | 90.74 |
| 22 | Table 3, entry 12 | 61 | 308.760 | 0.188 | 4.87 | 45.41 | 61 | 89.55 |
| 23 | Table 3, entry 13 | 44 | 353.280 | 0.155 | 5.87 | 37.90 | 44 | 90.75 |
| 24 | Table 3, entry 14 | 58 | 308.830 | 0.179 | 4.83 | 49.18 | 58 | 89.55 |
| 25 | Table 3, entry 15 | 60 | 322.790 | 0.193 | 4.81 | 45.09 | 60 | 89.96 |
| 26 | Table 3, entry 16 | 65 | 303.320 | 0.197 | 4.36 | 54.87 | 65 | 89.38 |
| 27 | Table 5, entry 1 | 85 | 414.416 | 0.352 | 3.14 | 58.08 | 85 | 85.19 |
| 28 | Table 5, entry 2 | 82 | 442.469 | 0.362 | 3.13 | 57.10 | 82 | 86.00 |
| 29 | Table 5, entry 3 | 75 | 446.548 | 0.334 | 3.41 | 52.35 | 75 | 86.11 |

product. In the same direction, the excellent yields with the catalyst produced good values of RME while moderate yield produced moderate RME values. Table 6 shows that all our reactions possess excellent AE values mostly being 89–90%. Thus all the reactions carried out using our methodology have very good green metrics correlations.

## CONCLUSION

It can be concluded that $MgSO_4 \cdot 7H_2O$ (10 mol %) in 0.5 mL water proves to be the best catalyst amongst all the alkaline Group II metals for dihydropyrimidone, bis-dihydropyrimidone and particularly, *N*,*N*′-dimethyl dihydropyrimidone formation. Since only 10 mol % of the catalyst and 0.5 mL of water are used, the reaction condition meets several green chemistry principles. The isolation of the reaction products is very simple and does not require column chromatography for most cases.

## EXPERIMENTAL

**General.** Ethanol was distilled before use. All the chemicals were purchased from Aldrich Chemical Company and Spectrochem (Mumbai, India). Silica Gel G with binder from Spectrochem was used for thin layer chromatography. $MgSO_4 \cdot 7H_2O$ was purchased from Spectrochem was used as such. $^1H$ and $^{13}C$ NMR spectra were obtained on Bruker 300 MHz instrument at 300 and 75 MHz, respectively. $CDCl_3$ and DMSO-$d_6$ were purchased from Aldrich Chemical Company. Melting points were determined on an electrical melting point apparatus with an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer RX/FTIR system.

**General experimental procedure for dihydropyrimidone/bis-dihydropyrimidone formation.** A mixture of aromatic aldehyde (1 mmol), β-keto ester or β-diketone (1.3 mmol/2.6 mmol), urea/thiourea/*N*,*N*′-dimethyl urea/*N*,*N*′-dimethyl thiourea (1.5 mmol/3.0 mmol) and $MgSO_4 \cdot 7H_2O$ (10 mol %) and 0.5 mL water were mixed thoroughly and then taken in a 5 mL conical flask. It was next placed in water bath at 90°C and heated for the specified time as mentioned in Tables 3–5. The reactions were monitored by TLC for the absence of the starting aldehyde. After completion of the reaction, the crude mass was cooled, poured into crushed ice, and stirred for further 10 min, when the dihydropyrimidones (solids) precipitated out. They were directly filtered and crystallized from hot aqueous ethanol to obtain the finally pure products. The liquid DHPMs products were extracted with (2 × 5) mL ethyl acetate, washed with brine, solvent removed to obtain the crude products. The pure products (liquids) were obtained by column chromatography with silica gel (100–200 mesh) and elution with ethyl acetate/petroleum ether (60–80°C). All the products were characterized by their spectral and analytical data.

The data for all the previously unknown compounds are given later:

***5-Acetyl-6-methyl-4-(2,5-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (Table 3, entry 6).*** Light brown solid; M.p. 252–254°C (MeOH). IR (KBr): 3247, 3107, 1705, 1628, 1495, 1454, and 1235 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 9.12 (s, 1H, NH), 7.33 (s, 1H, NH), 6.90 (d, $J$ = 8.7 Hz, 1H, aromatic $C_3$-H), 6.78 (dd, $J$ = 9.0, 3.0 Hz, 1H, aromatic $C_4$-H), 6.53 (d, $J$ = 3.3 Hz, 1H, aromatic $C_6$-H), 5.48 (d, $J$ = 3.0 Hz, 1H, $C_4$-H), 3.72 (s, 3H, $C_2$-OMe), 3.61 (s, 3H, $C_5$-OMe), 2.25 (s, 3H, —$COCH_3$), 2.00 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 194.6 (C=O), 153.2 ($C_2$=O), 152.3 (aromatic $C_2$), 150.5 (aromatic $C_5$), 148.2 ($C_6$), 132.4 (aromatic $C_1$), 113.9 (aromatic $C_3$), 112.3 (aromatic $C_4$), 112.2 (aromatic $C_6$), 108.0 ($C_5$), 56.0 ($C_2$-OMe), 55.4 ($C_5$-OMe), 48.9 ($C_4$), 29.8 (CO*C*$H_3$), 18.7 ($C_6$-*C*$H_3$). *Anal*. calcd. for $C_{15}H_{18}N_2O_4$; C: 62.06, H: 6.25, N: 9.65. Found: C: 62.17, H: 6.02, N: 9.71%.

***5-Methoxycarbonyl-6-methyl-4-(2,5-dimethoxyphenyl)-3.4-dihydropyrimidin-2(1H)-one (Table 3, entry 7).*** Off-white solid; M.p. 240–242°C (MeOH). IR (KBr): 3241, 3106, 2948, 1703, 1646, 1496, 1440, 1235, and 1092 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 9.16 (s, 1H, NH), 7.26 (s, 1H, NH), 6.91 (d, $J$ = 9.0 Hz, 1H, aromatic $C_3$-H), 6.79 (dd, $J$ = 8.9, 3.0 Hz, 1H, aromatic $C_4$-H), 6.54 (d, $J$ = 3.0 Hz, 1H, aromatic $C_6$-H), 5.41 (d, $J$ = 3.0 Hz, 1H, $C_4$-H), 3.73 (s, 3H, $C_2$-OMe), 3.64 (s, 3H, $C_5$-OMe), 3.47 (s, 3H, —$COOCH_3$), 2.27 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 165.9 (*CO*OMe), 153.0 ($C_2$=O), 152.3 (aromatic $C_2$), 150.8 (aromatic $C_5$), 149.3 ($C_6$), 132.6 (aromatic $C_1$), 113.9 (aromatic $C_3$), 112.4 (aromatic $C_4$), 112.0 (aromatic $C_6$), 97.4 ($C_5$), 56.1 ($C_2$-*OMe*), 55.3 ($C_5$-*OMe*), 50.8 ($C_4$), 49.0 (CO*OCH*$_3$), 17.8 ($C_6$-*C*$H_3$). *Anal*. calcd. for $C_{15}H_{18}N_2O_5$; C: 58.82, H: 5.92, N: 9.15. Found: C: 58.71, H: 5.84, N: 9.22%.

***5-Methoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-one (Table 3, entry 8).*** White solid; M.p. 176–178°C (MeOH). IR (KBr): 3329, 3120, 2235, 1634, 1223, and 1089 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 9.33 (s, 1H, NH), 7.85 (d, $J$ = 1.2 Hz, 1H, NH), 7.80 (d, $J$ = 8.4 Hz, 2H, aromatic $C_3$-, $C_5$-H), 7.38 (d, $J$ = 8.1 Hz, 2H, aromatic $C_2$-, $C_6$-H), 5.18 (d, $J$ = 3.3 Hz, 1H, $C_4$-H), 3.49 (s, 3H, —$COCH_3$), 2.22 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 165.7 (*CO*OMe), 152.0 ($C_2$=O), 149.9 (aromatic $C_1$), 149.7 ($C_6$), 132.7 (aromatic $C_3$, $C_5$), 127.4 (aromatic $C_2$, $C_6$), 118.8 ($C_5$), 110.3 (aromatic $C_4$), 98.2 (CN), 53.8 ($C_4$), 51.0 (CO*OCH*$_3$), 18.0 ($C_6$-*C*$H_3$). *Anal*. calcd. for $C_{14}H_{13}N_3O_3$; C: 61.99, H: 4.83, N: 15.49. Found: C: 61.84, H: 4.71, N: 15.63%.

***5-Acetyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-thione (Table 3, entry 11).*** White solid; M.p. 130–132°C (MeOH). IR (KBr): 3277, 3181, 2228, 1617, 1577, 1455, and 1186 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.38 (s, 1H, NH), 9.81 (d, $J$ = 2.4 Hz, 1H, NH), 7.80 (d, $J$ = 8.4 Hz, 2H, aromatic $C_3$-, $C_5$-H), 7.35 (d, $J$ = 8.1 Hz, 2H, aromatic $C_2$-, $C_6$-H), 5.32 (d, $J$ = 3.9 Hz, 1H, $C_4$-H), 2.31 (s, 3H, $COCH_3$), 2.18 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 194.7 (C=O), 174.6 (C=S), 148.1 (aromatic $C_1$), 145.5 ($C_6$), 132.8 (aromatic $C_3$, $C_5$), 127.6 (aromatic $C_2$, $C_6$), 118.8 ($C_5$), 110.5 (aromatic $C_4$), 110.3 (CN), 53.4 ($C_4$), 30.8 (CO*CH*$_3$), 18.5 ($C_6$-$CH_3$). *Anal*. calcd. for $C_{14}H_{13}N_3OS$; C: 61.97, H: 4.83, N: 15.49. Found: C: 61.84, H: 4.75, N: 15.61%.

***5-Methoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-thione (Table 3, entry 13).*** White solid; M.p. 158–160°C (MeOH). IR (KBr): 3327, 3146, 2926, 2228, 1689, 1526, and 1173 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.45 (s, 1H, NH), 9.72 (d, $J$ = 2.1 Hz, 1H, NH), 7.80 (d, $J$ = 8.4 Hz, 2H, aromatic $C_3$-, $C_5$-H), 7.35 (d, $J$ = 8.1 Hz, 2H, aromatic $C_2$-, $C_6$-H), 5.20 (d, $J$ = 3.3 Hz, 1H, $C_4$-H), 3.51 (s,

3H, $COOCH_3$), 2.25 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 175.1 (C=S), 165.3 (C=O), 147.0 (aromatic $C_1$), 143.6 ($C_6$), 132.8 (aromatic $C_3$, $C_5$), 127.5 (aromatic $C_2$, $C_6$), 118.3 ($C_5$), 112.4 (aromatic $C_4$), 102.0 (CN), 55.6 ($C_4$), 51.7 ($CO\mathit{OCH_3}$), 18.6 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{14}H_{13}N_3O_2S$; C: 58.52, H: 4.56, N: 14.62. Found: C: 58.64, H: 4.68, N: 14.74%.

***5-Ethoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-thione (Table 3, entry 15).*** White solid; M.p. 242–244°C (MeOH). IR (KBr): 3319, 3145, 2229, 1532, 1428, 1172, and 772 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H, NH), 7.85 (s, 1H, NH), 7.63 (d, $J$ = 8.1 Hz, 2H, aromatic $C_3$-, $C_5$-H), 7.42 (d, $J$ = 8.4 Hz, 2H, aromatic $C_2$-, $C_6$-H), 5.46 (d, $J$ = 3.0 Hz, 1H, $C_4$-H), 4.12 (q, $J$ = 6.8 Hz, 2H, $OCH_2CH_3$), 2.38 (s, 3H, $C_6$-$CH_3$), 1.20 (t, $J$ = 7.2 Hz, 3H, $OCH_2\mathit{CH_3}$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 174.7 (C=S), 164.9 (C=O), 147.1 (aromatic $C_1$), 143.6 ($C_6$), 132.7 (aromatic $C_3$, $C_5$), 127.5 (aromatic $C_2$, $C_6$), 118.3 ($C_5$), 112.2 (aromatic $C_4$), 102.1 (CN), 60.8 ($OCH_2$), 55.6 ($C_4$), 18.4 ($C_6$-$CH_3$), 14.1 ($OCH_2\mathit{CH_3}$). *Anal.* calcd. for $C_{15}H_{15}N_3O_2S$; C: 59.78, H: 5.02, N: 13.94. Found: C: 59.64, H: 5.16, N: 14.04%.

***4-(3-Hydroxyphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 17).*** Off-white solid; M.p. 220–222°C (EtOH). IR (KBr): 3315, 3189, 1669, 1576, 1478, 1284, 1194, 1117, and 752 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.32 (s, 1H, NH), 9.62 (brd, $J$ = 1.8 Hz, 1H, NH), 9.47 (s, 1H, OH), 7.12 (t, $J$ = 7.8 Hz, 1H, aromatic $C_5$-H), 6.65 (d, $J$ = 8.7 Hz, 3H, aromatic $C_2$-, $C_4$-, and $C_6$-H), 5.09 (d, $J$ = 3.6 Hz, 1H, $C_4$-H), 3.57 (s, 3H, —COOMe), 2.29 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 174.7 (C=S), 166.2 (C=O), 158.0 (aromatic $C_3$), 145.6 ($C_6$), 145.1 (aromatic $C_1$), 130.1 (aromatic $C_5$), 117.4 (aromatic $C_6$), 115.2 (aromatic $C_2$), 113.7 (aromatic $C_4$), 101.0 ($C_5$), 54.3 ($C_4$), 51.6 ($CO\mathit{OCH_3}$), 17.7 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{13}H_{14}N_2O_3S$: C: 56.10, H: 5.07, N: 10.06. Found: C: 56.03, H: 5.05, N: 10.10%.

***5-Acetyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 18).*** Brown solid; M.p. 254–256°C (EtOH). IR (KBr): 3419, 2927, 1719, 1607, 1527, 1355, 1268, 1202, 1093, 1013, and 668 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.41 (s, 1H, NH), 9.60 (s, 1H, NH), 7.92 (dd, $J$ = 9.0, 0.9 Hz, 1H, aromatic $C_3$-H), 7.72 (td, $J$ = 7.5,1.2 Hz, 1H, $C_4$-H), 7.54 (td, $J$ = 8.4, 1.2 Hz, 1H, aromatic $C_5$-H), 7.46 (dd, $J$ = 9.0, 1.2 Hz, 1H, aromatic $C_6$-H), 5.98 (d, $J$ = 3.0 Hz, 1H, $C_4$-H), 2.36 (s, 3H, —$COCH_3$), 2.16 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 194.0 (C=O), 173.7 (C=S), 147.0 (aromatic $C_2$), 144.6 ($C_6$), 137.0 (aromatic $C_1$), 133.6 (aromatic $C_5$), 128.7 (aromatic $C_6$), 128.6 (aromatic $C_4$), 123.9 (aromatic $C_3$), 110.1 ($C_5$), 48.9 ($C_4$), 30.3 ($CO\mathit{CH_3}$), 17.9 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H,4.50; N, 14.42%. Found: C, 53.53; H, 4.48; N,14.45%.

***5-Acetyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 19).*** Brown solid; M.p. 280–281°C (EtOH). IR (KBr): 3294, 3183, 2374, 1612, 1576, 1527, 1450, 1346, and 1186 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.45 (s, 1H, NH), 9.88 (brs, 1H, NH), 8.13–8.17 (m, 1H, aromatic $C_4$-H), 8.09 (brs, 1H, aromatic $C_2$-H), 7.63–7.70 (m, 2H, aromatic $C_5$-, $C_6$-H), 5.44 (d, $J$ = 3.9 Hz, 1H, $C_4$-H), 2.37 (s, 3H, —COOMe), 2.28 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 195.1 (C=O), 175.0 (C=S), 148.4 (aromatic $C_3$), 146.1 ($C_6$), 145.4 (aromatic $C_6$), 133.5 (aromatic $C_1$), 130.8 (aromatic $C_5$), 123.1 (aromatic $C_2$), 121.7 (aromatic $C_4$), 110.8 ($C_5$), 53.4 ($C_4$), 31.2 ($CO\mathit{CH_3}$), 18.9 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{13}H_{13}N_3O_3S$: C: 53.60, H: 4.50, N: 14.42. Found: C: 53.51, H: 4.54, N:14.39%.

***5-Acetyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 20).*** Yellowish-white solid; M.p. 228–230°C (EtOH). IR (KBr):3485, 3255, 3194, 1589, 1518, 1458, 1193, and 796 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.20 (s, 1H, NH), 9.65 (brs, 1H, NH), 9.05 (s, 1H, OH), 6.85 (d, $J$ = 1.8 Hz, 1H, aromatic $C_2$-H), 6.72 (d, $J$ = 7.8 Hz, 1H, aromatic $C_5$-H), 6.58 (dd, $J$ = 8.1, 1.8 Hz, 1H, aromatic $C_6$-H), 5.20 (d, $J$ = 3.6 Hz, 1H, $C_4$-H), 3.74 (s, 3H, aromatic —OMe), 2.32 (s, 3H, —$COCH_3$), 2.11 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 195.6 (C=O), 174.2 (C=S), 148.0 (aromatic $C_3$), 146.7 (aromatic $C_4$), 144.6 ($C_6$), 134.3 (aromatic $C_1$), 119.2 (aromatic $C_6$), 115.9 (aromatic $C_5$), 111.8 (aromatic $C_2$), 110.6 ($C_5$), 56.1 ($OCH_3$), 54.2 ($C_4$), 30.6 ($COCH_3$), 18.6 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{14}H_{16}N_2O_3S$: C: 57.52, H: 5.52, N: 9.58. Found: C: 57.39, H: 5.65, N: 9.47%.

***1,3,6-Trimethyl-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5 carboxylic acid methyl ester (Table 4, entry 1).*** Light yellow solid; M.p. 68–70°C (ethylacetate + petroleum ether). IR (KBr): 2949, 1669, 1506, 1431, and 1353 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.13 (td, $J$ = 8.4 Hz and 3 Hz, 2H, $C_2$-H, $C_6$-H), 6.81 (td, $J$ = 8.7 Hz and 3 Hz, 2H, $C_3$-H, $C_5$-H), 5.17 (s, 1H, $C_4$-H), 3.77 (s, 3H, –$OCH_3$), 3.67 (s, 3H, —$COOCH_3$), 3.28 (s, 3H, $N_1$-$CH_3$), 2.89 (s, 3H, $N_3$-$CH_3$), 2.47 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.4 (—$\mathit{C}OOCH_3$), 159.2 ($C_2$=O), 153.8 (aromatic-$C_4$), 149.1 ($C_1$), 133.9 (vinylic $C_6$), 127.7 (2C, $C_2$ + $C_3$), 114.0 (2C, $C_3$ + $C_5$), 103.7 (vinylic $C_5$), 60.2 ($C_4$), 55.2 (—$OCH_3$), 51.2 (—$COO\mathit{CH_3}$), 34.3 ($N_1$-$CH_3$), 31.0 ($N_3$-$CH_3$), 16.6 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{16}H_{20}N_2O_4$; C: 63.15, H: 6.62, N: 9.20. Found: C: 63.04, H: 6.77, N: 9.45%.

***1,3,6-Trimethyl-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 2).*** Off-white solid; M.p.184–186°C (ethylacetate + petroleum ether). IR (KBr): 3209, 2373, 1704, 1641, and 1449 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.02 (d, $J$ = 8.7 Hz, 2H, $C_2$-H, $C_6$-H), 6.68 (d, $J$ = 8.4 Hz, 2H, $C_3$-H, $C_5$-H), 5.16 (s, 1H, $C_4$-H), 4.13 (dq, $J$ = 7.8 Hz and 2.4 Hz, 2H, —$OCH_2CH_3$), 3.27 (s, 3H, $N_1$-$CH_3$), 2.91 (s, 3H, $N_3$-$CH_3$), 2.47 (s, 3H, $C_6$-$CH_3$), 1.73 (brs, 1H, OH), 1.22 (t, J = 7.2 Hz, 3H, —$OCH_2\mathit{CH_3}$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.1 (—$\mathit{C}OOCH_3$), 156.1 ($C_2$=O), 154.2 (aromatic $C_4$), 148.6 ($C_1$), 132.4 (vinylic $C_6$), 127.9 (2C, $C_2$ + $C_6$), 115.5 (2C, $C_3$ + $C_5$), 104.3 (vinylic $C_5$), 60.4 ($C_4$), 60.3 (—$OCH_2$), 34.5 ($N_1$-$CH_3$), 31.1 ($N_3$-$CH_3$), 16.6 ($C_6$-$CH_3$), 14.2 (—$OCH_2\mathit{CH_3}$). *Anal.* calcd. for $C_{16}H_{20}N_2O_4$; C: 63.15, H: 6.62, N: 9.20. Found: C: 63.03, H: 6.88, N: 9.37%.

***1,3,6-Trimethyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 3).*** Off-white solid; M.p. 86–88°C (ethylacetate + petroleum ether). IR (KBr): 2927, 1660, 1604, 1464, 1434, and 1268 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.06 (d, $J$ = 8.4 Hz, 2H, $C_2$-H, $C_6$-H), 6.96 (d, $J$ = 8.4 Hz, 2H, $C_3$-H, $C_5$-H), 5.03 (s, 1H, $C_4$-H), 3.48 (s, 3H, —$OCH_3$), 3.06 (s, 3H, $N_1$-$CH_3$), 2.71 (s, 3H, $N_3$-$CH_3$), 2.28 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.0 (—$\mathit{C}OOCH_3$), 153.4 ($C_2$=O), 149.6 ($C_4$), 139.3 (vinylic $C_6$), 133.4 (aromatic $C_1$), 128.6 (2C, $C_2$ + $C_6$), 127.7 (2C, $C_3$ + $C_5$), 102.8 (vinylic $C_5$), 60.0 ($C_4$), 51.1 (—$OCH_3$), 34.3 ($N_1$-$CH_3$), 30.9 ($N_3$-$CH_3$), 16.5 ($C_6$-$CH_3$).

*Anal.* calcd. for $C_{15}H_{17}N_2O_3Cl$; C:58.35, H: 5.55, N: 9.07. Found: C: 58.13, H: 5.83, N: 9.27%.

***1,3,6-Trimethyl-4-(3, 4-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 4).*** Light brown sticky liquid; IR (KBr): 3499, 2935, 1670, 1511 1031, and 753 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 6.77–6.71 (m, 3H, $C_2$-H, $C_5$-H, $C_6$-H), 5.16 (s, 1H,$C_4$-H), 4.13 (q, $J = 7.2$ Hz, 2H, —$OCH_2$), 3.82 (s, 3H, —$OCH_3$), 3.81 (s, 3H —$OCH_3$), 3.23 (s, 3H, $N_1$-$CH_3$), 2.90 (s, 3H, $N_3$-$CH_3$), 2.44 (s, 3H, $C_6$-$CH_3$), 1.24 (t, $J = 7.2$ Hz, 3H, —$CH_2CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.0 (—*C*$OOCH_2CH_3$), 153.8 ($C_2$=O), 148.9, 148.8, 148.6 (3C, aromatic $C_4$, $C_3$, $C_1$), 133.6 (vinylic $C_6$), 118.6 ($C_6$), 111.9 ($C_2$), 109.9 ($C_5$), 103.9 (vinylic $C_5$), 60.4 ($C_4$), 60.1 (—$OCH_2$), 55.8 (—$OCH_3$), 55.7 (—$OCH_3$), 34.3 ($N_1$-$CH_3$), 30.9 ($N_3$-$CH_3$), 16.5 ($C_6$-$CH_3$), 14.2 (—$OCH_2$*C*$H_3$). *Anal.* calcd. for $C_{18}H_{24}N_2O_5$; C: 62.05, H: 6.94, N: 8.04, O: 22.96%. Found: C: 62.13, H: 6.73, N: 8.27%.

***1,3,6-Trimethyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 5).*** Light brown sticky liquid; IR (KBr): 2944, 1670, 1618, 1534, and 1202 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.44 (dd, $J = 9$ Hz and 0.9 Hz, 1H, $C_3$-H), 7.31–7.23 (m, 2H, aromatic $C_4$ and $C_6$H), 7.13 (dt, $J = 7.4$ Hz and 2.4 Hz, 1H, $C_5$H), 5.71 (s, 1H, $C_4$-H), 3.24 (s, 3H, $N_1$-$CH_3$), 3.08 (s, 3H, —$OCH_3$), 2.74 (s, 3H, $N_3$-$CH_3$), 2.26 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 165.3 (—*C*$OOCH_3$), 152.8 ($C_2$=O), 150.4 ($C_2$), 148.8 ($C_1$) 137.0 (vinylic $C_6$), 133.2 ($C_5$), 128.7 (aromatic-$C_4$+$C_6$), 123.4 ($C_3$), 102.1 (vinylic $C_5$), 54.6 ($C_4$), 51.0 (—$OCH_3$), 33.7 ($N_1$-$CH_3$), 30.8 ($N_3$-$CH_3$), 16.3 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{15}H_{17}N_3O_5$; C: 56.42, H: 5.37, N: 13.16, O: 25.05%. Found: C: 56.33, H: 5.43, N: 13.27%.

***1,3,6-Trimethyl-4-(2,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 6).*** White solid; M.p. 100–102°C (ethylacetate + petroleum ether). IR (KBr): 2940, 2845, 1659, and 1434 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 6.76 (d, $J = 8.7$ Hz, 1H, $C_3$-H), 6.70 (dd, $J = 9$ Hz and 2.7 Hz, 1H, aromatic $C_4$-H), 6.67 (d, $J = 2.7$ Hz, 1H, $C_6$-H), 5.55 (s, 1H, $C_4$-H), 3.73, 3.68 (2S, 6H, 2—$OCH_3$), 3.57 (S, 3H, $N_1$-$CH_3$), 3.25, 3.23 (2s, 6H, $N_3$-$CH_3$, —$OCH_3$), 2.45 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.4 (—*C*$OOCH_3$), 153.6 ($C_2$=O), 151.3 ($C_2$/$C_5$), 149.2 ($C_5$/$C_2$), 129.7 (vinylic $C_6$), 115.1 ($C_3$), 112.8 (aromatic $C_4$/$C_6$), 112.0 ($C_6$/aromatic-$C_4$), 102.1 (vinylic $C_5$), 56.2 ($C_4$), 55.5, 55.4 (2 × $OCH_3$), 50.9 (*CO*$CH_3$), 31.0 ($N_1$-$CH_3$), 30.8 ($N_3$-$CH_3$), 16.4 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{17}H_{22}N_2O_5$; C: 61.07, H: 6.63, N: 8.38, O: 23.92%. Found: C: 61.13, H: 6.53, N: 8.27%.

***1,3,6-Trimethyl-4-(2,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 7).*** White solid; M.p. 68–70°C (ethylacetate + petroleum ether). IR (KBr): 2934, 1666, and 1492 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 6.78–6.73 (m, 2H, $C_3$-H, $C_4$-H), 6.71 (d, $J = 1.2$ Hz, 1H, $C_6$-H), 5.59 (s, 1H, $C_4$-H), 4.02 (dq, $J = 7.2$ Hz, 0.9 Hz, —$OCH_2$), 3.57 (s, 3H, —$OCH_3$), 3.26 (s, 3H, $N_1$-$CH_3$), 2.84 (s, 3H, $N_3$-$CH_3$), 2.48 (s, 3H, vinylic$C_6$), 1.14(t, $J = 7.2$ Hz, 3H, —$OCH_2CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.1 (—*C*$OOCH_2CH_3$), 153.6 ($C_2$=O, $C_1$), 151.3 ($C_2$/$C_5$), 149.2 ($C_5$/$C_2$), 129.9 (vinylic $C_6$), 115.5 ($C_3$), 112.8 (aromatic-$C_4$/$C_6$), 111.6 ($C_6$/aromatic-$C_4$), 102.3 (vinylic $C_5$), 59.8 ($C_4$), 56.0 (—$OCH_3$), 55.5 (—$OCH_3$,—$OCH_2$), 33.9 ($N_1$-$CH_3$), 30.8 ($N_3$-$CH_3$), 16.4 ($C_6$-$CH_3$), 14.0 (—$OCH_2$-*C*$H_3$). *Anal.* calcd. for $C_{18}H_{24}N_2O_5$; C: 62.05, H: 6.94, N: 8.04, O: 22.96%. Found: C: 62.13, H: 6.83, N: 8.27%.

***1,3,6-Trimethyl-4-(2-chlorophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1H)-one (Table 4, entry 8).*** Brown solid; M.p. 80–82°C (ethylacetate + petroleum ether). IR (KBr): 2926, 1660, and 1610 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.38–7.33 (m, 1H, aromatic$C_4$-H), 7.31–7.22 (m, 3H, $C_3$-H, $C_5$-H, $C_6$-H), 5.78 (s, 1H, $C_4$-H), 3.30 (s, 3H, $N_1$-$CH_3$), 2.96, 2.95 (2s, 3H, $N_3$-$CH_3$), 2.49 (2s, 3H, $C_6$-$CH_3$), 2.14 (S, 3H, —*CO*$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 196.3 (—*C*$OCH_3$), 152.7 ($C_2$=O), 148.6 ($C_1$), 137.7 ($C_2$), 132.5 (vinylic $C_6$), (129.8, 129.7, 129.4) ($C_3$, aromatic $C_4$, $C_6$), 128.3 ($C_5$), 112.1 (vinylic $C_5$), 57.5 ($C_4$), 33.9 ($N_1$-$CH_3$), 30.9 ($N_3$-$CH_3$), 30.1 ($COCH_3$), 17.1 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{15}H_{17}N_2O_2Cl$; C: 61.54, H: 5.85, N: 9.57, O: 10.93, Cl: 12.11%. Found: C: 61.33, H: 5.83, N: 9.27%.

***1,3,6-Trimethyl-4-(4-nitrophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (Table 4, entry 9).*** Light brown solid; M.p. 142–144°C (ethylacetate + petroleum ether). IR (KBr): 2931, 1675, 1621, and 1518 $cm^{-1}$. $^1H$ NMR ($CDCl_3$,300 MHz) δ: 8.16 (td, $J = 8.7$ Hz and 2.4 Hz, 2H, $C_2$-H, $C_6$-H), 7.39 (td, 8.7 Hz and 1.8 Hz, 2H, $C_3$-H, $C_5$-H), 5.46 (s, 1H, $C_4$-H), 3.34 (S, 3H, $N_1$-$CH_3$), 2.99 (s, 3H, $N_3$-$CH_3$), 2.42 (s, 3H, $C_6$-$CH_3$), 2.34 (s, 3H, —$COCH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 194.8 (—*C*$OCH_3$), 153.5 ($C_2$=O), 149.0 (aromatic $C_4$), 147.6 ($C_1$/vinylic $C_6$), 147.5 (vinylic $C_6$/$C_1$), 127.3 ($C_2$, $C_6$), 124.0 ($C_3$, $C_5$), 114.2 (vinylic $C_5$), 59.9 ($C_4$), 34.8 ($N_1$-$CH_3$), 31.4 ($N_3$-$CH_3$), 31.4 (—*CO*$CH_3$), 17.9 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{15}H_{17}N_3O_4$; C: 59.40, H: 5.65, N: 13.85, O: 21.10%. Found: C: 59.53, H: 5.83, N: 13.77%.

***1,3,6-Trimethyl-4-(4-bromophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (Table 4, entry 10).*** Light brown sticky liquid; IR (KBr): 2929, 1665, 1601, and 1403 $cm^{-1}$. $^1H$ NMR ($CDCl_3$,300 MHz) δ: 7.44 (td, $J = 8.4$ Hz and 1.8 Hz, 2H, $C_2$-H, $C_6$-H), 7.09 (td, $J = 8.4$ Hz and 1.8 Hz, 2H, $C_3$-H, $C_5$-H), 5.23 (s, 1H, $C_4$-H), 3.26 (s, 3H, $N_1$-$CH_3$), 2.95 (s, 3H, $N_3$-$CH_3$), 2.42 (s, 3H, vinylic $C_6$-$CH_3$), 2.25 (s, 3H, —$COCH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 195.3 (—$COCH_3$), 153.4 ($C_2$=O), 148.3 ($C_1$), 139.1 (vinylic $C_6$), 131.9 ($C_2$, $C_6$), 128.3 ($C_3$, $C_5$), 122.0 ($C_4$), 113.8 (vinylic $C_5$), 60.5 ($C_4$), 34.5 ($N_1$-$CH_3$), 31.2 ($N_3$-$CH_3$), 30.9 (—$COCH_3$), 17.5 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{15}H_{17}N_2O_2Br$; C:53.45, H: 5.08, N: 8.31, O: 9.49, Br: 23.69%. Found: C: 53.33, H: 5.13, N: 8.27%.

***1,3,6-Trimethyl-4-(4-bromophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 11).*** Light grey sticky liquid; IR (KBr): 2949, 1672, 1633, and 1415 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.42 (d, $J = 8.4$ Hz, 2H, $C_2$-H, $C_6$-H), 7.11 (d, $J = 8.4$ Hz,2H, $C_3$-H, $C_5$-H), 5.22 (s, 1H, $C_4$-H), 3.68 (s, 3H, $N_1$-$CH_3$), 3.26 (s, 3H, $N_3$-$CH_3$), 2.91 (s, 3H, —$OCH_3$), 2.48 (s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.0 (—*C*$OOCH_3$), 153.4 ($C_2$=O), 149.6 ($C_1$), 139.8 (vinylic $C_6$), 131.6 ($C_2$, $C_6$), 128.1 ($C_3$, $C_5$), 121.5 (aromatic $C_4$), 102.7 (vinylic $C_5$), 60.1 ($C_4$), 51.1 (—$OCH_3$), 34.3 ($N_1$-$CH_3$), 30.9 ($N_3$-$CH_3$), 16.5 ($C_6$-$CH_3$). *Anal.* calcd. for $C_{15}H_{17}N_2O_3Br$; C: 51.01, H: 4.85, N: 7.93, O: 13.59, Br: 22.63%. Found: C: 51.13, H: 4.83, N: 8.17%.

***1,3,6-Trimethyl-4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 12).*** Light brown solid; M.p. 54–56°C (ethyl acetate + petroleum ether). IR (KBr): 3596, 1661, 1604, and 1464 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) δ: 7.35–7.28 (m, 2H, aromatic$C_4$-H, $C_6$-H), 7.24–7.16 (m, 2H, $C_3$-H, $C_5$-H), 5.82 (s, 1H, $C_4$-H), 3.60 (s, 3H, $N_1$-$CH_3$), 3.32, 3.31 (2s, 3H, $N_3$-$CH_3$), 2.88 (s, 3H, —$OCH_3$), 2.57, 2.56 (2s, 3H, $C_6$-$CH_3$). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 166.1

(—*C*OOCH$_3$), 152.9 (C$_2$=O), 149.9 (C$_1$), 139.0 (C$_2$) 132.0 (vinylic C$_6$), 129.4,129.2, 129.0 (C$_3$, aromatic C$_4$,C$_6$), 127.8 (C$_5$), 102.4 (vinylic C$_5$), 57.1 (C$_4$), 51.1 (—COO*C*H$_3$), 33.7 (N$_1$-CH$_3$), 30.7 (N$_3$-CH$_3$), 16.4 (C$_6$-CH$_3$). *Anal*. calcd. for $C_{15}H_{17}N_2O_3Cl$; C: 58.35, H: 5.55, N: 9.07, O: 15.55, Cl: 11.48%. Found: C: 58.23, H: 5.73, N: 9.27%.

***1,3,6-Trimethyl-4-(4-bromophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (Table 4, entry 13).*** Light yellow sticky liquid; IR (KBr): 3133, 1612, and 1400 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz) δ: 7.14 (dd, *J* = 9.3 Hz and 1.8 Hz, 2H, C$_2$-H, C$_6$-H), 6.98 (dd, *J* = 8.1 and 1.5 Hz, 2H, C$_3$-H, C$_5$-H), 5.61 (s, 1H, C$_4$-H), 3.56 (s, 3H, N$_1$-CH$_3$), 3.49 (s, 3H, N$_3$-CH$_3$), 2.41 (s, 3H, C$_6$-CH$_3$), 2.39 (s, 3H, —COCH$_3$). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ:196.3 (—*C*OCH$_3$), 179.3 (C$_2$=S), 146.4 (C$_1$), 138.2 (vinylic C$_6$), 132.0 (C$_2$, C$_6$), 127.6 (C$_3$,C$_5$), 122.0 (aromatic C$_4$), 116.3 (vinylic C$_5$), 60.6 (C$_4$), 43.1 (N$_1$-CH$_3$), 38.2 (N$_3$-CH$_3$), 31.1 (—CO*C*H$_3$), 17.9 (C$_6$-CH$_3$). *Anal*. calcd. for $C_{15}H_{17}N_2OSBr$; C: 51.00, H: 4.85, N: 7.93, O: 4.53, S: 9.08, Br: 22.62%. Found: C: 51.13, H: 4.93, N: 8.17%.

***1,3,6-Trimethyl-4-(2chlorophenyl-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (Table 4, entry 14).*** Light yellow sticky liquid; IR (KBr): 3138, 1669, 1625, and 1399 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz) δ: 7.39–7.36 (m, 1H, aromatic-C$_4$-H), 7.27–7.23 (m, 2H, C$_6$-H, C$_3$-H), 7.17–7.14 (m, 1H, C$_5$-H), 5.95 (s, 1H, C$_4$-H), 3.66 (s, 3H, N$_1$-CH$_3$), 3.50 (s, 3H, N$_3$-CH$_3$), 2.45 (C$_6$-CH$_3$), 2.24 (—COCH$_3$). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ: 196.4 (—*C*OCH$_3$), 179.1 (C$_2$=S), 145.3 (C$_1$), 136.4 (C$_2$), 132.2 (vinylic C$_6$), (130.1, 130.0, 128.8, 128.3) (C$_3$, aromatic C$_4$,C$_6$,C$_5$), 114.6 (vinylic C$_5$), 58.5 (C$_4$), 42.5 (N$_1$-CH$_3$), 38.1 (N$_3$-CH$_3$), 30.1 (—CO*C*H$_3$), 17.4 (C$_6$-CH$_3$). *Anal*. calcd. for $C_{15}H_{17}N_2OSCl$; C: 58.34, H: 5.55, N: 9.07, O: 5.18, S: 10.38, Cl: 11.48%. Found: C: 58.23, H: 5.83, N: 9.27%.

***1,3,6-Trimethyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 15).*** Off-white solid; M.p. 60–62°C (ethylacetate + petroleum ether). IR (KBr): 3500, 1670, and 1427 cm$^{-1}$. $^1$H NMR (CDCl$_3$,300 MHz) δ: 7.27 (d, *J* = 8.4 Hz, 2H, C$_2$-H, C$_6$-H), 7.16 (d, *J* = 8.4 Hz, 2H, C$_3$-H,C$_5$-H), 5.22 (s, 1H, C$_4$-H), 4.12 (q, *J* = 7.2 Hz, 2H, —OCH$_2$), 3.26 (s, 3H, N$_1$-CH$_3$), 2.89 (s, 3H, N$_3$-CH$_3$), 2.47 (s, 3H, C$_6$-CH$_3$), 1.24 (t, *J* = 7.2 Hz, 3H, —OCH$_2$C*H*$_3$). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ: 164.7 (—*C*OOCH$_2$CH$_3$), 152.6 (C$_2$=O), 148.7 (C$_1$), 138.9 (C$_4$), 132.5 (vinylic C$_6$), 127.9 (C$_2$, C$_6$), 127.3 (C$_3$,C$_5$), 102.2 (vinylic C$_5$), 59.4 (C$_4$), 59.3 (—OCH$_2$), 33.5 (N$_1$-CH$_3$), 30.1 (N$_3$-CH$_3$), 15.2 (C$_6$-CH$_3$), 13.4 (—OCH$_2$*C*H$_3$). *Anal*. calcd. for $C_{16}H_{19}N_2O_3Cl$; C: 59.54, H: 5.93, N: 8.68, O: 14.87, Cl: 10.98%. Found: C: 59.43, H: 5.83, N: 8.77%.

***1,3,6-Trimethyl-4-(3-nitrophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (Table 4, entry 16).*** Light brown liquid; IR (KBr): 3485, 1672, 1605, and 1529 cm$^{-1}$. $^1$H NMR (CDCl$_3$,300 MHz) δ: 8.14 (qd, *J* = 8.1 Hz and 1.5 Hz, 1H, C$_6$-H), 8.08 (t, *J* = 1.8 Hz, 1H, C$_2$-H), 7.58 (td, *J* = 7.5 Hz and 1.5 Hz, 1H, aromatic-C$_4$-H), 7.50 (t, *J* = 7.8 Hz, 1H, C$_5$-H), 5.41 (s, 1H,C$_4$-H), 3.31 (S, 3H, N$_1$-CH$_3$), 2.99 (s, 3H, N$_3$-CH$_3$), 2.47 (S, 3H, C$_6$-CH$_3$), 2.32 (s, 3H, —COCH$_3$). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ:194.8 (—*C*OCH$_3$), 153.2 (C$_2$=O), 149.1 (C$_4$), 148.6 (C$_1$), 142.5 (vinylic-C$_6$), 132.7 (C$_6$), 129.8 (C$_5$), 123.0 (C$_2$/aromatic C$_4$), 121.6 (aromatc C$_4$/C$_2$), 113.9 (vinylic C$_5$), 60.2 (C$_4$), 34.7 (N$_1$-CH$_3$), 31.3 (N$_3$-CH$_3$), 31.2 (C$_6$-CH$_3$), 17.8 (—CO*C*H$_3$). *Anal*. calcd. for $C_{15}H_{17}N_3O_4$; C: 59.40, H: 5.65, N: 13.85, O: 21.10%. Found: C: 59.33, H: 5.83, N: 13.77%.

***(RR/RS) 4,4-(1,3-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-one (Table 5, entry 1).*** White solid; M.p. 309–311°C (MeOH). IR (KBr): 3339, 3304, 1668, 1441, 1343, 1237, and 1091 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-*d*$_6$) δ: 9.19 (s, 2H, 2 × NH), 7.71 (s, 2H, 2 × NH), 7.25 (t, *J* = 7.8 Hz, 1H, aromatic C$_5$-H), 7.20–7.05 (m, 3H, aromatic C$_2$, C$_4$, and C$_6$-H), 5.08 (d, *J* = 3.0 Hz, 2H, 2 × C$_4$-H), 3.50 (s, 6H, 2 × OCH$_3$), 2.20 (s, 6H, 2 × C$_6$-CH$_3$). $^{13}$C NMR (75 MHz, DMSO-*d*$_6$) δ: 165.9 (2 × *C*OOMe), 152.4 (2 × C$_2$=O), 148.6 (aromatic C$_1$, C$_3$), 145.2 (2 × C$_6$), 128.7 (aromatic C$_5$), 125.4 (aromatic C$_4$, C$_6$), 124.1 (aromatic C$_2$), 99.3 (2 × C$_5$), 54.0 (2 × C$_4$), 50.9 (2 × CO*OCH*$_3$), 17.9 (2 × C$_6$-*C*H$_3$). *Anal*. calcd. for $C_{20}H_{22}N_4O_6$; C: 57.97, H: 5.35, N: 13.52. Found: C: 57.84, H: 5.45, N: 13.61%.

***(RR/RS) 4,4-(1,3-phenylene)-bis[5-ethoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-one (Table 5, entry 2).*** White solid; M.p. 296–298°C (MeOH). IR (KBr): 3361, 3237, 3114, 1700, 1643, 1457, 1226, and 1093 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-*d*$_6$) δ: 9.14 (s, 2H, 2 × NH), 7.72 (s, 2H, 2 × NH), 7.24 (t, *J* = 7.2 Hz, 1H, aromatic C$_5$-H), 7.16–7.03 (m, 3H, aromatic C$_2$, C$_4$-, and C$_6$-H), 5.06 (s, 2H, 2 × C$_4$-H), 3.92 (s, 4H, 2 × —OC*H*$_2$CH$_3$), 2.19 (s, 6H, 2 × C$_6$-CH$_3$), 1.04 (t, *J* = 6.3 Hz, 6H, 2 × —OCH$_2$*C*H$_3$). $^{13}$C NMR (75 MHz, DMSO-*d*$_6$) δ: 165.3 (2 × *C*OOMe), 152.2 (2 × CO), 148.4 (aromatic C$_1$, C$_3$), 145.2 (2 × C$_6$), 128.6 (aromatic C$_5$), 125.4 (aromatic C$_4$, C$_6$), 124.2 (aromatic C$_2$), 99.4 (2 × C$_5$), 59.3 (2 × OCH$_2$), 54.1 (2 × C$_4$), 17.8 (2 × C$_6$-*C*H$_3$), 14.2 (2 × OCH$_2$*C*H$_3$). *Anal*. calcd. for $C_{22}H_{26}N_4O_6$; C: 59.72, H: 5.92, N: 12.66. Found: C: 59.87, H: 5.85, N: 12.81%.

***(RR/RS) 4,4-(1,3-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-thione (Table 5, entry 3).*** White solid; M.p. 280–282°C (MeOH). IR (KBr):3301, 3186, 2373, 1699, 1567, 1437, 1321, 1186, and 1108 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-*d*$_6$) δ: 10.39 (s, 2H, 2 × NH), 9.60 (s, 2H, 2 × NH), 7.31 (t, *J* = 7.8 Hz, 1H, aromatic C$_5$-H), 7.11 (d, *J* = 7.8 Hz, 2H, aromatic C$_4$, C$_6$-H), 7.02 (s, 1H, aromatic C$_2$-H), 5.10 (d, *J* = 3.3 Hz, 2H, 2×C$_4$-H), 3.54 (s, 6H, 2×—OCH$_3$), 2.30 (s, 6H, 2 × -CH$_3$). $^{13}$C NMR (75 MHz, DMSO-*d*$_6$) δ: 174.4 (2 × C=S), 165.6 (2 × *C*OOMe), 145.3 (aromatic C$_1$, C$_3$), 143.9 (2 × C$_6$), 129.0 (aromatic C$_5$), 125.9 (aromatic C$_4$, C$_6$), 124.2 (aromatic C$_2$), 100.5 (2 × C$_5$), 54.0 (2 × C$_4$), 51.2 (2×CO*OMe*), 17.3 (2×C$_6$-*C*H$_3$). *Anal*. calcd. for $C_{20}H_{22}N_4O_4S_2$; C: 53.80, H: 4.97, N: 12.55. Found: C: 53.94, H: 5.15, N: 12.41%.

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## REFERENCES AND NOTES

[1] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[2] Singh, K.; Arora, D.; Singh, S. Tetrahedron Lett 2006, 47, 4205.

[3] Ranu, B.C.; Hazra, A.; Dey, S. S. Org Process Res Dev 2002, 6, 817.

[4] Kinen, C. O.; Rossi, L. I.; de Rossi, R. H. Green Chem 2009, 11, 223.

[5] Hu, E.-H,Sidler, D. R.; Dolling, U.-H. J Org Chem 1998, 63, 3454.

[6] Biginelli, P. Gazz Chim Ital 1893, 23, 360.

[7] Suzuki, I.; Suzumura, Y.; Takeda, K. Tetrahedron Lett 2006, 47, 7861.

[8] Hassani, Z.; Islami, M. R.; Kalantari, M. Bioorg Med Chem Lett 2006, 16, 4479.

[9] Polshettiwar, V.; Varma, R. S. Tetrahedron Lett 2007, 48, 7343.

[10] Mukhopadhyay, C.; Datta, A.; Banik, B. K. Heterocycles 2007, 71, 181 and references cited therein.

[11] Mukhopadhyay, C.; Datta, A. J. Heterocycl Chem 2009, 46, 91.

[12] Mukhopadhyay, C.; Tapaswi, P. K.; Butcher, R. J. Aust J Chem 2009, 62, 140.

[13] Mukhopadhyay, C.; Datta, A.; Banik, B. K. J Heteterocycl Chem 2007, 44, 979.

[14] Tu, S.-J.; Zhu, X.-T.; Fang, F.; Zhang, X.-J.; Zhu, S.-L.; Li, T.-J.; Shi, D.-Q.; Wang, X.-S.; Ji., S.-J. Chin J Chem 2005, 23, 596.

[15] Folkers, K.; Johnson, T. B. J Am Chem Soc 1933, 55, 3784.

# Preparation of *NH*-Pyrazoleacetic Acid Anilides from Trilithiated Acetoacetanilide, Select Aromatic Esters, and Hydrazine



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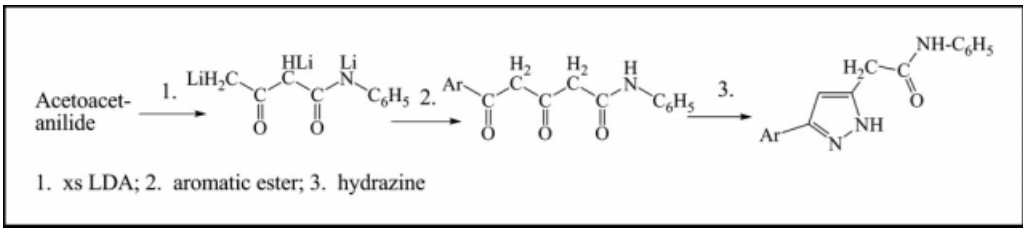


Acetoacetanilide was trilithiated with excess lithium diisopropylamide to form a reactive trianion-type intermediate. This was followed by a regioselective Claisen-type condensation of the trilithiated intermediate with a variety of aromatic esters to afford new *C*-acylated intermediates, 3,5-diketopentane-carboxanilides, that were not isolated but immediately condensed-cyclized with hydrazine to afford the *NH*-pyrazoleacetanilides, 5-aryl-1*H*-pyrazole-3-acetanilides, before these *C*-acylated intermediates had an opportunity to rearrange to anilino-pyranones, 4-anilino-6-aryl-2*H*-pyran-2-ones.

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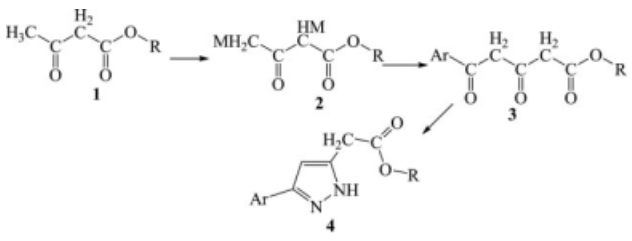
## INTRODUCTION

Pyrazoles of all substitution types continue to be prepared and studied, either as stand alone molecular systems, or as part of a fused-ring group of compounds, such as, indazoles and dihydrobenzindazoles [1]. *NH*-Pyrazole-3-acetic acids and their derivatives have received limited investigation [2], with a single recent citation dealing with the preparation of *NH*-pyrazole-3-acetanilides [3], and a single report for *NH*-pyrazole-3-acetic acid hydrazides [4]. Of the possible pyrazole substitution types, the *NH*-pyrazoles continue to receive increasing interest, especially in ligand investigations [5] (Scheme 1).

Claisen type strong base studies with β-ketoesters dianions **2** resulting from deprotonation of **1** with alkali metal amides (M = Li, Na, or K), lithium diisopropylamide (LDA), and other strong bases [6] was followed by condensation with carboxy electrophiles, usually an ester, and sometimes *N*-acylaziridines [7]. This afforded *C*-acylated products **3**, diketoesters, that could be isolated and transformed by condensation-cyclization with hydrazine into additional products, *NH*-pyrazoles **4**.

**Scheme 1.** Syntheses with dimetalated β-ketoesters.

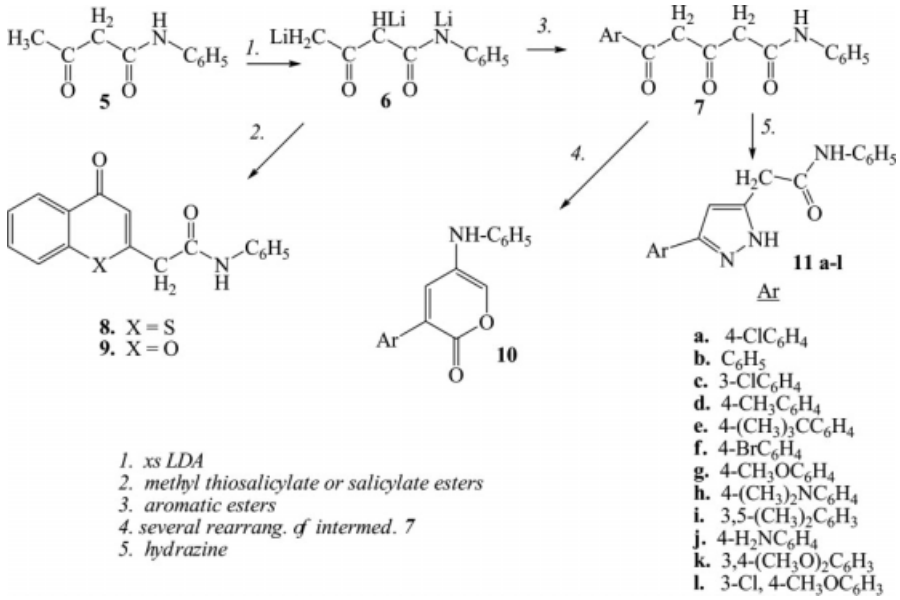


Some of the dianion-type β-ketoester systems **2** have been expanded to trianion-type β-ketoamide intermediates **6** that could be used in additional syntheses (Scheme 2). Recently, acetoacetanilide **5** has been trilithiated with excess LDA, and these intermediates **6** were regioselectively condensed at the terminal carbon atom with lithiated methyl thiosalicylate or a variety of lithiated methyl salicylates to afford *C*-acylation products **7** that were acid cyclized to 4*H*-1-benzothiopyran-4-ones (thiochromone-acetanilides) **8** [8] or 4*H*-1-benzopyran-4-ones (chromone-acetanilides) **9** [9], respectively. When the trilithiated intermediates **6** were condensed with other substituted benzoate esters, such as, methyl 4-methoxybenzoate, rearrangement products usually resulted and were identified as substituted 2-pyranones, 4-anilino-6-aryl-2*H*-pyran-2-ones **10** [10].

## RESULTS AND DISCUSSION

During this investigation, 2-[3-(phenyl or substituted phenyl)-1*H*-pyrazol-5-yl]-*N*-phenylacetamides, *NH*-pyrazole

**Scheme 2.** Syntheses with trilithiated acetoacetanilide including 5-aryl-1*H*-pyrazole-3-acetanilides **11a–l.**




acetanilides, **11a–l** were prepared by the immediate condensation-cyclization of 5-(phenyl or substituted phenyl)-3,5-dioxo-*N*-phenylpentamides, diketopentanilides **7**, (from **5** and **6**) intermediate compounds with hydrazine. Intermediate diketopentanilides **7** were prepared by modification and extension of some strong-base multiple anion procedures where trianion **6** resulted from treatment of acetoacetanilide **5** with excess LDA to **6**, and then condensed with a variety of substituted benzoate esters, that did not contain an ortho-substituted nucleophilic functional group (e.g., thiophenol).

The purification of these diketopentanilide intermediates **7** presented a good possibility of rearrangements to anilino-pyranones **10**; consequently, they were treated with excess hydrazine which resulted in the preferential condensation of a hydrazine nitrogen with one of the two carbonyl carbons of diketopentanilide intermediates **7** followed by cyclodehydration to the targeted pyrazoleacetic acid anilides **11a–l**. Anilino-pyranones **10** were not found.

The pyrazole acetanilides **11a–l** can be represented as a molecular system with numerous tautomeric forms (**I–VI**), including the keto-enol and annular tautomers with the pyrazole *N*—*H* hydrogen bonded to either of the adjacent nitrogen atoms (annular tautomers). IR carbonyl absorptions from crystalline products were noted at 1651–1676 $cm^{-1}$. Proton magnetic spectra indicated predominantly or exclusively keto tautomer, with the methylene absorptions appearing as a singlet at δ 3.44–3.78 ppm. The $C_4$—H absorptions of the pyrazole ring were noted at δ 6.31−6.69 ppm. Carbon-13 NMR spectra were indicative of structure but they were inconclusive. Even after extensive scans, the projected number of carbon absorptions were usually not obtained [3]. The C4 (CH carbon) resonance absorptions of the pyrazole ring in all cases were noted δ 101–107 ppm, which is in accord with estimates and recent experimental data reported by others [3,4]. DEPT taken after 5000 C-13 NMR scans on **11b** followed by HMQC indicated the presence of the methylene carbon absorptions at δ 35.8 ppm, which was matched with H-1 NMR methylene protons absorption at δ 3.72 ppm; the C-13 NMR absorption at δ 102.5 ppm was matched with H-1 NMR $C_4$—H of the pyrazole ring absorption at δ 6.61 ppm. Other C-13 NMR absorptions were noted for the methylene carbons from δ 32.9 to 40.2 ppm. LC-MS for all compounds, $(M+H)^+$, were also satisfactory and combustion analysis for the compounds were supportive. The single crystal X-ray analysis obtained for product **11c** indicated that a single tautomer in the keto form (**I**, Fig. 1) with a hydrogen bonded to the nitrogen adjacent to the pyrazole carbon also bonded to the methylene (C3 in the ORTEP diagram illustrated in Fig. 2) and that the pyrazole ring is nearly planar [12].

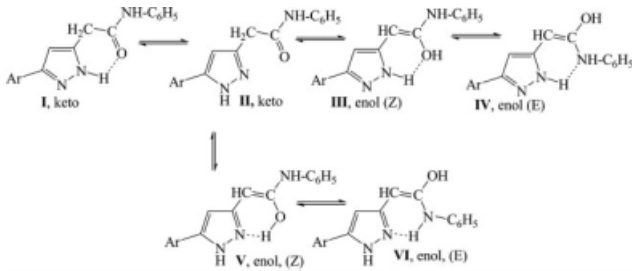



**Figure 1.** 5-Aryl-1*H*-pyrazole-3-acetanilide tautomers **I–VI**.

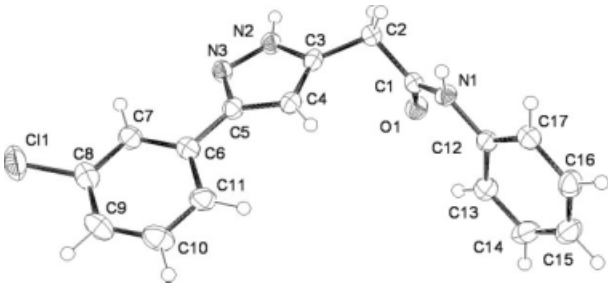



**Figure 2.** ORTEP diagram (50% ellipsoids for nonhydrogen atoms), $C_{17}H_{14}ClN_3O$ **11c** [11].

The molecular structure of **11c** is shown in Figure 2 and selected bond distances and angles are listed in Table 1. The bond lengths agree with the assignment of the double bond shown between C1 and O1 for the keto form (see ORTEP diagram for numbering of atoms).

The least squares best planes representing the rings containing C6 and C5 are nearly coplanar with an angle of 18.3° between them. There is likely some extended pi bonding between these rings. Each molecule is hydrogen bonded to four molecules: N3 to the H atom on N1, H on N2 to O1, O1 to the H atom on N2, and H on N1 to N3.

The overall yields for the two-step synthesis may not be optimal for an individual product, with the strong base reactions usually having the greatest variance. A practical side to the synthesis is the availability of starting materials, the use of less toxic acylating reagents (aromatic esters vs. acyl aziridines), a procedure that is reproducible by someone not necessarily familiar with strong base synthesis methods, and that the procedure is conducive to making targeted products which can be prepared in gram quantities after recrystallization from common solvents. Although not investigated extensively, tetramethylethylenediamine (TMEDA) did not markedly increase the overall yield, on occasion ~5% [6g]. In addition to all products targeted and prepared being new, they have the potential for use in agriculture and medicine, applications in other syntheses, and for spectral and theoretical studies.

## EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Fourier transform infrared spectra were obtained with a Mattson Genesis II FTIR with Specac Golden Gate Accessory. Proton and C-13 nuclear magnetic resonance spectra were obtained with a Varian Associates Mercury Oxford (300 MHz for H-1 and 75 MHz for C-13) nuclear magnetic resonance spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Whitehouse, NJ 08888. LCMS analyses were measured on a Thermo-Finnigan LCQ Advantage system with the Surveyor autosampler, Surveyor pump, and LCQ Advantage Max mass spectral detector using electrospray ionization; 2 mg samples were prepared in 2 mL $min^{-1}$ of acetonitrile; 10 μL injections were pumped at 1.00 mL $min^{-1}$ isocratically with 70% acetonitrile and 30% water, each buffered with 0.1% formic acid by volume; 15 min runs were reproduced in positive MS modes. Data were collected at full scan from 100 to 650 amu.

**General procedure for the preparation of 5-aryl-1*H*-pyrazole-3-acetic acid anilides (11a–l). Ratio of reagents—Acetoacetanilide:LDA:ester, 1:4:1 for 11a–g, and 1:5:1 for 11h and 11j.** In a typical reaction sequence, LDA was prepared in a round bottomed flask by the addition of 39–40 mL (50 mL for **11h** and **11j**) of 1.60*M* *n*-butyllithium (0.0630 mol/0.0788 mol for **11h** and **11j**) in hexanes (e.g., 500 mL), equipped with a nitrogen inlet tube, and a side-arm addition funnel (recommended). The flask was cooled in an ice water bath, and 6.41 g (0.0630 mol) or 8.01 g (0.0788 mol for **11h** and **11j**) of diisopropylamine (99.5%, Aldrich Chemical Co.), dissolved in 25–35 mL of dry THF was added from the addition funnel at a fast drop wise rate during a 5 min period. The solution was stirred for an additional 15–20 min, and then treated during 5 min with acetoacetanilide **6** (99.5%, Aldrich Chemical Co.),

**Table 1**

Selected bond distances (Å) and angles (°), $C_{17}H_{14}ClN_3O$ **11c.**

| | | | |
|---|---|---|---|
| C1—O1 | 1.235(4) | C1—N1—C12 | 128.5(3) |
| C1—N1 | 1.341(4) | O1—C1—N1 | 124.4(3) |
| N1—C12 | 1.420(4) | O1—C1—C2 | 120.9(3) |
| C1—C2 | 1.519(4) | N1—C1—C2 | 114.7(3) |
| C2—C3 | 1.500(4) | C3—C2—C1 | 108.7(3) |
| N2—C3 | 1.345(4) | C4—C3—C2 | 131.5(3) |
| N3—N2 | 1.353(4) | C3—C4—C5 | 105.8(3) |
| N3—C5 | 1.347(4) | N3—C5—C4 | 110.4(3) |
| C4—C5 | 1.403(4) | C5—N3—N2 | 104.7(2) |
| C3—C4 | 1.375(5) | C3—N2—N3 | 112.8(3) |
| C6—C5 | 1.473(5) | N2—C3—C2 | 122.1(3) |
| | | N2—C3—C4 | 106.4(3) |
| C11—C6—C5—C4 | −18.3(5) | C4—C3—C2—C1 | 50.5(5) |
| N1—C1—C2—C3 | −103.2(3) | C12—N1—C1—C2 | 174.5(3) |
| C1—N1—C12—C17 | 162.8(3) | | |

**Table 2**

Crystallographic data, $C_{17}H_{14}ClN_3O$ **11c**.

| | |
|---|---|
| CCDC deposit number [14] | 738,969 |
| Color/shape | Yellow/chip |
| Crystal dimensions (mm) | 0.34 × 0.14 × 0.12 |
| Formula | $C_{17}H_{14}ClN_3O$ |
| Formula mass | 311.76 |
| $T$ (K) | 163 |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| $a$ (Å) | 12.451(2) |
| $b$ (Å) | 9.642(2) |
| $c$ (Å) | 12.581(3) |
| β(°) | 104.884(7) |
| $V$ (Å$^3$) | 1459.8(5) |
| $Z$ | 4 |
| $d_{calc}$ (g cm$^{-3}$) | 1.419 |
| λ (Å) | 0.71073 |
| μ (mm$^{-1}$) | 0.267 |
| $F$(000) | 648 |
| θ range (°) | 2.70–25.15 |
| Reflections collected | 9944 |
| Miller indices | $-14 \leq h \leq 13$, $-10 \leq k \leq 11$, $-15 \leq l \leq 15$ |
| Unique reflections | 2605 |
| Unique reflections $I > 2\sigma(I)$ | 1915 |
| Max and min transmission | 1.000, 0.932 |
| Data, restraints, parameters | 2605, 0, 199 |
| Final $R$ indices $I > 2\sigma(I)$ | $R_1 = 0.0613$, $wR_2 = 0.1425$ |
| $R$ indices all data | $R_1 = 0.0883$, $wR_2 = 0.1687$ |
| Goodness of fit on $F^2$ | 1.052 |
| Largest diff peak and hole (e Å$^{-3}$) | 0.322, −0.403 |

2.65 g (0.015 mol) dissolved in 40–60 mL of THF. After 3 h, a solution of 0.0158 mol (5% molar excess) of substituted benzoate ester dissolved in 25–35 mL of THF, was added, during 5 min, to the trilithiated intermediate **7**, and the solution was stirred overnight ($N_2$) at room temperature. Finally, 100 mL of 3*M* hydrochloric acid was added all at once, followed by an additional 100 mL of reagent grade ether, and the two-phase mixture was separated, followed by extraction of the aqueous layer with ether (2 × 50 mL). The combined organic fractions were extracted with 25 mL of 5% sodium bicarbonate solution, then 25 mL water. The resulting solution was dried ($MgSO_4$), decanted, and evaporated (if rotoevap. used, temperature of water bath ~40°C). An oil usually resulted, which was taken up in 50–75 mL of methanol followed by 6 mL of hydrazine hydrate, 1 mL of acetic acid, and the solution heated under reflux for 2–4 h. The resulting solution was allowed to evaporate, and the resulting solid was recrystallized, usually from common solvents to afford products **11a–l**.

***2-[3-(4-Chlorophenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11a).*** Compound **11a** was obtained in 34% yield, mp 234–235°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-chlorobenzoate. IR: 1651, 3217, and 3332 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ 3.78 (s, 2H, $CH_2$), 6.63 (s, 1H, $C_4$—H, pyrazole), 7.05 (t, 1H, ArH, $J$ = 7.5 Hz), 7.31 (t, 2H, ArH, $J$ = 7.8 Hz), 7.45 (m, 2H, ArH), 7.63 (d, 2H, ArH, $J$ = 7.8 Hz), 7.79 (m, 2H, ArH), 10.22 (s, 1H, NH), and 12.86 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$): 31.37, 102.78 (C4, pyrazole), 119.8, 124.0, 127.4, 129.4, 139.8, 147.3, 174.1, 178.5. LCMS, theor. exact mass, 311.08: exp. $(M+H)^+$ 312.0. Anal. Calcd for $C_{17}H_{14}ClN_3O \cdot 1/8\ H_2O$ [13]: C, 65.02; H, 4.57; N, 13.38. Found: C, 64.97; H, 4.28; N, 12.98.

***2-[3-Phenyl-1H-pyrazol-5-yl]-N-phenylacetamide (11b).*** Compound **11b** was obtained in 31% yield, mp 222–224°C (methanol/benzene), from the two-step procedure for the condensation-cyclization of **6** and methyl benzoate. IR: 1668, 3195 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ 3.72 (s, 2H, $CH_2$), 6.61 (s, 1H, $C_4$—H, pyrazole), 7.04 (t, 1H, ArH, $J$ = 7.5 Hz), 7.31–7.43 (m, 5H, ArH), 7.64 (d, 2H, ArH, $J$ = 7.5 Hz), 7.76 (d, 2H, ArH, $J$ = 7.5 Hz), and 10.23 (NH). $^{13}$C NMR (DMSO-$d_6$): 35.8, 102.6 (C4, pyrazole), 119.8, 124.0, 125.7, 128.2, 129.5, 132.6, 139.9, 168.4. LCMS, theor. exact mass, 277.12: exp. $(M+H)^+$, 278.04. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.04. Found: C, 73.22; H, 5.47; N, 15.04.

***2-[3-(3-Chlorophenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11c).*** Compound **11c** was obtained in 49% yield, mp 191–194°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 3-chlorobenzoate. IR: 753, 1655, 3132, and 3194 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ 3.78 (s, 2H, $CH_2$), 6.69 (s, 1H, $C_4$—H, pyrazole), 7.06 (t, 1H, ArH, $J$ = 7.8 Hz), 7.29–7.44 (m, 4H, ArH), 7.63 (d, 2H, ArH, $J$ = 7.5 Hz), 7.76 (d, 2H, ArH, $J$ = 7.5 Hz), and 10.23 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$): 34.59, 103.5 (C4, pyrazole), 119.5, 124.7, 125.7, 127.8, 129.1, 131.7, 134.5, 139.9. LCMS, theor. exact mass, 311.08: exp. $(M+H)^+$, 312.01. Anal. Calcd for $C_{17}H_{14}\ ClN_3O \cdot 1/3\ H_2O$ [13]: C, 64.25; H, 4.65; N, 13.22. Found: C, 64.34; H, 4.84; N, 13.04.

***Single crystal X-ray structure determination.*** Yellow crystals of $C_{17}H_{14}ClN_3O$ **11c** were recrystallized from an ethanol-water solution in order to give satisfactory crystals for X-ray

determination. Crystal data for X-ray studies were collected at 20°C on a Mercury CCD area detector coupled with a Rigaku AFC8 diffractometer with graphite monochromated Mo-K radiation. Data were collected in 0.5° oscillations in ω with 40 s exposures. A sweep of data was done using ω oscillations from −40.0° to 90.0° at $\chi = 45°$ and $\phi = 0.0°$; a second sweep was performed using ω oscillations from −30.0° to 80.0° at $\chi = 45°$ and $\phi = 90.0°$. The crystal-to-detector distance was 27.7789 mm. Details of the data collection are reported in Table 2. Data were collected, processed, and corrected for Lorentz polarization and for absorption using CrystalClear (Rigaku) [15].

The nonhydrogen atoms were refined anistropically. Ideal hydrogen atom coordinates for the rings containing C6 and C12 (see numbering of atoms in ORTEP diagram, Fig. 2) were calculated and the hydrogen atoms were allowed to ride on their respective carbon atoms. The hydrogen atoms on N1, N2, C2, and C4 were located by difference and then ideal coordinates were calculated and these hydrogen atoms were allowed to ride on their respective atoms. The temperature factors of all hydrogen atoms were varied isotropically. Structure solution, refinement, and the calculation of derived results were performed using the SHELX-97 [16] package of computer programs. Neutral atom scattering factors were those of Cromer and Waber [16], and the real and imaginary anomalous dispersion corrections were those of Cromer [17].

***2-[3-(4-Methylphenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11d).*** Compound **11d** was obtained in 40% yield, mp 196–198°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-methylbenzoate. IR: 1338, 1660 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.51 (s, 2H, $CH_3$), 3.72 (s, 2H, $CH_2$), 6.56 (s, 1H, $C_4$—H, pyrazole), 7.05 (t, 1H, ArH, $J = 7.5$ Hz), 7.20–7.34 (m, 4H, ArH), 7.62–7.66 (m, 4H, ArH), 10.22 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): δ 25.79, 26.23, 39.51, 54.04, 106.98 (C4, pyrazole), 124.6, 128.7, 130.4, 134.2, 134.4, 134.8, 142.3, 144.6, 173.3. LCMS, theor. exact mass 291.14: exp. $(M+H)^+$, 292.08. Anal. Calcd for $C_{18}H_{17}N_3O \cdot 1/2\ H_2O$ [13]: C, 71.90; H, 6.04; N, 13.99. Found: C, 72.01; H, 6.26; N, 14.38.

***2-[3-(4-(1,1-Dimethylethyl)phenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11e).*** Compound **11e** was obtained in 37% yield, mp 262–265°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-(1,1-dimethylethyl)benzoate. IR: 1676, 3128 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 1.26 (s, 9H, $CH_3$), 3.44 (s, 2H, $CH_2$), 6.55 (s, 1H, $C_4$—H, pyrazole), 7.03 (t, 1H, ArH, $J = 7.5$ Hz), 7.29 (t, 2H, ArH, $J = 8.1$ Hz), 7.40 (d, 2H, ArH, $J = 8.4$ Hz), 10.20 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): 26.6, 31.8, 35.0, 102.3 (C4, pyrazole), 113.1, 119.9, 123.9, 125.5, 125.2, 126.2, 129.4, 139.9. LCMS, theor. exact mass 333.18: exp. $(M+H)^+$, 334.10. Anal. Calcd for $C_{20}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.28; H, 7.01; N, 12.54.

***2-[3-(4-Bromophenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11f).*** Compound **11f** was obtained in 19% yield, mp 246–249°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-bromobenzoate. IR: 1651, 3209 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 3.44 (s, 2H, $CH_2$), 6.54 (s, 1H, $C_4$—H, pyrazole), 7.03 (d, 1H, ArH, $J = 8.3$ Hz), 7.31 (t, 2H, ArH, $J = 5.4$ Hz), and 7.57–7.62 (m, 4H, ArH) and 10.20 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): δ 34.3, 102.6 (C4, pyrazole), 119.8, 124.0, 127.7, 129.4, 132.2, 139.0, 139.8, 142.2, 149.9, 172.2. LCMS, theor. exact mass 355.03: exp. $(M+H)^+$, 355.98. Anal. Calcd for $C_{17}H_{14}\ BrN_3O$: C, 57.32; H, 3.96; N, 11.85. Found: C, 56.94; H, 3.89; N, 11.83.

***2-[3-(4-Methoxyphenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11g).*** Compound **11g** was obtained in 40% yield, mp 201–203°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-methoxybenzoate. IR: 1660, 3283 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ $^1H$ NMR (DMSO-$d_6$): δ 3.66 (s, 2H, $CH_2$), 3.75 (s, 3H, $OCH_3$), 6.47 (s, 1H, $C_4$—H, pyrazole), 6.94–7.05 (m, 3H, ArH), 7.24–7.31 (m, 2H, ArH), 7.58–7.67 (m, 4H, ArH) and 10.16 (s, NH). $^{13}C$ NMR (DMSO-$d_6$): 36.01, 54.86, 78.36, 100.94 (C4, pyrazole), 113.8, 119.2, 123.1, 126.3, 128.4, 129.4, 138.9, 158.8, 167.8. LCMS, theor. exact mass, 307.13: exp. $(M+H)^+$, 308.06. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.11; H, 5.55; N, 13.51.

***2-[3-[4-(Dimethylamino)phenyl]-1H-pyrazol-5-yl]-N-phenylacetamide (11h).*** Compound **11h** was obtained in a 19% yield, mp 272–275°C (DMF), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-dimethylaminobenzoate. IR: 1610, 1670, 3184 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.92 (s, 6H, $CH_3$), 3.67(s, 2H, $CH_2$), 6.38 (s, 1H, $C_4$—H, pyrazole), 6.72 (d, 2H, ArH, $J = 9.0$ Hz), 7.02 (t, 1H, ArH, $J = 7.2$ Hz), 7.27 (t, 2H, $J = 7.8$ Hz, ArH), 7.55 (d, 2H, ArH, $J = 8.7$ Hz), 7.62 (d, 2H, ArH, $J = 7.5$ Hz), 8.17 (d, 2H, ArH), 10.09 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): 36.5, 44.0, 87.6, 101.0 (C4, pyrazole), 113.0, 119.8, 123.9, 126.6, 129.4, 139.2, 149.7, 139.9, 150.5. LCMS, theor. exact mass, 320.38: exp. $(M+H)^+$, 321.09. Anal. Calcd for $C_{19}H_{20}N_4O \cdot 1/4\ H_2O$ [13]: C, 70.24; H, 6.36; N, 17.34. Found: C, 70.30; H, 6.40; N, 17.49.

***2-[3-(3,5-Dimethylphenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11i).*** Compound **11i** was obtained in a 40% yield, 222–224°C (ethanol/benzene), from the two-step procedure for the condensation-cyclization of **6** and methyl 3,5-dimethylbenzoate. IR: 1660, 3238 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.29 (s, 6H, $CH_3$), 3.38 (s, 2H, $CH_2$), 6.55 (s, 1H, $C_4$—H, pyrazole), 6.92 (s, 1H, ArH), 7.05 (t, 1H, ArH, $J = 7.5$ Hz), 7.31 (t, 2H, ArH, $J = 7.5$ Hz), 7.37 (s, 1H, ArH), 7.61 (s, 2H, ArH), 7.64 (d, 2H, ArH, $J = 1.2$ Hz), 10.19 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): 21.7, 37.6, 102.5 (C4, pyrazole), 107.0, 112.7, 119.8, 123.5, 123.9, 129.4, 130.0, 138.6, 139.9, 160.8. LCMS, theor. exact mass, 305.15: exp. $(M+H)^+$, 306.17. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.34; H, 6.34; N, 13.66.

***2-[3-(4-Aminophenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11j).*** Compound **11j** was obtained in a 32% yield, 178–180°C (ethanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 4-aminobenzoate. IR: 1662, 2777, 3322 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 3.62 (s, 2H, $CH_2$), 5.32 (s, 1H, NH), 6.32 (s, 1H, $C_4$—H, pyrazole), 6.53 (s, 2H, NH), 6.58 (d, 2H, ArH, $J = 7.2$ Hz), 7.02 (t, 1H, ArH, $J = 7.5$ Hz), 7.28 (t, 2H, ArH), 7.36 (d, 2H, ArH, $J = 8.7$ Hz), 7.61 (d, 2H, ArH, $J = 7.5$ Hz), 10.18 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): 39.5, 100.8 (C4, pyrazole), 113.2, 115.1, 119.8, 120.8, 121.7, 123.9, 125.9, 126.7, 129.4, 130.1, 139.9, 168.9. LCMS, theor. exact mass, 292.34: exp. $(M+H)^+$ 293.04. Anal. Calcd for $C_{17}H_{16}N_4O \cdot 1/4\ H_2O$ [13]: C, 68.79; H, 5.60; N, 18.87. Found: C, 68.85; H, 5.49; N, 18.26.

***2-[3-(3,4-Dimethoxyphenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11k).*** Compound **11k** was obtained in a 19% yield, 198–

200°C (methanol), from the two-step procedure for the condensation-cyclization of **6** and methyl 3,4-dimethoxybenzoate. IR: 1655, 2931, 3193 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 3.68 (s, 2H, $CH_2$), 3.78 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 5.28 (s, 1H, NH), 6.35 (s, 1H, $C_4$—H, pyrazole), 6.54–6.76 (m, 3H, ArH) 6.94–7.18 (m, 3H, ArH), 7.49–7.57 (m, 3H, ArH), and 9.22 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$): 37.9, 56.2, 87.5, 102.1 (C4, pyrazole), 109.4, 112.6, 118.1, 119.8, 123.9, 129.4, 139.9, 147.9, 149.6, 168.0. LCMS, theor. exact mass, 337.37: exp. $(M+H)^+$ 338.08. Anal. Calcd for $C_{19}H_{19}N_3O_3 \cdot 1/4\ H_2O$ [13]: C, 66.75; H, 5.75; N, 12.29. Found: C, 67.11; H, 5.62; N, 12.23.

***2-[3-(3-Chloro-4-methoxyphenyl)-1H-pyrazol-5-yl]-N-phenylacetamide (11l).*** Compound **11l** was obtained in a 30% yield, 215–218°C (ethanol) from the two-step procedure for the condensation-cyclization of **6** and methyl 3-chloro-4-methoxybenzoate. IR: 1502, 1600, 1667, 2839, 3263 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 3.77 (s, 2H, $CH_2$), 3.85 (s, 3H, $CH_3O$), 5.41 (s, 1H, NH) 6.56 (s, 1H, $C_4$—H, pyrazole), 7.03 (t, 1H, ArH, $J$ = 7.2 Hz), 7.14 (d, 1H, ArH, $J$ = 8.4 Hz), 7.31 (t, 2H, ArH, $J$ = 7.5 Hz), 7.60 (d, 1H, ArH, $J$ = 1.8 Hz), 7.69 (d, 2H, ArH, $J$ = 1.8 Hz), 7.80 (s, 1H, ArH), 12.74 (s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$): 26.2, 40.2, 56.8, 103.3 (C4, pyrazole), 113.7, 119.8, 122.0, 124.0, 125.6, 126.9, 129.4, 139.8, 154.5, 167.9. LCMS, theor. exact mass, 341.09: exp. $(M+H)^+$, 342.01. Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 62.91; H, 4.79; N, 12.19.

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## REFERENCES AND NOTES

[1] (a) Elguero, J. In Comprehensive Heterocyclic Chemistry II: Pyrazoles; Katritsky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 1–7; (b) Elguero, J. In Comprehensive Heterocyclic Chemistry II: Pyrazoles; Katritsky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 8–75; (c) Elguero, J. In Comprehensive Heterocyclic Chemistry II: Pyrazoles; Katritsky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 817–932; (d) Coranago, P.; Claramunt, R. M.; Bouissane, L.; Elguero, J.; Tetrahedron 2008, 64, 3667; (e) Holzer, W.; Kautsch, C.; Laggner, C.; Claramunt, R. M.; Perez-Torallaba, M.; Alkorta, I.; Elguero, J.; Tetrahedron 2004, 60, 6791; (f) Knight, J. D.; Kramp, C. R.; Hilton, E. J.; Vella, J. H.; Grant, B. J.; Hajiaghamohseni, L. M.; Meierhoefer, M. A.; Dunn, S. P.; Walters, M. J.; Overby, J. S.; Metz, C. R.; Pennington, W. T.; VanDerveer, D. G.; Beam, C. F. Ind Eng Chem Res 2007, 46, 8959.

[2] (a) Bouveault, L.; Bongert, A.Bull Soc Chim Fr 1902, 27, 1095; (b) Claisen, L. Ber Deutschen Chem Gesellschaft 1903, 36, 3664; (c) O'Neill, D. J.; Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Zhang, H.-C.; Maryanoff, B. E.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. Bioorg Med Chem 2004, 12, 3167; (d) Jones, R. G.; Mann, M. J. J Am Chem Soc 1953, 75, 4048.

[3] (a) Sviridov, S. I.; Vasil'ev, A. A.; Shorshnev, S. V. Tetrahedron 2007, 63, 12195; (b) Their compound 2b (δ = 103.5 ppm) relative to this report made the statement that the signals of the rest of the carbon atoms were missing.

[4] Barker, J. M.; Huddleston, P. R.; Wood, M. L. J Chem Res Synop 1992, 291.

[5] Barszcz, B. Coord Chem Rev 2005, 249, 2259.

[6] (a) Huckin, S. N.; Weiler, L. Tetrahedron Lett 1972, 2405; (b) Sandifer, R. M.; Bhattacharya, A. K.; Harris, T. M. J Org Chem 1981, 46, 2260; (c) Boatman, S.; Hauser, C. R. J Org Chem 1966, 31, 1785; (d) Boatman, S.; Harris, T. M.; Hauser, C. R. J Am Chem Soc 1965, 87, 5198; (e) Hauser, C. R.; Eby, C. J. J Org Chem 1957, 22, 909; (f) Yamaguchi, M. Yuki Gosei Kagaku Kyokaishi 1987, 45, 969; (g) Narasimhan, N. S.; Ammanamanchi, R. J Org Chem 1983, 48, 3945; (h) Hauser, C. R.; Harris, T. M. J Am Chem Soc 1958, 80, 6360; (i) Miles, M. L.; Harris, T. M.; Hauser, C. R. J Org Chem 1965, 30, 1007; (j) Kirby, F. B.; Harris, T. M.; Hauser, C. R. J Org Chem 1963, 28, 2266; (k) Light, R. J.; Hauser, C. R. J Org Chem 1961, 26, 1296; (l) Light, R. J.; Hauser, C. R. J Org Chem 1960, 25, 538.

[7] (a) Schmidt, D.; Conrad, J.; Klaiber, I.; Beifuss, U. Chem Commun 2006, 4732; (b) Lygo, B. Tetrahedron 1995, 51, 12859.

[8] Angel, A. J.; Finefrock, A. E.; French, K. L.; Hurst, D. R.; Williams, A. R.; Rampey, M. E.; Studer-Martinez, S. L.; Beam, C. F. Can J Chem 1999, 77, 94.

[9] Hurst, D. R.; French, K. L.; Angel, A. J.; Williams, A. R.; Rampey, M. E.; Guion, T. S.; Chan, K. W.; Kassis, C. M.; Studer-Martinez, S. L.; Beam, C. F. J Heterocycl Chem 1998, 35, 1357.

[10] Downs, J. R.; Grant, S. P.; Townsend, J. D.; Schady, D. A.; Pastine, S. J.; Embree, M. C.; Metz, C. R.; Pennington, W. T.; Bailey Walsch, R. D.; Beam, C. F. Can J Chem, 2004, 82, 659.

[11] Farrugia, L. J Appl Crystallogr 1997, 30, 565.

[12] Ramos, M.; Alkorta, I.; Elguero, J. Tetrahedron 1997, 53, 1403.

[13] The incorporation of water and other molecules in recrystallized and pure azoles, especially pyrazoles, has been noted in many investigations. While the 8:1 ratio of water:product for **1a** is unlikely, analytical crystals of **1a** gave the combustion analysis presented. See also: ref. 1d and references cited therein.

[14] CCDC 738,969 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] (a) Rigaku Corporation. CrystalClear; Rigaku Corporation: Danvers, MA, 1999; (b) Jacobson, R. A. REQABS v 1.1; Molecular Structure Corp.: Texas, 1998.

[16] Sheldrick, G. M. SHELX-97, Crystallographic Computing System–Windows Version; University of Gottingen: Germany, 1997.

[17] International Tables for X-Ray Crystallography, Vol. IV: Tables 2.2 B and 2.3.1; Kluwer Academic Publisher: Dordrecht, 1974.

# A Simple, Mild, and Efficient Procedure for High-Yield Synthesis of Benzimidazoles Using Coppertriflate as Catalyst



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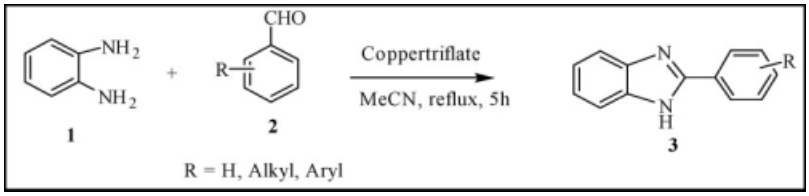


Copper triflate has been found to be an efficient catalyst for the synthesis of benzimidazoles from *o*-phenylenediamine and aldehydes at reflux temperature under acetonitrile solvent. This new method consistently has the advantage of excellent yields (74–95%) at reflux temperature.

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## INTRODUCTION

Benzimidazoles are highly biologically active compounds and exhibit antiviral, antinulcer, antihypertension, and anticancer properties [1]. Because of wide biological significance, the synthesis of these compounds has received a great deal of attention. The synthesis of benzimidazoles involves treatment of 1,2-phenylenediamines with carboxylic acids or various derivatives under strongly acidic conditions or with aldehydes followed by oxidation [2,3] for which various oxidative reagents have been used [4,5]. Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious work-up procedure. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of mild reaction conditions.

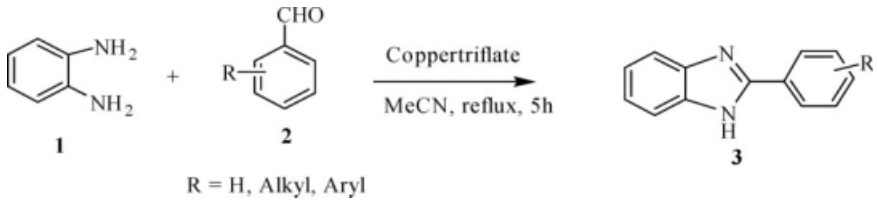
Recently, the use of copper triflate catalyst [6,7] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup. Among the various catalysts, particularly, copper triflate has advantages of low cost and ease of preparation. In view of this, we have used copper triflate as an efficient catalyst for the benzimidazole synthesis in our laboratory.

## RESULTS AND DISCUSSION

Initially, we have studied the condensation reaction of aldehyde (1.0 mmol) with 1,2-phenylenediamine (1.2 mmol) using copper triflate (1.0 mmol) under reflux temperature under acetonitrile solvent (Scheme 1). Copper triflate catalyst is acting as Lewis acid and the formation of benzimidazole may be through the following mechanism. (Scheme 2).

Encouraged by these results, we examined several aromatic aldehydes under the optimized conditions. This condensation proceeded smoothly in refluxing acetonitrile and also complete with in 5 h of reaction time. Several aldehydes (aromatic, heteroaromatic, and aliphatic) underwent the above conversion to form a series of benzimidazoles (Table 1). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well. The method is suitable for the preparation of benzimidazoles from an acid sensitive aldehyde such as furfuraldehyde (**3k**) and the sterically

**Scheme 1**



**Scheme 2.** Proposed mechanism for synthesis of benzimidazoles.

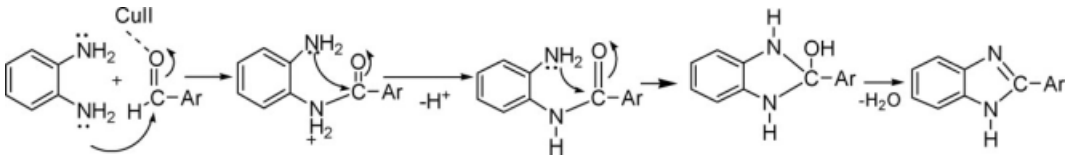
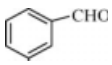
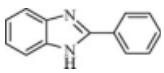
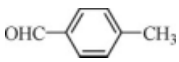
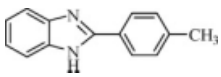
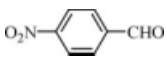
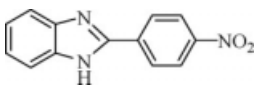
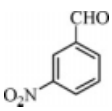
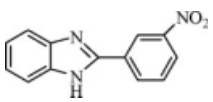
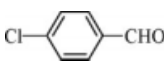
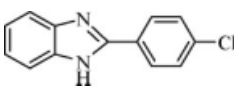
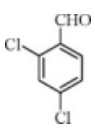
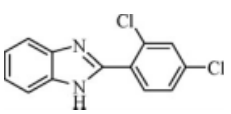
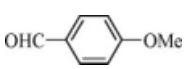
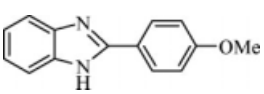
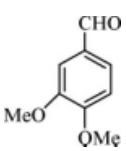
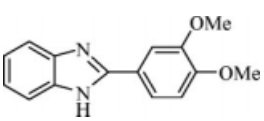
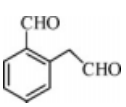
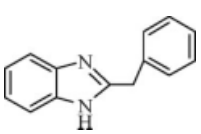
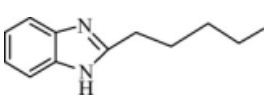
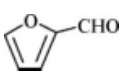
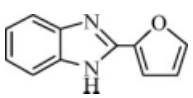
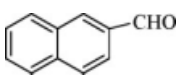
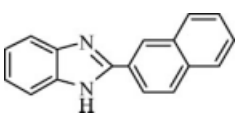


**Table 1**

Copper triflate catalyzed synthesis of benzimidazoles.

| Entry | Aldehyde | Product | Time (h) | Isolated yield (%) |
|---|---|---|---|---|
| **3a** |  |  | 3.5 | 95 |
| **3b** |  |  | 4.0 | 93 |
| **3c** |  |  | 4.0 | 93 |
| **3d** |  |  | 4.5 | 90 |
| **3e** |  |  | 4.5 | 88 |
| **3f** |  |  | 5.0 | 85 |
| **3g** |  |  | 4.5 | 88 |
| **3h** |  |  | 5.0 | 88 |
| **3i** |  |  | 5.0 | 85 |
| **3j** |  |  | 5.0 | 78 |
| **3k** |  |  | 5.0 | 75 |
| **3l** |  |  | 5.0 | 74 |

hindered aldehyde 2-naphthaldehyde (**3l**). Substituted aldehydes have been used with similar success to provide the corresponding benzimidazoles in high yields, which are also of much interest with regard to biological activity. The reaction conditions are mild and the experimental procedure is simple. The products were formed in high yields (74–95%). The structures of the products were determined from their spectral ($^1$H NMR, IR, and MS) data. Several examples illustrating this novel and general method for the synthesis of benzimidazoles are summarized in Table 1.

## CONCLUSIONS

In summary, we have developed a new methodology for the synthesis of various benzimidazoles by using 1,2-phenylenediamines and substituted aldehydes in the presence of copper triflate catalyst at reflux temperature. Thus, this method is a simple, high yielding, time saving, and the utility of copper triflate catalyst for synthesis of benzimidazoles would be precious addition to available methods.

## EXPERIMENTAL

**General procedure for the synthesis of benzimidazoles.** To a mixture of an aldehyde (0.5 mmol) and 1,2-phenylenediamine (0.6 mmol) in acetonitrile (5 mL) under a nitrogen atmosphere, coppertriflate (0.5 mmol) was added. The mixture was stirred at reflux temperature, and the reaction was monitored by TLC. After completion, the solvent was evaporated and the mixture was extracted with EtOAc (3 × 10 mL). The extract was concentrated, and the crude product was purified by silica gel column chromatography using ethyl acetate–*n*-hexane (1:9) as eluent to afford the desired product **3**. The residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain the pure benzimidazole. The spectral ($^1$H NMR, IR, and MS) data of some representative benzimidazoles are given below.

***Compound (3e).*** IR (KBr): ν 3189, 2980, 1625 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ 12.70 (1H, br s), 8.07 (2H, d, $J$ = 8.0 Hz), 7.57 (1H, m), 7.26–7.22 (3H, m), 7.19–7.06 (2H, m); FABMS: $m/z$ 231 ($^{37}$Cl $[M+H]^+$), 229 ($^{35}$Cl $[M+H]^+$); Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.27; H, 3.94; N, 12.25. Found: C, 68.42; H, 3.86; N, 12.38.

***Compound (3l).*** IR (KBr): ν 3055, 2925, 2853, 1624 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ 11.86 (1H, br s), 8.75 (1H, br s), 8.39 (1H, dd, $J$ = 8.0, 2.0 Hz), 8.02–7.90 (3H, m), 7.69–7.52 (4H, m), 7.26–7.18 (2H, m); FABMS: $m/z$ 245 $[M+H]^+$; Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.61; H, 4.92; N, 11.47. Found: C, 83.87; H, 4.88; N, 11.61.

## REFERENCES AND NOTES

[1] (a) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. J Med Chem 1994, 37, 4338; (b) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; La Voie, E. J. J Med Chem 1996, 39, 992; (c) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit R. W., Jr.; Michejda, C. J. J Med Chem 1997, 40, 4199; (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893.

[2] (a) Middleton, R. W.; Wibberley, D. G. J Heterocycl Chem 1980, 17, 1757; (b) Hisano, T.; Ichikawa, M.; Tsumoto, K.; Tasaki, M. Chem Pharm Bull 1982, 30, 2996; (c) Fairley, T. A.; Tidwell, R. R.; Donkor, I.; Naiman, N. A.; Ohemeng, K. A.; Lombardy, R. J.; Bentley, J. A.; Cory, M. J Med Chem 1993, 36, 1746; (d) Czarny, A.; Wilson, W. D.; Boykin, D. W. J Heterocycl Chem 1996, 33, 1393.

[3] (a) Stephens, F. F.; Bower, J. D. J Chem Soc 1949, 2971; (b) Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. Bull Chem Soc Jpn 1987, 60, 737; (c) Kumar, S.; Kansal, V.; Bhaduri, A. Ind J Chem 1991, 20B, 254; (d) Patzold, F.; Zeuner, F.; Heyer, T. H.; Niclas, H.-J. Syn Commun 1992, 22, 281; (e) Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. J Med Chem 1996, 39, 1452; (f) Beaulieu, P. L.; Hache, B.; Von Moos, E. Synthesis 2003, 1683.

[4] Lin, S.; Yang, L. Tetrahedron Lett 2005, 46, 4315.

[5] Das, B.; Holla, H.; Srinivas Y. Tetrahedron Lett 2007, 48, 61.

[6] Gupta, M. K. Synlett 2006, 6, 1044.

[7] Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. Tetrahedron Lett 2003, 44, 3305.

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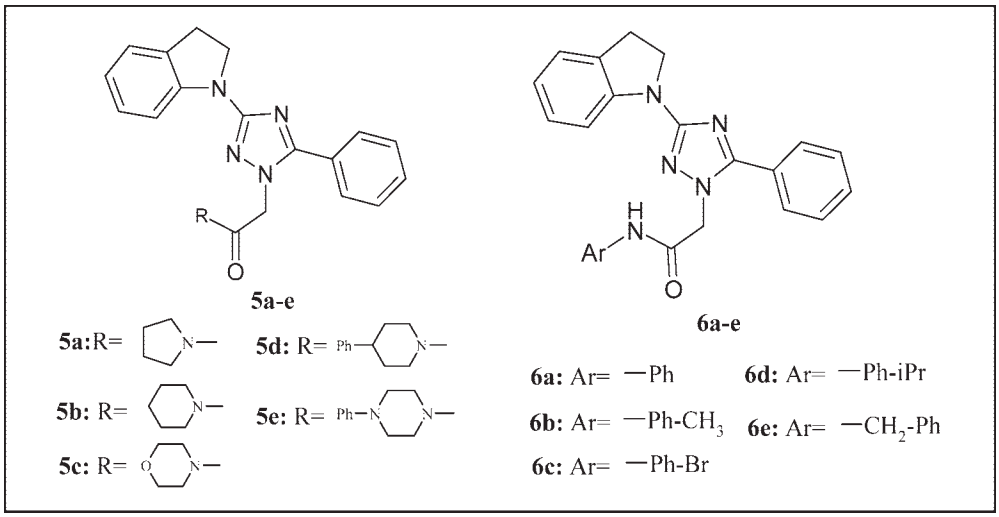


Triazole skeleton is ubiquitous in pharmaceutically important compounds. A novel series of indoline-containing triazole with different amides are described, which exhibit antibacterial and antifungal activities. The chemical synthesis strategies used, the complete characterization of the compounds, their *in vitro* screening, and the promising activity as reflected in the MIC values are reported.

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## INTRODUCTION

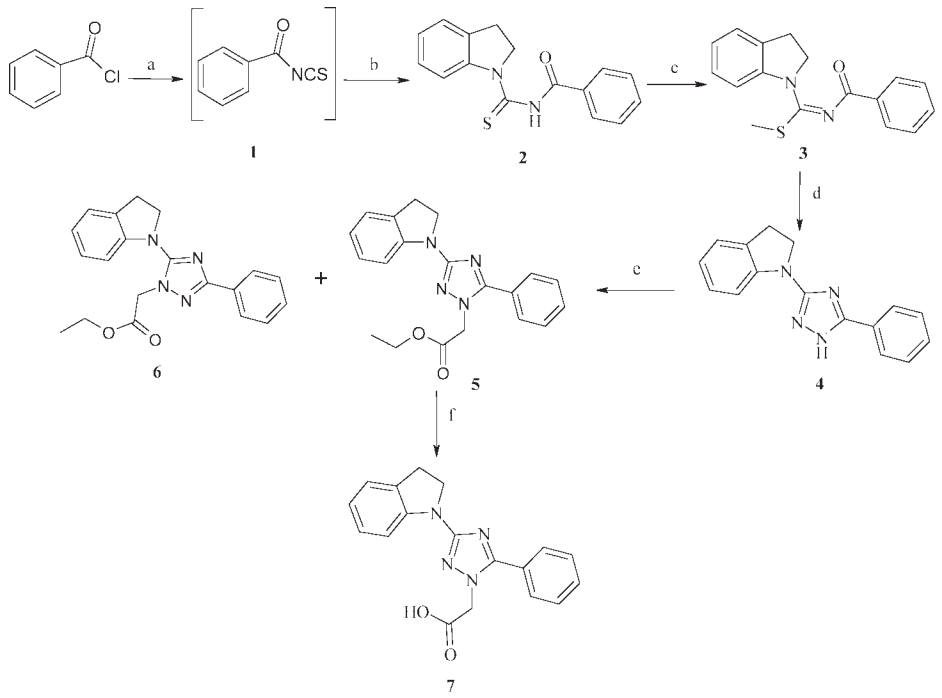
Developing new antimicrobial agents (antibacterial and antifungal) continues to attract attention and is an area of rigorous research. Although a large number of antibiotics and chemotherapeutics are available for medical use, the antimicrobial resistance created a substantial need of new class of antimicrobial agents in the last decades [1–3].

Triazole and its derivatives have distinct status as pharmaceutical agents. They have been found to have high therapeutic value as antifungal [4–6], anti-inflammatory [7], antimalarial [8], antiviral [9], antihypertensive [10], analgesic [11], antihyperuricemic [12], and anticancer agents [13,14]. Recently, synthesis of trisubstituted 1,2,4-triazole derivatives reported as a modulator of nicotinic receptor agonist [15] and antitumor and antiviral agents [16], in addition triazole derivatives revealing promising antimicrobial activities [17–23]. In continued quest of new antimicrobial agents, we designed and synthesized novel 1,2,4-triazole derivatives containing indoline ring. Structures of the products were characterized by IR, $^1$H-NMR, mass spectrometry, and elemental analysis. Results of biological activities indicate that some compounds possess potential antimicrobial activity.

## RESULTS AND DISCUSSION

**Chemistry.** The synthetic strategy involved in the synthesis of intermediate and target compounds is outlined in Schemes 1 and 2. The key intermediate [3-(2,3-dihydroindol-1-yl)-5-phenyl[1,2,4] triazol-1-yl]acetic acid **7** was prepared as outlined in Scheme 1 [24,25]. Benzoyl chloride reacted with ammonium thiocyanate to obtain benzoyl thiocyanate **1**, which was treated *in situ* with indoline to provide the addition product *N*-benzoyl thiourea **2** [26]. The addition product **2** was methylated by methyl iodide to produce *N*-benzoyl-S-methylisothiourea **3**, which was further cyclized with hydrazine hydrated in refluxing ethanol to give the triazole **4**. The triazole **4** was alkylated by ethyl bromoacetate in the presence of sodium hydride in dry THF to afford two regioisomers **5** and **6**. The isomer **5** was hydrolyzed in the presence of aqueous LiOH to give the corresponding

**Scheme 1.** Reagents and conditions: (a) ammonium thiocyanate, acetone, 56°C, 30 min; (b) indoline, acetone, 56°C, 1 h; (c) methyl iodide, $K_2CO_3$, DMF, rt, 1 h; (d) hydrazine hydrate, ethanol, reflux, 5 h; (e) ethyl bromoacetate, NaH, THF, rt, 4 h; (f) aq. $LiOH.H_2O$, THF-methanol, rt, 5 h.



acid derivative **7**, which was used as a key intermediate for the synthesis of target compounds.

The two regioisomers **5** and **6** were separated by chromatography on silica gel, and the resulting regioisomer ethyl [3-(2,3-dihydroindol-1-yl)-5-phenyl[1,2,4] triazol-1-yl]acetate **5** was the major product. The structures of these two regioisomers **5** and **6** were assigned based on NMR analysis and confirmed by NOE NMR experiments [24,27] (Fig. 1).

The synthesis of target compounds **8a–e** and **9a–e** is outlined in Scheme 2. The amide coupling of [3-(2,3-dihydroindol-1-yl)-5-phenyl[1,2,4] triazol-1-yl]acetic acid **7** was carried out with different amines, in the presence of EDCI in THF at room temperature, with excellent yield.

The structures of all the intermediates and final compounds **8a–e** and **9a–e** were found on the basis of elemental analysis and spectrographic (IR, $^1$H-NMR, and Mass) data. The physical characterization data are listed in Table 1.

**Biological activities.** The newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity against gram-negative *E. coli*, *P. aeruginosa*, gram-positive *S. aureus*, *S. pyogenes*, and antifungal activity against *C. albicans* and *A. niger* by microbroth dilution methods [28–30]. The standard strains used for screening of antibacterial and antifungal activities were procured from the Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in Table 2. The standard drug used for antibacterial activity was ciprofloxacin and nystatin for antifungal activity. Mueller Hinton broth was used as nutrient medium for bacteria and Sabouraud dextrose broth for fungal to grow. Inoculum size for test strain was adjusted to 108 CFU/mL by comparing the turbidity. Serial dilutions were prepared for primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO water at a concentration of 2.0 mg/mL. In primary screening, 500, 250, and 125 μg/mL

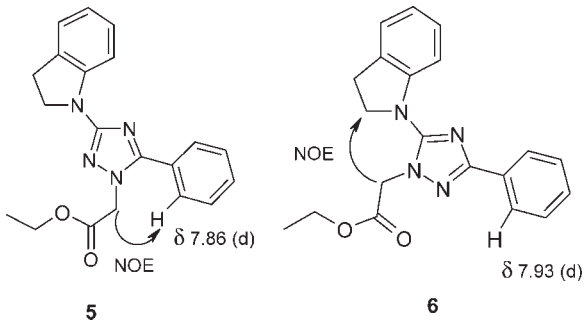
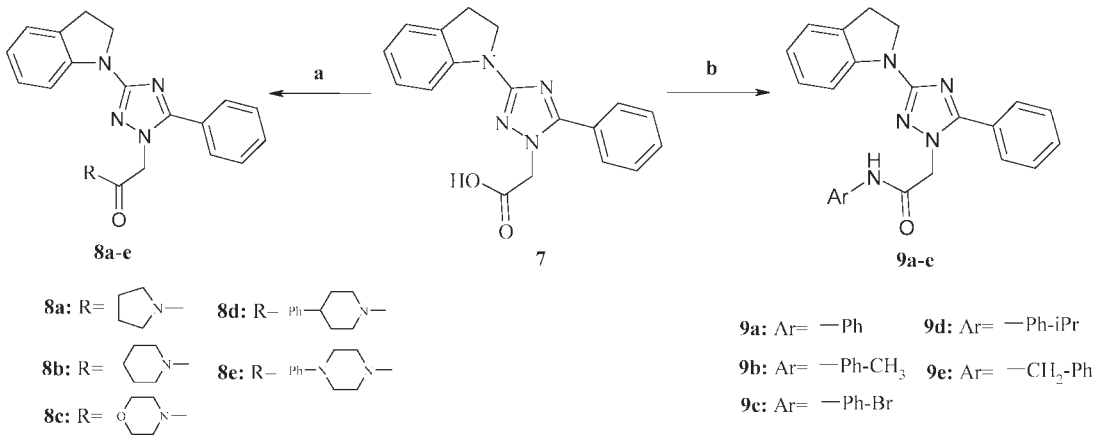



**Figure 1.** NOE was observed between 1-methylene and ortho-proton of phenyl group of compound **5** and between 1-methylene and *N*-methylene group of compound **6**. Chemical shift of ortho-hydrogen of phenyl in compound **6** was more downfield because of extra deshielding effect from the triazole ring.

**Scheme 2.** Reagents and conditions: (a) corresponding secondary cyclic amine, EDCI, DIPEA, THF, rt, 5–10 h and (b) corresponding aromatic amine, EDCI, DIPEA, THF, rt, 5–8 h.




concentrations of the synthesized drugs were taken. Data were not taken for the initial solution, because of the high DMSO concentration (10%). The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, and 6.250 μg/mL concentrations. The inoculated wells were incubated overnight at 37°C in a humid atmosphere. The highest dilution showing at least 99% inhibition zone is taken as MIC.

Results of antibacterial and antifungal activities of screened compounds indicate that some compounds possess comparable antibacterial activity with respect to reference drug ciprofloxacin. Compounds **8a–e** with secondary amide functionality exhibited moderate to excellent activity against all the tested bacterial strains, but not showed satisfactory activity against fungal strains. Compound **8a** exhibited excellent activity against *E. coli*, whereas moderate activity against *P. aeruginosa* and *S. aureus*. Compound **8b** showed very good active against *P. aeruginosa* only, whereas compound **8c** exhibited moderate activity against all the tested bacteria except *S. pyogenes*. Compound **8e** showed excellent activity against *S. aureus* and moderate activity against all the other tested bacteria. While the other series with aromatic amide functionality, compounds **9a–e**, did not show comparable inhibition with any tested bacterial and fungal organisms.

## EXPERIMENTAL

Melting points were determined with a Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PE-1600 FTIR spectrometer in KBr disc. $^1$H-NMR spectra were recorded on a Varian 400 spectrometer in DMSO-$d_6$ as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. EI-MS spectra were measured on a Waters mass spectrometer. Progress of the reaction was checked by thin layer chromatography (TLC) on silica gel-coated aluminum sheets (silica gel 60 F254) using a mixture of ethyl acetate and hexane (5:5 v/v). All of the solvents and materials were reagent grade and purified as required.

***N*-(2,3-Dihydroindole-1-carbothioyl)benzamide (2).** Benzoyl chloride was added to a stirred solution of $NH_4SCN$ (3.51 g, 0.046 mol) in acetone (30 mL), and the resultant suspension was refluxed for 30 min and then cooled to room temperature. A solution of indoline (5.0 g, 0.042 mol) in acetone (30 mL)

**Table 1**

Physical characterization data of compounds **8a–e** and **9a–e**.

| Compound | Physical state | Time (h) | Mp (°C) | Yield (%) | Molecular formula | $M_W$ |
|---|---|---|---|---|---|---|
| **8a** | Off-white crystal | 5 | 180–181 | 77 | $C_{22}H_{23}N_5O$ | 373 |
| **8b** | Off-white crystal | 5 | 178–180 | 73 | $C_{22}H_{23}N_5O_2$ | 389 |
| **8c** | White crystal | 4 | 129–131 | 69 | $C_{23}H_{25}N_5O$ | 387 |
| **8d** | Off-white crystal | 5 | 187–189 | 81 | $C_{29}H_{29}N_5O$ | 463 |
| **8e** | White crystal | 4 | 172–174 | 69 | $C_{28}H_{28}N_6O$ | 464 |
| **9a** | White crystal | 4 | 183–185 | 83 | $C_{24}H_{21}N_5O$ | 395 |
| **9b** | White crystal | 5 | 181–183 | 71 | $C_{25}H_{23}N_5O$ | 409 |
| **9c** | White crystal | 6 | 197–200 | 79 | $C_{24}H_{20}BrN_5O$ | 474 |
| **9d** | Off-white crystal | 5 | 179–181 | 73 | $C_{27}H_{27}N_5O$ | 437 |
| **9e** | White crystal | 4 | 199–201 | 81 | $C_{25}H_{23}N_5O$ | 409 |

**Table 2**

Antimicrobial activity data of newly synthesized compounds **8a–e** and **9a–e**.

| | Antibacterial MIC (μg/mL) | | | | Antifungal MIC (μg/mL) | |
|---|---|---|---|---|---|---|
| Compounds | *E.coli* MTCC 443 | *P. aeruginosa* MTCC 1688 | *S. aureus* MTCC 96 | *S. pyogenes* MTCC 442 | *C. albicans* MTCC 227 | *A. niger* MTCC 82 |
| **8a** | 50 | 100 | 125 | 500 | 1000 | 500 |
| **8b** | 125 | 62.5 | 125 | 250 | 1000 | 1000 |
| **8c** | 62.5 | 100 | 62.5 | 500 | 500 | 1000 |
| **8d** | 100 | 125 | 200 | 500 | 1000 | 500 |
| **8e** | 100 | 125 | 50 | 100 | 1000 | 1000 |
| **9a** | 250 | 500 | 500 | 500 | 500 | 1000 |
| **9b** | 500 | 500 | 250 | 500 | 1000 | 1000 |
| **9c** | 250 | 250 | 250 | 250 | 500 | 1000 |
| **9d** | 500 | 500 | 500 | 125 | 200 | 200 |
| **9e** | 500 | 500 | 500 | 500 | 200 | 200 |
| Ciprofloxacin | 25 | 25 | 50 | 50 | – | – |
| Nystatin | – | – | – | – | 100 | 100 |

was added and the mixture was refluxed for 1 h. Reaction mixture was cooled to room temperature and poured in to water, and the resulting white solid was filtered and washed with water. Solid was recrystallized in ethanol giving pure compound **3** as off-white solid. Yield 9.79 g (83.0%), m.p. 140–142°C; $^1$H-NMR (DMSO-$d_6$): δ 3.17–3.25 (t, 2H, $CH_2$, $J$ = 8.5 Hz), 4.10–4.21 (t, 2H, $CH_2$, $J$ = 8.6 Hz), 6.95–7.19 (m, 2H, ArH), 7.23–7.31 (d, 1H, ArH), 7.41–7.56 (m, 3H, ArH), 7.86–8.01 (m, 3H, ArH), 12.3 (bs, 1H, NH); ms: *m/z* 281 (M-1). Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; Found: C, 68.21; H, 4.89; N, 9.78.

***N*-[1-(2,3-Dihydroindol-1-yl)-1-methylsulfanyl-methylidene] benzamide (3).** Methyl iodide (2.38 mL, 0.038 mol) was added to a stirred suspension of compound **2** (9.0 g, 0.031 mol) and anhydrous $K_2CO_3$ (6.4 g, 0.046 mol) in DMF (50 mL) and stirred for 1 h at room temperature. Reaction mixture was poured in water (200 mL) and stirred for 15 min. The resulting off-white solid was filtered, washed with water, and dried *in vacuo*. Solid was crystallized from rectified spirit to give compound **3** as off-white solid. Yield 7.33 g (78.0%), m.p. 87–89°C; $^1$H-NMR (DMSO-$d_6$): δ 2.234 (s, 3H, $CH_3$); 3.17–3.25 (t, 2H, $CH_2$, $J$ = 8.5 Hz), 4.17–4.25 (t, 2H, $CH_2$, $J$ = 8.5 Hz), 7.02–7.20 (m, 2H, ArH), 7.28–7.32 (d, 1H, ArH), 7.43–7.58 (m, 3H, ArH), 8.02–8.09 (m, 3H, ArH); ms: *m/z* 297 (M+1). Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; Found: C, 68.77; H, 5.58; N, 9.33.

**1-(5-Phenyl-1*H*-[1,2,4]triazol-3-yl)-2,3-dihydro-1*H*-indole (4).** A solution of compound **3** (7.0 g, 0.023 mol) and hydrazine hydrate (1.78 mL, 0.035 mol) in ethanol (50 mL) was refluxed for 5 h, cooled, and poured into water (100 mL), and the mixture was stirred at room temperature. The resulting white solid was collected by filtration and washed with water to give a crude compound **3**. The solid was recrystallized in ethanol to give a pure compound **4** as white solid. Yield 4.64 g (75%), m.p. 131–133°C; $^1$H-NMR (DMSO-$d_6$): δ 3.16–3.25 (t, 2H, $CH_2$, $J$ = 8.2 Hz), 3.92–4.01 (t, 2H, $CH_2$, $J$ = 8.2 Hz), 6.72–6.81 (t, 1H, ArH), 7.13–7.21 (m, 2H, ArH), 7.49–7.53 (m, 3H, ArH), 7.69–7.73 (m, 2H, ArH), 7.81–7.86 (m, 1H, ArH), 12.9 (s, 1H, NH); ms: *m/z* 263 (M+1). Anal. Calcd. for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36; Found: C, 73.12; H, 5.51; N, 21.48.

**Ethyl[3-(2,3-dihydroindol-1-yl)-5-phenyl[1,2,4]triazol-1-yl] acetate (5) and ethyl[5-(2,3-dihydroindol-1-yl)-3-phenyl[1, 2,4]triazol-1-yl]acetate (6).** A solution of compound **4** (4.5 g, 0.017 mol) in dry THF was treated with NaH (1.0 g, 0.025 mol) at room temperature for 20 min, followed by ethyl bromoacetate (2.0 mL, 0.018 mol). The reaction mixture was stirred for 4 h at room temperature, and TLC indicated two products. The mixture was evaporated and the product was separated by chromatography on silica gel (20% EtOAc/hexane) to afford **5** and **6**.

***5*.** The major product, white solid. Yield 3.76 g (63%), m.p. 160–162°C; $^1$H-NMR (DMSO-$d_6$): δ 1.28–1.30 (t, 3H, $CH_3$, $J$ = 7.10 Hz), 3.17–3.20 (t, 2H, $CH_2$, $J$ = 8.30 Hz), 4.02–4.06 (t, 2H, $CH_2$, $J$ = 8.30 Hz), 4.11–4.13 (q, 2H, $CH_2$, $J$ = 7.11 Hz), 4.99 (s, 2H, $CH_2$), 6.77–6.81 (t, 1H, ArH), 7.11–7.15 (t, 1H, ArH), 7.17–7.19 (d, 1H, ArH), 7.55–7.57 (m, 3H, ArH), 7.70–7.73 (m, 2H, ArH), 7.84–7.86 (d, 1H, ArH); ms: *m/z* 349 (M+1). Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08; Found: C, 68.73; H, 5.93; N, 15.90.

***6*.** The minor product, white solid. Yield 0.59 g (10%), m.p. 171–163°C; $^1$H-NMR (DMSO-$d_6$): δ 1.27–1.29 (t, 3H, $CH_3$, $J$ = 7.10 Hz), 3.14–3.16 (t, 2H, $CH_2$, $J$ = 8.25 Hz), 3.28–3.34 (m, 2H, $CH_2$), 4.10–4.12 (q, 2H, $CH_2$, $J$ = 7.10 Hz), 5.05 (s, 2H, $CH_2$), 6.85–6.89 (t, 1H, ArH), 7.17–7.19 (t, 1H, ArH), 7.22–7.24 (t, 1H, ArH), 7.57–7.60 (m, 3H, ArH), 7.77–7.79 (m, 2H, ArH), 7.91–7.93 (dd, 1H, ArH); ms: *m/z* 349 (M+1). Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08; Found: C, 68.76; H, 5.87; N, 15.88.

**[3-(2,3-Dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]acetic acid (7).** A solution of compound **6** (3.70 g, 0.010 mol) in THF-MeOH (20:20 mL) was treated with LiOH.$H_2$0 (0.89 g, 0.021 mol) at room temperature for 5 h, and the mixture was evaporated *in vacuo*. Water (50 mL) was added to the residue and washed with ethyl acetate (20 mL). Aqueous layer was acidified to pH 4 by adding dil. HCl, and the resulting precipitate was filtered, washed with water, and dried *in vacuo* to give compound **7** as white solid. Yield 2.75 g (81%), m.p. 200–202°C; $^1$H-NMR (DMSO-$d_6$): δ 3.13–3.21 (t, 2H, $CH_2$, $J$ = 8.31 Hz), 4.00–4.08 (t, 2H, $CH_2$, $J$ = 8.31 Hz), 4.99 (s, 2H, $CH_2$), 6.75–6.83 (t, 1H, ArH), 7.10–7.20 (m, 2H, ArH), 7.54–7.57 (m, 3H, ArH), 7.70–7.74 (m, 2H, ArH), 7.84–7.88 (d, 1H,

ArH), 13.51 (s, 1H, COOH); ms: *m/z* 319 (M-1). Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49; Found: C, 67.57; H, 5.16; N, 17.31.

**General procedure for the synthesis of compounds 8a–e and 9a–e.** A stirred solution of compound **6** (0.625 mmol), corresponding amino derivative (0.687 mmol), and diisopropylethylamine (1.25 mmol) in anhydrous THF (10 mL) was cooled to 0°C. EDCI (0.750 mmol) was added to the above mixture, and the resulting solution was stirred at room temperature for 5–7 h. The reaction mixture was evaporated *in vacuo*, and water (50 mL) was added to the residue and acidified to pH 4 by adding dil. HCl. The solid separated was collected by filtration, washed with water, and dried. Compound was recrystallized from 95% ethanol to give pure compounds **8a–e** and **9a–e**. The yield, the reaction time, and the physical properties are reported in Table 1.

***2-[3-(2,3-Dihydro-indol-1-yl)-5-phenyl-[1,2,4]triazol-1-yl]-1-pyrrolidin-1-yl-ethanone (8a).*** IR υ ($cm^{-1}$): 1675 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 2.12–2.20 (m, 4H, $2CH_2$), 3.12–3.23 (t, 2H, $CH_2$, $J$ = 8.25 Hz), 3.41–3.63 (m, 4H, $2CH_2$), 3.91–4.00 (t, 2H, $CH_2$, $J$ = 8.25 Hz), 5.21 (s, 2H, $CH_2$), 6.78–6.80 (t, 1H, ArH), 7.13–7.19 (m, 2H, ArH), 7.52–7.55 (t, 3H, ArH), 7.66–7.80 (m, 2H, ArH), 7.85–7.90 (dd, 1H, ArH); ms: *m/z* 374 (M+1). Anal. Calcd. for $C_{22}H_{23}N_5O$: C, 70.76; H, 6.21; N, 18.75; Found: C, 70.89; H, 6.09; N, 18.84.

***2-[3-(2,3-Dihydro-indol-1-yl)-5-phenyl-[1,2,4]triazol-1-yl]-1-morpholin-4-yl-ethanone (8b).*** IR υ ($cm^{-1}$): 1678 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 3.11–3.25 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 3.45–3.68 (m, 8H, $4CH_2$), 3.99–4.05 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 5.22 (s, 2H, $CH_2$), 6.77–6.80 (t, 1H, ArH), 7.11–7.19 (m, 2H, ArH), 7.54–7.57 (t, 3H, ArH), 7.68–7.85 (m, 2H, ArH), 7.87–7.94 (dd, 1H, ArH); ms: *m/z* 390 (M+1). Anal. Calcd. for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98; Found: C, 67.91; H, 5.81; N, 17.81.

***2-[3-(2,3-Dihydro-indol-1-yl)-5-phenyl-[1,2,4]triazol-1-yl]-1-piperidin-1-yl-ethanone (8c).*** IR υ ($cm^{-1}$): 1664 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 1.62–1.71 (m, 6H, $3CH_2$), 3.13–3.24 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 3.38–3.43 (m, 4H, $2CH_2$), 3.91–3.99 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 5.20 (s, 2H, $CH_2$), 6.80–7.19 (m, 3H, ArH), 7.54–7.57 (t, 3H, ArH), 7.69–7.81 (m, 2H, ArH), 7.85–7.90 (m, 1H, ArH); ms: *m/z* 388 (M+1). Anal. Calcd. for $C_{23}H_{25}N_5O$: C, 71.29; H, 6.50; N, 18.07; Found: C, 71.42; H, 6.37; N, 18.23.

***2[3-(2,3-Dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]-1-(4-phenyl-piperidin-1-yl) ethanone (8d).*** IR υ ($cm^{-1}$): 1679 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 1.80–1.86 (m, 4H, $2CH_2$), 2.78–2.81 (m, 1H, CH), 3.13–3.24 (t, 2H, $CH_2$, $J$ = 8.25 Hz), 3.40–3.44 (m, 4H, $2CH_2$), 3.96–4.07 (t, 2H, $CH_2$, $J$ = 8.25 Hz), 5.21 (s, 2H, $CH_2$), 6.80–7.19 (m, 3H, ArH), 7.54–7.57 (t, 5H, ArH), 7.69–7.81 (m, 5H, ArH), 7.85–7.90 (m, 1H, ArH); ms: *m/z* 464 (M+1). Anal. Calcd. for $C_{29}H_{29}N_5O$: C, 75.14; H, 6.31; N, 15.11; Found: C, 75.29; H, 6.19; N, 15.23.

***2[3-(2,3-Dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]-1-(4-phenyl-piperazin-1-yl) ethanone (8e).*** IR υ ($cm^{-1}$): 1668 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 3.13–3.24 (t, 2H, $CH_2$, $J$ = 8.22 Hz), 3.40–3.44 (m, 4H, $2CH_2$), 3.61–3.64 (m, 4H, $2CH_2$), 3.96–4.07 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 5.23 (s, 2H, $CH_2$), 6.83–7.21 (m, 3H, ArH), 7.58–7.62 (t, 5H, ArH), 7.71–7.83 (m, 5H, ArH), 7.85–7.90 (m, 1H, ArH); ms: *m/z* 465 (M+1). Anal. Calcd. for $C_{28}H_{28}N_6O$: C, 72.39; H, 6.08; N, 18.09; Found: C, 72.21; H, 6.22; N, 18.21.

***2[3-(2,3-Dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]-N-phenyl-acetamide (9a).*** IR υ ($cm^{-1}$): 3415 (N—H), 1674 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 3.16–3.18 (t, 2H, $CH_2$, $J$ = 8.24 Hz), 3.97–4.12 (t, 2H, $CH_2$, $J$ = 8.22 Hz), 5.13 (s, 2H, $CH_2$), 6.78–6.86 (t, 1H, ArH), 7.08–7.18 (m, 3H, ArH), 7.32–7.41 (t, 2H, ArH), 7.55–7.60 (m, 5H, ArH), 7.81–7.97 (m, 3H, ArH), 10.56 (bs, 1H, NH); ms: *m/z* 396 (M+1). Anal. Calcd. for $C_{24}H_{21}N_5O$: C, 72.89; H, 5.35; N, 17.71; Found: C, 72.77; H, 5.43; N, 17.83.

***2[3-(2,3-Dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]-N-p-tolyl-acetamide (9b).*** IR υ ($cm^{-1}$): 3450 (N—H), 1679 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 2.41 (s, 3H, $CH_3$), 3.20–3.21 (t, 2H, $CH_2$, $J$ = 8.21 Hz), 3.89–3.93 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 5.10 (s, 2H, $CH_2$), 6.80–6.82 (m, 1H, ArH), 7.10–7.16 (m, 3H, ArH), 7.30–7.37 (m, 2H, ArH), 7.60–7.65 (m, 4H, ArH), 7.91–7.97 (m, 3H, ArH), 10.66 (bs, 1H, NH); ms: *m/z* 410 (M+1). Anal. Calcd. for $C_{25}H_{23}N_5O$: C, 73.33; H, 5.66; N, 17.10; Found: C, 73.47; H, 5.51; N, 16.91.

***N-(4-Bromo-phenyl)-2-[3-(2,3-dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]acetamide (9c).*** IR υ ($cm^{-1}$): 3446 (N—H), 1683 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 3.18–3.21 (t, 2H, $CH_2$, $J$ = 8.22 Hz), 3.96–4.10 (t, 2H, $CH_2$, $J$ = 8.21 Hz), 5.31 (s, 2H, $CH_2$), 6.78–6.86 (t, 1H, ArH), 7.12–7.16 (m, 3H, ArH), 7.55–7.60 (m, 5H, ArH), 7.81–7.97 (m, 4H, ArH), 10.86 (bs, 1H, NH); ms: *m/z* 475 (M+1). Anal. Calcd. for $C_{24}H_{20}BrN_5O$: C, 60.77; H, 4.25; N, 14.76; Found: C, 60.81; H, 4.38; N, 14.59.

***2[3-(2,3-Dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]-N-(4-isopropyl-phenyl)acetamide (9d).*** IR υ ($cm^{-1}$): 3433 (N—H), 1678 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 1.32–1.41 (d, 6H, $2CH_3$), 3.16–3.23 (m, 3H, $CH_2$ and CH), 3.93–4.02 (t, 2H, $CH_2$, $J$ = 8.22 Hz), 5.23 (s, 2H, $CH_2$), 6.86–7.16 (m, 4H, ArH), 7.55–7.60 (m, 5H, ArH), 7.81–7.97 (m, 4H, ArH), 10.71 (bs, 1H, NH); ms: *m/z* 438 (M+1). Anal. Calcd. for $C_{27}H_{27}N_5O$: C, 74.12; H, 6.22; N, 16.01; Found: C, 74.01; H, 6.37; N, 16.17.

***N-Benzyl-2-[3-(2,3-dihydro-indol-1-yl)-5-phenyl[1,2,4]triazol-1-yl]acetamide (9e).*** IR υ ($cm^{-1}$): 3411 (N—H), 1683 (C=O); $^1$H-NMR (DMSO-$d_6$): δ 3.26–3.31 (t, 2H,$CH_2$, $J$ = 8.20 Hz), 3.93–4.17 (t, 2H, $CH_2$, $J$ = 8.20 Hz), 4.56–4.61 (d, 2H, $CH_2$), 5.23 (s, 2H, $CH_2$), 6.89–7.14 (m, 4H, ArH), 7.32–7.41 (m, 5H, ArH), 7.55–7.60 (m, 3H, ArH), 7.73–7.80 (m, 2H, ArH), 9.81 (bs, 1H, NH); ms: *m/z* 410 (M+1). Anal. Calcd. for $C_{25}H_{23}N_5O$: C, 73.33; H, 5.66; N, 17.10; Found: C, 73.12; H, 5.79; N, 17.22.

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## REFERENCES AND NOTES

[1] Lee, C. Int J Antimicrob Agents 2008, 32, 197.

[2] Byarugaba, D. K. Int J Antimicrob Agents 2004, 24, 105.

[3] Kauffman, C. A.; Malani, A. N.; Easley, C.; Kirkpatrick, P. In Nature Reviews Drug Discovery; Kirkpatrick, P. C., Ed. Nature Publishing group: London, 2007; p 183.

[4] Ezabadi, I. R.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Sokovic, M.; Glamocilija, J. Bioorg Med Chem Lett 2008, 16, 1150.

[5] Liu, P.; Zhu, S.; Li, P.; Xie, W.; Jin, Y.; Sun, Q.; Wu, Q.; Sun, P.; Zhang, Y.; Yang, X.; Jiang, Y.; Zhang, D. Bioorg Med Chem Lett 2008, 18, 3261.

[6] Sun, Q. Y.; Zhang, W. N.; Xu, J. M.; Cao, Y. B.; Wu, Q. Y.; Zhang, D. Z.; Liu, C. M.; Yu, S. C.; Jiang, Y. Y. Eur J Med Chem 2007, 42, 1151.

[7] Safwat, M. R.; Nawal, A. E.; Hoda, Y.; Tarek, A. F. Archiv Der Phaemazie 2006, 339, 32.

[8] Invidiata, F. P.; Grimaudo, S.; Giammanco, P.; Giammanco, L. Farmaco 1991, 46, 1489.

[9] Kucukguzela, I.; Tatara, E.; Kucukguzela, S. G.; Rollasa, S. Eur J Med Chem 2008, 43, 381.

[10] Kakefuda, A.; Suzuki, T.; Tobe, T.; Tahara, A.; Sakamoto, S.; Tsukamoto, S. Bioorg Med Chem 2002, 10, 1905.

[11] Birsen, T.; Esra, K.; Erdem, Y.; Mevlut, E. Bioorg Med Chem 2007, 15, 1808.

[12] Takahiro, S.; Ashizawa, N.; Iwanaga, T.; Nakamura, H.; Matsumoto, K. Bioorg Med Chem Lett 209, 19, 184.

[13] Sanghvi, Y. S.; Bhattacharya, B. K.; Kini, G. D.; Matsumoto, S. S.; Larson, S. B.; Jolley, W. B.; Robins, R. K.; Revankar, G. R. J Med Chem 1990, 33, 336.

[14] Lin, R.; Connolly, P. J.; Huang, S.; Wetter, S. K.; Lu, Y.; Murray, W. V.; Emanuel, S. L.; Gruninger, R. H. J Med Chem 2005, 48, 4208.

[15] Thuring, J. W.; McDonald, G. J.; Lesage, A. S.; Zhuang, W.; De Bruyn, M. F.; Dinklo, T.; James, E. S. WO Pat. 2007, 118, 903-A1 (2007).

[16] Al-Masoudi, N. A.; Yaseen, A. S.; Al-Dweri, M. N. Farmaco 2004, 59, 775.

[17] Holla, B. S.; Rao, B. S.; Sarojini, B. K.; Akberali, P. M. Eur J Med Chem 2006, 41, 657.

[18] Holla, B. S.; Akberali, P. M.; Shivananda, M. K. Farmaco 2001, 56, 919.

[19] Hui, X. P.; Zhang, Y.; Xu, P. F.; Wang, Q.; Zhang, Z. Y. Chin J Org Chem 2005, 25, 700.

[20] Sztanke, K.; Pasternak, K.; Wojtowicz, A. S. Bioorg Med Chem 2006, 14, 3635.

[21] Colanceska, K.; Dimova, V.; Kakurinov, V.; Gabor, D. M. Molecules 2001, 6, 815.

[22] Janjic, N. P.; Acinski, M.; Janjic, N.; Lazarevic, M. J Planar Chromatogr 2000, 13, 281.

[23] Lazarevic, M.; Dimova, V.; Gabor, D. M.; Kakurinov, V. Heterocycl Commun 2001, 7, 577.

[24] Lowe, R. F.; Nelson, J.; Dang, T. N.; Crowe, P. D.; Pahuja, A.; McCarthy, J. R.; Grigoriadis, D. E.; Conlon, P.; Saunders, J.; Chen, C.; Szabo, T.; Chen, T. K.; Bozigian, H. J Med Chem 2005, 48, 1540.

[25] Whitfield, L. L.; Papadopoulos, E. P. J Hetrocycl Chem 1981, 18, 1197.

[26] Chern, J.; Hsu, T.; Kang, I.; Wang, L.; Lee, C. U.S. Pat. 2008,255,189-A1 (2008).

[27] Chen, C.; Dagnino, R.; Huang, C. Q.; McCarthy, J. R.; Grigoriadis, D. E. Bioorg Med Chem Lett 2001, 11, 3165.

[28] National Committee for Clinical Laboratory Standards. Methods for Dilution, Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard (M7A5), 5th ed.; National Committee for Clinical Laboratory Standards: Wayne, PA, 2000.

[29] Shadomy, S. In Manual of Clinical Microbiology; Albert, B., Ed.; ASM Press: Washington, 1991; p 1173.

[30] Rattan, A. Antimicrobials in Laboratory Medicine; B. I. Churchill Livingstone: India, 2000; p 85.

# Synthesis and Herbicidal Activity of *O,O*-Dialkyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-substitutedbenzyl Phosphonates

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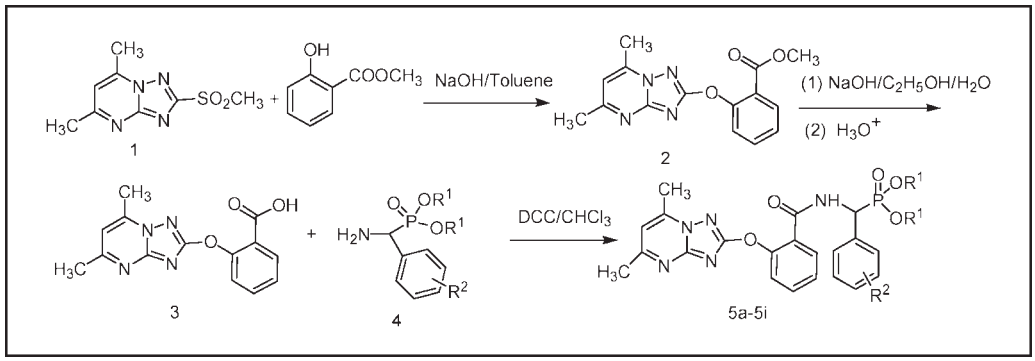


A series of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives containing an α-amino phosphonate moiety **5** were designed and synthesized by the multi-step reactions. Their structures were clearly confirmed by spectroscopic data (IR, $^{1}$H NMR, $^{31}$P NMR, MS) and elemental analysis, compound **5b** was further determined by X-ray diffraction crystallography. The results of preliminary bioassay indicated that some of the title compounds **5** possessed moderate herbicidal activities against dicotyledonous plants (*Brassica campestris L*) at the concentration of 100 mg/L. For example, compound **5i** possessed 92.0% inhibitory activity against *B. campestris L* and showed better activity than that of the commercialized herbicide Bispyribac-sodium; however, compounds **5** displayed weak herbicidal activity at the concentration of 10 mg/L.

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## INTRODUCTION

α-Amino phosphonic acid and their ester derivatives, as bioisosteres of natural amino acids, are receiving an increasing attention in medicinal chemistry and pesticide science due to their wide biological activities, such as enzyme inhibition, antibiotics, and haptens of catalytic antibodies, fungicides, herbicides, plant regulators and plant virucides [1–7]. Recently, 1,2,4-Triazolopyrimidine derivatives exhibited wide biological activities and were used as herbicides in plant protection [8–12]. A lot of triazolopyrimidine sulfonamide herbicides, such as Cloransulam-methyl, Flumetsulam, Diclosulam, Penoxsulam and Metosulam (Fig. 1), were commercialized, these herbicides acted as acetolactate synthase (ALS) inhibitors, which have been identified as a very fruitful acting target for herbicides in the last decades [13]. To find novel potent and selective herbicide lead compounds, we have designed a series of novel 1,2,4-triazolo[1, 5-a]pyrimidine derivatives containing an α-amino phosphonate moiety **5**. The target compounds **5** were evaluated for herbicidal activities in this paper. The synthetic route is listed in Scheme 1, the molecular structure of compound **5b** is shown in Figure 2. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC No. 734888 (available free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving/html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK).

## RESULTS AND DISCUSSION

**Synthesis and structure determination of title compounds 5.** 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-methylsulfone **1** were prepared using 3-amino-1,2,4-triazole-5-thiol and acetyl acetone as the starting materials, followed by S-alkylation and oxidation by $H_2O_2$ and $NaWO_4$ in good yield. 2-(5,7-Dimethyl-[1,2,4] triazolo[1,5-a]pyrimidin-2-yloxy)benzoic acid **3** was prepared by the reaction of **1** and methyl 2-hydroxybenzoate in the presence of sodium hydroxide in refluxing toluene, followed by the saponification in the presence

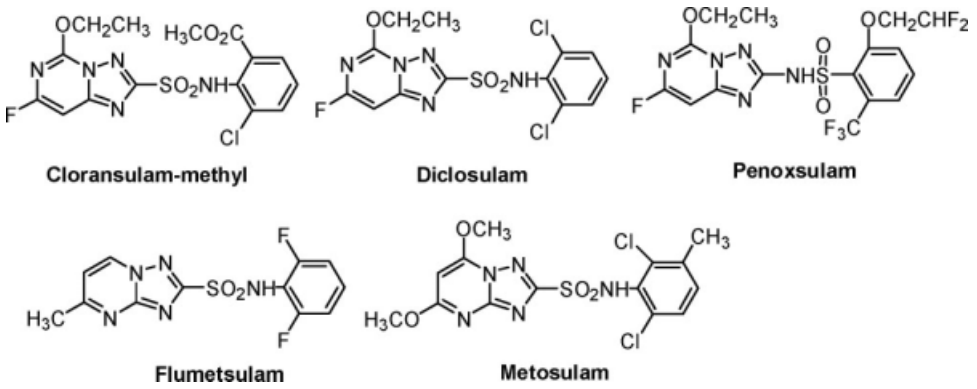



**Figure 1.** Structures of some commercial triazolopyrimidine-2-sulfonamide herbicides.

of aqueous sodium hydroxide. **3** reacted with α-amino-phosphonates **4** to generate the target compounds **5** in good yields in mild condition using dicyclohexylcarbodiimide (DCC) as the dehydration agent. The structures of target compounds **5** were characterized from their spectral data (IR, $^{1}$H NMR, $^{31}$P NMR, EI-MS) and elemental analysis, compound **5b** was further determined by single crystal X-ray diffraction analysis (see Fig. 2). In the $^{1}$H NMR spectra of **5**, the CH proton linking with the phosphonyl group displayed doublet of doublet due to coupling with P atom and NH proton with the coupling constant of 21 and 9.0 Hz, respectively. While the NH and pyrimidine protons appeared as a singlet with chemical shift atδ 6.8 and 8.0, respectively. The IR spectra of compounds **5** showed normal stretching absorption bands indicating the existence of the NH (∼3240 $cm^{-1}$), C═O (∼1660 $cm^{-1}$), P═O (∼1225 $cm^{-1}$), P─O─C (∼1025 $cm^{-1}$) moieties. The ESI-MS of compounds **5** revealed the existence of their molecular ion peaks, which were in accordance with the given structures of products **5**.

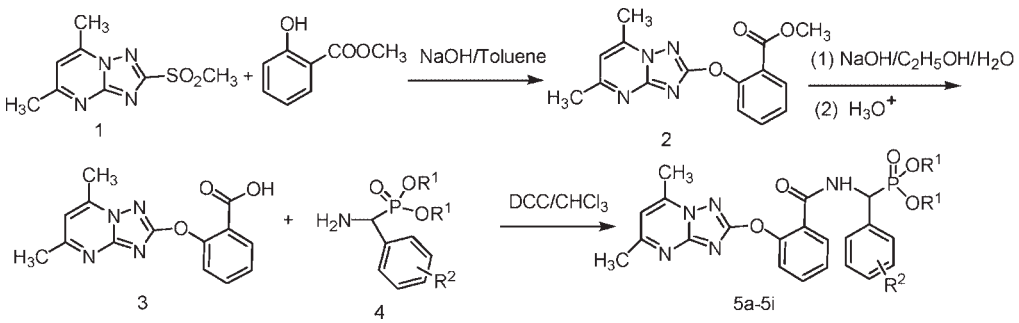
**Herbicidal activities.** The herbicidal activity values of the title compounds **5** against *Brassica campestris L* (rape) and *Echinochloa crus-galli* (barnyard grass) has been investigated at the dosages of 100 and 10 mg/L compared with the commercially available herbicide, Bispyribac-sodium according to the method described in the experimental section. The results of preliminary bioassy indicated that some of the title compounds **5** possessed moderate herbicidal activities against dicotyledonous plants (*B. campestris L*) at the concentration of 100 mg/L. For example, compound **5i** possessed 92.0% inhibitory activity against *B. campestris L* and showed better herbicidal activity than that of the commercialized herbicide Bispyribac-sodium. Futhermore, most of compounds **5** showed stronger inhibitory activity against dicotyledonous plants (*B. campestris L*) than that of monocotyledonous plants (*Radix E. crus-galli*). However, compounds **5** displayed weak herbicidal activity at the concentration of 10 mg/L. Further herbicidal evaluation (*in vivo*) and the structure–activity relationships are under investigation.

**Conclusion.** In summary, we have designed and synthesized one series of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives containing an α-amino phosphonate moiety **5**. The results of preliminary bioassy indicated that some of the title compounds **5** possessed moderate herbicidal activities against dicotyledonous plants (*B. campestris L*) at the concerntration of 100 mg/L.

## EXPERIMENTAL

The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument, Beijing,

**Scheme 1.** Synthesis of the title compounds **5**.



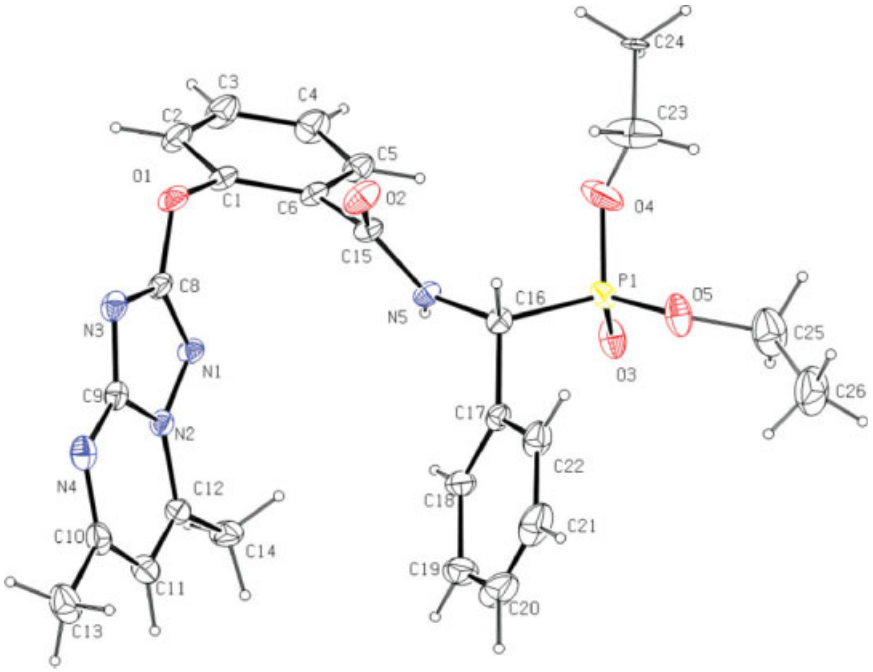



**Figure 2.** Molecular structure of compound **5b**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

China) and were uncorrected. The IR spectra were recorded on a Nicolet NEXUS470 spectrometer as KBr pellets with absorption given in $cm^{-1}$. $^1H$ and $^{31}P$ NMR spectra were performed on a Varian Mercury-PLUS400 (400 MHz) or Varian Mercury Plus-600 (600 MHz) spectrometer at room temperature in $CDCl_3$ with TMS and 85% $H_3PO_4$ as the internal and external standards, respectively. Mass spectra was measured on an Applied Biosystems API 2000 LC/MS/MS (ESI-MS) spectrometer. Elemental analysis was taken on a Elementar Vario EL III elemental analysis instrument. X-ray diffraction was carried out on a Bruker Smart 1000 CCD diffractometer (Germany). Analytical thin layer chromatography (TLC) was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were dried and redistilled before use. 5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-methylsulfone **1** were prepared by the annulation reaction of 3-amino-1,2,4-triazole-5-thiol with acetyl acetone, followed by S-alkylation and oxidation by $H_2O_2$ and $NaWO_4$ according to the reported procedure [14], yield 82%, m.p. 187–188°C. Dialkyl α-amino phosphonates **4** were prepared from aromatic aldehyde, ammonium hydroxide and dialkyl phosphites in moderate yields according to the reported synthetic protocols [15,16].

**Synthesis of methyl 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoate 2.** Methyl 2-hydroxy-benzoate (0.91 g, 6 mmol), sodium hydroxide (0.24 g, 6 mmol) and anhydrous toluene (60 mL) were stirred under reflux for 3h, while the water was removed away during the reaction time. 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-methylsulfone **1** (2.26 g, 10 mmol) was added and stirred under reflux for 10 h till the reaction completed (monitored by TLC). The solid was filtered off, and the solvent was removed under a reduced pressure, the residue was purified by column chromatography on silica gel using petroleum ether/acetone (1:1 *v*/*v*) as the eluent, giving a white solid, yield: 68%, mp: 141–142°C. Anal. Cacld for $C_{15}H_{14}N_3O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.17; H, 4.91; N, 18.55.

**Synthesis of 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoic acid 3.** Methyl 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-loxy)benzoate **2** (1.19 g, 4 mmol), sodium hydroxide (0.32 g, 8 mmol), water (10 mL) and ethanol (10 mL) were stirred at 80–90°C for 1–2 h. The solution was acidified by dilute hydrochloride, The crude product was collected by filtration, washed by ethyl ether, the product was obtained as a yellow solid, yield: 80%, mp: 103–104°C. Anal. Cacld for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.30; H, 4.19; N, 19.47.

**General synthetic procedure for *O,O*-dialkyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-substitutedbenzyl phosphonate 5.** 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoic acid **3** (0.284 g, 1.0 mmol), *O,O′*-diethyl α-amino (substituted phenyl) methylphosphonate **4** (1.0 mmol) and anhydrous chloroform (5 mL) were added to a 50 mL three-necked flask at 273 K, DCC (0.225 g, 1.1 mmol) in anhydrous chloroform (5 mL) was added dropwise slowly. The mixture was allowed to be stirred at room temperature overnight. After the solvent was removed under a reduced pressure, the residue was purified by column chromatography on silica gel using petroleum ether/acetone (1:2 *v*/*v*) as the eluent, giving the target compounds as a light yellow solid or liquid.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(*p*-tolyl) methyl phosphonate (5a).** Yellow oil, yield 68%; IR (KBr): υ 3230 (N—H), 2985 (Ph-H), 1652 (C=O), 1562, 1465, 1426 (Ph), 1248 (P=O), 1025 (P—O—C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 600 MHz): δ 1.12 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.21 (t, $J$ = 7.2

Hz, 3H, $CH_2\mathbf{CH_3}$), 2.26 (s, 3H, $CH_3$), 2.64 (s, 3H, $CH_3$), 2.67 (s, 3H, $CH_3$), 3.83–3.85 (m, 1H, $CH_2$), 3.95–3.97 (m, 1H, $CH_2$), 4.00–4.04 (m, 2H, $CH_2$), 5.67 (dd, $J$ = 9.6 Hz, $J$ = 20.1 Hz, 1H, PCH), 6.80 (s, 1H, pyrimidine-H), 7.01 (d, $J$ = 7.8 Hz, 2H, ArH), 7.28–7.37 (m, 4H, ArH), 7.49 (t, $J$ = 7.8 Hz, 1H, ArH), 7.99 (d, $J$ = 7.8 Hz, 1H, ArH), 8.09 (s, 1H, NH); ESI-MS: *m/z* 562 ($M^+$ + K-1, 5%), 546 ($M^+$ + Na-1, 23%), 523.7 ($M^+$, 100%), 267 (10%). Anal. Cacld for $C_{26}H_{30}N_5O_5P$: C, 59.65; H, 5.78; N, 13.38. Found: C, 59.47; H, 5.51; N, 13.24.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-phenylmethyl phosphonate (5b).** Yellow solid, m.p. 136–137°C, yield 69%; IR (KBr): υ 3238 (N—H), 2982 (Ph-H), 1658 (C=O), 1558, 1463, 1420 (Ph), 1252 (P=O), 1026 (P—O—C) $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.21 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.65 (s, 3H, $CH_3$), 2.69 (s, 3H, $CH_3$), 3.81–3.87 (m, 1H, $CH_2$), 3.93–4.05 (m, 3H, $2CH_2$), 5.71 (dd, $J$ = 9.6 Hz, $J$ = 20.6 Hz, 1H, PCH), 6.81 (s, 1H, pyrimidine-H), 7.18–7.25 (m, 3H, ArH), 7.27–7.43 (m, 4H, ArH), 7.50 (t, $J$ = 8.0 Hz, 1H, ArH), 8.01 (d, $J$ = 7.6 Hz, 1H, ArH), 8.15 (dd, $J$ = 4.0 Hz, $J$ = 9.0 Hz, 1H, NH); $^{31}$P NMR ($CDCl_3$, 162 MHz): δ 19.58; ESI-MS: *m/z* 547 ($M^+$ + K-1, 5%), 531.5 ($M^+$ + Na-1, 14%), 509.1 ($M^+$, 100%), 266.6 (5%). Anal. Cacld for $C_{25}H_{28}N_5O_5P$: C, 58.93; H, 5.54; N, 13.75. Found: C, 59.12; H, 5.68; N, 13.51.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(4-chlorophenyl) methyl phosphonate (5c).** yellow solid, m.p. 121–123°C, yield 75%; IR (KBr): υ 3228 (N—H), 2987 (Ph-H), 1663 (C=O), 1561, 1468, 1418 (Ph), 1246 (P=O), 1019 (P—O=C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.23 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.66 (s, 6H, $CH_3$), 3.88–4.07 (m, 4H, $2CH_2$), 5.68 (dd, $J$ = 8.0 Hz, $J$ = 20.8 Hz, 1H, PCH), 6.83 (s, 1H, pyrimidine-H), 7.15 (d, $J$ = 8.0 Hz, 2H, ArH), 7.34–7.38 (m, 4H, ArH), 7.52 (t, $J$ = 6.8 Hz, 1H, ArH), 8.00 (d, $J$ = 8.0 Hz, 1H, ArH), 8.07 (s, 1H, NH); ESI-MS: *m/z* 565.8 ($M^+$ + Na-1, 17%), 543.8 ($M^+$, 100%), 266.9 (12%). Anal. Cacld for $C_{25}H_{27}ClN_5O_5P$: C, 55.20; H, 5.00; N, 12.88. Found: C, 55.03; H, 4.87; N, 12.95.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(4-methoxyphenyl) methyl phosphonate (5d).** Yellow solid, m.p. 89–90°C, yield 67%; IR (KBr): υ 3236 (N—H), 2992 (Ph-H), 1661 (C=O), 1564, 1466, 1425 (Ph), 1242 (P=O), 1025 (P—O—C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.12 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.24 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.67 (s, 3H, $CH_3$), 2.68 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 3.86–4.05 (m, 4H, $2CH_2$), 5.68 (dd, $J$ = 9.4 Hz, $J$ = 20.8 Hz, 1H, PCH), 6.83 (s, 1H, pyrimidine-H), 7.01 (d, $J$ = 8.8 Hz, 2H, ArH), 7.27–7.37 (m, 4H, ArH), 7.51 (d, $J$ = 7.6 Hz, 1H, ArH), 7.98 (d, $J$ = 9.6 Hz, 1H, ArH), 8.10 (s, 1H, NH). Anal. Cacld for $C_{26}H_{30}N_5O_6P$: C, 57.88; H, 5.60; N, 12.98. Found: C, 58.05; H, 5.85; N, 12.81.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(2,4-dichlorophenyl) methyl phosphonate (5e).** Yellow solid, m.p. 96–97°C, yield 85%; IR (KBr): υ 3232 (N—H), 2996 (Ph-H), 1668 (C=O), 1560, 1461, 1432 (Ph), 1246 (P=O), 1028 (P—O—C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.13 (t, $J$ = 8.0 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.29 (t, $J$ = 8.0 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.66 (s, 3H, $CH_3$), 2.68 (s, 3H, $CH_3$), 3.86–3.99 (m, 2H, $CH_2$), 4.11–4.15 (m, 2H, $CH_2$), 6.18 (dd, $J$ = 8.8 Hz, $J$ = 21.0 Hz, 1H, PCH), 6.83 (s, 1H, pyrimidine-H), 7.08 (d, $J$ = 8.0 Hz, 1H, ArH), 7.29–7.39 (m, 3H, ArH), 7.46–7.53 (m, 2H, ArH), 8.02 (d, $J$ = 8.0 Hz, 1H, ArH), 8.22 (s, 1H, NH). Anal. Cacld for $C_{25}H_{26}Cl_2N_5O_5P$: C, 51.91; H, 4.53; N, 12.11. Found: C, 52.13; H, 4.27; N, 12.04.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(4-bromophenyl) methyl phosphonate (5f).** Yellow solid, m.p. 119–120°C, yield 88%; IR (KBr): υ 3235 (N—H), 2992 (Ph-H), 1672 (C=O), 1556, 1459, 1430 (Ph), 1245 (P=O), 1026 (P—O—C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.24 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.66 (s, 6H, $2CH_3$), 3.90–4.06 (m, 4H, $2CH_2$), 5.65 (dd, $J$ = 9.2 Hz, $J$ = 20.6 Hz, 1H, PCH), 6.83 (s, 1H, pyrimidine-H), 7.29–7.38 (m, 4H, ArH), 7.51 (t, $J$ = 7.6 Hz, 1H, ArH), 7.98 (d, $J$ = 8.0 Hz, 1H, ArH), 8.10 (s, 1H, NH). Anal. Cacld for $C_{25}H_{27}BrN_5O_5P$: C, 51.03; H, 4.63; N, 11.90. Found: C, 51.34; H, 4.90; N, 11.73.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(2-chlorophenyl) methyl phosphonate (5g).** white solid, m.p. 144–145°C, yield 68%; IR (KBr): υ 3417, 3236 (N—H), 2990 (Ph-H), 1665(C=O), 1626, 1557, 1479 (Ph), 1233 (P=O), 1025 (P—O—C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 600 MHz): δ 1.10 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.26 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.65 (s, 3H, $CH_3$), 270 (s, 3H, $CH_3$), 3.80–3.82 (m, 1H, $CH_2$), 3.92–3.95 (m, 1H, $CH_2$), 4.11–4.14 (m, 2H, $CH_2$), 6.26 (dd, $J$ =9.0 Hz, $J$ = 20.7 Hz, 1H, PCH), 6.81 (s, 1H, pyrimidine-H), 7.10–7.14 (m, 2H, ArH), 7.32 (d, $J$ = 10.2 Hz, 2H, ArH), 7.37 (d, $J$ = 7.8 Hz, 1H, ArH), 7.49 (d, $J$ = 7.8 Hz, 1H, ArH), 7.53 (d, $J$ = 7.2 Hz, 1H, ArH), 8.02 (d, $J$ = 8.4 Hz, 1H, ArH), 8.27 (s, 1H, NH); $^{31}$P NMR ($CDCl_3$, 243 MHz): δ 18.89; ESI-MS: *m/z* 581.6 ($M^+$ + K-1, 3%), 563.8 ($M^+$ + Na-1, 7%), 543.4 ($M^+$, 100%), 266.8 (2%). Anal. Cacld for $C_{25}H_{27}ClN_5O_5P$: C, 55.20; H, 5.00; N, 12.88. Found: C, 54.97; H, 4.73; N, 12.60.

***O,O*-Diethyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(4-fluorophenyl) methyl phosphonate (5h).** Yellow solid, m.p. 147–148°C, yield 73%; IR (KBr): υ 3241 (N—H), 2995 (Ph-H), 1662 (C=O), 1622, 1554, 1485 (Ph), 1230 (P=O), 1021 (P—O—C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 600 MHz): δ 1.14 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.22 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.65 (s, 3H, $CH_3$), 2.67 (s, 3H, $CH_3$), 3.87–3.90 (m, 1H, $CH_2$), 3.96–3.99 (m, 1H, $CH_2$), 4.00–4.06 (m, 2H, $CH_2$), 5.68 (dd, $J$ = 9.0 Hz, $J$ = 20.4 Hz, 1H, PCH), 6.81 (s, 1H, pyrimidine-H), 6.88 (t, $J$ = 9.0 Hz, 2H, ArH), 7.33–7.42 (m, 4H, ArH), 7.51 (t, $J$ = 7.2 Hz, 1H, ArH), 8.00 (d, $J$ = 8.4 Hz, 1H, ArH), 8.08 (s, 1H, NH). Anal. Cacld for $C_{25}H_{27}FN_5O_5P$: C, 56.92; H, 5.16; N, 13.28. Found: C, 57.12; H, 5.27; N, 13.65.

***O,O*-Dibutyl *N*-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-(phenyl) methyl phosphonate (5i).** Yellow oil, yield 52%; IR (KBr): υ 3236 (N—H), 2998 (Ph-H), 1654 (C=O), 1618, 1550, 1482 (Ph), 1225 (P=O), 1025 (P—O—C) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 600 MHz) δ: 0.79 (t, $J$ = 7.8 Hz, 3H, $CH_2\mathbf{CH_3}$), 0.83 (t, $J$ = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 1.20–1.53 (m, 8H, $2CH_2CH_2$), 2.68 (s, 3H, $CH_3$), 2.70 (s, 3H, $CH_3$), 3.72–3.75 (m, 1H, $CH_2$), 3.87–3.90 (m, 1H, $CH_2$), 3.93–3.99 (m, 2H, $CH_2$), 5.72 (dd, $J$ = 9.0 Hz, $J$ = 20.4 Hz, 1H, PCH), 6.80 (s, 1H, pyrimidine-H), 7.17–7.22 (m, 3H, ArH), 7.33 (t, $J$ = 7.2 Hz, 1H, ArH), 7.35 (d, $J$ = 8.0 Hz, 1H, ArH), 7.42 (d, $J$ = 7.2 Hz, 2H, ArH), 7.49 (t, $J$ = 7.2

**Table 1**

The herbicidal activities of compounds **5a–5i** (*in vitro*, relative inhibitory rate %, concentration, mg/L).

| | *Brassica campestris* root test | | *Echinochloa crusgalli* cup test | |
|---|---|---|---|---|
| Compounds | 100 | 10 | 100 | 10 |
| **5a** | 42.9 | 15.4 | 25.9 | 13.1 |
| **5b** | 52.1 | 26.6 | 30.5 | 21.0 |
| **5c** | 39.7 | 0 | 29.5 | 0 |
| **5d** | 29.0 | 19.2 | 19.5 | 11.7 |
| **5e** | 45.3 | 14.0 | 15.1 | 9.0 |
| **5f** | 33.6 | 4.7 | 14.6 | 0 |
| **5g** | 34.1 | 0 | 11.6 | 6.2 |
| **5h** | 7.0 | 0 | 20.0 | 6.2 |
| **5i** | 92.0 | 31.3 | 23.4 | 7.6 |
| Bispyribac-sodium | 69.8 | 65.6 | 72.4 | 46.9 |

Hz, 1H, ArH), 8.00 (d, $J$ = 7.2 Hz, 1H, ArH ), 8.15 (s, 1H, NH); $^{31}$P NMR ($CDCl_3$, 243 MHz): δ 19.61. Anal. Cacld for $C_{29}H_{36}N_5O_5P$: C, 61.58; H, 6.42; N, 12.38. Found: C, 61.84; H, 6.35; N, 12.07.

**Herbicidal activity (*in vitro*).** The herbicidal evaluation of compounds **5** were carried out in the laboratory of biological activities test, Nankai University, China. Compounds **5** were determined with *B. campestris L.* and *Radix E. crus-galli* as samples of annual dicotyledonous and monocotyledonous plants, respectively, using a previously reported procedure [17]. For all of the bioassay tests, each treatment was repeated two times.

***Treatment.*** The emulsions of purified compounds were prepared by dissolving them in 100 μL of *N*,*N*-dimethylformamide with the addition of 2 μL of Tween 20. The mixture of the same amount of water, *N*,*N*-dimethylformamide, and Tween 20 was used as control. The commercially available herbicide, Bispyribac-sodium was used as a compared sample to evaluate the herbicidal activity of the target compounds **5**.

**Inhibition of the root-growth of rape (*B. campestris* L.).** Rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6 cm Petri plate, to which 2 mL of inhibitor solution had been added in advance. Usually, 10 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 72 h at 28 ± 1°C. The lengths of 10 rape roots selected from each plate were measured, and the means were calculated. The percentage inhibition was used to describe the control efficiency of the compounds. The herbicidal activity was listed in Table 1.

**Inhibition of the seedling growth of barnyard grass [*Radix Echinochloa crus-galli*].** Ten *Radix E. crus-galli* seeds were placed into a 50 mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 6 mL of inhibitor solution had been added in advance. The cup was placed in a bright room, and the seeds were allowed to germinate for 72 h at 28 ± 1°C. The heights of the above-ground parts of the seedlings in each cup were measured, and the mean values were calculated. The percentage inhibition was used to describe the control efficiency of the compounds. The herbicidal activity is also listed in Table 1.

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## REFERENCES AND NOTES

[1] Kuhkar, V. P.; Hudson, H. R.; eds. Synthesis of α-aminoalkanephosphonic and α-aminophosphinic Acids; John Wiley and Sons: Chichester, UK, 2000.

[2] Palacios, F.; Alonso, C.; de los Santos, J. M. Chem Rev 2005, 105, 899.

[3] Gioia, P. L.; Chuah, P. H.; Sclapari, T. WO 2007,054,540, 2007.

[4] Kafarski, P.; Lejczak, B. Curr Med Chem Anti-Cancer Agents 2001, 1, 301.

[5] Lintunen, T.; Yli-Kauhaluoma, J. T. Bioorg Med Chem Lett 2000, 10, 1749.

[6] Kafarski, P.; Lejczak, B. Phosphorus Sulfur 1991, 63, 193.

[7] Chen, M.-H.; Chen, Z.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Cai, X.-J.; Hu, D.-Y.; Xue, W.; Zeng, S. J Agric Food Chem 2009, 57, 1383.

[8] Willam, K. M.; Barrington, C. Pestic Sci 1990, 29, 241.

[9] Kleschick, W. A.; Her, R. J.; Gerwick, B. C. EP 142,152, 1985.

[10] Kleschick, W. A.; Costales, M. J.; Dunbar, J. E. Pestic Sci 1990, 29, 341.

[11] Tomlin, C. D. S. The Pesticide Manual, A World Compendium, 14th ed.; British Crop production Council: Alton, Hampshire, UK, 2006, pp 208, 316, 470, 489, 720, and 807.

[12] (a) Ji, F. Q.; Niu, C. W.; Chen, C. N.; Chen, Q.; Yang, G. F.; Xi, Z.; Zhan, C. G. ChemMedChem 2008, **3**, 1203; (b) Yang, G.; Yang, H.; Wang, H. CN 1417210 A. 2003, Chem Abstr 2003, 143, 133379.

[13] Stetter, J., ed. Herbicides Inhibiting Branched Chain Amino Acid Biosynthesis, Chemistry of Plant Protection 10; Springer: New York, 1994.

[14] Chen, Q.; Liu, Y. C.; Zhang, M. Z.; Yang, G. F. Chin J Pestic Sci 2009, 11, 31.

[15] Kaboudin, B.; Morad, K. Tetrahedron Lett 2005, 46, 2989.

[16] Takahashi, H.; Yoshioka, M. Synthesis 1994, 763.

[17] Chen, X. B.; Shi, D. Q. Chin J Org Chem 2009, 29, 1096.

# Bichalcophenes: A Concise Synthesis of Formyl Ester- and Cyano Ester-Substituted Bithiophenes, Bifurans, and Furanothiophenes



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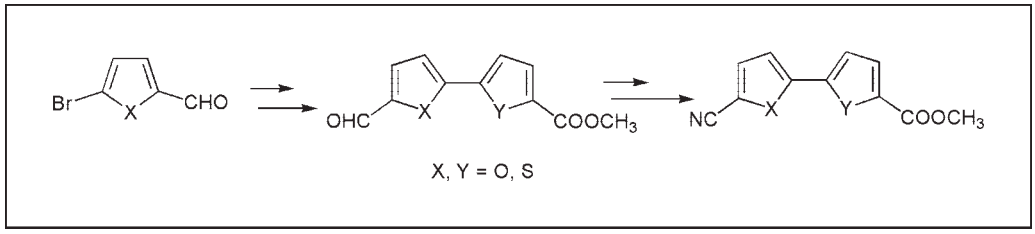


Syntheses of new formyl ester- and cyano ester-substituted bithiophenes, bifurans, and furanothiophenes in good yield are described. The key synthetic step uses Stille coupling of appropriately substituted bromo 5-ring heterocycles with stannyl-substituted 5-ring heterocycles.

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## INTRODUCTION

Compounds containing 2,2′-bithiophene, 2,2′-bifuran, and 2,2′-furanothiophene cores play important roles in material sciences [1], pharmaceutical [2], and agrochemical [3] fields. The various optical properties of these bichalcophenes have lead to their extensive use in nonlinear optical devices [4], sensors [5], solar cells [6], and other advanced materials. These bichalcophene units appear in important medicinal chemical applications including antibacterial [7] and anticancer studies [8]. Bichalcophene diamidines of the type I and II from our laboratory have been shown to recognize G-quadruplex DNA [9]. Formyl and ester bichalcophene analogs can undergo a variety of condensation reactions to prepare more complex molecules of importance to material science as well as for the generation of useful bioactive molecules. Cyano derivatives are key intermediates for the preparation of amidine molecules, which are important molecules in such diverse fields as medicinal chemistry [9] and catalyst development [10]. In view of our interest in molecules that recognize G-quadruplex DNA [9] and other ones, which can potentially function as diagnostics [11] for parasites and as an expansion of our previous bichalcophene work [12(a)]. We report here the synthesis of new bichalcophenes with formyl, ester, and cyano substituents that can serve as versatile building blocks for the preparation of more complex molecules (Fig. 1).

## RESULTS AND DISCUSSION

Scheme 1 outlines our approach to the synthesis of both the bichalcophene formyl and cyano esters. We chose to use the Stille approach for the coupling to form the bichalcophene units because this methodology is known to be quite robust and can be performed under neutral conditions [1(b),2,12(b)]. For ease of preparation of the Stille reagent, we chose to use the acetal-protected formyl furan **2a** and thiophene **2b**. The commercially available aldehydes **1a**, **b** were converted into the previously unreported acetals **2a**, **b** in high yields (>95%) using NBS as a catalyst, under mild conditions [13].The new tri-*n*-butylstannyl reagents were prepared in good yields (>80%) by a conventional *n*-butyllithium debromination of **2a**, **b** at −78°C followed by reaction with tri-*n*-butyltin chloride. The Stille coupling reaction between **3a**, **b** and commercially available **4a**, **b** in the presence of a 5 mol % of Pd $(PPh_3)_4$ using 1,4-dioxane as solvent at 100°C for 24 h followed by deprotection of the acetal product by stirring with conc. HCl solution for 6 h gave the desired new formyl analogs **5a–d** in good yields (>73%). The formyl esters were converted into the cyano esters (**6a–d**) using a conventional two-step process of conversion of the aldehydes into the corresponding oximes followed by acetic anhydride-facilitated dehydration to provide the new nitriles in good isolated yields (>75%).

In conclusion, we have reported a concise synthesis, in good yields, of new cyano and formyl ester-substituted bichalcophenes, which can be used for the

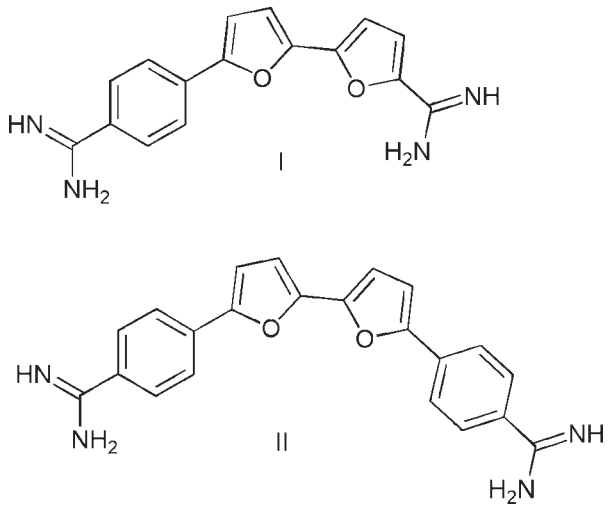



**Figure 1.** Bichalcophenes which recognize G-quadruplex DNA.

preparation of more complex molecules for multiple applications.

## EXPERIMENTAL

All commercial reagents were used without purification. Melting points were determined on a Mel-Temp 3.0 melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets using UV light for detection. $^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker 400 MHz spectrometer using the indicated solvents. Mass spectra were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA. Elemental analysis were performed by Atlantic Microlab, Norcross, GA.

**General procedure for the synthesis of 2a, b.** A 1.06 g NBS (6 mmol) was added in portions to a stirred mixture of **1a**, **b** (130 mmol) and 19.55 mL trimethyl orthoformate (190 mmol) in 150 mL anhydrous $CH_2Cl_2$ and 15 mL anhydrous $CH_3OH$ at 0°–5°. After the addition was completed, the resulting mixture was stirred overnight at room temperature, quenched with water, and the organic layer was separated, washed with water again, dried (sodium sulfate), and evaporated. The resulting oil was purified by distillation.

***2-Bromo-5-(dimethoxymethyl) furan (2a).*** Colorless liquid, yield 95%; bp 45°C (0.35 mmHg); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 6.91$ (d, $J = 2.8$ Hz, 1 H), 6.85 (d, $J = 2.8$ Hz, 1 H), 5.38 (s, 1 H), 3.36 (s, 6 H); $^{13}$C-NMR ($CDCl_3$): $\delta = 52.3$, 99.6, 112.7, 125.7, 130.4, 143.1; ESI-MS: *m/z* calculated for $C_7H_9BrO_3$: 221.05, Found: 222.1 ($M^+ + 1$), 223.1 ($M^+ + 2$); Anal. Calcd. for $C_7H_9BrO_3$: C, 38.03; H, 4.10; Found: C, 37.81; H, 4.25.

***2-Bromo-5-(dimethoxymethyl) thiophene (2b).*** Colorless liquid, yield 97%; bp 69°C (0.25 mm Hg). $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (d, $J = 4$ Hz, 1 H), 6.83 (dd, $J = 1.2$, 4 Hz, 1 H), 5.54 (d, $J = 1.2$, 1 H), 3.33 (s, 6 H); $^{13}$C-NMR ($CDCl_3$): $\delta = 52.5$, 99.7, 112.5, 125.9, 131.1, 142.8; ESI-MS: *m/z* calculated for $C_7H_9BrO_2S$: 237.11, Found: 238.3 ($M^+ + 1$), 239.3 ($M^+ + 2$); Anal. Calcd. for $C_7H_9BrO_2S$: C, 35.46; H, 3.83; Found: C, 35.22; H, 4.15.

**General procedure for the synthesis of 3a, b.** A 101 mL 1.6*M* *n*-butyllithium solution in hexane (150 mmol) was added slowly to a stirred solution of **2a**, **b** (130 mmol) in 150 mL anhydrous THF under nitrogen atmosphere at –78°C. After the addition was completed, the mixture was stirred for 4 h and then 40.6 mL tri-*n*-butyltin chloride (150 mmol) was added slowly at –78°C. After stirring overnight, the solution was quenched with 50 mL water and solvents were removed under reduced pressure. The residue was extracted with 200 mL ether, the organic layer was washed with 30 mL 10% NaF solution and 100 mL water, dried (sodium sulfate), and concentrated. The resulting oil was purified by distillation.

***5-(Dimethoxymethyl)furan-2-yl-tri-n-butylstannane (3a).*** Yellow oil, yield 84%; bp 145°C (0.6 mm Hg); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 6.53$ (d, $J = 2.8$ Hz, 1 H), 6.44 (d, $J = 2.8$ Hz, 1 H), 5.50 (s, 1 H), 3.39 (s, 6 H). 1.64 (m, 6 H), 1.53 (m, 6 H), 1.25 (m, 6 H), 1.09 (m, 9 H); $^{13}$C-NMR ($CDCl_3$): $\delta = 12.5$, 15.5, 26.9, 28.9, 52.4, 100.4, 126.4, 134.8, 135.1, 146.9; ESI-MS: *m/z* calculated for $C_{19}H_{36}O_3Sn$: 431.20, Found: 432.3 ($M^+ + 1$); Anal. Calcd. for $C_{19}H_{36}O_3Sn$: C, 52.92; H, 8.42; Found: C, 52.71; H, 8.55.

***5-(Dimethoxymethyl)thiophen-2-yl-tri-n-butylstannane (3b).*** Yellow oil, yield 81%; bp 185°C (0.7 mm Hg); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 2.8$ Hz, 1 H), 7.15 (d, $J = 2.8$ Hz, 1 H), 5.69 (s, 1 H), 3.48 (s, 6 H), 1.78 (m, 6 H), 1.60 (m, 6 H), 1.48 (m, 6 H), 1.17 (m, 9 H); $^{13}$C-NMR ($CDCl_3$): $\delta = 13.2$, 17.3, 27.4, 28.5, 52.7, 101.1, 126.9, 134.2, 135.7, 146.3; ESI-MS: *m/z* calculated for $C_{19}H_{36}O_2SSn$: 447.26, Found: 448.2 ($M^+ + 1$); Anal. Calcd. for $C_{19}H_{36}O_2SSn$: C, 51.02; H, 8.11; Found: C, 51.17; H, 7.99.

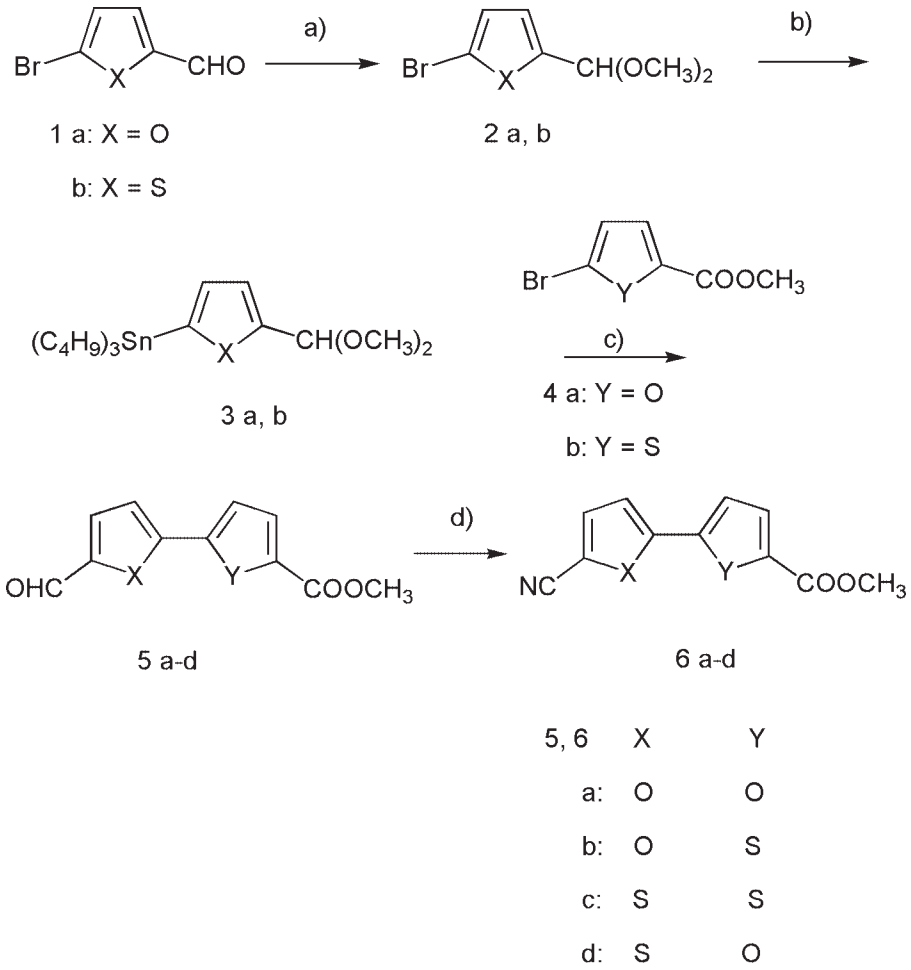
**General procedure for the synthesis of 5a–d.** A 1.15 g tetrakis-triphenyl-phosphine palladium (1 mmol) was added to a stirred mixture of **3a**, **b** (20 mmol) and **4a**, **b** (20 mmol) in deaerated dry 40 mL dioxane under nitrogen atmosphere. The vigorously stirred mixture was warmed to 90–100°C for 24 h. The solvent was removed under reduced pressure; the residue was dissolved in 150 mL dichloromethane containing 5 mL of concentrated ammonia, then washed with water, and passed through celite. The solution was mixed with conc. 5 mL HCl, stirred for 6 h, separated and washed with water, dried (sodium sulfate), and evaporated. The product was purified by column chromatography on silica gel, using dichloromethane as eluent.

***Methyl 5′-formyl-2,2′-bifuran-5-carboxylate (5a).*** Yellow solid, yield (two steps) 79%; mp 129–130°C; $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 9.65$ (s, 1 H), 7.69 (d, $J = 3.6$ Hz, 1 H), 7.49 (d, $J = 3.6$ Hz, 1 H), 7.24 (brs, 1 H), 7.25 (brs, 1 H), 3.86 (s, 3 H); $^{13}$C-NMR ($CDCl_3$): $\delta = 53.1$, 111.2, 125.6, 127.6, 133.8, 135.2, 137.4, 152.3, 152.7, 161.9, 178.5; ESI-MS: *m/z* calculated for $C_{11}H_8O_5$: 220.18, Found: 221 ($M^+ + 1$); Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66; Found: C, 60.28; H, 3.79.

***Methyl 5-(5-formylfuran-2-yl) thiophene-2-carboxylate (5b).*** Yellowish white solid, yield (two steps) 85%; mp 143–143.5°C. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 9.62$ (s, 1 H), 7.85 (d, $J = 4$ Hz, 1 H), 7.79 (d, $J = 4$ Hz, 1 H), 7.68 (d, $J = 4$ Hz, 1 H), 7.34 (d, $J = 4$, 1 H), 3.91 (s, 3 H); $^{13}$C-NMR ($CDCl_3$): $\delta = 53.1$, 111.3, 125.7, 127.8, 133.8, 135.1, 137.9, 152.3, 152.9, 162.1, 177.3; ESI-MS: *m/z* calculated for $C_{11}H_8O_4S$: 236.24, Found: 237 ($M^+ + 1$); Anal. Calcd. for $C_{11}H_8O_4S$: C, 55.92; H, 3.41; Found: C, 56.21; H, 3.48.

***Methyl-5′-formyl-2,2′-bithiophene-5-carboxylate (5c).*** White solid, yield (two steps) 73%; mp 161°C. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 9.93$ (s, 1 H), 8.05 (d, $J = 4$ Hz, 1 H), 7.82 (d, $J$

**Scheme 1**




Reagents and conditions: a) Trimethyl orthoformate, NBS, $CH_2Cl_2$, $CH_3OH$; b) *n*-Bu Li(1.6mol), $(Bu)_3SnCl$, THF; c) (i) $Pd(PPh_3)_4$, 1,4-dioxane; (ii) Aq HCl; d) (i) $NH_2OH.HCl$, $Na_2CO_3$, $H_2O$, $CH_3OH$; (ii) $Ac_2O$.

= 4 Hz, 1 H), 7.79 (d, *J* = 4, 1 H), 7.50 (d, *J* = 4, 1 H), 3.89 (s, 3 H); $^{13}$C-NMR ($CDCl_3$): δ = 51.5, 111.6, 121.9, 126.4, 139.3, 139.4, 142.2, 144.8, 150.7, 162.4, 181.1; ESI-MS: *m/z* calculated for $C_{11}H_8O_3S_2$: 252.31, Found: 253 ($M^+$ + 1); Anal. Calcd. for $C_{11}H_8O_3S_2$: C, 52.36; H, 3.2; Found: C, 52.46; H, 3.13.

***Methyl-5-(5-formylthiophen-2-yl) furan-2-carboxylate (5d).*** Yellowish brown solid, yield (two steps) 78%; mp 178–180°C. $^1$H-NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 8.07 (d, *J* = 4 Hz, 1 H), 7.78 (d, *J* = 4 Hz, 1 H), 7.48 (d, *J* = 4, 1 H), 7.30 (d, *J* = 4, 1 H), 3.86 (s, 3 H); $^{13}$C-NMR ($CDCl_3$): δ = 52.5, 111.6, 121.2, 127.1, 139.1, 139.5, 143.4, 144.2, 151.3, 158.4.1, 184.7. ESI-MS: *m/z* calculated for $C_{11}H_8O_4S$: 236.24, Found: 237 ($M^+$ + 1); Anal. Calcd. for $C_{11}H_8O_4S$: C, 55.92; H, 3.41; Found: C, 56.01; H, 3.44.

**General procedure for the synthesis of 6a–d.** A 10 mL aqueous solution of 0.7 g hydroxylamine hydrochloride (10 mmol) and 1.06 g sodium carbonate (10 mmol) was added to a stirred solution of **5a–d** (10 mmol) in 25 mL methanol and heated at reflux for 24 h. Evaporation of the solvent under reduced pressure to yield a precipitate that was partitioned between water and 100 mL ethyl acetate, and the organic layer was dried (sodium sulfate) and then concentrated to dryness under reduced pressure. The crude oxime was allowed to reflux in 20 mL acetic anhydride for 24 h, and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel, using hexanes/ethyl acetate (80/20, v/v) as eluent.

***Methyl 5′-cyano-2,2′-bifuran-5-carboxylate (6a).*** Yellowish brown solid, yield (two steps) 81%; mp 99–100°C. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ = 7.77 (d, *J* = 3.6 Hz, 1 H), 7.46 (d, *J* = 3.6 Hz, 1 H), 7.20 (brs, 2 H), 3.85 (s, 3 H); $^{13}$C-NMR (DMSO-$d_6$): δ = 52.5, 108.5, 111.3, 114.5, 121, 126.3, 138.5, 140.6, 144.2, 150.6, 158.4; ESI-MS: *m/z* calculated for $C_{11}H_7NO_4$: 217.18, Found: 218 ($M^+$ + 1); Anal. Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45; Found: C, 60.88; H, 3.38; N, 6.08.

***Methyl 5-(5-cyanofuran-2-yl)thiophene-2-carboxylate (6b).*** Yellowish brown solid, yield (two steps) 78%; mp 115-116°C. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ = 7.85 (d, $J$ = 4 Hz, 1 H), 7.80 (d, $J$ = 4 Hz, 1 H), 7.70 (d, $J$ = 3.6, 1 H), 7.31 (d, $J$ = 3.6, 1 H), 3.86 (s, 3 H); $^{13}$C-NMR (DMSO-$d_6$): δ = 49.9, 107.1, 111.9, 113.2, 121, 126.1, 138.9, 139.2, 145.8, 151.9, 165.9; ESI-MS: *m/z* calculated for $C_{11}H_7NO_3S$: 233.24, Found: 234 ($M^+$ + 1); Anal. Calcd. for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01; Found: C, 56.95; H, 3.16; N, 5.77.

***Methyl 5′-cyano-2,2′-bithiophene-5-carboxylate (6c).*** Yellow solid, yield (two steps) 75%; mp 142-144°C. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ = 8.01 (d, $J$ = 4 Hz, 1 H), 7.71 (d, $J$ = 4 Hz, 1 H), 7.45 (d, $J$ = 3.6, 1 H), 7.28 (d, $J$ = 3.6, 1 H), 3.85 (s, 3 H); $^{13}$C-NMR (DMSO-$d_6$): δ = 55.1, 105.2, 110.2, 113.8, 121.2, 126.7, 134.5, 137.2, 147.1, 152.4, 162.4; ESI-MS: *m/z* calculated for $C_{11}H_7NO_2S_2$: 249.31, Found: 250.2 ($M^+$ + 1); Anal. Calcd. for $C_{11}H_7NO_2S_2$: C, 52.99; H, 2.83; N, 5.62; Found: C, 53.12; H, 3.06; N, 5.39.

***Methyl 5-(5-cyanothiophen-2-yl) furan-2-carboxylate (6d).*** Brown solid, yield (two steps) 78%; mp 126-126.5°C. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ = 7.61 (d, $J$ = 4 Hz, 1 H), 7.54 (d, $J$ = 4 Hz, 1 H), 7.25 (d, $J$ = 4, 1 H), 6.80 (d, $J$ = 4, 1 H), 3.94 (s, 3 H); $^{13}$C-NMR (DMSO-$d_6$): δ = 51.3, 109.2, 111.9, 115.4, 120.7, 124.9, 137.7, 140.1, 144.7, 151.1, 161.8; ESI-MS: *m/z* calculated for $C_{11}H_7NO_3S$: 233.24, Found: 234 ($M^+$ + 1); Anal. Calcd. for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01; Found: C, 56.67; H, 3.09; N, 5.98.

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## REFERENCES AND NOTES

[1] (a) Herbivo, C.; Comel, A.; Kirsch, G.; Raposo, M. M. M. Tetrahedron 2009, 65, 2079; (b) Raposo, M. M. M.; Fonseca, A. M. C.; Kirsch, G. Tetrahedron 2004, 60, 4071; (c) Shirota, Y. J Mater Chem 2000, 10, 1.

[2] Stanforth, S. P. Tetrahedron 1998, 54, 263.

[3] Kober, R.; Leyendecker, J.; Seel, R.; Fischer, K.; Theobald, H.; Wuerzer, B.; Westphalen, K. O.; Meyer, N. Eur Pat Appl (BASF A.-G., Germany), 1990, p 45; CODEN: EPXXDW EP353667 A1 19900207.

[4] (a) Garcia, M. H.; Mendes, J. P.; Robalo, M. P.; Dias, A. R.; Campo, J.; Wenseleers, W.; Goovaerts, E. J Org Metal Chem 2007, 692, 3027; (b) Zhang, T.-G.; Zhao, Y.; Asselberghs, I.; Persoons, A.; Clays, K.; Therien, M. J. J Am Chem Soc 2005, 127, 9710; (c) Fillaut, J. L.; Perruchon, J.; Blanchard, P.; Roncali, J.; Golhen, S.; Allain, M.; Migalsaka-Zalas, A.; Kityk, I. V.; Sahraoui, B. Organometallics 2005, 24, 687; (d) Cai, C.; Liakatas, I.; Wong, M. S.; Bosch, M.; Bosshard, C.; Gunter, P.; Concilio, S.; Tirelli, N.; Suter, U. W. Org Lett 1999, 1, 1847.

[5] (a) Yan, P.; Xie, A.; Wei, M.; Loew, L. M. J Org Chem 2008, 73, 6587; (b) Gallaz, M. C.; Tassoni, L.; Bertarelli, C.; Pioggia, G.; Di Francesco, F.; Montoneri, E. Sens Actuators B 2003, 88, 178.

[6] (a) Yum, J. H.; Hagberg, D. P.; Moon, S. J.; Karlsson, K. M.; Marinado, T.; Sun, L.; Hagfeldt, A.; Nazeeruddin, M. K.; Gratzel, M. Angew Chem 2009, 48, 1576; (b) Lin, T. J.; Chen, P. C.; Yen, Y. S.; Hsu, Y. C.; Chou, H. H.; Yeh, M. C. Org Lett 2009, 11, 97.

[7] Zajac, M.; Hrobarik, P.; Magdolen, P.; Foltinova, P.; Zahradnik, P. Tetrahedron 2008, 64, 10605.

[8] (a) Rheault, T. R.; Caferro, T. R.; Dickerson, S. H.; Donaldson, K. H.; Gaul, M. D.; Goetz, A. S.; Mullin, R. J.; McDonald, O. B.; Petrov, K. G.; Rusnak, D. W.; Shewchuk, L. M.; Spehar, G. M.; Truesdale, A. T.; Vanderwall, D. E.; Wood, E. R.; Uehling, D. E. Bioorg Med Chem Lett 2009, 19, 817; (b) Boschelli, D. H.; Wu, B.; Sosa, A. C. B.; Chen, J. J.; Golas, J. M.; Boschelli, F. Bioorg Med Chem Lett 2005, 15, 4681; (c) Mertins, S. D.; Myers, G. T.; Hollingshead, M.; Dykes, D.; Bodde, E.; Tasi, P.; Jefferis, C. A.; Gupta, R.; Linehan, W. M.; Alley, M.; Bates, S. E. Clin Cancer Res 2001, 7, 620.

[9] (a) White, E. W.; Tanious, F. A.; Ismail, M. A.; Reszka, A. P.; Neidle, S.; Boykin, D. W.; Wilson, D. W. Biophys Chem 2007, 126, 140; (b) Tidwell, R. R.; Boykin, D. W.; Ismail, M. A.; Wilson, D. W.; White, E. A. W.; Kumar, A.; Nanjunda, R. Eur Pat Appl 2007, p 110; CODEN: EPXXDW EP1792613 A2 20070606.

[10] (a) Desset, S. L.; Cole-Hamilton, D. J. Angew Chem 2009, 48, 1472; (b) Joannesse, C.; Simal, C.; Concellon, C.; Thomson, J. E.; Campbell, C. D.; Salwin, A. M. Z.; Smith, A. D. Org Biomol Chem 2008, 6, 2900; (c) Saitoth, A.; Morimoto, T.; Achiwa, K. Tetrahedron: Asymmetry 1997, 21, 3567.

[11] Stewart, M. L.; Krishna, S.; Burchmore, R. J. S.; Brun, R.; Koning, H. P.; Boykin, D. W.; Tidwell, R. R.; Hall, J. E.; Barrett, M. P. Lancet 2005, 366, 486.

[12] (a) Ismail, M. A.; Boykin, D. W.; Stephens, C. E. Tetrahedron Lett 2006, 47, 795; (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille Reaction; Wiley: New York, 1998.

[13] (a) Karimi, B.; Seradj, H.; Ebrahimian, G.-R. Synlett 1999, 9, 1456; (b) Karimi, B.; Hazarkhani, H.; Maleki, J. Synthesis 2005, 2, 279.

# Facile Synthesis and Herbicidal Activity of Novel Multisubstituted Pyridine Derivatives



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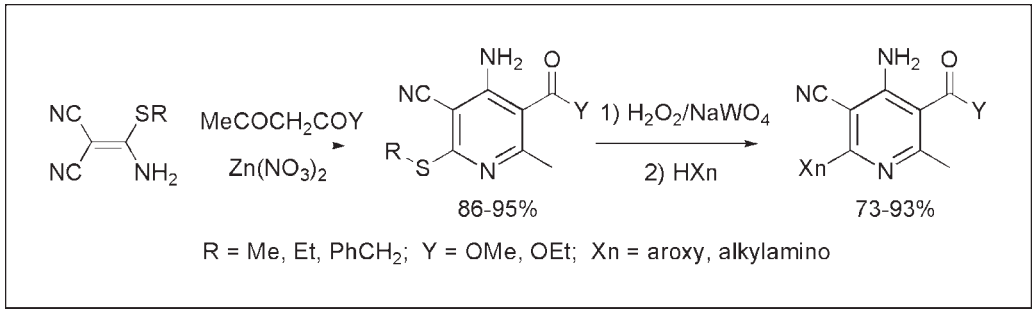


Ketene *N*,*S*-acetals reacted with β-ketoesters in the presence of $Zn(NO_3)_2 \cdot 6H_2O$ as catalyst, in ethanol solvent, giving 6-alkylsulfanylpyridines **4** in good yields without complicated purification procedures. Oxidization of compounds **4** with aqueous hydrogen peroxide in the presence of catalytic sodium wolframate led to the formation of 6-alkylsulfonylpyridine derivatives **5**, which could be further derivatized in the 6-position by nucleophilic reactions with phenols or amines to give multisubstituted pyridine compounds **8**. Bioassays indicated that some of the compounds of the type **8** have good herbicidal activity at a dose of 100 mg/L on the roots of oil rape and barnyard grass.

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## INTRODUCTION

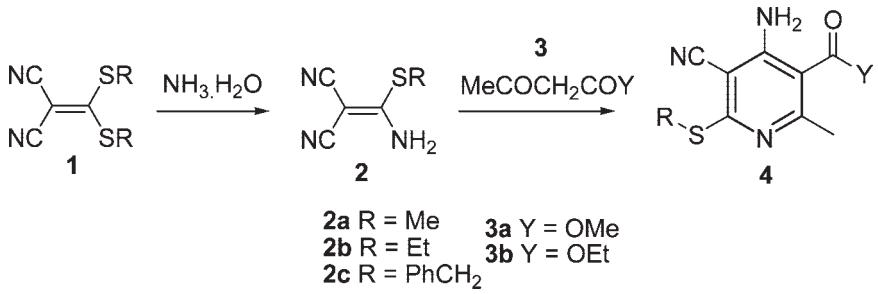
Muti-substituted pyridine derivatives occupy a central position in modern heterocyclic chemistry particularly in the pharmaceutical and agrochemical fields [1–4]. Therefore, new and improved synthetic studies about the preparation of this important heterocyclic ring system are of contemporary interest. The Hantzsch reaction has been proved to be a versatile method for the preparation of a large range of pyridines and dihydropyridines with symmetrical substitution patterns [5,6]. But the synthesis of multi-substituted pyridines with unsymmetrical substitution patterns is often difficult and involves multistep sequences, so there is still a great need to develop new approaches to pyridines of this type.

Our interests in the preparation of new heterocyclic compounds prompted us to elaborate novel methods for the synthesis of unsymmetrical multi-substituted pyridines and the evaluation of their biological activities. In this context, we report here an improved and convenient synthesis of the unsymmetrical multisubstituted pyridines **4** from easily accessible staring materials ketene *N*,*S*-acetals **2** and β-ketoesters **3**, as well as the preparation of various functional derivatives **5** and **8** resulting from a oxidization sequence and nucleophilic reactions. A preliminary *in vitro* bioassay indicated that some of the compounds of the type **8** have good herbicidal activity.

## RESULTS AND DISCUSSION

The intermediates 1 and **2** can be prepared according to a published method [7]. It was reported that 4-aminopyridine **4** (Scheme 1) was prepared in moderate yield (48%) by using anhydrous stannic chloride as catalyst [8,9]. However, we found that there were some drawbacks with this method which need to be addressed. First, this method requires anhydrous conditions because tin (IV) chloride is readily hydrolyzed in water. Furthermore, the poor solubility of the reactants and the $SnCl_4$ catalyst in toluene, used as the solvent for the reaction, often leads to a low yield and prolonged reaction time. And finally, the complex and cockamamie workup procedure involves a dilution of the reaction mixture with a saturated aqueous solution of sodium carbonate and an extraction of the reactant mixture with ethyl acetate

**Scheme 1.** Synthesis of 6-alkylsulfanyl substituted pyridines **4**.




before the title compound can be isolated and purified by a flash chromatography on silica gel.

In this study, various catalysts, different solvents as well as the reaction times and the molar ratios of reactants were tested to optimize the reaction conditions. The survey of reaction conditions and results are summarized in Table 1. The initial study was performed on the reaction of 2-(amino-methylthio-methylene)-malononitrile with ethyl acetoacetate in the presence of anhydrous $SnCl_4$ (2 equiv.) in refluxing toluene, which gave a yield of 38% of **4b** (entry 1). Corresponding reactions carried out in polar solvents such as ethanol led to none of the required product being observed (entry 2).

It was found that catalysts and solvents have a dramatic influence on the efficiency of the reaction. A variety of catalysts, such as $ZnCl_2$ (entries 3–4), $Zn(OAc)_2 \cdot 2H_2O$ (entry 6), $Zn(NO_3)_2 \cdot 6H_2O$ (entries 7–9), catalyze the reactions more efficiently than $SnCl_4$ (entries 1–2). And when ethanol was used as the solvent, $Zn(NO_3)_2 \cdot 6H_2O$ provided the best catalytic efficiency. We also found that the higher concentration of β-ketoesters (2 equiv.) slightly increased the yield (entry 7 *vs*. entry 8).

When using $Zn(NO_3)_2 \cdot 6H_2O$ as catalyst, we found that there was almost no change on the reaction yields when the reaction time changed from 12 h to 6 h whereas other variables were kept constant (entry 8 *vs*. entry 9). However, when a catalytic amount of triethylbenzylammonium chloride (TEBA) was added to the reaction, a maximum amount of the title compound **4b** was obtained (entry 10).

To investigate the scope of this reaction and to establish its tolerance of different substrates under the optimized conditions, a range of different β-ketoesters **3** and ketene *N,S*-acetals **2** were heated at reflux in ethanol in the presence of stoichiometric amounts of zinc(II) nitrate and a catalytic amount of TEBA. In all the cases investigated (Table 2), the expected pyridine **4** was isolated in good to excellent yield (86–95%), and no regioisomeric products were detected.

Bearing in mind the fact that the alkylsulfanyl group of compound **4** can be oxidized into alkylsulfonyl group, we became interested in identifying new ways to synthesize pyridines in which the methylsulfonyl group could serve as a leaving group to facilitate C—C bond-forming in the reactions. 6-Alkylsulfanyl pyridine derivatives **4** was treated with aqueous hydrogen peroxide in the presence of sodium wolframate as catalyst to give 6-alkylsulfonyl pyridine derivatives **5**. Acetic acid was a solvent of choice for the reaction stated in the literature [10]. In our case, however, acetic acid was not the best candidate as the reaction proceed in acetic acid at room

**Table 1**

Optimization of the reaction conditions.

| Entry | Catalyst | Ratio **2a**:**3b**:catalyst | Conditions | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $SnCl_4$ | 1:1:2 | Toluene/reflux | 8 | 38 |
| 2 | $SnCl_4$ | 1:1:2 | Ethanol/reflux | 8 | Failed |
| 3 | $ZnCl_2$ | 1:1:2 | Toluene/reflux | 12 | 48 |
| 4 | $ZnCl_2$ | 1:1:2 | Ethanol/reflux | 12 | 60 |
| 5 | $ZnSO_4 \cdot 7H_2O$ | 1:1:2 | Ethanol/reflux | 12 | 31 |
| 6 | $Zn(OAc)_2 \cdot 2H_2O$ | 1:1:2 | Ethanol/reflux | 12 | 70 |
| 7 | $Zn(NO_3)_2 \cdot 6H_2O$ | 1:1:2 | Ethanol/reflux | 12 | 73 |
| 8 | $Zn(NO_3)_2 \cdot 6H_2O$ | 1:2:2 | Ethanol/reflux | 12 | 80 |
| 9 | $Zn(NO_3)_2 \cdot 6H_2O$ | 1:2:2 | Ethanol/reflux | 6 | 78 |
| 10 | $Zn(NO_3)_2 \cdot 6H_2O$ + TEBA | 1:2:2 | Ethanol/reflux | 6 | 95 |

[a] Yield of pure isolated product.

**Table 2**

Yields of compounds **4–7**.

| Compounds | R | Y | Yield (%)[a,b] | Compds | R | Y | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| **4a** | Me | MeO | 90 | **5a** | Me | MeO | 85 |
| **4b** | Me | EtO | 95 | **5b** | Me | EtO | 91 |
| **4c** | Et | MeO | 86 | **5c** | Et | MeO | 78 |
| **4d** | Et | EtO | 91 | **5d** | Et | EtO | 83 |
| **4e** | $PhCH_2$ | MeO | 87 | **6** | \ | EtO | 50 |
| **4f** | $PhCH_2$ | EtO | 89 | **7** | \ | EtO | 67 |

[a] Yield of pure isolated product.
[b] Using $Zn(NO_2)_{2.} \cdot 6H_2O$ and TEBA as catalyst.

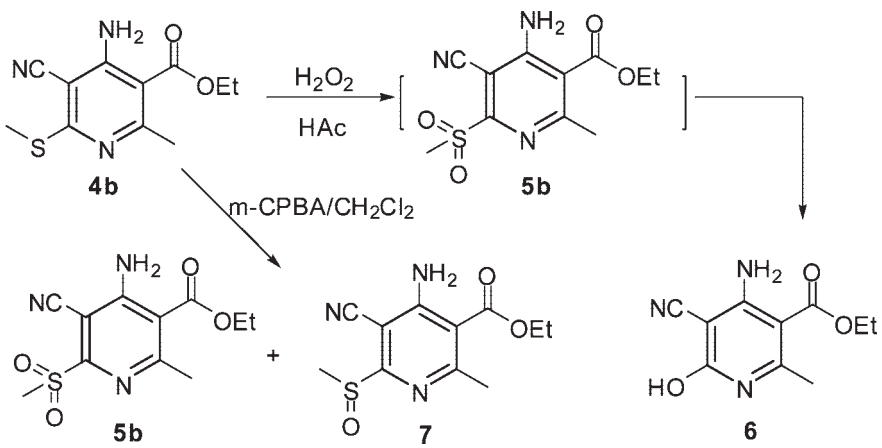
temperature or refluxing temperature gave mainly the byproduct of 4-amino-5-cyano-6-hydroxy-2-methyl-3-ethyloxycarbonyl pyridine **6** (Scheme 2). It may be due in part to the instability of 6-methylsulfonyl pyridine **5b** which could be hydrolyzed under the strong polar conditions.

On the other hand, when the reaction was performed in a less polar solvent of dichloromethane with *m*-chloroperbenzoic acid (*m*-CPBA) as oxidizing reagent, a mixture of 6-methylsulfonyl pyridine **5b** and 6-methylsulfinyl pyridine **7** were obtained (Scheme 2). In addition to these observations, we also attempted to use other solvents such as ethanol, methanol, acetonitrile, or even mixtures of these solvents coupled with different oxidizing reagents. Finally, $H_2O_2$-DMF was identified as the best oxidizing reagent-solvent combination in terms of both operational simplicity and yield. Under the optimized conditions, compound **4** was easily transformated into compound **5** with a high yield after refluxing for 2 h in DMF with aqueous hydrogen peroxide in the presence of sodium wolframate as catalyst (Scheme 3). The workup and purification of the reaction products were easy and efficient.

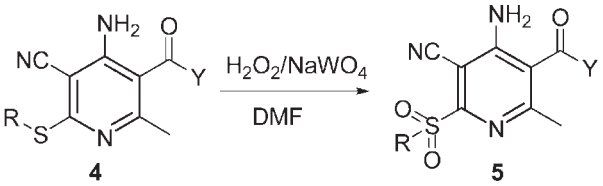
With robust synthesis procedure of 6-methylsulfonyl pyridine **5** in hand, a series of studies on compound **5** were performed to access other 6-substitued pyridine derivatives. The direct reaction of compound **5** with phenols failed to produce 6-aryloxy substituted pyridine **8a–j**. However, when performed in the presence of catalytic potassium carbonate in acetonitrile, the reaction took place and offered **8a–j** in good yield (Scheme 4). Irrespective of the fact whether the substituents on the phenols were electron-withdrawing or electron-releasing groups, the reaction was completed smoothly at refluxing temperature for 1–3 h. On the other hand, when the reaction was performed with NaH as the catalyst, no title product was separated out. This suggested that the compound **5** was unstable and the $SO_2R$ group can be replaced by hydride ion of NaH firstly, which led to the next nucleophilic attack of phenoxides to methylsulfonyl group not occurring.

Conversion of compound **5** into 6-alkylamino substituted pyridine **8k–p** (Scheme 4) was effectively carried out by treatment of acetonitrile solutions of the 6-methylsulfonyl substituted pyridine **5** with 2 equivalent of amines at ambient temperature overnight followed by straight-forward purification of recrystallization. It was noteworthy that the isolated yield of **8k–p** was good despite that the amine is alkylamino or bulkyl heterocycle amino group (Table 3).

**Scheme 2.** Oxidization of **4b** using HAc and $CH_2Cl_2$ as solvent.



**Scheme 3.** Synthesis of 6-alkylsulfonyl pyridines **5**.




The compounds obtained were characterized fully by using spectroscopic methods (IR, $^1$H NMR and EI-MS) and elemental analysis. For example, the IR spectra of **8a** revealed CN and C=O absorption bands at 2225 and 1689 cm$^{-1}$ respectively, the signals attributable to the $NH_2$ are found at 3450 and 3346 cm$^{-1}$. The $^1$H NMR spectrum of **8a** also shows the signals of $NH_2$ at 6.66 ppm as a broad absorption. The MS spectrum of **8a** shows strong molecular ion peak at *m/z* 331 with 100% abundance. In the case of **8h** [11], the structure was additionally confirmed by single-crystal X-ray diffraction (Fig. 1).

The preliminary herbicidal activity of compounds **8** series was evaluated comparable to a commercial herbicide 2,4-D, against two representative targets, oil rape and barnyard grass, at concentrations of 100 mg/L and 10 mg/L, according to a literature method [12]. The results are listed in Table 3 and show that these compounds have moderate to good herbicidal activity against the roots of these two species at the rate of 100 mg/L, especially against the root of oil rape. Compound with substituted phenoxy moiety in position 6 of the pyridine ring showed much better activity than 6-amino-substituted compounds. Switching the substituent Y from methoxy to ethoxy has no obvious effect on the inhibition rates.

In summary, we have developed an improved and convenient synthetic method for the preparation of multisubstituted pyridine derivatives with unsymmetrical substitution patterns. Some multisubstituted pyridines-containing compounds could be synthesized from simple precursors which are assembled in a modular fashion from readily available and inexpensive starting materials. The biological evaluation showed that some compounds have good herbicidal activities and we feel that this method will further facilitate exploration of this increasingly important pharmacophore.

## EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. Mass spectra were measured on a Finnigan Trace MS 2000 spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm$^{-1}$. $^1$H NMR spectra were recorded in $CDCl_3$ or DMSO on a Varian Mercury 400 spectrometer and resonances were given in ppm (δ) relative to TMS (δ 0.00 ppm). $^{13}$C NMR spectra were recorded using $CDCl_3$ as the solvent on a Varian Mercury 600 spectrometer and resonances are given in ppm (δ) relative to $CDCl_3$ (δ 77.00 ppm). The elementary analysis was performed on a Vario EL III elementary analysis instrument. All of the solvents and materials were reagent grade and purified as required.

**General procedure for the preparation of compounds (4a–f).** A mixture of 2-(alkylsulfanyl-amino-methylene)-malononitrile **2** (10 mmol) and $Zn(NO_2)_2 \cdot 6H_2O$ (20 mmol) and a catalytic amount of TEBA (0.2 mmol) were added to a stirred solution of β-ketoesters **3** (20 mmol) in ethanol (30 mL). The solution was heated in an oil bath and refluxed for 6–8 h, and then cooled to room temperature. The crude precipitated product was collected by filtration. Further purification was accomplished by recrystallization from ethanol to give pure products **4a–f**.

***4-Amino-5-cyano-2-methyl-6-methylsulfanyl-nicotinic acid methyl ester (4a).*** This compound was obtained as white solid, mp 141.2–143.2°C, yield 90%; IR: 3418, 3315, 3197, 3002, 2214(CN), 1690(C=O), 1610, 1550, 1238, 1096 cm$^{-1}$ ; $^1$H NMR ($CDCl_3$): δ 2.61 (s, 3H, $SCH_3$), 2.68 (s, 3H, py-$CH_3$), 3.92 (s, 3H, $OCH_3$), 6.70 ppm (s, 2H, $NH_2$); $^{13}$C NMR ($CDCl_3$): δ 12.8, 27.6, 52.0, 89.1, 104.5, 114.5, 156.4, 163.7, 165.1, 168.2 ppm; ms: *m/z* 238 ($M^+$ +1, 15), 237 ($M^+$, 100), 236 ($M^+$ −1, 32), 205 (21), 177 (29); *Anal.* Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.51. Found: C, 50.90; H, 4.92; N, 17.78; S, 13.88.

***4-Amino-5-cyano-2-methyl-6-methylsulfanyl-nicotinic acid ethyl ester (4b).*** This compound was obtained as white solid, mp 136.0–138.0°C, yield 95%; IR: 3406, 3309, 3200, 2983, 2219(CN), 1682(C=O), 1618, 1546, 1241, 1097 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.41 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.62 (s, 3H, $SCH_3$), 2.70 (s, 3H, py-$CH_3$), 4.39 (q, 2H, $OCH_2$, $J$ = 7.2 Hz), 6.68 ppm (s, 2H, $NH_2$); $^{13}$C NMR ($CDCl_3$): δ 12.8, 14.1, 27.6, 61.4, 89.1, 104.7, 114.5, 156.4, 163.6, 164.9, 167.8 ppm; ms: *m/z* 252 ($M^+$ +1, 23), 251 ($M^+$, 100), 250 ($M^+$ −1, 41), 223 (47), 205 (31), 177(30); *Anal.* Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.75; H, 4.80; N, 16.89; S, 12.72.

***4-Amino-5-cyano-6-ethylsulfanyl-2-methyl-nicotinic acid methyl ester (4c).*** This compound was obtained as white solid, mp 137.2–139.2°C, yield 86%; IR: 3406, 3310, 3276, 2951,

**Scheme 4.** Synthesis of 6-aroxy and 6-alkylamino substituted pyridines **8**.

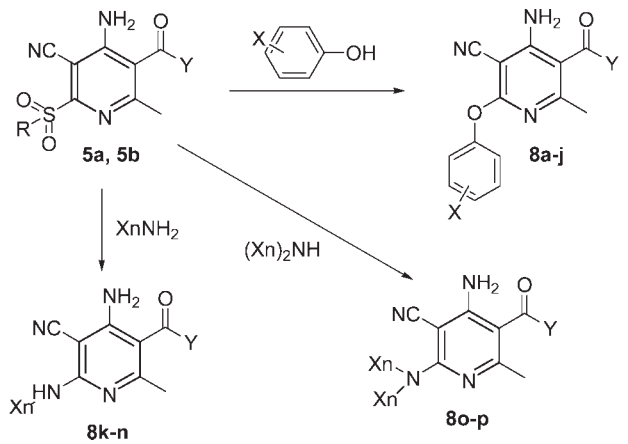
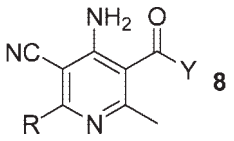


**Table 3**

Yields and heribicidal activity (% inhibition) of compounds **8**.




| Compounds | R | Y | Yield (%)[a] | Oil rape (root/stalk) | | Barnyard grass (root/stalk) | |
|---|---|---|---|---|---|---|---|
| | | | | 100 mg/L | 10 mg/L | 100 mg/L | 10 mg/L |
| **8a** | 4-Br-$C_6H_4O$ | MeO | 77 | 85/69 | 38/31 | 79/52 | 59/35 |
| **8b** | 4-Cl-2-F-$C_6H_3O$ | MeO | 75 | 60/27 | 16/12 | 72/13 | 48/13 |
| **8c** | 3-MeO-$C_6H_4O$ | MeO | 83 | 52/27 | 28/8 | 69/44 | 62/44 |
| **8d** | 3-NO2-$C_6H_4O$ | MeO | 75 | 74/62 | 45/19 | 83/39 | 59/22 |
| **8e** | $C_6H_5O$ | MeO | 79 | 90/65 | 54/27 | 73/48 | 52/35 |
| **8f** | $C_6H_5O$ | EtO | 88 | 79/42 | 16/19 | 79/39 | 52/30 |
| **8g** | 4-Cl-$C_6H_4O$ | EtO | 93 | 68/27 | 45/0 | 79/39 | 59/28 |
| **8h** | 2-NO2-$C_6H_4O$ | EtO | 87 | 90/65 | 54/27 | 72/48 | 52/35 |
| **8i** | 2,3-diMe-$C_6H_3O$ | EtO | 90 | 59/50 | 35/19 | 90/44 | 72/44 |
| **8j** | 4-Me-$C_6H_4O$ | EtO | 89 | 77/52 | 67/44 | 84/28 | 33/14 |
| **8k** | EtNH | EtO | 90 | /[b] | /[b] | /[b] | /[b] |
| **8l** | *n*-PrNH | EtO | 89 | /[b] | /[b] | /[b] | /[b] |
| **8m** | *n*-BuNH | MeO | 87 | 48/47 | 40/33 | 55/33 | 27/7 |
| **8n** | $PhCH_2NH$ | MeO | 73 | 63/47 | 48/40 | 67/48 | 52/30 |
| **8o** | Triazol-1-yl | EtO | 78 | 73/40 | 32/8 | 75/39 | 41/28 |
| **8p** | Piperdin-1-yl | EtO | 82 | /[b] | /[b] | /[b] | /[b] |
| | 2,4-D | | | 99/94 | 99/81 | 99/72 | 90/70 |

[a] Yield of pure isolated product.
[b] Not tested.

2213(CN), 1689(C=O), 1612, 1546, 1240, 1093 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.37 (t, 3H, $SCH_2\underline{CH_3}$, $J$ = 7.2 Hz), 2.68 (s, 3H, Py-$\underline{CH_3}$), 3.25(q, 2H, $S\underline{CH_2}CH_3$, $J$ = 7.2 Hz), 3.92(s, 3H, $OCH_3$), 6.72 ppm (s, 2H, $NH_2$); $^{13}C$ NMR ($CDCl_3$): δ 14.6, 24.4, 27.6, 51.9, 89.2, 104.4, 114.5, 156.5, 163.7, 164.9, 168.2 ppm; ms: $m/z$ 251 ($M^+$, 66), 236 (26), 218 (81), 204 (15), 191

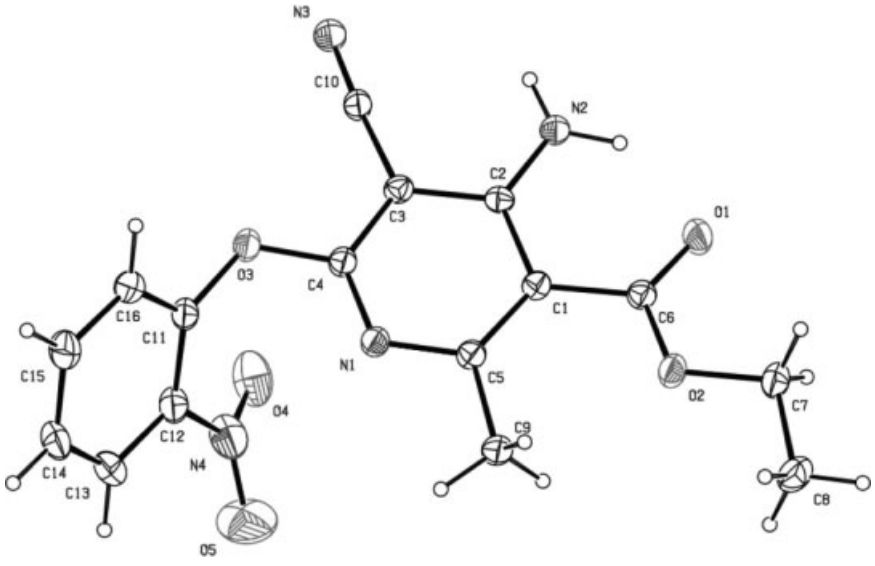



**Figure 1.** The molecular structure of compound **8h**.

(100), 186 (41), 159 (47), 130 (29); *Anal.* Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.90; H, 4.97; N, 16.60; S, 12.36.

***4-Amino-5-cyano-6-ethylsulfanyl-2-methyl-nicotinic acid ethyl ester (4d).*** This compound was obtained as white solid, mp 145.0–146.9°C, yield 91%; IR: 3411, 3305, 3268, 2978, 2213(CN), 1680(C=O), 1609, 1544, 1240, 1092 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ (ppm): 1.37 (t, 3H, $CH_3$, $J$ = 7.2 Hz), 1.41 (t, 3H, $CH_3$, $J$ = 7.2 Hz), 2.68 (s, 3H, Py-$CH_3$), 3.25 (q, 2H, S$CH_2CH_3$, $J$ = 7.6 Hz), 4.38 (q 2H, O$CH_2CH_3$, $J$ = 7.2 Hz,), 6.69 ppm (s, 2H, $NH_2$); $^{13}C$ NMR ($CDCl_3$): δ 14.6, 24.4, 27.6, 51.9, 61.3, 89.2, 104.4, 114.5, 156.5, 163.7, 164.9, 168.2 ppm; ms: *m/z* 265 ($M^+$, 36), 250 (7), 232 (30), 204 (62), 191 (99), 186 (57), 159 (100), 131 (50); *Anal.* Calcd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84; S, 12.08. Found: C, 54.53; H, 5.41; N, 16.04; S, 12.35.

***4-Amino-6-benzylsulfanyl-5-cyano-2-methyl-nicotinic acid methyl ester (4e).*** This compound was obtained as yellow solid, mp 139.4–141.7°C, yield 87%; IR: 3426, 3307, 3004, 2211(CN), 1677(C=O), 1603, 1547, 1250 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.71 (s, 3H, Py-$CH_3$), 3.92 (s, 3H, $OCH_3$), 4.51 (s, 2H, Ph$CH_2$), 6.69 (s, 2H, $NH_2$), 7.24–7.41 ppm (m, 5H, Ph-H); $^{13}C$ NMR ($CDCl_3$): δ 27.6, 33.9, 52.1, 89.1, 104.8, 114.4, 127.3, 128.4, 129.1, 137.4, 156.6, 163.7, 164.2, 168.2 ppm; ms: *m/z* 314 ($M^+$ +1, 17), 313 ($M^+$, 100), 312 ($M^+$ −1, 27), 280 (18), 255 (4); *Anal.* Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.41; H, 4.39; N, 13.33; S, 10.53.

***4-Amino-6-benzylsulfanyl-5-cyano-2-methyl-nicotinic acid ethyl ester (4f).*** This compound was obtained as yellow solid, mp 109.7–112.0°C, yield 89%; IR: 3419, 3312, 2986, 2211(CN), 1673(C=O), 1606, 1546, 1237 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.41 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.72 (s, 3H, Py-$CH_3$), 4.38 (q, 2H, O$CH_2CH_3$, $J$ = 7.2 Hz), 4.51 (s, 2H, Ph$CH_2$), 6.70 (s, 2 H, $NH_2$), 7.24–7.41 ppm (m, 5 H, Ph-H); $^{13}C$ NMR ($CDCl_3$): δ 14.1, 27.5, 33.9, 61.2, 88.9, 104.9, 114.3, 127.2, 128.4, 129.1, 137.4, 156.6, 163.5, 163.9, 167.7 ppm; ms: *m/z* 328 ($M^+$ +1, 18), 327 ($M^+$, 100), 326 ($M^+$ −1, 74), 299 (11), 255 (28), 212 (38); *Anal.* Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.14; H, 4.97; N, 12.76; S, 9.63.

**General procedure for the preparation of compounds (5a–d, 6,7).** A mixture of 4-amino-5-cyano-2-methyl-6-alkylsulfanyl-nicotinic acid alkyl esters **4a–d** (10 mmol) and the catalysis sodium wolframate (0.1 mmol) were added to DMF (30 mL) and heated to 40°C. A solution of aqueous hydrogen peroxide (12 mmol) in ethanol (5 mL) was added at a rate of 1d/s to keep the internal temperature below 50°C. The mixture stirred at 60°C for 3 h and then cooled. The reaction mixture poured into 300 mL of water and the solution was stirred for 4–6 h at room temperature and the precipitate was collected by filtration. The products were air dried and recrystallized from ethanol to give pure product 4-amino-5-cyano-6-alkylsulfonyl- 2-methyl-nicotinic acid alkyl esters **5a–d.**

When this reaction was performed in a solvent of acetic acid, the product **6** was obtained in 50% yield. And when the same reaction was carried out in presence of m-chloroperbenzoic acid (m-CPBA), as oxidizing reagent in $CH_2Cl_2$, a mixture of 6-methylsulfonyl pyridine **5b** and 6-methylsulfinyl pyridine **7** were obtained. The purification procedure was carried out by flash silica gel chromatography using petroleum ether/ethyl acetate (3:1, v/v) as eluent to give product **7** in 67% yield and **5b** in 25% yield.

***4-Amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid methyl ester (5a).*** This compound was obtained as white solid, mp 172.0–174.0°C, yield 85%; IR: 3409, 3298, 2928, 2223(CN), 1697(C=O), 1613, 1554, 1307, 1255, 1138 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ2.76 (s, 3H, Py-$CH_3$), 3.32 (s, 3H, $SO_2CH_3$), 3.99 (s, 3H, $OCH_3$), 7.05 ppm (s, 2H, $NH_2$); ms: *m/z* 269 ($M^+$, 7), 237 (5), 218 (9), 205 (51), 190 (14), 175 (52), 158 (21), 129 (28); *Anal.* Calcd for $C_{10}H_{11}N_3O_4S$: C, 44.60; H, 4.12; N, 15.60; S, 11.91. Found: C, 44.73; H, 4.00; N, 15.42; S, 12.27.

***4-Amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid ethyl ester (5b).*** This compound was obtained as white solid, mp 154.3–156.0°C, yield 91%; IR: 3415, 3287, 2924, 2224(CN), 1690(C=O), 1606, 1550, 1274, 1139 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.45 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.76 (s, 3H, Py-$CH_3$), 3.32 (s, 3H, $SO_2CH_3$), 4.46 (q, 2H, O$CH_2CH_3$, $J$ = 7.2 Hz), 7.05 ppm (s, 2H, $NH_2$); $^{13}C$ NMR ($CDCl_3$): δ 14.0, 27.0, 39.3, 62.4, 89.3, 110.3, 111.8, 157.5, 159.6, 163.8, 166.5 ppm; ms: *m/z* 284 ($M^+$ +1, 4), 283 ($M^+$, 25), 237 (14), 219 (100), 191 (19), 175 (63), 131 (36); *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83; S, 11.32. Found: C, 46.87; H, 4.54; N, 15.04; S, 11.25.

***4-Amino-5-cyano-6-ethylsulfonyl-2-methyl-nicotinic acid methyl ester (5c).*** This compound was obtained as white solid, mp 128.0–129.3°C, yield 78%; IR: 3427, 3342, 2926, 2226(CN), 1731(C=O), 1640, 1529, 1570, 1324, 1252, 1137 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.41(t, 3H, $SO_2CH_2CH_3$, $J$ = 7.2 Hz), 2.76 (s, 3H, Py-$CH_3$), 3.53(q, 2H, $SO_2CH_2CH_3$, $J$ = 7.2 Hz), 3.99(s, 3H, $OCH_3$), 7.10 ppm (s, 2H,$NH_2$); ms: *m/z* 283 ($M^+$, 2), 252 (8), 218 (36), 205 (52), 192 (100), 191 (87), 176 (24), 160 (25), 131 (49); *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$: $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83; S, 11.32. Found: C, 46.73; H, 4.34; N, 14.83; S, 11.51.

***4-Amino-5-cyano-6-ethylsulfonyl-2-methyl-nicotinic acid ethyl ester (5d).*** This compound was obtained as white solid, mp 102.5–103.7°C, yield 83%, IR: 3421, 3327, 2921, 2226(CN), 1694(C=O), 1611, 1526, 1553, 1316, 1140 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.39–1.59 (m, 6H, 2* $CH_3$), 2.76 (s, 3H, Py-$CH_3$), 3.52(q, 2H, $SO_2CH_2CH_3$, $J$ = 7.2 Hz), 4.47(q, 2H, O$CH_2CH_3$, $J$ = 6.8 Hz), 7.12 ppm (s, 2H, $NH_2$); ms: *m/z* 298 ($M^+$ +1, 2), 297 ($M^+$, 3), 233 (9), 205 (25), 187 (5), 161 (12), 132 (20); *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$: $C_{12}H_{15}N_3O_4S$: C, 48.47; H, 5.08; N, 14.13; S, 10.78. Found: C, 48.73; H, 4.78; N, 14.12; S, 11.06.

***4-Amino-5-cyano-6-hydroxy-2-methyl-nicotinic acid ethyl ester (6).*** This compound was obtained as white solid, mp >270°C, yield 50%; $^1H$ NMR (DMSO): δ 1.28 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.42 (s, 3H, Py-$CH_3$), 4.26 (q, 2H, O$CH_2CH_3$, $J$ = 7.2 Hz), 7.58 (s, 2H, $NH_2$), 11.68 ppm (s, 1H, OH); *Anal.* Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.43; H, 4.97; N, 18.83.

***4-Amino-5-cyano-6- methylsulfinyl-2-methyl-nicotinic acid ethyl ester (7).*** This compound was obtained as white solid, mp 132.2–134.4°C, yield 67%; $^1H$ NMR ($CDCl_3$): δ 1.44 (t 3H, $OCH_2CH_3$, $J$ = 7.2 Hz,), 2.76 (s, 3H, Py-$CH_3$), 2.94 (s, 3H, $SOCH_3$), 4.46 (q, 2H, O$CH_2CH_3$, $J$ = 7.2 Hz), 7.04 ppm (s, 2H, $NH_2$); ms: *m/z* 267 ($M^+$, 12), 250 (10), 219 (72), 175 (100), 131 (11); *Anal.* Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72; S, 12.00. Found: C, 49.51; H, 4.44; N, 15.62; S, 12.26.

**General procedure for the preparation of compounds (8a–j).** A mixture of 4-amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid alkyl ester **5a** or **5b** (5mmol) and

catalytic amount of $K_2CO_3$ (0.1 mmol) were added to a solution of substituted phenol (5 mmol) in anhydrous acetonitrile (20 mL). The solution was heated to 80°C in an oil bath to bring the mixture to reflux for 1–2 h and then cooled to room temperature. The precipitated crude product was collected by filtration. The filtrate was recrystallized from dichloromethane/petroleum ether to give pure 4-amino-5-cyano-2-methyl-6-substitutedphenoxy- nicotinic acid alkyl ester **8a–j.**

***4-Amino-5-cyano-6-(4-bromophenoxy)-2-methyl-nicotinic acid methyl ester (8a).*** This compound was obtained as white solid, mp 161.0–163.0°C, yield 77%; IR: 3400, 3308, 2955, 2225(CN), 1689(C=O), 1616, 1546, 1567, 1270, 1160 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.07 (s, 3H, Ar-$CH_3$), 2.32 (s, 3H, Ar-$CH_3$), 2.48 (s, 3H, Py-$CH_3$), 3.90 (s, 3H, $OCH_3$), 6.80 (s, 2H, $NH_2$ ), 6.92–7.11 ppm (m, 3H, Ar-H); ms: *m/z* 311 ($M^+$, 29), 310 (10), 296 (49), 264 (28), 236 (19), 103 (41), 91 (44), 77 (100), 66(19); *Anal*. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.35; H, 5.11; N, 13.41.

***4-Amino-5-cyano-6-(4-chloro-2-fluorophenoxy)-2-methyl-nicotinic acid methyl ester (8b).*** This compound was obtained as white solid, mp 184.0–184.7°C, yield 75%; IR: 3409, 3318, 2959, 2223(CN), 1692(C=O), 1627, 1551, 1497, 1574, 1269, 1094 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.49 (s, 3H, Py-$CH_3$), 3.90 (s, 3H, $OCH_3$), 6.90 (s, 2H, $NH_2$), 7.15–7.18 ppm (m, 3H, Ar-H). ms: *m/z* 335 ($M^+$, 49), 303 (29), 275 (82), 236 (24) 213 (22), 170 (100), 169 (83), 129 (43), 77 (31), 66 (75); *Anal*. Calcd. for $C_{15}H_{11}ClFN_3O_3$: C, 53.66; H, 3.30; N, 12.52. Found: C, 53.99; H, 3.30; N, 12.41.

***4-Amino-5-cyano-6-(3-methoxyphenoxy)-2-methyl-nicotinic acid methyl ester (8c).*** This compound was obtained as white solid, mp 188.0–190.0°C, yield 83%; IR: 3412, 3313, 2964, 2221(CN), 1688(C=O), 1613, 1568, 1501, 1263, 1090 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.46 (s, 3H, $CH_3$), 3.75 (s, 3H, Ar-$OCH_3$), 3.89 (s, 3H, $OCH_3$), 6.80 (s, 2H, $NH_2$), 6.96–7.22 ppm (m, 4H, Ar-H). $^{13}C$ NMR ($CDCl_3$): δ 27.4, 51.9, 55.9, 78.3, 104.4, 112.8, 114.1, 120.7, 122.9, 126.4, 141.5, 151.6, 159.1, 164.0, 165.3, 168.1 ppm; ms: *m/z* 313 ($M^+$, 11), 298 (26), 250 (62), 222 (34), 210 (18), 194 (15), 173 (19), 147 (24), 91 (46), 77 (100); *Anal*. Calcd for $C_{16}H_{15}N_3O_3$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.56; H, 4.51; N, 13.23.

***4-Amino-5-cyano-6-(3-nitrophenoxy)-2-methyl-nicotinic acid methyl ester (8d).*** This compound was obtained as yellow solid, mp 141.0–143.0°C, yield 75%; IR: 3387, 3281, 2954, 2232(CN), 1695(C=O), 1630, 1598, 1531, 1575, 1269, 1097 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.42 (s, 3H, Py-$CH_3$), 3.90 (s, 3H, $OCH_3$), 6.90 (s, 2H, $NH_2$), 7.34–8.12 ppm (m, 4H, Ar-H); ms: *m/z* 296 ($M^+ - O_2$, 11), 283 ($M^+ - NO_2$, 44), 282 (100), 250 (43), 222 (9), 206 (10), 91 (7), 77 (6); *Anal*. Calcd. for $C_{15}H_{12}N_4O_5$: C, 54.88; H, 3.68; N, 17.07. Found: C, 55.16; H, 3.64; N, 16.89.

***4-Amino-5-cyano-2-methyl-6-phenoxy-nicotinic acid methyl ester (8e).*** This compound was obtained as white solid, mp 171.0–173.0°C, yield 79%; IR: 3393, 3286, 2957, 2229(CN), 1692(C=O), 1630, 1594, 1492, 1267, 1096 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.41 (s, 3H. Py-$CH_3$), 3.90 (s, 3H, $OCH_3$), 6.90 (s, 2H, $NH_2$) 7.34–8.12 ppm (m, 5H, Ar-H); $^{13}C$ NMR ($CDCl_3$): δ 27.4, 52.0, 78.8, 104.6, 113.9, 121.6, 125.3, 129.2, 152.3, 159.1, 163.8, 165.4, 167.9 ppm; ms: *m/z* 284 ($M^+$ +1, 7), 283 ($M^+$, 55), 282 ($M^+$ −1, 23), 251(17), 225 (63), 222 (44), 194 (28), 130 (22), 118 (75), 77 (100); *Anal*. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.89; H, 4.57; N, 14.70.

***4-Amino-5-cyano-2-methyl-6-phenoxy-nicotinic acid ethyl ester (8f).*** This compound was obtained as white solid, mp 126.9–128.5°C, yield 88%; IR: 3402, 3308, 2984, 2230(CN), 1680(C=O), 1625, 1491, 1566, 1265, 1096 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.40 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.52 (s, 3H, Py-$CH_3$),4.38(q 2H, $OCH_2CH_3$, $J$ = 7.2 Hz,), 6.88 (s, 2H, $NH_2$), 7.15–7.41 ppm (m, 5 H, Ar-H); ms: *m/z* 298 ($M^+$ +1, 15), 297 ($M^+$, 47), 250 (35), 226 (41), 225 (54), 224 (100), 194 (27), 176 (24), 183 (55), 118 (61), 77 (46); *Anal*. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.54; H, 4.79; N, 14.11.

***4-Amino-6-(4-chloro-phenoxy)-5-cyano-2-methyl-nicotinic acid ethyl ester (8g).*** This compound was obtained as white solid, mp 184.0–184.7°C, yield 93%; IR: 3450, 3346, 2982, 2222(CN), 1708(C=O), 1570, 1490, 1230 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.40 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.51 (s, 3H, Py-$CH_3$), 4.38 (q, 2H, $OCH_2CH_3$, $J$ = 7.2 Hz), 6.66 (s, 2H, $NH_2$), 7.10–7.36 ppm (m, 4H, Ar-H); $^{13}C$ NMR ($CDCl_3$): δ 14.1, 27.4, 61.5, 78.8, 105.0, 113.7, 123.1, 129.2, 130.5, 150.8, 159.2, 163.3, 165.1, 167.4; ms: *m/z* 332 ($M^+$ +1, 9), 331 ($M^+$, 100), 302 (15), 284 (33), 258 (91), 222 (19), 194 (21), 152 (64); *Anal*. Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.88; H, 4.03; N, 12.62.

***4-Amino-5-cyano-2-methyl-6-(2-nitrophenoxy)-nicotinic acid ethyl ester (8h).*** This compound was obtained as yellow solid, mp 141.0–143.0°C, yield 87%; IR: 3386, 3298, 2979, 2229(CN), 1684(C=O), 1618, 1569, 1272 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.38 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.42 (s, 3H, Py-$CH_3$), 4.37 (q, 2H, $OCH_2CH_3$, $J$ = 7.2 Hz), 6.90 (s, 2H, $NH_2$), 7.34–8.12 ppm (m, 4H, Ar-H); $^{13}C$ NMR ($CDCl_3$): δ 14.1, 27.4, 61.5, 78.7, 105.4, 113.4, 125.2, 125.5, 126.2, 134.6, 142.2, 145.2, 159.2, 162.3, 164.9, 167.3 ppm; ms: *m/z* 342 ($M^+$, 10), 331 (21), 296 (50), 268 (100), 250 (22), 224 (26), 194 (12), 176 (15), 152 (16); *Anal*. Calcd for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.29; H, 3.81; N, 16.51.

***4-Amino-5-cyano-2-methyl-6-(2,3-dimethylphenoxy)-nicotinic acid ethyl ester (8i).*** This compound was obtained as yellow solid, mp 159.8–161.8°C, yield 90%; IR: 3391, 3297, 2980, 2229(CN), 1679(C=O), 1617, 1543, 1565, 1271, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.39 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.07 (s, 3H, Ar-$CH_3$), 2.32 (s, 3H, Ar-$CH_3$); 2.48(s, 3H, Py-$CH_3$), 4.37 (q, 2H, $OCH_2CH_3$, $J$ = 7.2 Hz), 6.90 (s, 2H, $NH_2$), 6.92–7.10 ppm (m, 3H, Ar-H); ms: *m/z* 325 ($M^+$, 100), 310 (92), 296 (23), 282 (45), 264 (69), 253 (36), 236 (48), 218 (12), 208 (15), 146 (15), 102 (53), 91 (44); *Anal*. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.47; H, 5.52; N, 13.06.

***4-Amino-5-cyano-2-methyl-6-(4-methylphenoxy)-nicotinic acid ethyl ester (8j).*** This compound was obtained as white solid, mp 106.9–108.3°C, yield 89%; IR: 3397, 3279, 2942, 2224(CN), 1689(C=O), 1626, 1505, 1566, 1266, 1097 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.39 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.37 (s, 3H, Ar-$CH_3$), 2.52(s, 3H, Py-$CH_3$), 4.37 (q, 2H, $OCH_2CH_3$, $J$ = 7.2 Hz), 6.92 (s, 2H, $NH_2$), 7.03–7.19 ppm (m, 3H, Ar-H); ms: *m/z* 311 ($M^+$, 100), 296 (6), 282 (14), 265 (52), 239 (82), 237 (46), 222 (7), 132 (30), 91 (16), 77 (8); *Anal*. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.86; H, 5.97; N, 13.57.

**General procedure for the preparation of compounds (8k–p).** A mixture of 4-amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid alkyl ester **5a** or **5b** (5 mmol),

alkylamines or heterocycleamines (10 mmol), and 20 mL of acetonitrile was stirred for 4–5 h at room temperature. The color of the reaction mixture was changed into yellow. The reaction mixture was poured into 100 mL of water and this solution was stirred for 2 h. The crude product that precipitated was collected by filtration. The filtrate was recrystallized from dichloromethane/petroleum ether to give pure 4-amino-5-cyano-2-methyl-6-alkylamino-nicotinic acid alkyl esters **8 k–p.**

***4-Amino-5-cyano-2-methyl-6-ethylamino-nicotinic acid ethyl ester (8k).*** This compound was obtained as white solid, mp 151.0–154.0°C, yield 90%; $^1$H NMR ($CDCl_3$): δ 1.24(t, 3H, $NHCH_2\underline{CH_3}$, $J$ = 7.2 Hz), 1.38(t, 3H, $OCH_2\underline{CH_3}$, $J$ = 7.2 Hz), 2.60 (s, 3H, Py-$CH_3$), 3.55–3.61(m, 2H, $\underline{NHCH_2}CH_3$), 4.33(q, 2H, $O\underline{CH_2}CH_3$, $J$ = 6.8 Hz), 5.08(s, 1H, $\underline{NH}$), 6.68 ppm (s, 2H, $\underline{NH_2}$); ms: $m/z$ 248 ($M^+$, 100), 233(88.0), 219 (84.8), 205(64.9), 187 (46.8), 174 (98.7), 159 (38.0), 117 (6.0), 44 (7.9); *Anal*. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.75; H, 6.02; N, 22.77.

***4-Amino-5-cyano-2-methyl-6-propylamino-nicotinic acid ethyl ester (8l).*** This compound was obtained as white solid, mp 141.0–142.0°C, yield 89%; $^1$H NMR ($CDCl_3$): δ 0.97(t, $J$ = 7.2 Hz, 3H, $NHCH_2\underline{CH_3}$), 1.38(t, $J$ = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.63(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.60 (s, 3H, Py-$CH_3$), 3.50(q, $J$ = 6.8 Hz, 2H, $NH\underline{CH_2}CH_2$), 4.33(q, $J$ = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 5.12(s, 1H, $\underline{NH}$), 6.68 ppm (s, 2H, $NH_2$); $^{13}$C NMR ($CDCl_3$): δ 11.3, 14.3, 22.9, 28.3, 42.8, 60.6, 72.5, 99.5, 116.3, 158.4, 158.5, 166.3, 168.2 ppm; *Anal*. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.46; H, 6.74; N, 21.50.

***4-Amino-5-cyano-2-methyl-6-butylamino-nicotinic acid methyl ester (8m).*** This compound was obtained as white solid, m.p. 139.9–141.3°C, yield 87%; IR: 3424, 3349, 2959, 2201(CN), 1669(C=O), 1611, 1507, 1565, 1274, 1092 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 0.95(t, $J$ = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 1.37–1.42(m, 2H, $CH_2\underline{CH_2}CH_3$), 1.55–1.62 (m, 2H, $\underline{CH_2}CH_2CH_3$), 2.60 (s, 3H, Py-$\underline{CH_3}$), 3.54(q, $J$ = 6.4 Hz, 2H, $\underline{NHCH_2}CH_2$), 3.87(s, 3H, $O\underline{CH_3}$), 5.12(s, 1H, NH), 6.68 ppm (s, $\underline{2H}$, $\underline{NH_2}$); ms: $m/z$ 262 ($\underline{M^+}$, 38), 247 (7), 233 (55), 219 (100), 206 (46), 187 (78), 174 (49), 159 (19); *Anal*. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.30; H, 7.12; N, 21.05.

***4-Amino-5-cyano-2-methyl-6-benzylamino-nicotinic acid methyl ester (8n).*** This compound was obtained as white solid, m.p. 138.8–140.8°C, yield 73%; IR: 3423, 3345, 2949, 2202(CN), 1673(C=O), 1602, 1503, 1562, 1284, 1091 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.62 (s, 3H, Py-$CH_3$), 3.88(s, 3H, $OCH_3$), 4.75(d, $J$ = 5.6 Hz, 2H, $NH\underline{CH_2}$), 5.44(s, 1H, NH), 6.74 (s, 2H, $NH_2$), 7.28–7.37 ppm (m, $\underline{5H}$, Ph-H); $^{13}$C NMR ($CDCl_3$): δ 28.2, 44.8, 51.5, 72.8, 99.8, 116.0, 127.5, 127.8, 128.6, 138.5, 158.1, 158.4, 166.4, 168.5 ppm; ms: $m/z$ 296 ($M^+$, 100), 263 (11), 236 (6), 218 (8), 191 (16), 159 (10), 106 (66), 91 (27); *Anal*. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.28; H, 5.39; N, 18.74.

***4-Amino-5-cyano-2-methyl-6-triazolyl-nicotinic acid ethyl ester (8o).*** This compound was obtained as yellow solid, m.p. 196.0–198.0°C, yield 78%; $^1$H NMR ($CDCl_3$): δ 1.45(t, $J$ = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.75 (s, 3H, Py-$CH_3$), 4.45(q, $J$ = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 7.08 (s, 2H, $NH_2$), 8.19(s, 1H, triazole-H), 9.18 ppm (s, 1H, triazole-H); ms: $m/z$ 272 ($M^+$, 44.9), 227 (91.4), 225(100), 199 (26), 173 (10), 144 (6); *Anal*. Calcd. for $C_{12}H_{12}N_6O_2$: C, 52.94; H, 4.44; N, 30.87. Found: C, 53.22; H, 4.64; N, 31.12.

***4-Amino-5-cyano-2-methyl-6-piperdinyl-nicotinic acid ethyl ester (8p).*** This compound was obtained as yellow solid, m.p. 108.0–110.0°C, yield 82%; $^1$H NMR ($CDCl_3$): δ 1.38(t, $J$ = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.67(d, $J$ = 7.2 Hz, 6H, 3*$CH_2$), 2.56 (s, 3H, Py-$CH_3$), 3.82(d, $J$ = 7.2 Hz, 4H, 2*$CH_2$), 4.32(q, $J$ = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 6.88 ppm (s, 2H, $NH_2$); $^{13}$C NMR ($CDCl_3$): δ 14.2, 24.6, 26.0, 28.1, 48.3, 60.5, 73.3, 98.9, 117.7, 158.9, 160.3, 164.4, 168.2 ppm; ms: $m/z$ 288 ($M^+$, 100), 259 (46), 245 (33), 231 (26), 205(64), 187 (37), 173 (52), 158 (35), 84 (75); *Anal*. Calcd. for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.18; H, 7.26; N, 19.21.

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## REFERENCES AND NOTES

[1] Yildiz, D. Toxicon 2004, 43, 619.

[2] Cutshall, N. S.; Kucera, K. A.; Ursion, R.; Latham, J.; Ihle, N. C. Bioorg Med Chem Lett 2002, 12, 1517.

[3] Roth, H. J.; Kleemann, A. In Pharmaceutical Chemistry. Drug Synthesis; Wiley: New York, 1988; Vol.1.

[4] Gilchrist, T. L. In Heterocyclic Chemistry, 3rd ed.; Addison Wesley Longman: Harlow, 1997; p 127.

[5] Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. Synthesis 2006, 55.

[6] Rabin, J. C.; Kirsch, G.; Beley, M. J Heterocycl Chem 2000, 37, 1077.

[7] Zhao, W. G.; Wang, S. H.; Wang, W. Y.; Li, Z. M. Huaxue Shiji 2000, 22, 376.

[8] Veronese, A. C.; Callegari, R.; Morellic, C. F. Tetrahedron 1995, 51, 12277.

[9] Zhao, W. G.; Liu, Z. X.; Li, Z. M.; Wang, B. L. Synth Commun 2003, 33, 4229.

[10] Liu, H.; Wang, H. Q.; Ding, M. W.; Liu, Z. J.; Xiao, W. J. J Fluorine Chem 2006, 127, 1584.

[11] Crystal structure of compound **8h** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 662948.

[12] Yang, F. L.; Liu, Z. J.; Huang, X. B.; Ding, M. W. J Heterocycl Chem 2004, 41, 77.

# Microwave-Assisted Synthesis and Evaluation of Antimicrobial Activity of 3-{3-(s-Aryl and s-Heteroaromatic)acryloyl}-2*H*-chromen-2-one Derivatives



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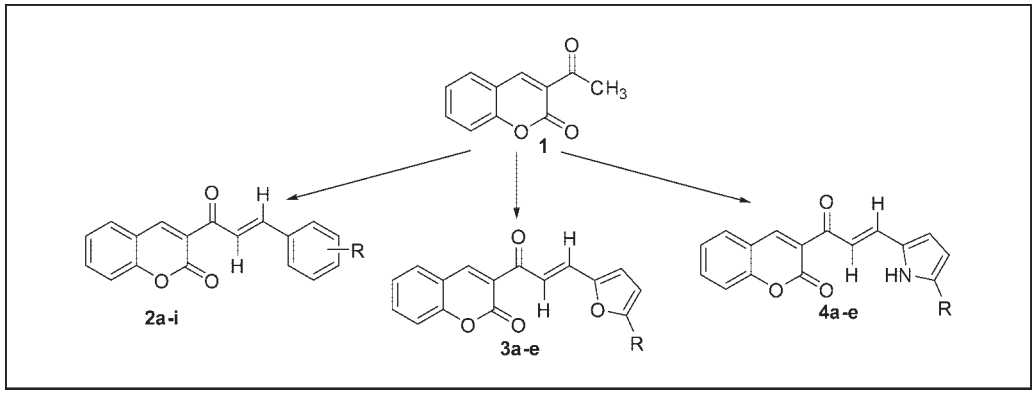


The exploration of potential utilization of microwaves as an energy source for heterocyclic synthesis was herein investigated using condensation of 3-acetylcoumarin (**1**) with aromatic and heteroaromatic aldehydes to afford the corresponding aromatic chalcones (**2a–j**) and heteroaromatic chalcones (**3a–e** and **4a–e**), respectively, in good to excellent yield within 1–3 min. The chemical structures were confirmed by analytical and spectral data. All the synthesized compounds were screened for their antibacterial activity and 3-{3-(4-dimethylaminophenyl)acryloyl}-2*H*-chromen-2-one (**2i**) was discovered to be the most active at minimum inhibitory concentration (MIC) value of 7.8 μg/mL.

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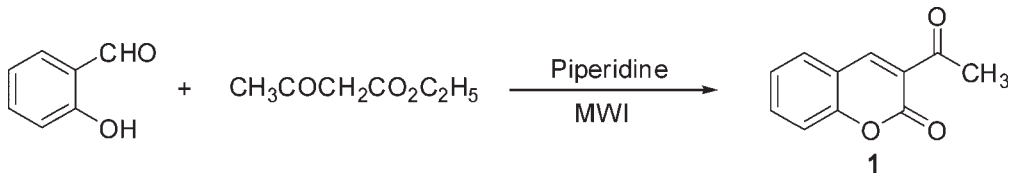
## INTRODUCTION

Over the years, coumarins have been established as well-known naturally occurring oxygen-heterocyclic compounds isolated from various plants [1–4]. They are the family of lactones containing benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory. The plant extracts containing coumarin-related heterocycles are employed as herbal remedies in traditional systems of medicine. The synthesis of coumarin (2-oxo-2*H*-chromene) derivatives has attracted considerable attention of organic and medicinal chemists due to its wide usage in food additives [5], fragrances, pharmaceuticals, and agrochemicals [6]. Furthermore, the pharmacological and biochemical properties as well as therapeutic applications of coumarins depend upon the pattern of substitution [7]. In view of this, coumarins have attracted intense interest in recent years because of their diverse pharmacological properties. Hence, coumarins have been reported to possess, among others, anticoagulant [8,9], antitubercular [10], antileucemic [11], antimicrobial [12,13], anti-inflammatory [14,15], anti-HIV [16], analgesic [17,18], anticancer [19], antitumoral [20], anticonvulsant [21,22], antiplatelet [23], antifungal [24,25] antiviral [26,27], antibacterial [28–31], and antimalarial [32] activities.

Some coumarin derivatives can be utilized beneficially for the synthesis of valuable heterocyclic ring systems. In like fashion, chalcones are essential building blocks [33] and valuable reactive intermediates for the synthesis of various heterocyclic compounds [34–36] as well as metal complexes [37–39] of high-biological relevance. Many techniques have been employed in the synthesis of coumarin frameworks [40,41] and chalcone moieties [42,43]. However, microwave-assisted approach toward the synthesis of coumarin chalcones has not been extensively explored.

The continuing drive to develop more economical and environmentally friendly chemical processes has spurred synthetic chemists to seek more versatile methods such as microwave method, for running reactions with less waste and short reaction time [44,45]. On the basis of the experimental data from various studies, chemists

**Scheme 1.** Microwave assisted synthesis of 3-acetylcoumarin, **1**.




have found that microwave-enhanced chemical reaction rates can be faster than those of conventional heating methods by as much as a 1000-fold [46].

In view of our current trust in the microwave-assisted organic synthesis [47] and various findings mentioned earlier, there is merit in developing a facile route for the formation of coumarins incorporated with chalcone templates *via* microwave synthetic approach to investigate the antimicrobial properties of such targeted library.

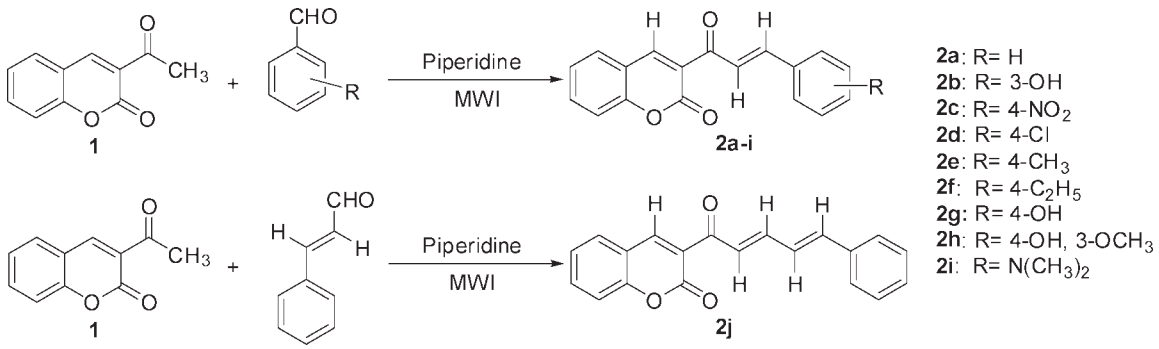
## RESULTS AND DISCUSSION

**Chemistry.** In a continuing effort to obtain new antimicrobial drug candidates, the synthesis of s-phenyl- and s-furan-2-ylcoumarin derivatives were attempted in the presence of catalytic amount of piperidine in a solvent less medium. 3-Acetylcoumarin, **1**, used as the essential precursor in this study, was synthesized by the reaction of salisaldehyde with ethyl acetoacetate in the presence of catalytic amount of piperidine (Scheme 1). Furthermore, 3-acetylcoumarin, **1** was made to undergo condensation reaction with substituted benzaldehdye to afford chalcones 3-{3-(s-aryl)acryloyl)}-2*H*-chromen-2-one, **2a–i**, whereas the replacement of benzaldehyde with cinnamaldehyde resulted in the formation of chalcone 3-(5-phenylpenta-2,4-dienoyl)-2*H*-chromen-2-one **2j** under microwave irradiation (Scheme 2). The reaction of **1** with heteroaromatic aldehyde; furfural and pyrrole-2-carbaladehyde furnished chalcones 3-{3-(s-heteroaromatic) acryloyl)}-2*H*-chromen-2-one **3a–e** and **4a–e**, respectively (Scheme 3) in moderate yields.

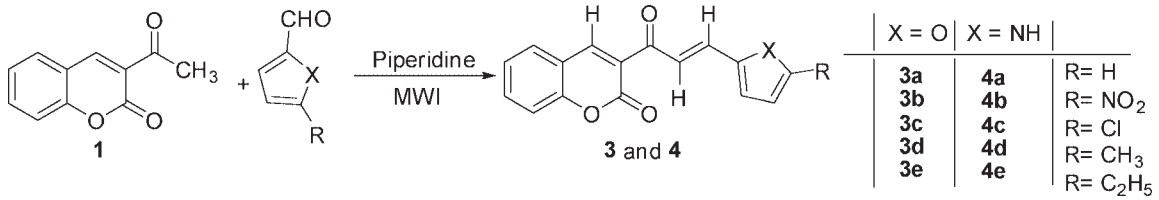
Preliminary optimization of reaction conditions was done by comparing the synthesis of **2a** in the presence of two solvents and solvent-free media (Table 1). It was observed that the solvent free medium gave the most suitable condition for the synthesis of **2a**, and therefore, it was used in all subsequent experiments. The effect of temperature was studied by carrying out the synthesis of **2a** at different temperatures; 50, 100, and 140°C (Table 2) using neat reaction condition in solvent free media. It was discovered that yield is a function of temperature, since the yield increased as the reaction temperature was raised. In fact, **2a** had the highest yield (97%) at 140°C. The results show that neat preparation of **2a** in solvent free medium at 140°C provides an efficient way to access diverse, highly functionalized coumarin containing chalcones. Hence, these optimum conditions were applied for the synthesis of a series of 3-{3-(s-aryl and (s-heteroaryl)acryloyl}-2*H*-chromen-2-one derivatives **2a–j**, **3a–e**, and **4a–e**, respectively. The melting points of the compounds varied between 119 and 289°C for all the compounds except **3c** and **4e** which did not melt even at 300°C. The progress of the reaction was monitored by TLC spotting with $R_f$ values ranging between 0.44 and 0.85 in acetone/methanol (3:1, v/v) solvent system.

The structures of newly synthesized compounds were elucidated by IR, UV, NMR, mass spectral studies, and elemental analysis. The IR spectrum, of **2a**, for instance, exhibited the absorption band at 1740 $cm^{-1}$ due to the presence of C=O (ester) which was confirmed by the presence of C—O of lactone at 1363 $cm^{-1}$. The band at 1673 $cm^{-1}$ and 1606 $cm^{-1}$ depicted the presence of C=O (conjugated ketone) and C=C (aromatic), respectively. The UV–visible spectrum of **2a** gave rise to wavelength ($\lambda_{max}$) at 224 nm and 348 nm with log ε

**Scheme 2.** Microwave assisted synthesis of various s-arylchalcones, **2a–j**.



**Scheme 3.** Microwave assisted synthesis of various s-heteroaromatic chalcones, **3a–e** and **4a–e**.




values of 3.99 and 3.47, respectively, whereas a shoulder was observed at 375 nm. The wavelength at 224 nm was as a result of $\pi \rightarrow \pi^*$ transition of phenyl ring, whereas 348 nm was as a result of $n \rightarrow \pi^*$ transition of the enone attached to coumarin moiety at 3-position, whereas a bathochromic shift observed as a shoulder at 375 nm was due to the presence of extensive conjugation of the π-electron systems. In $^1$H-NMR spectrum ($CD_3OD$) of **2a**, a doublet at δ 7.03 (1H, $J$ = 8.5 Hz, CO—CH=C); a multiplet at δ 7.33–7.84 (9H, which was made up of four protons of benzofused coumarin and five phenyl protons); a doublet at δ 7.82 (1H, $J$ = 8.5 Hz, CO—C=CH) and a singlet at δ 8.57 (1H, Coumarin-H) were all observed down field of TMS scale. The $^{13}$C-NMR spectrum showed peaks at δ 183.7 ppm due to C=O (conjugated ketone), whereas the peak at δ 159.4 ppm was due to the presence of C=O (ester). Other peaks which were observed between δ 153.0 and 116.1 ppm were due to sixteen $sp^2$ hybridized carbon atoms. The mass spectrum of **2a** showed the molecular ion peak at m/z 276 corresponding to its molecular weight. The base peak was observed at 173, whereas other daughter fragment noticed at m/z 199 was due to loss of phenyl free radical. The result of elemental analysis (Table 3) did not only correlate well with the molecular masses of the compounds but also showed a consistent minimum difference of not more than ±0.40 between % calculated and % found for the carbon, hydrogen, and nitrogen of the prepared compounds.

**Antibacterial activities.** The antibacterial activity of 21 synthesized compounds, **1**–**4e**, was determined *in vitro* by agar well diffusion technique [48]. The media were inoculated with test organisms and a solution of the tested compound in DMSO solvent. The zones of inhibition were measured after 24 h of incubation. The *in vitro* general sensitivity testing of the prepared compounds, **1**–**4e** was carried out against five gram positive bacteria [*Bacillus anthracis* (LIO), *Bacillus stearothermophilus* (NCIB 8222), *Bacillus subtilis* (NCIB 3610), *Bacillus cereus* (NCIB 6349), *Staphylococcus aureus* (NCIB 8588)] and five gram negative bacteria [*Escherichia coli* (NCIB 86), *Klebsiella pneumonia* (NCIB 418), *Pseudomonas aeruginosa* (NCIB 950), *Pseudomonas fluorescence* (NCIB 3756), *Shigella dysenteriae* (LIO)] as well as the standard drug streptomycin (Table 4). It was observed that the zones of inhibition of **1**, **2a**, **2d**, **2f**, **2g** on growth of various bacteria varied between 10 mm and 23 mm, whereas that of **2b**, **2c**, **2j**, **3a**, **4c** was between 10 mm and 21 mm. Others include **3b**, **3d**, **4d**, **4e** with zones of inhibition of 11–23 mm and **2e**, **2i**, **3c**, **4a** with inhibition zones of 15–31 mm.

In like fashion, the zones of inhibition of **2h** on the bacteria growth ranged between 14 mm and 18 mm, whereas that of **3e** ranged between 14 mm and 22 mm. Furthermore, streptomycin standard was active on all bacteria with the zones of inhibition ranging from 17 mm to 28 mm, except on *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* where resistance was noticed. Compared with streptomycin, compounds **2e**, **2i**, and **4a** revealed larger zones of inhibition against *Bacillus stearothermophilus* (*i.e.*, >23 mm) and *Bacillus subtilis* (*i.e.*, >27 mm), whereas **2d** and **4e** showed the same zones of inhibition as streptomycin upon *Bacillus cereus* (23 mm).

However, high degree of resistance as well as small zones of inhibition were observed upon the screening of synthesized compounds against *Bacillus cereus*, *Staphylococcus aureus, Pseudomonas aeruginosa*, *Pseudomonas fluorescence*, and *Shigella dysenteriae*. In view of these, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) tests were selectively carried out on the remaining five

**Table 1**

Synthesis of 3-cinnamoyl-2*H*-chromen-2-one, **2a**, in different solvents at 140°C.

| Entry | Solvent | Time/mins | Yield/% |
|---|---|---|---|
| 1 | Ethanol | 1 | 52 |
| 2 | Chloroform | 1 | 45 |
| 3 | Solvent free | 1 | 97 |

**Table 2**

Synthesis of 3-cinnamoyl-2*H*-chromen-2-one, **2a**, at different temperatures.

| Entry | Solvent | Temperature/°C | Yield/% |
|---|---|---|---|
| 1 | Solvent free | 140 | 97 |
| 2 | Solvent free | 100 | 83 |
| 3 | Solvent free | 50 | 58 |

**Table 3**

Physicochemical properties of compounds synthesized (**1–4e**).

| Comp no. | Molecular formula | Mol. wt. | Yield (%) | M.P. (°C) | $R_f$[a] | Color | Elem. Anal. %Calcd. (%Found) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| **1** | $C_{11}H_8O_3$ | 188 | 92.6 | 119–121 | 0.52 | yellow | 70.2(70.1) | 4.3(4.4) | – |
| **2a** | $C_{18}H_{12}O_3$ | 276 | 97.0 | 142–143 | 0.50 | yellow | 78.3(78.1) | 4.3(4.5) | – |
| **2b** | $C_{18}H_{12}O_4$ | 292 | 89.1 | 139–140 | 0.61 | yellow | 74.0(74.4) | 4.1(3.9) | – |
| **2c** | $C_{18}H_{11}NO_5$ | 321 | 78.3 | 170–172 | 0.69 | orange | 67.3(67.2) | 3.4(3.2) | 4.4(4.6) |
| **2d** | $C_{18}H_{11}ClO_3$ | 310.5 | 77.1 | 222–223 | 0.59 | yellow | 69.7(69.4) | 3.5(3.7) | – |
| **2e** | $C_{19}H_{14}O_3$ | 290 | 92.5 | 161–163 | 0.54 | yellow | 78.6(78.3) | 4.8(4.5) | – |
| **2f** | $C_{20}H_{16}O_3$ | 304 | 95.1 | 172–174 | 0.66 | cream | 78.9(78.6) | 5.3(5.1) | – |
| **2g** | $C_{18}H_{12}O_4$ | 292 | 97.8 | 246–249 | 0.68 | yellow | 74.0(73.8) | 4.1(4.3) | – |
| **2h** | $C_{19}H_{14}O_5$ | 322 | 77.1 | 230–231 | 0.70 | yellow | 70.8(70.9) | 4.3(4.1) | – |
| **2i** | $C_{20}H_{17}NO_3$ | 319 | 81.6 | 217–218 | 0.71 | red | 75.2(74.9) | 5.3(5.0) | 4.4(4.7) |
| **2j** | $C_{20}H_{14}O_3$ | 302 | 73.3 | 184–186 | 0.63 | yellow | 79.5(79.3) | 4.6(4.4) | – |
| **3a** | $C_{16}H_{10}O_4$ | 266 | 87.2 | 135–137 | 0.57 | brown | 72.2(72.4) | 3.8(3.5) | – |
| **3b** | $C_{16}H_9NO_6$ | 311 | 66.8 | 194–196 | 0.81 | yellow | 61.7(61.4) | 2.9(3.1) | 4.5(4.3) |
| **3c** | $C_{16}H_9ClO_4$ | 300.5 | 59.2 | > 300 | 0.44 | green | 63.9(64.1) | 3.0(2.8) | – |
| **3d** | $C_{17}H_{12}O_4$ | 280 | 74.8 | 200–201 | 0.49 | green | 72.9(72.6) | 4.3(4.5) | – |
| **3e** | $C_{18}H_{14}O_4$ | 294 | 66.5 | 240–241 | 0.85 | orange | 73.5(73.8) | 4.8(4.7) | – |
| **4a** | $C_{16}H_{11}NO_3$ | 265 | 71.4 | 209(dec) | 0.69 | black | 72.5(72.4) | 4.2(4.4) | 5.3(5.5) |
| **4b** | $C_{16}H_{10}N_2O_5$ | 310 | 63.7 | 268–269 | 0.85 | yellow | 61.9(62.2) | 3.2(3.3) | 9.0(9.2) |
| **4c** | $C_{16}H_{10}NClO_3$ | 299.5 | 55.8 | 288–289 | 0.55 | yellow | 64.1(61.5) | 3.3(3.5) | 4.7(4.5) |
| **4d** | $C_{17}H_{13}NO_3$ | 279 | 50.1 | 214–216 | 0.77 | orange | 73.1(73.5) | 4.7(4.6) | 5.0(4.8) |
| **4e** | $C_{18}H_{15}NO_3$ | 293 | 50.8 | > 300 | 0.83 | yellow | 73.7(73.3) | 5.1(5.0) | 4.8(4.6) |

[a] Solvent system: $CH_3COCH_3$:$CH_3OH$ (3:1, v/v) solvent system.

**Table 4**

Result of antibacterial screening (sensitivity testing) on bacteria with zones of inhibition (in mm).

| Comp. no. | Bacteria | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *B.a* | *B.c* | *B.s* | *B.su* | *S.a* | *E.c* | *K.p* | *P.a* | *P.f* | *S.d* |
| **1** | 10 | 10 | 11 | 23 | – | 14 | 12 | 13 | 10 | – |
| **2a** | – | 14 | 18 | 20 | – | 10 | 23 | – | 10 | – |
| **2b** | – | – | 20 | – | – | 17 | 19 | – | – | – |
| **2c** | 12 | – | – | 21 | 14 | 10 | 16 | – | – | – |
| **2d** | 17 | 23 | 23 | 16 | 10 | 14 | – | 16 | – | – |
| **2e** | 18 | 20 | 24 | 31 | 18 | 16 | 29 | 21 | 15 | 18 |
| **2f** | 21 | 15 | – | 23 | – | 15 | 19 | 11 | 10 | – |
| **2g** | – | – | 20 | 23 | – | 18 | 10 | – | – | – |
| **2h** | 18 | 18 | 15 | 11 | – | 16 | 14 | – | – | – |
| **2i** | 18 | 25 | 25 | 28 | – | 31 | 22 | 17 | – | 15 |
| **2j** | – | 10 | 20 | 20 | – | 21 | 16 | – | 12 | 18 |
| **3a** | – | – | 14 | 10 | 10 | 21 | 17 | – | – | – |
| **3b** | 11 | 8 | – | 11 | – | 19 | 23 | – | – | – |
| **3c** | – | – | 15 | 19 | – | 31 | 18 | 15 | – | – |
| **3d** | 13 | – | 12 | 18 | – | 17 | 23 | 15 | 13 | 11 |
| **3e** | 15 | – | 20 | 14 | 15 | 13 | 22 | 17 | – | – |
| **4a** | 18 | – | 31 | 28 | – | 16 | 15 | – | – | – |
| **4b** | 12 | – | – | 13 | – | 9 | 15 | 12 | – | – |
| **4c** | 18 | – | 12 | 15 | 13 | 21 | 13 | 13 | – | 10 |
| **4d** | 15 | 13 | 16 | 14 | – | 14 | 23 | – | – | 11 |
| **4e** | 17 | 23 | 22 | – | – | 13 | – | 11 | – | – |
| **str** | 20 | 23 | 23 | 27 | 21 | – | – | – | 22 | 17 |

–Indicates bacteria are resistant to the compounds >1000 μg/mL.

*B.a, Bacillus anthracis* (LIO)$^{G+}$; *B.c, Bacillus cereus* (NCIB 6349)$^{G+}$; *B.s, Bacillus stearothermophilus* (NCIB 8222)$^{G+}$; *B.su, Bacillus subtilis* (NCIB 3610)$^{G+}$; *S.a, Staphylococcus aureus* (NCIB 8588)$^{G+}$; *E.c, Escherichia coli* (NCIB 86)$^{G-}$; *K.p, Klebsiella pneumonia* (NCIB 418)$^{G-}$; *P.a, Pseudomonas aeruginosa* (NCIB 950)$^{G-}$; *P.f, Pseudomonas fluorescence* (NCIB 3756)$^{G-}$; *S.d, Shigella dysenteriae* (LIO)$^{G-}$; str, streptomycin; $^{G+}$, Gram positive; $^{G-}$, Gram negative.

**Table 5**

Results of MIC and MBC of synthesized compounds on some selected bacteria (in μg/mL).

| | Bacteria | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *B. anthracis* | | *B. stearotherm* | | *B. subtilis* | | *E. coli* | | *K. pneumonia* | |
| Comp. no. | MIC | MBC | MIC | MBC | MIC | MBC | MIC | MBC | MIC | MBC |
| **1** | 31.2 | 62.4 | 31.2 | 62.4 | 15.6 | 15.6 | 31.2 | 31.2 | 31.2 | 31.2 |
| **2a** | – | – | 15.6 | 15.6 | 7.8 | 7.8 | 31.2 | 62.4 | 7.8 | 31.2 |
| **2b** | – | – | 7.8 | 31.2 | – | – | 15.6 | 15.6 | 7.8 | 15.6 |
| **2c** | 31.2 | 62.4 | – | – | 7.8 | 7.8 | 31.2 | 62.4 | 15.6 | 62.4 |
| **2d** | 15.6 | 62.4 | 7.8 | 31.2 | 15.6 | 15.6 | 15.6 | 31.2 | – | – |
| **2e** | 7.8 | 15.6 | 7.8 | 15.6 | 7.8 | 7.8 | 15.6 | 31.2 | 7.8 | 31.2 |
| **2f** | 7.8 | 31.2 | – | – | 7.8 | 7.8 | 15.6 | 15.6 | 15.6 | 62.4 |
| **2g** | – | – | 7.8 | 7.8 | 7.8 | 7.8 | 15.6 | 15.6 | 31.2 | 62.4 |
| **2h** | 15.6 | 15.6 | 15.6 | 62.4 | 31.2 | 31.2 | 31.2 | 31.2 | 31.2 | 63.4 |
| **2i** | 7.8 | 7.8 | 7.8 | 15.6 | 7.8 | 7.8 | 7.8 | 7.8 | 7.8 | 7.8 |
| **2j** | – | – | 15.6 | 62.4 | 7.8 | 7.8 | 7.8 | 15.6 | 15.6 | 31.2 |
| **3a** | – | – | 31.2 | 31.2 | 31.2 | 31.2 | 7.8 | 7.8 | 7.8 | 15.6 |
| **3b** | 31.2 | 62.4 | – | – | 31.2 | 31.2 | 15.6 | 15.6 | 15.6 | 15.6 |
| **3c** | – | – | 31.2 | 93.6 | 7.8 | 7.8 | 7.8 | 7.8 | 15.6 | 31.2 |
| **3d** | 31.2 | 62.4 | 31.2 | 31.2 | 15.6 | 15.6 | 15.6 | 31.2 | 7.8 | 15.6 |
| **3e** | 15.6 | 31.2 | 7.8 | 15.6 | 31.2 | 62.4 | 31.2 | 62.4 | 7.8 | 31.2 |
| **4a** | 7.8 | 31.2 | 7.8 | 7.8 | 7.8 | 31.2 | 15.6 | 62.4 | 31.2 | 62.4 |
| **4b** | 31.2 | 31.2 | – | – | 15.6 | 31.2 | 31.2 | 31.2 | 7.8 | 15.6 |
| **4c** | 7.8 | 15.6 | 31.2 | 31.2 | 15.6 | 15.6 | 7.8 | 31.2 | 31.2 | 93.6 |
| **4d** | 15.6 | 62.6 | 15.6 | 31.2 | 15.6 | 31.2 | 15.6 | 15.6 | 7.8 | 31.2 |
| **4e** | 15.6 | 31.2 | 7.8 | 15.6 | – | – | 31.2 | 31.2 | – | – |
| **str** | 7.8 | 15.6 | 15.6 | 15.6 | 7.8 | 7.8 | – | – | – | – |

– Indicates bacteria are resistant to the compounds >100 μg/mL.
MIC, minimum inhibitory concentration, i.e. the lowest concentration to completely inhibit bacterial growth; MBC, minimum bactericidal concentration, i.e. the lowest concentration to completely kill bacteria.

microorganisms comprising three gram +ve (*Bacillus anthracis, Bacillus subtilis*, and *Bacillus stearothermophilus*) and two gram –ve (*Escherichia coli* and *Klebsiella pneumonia*e) bacterial strains (Table 5). MIC is defined as the lowest concentration of the compounds that completely inhibit the growth of microorganism, whereas MBC is the lowest concentration at which 99.9% of the inoculum was killed. The MIC values of the compounds varied between 7.8 and 31.2 μg/mL, whereas that of streptomycin was between 7.8 and 15.6 μg/mL. The MBC of few compounds was found to be the same as MIC but in most of the compounds, it was twofold or threefold or fourfold higher than their corresponding MIC values. In the long run, **2i** emerged as the most active antibacterial agent at 7.8 μg/mL.

## CONCLUSIONS

It was discovered that microwave-assisted approach is highly efficient procedure for the preparation of various coumarin chalcones, especially in the solvent-free media. By visualizing the antimicrobial data, the results revealed that the compounds exhibited high potency as antibacterial agents. The most active compound was 3-{(3-(4-dimethylamino phenyl)acryloyl}-2*H*-chromen-2-one (**2i**) with an MIC value of 7.8 μg/mL. Thus, 3-(substituted aryl and substituted heteroaromatic)acryloyl)-2*H*-chromen-2-one derivatives synthesized as well as the starting material may seem promising for further activity optimization studies.

## EXPERIMENTAL

**General condition (chemical synthesis).** Melting points were determined with open capillary tube on a Gallenkamp (variable heater) melting point apparatus and were uncorrected. Infra red spectra were recorded as KBr disc using a Shimadzu IR-740 Spectrophotometer, whereas UV–visible spectra were recorded on a Heλiosεα v2.02 Unicam Spectrophotometer using methanol solvent. $^{1}$H- and $^{13}$C-NMR were run on a Jeol EX 400 Spectrometer using deuteriated methanol with tetramethylsilane as the internal standard and δ values recorded in ppm. Mass spectra were run on Finnigan MAT 312 machine. All compounds were routinely checked by TLC on silica gel G plates using $CH_3COCH_3$:$CH_3OH$ (3:1, v/v) solvent system and the developed plates were visualized under UV light. The elemental analysis (C, H, N) of compounds were performed using a Carlo Erba-1108 elemental analyzer. The microwave-assisted syntheses were carried out in a CEM Discover monomode oven using sealed tube, with magnetic stirring, and the temperature control was fixed at 140°C. All reagents used

were obtained from Sigma-Aldrich Chemicals, except piperidine and furfural derivatives which were obtained from BDH Chemical Limited. Solvents used were of analytical grade and, when necessary, were purified and dried by standard method.

**3-Acetylcoumarin (1).** To a mixture of salicyaldehyde (0.86 mL, 81.89 mmoles) and ethyl acetoacetate (11.5mL, 90.13 mmoles) was added catalytic amount of piperidine (0.2 mL, 1.64 mmoles) and swirled thoroughly. The mixture was irradiated in microwave oven at 400 W for 1 min. The solid product was filtered, dried, and recrystallized from methanol to afford pure 3-acetyl coumarin **1** in appropriate yield (Table 3). $\lambda_{max}$ (Log ε): 216 (5.29), 236 (4.65), 288 (4.57), 327 (4.57), 348 (4.49), 355 (4.24), 369 (4.01). IR (KBr): 2925 (CH aliphatic), 1746 (C=O ester), 1685 (C=O), 1606 (C=C), 1369 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 2.27 (s, 3H, $CH_3$), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 198.7 (C=O), 159.4 (C=O), 153.0, 137.4, 131.2, 128.3, 127.9, 125.4, 118.1, 116.1, 29.6 ($CH_3$) ppm. MS: m/z 188 ($M^+$, 80%), 145 (100%), 94 (50%).

**General procedure for synthesis of (2a–j).** To an equimolar mixture of 3-acetylcoumarin, **1** (1 g, 5.3 mmoles) and substituted benzaldehyde (5.3 mmoles) was added piperidine (0.2 mL, 1.64 mmoles) drop wisely with continuous stirring until homogeneity was achieved. The mixture was irradiated in microwave oven at 400 W for 1–3 min. The crude product was filtered, dried, and recrystallized from appropriate solvent to afford **2a–j** in varied yields (Table 3).

***3-Cinnamoyl-2H-chromen-2-one (2a).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), benzaldehyde (0.5 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 3 min, 140°C. Purification: recrystallization (ethanol). $\lambda_{max}$ (Log ε): 224 (3.99), 348 (3.47), 375 (3.01s). IR (KBr): 1740, 1673, 1606, 1363 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.33–7.84 (m, 9H, Benzofused coumarin-4H and Ar-5H), 7.82 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 147.2, 142.2, 135.2, 134.2, 128.6, 128.6, 128.5, 128.5, 128.3, 127.9, 127.9, 125.4, 125.4, 118.1, 116.1 ppm. MS: m/z 276 ($M^+$, 75%), 199 (60%), 173 (100%).

***3-(3-(3-Hydroxyphenyl)acryloyl)-2H-chromen-2-one (2b).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), *m*-hydroxybenzaldehyde (0.65 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2 min, 140°C. Purification: recrystallization (methanol). $\lambda_{max}$ (Log ε): 208 (3.82), 280 (3.32), 348 (3.46), 361 (3.46), 369 (3.45). IR (KBr): 3302, 1703, 1648, 1600, 1375 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 5.35 (s, 1H, OH, $D_2O$ exchangeable), 6.70 (s, 1H, Ar-H), 6.83 (d, 1H, Ar-H), 7.03 (d, 1H, $J$ = 8.8 Hz, CO—CH=C), 7.16 (d, 1H, Ar-H), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.53 (t, 1H, Ar-H), 7.96 (d, 1H, $J$ = 8.8 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 158.4, 153.0, 147.2, 142.2, 135.4, 134.2, 130.0, 128.3, 127.9, 125.4, 125.4, 121.1, 118.1, 117.6, 116.1, 115.1 ppm. MS: m/z 292 ($M^+$, 30%), 275 (50%), 199 (25%), 145 (100%).

***3-(3-(4-Nitrophenyl)acryloyl)-2H-chromen-2-one (2c).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), *p*-nitrobenzaldehyde (0.80 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 1 min, 140°C. Purification: recrystallization (methylated spirit). $\lambda_{max}$ (Log ε): 220 (4.22), 328 (3.76), 368 (3.87). IR (KBr): 1740, 1673, 1606, 1364, 738 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 7.32 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.96 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 8.03 (d, 2H, Ar-H), 8.21 (d, 2H, Ar-H), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 147.2, 147.1, 142.2, 141.3, 134.2, 129.0, 129.0, 128.3, 127.9, 125.4, 125.4, 123.8, 123.8, 118.1, 116.1 ppm. MS: m/z 321 ($M^+$, 70%), 275 (47%), 145 (100%).

***3-(3-(4-Chlorophenyl)acryloyl)-2H-chromen-2-one (2d).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), *p*-chlorobenzaldehyde (0.74 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 1.5 min, 140°C. Purification: recrystallization (methanol). $^1$H-NMR ($CD_3OD$, 400 Hz): δ 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.82 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 7.44 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 153.0, 147.2, 142.2, 134.2, 133.5, 133.3, 129.0, 129.0, 128.7, 128.7, 128.3, 127.9, 125.4, 125.4, 118.1, 116.1 ppm. MS: m/z 310.5 ($M^+$, 80%), 275 (40%).

***3-(3-(3-p-Tolylacryloyl)-2H-chromen-2-one (2e).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), *p*-methylbenzaldehyde (0.65 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2 min, 140°C. Purification: recrystallization (methanol). $^1$H-NMR ($CD_3OD$, 400 Hz): δ 2.34 (s, 3H, $CH_3$), 7.18 (d, 2H, Ar-H), 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.59 (d, 2H, Ar-H), 7.82 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 153.0, 147.2, 142.2, 137.6, 134.2, 132.2, 128.9, 128.9, 128.5, 128.5, 128.3, 127.9, 125.4, 125.4, 118.1, 116.1, 21.3 ($CH_3$) ppm. MS: m/z 290 ($M^+$, 50%), 199 (100%).

***3-(3-(4-Ethylphenyl)acryloyl)-2H-chromen-2-one (2f).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), *p*-ethylbenzaldehyde (0.72 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2 min, 140°C. Purification: recrystallization (methanol). $^1$H-NMR ($CD_3OD$, 400 Hz): δ 1.25 (t, 3H, $J$ = 7.0 Hz, $CH_3$), 2.60 (q, 2H, $J$ = 7.0 Hz, $CH_2$), 6.77 (d, 2H, Ar-H), 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.42–7.84 (m, 6H, Benzofused coumarin-4H and Ar-2H), 7.82(d, 1H, $J$ = 8.5 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 153.0, 142.2, 143.5, 142.2, 134.2, 132.4, 128.5, 128.5, 128.3, 127.9, 127.6, 127.6, 125.4, 125.4, 118.1, 116.1, 28.2 ($CH_2$), 14.5 ($CH_3$). MS: m/z 304 ($M^+$, 80%), 285 (35%), 145 (100%).

***3-(3-(4-Hydroxyphenyl)acryloyl)-2H-chromen-2-one (2g).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), *p*-hydroxybenzaldehyde (0.65 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 3 min, 140°C. Purification: recrystallization (ethanol). $\lambda_{max}$ (Log ε): 211 (3.52), 336 (3.41), 368 (3.56). IR (KBr): 3241, 1734, 1685, 1612, 1375 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 5.35 (s, 1H, OH, $D_2O$ exchangeable), 6.65 (d, 2H, Ar-H), 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.56 (d, 2H, Ar-H), 7.82 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 157.7 (C—OH), 153.0, 147.2, 142.2, 134.2, 130.6, 130.6, 128.3, 127.9, 127.8, 125.4, 125.4, 118.1, 116.1, 115.8 ppm. MS: m/z 292 ($M^+$, 40%), 275 (75%), 199 (50%), 145 (100%).

***3-(3-(4-Hydroxy-3-methoxyphenyl)acryloyl)-2H-chromen-2-one (2h).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), vanillin

(0.81 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 1 min, 140°C. Purification: recrystallization (ethanol). $\lambda_{max}$ (Log ε): 208 (4.03), 244 (3.91), 352 (3.42). IR (KBr): 1740, 1685, 1600, 1338 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 3.83 (s, 3H, $OCH_3$), 5.35 (s, 1H, OH, $D_2O$ exchangeable), 6.79 (d, 1H, Ar-H), 6.99 (d, 1H, Ar-H), 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.16 (s, 1H, Ar-H), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.82 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 149.1 (*C*—$OCH_3$), 147.9 (C—OH), 147.2, 142.2, 134.2, 128.3, 127.9, 127.6, 125.4, 125.4, 122.9, 118.1, 116.8, 116.1, 111.9, 56.1 ($OCH_3$) ppm. MS: m/z 323 ($M^+$, 68%), 275 (60%), 199 (50%).

***3-(3-(4-Dimethylaminophenyl)acryloyl)-2H-chromen-2-one (2i).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 4-(*N*,*N*-dimethylamino)benzaldehyde (1.27 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2.5 min, 140°C. Purification: recrystallization (ethanol). $\lambda_{max}$ (Log ε): 208 (4.00), 327 (3.90s), 344 (3.97), 448 (3.84). IR (KBr): 1746, 1685, 1594, 1375 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 3.06 (s, 6H, 2×$CH_3$), 6.71 (d, 2H, Ar-H), 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.72 (d, 2H, Ar-H), 7.42–7.84 (m, 4H, Ar-H), 7.82 (d, 1H, $J$ = 8.5 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 150.3, 147.2, 142.2, 134.2, 129.7, 129.7, 128.3, 127.9, 125.4, 125.4, 124.7, 118.1, 116.1, 111.7, 111.7, 41.3 (2×$CH_3$) ppm. MS: m/z 319 ($M^+$, 70%), 199 (100%).

***3-(5-Phenylpenta-2,4-dienoyl)-2H-chromen-2-one (2j).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), cinnamaldehyde (0.67 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 1 min, 140°C. Purification: recrystallization (ethanol). $\lambda_{max}$ (Log ε): 212 (3.72), 300 (3.49), 330 (3.49), 347 (3.53), 360 (3.53), 366 (3.53), 369 (4.01). IR (KBr): 1740, 1648, 1612, 1375 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 6.69 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 6.71 (d, 1H, $J$ = 8.5 Hz, 9.2 Hz, CO—C=C—CH), 7.02 (d, 1H, $J$ = 9.2 Hz, COC=C—C=CH), 7.52 (d, 1H, $J$ = 8.5 Hz, 9.2 Hz, CO—C=CH), 7.33–7.84 (m, 9H, Benzofused coumarin-4H and Ar-5H), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 151.9, 147.2, 141.0, 135.2, 134.2, 128.6, 128.6, 128.5, 128.5, 128.3, 127.9, 127.9, 125.4, 125.2, 121.2, 118.1, 116.1 ppm. MS: m/z 302 ($M^+$, 55%).

**General procedure for synthesis of (3a–e) and (4a–e).** A catalytic amount of piperidine (0.2 mL, 1.64 mmoles) was cautionly added to a well-ground mixture of 3-acetyl coumarin **1**(1.0 g, 5.3 mmoles) and substituted heteroaromatic aldehyde (5.3 mmoles). The reaction mixture was irriadiated in microwave oven at an emitted power of 400 W for an appropriate time. Then, it was poured in crushed ice and the product was filtered and recrystallized from appropriate solvent to give **3a**–**e** and **4a**–**e**.

***3-(3-(Furan-2-yl)acryloyl)-2H-chromen-2-one (3a).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), furfural (0.33 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 3 min, 140°C. Purification: recrystallization (methylated spirit). $\lambda_{max}$ (Log ε): 220 (3.88), 348 (3.49), 368 (3.65). IR (KBr): 1734, 1648, 1606, 1380 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 6.87 (t, 1H, Furan-H), 7.03 (d, 1H, $J$ = 8.7 Hz, CO—CH=C), 7.42–7.84 (m, 5H, Benzofused coumarin-4H & Furan-1H), 7.66 (d, 1H, $J$ = 8.7 Hz, CO—C=CH), 8.17 (d, 1H, Furan-H), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 151.5, 147.2, 143.7, 138.9, 134.2, 129.3, 128.3, 127.9, 125.4, 118.1, 116.1, 113.8, 112.7. MS: m/z 266 ($M^+$, 25%), 199 (75%), 68 (33%).

***3-(3-(5-Nitrofuran-2-yl)acryloyl)-2H-chromen-2-one (3b).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-nitrofurfural (0.47 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 1.5 min, 140°C. Purification: recrystallization (aqueous ethanol, 1:1). $\lambda_{max}$ (Log ε): 216 (4.03), 372 (3.77). IR (KBr): 1734, 1685, 1600, 1376 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 7.03 (d, 1H, $J$ = 8.7 Hz, CO—CH=C), 7.42–7.85 (m, 5H, Benzofused coumarin-4H & Furan-1H), 7.66 (d, 1H, $J$ = 8.7 Hz, CO—C=CH)), 7.94 (d, 1H, Furan-H), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 155.4, 153.8, 153.0, 147.2, 138.9, 134.2, 129.3, 128.3, 127.9, 125.4, 118.1, 117.5, 116.1, 114.5. MS: m/z 311 ($M^+$, 20%), 265 (45%).

***3-(3-(5-Chlorofuran-2-yl)acryloyl)-2H-chromen-2-one (3c).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-chlorofurfural (0.69 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 1 min, 140°C. Purification: recrystallization (ethanol). $\lambda_{max}$ (Log ε): 216 (4.28), 368 (4.41), 388 (3.95). IR (KBr): 1744, 1648, 1605, 1380 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 6.89 (d, 1H, $J$ = 9.3 Hz, Furan-H), 7.03 (d, 1H, $J$ = 8.7 Hz, CO—CH=C), 7.24 (d, 1H, $J$ = 9.3 Hz, Furan-H), 7.42–7.84 (m, 4H, Benzofused coumarin-H ), 7.66 (d, 1H, $J$ = 8.7 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 151.9, 147.2, 138.9, 138.7, 134.2, 129.3, 128.3, 127.9, 125.4, 118.1, 116.1, 114.1, 109.8. MS: m/z 300.5 ($M^+$, 60%), 199 (80%), 103.5 (38%).

***3-(3-(5-Methylfuran-2-yl)acryloyl)-2H-chromen-2-one (3d).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-methylfurfural (0.53 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2.5 min, 140°C. Purification: recrystallization (methylated spirit). $\lambda_{max}$ (Log ε): 208 (4.03), 244 (3.91), 352 (3.42). IR (KBr): 1740, 1685, 1600, 1338 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 2.30 (s, 3H, $CH_3$), 6.43 (d, 1H, $J$ = 9.5 Hz, Furan-H), 7.03 (d, 1H, $J$ = 8.5 Hz, CO—CH=C), 7.28 (d, 1H, $J$ = 9.5 Hz, Furan-H), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.66 (s, 1H, CO—C=CH). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 157.6, 153.0, 152.4, 147.2, 138.9, 134.2, 129.3, 128.3, 127.9, 125.4, 118.1, 117.5, 116.1, 109.5, 13.8 ($CH_3$). MS: m/z 280 ($M^+$, 83%), 265 (52%), 68 (30%).

***3-(3-(5-Ethylfuran-2-yl)acryloyl)-2H-chromen-2-one (3e).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-ethyl-2-furaldehyde (0.63 mL, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2 min, 140°C. Purification: recrystallization (methylated spirit). $\lambda_{max}$ (Log ε): 212 (4.07), 248 (3.84), 368 (3.42). IR (KBr): 1734, 1648, 1606, 1380 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 1.25 (t, 3H, $J$ = 6.0 Hz, $CH_3$), 2.44 (q, 2H, $J$ = 6.0 Hz, $CH_2$), 6.43 (d, 1H, $J$ = 10.0 Hz, Furan-H), 7.03 (d, 1H, $J$ = 8.6 Hz, CO—CH=C), 7.28 (d, 1H, $J$ = 10.0 Hz, Furan-H), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.66 (d, 1H, $J$ = 8.6 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 157.4, 153.0, 151.8, 147.2, 138.9, 134.2, 129.3, 128.3, 127.9, 125.4, 120.0, 118.1, 116.1, 108.7, 21.4 ($CH_2$), 12.7 ($CH_3$). MS: m/z 294 ($M^+$, 40%). 280 (45%).

***3-(3-(1H-Pyrrol-2-yl)acryloyl-2H-chromen-2-one (4a).*** Reagents: Compound **1** (1.0 g, 5.3 mmol), pyrrole-2-carboxaldehyde (0.50 g, 5.3 mmol), piperidine (0.2 mL). Conditions: MWI for

2.5 min, 140°C. Purification: recrystallization (DMF/ethanol, 1:9). $\lambda_{max}$ (Log ε): 212 (4.16), 344 (3.62). IR (KBr): 3445, 1685, 1600, 1348 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 5.00 (s, 1H, NH, $D_2O$ exchangeable), 6.15 (t, 1H, $J$ = 12.5 Hz, 15 Hz, Pyrrolo-H), 6.51 (d, 1H, $J$ = 12.5 Hz, Pyrrolo-H), 6.95 (d, 1H, $J$ = 15 Hz, Pyrrolo-H), 7.03 (d, 1H, $J$ = 8.0 Hz CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.66 (d, 1H, $J$ = 8.0 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 153.0, 147.2, 143.4, 134.2, 129.8, 129.3, 128.3, 127.9, 125.4, 118.3, 118.1, 116.1, 111.9, 108.2. MS: m/s 266 ($M^+$, 62%), 199 (100%), 67 (48%).

***3-(3-(5-Nitro-1H-pyrrol-2-yl)acryloyl)-2H-chromen-2-one (4b).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-nitro-1*H*-pyrrole-2-carboxaldehyde (0.74 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2.5 min, 140°C. Purification: recrystallization (DMF/ethanol, 1:9). $\lambda_{max}$ (Log ε): 210 (3.93), 368 (3.52). IR (KBr): 3302, 1740, 1685, 1600, 1338 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 5.0 (s, 1H, NH; $D_2O$ exchangeable), 6.75 (d, 1H, $J$ = 12.3 Hz, Pyrrolo-H), 7.03 (d, 1H, $J$ = 7.5 Hz, CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-4H), 7.46 (d, 1H, $J$ = 12.3 Hz, Pyrrolo-H), 7.66 (d, 1H, $J$ = 7.5 Hz, CO—C=CH), 8.57 (d, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 147.2, 143.4, 139.9, 134.2, 134.0, 129.3, 128.3, 127.9, 125.4, 118.1, 116.1, 112.5, 109.3. MS: m/z 311 ($M^+$, 55%), 67 (35%).

***3-(3-(5-Chloro-1H-pyrrol-2-yl)acryloyl)-2H-chromen-2-one (4c).*** Reagents: Compound 1 (1.0 g, 5.3 mmoles), 5-chloro-1*H*-pyrrole-2-carboxaldehyde (0.69 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2.5 min, 140°C. Purification: recrystallization (DMF/ethanol, 3:7). $\lambda_{max}$ (Log ε): 212 (4.29), 252 (3.84), 350 (3.42s). IR (KBr): 3241, 1734, 1685, 1612, 1375, 980 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 5.0 (s, 1H, NH; $D_2O$ exchangeable), 6.40 (d, 1H, $J$ = 11.2 Hz, Pyrrolo-H), 6.51 (d, 1H, $J$ = 11.2 Hz, Pyrrolo-H), 7.03 (d, 1H, $J$ = 8.1 Hz, CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.66 (d, 1H, $J$ = 8.1 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7, 159.4, 153.0, 147.2, 143.4, 134.2, 129.8, 129.3, 128.3, 127.9, 125.4, 121.8, 118.1, 116.3, 116.1, 112.1. MS: m/z 300.5 ($M^+$, 55%).

***3-(3-(5-Methyl-1H-pyrrol-2-yl)acryloyl)-2H-chromen-2-one (4d).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-methyl-1*H*-pyrrole-2-carboxaldehyde (0.58 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2.5 min, 140°C. Purification: recrystallization (methanol). $\lambda_{max}$ (Log ε): 220 (3.87), 368 (4.15), 388 (3.72). IR (KBr): 3302, 2929, 1734, 1648, 1600, 1375 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 2.14 (s, 3H, $CH_3$), 5.0 (s, 1H, NH; $D_2O$ exchangeable), 6.07 (d, 1H, $J$ = 11.5 Hz, Pyrrolo-H), 6.35 (d, 1H, $J$ = 11.5 Hz, Pyrrolo-H), 7.03 (d, 1H, $J$ = 8.1 Hz, CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.66 (d, 1H, $J$ = 8.1 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 147.2, 143.4, 134.2, 130.1, 129.5, 129.3, 128.3, 127.9, 125.4, 118.1, 116.1, 112.0, 106.5, 17.3 ($CH_3$).

***3-(3-(5-ethyl-1H-pyrrol-2-yl)acryloyl)-2H-chromen-2-one (4e).*** Reagents: Compound **1** (1.0 g, 5.3 mmoles), 5-ethyl-1*H*-pyrrole-2-carboxaldehyde (0.65 g, 5.3 mmoles), piperidine (0.2 mL). Conditions: MWI for 2.5 min, 140°C. Purification: recrystallization (methylated spirit). $\lambda_{max}$ (Log ε): 220 (4.11), 250 (3.91), 368 (3.42). IR (KBr): 3241, 1746, 1740, 1650, 1594, 1375 $cm^{-1}$. $^1$H-NMR ($CD_3OD$, 400 Hz): δ 1.24 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 3.11 (q, 2H, $J$ = 7.2 Hz, $CH_2$), 5.0 (s, 1H, NH; $D_2O$ exchangeable), 6.07 (d, 1H, $J$ = 11.5 Hz, Pyrrolo-H), 6.35 (d, 1H, $J$ = 11.5 Hz, Pyrrolo-H), 7.03 (d, 1H, $J$ = 8.2 Hz, CO—CH=C), 7.42–7.84 (m, 4H, Benzofused coumarin-H), 7.66 (d, 1H, $J$ = 8.2 Hz, CO—C=CH), 8.57 (s, 1H, Coumarin-H). $^{13}$C-NMR ($CD_3OD$, 400 Hz): δ 183.7 (C=O), 159.4 (C=O), 153.0, 147.2, 143.4, 136.1, 134.2, 129.5, 129.3, 128.3, 127.9, 125.4, 118.1, 116.1, 112.0, 107.7, 21.4 ($CH_2$), 13.7 ($CH_3$).

**Antibacterial activity assays.** Most of the organisms used were standard bacteria of National Collection for Industrial Bacteria (NCIB), whereas few others were Locally Isolated Organisms (LIO). The organisms were *Bacillus cereus* (NCIB 6349), *Bacillus stearothermophilus* (NCIB 8222), *Bacillus subtilis* (NCIB 3610), *Bacillus anthracis* (LIO), *Bacillus polymyxa* (LIO), *Corynebacterium pyogenes* (LIO), *Streptococcus faecalis* (NCIB775), *Staphylococcus aureus* (NCIB 8588), *Clostridium sporogenes* (LIO), *Escherichia coli* (NCIB 86), *Pseudomonas fluorescence* (NCIB 3756), *Klebsiella pneumonia* (NCIB 418), *Shigella dysenteriae* (LIO), *Pseudomonas aeruginosa* (NCIB 950), and *Candida albican* (LIO).

**Antibacterial sensitivity testing of compounds, 1–4e.** All the synthesized compounds (**1–4e**) and streptomycin were screened for antibacterial activity on nine gram positive and five gram negative bacterial strains using agar well diffusion method [48]. The medium employed was diagnostic sensitivity test agar (Biotech Ltd.). With the aid of a sterile 1 mL pipette, about 0.2 mL of the broth culture of test organism was added to 18 mL sterile molten diagnostic sensitivity test agar (Biotech Ltd.) which had already cooled down to 45°C. This was well mixed and poured into previously sterilized Petri dishes, which had been properly labeled according to the test organisms. The medium was then allowed to set. With the aid of a sterile cork borer, the required numbers of holes were bored into the medium. The wells were made of about 5 mm to the edge of the plate. The wells were then filled up aseptically with the solution of the compound in DMSO using Pasteur pipettes. Streptomycin was used as the standard antibacterial agent at a concentration of 1000 μg/mL. The plates were allowed to stand for about 1 h on the bench for proper diffusion of the antibacterial agents into the medium and then incubated uprightly at 37°C for 24 h. Care was taken not to stockpile the plates. Clear zones of inhibition in millimetres indicated the relative susceptibility of the bacteria to the compounds (**1–4e**) and streptomycin standard.

**Determination of MIC and MBC.** The minimum inhibitory concentration (MIC) was done using the method of Russell and Furr [48]. Based on the level of resistance of some organisms and large zones of inhibition experienced in others, minimum inhibitory concentration (MIC) was selectively done for five gram positive and five gram negative bacterial strains. Different concentrations (7.8 and 100.0 μg/mL) of the compounds and standard were prepared using a twofold dilution which was prepared in a sterile plate with the aid of sterile pipette and then mixed with 18 mL of molten nutrient agar. This was then allowed to set. The surface of the nutrient agar plate was allowed to dry before streaking with overnight broth cultures of the bacterial strains. The plates were then labeled accordingly and incubated at 37°C for up to 72 h. They were subsequently examined for the presence or absence of growth.

The lowest concentration preventing the growth of bacteria was taken as the minimum inhibitory concentration of the compounds. This procedure was likewise repeated for the streptomycin (standard).

To obtain minimum bactericidal concentration (MBC), 0.1 mL volume was taken from each tube and spread on agar plates. The number of c.f.u was counted after 18–24 h of incubation at 35°C.

## REFERENCES AND NOTES

[1] Lévai, A.; Jekó, J. ARKIVOC 2009, vi, 63.

[2] Curir, P.; Galeotti, F.; Marcello, D.; Barile, E.; Lanzotti, V. J Nat Prod 2007, 70, 1668.

[3] Tran, Q. L.; Tezuka, Y.; Ueda, J.-Y.; Nguyen, N. T.; Maruyawa, Y.; Begum, K.; Kim, H. S.; Tran, Q. K.; Kadota, S. J Ethnopharmacol 2003, 86, 249.

[4] Yenjai, C.; Sripontan, S.; Sriprajun, P.; Kittakoop, P.; Jintasirikul, A.; Tanticharoen, M.; Thebtaranonth, Y. Planta Med 2000, 66, 277.

[5] Ragitha, B.; Kumar, N. V.; Someshwar, P.; Madhav, J. V.; Reddy, P. N.; Reddy, Y. T. ARKIVOC 2006, xii, 23.

[6] Dekić, S. V.; Dekić, V. S.; Vučić, B.; Dekić, B. R.; Dekić, M. S. Phys Chem Technol 2007, 5, 85.

[7] Kostova, I.; Raleva, S.; Genova, P.; Argirova, R. Bioinorg Chem Appl 2006, 2006, 68274.

[8] Anderson, D. M.; Shelley, S.; Crick, N.; Buraglio, M. J Clin Pharmacol 2002, 42, 1358.

[9] Tassies, D.; Freire, C.; Puoan, J.; Maragall, S.; Monteagudo, J.; Ordinas, A.; Reverter, J. C. Haematologica 2002, 87, 1185.

[10] Gürsoy, A.; Karali, N. Turk J Chem 2003, 27, 545.

[11] Kotali, A.; Lafazanis, I. S.; Papageorgiou, A.; Chrysogelou, E.; Liarliaris, T.; Sinakos, Z. Molbank 2008, M574, 1.

[12] Satyanarayana, V. S. V.; Sreevani, P.; Sivakumar, A.; Vijayakumar, V. ARKIVOC 2008, vii, 221.

[13] Raviraj, A. K.; Manohar, V. K. Indian J Chem 2005, 44B, 591.

[14] Kontogiorgis, C. A.; Savvoglou, K.; Hadjipavlou-Litina, D. J. J Enzyme Inhib Med Chem 2006, 21, 21.

[15] Srinivas, K. K.; Hager, E.; Pehit, C.; Davidson, N. E.; Khan, S. R. J Med Chem 2003, 46, 2831.

[16] Meteeva, N. N.; Kode, R. M.; Redda, K. K. J Heterocycl Chem 2002, 39, 1251.

[17] Jayashree, B. K.; Sameer, A.; Yogendra, N. Pharmacologyonline 2008, 2, 404.

[18] Venugopala, K. N.; Jayashree, B. S. Asian J Chem 2004, 16, 407.

[19] Lacy, A.; O'Kennedy, R. Curr Pharm Des 2004, 10, 3797.

[20] Al-Soud, Y. A.; Al-Sa'doni, H. H.; Amajaour, H. A. S.; Salih, K. S. M.; Mubarak, M. S.; Al-Masoudi, N. A.; Jaber, I. H. Z Naturforsch B 2008, 63, 83.

[21] Luszcski, J. J.; Andres-Mach, M.; Cisowswi, W.; Mazol, I.; Glowniak, K.; Czuczwar, S. J. Eur J Pharmacol 2009, 607, 107.

[22] Tosun, F.; Kizilay, Ç. A.; Erol, K.; Kiliç, F. S.; Kürkçüoğlu, M.; Başer, K. H. C. Food Chem 2008, 107, 990.

[23] Roma, G.; Di Braccio, M.; Grossi, G.; Piras, D.; Leoncini, G.; Bruzzese, D.; Grazia, S. M.; Fossa, P.; Mosta, L. J Med Chem 2007, 50, 2886.

[24] Montagner Souza, S. M. D.; Groposo, C.; Monache, F. D.; Smania, E. F. A.; Smania, A., Jr.; Z Naturforsch C 2008, 63, 21.

[25] Mouri, T.; Yano, T.; Kochi, S. I.; Ando, T.; Hori, M. J Pestic Sci 2005, 30, 209.

[26] Neyts, J.; De Clercq, E.; Singha, R.; Chang, Y. H.; Das, A. R.; Chakraborty, S. K.; Hong, S. C.; Tsay, S.-C.; Hsu, M.-H.; Hwu, J. R. J Med Chem 2009, 52, 1486.

[27] Hwu, J. R.; Singha, R.; Hong, S. C.; Chang, Y. H.; Das, A. R.; Vliengen, I.; De Clercq, E.; Neyts, J. Antiviral Res 2008, 77, 157.

[28] Govori, S. R.; Spahiu, S.; Haziri, A. FASEB J 2008, 22, 1061.

[29] Siddiqui, Z. N.; Asad, M.; Praveen, S. Med Chem Res 2008, 17, 318.

[30] Mashelkar, U. C.; Audi, A. A. J Indian Chem Soc 2005, 82, 254.

[31] Lee, S.; Shin, S.-D.; Kim, J. S.; Oh, K.-B.; Kang, S. S. Arch Pharm Res 2003, 26, 449.

[32] Lisgarten, J. N.; Potter, B. S.; Aymami, J.; Oketch-Rabah, H.; Palmer, R. A. J Chem Crystallogr 2003, 33, 149.

[33] Yun, J. M.; Kweon, M. H.; Kwon, H.; Wang, J. K.; Mukhtar, H. Carcinogenesis 2006, 27, 1454.

[34] Gaber, M.; Fayed, T. A.; El-Daly, S. A.; El-Sayed, Y. S. Photochem Photobiol Sci 2008, 7, 257.

[35] Larsen, M.; Kromann, H.; Kharazmi, A.; Nielsen, S. F. Bioorg Med Chem Lett 2005, 15, 4858.

[36] Anzari, F. L.; Umbreen, S.; Hussain, L.; Makhmoor, T.; Nawaz, S. A.; Lodhi, M. A.; Khan, S. N.; Shaheen, F.; Choudhary, M. I.; Rahman, A. U. Chem Biodivers 2005, 2, 487.

[37] Son, K. I.; Kang, S. Y.; Noh, D. Y. Bull Korean Chem Soc 2009, 30, 513.

[38] Schobert, R.; Biersack, B.; Dietrich, A.; Knauer, S.; Zoldakova, M.; Freuhauf, A.; Mueller, T. J Med Chem 2009, 52, 241.

[39] Devi, J. M.; Tharmaraj, P.; Ramakrishnan, S. K.; Ramachandran, K. Mater Lett 2008, 62, 852.

[40] Majumdar, K. C.; Mondal, S. Tetrahedron Lett 2008, 49, 2418.

[41] Yamamoto, Y.; Kirai, N. Org Lett 2008, 10, 5513.

[42] Saxena, O. M.; Faridi, U.; Kumar, J. K.; Luqman, S.; Darokar, M. P.; Shanker, K.; Chanotiya, C. S.; Gupta, M. M.; Negi, A. S. Steroids 2007, 72, 892.

[43] Tamilvanan, M.; Pandurangan, A.; Reddy, B. S. R.; Subramanian, K. Polym Int 2006, 56, 104.

[44] Lewis, I. Process Column 2005, 17, 1.

[45] Pivonka, D. E.; Empfiled, J. R. Appl Spectrosc 2004, 58, 41.

[46] Hayes, B. L. Aldrichim Acta 2004, 37, 66.

[47] Ajani, O. O.; Obafemi, C. A.; Ikpo, C. O.; Ajanaku, K. O.; Ogunniran, K. O.; James, O. O. Int J Phys Sci 2009, 4, 156.

[48] Russell, A. D.; Fur, J. R. J Appl Bacteriol UK 1977, 43, 253.

# The Synthesis and Characterization of Solvatochromic Maleimide-Fused *N*-Allyl- and *N*-Alkyl-Substituted 1,4-Dithiines and Diels–Alder Reactions with Anthracene

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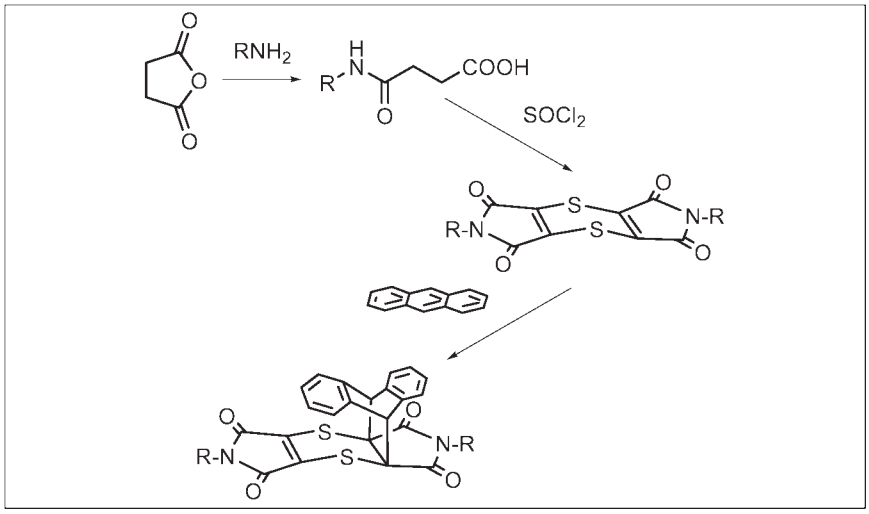


A simple and facile access to new solvatochromic maleimide-fused *N*-allyl- and *N*-alkyl-substituted 1,4-dithiines from the corresponding *N*-substituted succinamic acid derivatives in one-pot with oxidation by thionyl chloride is described. The Diels–Alder reaction of these 1,4-dithiines with anthracene has been investigated. The 1,4-dithiine derivatives react smoothly with anthracene *via* charge-transfer complexes to form the Diels–Alder adducts in excellent yields.

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## INTRODUCTION

Sulfur-containing heterocyclic compounds have held the focus of researchers along decades of historical development of organic synthesis. Their biological activities and unique structures allow several applications in different parts of pharmaceutical and agrochemical research or in material science [1].

The synthesis of 1,4-dithiines has recevied much attention because of their biological activity, particularly as fungicides and antibacterials [2], their application in synthetic organic and medicinal chemistry, their structural and electronic properties, their ability to act as electron donors [3], and the wide variety of synthetic transformation they undergo [3]. Some derivatives of 1,4-dithiines show activities as nonpeptide antagonists of the human Galanin hGAL-1 receptors [4], and some 1,4-dithiine-2,3,5,6-tetracarboxydiimides have been used as anthelmintics [5]. Detailed research of 1,4-dithiines has been limited by a lack of suitable synthetic approaches. Some 1,4-dithiines have been known for more than 100 years, although the correct stuctures were assigned recently [1,6,7]. Many polycyclic 1,4-dithiine derivatives are useful as pigments and functional materials for electrooptical applications [7].

For 80 years, the Diels–Alder reaction has remained as one of the best and most powerful methods of synthesis of six-membered rings and bicyclic molecules [8]. Many factors, such as its versatility, its high regio- and stereoselectivity, and its ability to rapidly give polyfunctionality have contributed to the popularity of this reaction in organic syntheses.

Anthracene and its derivatives are among the most useful polycyclic aromatic compounds and efficient photochromic systems. In view of their fluorescent properties, they are of practical interest as sensors and markers in biological or supramolecular systems [9]. Anthracenes are well-known as fairly reactive dienes that easily undergo both thermal and photochemical Diels–Alder cycloadditions with a variety of dienophiles [10]. In the thermal [4+2] cycloaddition reaction mechanism, new

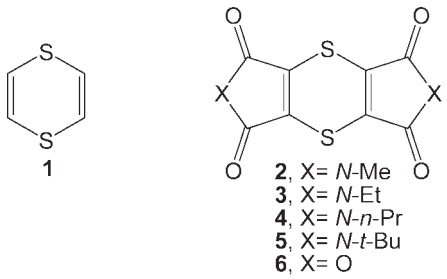



**Figure 1.** 1,4-Dithiine and its derivatives.

sigma bonds are formed simultaneously, either by direct addition or *via* intermediate charge-transfer (CT) complex (electron donor-acceptor molecular complex). Many studies have indicated the observation of transient color that disappears as the thermal Diels–Alder reaction proceeds. This has been shown to be due to the formation of a CT complex during the course of the reaction [11].

Very few articles deal with the synthesis, characterization, reactions, and properties of maleimide-fused 1,4-dithiines [7,12–15]. Hayakawa *et al*. [12] and Kim *et al*. [13] have reported the preparation of the methyl, ethyl, propyl, and *t*-butyl derivatives of maleimide-fused 1,4-dithiine with short experimental details. The mechanistic pathway was not suggested in these reports. Valla *et al*. [14] and Zentz *et al*. [15] have reported the preparation of the propyl, isopropyl, butyl, and benzyl derivatives of maleimide-fused 1,4-dithiine with experimental details and investigated the mechanistic pathway by using a Pummerer rearrangement-like reaction. 1,4-Dithiines **2, 3, 4,** and **5** were used as a dienophile for Diels–Alder reactions by Hayakawa *et al*. [12] and Kim *et al*. [13] (Fig. 1).

1,4-Dithiine **1** and its derivatives undergo thermal elimination of sulfur to produce corresponding thiophene derivatives [16]. Nevertheless, thermal stability of *N*,*N*′-dimethyl-dipyrrole-fused dithiine **2** and the dianhydride **6** was observed by Draber [17], along with the formation of cycloadducts with anthracene (Fig. 1).

Draber [17] has suggested the planar structure of **2** and **6** based on strong ultraviolet absorptions at long wavelenghts, thermal stability, and the ability to form CT complexes. Indeed, various molecular orbital calculations have indicated **2** and **6** to be nearly planar [12]. 1,4-Ditihiine **3** exhibits a planar structure that makes easy the formation of CT crystals with anthracene in alternate donor-acceptor stacks [13].

## RESULTS AND DISCUSSION

This study describes synthesis of new solvatochromic maleimide-fused *N*-allyl- and *N*-alkyl-substituted 1,4-dithiines (**9a–d**) from succinamic acid derivatives (**8a–d**) in one-pot with oxidation by thionyl chloride and their subsequent Diels–Alder cycloaddition reactions with anthracene.

**Maleimide-fused *N*-allyl- and *N*-alkyl-substituted 1,4-dithiines.** The initial study began with the reaction between succinic anhydride **7** and the appropriate amines to give *N*-substituted succinamic acid derivatives. Maleimide-fused *N*-allyl [18] and *N*-alkyl 1,4-dithiines were prepared in high yields from corresponding *N*-substituted succinamic acid derivatives using $SOCl_2$ according to the earlier reported procedure (Table 1) by Michaïlidis *et al*. [19], who reported without experimental details. 1,4-Dithiines **9a–d** are green and deep green crystals, but their solutions in various solvents (diethyl ether, ethanol, chloroform, acetone, and benzene) are coloured yellow (**9a** in diethyl ether, ethanol, and acetone; **9c** in ethanol), green (**9a** in benzene; **9c** in acetone; **9d** in ethanol), deep geen (**9a** in chloroform; **9c** in diethyl ether and chloroform), deep blue (**9c** in benzene; **9d** in diethyl ether), purple (**9b** in acetone), deep blue-green (**9d** in benzene and chloroform), deep blue-purple (**9b** in benzene and chloroform; **9d** in acetone); thus, products **9a–d** are higly solvatochromic. Maleimide-fused *N*-allyl 1,4-dithiine **9a** is partly soluble in diethyl ether and ethanol, whereas **9b** is insoluble in diethyl ether and ethanol.

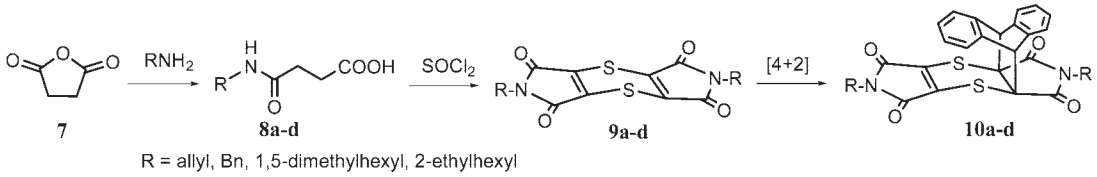
The conjugation of double bond with carbonyl groups in 1,4-dithiines **9a–d** leads to both the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ transitions being shifted to longer wavelengths. The absorptions are found between 300 and 310 nm for $\pi \rightarrow \pi^*$ transition and between 378 and 389 nm for $n \rightarrow \pi^*$ transition in **9a–d**. The $n \rightarrow \pi^*$ transitions are much less intense ($\epsilon$ = 1271–1803) than $\pi \rightarrow \pi^*$ transition ($\epsilon$ = 1657–2439).

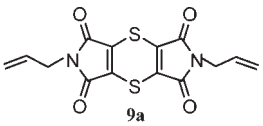
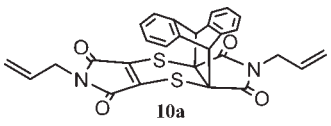
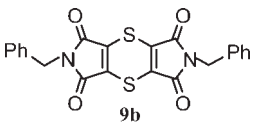
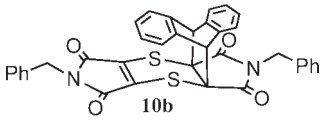
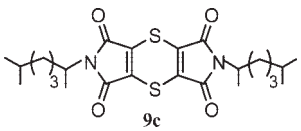
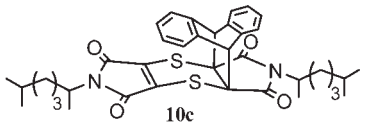
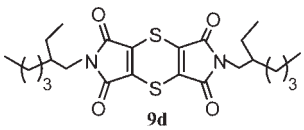
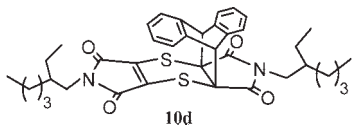
The reaction is straightforward and requires simple and inexpensive starting materials. We have, thus, introduced a highly efficient methodology for the synthesis of maleimide-fused *N*-allyl- and *N*-alkyl-substituted 1,4-dithiines. It may be widely applicable for the preparation of a variety of 1,4-dithiines.

**Diels–Alder cycloaddition reactions.** When anthracene was allowed to react with 1,4-dithiines **9a–d** in refluxing benzene, the characteristic green, deep blue, deep blue-green, and deep blue-purple colors of **9a–d** disappeared, and the corresponding Diels–Alder cycloadducts **10a–d** were obtained in 95, 89, 94, and 90% yields, respectively (Table 1). Much longer reaction times were needed for **9c** and **9d** than for the reaction of **9a** and **9b**, probably, because of the increased steric bulk. Anthracene and **9a–b** in $CHCl_3$ underwent a slow reaction at room temperature in the dark in 2 weeks, giving the Diels–Alder cycloadducts **10a** and **10b** in 99 and 94% yield, respectively. The same reaction was

**Table 1**

Formation of 1,4-dithiines and the Diels-Alder cycloadducts.




| Entry | 1,4-Dithiine | Yield (%) | Diels-Alder cycloadduct | Time | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **9a** | 63 |  **10a** | 24 h<br>2 weeks | 95[a]<br>99[b] |
| 2 |  **9b** | 60 |  **10b** | 22 h<br>2 weeks | 89[a]<br>94[b] |
| 3 |  **9c** | 88 |  **10c** | 5 days<br>4 weeks | 94[a]<br>74[b] |
| 4 |  **9d** | 87 |  **10d** | 3 days<br>4 weeks | 90[a]<br>79[b] |

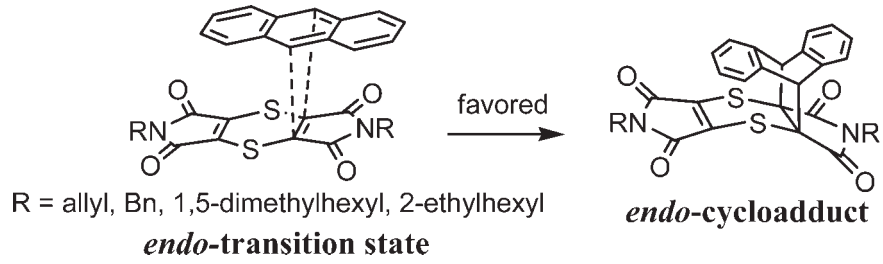
The Diels–Alder reaction conditions: [a]: benzene, reflux; [b]: $CHCl_3$, rt, in the dark.

carried out using **9c** and **9d** under the same reaction conditions but over a time of 4 weeks, giving **10c** and **10d** in 74 and 79% yield, respectively (Table 1). The Diels–Alder cycloadducts **10a–d** were bright yellow crystals, which were reasonably soluble in dichloromethane, chloroform, and ethanol. Only *endo*-cycloadducts **10a** and **10b** were obtained, while the Diels–Alder cycloadducts **10c** and **10d** were shown to be a mixture of two diastereoisomers in a 1:1 ratio as shown by integration of signals in the $^1$H NMR spectrum. The structure of these adducts **10a–d** were determined on the basis of $^1$H and $^{13}$C NMR spectroscopy, mass spectroscopy, and elemental analysis.

When anthracene and 1,4-dithiine approach each other in the Diels–Alder reaction, the best overlap is achieved when the reactants lie directly on top of one another, a geometry that leads to *endo*- rather than *exo*-product. The kinetically favorable *endo*-Diels–Alder cycloadduct is formed faster (lowest activation energy), even though the thermodynamically favorable *exo*-product is more stable. Secondary orbital overlap in the transition state between the orbitals on the carbonyl groups in the 1,4-dithiine and the orbitals in the anthracene not directly involved in bonding. These interactions do not lead to bond formation, but they do lower the energy of the transition state (Scheme 1).

The IR spectra exhibited characteristic imide bands at 1771 and 1707 $cm^{-1}$ for **10a**, at 1776 and 1708 $cm^{-1}$ for **10b**, at 1773 and 1706 $cm^{-1}$ for **10c**, and at 1767 and 1703 $cm^{-1}$ for **10d**. $^1$H NMR spectra showed two *N*-allyl or *N*-alkyl proton signals for one isomer, one of them being shifted upfield as a result of shielding effect

**Scheme 1.** Formation of the *endo*-Diels–Alder cycloadduct.




of the anthracene ring. Characteristic absorptions of anthracene have disappeared, indicating destruction of the anthracene conjugated system by the Diels–Alder cycloadditon. The UV–vis spectroscopic analysis of the Diels–Alder cycloadducts **10a–d** revealed the appearance of new absorption bands at 405, 412, 410, and 411 nm, respectively.

In accordance with the reported early experimental results [13], there are two pathways for the formation of the Diels–Alder cycloadducts of 1,4-dithiines **9a–d** and anthracene (Fig. 2). The choice of these reaction pathways only depends on the electronic properties of dienophile (1,4-dithiine) and diene (anthracene). Electron-rich dienes (anthracene, 9-methylanthracene, 9,10-dimethylanthracene) give a cycloadduct *via* pathway I, modestly electron-deficient diene (9-anthracenecarboxaldehyde) give a cycloadduct *via* pathway II, and no reaction occurs to the strongly electron-deficient diene (9-nitroanthracene) [12]. 1,4-Dithiine derivatives 9a–d act as strong acceptors in CT complex formation and possess high reactivity as planar electron-rich dienes.

According to the preliminary investigation by Draber [17], the reaction of 1,4-dithiines **9a–d** with the electron-rich anthracene occurred *via* CT complexes, as evidenced by unusual color change during the reaction.

We, herein, report new 1,4-dithiine derivatives and their Diels–Alder cycloadducts. The oxidation reaction by thionyl chloride was succesfully applied to **8a–d**, which gave the corresponding ring-closed 1,4-dithiines **9a–d** in good yields. To the best of our knowledge, three of the synthesized 1,4-dithiines, **9a, 9c,** and **9d,** and all Diels–Alder cycloadducts **10a–d** are new compounds. To the best of our knowledge, this method is the first example of a one-step synthesis of maleimide-fused *N*-allyl- and sterically-bulky *N*-alkyl-substituted 1,4-dithiines directly from succinamic acid derivatives by thionyl chloride oxidation. This one-pot reaction converts various succinamic acid derivatives to solvatochromic 1,4-dithiines, which underwent the Diels–Alder reactions with anthracene in excellent yields.

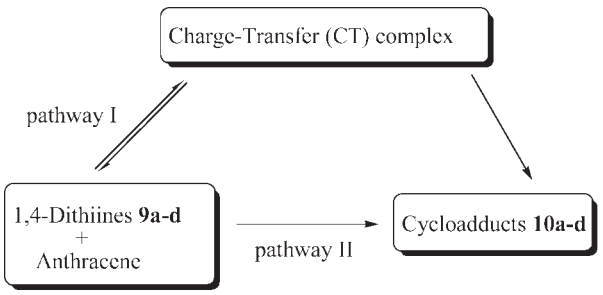



**Figure 2.** Pathway I: The cycloaddition *via* CT complex, pathway II: Direct cycloaddition.

## EXPERIMENTAL

The melting points were measured on an Electrothermal 9100 melting point apparatus and are uncorrected. The UV–vis absorption spectra were determined with a Perkin Elmer Lamda 25 spectrophotometer in chloroform solutions using 10-mm quartz cells. The IR spectra were recorded on a One FTIR ATR Perkin Elmer spectrometer. The $^{1}H$ and $^{13}C$ NMR spectra were taken with a Varian NMR Gemini 300 and Bruker 400 Ultra Shield spectrometers and chemical shifts were recorded as ppm downfield from internal tetramethylsilane. The mass spectra were taken on a Waters ZQ Micromass LC/MS spectrometer. Elemental analyses were performed on a Leco 932 CHNS instrument. All chemicals were purchased from commercial suppliers and used directly without any further purification. Organic solvents were dried by standard methods and were distilled before use. All the reactions were performed under a nitrogen atmosphere. Reaction progress was monitored by TLC on precoated aluminum-backed plates (Merck SIL G/$UV_{254}$), and chromophoric compounds were visualised by UV light and subsequent staining with alkaline potassium permanganate solution or iodine. Petroleum ether refers to light petroleum (bp 40–60°C).

**General procedure for the preparation of *N*-substituted succinamic acids (8a–d).** Reaction of succinic anhydride **7** (16 mmol) with the appropriate amine (20 mmol) in the presence of the dry appropriate solvent (10 mL, THF, MeCN, acetone, or 1,4-dioxane) at room temperature with stirring for a few hours generated the corresponding *N*-substituted succinamic acids **8a–d**. After the reaction was completed, the solvent was removed under reduced pressure and recrystallized from the appropriate solvent ($Et_2O$, 1,4-dioxane, or water).

***4-Oxo-4-(prop-2-enylamino)butanoic acid (8a).*** White crystals; 70% yield (1.76 g); mp 93–94°C; IR-ATR ($\nu_{max}$, $cm^{-1}$): 3500–2600, 3302, 1690, 1639, 1618, 1544; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): 2.54 (t, $J$ = 6.9 Hz, 2H, $CH_2$CONH), 2.72 (t, $J$ = 6.9 Hz, 2H, $CH_2$COOH), 3.90 (m, 2H, CONHC$H_2$), 5.20–5.15 (skew dq, 2H, CH=C$H_2$), 5.80 (m, 1H, C$H$=$CH_2$),

5.97–6.34 (br s, 1H, NH), 7.34–10.45 (br s, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 29.70 (*C*$H_2$CONH), 30.64 (*C*$H_2$COOH), 41.55 (CONH*C*$H_2$), 115.37 (CH=*C*$H_2$), 135.04 (*C*H=$CH_2$), 171.63 (CONH), 174.35 (COOH); MS (ESI+): m/z (%): 158 (44, $[M + H]^+$), 152 (14), 140 (100); Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.55; H, 7.19; N, 8.94.

***4-Oxo-4-(phenylmethylamino)butanoic acid (8b).*** White crystals; 83% yield (2.75 g); mp 132–133°C (lit. [20] mp 137.7–138.2°C; lit. [14,15] mp 144°C ); IR-ATR ($\nu_{max}$, $cm^{-1}$): 3300–2500, 3296, 1689, 1639, 1540; $^1$H NMR (400 MHz, DMSO-$d_6$): 2.61 (m, 2H, $CH_2$), 2.46 (m, 2H, $CH_2$), 3.4 (br s, 1H, NH), 4.36 (d, $J$ = 5.71 Hz, 2H, $CH_2$NH), 6.02 (br s, 1H, OH), 7.3–7.2 (m, 5H, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$): 30.17 ($CH_2$), 31.03 ($CH_2$), 43.84 ($CH_2$), 127.78 (CH), 128.71 (CH), 128.84 (CH), 137.77 (Q), 172.43 (CONH), 174.66 (COOH); MS (ESI−): *m/z* (%): 206 (100, $[M - H]^-$); MS (ESI+): *m/z* (%): 208 (35, $[M + H]^+$), 230 (100, $[M + Na]^+$).

***4-[(6-Methylheptan-2-yl)amino]-4-oxobutanoic acid (8c).*** White crystals; 93% yield (3.40 g); mp 79–80°C; IR-ATR ($\nu_{max}$, $cm^{-1}$): 3200–2500, 3287, 1714, 1648, 1550; $^1$H NMR (300 MHz, $CDCl_3$): 0.84 (d, $J$ = 6.44 Hz, 6H, $CH_3$), 1.09 (d, $J$ = 6.44 Hz, 3H, $CH_3$), 1.10–1.16 (m, 1H, CH), 1.2–1.3 (m, 2H, $CH_2$), 1.38–1.42 (m, 2H, $CH_2$), 1.44–1.53 (m, 2H, $CH_2$), 2.49 (skew t, 2H, $CH_2$), 2.67 (skew t, 2H, $CH_2$), 3.30–3.95 (m, 1H, CH), 5.95 (d, $J$ = 8.5 Hz, 1H, NH); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 20.96 ($CH_3$), 22.78 ($CH_3$), 22.81 ($CH_3$), 23.99 ($CH_2$), 28.07 (CH), 30.29 ($CH_2$), 31.12 ($CH_2$), 37.16 ($CH_2$), 38.92 ($CH_2$), 45.99 (CH), 172 (CONH), 176.81 (COOH); MS (ESI−): *m/z* (%): 228 (100, $[M - H]^-$); MS (ESI+): *m/z* (%): 230 (100, $[M + H]^+$), 252 (98, $[M + Na]^+$); Anal. Calcd. for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.59; H, 9.71; N, 6.30.

***4-[(2-Ethylhexyl)amino]-4-oxobutanoic acid (8d).*** White crystals; 80% yield (2.92 g); mp 65–67°C; IR-ATR ($\nu_{max}$, $cm^{-1}$): 3310–2500, 3318, 1691, 1631, 1544; $^1$H NMR (300 MHz, $CDCl_3$): 0.85–0.88 (m, 6H, $CH_3$), 1.22–1.32 (m, 8H, $CH_2$), 1.35–1.45 (m, 1H, CH), 2.5 (skew t, 2H, $CH_2$), 2.66 (skew t, 2H, $CH_2$), 3.16 (dt, $J$ = 1.46, 4.7 Hz, 2H, $CH_2$), 6.00 (br s, 1H, NH); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 11.01 ($CH_3$), 14.29 ($CH_3$), 23.20 ($CH_2$), 24.30 ($CH_2$), 29.01 ($CH_2$), 30.20 ($CH_2$), 31.01 ($CH_2$), 31.09 ($CH_2$), 39.40 (CH), 42.87 ($CH_2$), 172.75 (CONH), 176.89 (COOH); MS (ESI−): *m/z* (%): 228 (100, $[M - H]^-$); MS (ESI+): *m/z* (%): 230 (95, $[M + H]^+$), 252 (100, $[M + Na]^+$); Anal. Calcd. for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.50; H, 9.81; N, 6.45.

**General procedure for the preparation of maleimide-fused *N*-allyl- and *N*-alkyl-substituted 1,4-dithiines (9a–d).** To a solution of *N*-substituted succinamic acid **8a–d** (3.82 mmol) in dry 1,4-dioxane (10 mL) was added dropwise a solution of thionyl chloride (30.56 mmol) in dry 1,4 dioxane (2 mL) at room temperature with stirring. The solution was heated at 50°C for 6 h. After the reaction was completed, the solution was concentrated *in vacuo*, column chromatography of the residue over silica eluting with petroleum ether-EtOAc (9:1) furnished **9a–d**.

The same reactions of **8a–d** were conducted at room temperature with stirring overnight.

***2,6-Di(prop-2-en-1-yl)-1H,5H-[1,4]dithiino[2,3-c:5,6-c′]dipyrrole-1,3,5,7(2H,6H)-tetrone (9a).*** Dark green crystals; 63% yield (400 mg); mp 225–227°C; UV ($CHCl_3$) $\lambda_{max}$ : 300 nm sh (Є 1657), 378 (1271), 600 (29); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1777, 1710, 1661, 1566; $^1$H NMR (400 MHz, DMSO-$d_6$): 4.02 (skew dt, 4H, C$H_2$CH=$CH_2$), 5.17 (dt, $J$ = 1.22, 18.6 Hz, 4H, CH=C$H_2$), 5.80 (m, 2H, C*H*=$CH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 40.86 (*C*$H_2$CH=$CH_2$), 117.30 (CH=*C*$H_2$), 131.08 (*C*H=$CH_2$), 132.20 (Q), 164.39 (CO); MS (API−): *m/z* (%): 334 (100, $[M^+]$); Anal. Calcd. for $C_{14}H_{10}N_2O_4S_2 \cdot 1.07H_2O$: C, 47.55; H, 3.46; N, 7.92; S, 18.18. Found: C, 47.42; H, 3.21; N, 7.52; S, 18.16.

***2,6-Dibenzyl-1H,5H-[1,4]dithiino[2,3-c:5,6-c′]dipyrrole-1,3,5,7(2H,6H)-tetrone (9b).*** Dark green pellets; 60% yield (500 mg); mp 216–218°C (lit. [14,15] mp 224°C); UV ($CHCl_3$) $\lambda_{max}$: 301 nm sh (Є 1980), 387 (1300), 594 (40); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1775, 1707, 1693, 1596; $^1$H NMR (400 MHz, DMSO-$d_6$): 4.6 (s, 4H, $CH_2$), 7.34–7.45 (m, 10H, Ar); $^{13}$C NMR (100 MHz, DMSO-$d_6$): 42.53 ($CH_2$), 128.36 (CH), 128.67 (CH), 128.88 (CH), 131.65 (Q), 135.03 (Q), 163.66 (CO); MS (API−): *m/z* (%): 434 (100, $[M^+]$).

***2,6-Di(6-methylheptan-2-yl)-1H,5H-[1,4]dithiino[2,3-c:5,6-c′]dipyrrole-1,3,5,7(2H,6H)-tetrone (9c).*** Green solid; 88% yield (800 mg); mp 99–100°C; UV ($CHCl_3$) $\lambda_{max}$: 310 nm sh (Є 1955), 388 (1636), 595 (45); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1771, 1692, 1573; $^1$H NMR (400 MHz, $CDCl_3$): 0.77 (d, $J$ = 6.6 Hz, 6H, $CH_3$), 0.79 (d, $J$ = 6.6 Hz, 6H, $CH_3$), 1.07–1.13 (m, 8H, $CH_2$), 1.26 (d, $J$ = 6.93 Hz, 6H, $CH_3$), 1.41–1.53 (m, 4H, $CH_2$), 1.73–1.79 (m, 2H, CH), 3.84–4.19 (m, 2H, CH); $^{13}$C NMR (100 MHz, $CDCl_3$): 18.54 ($CH_3$), 22.45 ($CH_3$), 22.61 ($CH_3$), 24.39 ($CH_2$), 27.75 (CH), 33.81 ($CH_2$), 38.32 ($CH_2$), 48.89 (CH), 131.35 (Q), 164.21 (CO); MS (API−): *m/z* (%): 478 (100, $[M^+]$); Anal. Calcd. for $C_{24}H_{34}N_2O_4S_2 \cdot 0.8H_2O$: C, 58.46; H, 7.28; N, 5.68; S, 13.00. Found: C, 58.15; H, 7.19; N, 5.62; S,12.87.

***2,6-Di(2-ethylhexyl)-1H,5H-[1,4]dithiino[2,3-c:5,6-c′]dipyrrole-1,3,5,7(2H,6H)-tetrone (9d).*** Dark green solid; 87% yield (790 mg); mp 57–58°C; UV ($CHCl_3$) $\lambda_{max}$: 310 nm sh (Є 2439), 389 (1803), 601 (45); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1776, 1703, 1571; $^1$H NMR (400 MHz, $CDCl_3$): 0.78–0.84 (skew t, 12H, $CH_3$), 1.10–1.22 (m, 16H, $CH_2$) 1.60 (m, 2H, CH), 3.30 (d, $J$ = 7.12 Hz, 4H, $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): 10.23 ($CH_3$), 14.03 ($CH_3$), 22.93 ($CH_2$), 23.65 ($CH_2$), 28.37 ($CH_2$), 30.30 ($CH_2$), 38.19 (CH), 42.79 ($CH_2$), 131.42 (Q), 164.42 (CO); MS (API−): *m/z* (%): 478 (100, $[M^+]$); Anal. Calcd. for $C_{24}H_{34}N_2O_4S_2 \cdot 0.4H_2O$: C, 59.33; H, 7.22; N, 5.77; S, 13.20. Found: C, 59.04; H, 6.89; N, 5.84, S, 13.20.

**General procedure for the Diels–Alder cycloadditions (10a–d).** To a solution of anthracene (0.49 mmol) in benzene (15 mL) was added 1,4-dithiines 9a–d (0.45 mmol), and the reaction mixture was refluxed until the green, deep blue, deep blue-green, and deep blue-purple colors of 9a–d faded away, indicating the complete consumption of 9a–d. The solution was concentrated *in vacuo*, purification by column chromatography on silica, eluting with petroleum ether-EtOAc (9:1) gave the corresponding *endo*-cycloadducts **10a** and **10b** and a 1:1 mixture of diastereoisomers of **10c** and **10d**.

The same reactions of **9a–d** were conducted at room temperature in $CHCl_3$ and in the dark for 2 and 4 weeks.

***5,10-Dihydro-2,13-di(prop-2-en-1-yl)-5,10[1′,2′]-benzeno-4a,10a-(methaniminomethano)-1H-naphtho[2′,3′:5,6][1,4]dithiino[2,3-c]pyrrole-1,3,12,14(2H)-tetrone (10a).*** Bright yellow solid; 95% yield (218 mg); mp 258–260°C (melts with dec.); UV ($CHCl_3$) $\lambda_{max}$: 292 nm sh (Є 2060), 405 (440); IR-ATR ($\nu_{max}$,

$cm^{-1}$): 1771, 1707, 1650, 1579; $^1H$ NMR (400 MHz, $CDCl_3$): 3.76 (d, $J = 3.7$ Hz, 2H, $CH_2$), 3.88 (d, $J = 3.7$ Hz, 2H, $CH_2$), 4.68 (s, 2H, CH), 4.80–4.85 (m, 2H), 5.12–5.15 (m, 2H, CH), 5.60–5.75 (m, 2H, CH), 7.03–7.05 (m, 2H, Ar), 7.08–7.10 (m, 2H, Ar), 7.20–7.23 (m, 2H, Ar), 7.26–7.29 (m, 2H, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$): 40.60, 41.76, 55.84, 68.80, 118.64, 119.43, 125.76, 127.22, 127.88, 128.04, 128.79, 131.11, 136.99, 137.50, 137.66, 164.14, 172.57; MS (API+): *m*/*z* (%): 513 (38, $[M + H]^+$); Anal. Calcd. for $C_{28}H_{20}N_2O_4S_2 \cdot 1.7H_2O$: C, 61.91; H, 4.34; N, 5.16; S, 11.81. Found: C, 61.54; H, 4.67; N, 5.29; S,12.20.

***5,10-Dihydro-2,13-dibenzyl-5,10[1′,2′]-benzeno-4a,10a-(methaniminomethano)-1H-naphtho[2′,3′:5,6][1,4]dithiino[2,3-c]pyrrole-1,3,12,14(2H)-tetrone (10b).*** Bright yellow crystals; 89% yield (244 mg); mp 278–280°C (melts with dec.); UV ($CHCl_3$) $\lambda_{max}$: 290 nm sh (Є 2583), 412 (569); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1776, 1708, 1581; $^1H$ NMR (400 MHz, $CDCl_3$): 4.33 (s, 2H, CH), 4.42 (s, 2H, $CH_2$), 4.6 (s, 2H, $CH_2$), 6.50–6.54 (m, 2H, Ar), 6.79–6.81 (m, 4H, Ar), 7.02–7.09 (m, 7H, Ar), 7.25–7.35 (m, 5H, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$): 42.10, 43.43, 55.67, 68.87, 125.32, 126.93, 127.66, 127.93, 127.99, 128.22, 128.44, 128.60, 128.64, 129.46, 133.63, 135.42, 136.77, 137.11, 137.40, 164.24, 172.75; MS (API+): *m*/*z* (%): 613 (85, $[M + H]^+$); Anal. Calcd. for $C_{36}H_{24}N_2O_4S_2$: C, 70.57; H, 3.95; N, 4.57; S, 10.47. Found: C, 70.69; H, 3.96; N, 4.55; S, 10.02.

***5,10-Dihydro-2,13-di(6-methylheptan-2-yl)-5,10[1′,2′]-benzeno-4a,10a-(methaniminomethano)-1H-naphtho[2′,3′:5,6][1,4]dithiino[2,3-c]pyrrole-1,3,12,14(2H)-tetrone (10c).*** Yellow oil slowly crystallized to bright yellow crystals; 94% yield (277 mg); mp 99–101°C; UV ($CHCl_3$) $\lambda_{max}$: 284 nm sh (Є 1895), 410 (313); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1773, 1706, 1580; $^1H$ NMR (400 MHz, $CDCl_3$): 0.71 (d, $J = 6.5$ Hz, 6H, $CH_3$), 0.73 (d, $J = 6.7$ Hz, 6H, $CH_3$), 0.76 (d, $J = 6.6$ Hz, 6H, $CH_3$), 0.77 (d, $J = 6.6$ Hz, 6H, $CH_3$), 0.94–0.97 (m, 8H, $CH_2$), 1.03–1.08 (m, 8H, $CH_2$), 1.20 (d, $J = 6.9$ Hz, 12 H, $CH_3$), 1.33–1.44 (m, 8H, $CH_2$), 1.63–1.68 (m, 4H, CH), 3.75–3.84 (m, 2H, CH), 3.86–3.95 (m, 2H, CH), 4.67 (s, 4H, CH), 7.04–7.06 (m, 4H, Ar), 7.08–7.11 (m, 4H, Ar), 7.22–7.24 (m, 4H, Ar), 7.28–7.30 (m, 4H, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$): 16.85, 18.29, 22.49, 22.57, 23.89, 24.43, 25.52, 27.74, 29.70, 30.94, 32.31, 33.91, 38.17, 38.45, 48.22, 49.33, 55.89, 55.91, 67.94, 67.96, 125.73, 125.79, 126.98, 127.25, 127.87, 127.90, 134.14, 135.98, 136.28, 137.64, 137.67, 137.91, 137.93, 164.68, 164.74, 173.23, 173.33; MS (API+): *m*/*z* (%): 657 (100, $[M + H]^+$); Anal. Calcd. for $C_{38}H_{44}N_2O_4S_2$: C, 69.48; H, 6.75; N, 4.26; S, 9.76. Found: C, 69.22; H, 6.58; N, 3.88; S, 9.55.

***5,10-Dihydro-2,13-di(2-ethylhexyl)-5,10[1′,2′]-benzeno-4a,10a-(methaniminomethano)-1H-naphtho[2′,3′:5,6][1,4]dithiino[2,3-c]pyrrole-1,3,12,14(2H)-tetrone (10d).*** Bright yellow crystals; 90% yield (265 mg); mp 188–189°C; UV ($CHCl_3$) $\lambda_{max}$: 288 nm sh (Є 4328), 411 (852); IR-ATR ($\nu_{max}$, $cm^{-1}$): 1767, 1703, 1581; $^1H$ NMR (400 MHz, $CDCl_3$): 0.62–0.66 (t, $J = 7$ Hz, 6H, $CH_3$), 0.77–0.84 (m, 18H, $CH_3$), 1.06–1.21 (m, 24H, $CH_2$), 1.48 (m, 4H, CH), 3.07 (d, $J = 6.97$ Hz, 4H, $CH_2$), 3.16 (d, $J = 6.97$ Hz, 4H, $CH_2$), 4.68 (s, 4H, CH), 7.03 (m, 4H, Ar), 7.09 (m, 4H, Ar), 7.22 (m, 4H, Ar), 7.27 (m, 4H, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$): 10.31,10.34, 14.03, 14.09, 22.88, 23.01, 23.33, 23.64, 28.03, 28.41, 30.02, 30.30, 37.55, 38.47, 42.23, 43.75, 55.64, 68.54, 68.60, 125.63, 125.68, 127.11, 127.14, 127.49, 127.54, 128.04, 128.06, 136.50, 136.52, 136.57, 137.76, 137.77, 137.79, 165.04, 173.47, 173.49; MS (API+): *m*/*z* (%): 657 (38, $[M + H]^+$); Anal. Calcd. for $C_{38}H_{44}N_2O_4S_2 \cdot 0.4H_2O$: C, 68.79; H, 6.81; N, 4.22; S, 9.66. Found: C, 68.39; H, 6.46; N, 4.26; S, 9.40.

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## REFERENCES AND NOTES

[1] García-Valverde, M.; Torroba, T. Eur J Org Chem 2006, 849.

[2] Guillaumet, G. In Comprehensive Heterocyclic Chemistry II; Boulton, A. J., Ed.; Pergamon: Oxford, 1996; Vol. 6, p 448.

[3] (a) Andreu, R.; Garín, J.; Orduna, J.; Royo, J. K. Tetrahedron Lett 2001, 42, 875; (b) Murru, S.; Kavala, V.; Singh, C. B.; Patel, B. K. Tetrahedron Lett 2007, 48, 1007.

[4] Scott, M. K.; Ross, T. M.; Lee, D. H. S.; Wang, H.-Y.; Shank, R. P.; Wild, K. D.; Davis, C. B.; Crooke, J. J.; Potocki, A. C.; Reitz, A. B. Bioorg Med Chem 2000, 8, 1383.

[5] Draber, W.; Korte, F. U.S. Pat. 3,364,229 (1968).

[6] Link, T.; Oberjat, M.; Klar, G. J Chem Res S 1997, 435.

[7] (a) Matsuoka, M.; Iwamoto, A.; Furukawa, N.; Kitao, T. J Heterocycl Chem 1992, 29, 439; (b) Katrizky, A. R.; Fan, W.-Q. J Heterocycl Chem 1993, 30, 1679.

[8] Diels, O.; Alder, K. Liebigs Ann 1928, 460, 98.

[9] Ihmels, H. Eur J Org Chem 1999, 1595, and references therein.

[10] Atherton, J. C. C.; Jones, S. Tetrahedron 2003, 59, 9039.

[11] Atherton, J. C. C.; Jones, S. Tetrahedron 2003, 59, 9039, and references therein.

[12] Hayakawa, K.; Mibu, N.; Ōsawa, E.; Kanematsu, K. J. Am Chem Soc 1982, 104, 7136.

[13] Kim, J. H.; Hubig, S. M.; Lindeman, S. V.; Kochi, J. K. J Am Chem Soc 2001, 123, 87.

[14] Valla, A.; Cartier, D.; Zentz, F.; Labia, R. Synth Commun 2006, 36, 3591.

[15] Zentz, Z.; Labia, R.; Sirot, D.; Faure, O.; Grillot, R.; Valla, A. II Farmaco 2005, 60, 944.

[16] Hayakawa, K.; Mibu, N.; Ōsawa, E.; Kanematsu, K. J Am Chem Soc 1982, 104, 7136, and references therein.

[17] Draber, W. Chem Ber 1967, 100, 1559.

[18] Gülten, S. Drugs Fut 2007, 32(Suppl A), 14.

[19] Michaïlidis, A.; Giraud, M.; Molho, D. In Organic Sulphur Chemistry; Stirling, C. J., Ed.; Butterworths: London, 1975; p 466.

[20] Pressman, D.; Bryden, J. H.; Pauling, L. J. Am Chem Soc 1948, 70, 1352.

# Glycine-Catalyzed Easy and Efficient One-Pot Synthesis of Polyhydroquinolines Through Hantzsch Multicomponent Condensation under Controlled Microwave



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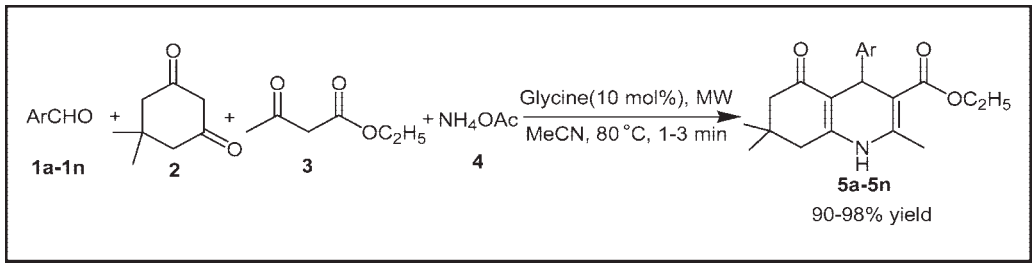


Glycine, a novel heterogeneous organocatalyst, is found to be highly effective for the synthesis of polyhydroquinoline derivatives in a one-pot multicomponent reaction *via* Hantzsch condensation under controlled microwave (MW) irradiation. The combination of glycine and MW has promising features for the reaction response, such as the shortest reaction time, excellent product yields, and simple work-up of the products.

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## INTRODUCTION

Microwave (MW) irradiation has evolved as a powerful method to perform organic synthesis with great success, particularly in the light of the current paradigm shift to ''green chemistry.'' It provides chemical processes with special attributes, such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimization of reactions, and several eco-friendly advantages [1]. An important way to improve synthetic efficiency and to give access to a multitude of diversified molecules from simple building blocks is the development of multicomponent synthesis. Multicomponent reactions (MCRs) have recently taken a new dimension in organic synthesis, as they comply well with the requirements for ideal organic syntheses [2,3]. According to the current synthetic and environmental requirements, MCRs using MW methodology are of great interest.

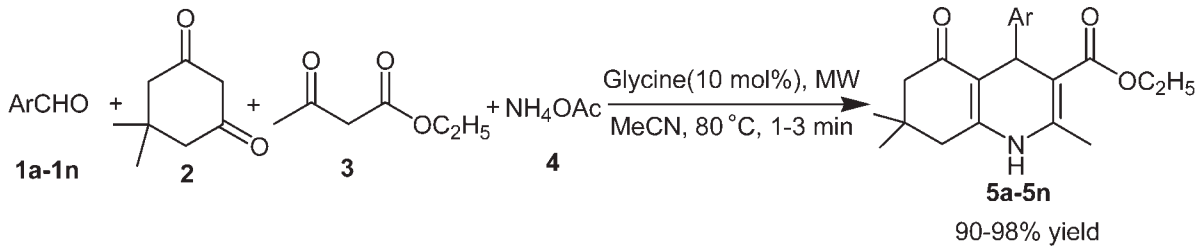
Polyhydroquinoline derivatives have a great deal of importance because of their diverse medicinal applications, which include calcium channel activity, vasodilators, bronchodilators, antiatherosclerotics, hepatoprotective, antidiabetic, antihypertensive, neuroprotectant, platelet antiaggregatory activity, cerebral antischemic activity, and chemosensitizer activity [4–10]. Owing to the remarkable potential of these compounds as a source of valuable drugs, various methods have been reported using conditions such as conventional heating [11], solar thermal energy [12], ionic liquid [13], TMSCl-NaI [14], metal triflates [15], grinding [16], Hy-Zeolite [17], montmorillonite K-10 [18], cerium(IV) ammonium nitrate [19], iron(III) trifluoroacetate [20], $HClO_4$-$SiO_2$ [21], heteropoly acid [22], molecular iodine [23], PTSA [24], L-proline and derivatives [25], nickel [26], polymers [27], and Baker's yeast [28]. Most of these processes, however, suffer from one or other drawbacks such as longer reaction time, lower product yield, harsh conditions, high costs, and use of hazardous catalysts. As a result, an eco-safe and efficient alternative method for the preparation of polyhydroquinoline is highly desirable. As there is no report on the use of glycine as an organocatalyst in the Hantzsch condensation, we wish to demonstrate the catalytic activity of this organocatalyst in the synthesis of polyhydroquinolines.

## RESULTS AND DISCUSSION

We report herein a benign, rapid, and efficient four-component, one-pot synthesis of polyhydroquinolines in excellent yields using aromatic aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate in the presence of catalytic amount of glycine (10 mol %) in acetonitrile under monomode MW irradiation (Scheme 1).

To optimize the synthesis, a typical four-component reaction of benzaldehyde **1a**, dimedone **2**, ethyl acetoacetate **3**, and ammonium acetate **4** was undertaken using

**Scheme 1**




a catalytic amount of different amino acids such as L-alanine, L-valine, and glycine in different solvents such as acetonitrile, ethanol, and water under varying reaction conditions to obtain the corresponding polyhydroquinoline derivative **5a** (Table 1). Consistent with Table 1, the optimum yield (95%) of product **5a** was obtained in the presence of catalytic amount of glycine (10 mol %) in solvent acetonitrile (entry 6) in 1 min under single-mode MW heating (180 W, 80°C). Decreasing the catalyst levels, MW power or temperature reduced the product yield considerably (Table 1; Entries 13, 16, and 17). An increase in the molar proportion of catalyst, MW power, and temperature did not bring about any further increase in the product yield, rather, a bit diminution was observed (Table 1; entries 14, 15, 18, and 19). It is assumed that the acidic hydrogen of carboxylic function and the small size of glycine play a key role in the catalysis of the reaction. Under the optimized set of reaction conditions (entry 6), a number of aromatic aldehydes **1** were allowed to undergo MCR with **2**, **3**, and **4** in a molar ratio of 1:1:1:1.2 in the presence of glycine (10 mol %) in acetonitrile under MW (180 W, 80°C) heating. The results are given in Table 2. All the electron-rich and electron-deficient aldehydes worked well leading to excellent yields of products.

After completion of the reaction, the resulting precipitate was filtered and recrystallized from methanol to yield pure substituted polyhydroquinolines **5a–5n**. All the products were crystalline and fully characterized on the basis of their melting points, elemental analyses, and spectral data (IR, $^1$H-NMR, and $^{13}$C-NMR).

**Table 1**

Optimization of reaction conditions for the multicomponent synthesis of **4a**.

| | | | Reaction conditions | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Room temperature | | Reflux | | Microwave[b] | |
| Entry | Catalyst[a] | Solvent | Time (h) | Yield (%) | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 1 | – | Water | 3.0 | 14 | 60 | 28 | 5 | 46 |
| 2 | – | Ethanol | 3.0 | 15 | 60 | 29 | 5 | 50 |
| 3 | – | MeCN | 3.0 | 15 | 60 | 32 | 5 | 54 |
| 4 | Glycine | Water | 1.0 | 54 | 30 | 61 | 1 | 75 |
| 5 | Glycine | Ethanol | 1.0 | 57 | 20 | 68 | 1 | 84 |
| 6 | Glycine | MeCN | 1.0 | 64 | 20 | 86 | 1 | 95 |
| 7 | L-Alanine | Water | 1.0 | 42 | 20 | 51 | 1 | 63 |
| 8 | L-Alanine | Ethanol | 1.0 | 46 | 20 | 58 | 1 | 72 |
| 9 | L-Alanine | MeCN | 1.0 | 52 | 20 | 66 | 1 | 78 |
| 10 | L-Valine | Water | 1.0 | 46 | 20 | 57 | 1 | 70 |
| 11 | L-Valine | Ethanol | 1.0 | 50 | 20 | 61 | 1 | 78 |
| 12 | L-Valine | MeCN | 1.0 | 56 | 20 | 72 | 1 | 86 |
| 13 | Glycine | MeCN | 1.0 | 57 | 30 | 79 | 3 | 87 |
| 14 | Glycine | MeCN | 1.0 | 64 | 30 | 84 | 2 | 95 |
| 15 | Glycine | MeCN | 1.0 | 63 | 30 | 80 | 2 | 93 |
| 16 | Glycine | MeCN | – | – | – | – | 3 | 89 |
| 17 | Glycine | MeCN | – | – | – | – | 3 | 88 |
| 18 | Glycine | MeCN | – | – | – | – | 2 | 93 |
| 19 | Glycine | MeCN | – | – | – | – | 2 | 95 |

[a] Catalyst concentration 10 mol % except for entries 13 (5 mol %), 14 (15 mol %), and 15 (20 mol %).
[b] Microwave heating performed on 180 W power and 80°C temperature except for entries 16 (120 W, 80°C), 17 (180 W, 50°C), 18 (250 W, 80°C), and 19 (180 W, 100°C).

**Table 2**

Glycine-catalyzed Hantzsch condensation to polyhydroquinoline derivatives.[a]

| Product | Ar | Time (min) | Yield[b] (%) | Mp (°C) Obs | Mp (°C) Lit |
|---|---|---|---|---|---|
| **5a** | $C_6H_5$ | 1 | 95 | 203–205 | 202–204 [15(a)] |
| **5b** | 4-$CH_3C_6H_4$ | 1 | 96 | 259–260 | 260–261 [15(a)] |
| **5c** | 4-$CH_3OC_6H_4$ | 1 | 98 | 256–257 | 257–259 [15(a)] |
| **5d** | 4-$ClC_6H_4$ | 2 | 97 | 246–248 | 245–246 [21] |
| **5e** | 3-$ClC_6H_4$ | 2 | 94 | 192–193 | – |
| **5f** | 4-$BrC_6H_4$ | 2 | 96 | 254–256 | 253–255 [15(a)] |
| **5g** | 3-$BrC_6H_4$ | 2 | 93 | 235–237 | 234–236 [16] |
| **5h** | 4-$FC_6H_4$ | 2 | 95 | 184–186 | 184–186 [15(a)] |
| **5i** | 4-$NO_2C_6H_4$ | 3 | 93 | 243–245 | 243–244 [21] |
| **5j** | 3-$NO_2C_6H_4$ | 3 | 91 | 176–177 | 178–179 [21] |
| **5k** | 4-OH-3-$CH_3OC_6H_3$ | 2 | 94 | 211–213 | 211–212 [21] |
| **5l** | 4-$(CH_3)_2NC_6H_4$ | 2 | 95 | 232–233 | 229–231 [15(a)] |
| **5m** | 2-Furyl | 2 | 90 | 247–249 | 246–248 [15(a)] |
| **5n** | 2,4-$Cl_2C_6H_3$ | 2 | 94 | 243–245 | 242–244 [21] |

[a] Microwave heating performed on 180 W power and 80°C temperature.
[b] Isolated yield.

## CONCLUSIONS

In conclusion, the present MW irradiation procedure provides an easy and efficient access to polyhydroquinolines *via* Hantzsch condensation using glycine as an organocatalyst. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent product yield, shorter reaction time, and the easy work-up procedure make this approach more attractive in synthesizing a variety of such derivatives.

## EXPERIMENTAL

All the chemicals were procured from Aldrich, USA and E. Merck, Germany and were purified before use. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as an internal standard. Elemental microanalysis was performed on Exeter Analytical Model CE-440 CHN analyzer. Melting points were measured in open capillaries and are uncorrected. The MW irradiation was effected using the CEM's Discover Bench Mate (magnetron frequency 2455 MHz) single-mode MW synthesis system using safe pressure regulation 10-mL pressurized vials with ''snap-on'' cap.

**General procedure for the synthesis of polyhydroquinolines 5.** A mixture of aldehyde **1** (1 mmol), dimedone **2** (1 mmol), ethyl acetoacetate **3** (1 mmol), ammonium acetate **4** (1.2 mmol), glycine (10 mol %), and acetonitrile (1 mL) was placed in a sealed pressure regulation 10-mL pressurized vial with ''snap-on'' cap and was irradiated in the single-mode MW synthesis system at 180 W power and 80°C temperature for 1–3 min. After completion of reaction (TLC), the mixture was cooled and the resulting product was washed with cold water to remove any unreacted ammonium acetate. The crude product was finally recrystallized from methanol to afford the pure products **5a–5n**.

***Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a).*** IR (KBr): 3289, 3080, 2961, 1699, 1612 $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.26–7.31 (m, 2H), 7.17–7.22 (m, 2H), 7.07–7.11 (m, 1H), 5.85 (s, 1H), 5.05 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 2.18–2.31 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.70, 167.47, 148.72, 147.05, 143.67, 127.96, 127.83, 125.98, 111.92, 105.93, 59.78, 50.72, 40.85, 36.55, 32.64, 29.41, 27.08, 19.24, 14.17; Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13; Found: C, 74.23; H, 7.48; N, 4.19.

***Ethyl 4-(4-methylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5b).*** IR (KBr): 3276, 3078, 2960, 1702, 1646 $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.69 (s, 1H), 5.07 (s, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 2.16–2.29 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 3H), 0.95 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.68, 167.39, 148.74, 146.95, 143.71, 127.97, 127.83, 126.07, 112.01, 105.98, 59.83, 50.77, 40.92, 36.59, 32.73, 29.45, 27.06, 19.81, 19.23, 14.16; Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96; Found: C, 74.85; H, 7.66; N, 3.90.

***Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5c).*** IR (KBr): 3279, 3079, 2959, 1702, 1646 $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 5.75 (s, 1H), 4.99 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 2.37 (s, 3H), 2.17–2.30 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 3H), 0.94 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.65, 167.51, 157.72, 148.18, 143.21, 139.60, 128.91, 113.20, 112.21, 106.24, 59.75, 55.08, 50.73, 40.95, 35.67, 32.64, 29.41, 27.13, 19.31, 14.21; Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79; Found: C, 71.61; H, 7.40; N, 3.70.

***Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5d).*** IR (KBr): 3274, 3206, 3085, 2938, 1705, 1606 $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$):

δ = 7.14–7.23 (m, 2H), 7.05–7.11 (m, 2H), 5.77 (s, 1H), 5.02 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 2.16–2.37 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.64, 167.31, 149.20, 144.53, 133.55, 129.11, 128.08, 126.23, 111.14, 105.12, 59.79, 50.67, 40.64, 36.58, 32.59, 29.34, 27.01, 19.06, 14.13; Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75; Found: C, 67.34; H, 6.52; N, 3.78.

***Ethyl 4-(3-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e).*** IR (KBr): 3274, 3202, 3074, 2934, 1704, 1605 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.08–7.24 (m, 4H), 5.78 (s, 1H), 5.03 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.19–2.39 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 3H), 0.95 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.66, 167.25, 149.28, 144.41, 133.53, 129.10, 128.05, 126.19, 111.11, 105.10, 59.78, 50.64, 40.61, 36.57, 32.55, 29.31, 27.04, 19.05, 14.13; Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75; Found: C, 67.51; H, 6.44; N, 3.70.

***Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5f).*** IR (KBr): 3274, 3205, 3072, 2955, 1702, 1604 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.18–7.23 (m, 2H), 7.02–7.08 (m, 2H), 6.56 (s, 1H), 5.03 (s, 1H), 4.02–4.11 (m, 2H), 2.34 (s, 3H), 2.12–2.28 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.95 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.38, 167.76, 148.87, 145.69, 143.71, 131.03, 129.73, 111.14, 106.05, 59.79, 50.67, 40.64, 36.28, 32.59, 29.34, 27.01, 19.16, 14.15; Anal. Calcd. for $C_{21}H_{24}BrNO_3$: C, 60.29; H, 5.78; N, 3.35; Found: C, 60.42; H, 5.71; N, 3.29.

***Ethyl 4-(3-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5g).*** IR (KBr): 3275, 3204, 3074, 2957, 1703, 1605 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 7.21–7.26 (m, 2H), 7.04–7.09 (m, 1H), 6.60 (s, 1H), 5.02 (s, 1H), 4.02–4.12 (m, 2H), 2.35 (s, 3H), 2.13–2.29 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 3H), 0.95 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.56, 167.16, 149.08, 144.00, 131.04, 129.25, 126.87, 122.02, 111.42, 105.43, 59.90, 50.67, 40.89, 36.63, 32.69, 29.36, 27.13, 19.31, 14.17; Anal. Calcd. for $C_{21}H_{24}BrNO_3$: C, 60.29; H, 5.78; N, 3.35; Found: C, 60.20; H, 5.83; N, 3.42.

***Ethyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5h).*** IR (KBr): 3287, 3209, 2960, 1697, 1615 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.21–7.26 (m, 2H), 6.89–7.03 (m, 2H), 5.69 (s, 1H), 5.11 (s, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 2.14–2.28 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.65, 167.55, 153.72, 149.27, 144.60, 138.63, 129.51, 112.17, 106.25, 59.84, 50.78, 40.97, 36.12, 32.71, 29.42, 27.15, 19.31, 14.22; Anal. Calcd. for $C_{21}H_{24}FNO_3$: C, 70.57; H, 6.77; N, 3.92; Found: C, 70.46; H, 6.74; N, 3.88.

***Ethyl 4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i).*** IR (KBr): 3285, 3203, 3078, 2964, 1676, 1605, 1515 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 5.75 (s, 1H), 5.15 (s, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.11–2.35 (m, 4H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 3H), 0.91 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.38, 166.82, 154.50, 148.88, 146.16, 144.48, 128.92, 123.28, 110.99, 104.83, 60.04, 50.57, 40.93, 37.18, 32.67, 29.32, 27.01, 19.37, 14.15; Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29; Found: C, 65.56; H, 6.33; N, 7.37.

***Ethyl 4-(3-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j).*** IR (KBr): 3283, 3210, 3079, 2958, 1705, 1608, 1532 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 5.88 (s, 1H), 5.15 (s, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 2.41 (s, 3H), 2.12–2.36 (m, 4H), 1.19 (t, *J* = 6.9 Hz, 3H), 1.10 (s, 3H), 0.94 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.52, 166.90, 149.15, 148.20, 144.52, 134.73, 128.54, 122.81, 121.23, 111.09, 104.99, 60.02, 50.54, 40.84, 36.95, 32.70, 29.32, 27.02, 19.33, 14.13; Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29; Found: C, 65.70; H, 6.34; N, 7.20.

***Ethyl 4-(4-hydroxy-3-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5k).*** IR (KBr): 3399, 3292, 2934, 1698, 1591 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ = 8.99 (s, 1H), 8.63 (s, 1H), 6.69 (s, 1H), 6.49–6.58 (m, 2H), 4.74 (s, 1H), 4.40 (q, *J* = 6.9 Hz, 2H), 2.50 (s, 3H), 1.95–2.39 (m, 7H), 1.16 (t, *J* = 6.9 Hz, 3H), 1.01 (s, 3H), 0.88 (s, 3H); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ = 194.49, 167.10, 149.39, 146.78, 144.49, 139.10, 119.59, 114.98, 112.03, 110.22, 104.14, 59.05, 55.49, 50.35, 35.07, 32.16, 29.29, 26.42, 18.28, 14.28; Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63; Found: C, 68.61; H, 7.11; N, 3.58.

***Ethyl 4-(4-dimethylaminophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5l).*** IR (KBr): 3280, 3207, 3079, 2954, 1700, 1607 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 5.70 (s, 1H), 4.95 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.87 (s, 6H), 2.18–2.36 (m, 7H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 3H), 0.97 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.56, 167.65, 148.97, 147.59, 142.75, 135.81, 128.58, 112.47, 106.55, 59.72, 50.76, 40.94, 35.29, 32.70, 29.41, 27.33, 19.42, 14.25; Anal. Calcd. for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32; Found: C, 72.10; H, 7.95; N, 7.38.

***Ethyl 4-(furan-2-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5m).*** IR (KBr): 3287, 3220, 3086, 2932, 1675, 1605 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.18 (s, 1H), 6.20 (s, 1H), 6.00 (s, 1H), 5.89 (s, 1H), 5.25 (s, 1H), 4.12–4.16 (m, 2H), 2.19–2.39 (m, 7H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.10 (s, 3H), 1.02 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.57, 167.34, 157.94, 150.61, 144.26, 140.85, 111.13, 105.03, 103.07, 59.83, 50.63, 36.88, 32.48, 29.71, 27.03, 19.08, 14.17; Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; Found: C, 69.17; H, 7.10; N, 4.28.

***Ethyl 4-(2,4-dichlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5n).*** IR (KBr): 3287, 3204, 3088, 2936, 1703, 1607 cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, 1H), 7.22 (s, 1H), 7.10 (d, 1H), 6.13 (s, 1H), 5.23 (s, 1H), 3.97–4.06 (m, 2H), 2.38 (s, 3H), 2.18–2.36 (m, 4H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 3H), 0.94 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 195.41, 167.23, 149.38, 142.42, 133.67, 132.78, 132.04, 129.13, 126.86, 111.13, 104.59, 60.11, 50.58, 41.07, 32.73, 29.12, 27.37, 19.11, 14.17; Anal. Calcd. for $C_{21}H_{23}Cl_2NO_3$: C, 61.77; H, 5.68; N, 3.43; Found: C, 61.84; H, 5.71; N, 3.39.

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## REFERENCES AND NOTES

[1] (a) Caddick, S.; Fitzmaurice, R. Tetrahedron 2009, 65, 3325; (b) Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250; (c) Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563; (d) Tierney, J. P.; Lidstrom, P. Microwave Assisted Organic Synthesis; Blackwell: Oxford, UK, 2005; p 1; (e) Kappe, C. O.; Stadler, A. Microwaves in Organic and Medicinal Chemistry; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2005; p 1.

[2] (a) Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2005; p 1; (b) Ganem, B. Acc Chem Res 2009, 42, 463; (c) Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471; (d) Syamal, M. Org Prep Proc Int 2009, 41, 1; (e) Jiang, B.; Yang, C.-G.; Wang, J. J Org Chem 2001, 66, 4865.

[3] (a) Domling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3168; (b) Jimenez-Abnso, S.; Chavez, H.; Estevez-Braan, A.; Ravelo, A.; Feresin, G.; Tapia, A. Tetrahedron 2008, 64, 8938; (c) Ramon, D. J.; Yus, M. Angew Chem Int Ed 2005, 44, 1602.

[4] Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schravan, K. Eur J Med Chem 1992, 27, 229.

[5] Bossert, F.; Meyer, H.; Wehinger, E. Angew Chem Int Ed 1981, 20, 762.

[6] Nakayama, H.; Kasoaka, Y. Heterocycles 1996, 42, 901.

[7] Klusa, V. Drugs Future 1995, 20, 135.

[8] Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. Am J Kidney Dis 1993, 21, 53.

[9] Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. Drugs Future 1992, 17, 465.

[10] Boer, R.; Gekeler, V. Drugs Future 1995, 20, 499.

[11] (a) Sufirez, M.; Ochoa, E.; Verdecia, Y.; Verdecia, B.; Moran, L.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Novoa, H.; Blaton, N.; Peters, O. M. Tetrahedron 1999, 55, 875; (b) Suresh; Kumar, D.; Sandhu, J. S. Synth Commun 2009, 39, 1957.

[12] Mekheimer, R. A.; Hameed, A. A.; Sadek, K. U. Green Chem 2008, 10, 592.

[13] (a) Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loa, T. P. Synlett 2004, 831; (b) Zhang, X. Y.; Li, Y. Z.; Fan, X. S.; Qu, G. R.; Hu, X. Y.; Wang, J. J Chin Chem Lett 2006, 17, 150.

[14] Sabitha, G.; Reddy, G. S. K.; Reddy, C. S.; Yadav, J. S. Tetrahedron Lett 2003, 44, 4129.

[15] (a) Wang, L. M.; Sheng, J.; Zhang, L.; Han, J. W.; Fan, Z. Y.; Tian, H.; Qian, C. T. Tetrahedron 2005, 61, 1539; (b) Donelson, J. L.; Gibbs, A.; De, S. K. J Mol Catal A: Chem 2006, 256, 309.

[16] Kumar, S.; Sharma, P.; Kapoor, K. K.; Hundal, M. S. Tetrahedron 2008, 64, 536.

[17] Das, B.; Ravikanth, B.; Ramu, R.; Rao, V. B. Chem Pharm Bull 2006, 54, 1044.

[18] Song, G.; Wang, B.; Wu, X.; Kang, Y.; Yang, L. Synth Commun 2005, 35, 2875.

[19] Reddy, C. S.; Raghu, M. Chin Chem Lett 2008, 19, 775.

[20] Adibi, H.; Samimi, H. A.; Beygzadeh, M. Catal Commun 2007, 8, 2119.

[21] Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, C. V. Arkivoc 2006, 2, 201.

[22] (a) Heravi, M. M.; Bakhtiri, K.; Javadi, N. M.; Bamoharram, F. F.; Saeedi, M.; Oskooi, H. A. J Mol Catal A: Chem 2007, 264, 50; (b) Nagarapu, L.; Apuri, S.; Gaddam, S.; Bantu, R.; Mahankhali, V. C.; Kantevari, S. Lett Org Chem 2008, 5, 60.

[23] Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. Tetrahedron Lett 2005, 46, 5771.

[24] Cherkupally, S. R.; Mekalan, R. Chem Pharm Bull 2008, 56, 1002.

[25] (a) Evans, C. G.; Gestwicki, J. E. Org Lett 2009, 11, 2957; (b) Kumar, A.; Maurya, R. A. Tetrahedron 2007, 63, 1946.

[26] Sapkal, S. B.; Shelke, K. F.; Shingate, B. B.; Shingare, M. Tetrahedron Lett 2009, 50, 1754.

[27] (a) Breitenbucher, J. G.; Figliozzi, G. Tetrahedron Lett 2000, 41, 4311; (b) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Tetrahedron 2004, 60, 2311.

[28] Kumar, A.; Maurya, R. A. Tetrahedron Lett 2007, 48, 3887.

# Solvent-Dependent Fluorescence Emission in Heterocyclic Compounds Having Isoquinoline Backbone



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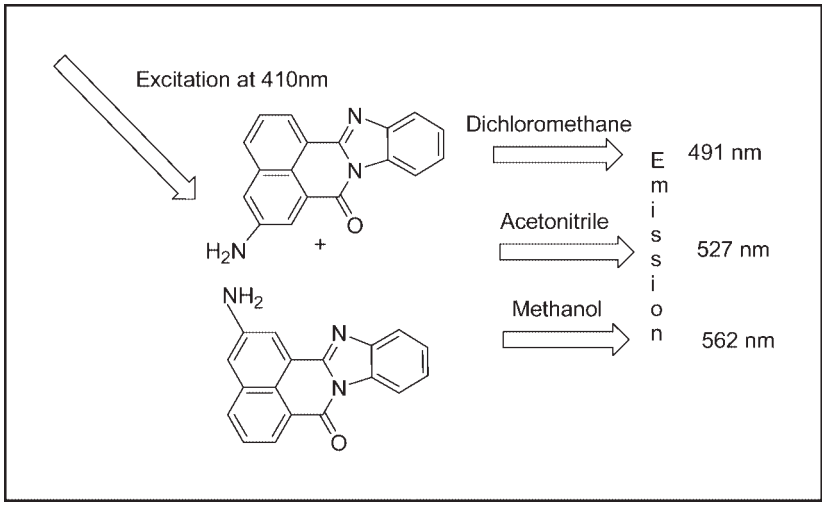


Few amino derivatives of benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one having amino groups at different positions of the rings are prepared and characterized. Solvent-dependent emission and changes in emission properties on protonation of amine group are observed.

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## INTRODUCTION

The organic compounds having fluorophores that are sensitive to environment are of great importance [1–5] in chemistry and biology. The fluorescence emission spectra of some heterocyclic compounds such as benzo [de]benzo[4,5]imidazo[2,1-a]isoquinoline (Fig. 1) are sensitive to environment [6–8], and some of such heterocyclic compounds are used as organic photoconductive materials [9]. Therefore, the functionalization of such heterocyclic compounds is expected to form derivatives that may possess interesting optical properties [10]. Heterocyclic compounds having more numbers of delocalized aromatic rings in conjugation to each other would lead to better as well as novel optical properties [9]. With an interest to identify and characterize and also to understand optical properties of compounds bearing fluorophores that are sensitive to environment, we have synthesized few heterocyclic compounds as shown in Figure 1. We have studied fluorescence emission of these compounds and compared with some of their derivatives.

## RESULTS AND DISCUSSION

**Synthesis of the heterocycles.** The compounds **2** and **4** were prepared by the reactions as depicted in Schemes 1 and 2. The condensation of 1,8-naphthalic anhydride with 4-nitro 1,2-diaminobenzene in acetic acid gave 11-nitro-benzo[de] benzo[4,5] imidazo[2,1-a] isoquinolin-7-one (**1**). Although this reaction is expected to give two isomeric products, we obtained a single isomeric product. This is due to the fact that such cyclization process passes through imide intermediates. It is recently shown that only one imide isomer is formed in this reaction before cyclization. This was shown by trapping the intermediate imide derivative in dimethylformamide (DMF) as a solvent. The formation of specific imide in this reaction, between the two possible isomers, may be attributed to the ease of attack of the less sterically crowded [11] amino group at *p*-position to the nitro group of 4-nitro 1,2-diaminobenzene. The reduction of the nitro group of the compound **1** resulted in the formation of the corresponding amine **2**. Acetic acid is found

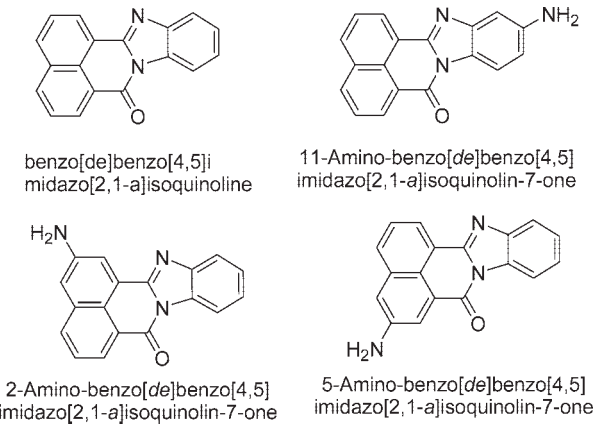
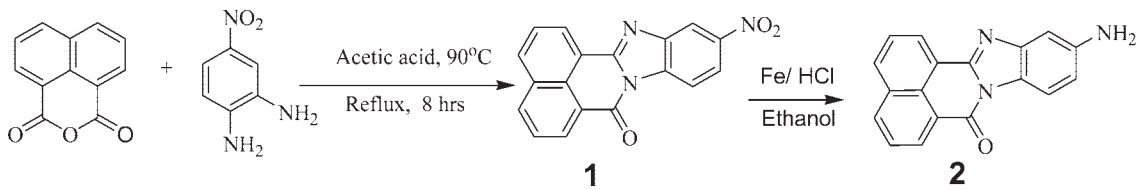



**Figure 1.** Structure of the heterocycles.

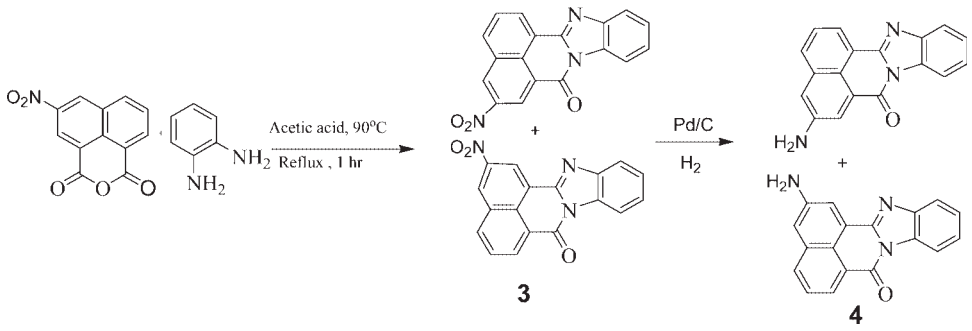
to be appropriate solvent for the synthesis of **2**. Recently, we have discussed about the role of solvent in the formation of similar heterocycles [11] and also mentioned about the usefulness of acetic acid in the synthesis of such heterocycles. Similarly, the condensation reaction of 3-nitro-1,8-naphthalic anhydride with 1,2-diaminobenzene gave a mixture of isomeric products, namely 2-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]one-methane and 5-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one (**3**). We could not separate the two isomers by conventional chromatographic techniques such as preparative thin layer (TLC) or column chromatography. The $^1$H-NMR chemical shift and the integration values of the mixture of isomers suggest formation of almost an equimolar mixture of the two isomers. In an earlier report, it was suggested that similar reaction under microwave irradiation in the presence of alumina resulted only one isomer [12], but in our case we have failed to obtain pure isomer through the reaction condition described herein, and the isomeric product separation of **3** was not successful. However, the condensation reaction of 3-nitro-1,8-naphthalic anhydride with 1,2-diaminobenzene under solvothermal condition in acetic acid at 150°C in an autoclave gave only one isomer. The $^1$H-NMR spectra of this isomer obtained from this reaction is given as Supporting Information. It has eight peaks in aromatic region and tallies the structure of 2-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]one methane. The assignment of the $^1$H-NMR of this compound is on the assumption that the simulated $^1$H-NMR of other isomer namely 5-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one shows proton signals at relatively high chemical shift than the 2-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]one methane. As the optical properties of these two isomers and derivatives are indistinguishable, we proceeded to take the mixture of isomers for optical study described in the Experimental section. The reduction of the nitro groups of these isomers (**3**) was carried out by hydrogen gas with a catalytic amount of palladized carbon to prepare two isomeric amine derivatives **4** (Scheme 2). In the case of **1**, we have obtained only one isomer because of the presence of nitro-group on diamino benzene ring, which could differentiate the two amino groups on the ring in terms of reactivity. The nitro group on the compound **1** was reduced to amino group, and the amino group was further functionalized to various derivatives **5–8** as illustrated in Scheme 3. Methyl and acyl derivatives (**9–12**) of compound **4** were also synthesized by similar procedure (Scheme 4).

**Optical properties.** The compounds **2** and **4** show solvatochromic properties, and the absorption features of **2** and **4** differ in different solvents, which are listed in Table 1. The compounds **2** and **4** are derived from a planar aromatic ring system, which is derived from 1,8-naphthalic anhydride [6]. The imides derived from naphthalic anhydride are useful as fluorescence probes, and their applications are decided by the presence of tether connecting two similar or dissimilar molecules [12]. The compounds **2** and **4** have reasonable fluorescence emission properties on excitation at appropriate wavelengths. The UV–visible absorption spectra as well as fluorescence emission spectra of several derivatives of 11-amino benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one (**2**) are recorded and listed in Table 2. Among the nitro and amino group (compounds **1** and **2**), the later shifts the fluorescence emission towards higher wavelength. In the case of substituted amines, it is observed that the substituent attached on nitrogen also leads to emission to higher wavelength. Among the *N*-substituent compounds **5–8**, the highest shift is observed in *N*-benzoylated derivative (**7**). It is attributed to the fact that benzoate group participates in delocalization of electrons with the aromatic ring of the heterocycle. The fluorescence emission of **2** in dichloromethane solution is

**Scheme 1**



**Scheme 2**



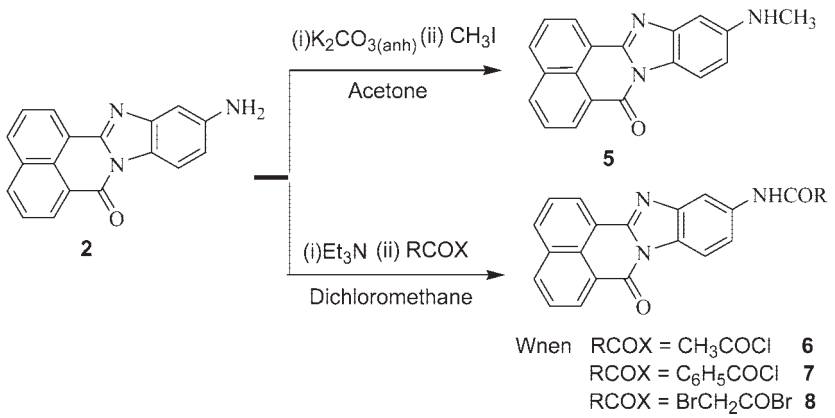

observed at 508 nm upon excitation at 410 nm. The compound **2** is found to be fluorescence inactive in methanol. Accordingly, the fluorescence emission of the **2** observed from dichloromethane solution also gets quenched on addition of methanol (Fig. 2). The fluorescence emission spectra of various derivatives of 11-amino-benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one (**2**) and mixture of 2-amino-benzo[de]benzo[4,5]-imidazo[2,1-a]isoquinolin-7-one and 5-amino-benzo[de]-benzo[4,5]imidazo[2,1-a]isoquinolin-7-one (**4**) were also recorded, and the emission wavelengths and quantum yields are listed in Table 2. Although the compound **4** is a mixture of two isomers, in none of the cases, we could obtain any distinguishable fluorescence emission features of the two isomers. The wavelength shifts and intensity changes in various derivatives of **2** and **4** predominantly occur from the electronic effect caused to the overall electronic environment by the presence of the substituents. It is important to note that the emission spectra of naphthalimide fluorophores having amine groups are proton responsive [13], and such compounds have relevance in recognition of anions [14].

In the case of compound **2**, the protonation causes shift in the fluorescence emission to a lower wavelength from the parent compound. For example, the parent compound **2** in dichloromethane on excitation at 410 nm emits at 514 nm, and the shifts to 508 and 498 nm, respectively, on addition of 1 and 2 equiv of hydrochloric acid (HCl).

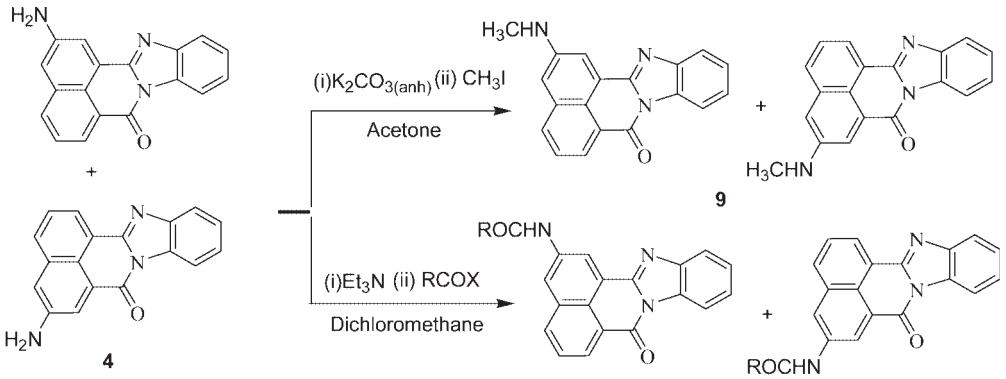
The emission spectra of **4** are highly solvent dependent. A solution of **4** on excitation at 410 nm in dichloromethane, acetonitrile, and methanol shows fluorescence emission at 491 ($\Phi = 0.458$), 527, and 562 nm, respectively [Fig. 3(a)]. Such large characteristic shifts in emission spectra make it possible to distinguish these three solvents. From Table 1, it is clear that the compound **4** shows very small solvatochromicity in visible spectra, whereas it shows a large shift in emission spectra on change of solvents. This suggests that a polar excited state capable of forming exciplex with different solvents is involved in the fluorescence emission.

Addition of methanol to dichloromethane solution of **4** changes its fluorescence emission; initially, the emission occurring due to excitation at 410 nm decreases, but the emission shifts to a higher wavelength and on gradual addition of methanol it once again increases and reaches the emission wavelength that corresponds to the observed emission wavelength from a methanolic solution of **4** [Fig. 3(b)]. Similarly, the addition of methanol to an acetonitrile solution of **4** shifts the fluorescence emission to higher wavelength [Fig. 3(c)]. The compound **4** also shows proton responsive fluorescence

**Scheme 3**



**Scheme 4**



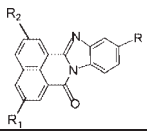

emission, which is dependent on the hydrogen ion concentrations. For example, treatment of a solution of **4** with HCl (1 equiv) causes a change of fluorescence emission from 491 to 501 nm, and on addition of 2 equiv of the acid, the emission occurs at 510 nm [Fig. 3(d)]. These results suggest that the protonation effects the delocalization of electrons of the amino group, which in turn contributes to the changes in the emission spectra of these compounds. The solvato-emissive properties can be attributed to the stabilization of polar exited state by polar solvent, whereas the proton responsive nature is attributed to the hydrogen bonding by protic solvent and protonation by mineral acid. Similar properties are seen in receptors of carboxylic acids [15].

## CONCLUSIONS

A large shift in fluorescence emission wavelength is observed on introduction of amino group at different positions of benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one. Different organic solvents such as dichloromethane, acetonitrile, and methanol can be distinguished from the emission wavelengths of the **4** in these solvents. Depending on the position of an amino group on the rings and protonation of the amino groups at different positions, the fluorescence emissions shifts to higher or lower wavelength.

**Table 1**

Effect of solvent on the visible spectra of **2** and **4**.

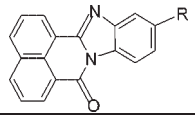
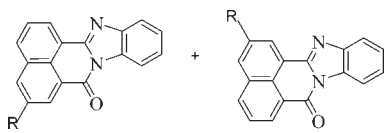
|  | Solvent | $\lambda_{max}$ (nm) | ε ($M^{-1}$ $cm^{-1}$) |
|---|---|---|---|
| R = $NH_2$, $R_1$, $R_2$ = H (**2**) | Dichloromethane | 430 | 12,727 |
| R = $NH_2$, $R_1$, $R_2$ = H (**2**) | Methanol | 437 | 10,227 |
| R = $NH_2$, $R_1$, $R_2$ = H (**2**) | Acetonitrile | 444 | 9545 |
| R = H, $R_1$, $R_2$ = H/$NH_2$ (**4**) | Dichloromethane | 427 | 11,212 |
| R = H, $R_1$, $R_2$ = H/$NH_2$ (**4**) | Acetonitrile | 432 | 10,000 |
| R = H, $R_1$, $R_2$ = H/$NH_2$ (**4**) | Methanol | 438 | 9696 |

## EXPERIMENTAL

UV–visible spectra were recorded on Perkin Elmer Lamda 25 UV–visible spectrometer, and the fluorescence spectra were recorded on Perkin Elmer LS-55 fluorescence spectrometer.

**Table 2**

The visible spectra and fluorescence emission ($\lambda_{ex}$ = 410 nm) of derivatives of **2** and **4**.

| | Dichloromethane | | | |
|---|---|---|---|---|
|  | $\lambda_{max}$ (nm) | ε ($M^{-1}$ $cm^{-1}$) | $\lambda_{em}$ (nm) | Φ |
| R = $NO_2$ (**1**) | 390 | 19,772 | 463 | 0.134 |
| R = $NH_2$ (**2**) | 430 | 12,727 | 508 | 0.252 |
| R = $NHCH_3$ (**5**) | 395 | 6818 | 515 | 0.060 |
| R = $NHCOCH_3$ (**6**) | 397 | 6136 | 545 | 0.350 |
| R = $NHCOC_6H_5$ (**7**) | 401 | 8409 | 546 | 0.452 |
| R=$NHCOCH_2Br$ (**8**) | 393 | 10,909 | 518 | 0.343 |
|  | | | | |
| R=$NH_2$ (**4**) | 427 | 11,212 | 491 | 0.288 |
| R=$NHCH_3$ (**9**) | 375 | 18,909 | 538 | 0.156 |
| R=$NHCOCH_3$ (**10**) | 401 | 10,303 | 493 | 0.290 |
| R=$NHCOC_6H_5$ (**11**) | 401 | 19,181 | 493 | 0.324 |
| R=$NHCOCH_2Br$ (**12**) | 395 | 10,393 | 495 | 0.215 |

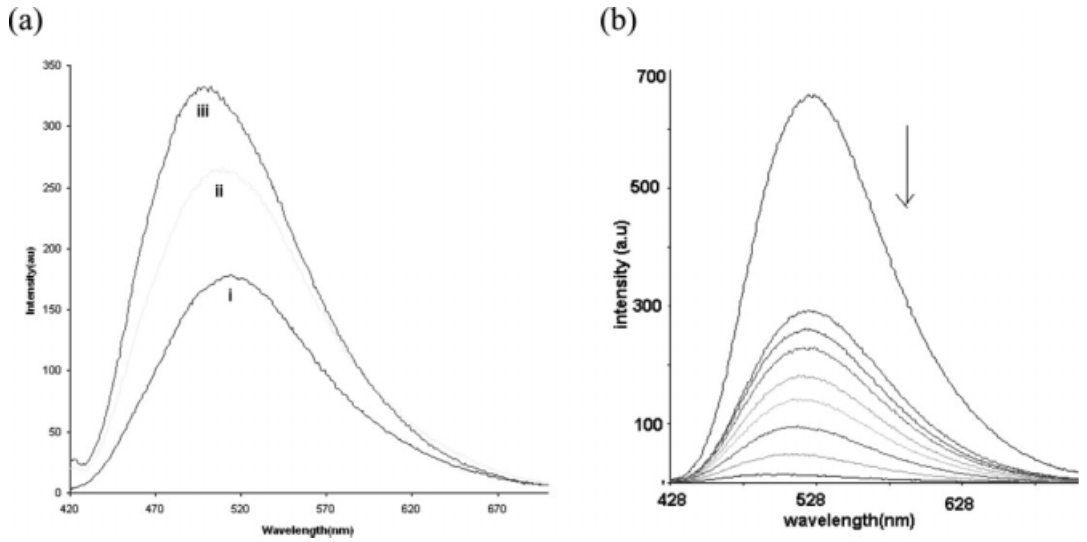



**Figure 2.** (a) Fluorescence emission ($\lambda_{ex}$ = 410 nm) spectra of (i) **2** in dichloromethane: (ii) on addition of 1 mol equiv of HCl and (iii) on addition of 2 mol equiv of HCl (in each cases 3 mL of 1.1 × $10^{-5}M$ solution). (b) Effect of the addition of methanol (100 μL aliquots) to a solution of **2** in dichloromethane.

The NMR spectra were recorded on a 400 MHz Varian FT-NMR instrument with TMS as an internal standard. Mass spectra were recorded in a Water LC-MS. The melting points of the compounds were determined in a Buchi B-540 melting point apparatus. All the optical measurements were carried out by dissolving calculated amount of the compounds in spectroscopic grade solvents. The fluorescence titrations were carried out in quartz cuvette by adding different aliquots of titrant/s by micropipette to a parent solution (3 mL).

**Determination of fluorescence quantum yield.** Fluorescence quantum yields were determined by calibrating with perylene (Φ = 0.94) by fluorescence excitation at 410 nm as standard. The fluorescence quantum yield was calculated by using the following formula [16]:

$$\frac{(\text{Quantum yield})_{\text{sample}}}{(\text{Quantum yield})_{\text{standard}}} = \frac{\text{Absorption of standard}\,(\text{Area under the graph of emission spectra})_{\text{Sample}}}{\text{Absorption of sample}\,(\text{Area under the graph of emissio spectra})_{\text{Standard}}}.$$

For calculation of the quantum yield of the other samples, the identical procedures were used.

**Synthesis and characterization of various compounds.**

***Compound 1.*** A mixture of 1,8-naphthalic anhydride (0.99 g, 5 mmol) and 4-nitro 1,2 diaminobenzene (0.77 g, 5 mmol) was refluxed in acetic acid (10 mL) for 4 h. The reaction mixture was cooled and water (20 mL ) was added to the reaction mixture and stirred for 20 min. The precipitate was filtered and washed several times with water to remove acetic acid. The product was air dried to obtain 11-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one in 77% yield. Elemental Anal. Calcd. for $C_{19}H_9N_3O_3$; C, 68.57; H, 2.88; Found C, 68.60, H, 2.86. $^1$H-NMR (400 MHz, $CDCl_3$): 9.17 (d, 1H, $J$ = 2.4), 8.75 (m, 4H), 8.51 (dm, 1H, $J$ = 7.2), 8.19 (s, 1H), 7.87 (m, 2H). IR (KBr, $cm^{-1}$): 1699 (s), 1517 (s), 1335 (s). ESI-MS: 316.1757 ($M + H^+$) m.p. 415°C.

***Compound 2.*** To a solution of 11-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one (0.32 g, 1 mmol) in ethanol/water (2:1, 20 mL), iron powder (35 mmol) and aqueous HCl (10%, 5 mL) were added. The mixture was kept at 90°C for 2 h. The reaction mixture was brought to room temperature and then water (10 mL) was added to the reaction mixture and filtered. The solid product obtained was washed with water and the product was purified by preparative TLC. Yield: 55%. Elemental Anal Calcd. for $C_{18}H_{11}N_3O$; C, 75.78; H, 3.89; Found C, 75.80, H, 3.90. $^1$H-NMR (400 MHz, $CDCl_3$) 8.76 (m, 2H), 8.26 (d, 1H, $J$ = 8.4 Hz), 8.1 (d, 1H, $J$ = 8 Hz), 7.9 (d,1H, $J$ = 2.4 Hz), 7.8 (m, 2H), 7.66 (d, 1H, $J$ = 8.4 Hz), 6.85 (d, 1H, $J$ = 8.4 Hz), 5.0 (s, 2H).$^{13}$C-NMR ($CDCl_3$): 158.9, 145.8, 137.4, 134.3, 134.2, 131.6, 130.8, 129.7, 129.5, 129.3, 127.4, 125.9, 125.7, 123.1, 120.2, 120.1, 118.5, 115.3. IR (KBr, $cm^{-1}$): 3232 (w), 3363 (s), 1589 (m), 1621 (s), 1697 (s). ESI-MS = 286.1864 ($M + H^+$). m.p. 406°C.

***Compound 3.*** A mixture of 3-nitro-1,8-naphthalic anhydride (1.22 g, 5 mmol) and 1,2 diaminobenzene (0.54 g, 5 mmol) was refluxed in acetic acid (20 mL) at 90°C for 4 h. The reaction mixture was cooled and then water (20 mL) was added to the reaction mixture and stirred for 20 min. The precipitate was filtered and washed several times with water to remove acetic acid, and the product was air dried to obtain a mixture of 2-nitro-benzo[de]benzo[4,5]imidazo[2,1-a]onemethane and 5-nitro-benzo[de]benzo[4,5]imidazo [2,1-a]isoquinolin-7-one in

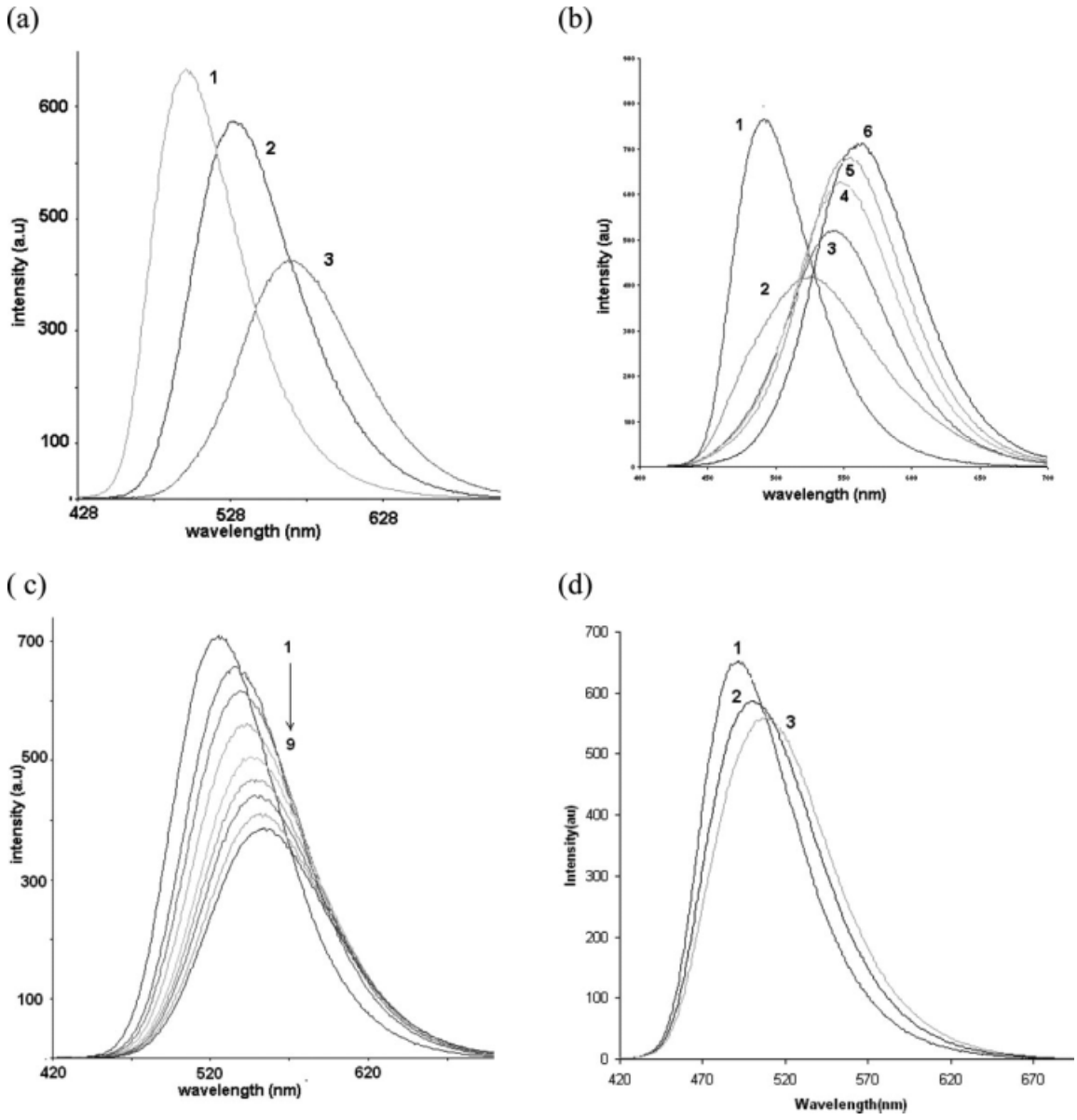



**Figure 3.** The fluorescence emission of ($\lambda_{ex}$ = 410 nm): (a) **4** in (i) dichloromethane, (ii) acetonitrile, and (iii) methanol (in each cases 3 mL of $1.1 \times 10^{-5}M$ solution **4**); (b) **4** on addition of different aliquots of methanol (50 μL each from 2–6) to a dichloromethane solution of **4**; (c) **4** on addition of different aliquots of methanol (50 μL each from 2–6) to an acetonitrile solution of **4**; (d) **4** (1) in dichloromethane and on addition of (2) 1 equiv of HCl or (3) 2 equiv of HCl.

86% yield. $^1$H-NMR (400 MHz, $CDCl_3$): 9.55 (d, $J$ = 4 Hz, 1H) 9.48 (d, $J$ = 4 Hz, 1H), 9.18 (d, $J$ = 4 Hz, 1H), 9.0 (d, $J$ = 4 Hz, 1H), 8.98 (d, 1H, $J$ = 8 Hz), 8.95 (d, 1H, $J$ = 8 Hz), 8.54 (m, 2H), 8.48 (d, 1H, $J$ = 8 Hz), 8.35 (d, $J$ = 8 Hz, 1H), 7.99 (t, $J$ = 8 Hz, 2H), 7.91–7.94 (m, 2H), 7.50–7.53 (m, 4H). IR (KBr, cm$^{-1}$): 3444 (m), 3067 (m), 1696 (s), 1596 (m), 1531 (m), 1443 (w), 1343 (s), 1234 (m), 1152 (w), 1039 (w), 751 (m), 557 (w). ESI-MS: 316.1814 ($M + H^+$). m.p. 410°C.

***Compound 4.*** To a solution of mixture of 2-nitro-benzo[de]-benzo[4,5]imidazo[2,1-a]onemethane and 5-nitro-benzo[de]-benzo[4,5]imidazo [2,1-a]isoquinolin-7-one (1.58 g, 5 mmol) in tetrahydrofuran (20 mL), palladized carbon (10%, 0.1 g) was added. The mixture was stirred under hydrogen atmosphere (50 psi) for 24 h, filtered, and the solvent was removed from filtrate under reduced pressure to get the desired product. The yield after purification was 85%. $^1$H-NMR (400 MHz, $CDCl_3$): 8.48–8.56 (m, 4H), 8.25 (d, $J$ = 3 Hz, 1H), 8.18 (d, 1H, $J$ = 3 Hz), 7.96 (d, $J$ = 8 Hz, 1H), 7.83–7.85 (m, 2H), 7.62–7.67 (m, 2H), 7.43–7.48 (m, 4H), 7.35 (d, $J$ = 3 Hz, 1H) 4.2 (broad s, 2H). $^{13}$C-NMR ($CDCl_3$): 158.1, 145.4, 134.2,

133.3, 130.0, 128.2, 127.8, 127.4, 125.9, 125.6, 125.4, 123.9, 122.4, 120.1, 118.0, 116.1, 115.7, 112.5. IR (KBr, $cm^{-1}$): 3448 (w), 3362 (s), 2924 (m), 2851 (m), 1690 (s), 1627 (s), 1550 (w), 1448 (w), 1352 (s), 1330 (s), 1166 (w), 1050 (w), 872 (w), 764 (w). ESI-MS: 286.1957 ($M + H^+$). m.p. 405°C.

***Compounds 5–8.*** The 11-amino-benzo[de]benzo[4,5]imidazo[2,1-a]isoquinolin-7-one (**2**) was converted to corresponding *N*-methyl (**5**), *N*-acetyl (**6**), *N*-benzoyl (**7**), and *N*-bromoacetyl derivatives (**8**) by reactions with suitable reagents as follows:

***Compound 5.*** A mixture of compound **1** (0.1 g, 0.35 mmol) and anhydrous potassium carbonate was refluxed in dry acetone with methyl iodide (0.08 g, 0.53 mmol) for 24 h. The reaction mixture was evaporated, water (15 mL) and dichloromethane (15 mL) were added, the organic layer was separated, and the product was extracted from the dichloromethane by evaporation. The compound was further purified by TLC. Yield: 25 %. $^1$H-NMR (400 MHz, DMSO-$d_6$): 8.65 (d, 1H, $J = 7.2$ Hz), 8.16 (d, 1H, $J = 8.4$ Hz), 7.98 (d, 1H, $J = 8.4$ Hz), 7.82 (d, 1H, $J = 2.8$ Hz), 7.7 (m, 4H), 6.86 (dd, 1H, $J = 2.8$ Hz), 3.0 (s, 3H). IR (KBr, $cm^{-1}$): 3390 (s), 2924 (s), 2853 (m), 1693 (s), 1621 (s), 1502 (s), 1318 (m). ESI-MS: 300.1132 ($M + H^+$). m.p. 386°C.

***Compounds 6–8.*** The compound **2** (0.06 g, 0.2 mmol) was mixed with RCOX (for **6**, **7** R = $CH_3$, Ph and X = Cl, respectively, whereas for **8** R = $BrCH_2CO$- and X = Br) and triethylamine (0.4 mL) in dry dichloromethane (10 mL). The mixture was stirred overnight at room temperature. On adding 40 mL water to the reaction mixture, the solid products in pure form were obtained from dichloromethane in quantitative yield.

***Compound 6.*** $^1$H-NMR (400 MHz, DMSO-$d_6$): 10.26 (s,1H), 8.9 (s,1H), 8.72 (d, 2H, $J = 8$ Hz ), 8.54 (d, 1H, $J = 8.4$ Hz), 8.38 (d, 1H, $J = 8.4$ Hz), 7.94 (m, 2H), 7.8 (d, 1H, $J = 8.8$ Hz ), 7.64 (d, 1H, $J = 8.4$ Hz), 2.1 (s, 3H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 168.4, 159.8, 149.9, 143.7, 139.2, 137.2, 135.5, 132.1, 131.7, 131.1, 127.4, 127.1, 126.7, 122.5, 119.92, 117.5, 116.9, 115.0, 109.6, 105.9, 24.1. IR (KBr, $cm^{-1}$): 3302 (s), 2923 (s), 2852 (m), 1702 (s), 1662 (s), 1597 (m). ESI-MS: 328.1220 ($M + H^+$). m.p. 395°C.

***Compound 7.*** $^1$H-NMR (400 MHz, DMSO-$d_6$) 10.57 (s, 1H), 8.7 (d, 1H, $J = 3.6$ Hz), 8.52 (d, 1H, $J = 7.6$ Hz), 8.36 (d, 1H, $J = 7.2$ Hz), 8.15 (d,1H, $J = 4.8$ Hz), 8.04 (d,1H, $J = 4.8$ Hz), 7.94 (d, 2H, $J = 4.8$ Hz), 7.9 (s, 1H), 7.83 (d, 1H, $J = 7.2$ Hz), 7.63 (d, 2H, $J = 4.8$ Hz), 7.57 (s, 1H), 7.51 (d, 2H, $J = 4.8$ Hz). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 165.5, 160.0, 148.63, 139.5, 136.7, 135.3, 135.0, 131.7, 131.4, 131.0, 129.3, 128.4, 127.8, 127.3, 127.0, 126.1, 122.5, 120.0, 119.2, 118.7, 115.0, 111.1, 107.2. IR (KBr, $cm^{-1}$): 3301 (m), 3071 (m), 1703 (s), 1601 (m), 1699 (s). ESI-MS: 390.1217 ($M + H^+$). m.p. 385°C.

***Compound 8.*** $^1$H-NMR (400 MHz, DMSO-$d_6$): 10.72 (s, 1H), 8.90 (s, 1H), 8.70 (d, 2H, $J = 8.4$ Hz), 8.53 (d, 1H, $J = 8.4$ Hz), 8.37 (d, 1H, $J = 8.4$ Hz), 7.9 (m, 2H), 7.8 (m, 1H), 7.65 (d, 1H, $J = 8.4$ Hz), 4.1 (s, 2H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 170.9, 160.0, 148.5, 136.5, 136.1, 135.5, 132.4, 131.8, 131.3, 127.4, 127.1, 126.2, 122.5, 119.8, 119.47, 119.2, 118.3, 117.6, 106.5, 62.0. IR (KBr, $cm^{-1}$): 3253 (s), 2959 (s), 1698 (m), 1654 (s), 1737 (s), 1591 (m), 1233 (m). ESI-MS: 405.9840 and 407.9832 ($M + H^+$). m.p. 378°C.

***Compounds 9–12.*** The compounds **9**, **10**, **11**, and **12** were synthesized from compound **4** by identical procedure that is described for **5**, **6**, **7**, and **8**, respectively.

***Compound 9.*** Yield: 28%. $^1$H-NMR (400 MHz, $CDCl_3$): 8.53 (m,4H), 8.43 (d, 1H, $J = 6.4$ Hz), 8.39 (d, 1H, $J = 2.8$ Hz), 8.32 (d, 1H, $J = 2.8$ Hz), 8.00 (d, 1H, $J = 8.0$ Hz), 7.85 (m, 4H), 7.62 (m, 2H), 7.45 (m, 4H), 7.21 (d, 1H, $J = 2.4$ Hz), 7.10 (d, 1H, $J = 2.4$ Hz), 3.07 (d, 6H, $J = 6.8$ Hz). IR (KBr, $cm^{-1}$): 3445 (s), 2924 (m), 2852 (w), 2357 (w), 1622 (s), 1430 (m), 1327 (s), 1231 (m), 1159 (w), 927 (w), 842 (w), 763 (m). ESI-MS: 300.1147 ($M + H^+$). m.p. 367°C.

***Compound 10.*** Yield: 82%. $^1$H-NMR (400 MHz, $CDCl_3$): 9.92 (s,1H), 9.85 (s,1H), 8.43 (s,1H), 8.28 (d, 2H, $J = 4.0$ Hz), 8.26 (s,1H), 8.15 (d, 1H, $J = 4.0$ Hz), 8.08 (d, 1H, $J = 7.2$ Hz), 8.00 (t, 2H, $J = 5.6$ Hz), 7.73 (d, 1H, $J = 8.4$ Hz), 7.60 (d, 1H, $J = 7.2$ Hz), 7.34 (m, 2H), 7.28 (t, 2H, $J = 8.0$ Hz), 6.98 (dd, 4H, $J = 3.6$ Hz), 2.08 (s, 4H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 169.1, 160.0, 148.6, 143.2, 138.3, 134.7, 132.4, 131.3, 129.2, 127.2, 125.4, 125.0, 122.8, 122.2, 120.2, 119.7, 119.5, 118.4, 115.1, 45.3. IR (KBr, $cm^{-1}$): 3433 (s), 2983 (m), 2738 (w), 2678 (w), 1657 (s), 1558 (m), 1347 (m), 1262 (m), 1161 (w), 1035 (m), 878 (w), 767 (m). ESI-MS: 328.1239 ($M + H^+$). m.p. 356°C.

***Compound 11.*** Yield: 84%. $^1$H-NMR (400 MHz, $CDCl_3$): 10.24 (s, 1H), 10.18 (s, 1H), 8.72 (s, 1H), 8.58 (s, 1H), 8.22 (d, 1H, $J = 7.2$ Hz), 8.10 (dd, 2H, $J = 3.6$ Hz), 7.87 (d, 1H, $J = 8.4$ Hz), 7.70 (t, 4H, $J = 8.0$ Hz), 7.59 (d, 4H, $J = 6.4$ Hz), 7.40 (dd, 2H, $J = 6.0$ Hz), 7.31 (t, 2H, $J = 7.6$ Hz), 7.15 (m, 5H), 7.04 (m,5H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 168.2, 166.6, 163.1, 143.5, 138.3, 135.8, 134.6, 133.6, 132.6, 131.5, 131.1, 130.8, 129.91, 129.8, 129.2, 128.4, 128.3, 125.6, 120.0, 115.0. IR (KBr, $cm^{-1}$): 3394 (s), 3054 (w), 2923 (w), 1788 (m), 1705 (s), 1657 (m), 1543 (s), 1351 (m), 1243 (s), 1174 (m), 1040 (m), 877 (w), 750 (w), 705 (m). ESI-MS: 390.1074 ($M + H^+$). m.p. 362°C

***Compound 12.*** Yield: 80%. $^1$H-NMR (400 MHz, $CDCl_3$): 10.44 (s, 1H), 10.38 (s, 1H), 8.46 (s, 1H), 8.37 (s, 1H), 8.31 (s, 2H), 8.22 (d, 1H, $J = 7.6$ Hz), 8.16 (d, 1H, $J = 7.2$ Hz), 8.03 (t, 1H, $J = 6.8$ Hz), 7.79 (d, 1H, $J = 8.4$ Hz), 7.66 (d, 1H, $J = 8.0$ Hz), 7.35 (m, 3H), 7.14 (m, 2H), 7.05 (dd, 4H, $J = 3.2$ Hz), 3.64 (s, 4H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): 172.4, 160.5, 149.4, 143.8, 138.2, 135.6, 133.1, 132.0, 130.2, 128.1, 126.2, 125.8, 123.8, 123.0, 120.8, 120.2, 119.9, 115.9, 62.7. IR (KBr, $cm^{-1}$): 3437 (s), 3274 (s), 1697 (s), 1673 (s), 1599 (m), 1552 (m), 1492 (w), 1431 (m), 1347 (m), 1050 (w), 868 (w), 766 (m), 677 (w). ESI-MS: 405.9780 and 407.9749 ($M + H^+$). m.p. 360°C.

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## REFERENCES AND NOTES

[1] Kolosov, D.; Adamovich, V.; Djurovich, P.; Mark, E. T.; Adachi, C. J Am Chem Soc 2002, 124, 9945.

[2] Hoeben, J. M.; Jonkheijm, P.; Meijer, E. W.; Schenning, P. H. J. Chem Rev 2005, 105, 1491.

[3] Callan, J.; deSilva, A. P.; Magri, D. Tetrahedron 2005, 61, 8551.

[4] Zhu, W.; Hu, C.; Chen, K.; He, J.; Songs, Q.; Hou, X. J Mater Chem 2002, 12, 1262.

[5] Guo, X.; Qian, X.; Jia, L. Tetrahedron Lett 2004, 45, 113.

[6] Tamuly, C.; Barooah, N.; Laskar, M.; Sarma, R. J.; Baruah, J. B. Supramol Chem 2006, 18, 605.

[7] Galunov, N. Z.; Krasovitskii, B. M.; Lyubenko, O. N.; Yermolenko, I. G.; Patsenker, I. D.; Doroshenko, A. O. J Lumin 2003, 102/103, 119.

[8] Brana, M. F.; Ramos, A. Curr Med Chem 2001, 1, 237.

[9] Law, K.-Y. Chem Rev 1993, 93, 449.

[10] Langthals, H.; Jaschke, H. Chem Eur J 2006, 12, 2815.

[11] Singh, D.; Baruah, J. B. Tetrahedron Lett 2008, 49, 4374.

[12] Pourjavadi, A.; Marandi, G. B. J Chem Res 2001, 11, 485.

[13] Bhosale, S.; Jani, C. H.; Langford, S. J. Chem Soc Rev 2008, 37, 331.

[14] Gunnalaugsson, T.; Kruger, P. D.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. Tetrahedron Lett 2003, 44, 8909.

[15] Karmakar, A.; Baruah, J. B. Supramol Chem 2008, 20, 667.

[16] Lakowicz, J. R. Principles of Fluorescence Spectroscopy, 2nd ed.; Kluwer Academic/Plenum Publishers: New York, 1999; p 52.

# Gas-Phase Pyrolysis in Organic Synthesis: A Route for Synthesis of Cyanamides



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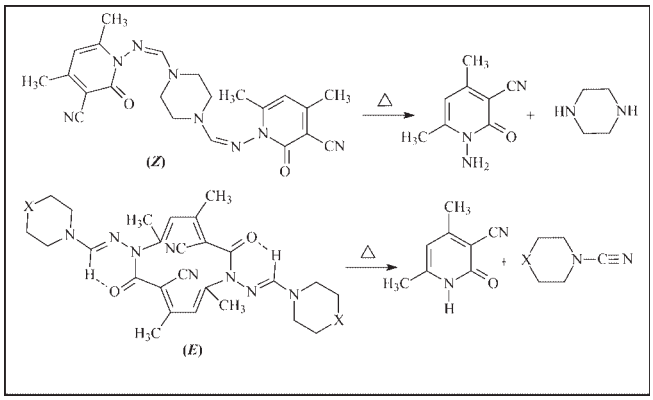

Pyrolysis of 1,7-di-[(*E*)-1-morpholinomethylidene]- and 1,7-di-[(*E*)-1-piperidino-methylidene]-4,6,10,12-tetramethylamino-2,8-dioxo-1,7-diaza-3,5,9,11-cyclododecatetraene-3,9-dicarbonitrile **6a,b** afforded pyridone **10** in addition to cyanamides **11a,b**. On the other hand, pyrolysis of 1-[*E*-(4-(*E*-3-cyano-4,6-dimethyl-2-oxopyridin-1(*2H*)-ylimino) methylpiperazin-1-yl] methylenamino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **8** gave 1-amino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **13** as well as piperazine. The mechanism of pyrolysis and the effect of stereochemistry of pyrolyzed substrates on the nature of the pyrolysates are discussed.

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## INTRODUCTION

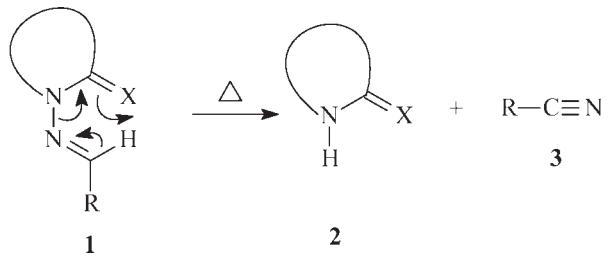
*N*-Aminoheteroaromatics are readily obtainable precursors [1–5]. The amino function could then be condensed with aromatic aldehydes into **1**. The gas-phase pyrolysis of this derivative produces pyridones **2** and nitriles **3** [6,7]. This approach offers an ideal and environmentally friendly methodology for synthesis of nitriles and related compounds, as no reagents, solvents, or catalysts are used in these thermal gas-phase reactions [8]. It seemed to us quite feasible that simple alternation in the structure of starting substrates could also be adopted as a strategy to synthesize cyanamides as well as organic cyanates (Scheme 1).

## RESULTS AND DISCUSSION

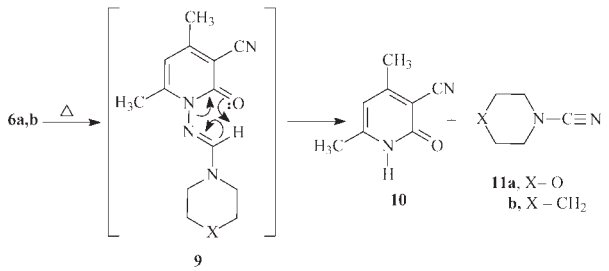
In the present article, we report synthesis of different substituted 1,7-diaza-3,5,9,11-cyclododecatetraene derivatives **4** as well as the results of their pyrolysis in the gas phase. In a recent investigation, we established that the reaction of acetylacetone with 2-cyanoacetohydrazide in the presence of diethylamine gave a dimeric product **4** of $m/z = 327$ ($M^{+\cdot} + 1$) [7]. Here, the reaction of the dimeric product **4** with triethylorthoformate afforded the diiminoformate **5,** which is then converted into **6a,b** and **8** through reaction with secondary amines, namely, morpholine, piperidine, and piperazine. Compound **5** could as well be generated *in situ* in a one-pot synthesis by mixing the three products under reflux in *N*,*N*-dimethylformamide. The reaction is facile, clean, and efficient, and is free from by-products. The structural assignments of compounds **5–8** were inferred from their mass spectra and other analytical data. Formation of **8** is believed to occur via initial conversion of diiminoformate **5** to the intermediate iminoformate **7** and subsequent condensation of two molecules of **7** with one molecule of piperazine (Scheme 2).

Pyrolysing **6a,b** in the gas phase gave the expected 1,2-dihydropyridine-3-carbonitrile derivative **10** and cyanamide **11a,b** via the methyleneamino-1,2-dihydropyridine-3-carbonitrile derivative **9** (Scheme 3). Formation of these products was confirmed by LCMS and by TLC, as well as $^1$H NMR of products of pyrolysis against

**Scheme 1**



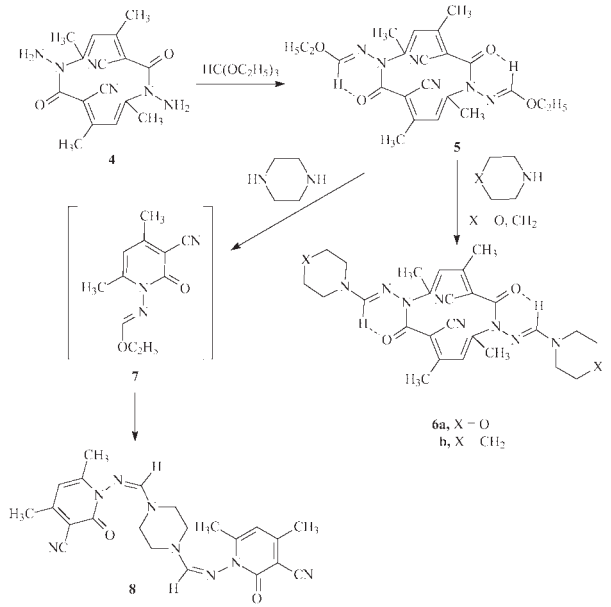
**Scheme 3**



authentic specimens of pyridone **10**. On the other hand, pyrolysis of **8** afforded **13** without formation of **12** (Scheme 4).

The difference in the pyrolytic behavior of **6a,b** and **8** is most likely a result of their stereochemistry. Thus, the pyrolyzed compounds **6a,b** exist in the (*E*) form, while **8** exists in the (*Z*) form. If one assumes that the pyrolysis of **8** (***E***) occurred via the H-bonded intermediate (Scheme 3), one would obtain pyridine **10** and dicyanamide **12** as pyrolytic products. As the *N*-aminopyridone **13** was the pyrolytic product obtained from **8** and no trace of the dicyanamide **12** was detected, it can thus be expected that **8** exists in the non-H-bonded (*Z*) form. In fact here, hydrolysis of **8** under the pyrolytic reaction conditions took place. To our knowledge such a hydrolysis has not been reported earlier. In conclusion, we could determine structures of pyrolysis products of **6a,b** and **8**. In addition, a new and safe route for synthesis of cyanamide **11a,b** is reported. Although **11a,b** could be obtained by treating cyanogen bromide with Mannich bases [9] and with morpholine compounds [10,11], this route required the use of hazardous and explosive cyanogen bromide reagents.

**Scheme 2**



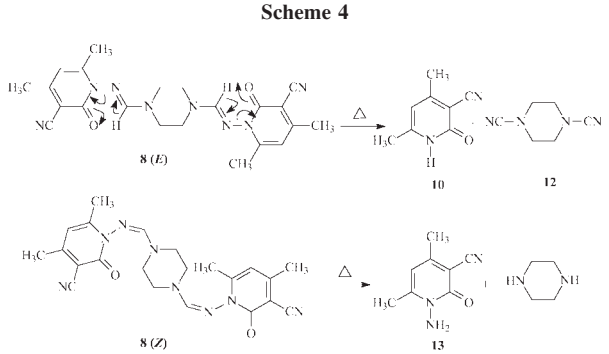
## EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analysis was by means of a LECO CHNS-932 Elemental Analyzer. NMR spectra were measured using a Bruker DPX 400 MHz superconducting spectrometer, and FT-IR measurements were from a Perkin Elmer 2000 FT-IR system. Mass spectrometric analysis was carried out on a VG-Autospec-Q high performance tri-sector GC/MS/MS, and the instrument for HPLC was an Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode.

**1,7-Diamino-4,6,10,12-tetramethyl-2,8-dioxo-1,7-diazacyclododeca-3,5,9,11-tetraene-3,9-dicarbonitrile 4.** This compound was prepared following published procedure. It was obtained as white crystals from ethanol (yield 94%); m.p. 171–172°C, Lit. mp. 174°C [7]; IR (KBr): λ max/cm$^{-1}$: 3420, 3332 ($NH_2$), and 2216 (CN); MS: $m/z$ = 327 ($M^{+\cdot}$+1). $^1$H NMR (DMSO): δ = 2.31 (s, 6H, $2CH_3$), 2.42 (s, 6H, $2CH_3$), 6.15 (br s, 4H, $2NH_2$ $D_2O$ exchangeable), 6.33 (s, 2H). Anal. Calcd. for $C_{16}H_{18}N_6O_2$ (326.36): C 58.89, H 5.56, N 25.75. Found C 59.00, H 5.49, N 25.89.

**4,6,10,12-Tetramethyl-1,7-(diethoxy-dimethylene-amino)-2,8-dioxo-1,7-diaza-3,5,9,11-cyclododeca-tetraene-3,9-dicarbonitrile 5.** To a stirred mixture of compound **4** (0.01 mol, 3.26g) in 10 mL of *N*,*N*-dimethylformamide was added triethyl orthoformate (0.01 mol, 1.48 g). The resulted mixture was refluxed for 15 min. The solvent was removed and resulting solid was recrystallized from ethanol. Yield 86% (3.77g); m.p. 150°C; IR (KBr): λ max/cm$^{-1}$: 2218 (CN), 1658 (C=O); MS: $m/z$ = 439 ($M^{+\cdot}$+ 1); $^1$H NMR (DMSO): δ = 1.35 (t, 6H, $J$ = 7.04 Hz $2CH_3$), 2.28 (s, 6H, $2CH_3$), 2.33 (s, 6H, $2CH_3$), 4.35

**Scheme 4**



(q, 4H, $J$ = 7.04 Hz $2CH_2$), 6.37 (s, 2H, cycloalkene-H), 8.36 (s, 2H, amidine-H). Anal. Calcd. for $C_{22}H_{26}N_6O_4$ (438.49): C 60.26, H 5.98, N 19.17. Found C 60.06, H 5.94, N 19.25.

**General procedure for the preparation of compounds 6a,b and 8.** To a stirred mixture of compound **5** (0.01 mol, 4.38 g) in 20 mL of DMF was added the appropriate amine (0.01 mol). The mixture thus obtained was heated under reflux for 20 hours. The solvent was removed and the resulting solid was recrystallized from DMF.

**4,6,10,12-Tetramethyl-1,7-di-[(*E*)-1-morpholino-methylidene] amino-2,8-dioxo-1,7-diaza-3,5,9,11-cyclododecatetraene-3,9-dicarbonitrile 6a.** Yield 85% (4.42 g); m.p. 190°C, brown crystals from DMF; IR (KBr): ν/cm$^{-1}$: 2216 (CN), 1647 (C=O); MS: $m/z$ = 521 ($M^{+\cdot}$ + 1); $^1$H NMR (DMSO-$d_6$): δ (ppm) = 2.26 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 3.50–3.54 (m, 8H, morpholino-H), 3.62–3.65 (m, 8H, morpholino-H), 6.30 (s, 2H, cycloalkene-H), 7.93 (s, 2H, amidine-H). Anal. Calcd. for $C_{26}H_{32}N_8O_4$ (520.59): C 59.99, H 6.20, N 21.52. Found C 60.06, H 6.26, N 21.58.

**4,6,10,12-Tetramethyl-2,8-dioxo-1,7-di-[(*E*)-1-piperidinomethylidene]amino-1,7-diaza-3,5,9,11-cyclododecatetraene-3,9-dicarbonitrile 6b.** Yield 92% (4.75 g); m.p. 115°C, brownish crystals from ethanol; IR (KBr): ν/cm$^{-1}$: 2213 (CN), 1652 (C=O); MS: $m/z$ = 517 ($M^{+\cdot}$+1); $^1$H NMR (DMSO-$d_6$): δ (ppm) = 1.50–1.57 (m, 8H, piperidinyl-H), 1.63–1.66 (m, 4H, piperidinyl-H), 2.25 (s, 6H, $2CH_3$), 2.29 (s, 6H, $2CH_3$), 3.29–3.31(m, 4H, piperidinyl-H), 3.48–3.52 (m, 4H, piperidinyl-H), 6.26 (s, 2H, cycloalkene-H), 7.81 (s, 2H, amidine-H). Anal. Calcd. for $C_{28}H_{36}N_8O_2$ (516.65): C 65.09, H 7.02, N 21.69. Found C 64.67, H 6.71, N 21.57.

**1,1'-{Piperazine-1,4-diylbis[(*Z*)-methylylidenenitrilo]} bis (4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 8.** Yield 62% (2.67 g); m.p. >300 °C, buff crystals from DMF; IR (KBr): ν/cm$^{-1}$: 2217 (CN), 1642 (C=O); MS: $m/z$ = 433 ($M^{+\cdot}$+1); $^1$H NMR (DMSO-$d_6$): δ (ppm) = 2.29 (s, 6H, $2CH_3$), 2.31 (s, 6H, $CH_3$), 3.44–3.48 (m, 4H, piperidinyl-H), 3.57–3.64 (m, 4H, piperidinyl-H), 6.30 (s, 2H, pyridyl H-5), 8.00 (s, 2H, amidine-H). Anal. Calcd. for $C_{22}H_{24}N_8O_2$ (432.48): C 61.10, H 5.59, N 25.91. Found C 60.69, H 5.72, N 25.68.

**General Procedure for Pyrolysis of 6a,b and 8.** Each of compounds **6a–c** and **8** was introduced in the reaction tube (1.5 × 12 cm$^2$ Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and placed in the pyrolyser for 900 s at a temperature of complete pyrolysis. The pyrolysate was then separated into its constituents by preparative TLC (MERCK, 12 PSC-Platten 20 × 20 cm$^2$, Silica gel 60 $F_{254}$ 2 mm) using chloroform: petroleum ether (bp 40:60) in 80:20 ratio as eluent, and each constituent was collected, analyzed and characterized. The techniques used include $^1$H NMR and GC/MS.

**Morpholine-4-carbonitrile 11a.** MS: $m/z$ = 112 ($M^{+\cdot}$) for $C_5H_8N_2O$ (112.13). IR = 2220 cm$^{-1}$ (CN). $^1$H NMR ($CDCl_3$): δ (ppm) = 3.05–3.08 (m, 2H, morpholinyl-H), 3.21–3.23 (m, 2H, morpholinyl-H), 3.43–3.49 (m, 2H, morpholinyl-H), 3.59–3.68 (m, 2H, morpholinyl-H). [Lit $^1$H NMR 90 MHz ($CDCl_3$) [12]: δ (ppm) = 3.2–3.3 (m, 4H), 3.6–3.7 (m, 4H)].

**Piperidine-1-carbonitrile 11b.** MS: $m/z$ = 110 ($M^{+\cdot}$) for $C_6H_{10}N_2$ (110.16). $^1$H NMR ($CDCl_3$): δ (ppm) = 1.41–1.52 (m, 6H, piperidinyl-H), 3.56–3.78 (m, 4H, piperidinyl-H). Lit $^1$H NMR 90 MHz ($CDCl_3$) [13]: δ (ppm) = 1.45–1.68 (m, 6H), 3.2–3.5 (m, 4H)].

**4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 10.** MS: $m/z$ = 163 ($M^{+\cdot}$) for $C_8H_8N_2O$ (148.16). $^1$H NMR ($CDCl_3$): δ (ppm) = 2.33 (s, 3H, $CH_3$), 2.40 (s, 2H, $CH_3$), 3.60 (br s, 1H, NH $D_2O$ exchangeable), 6.21 (s, 1H, pyridyl H-5). [Lit $^1$H NMR 200 MHz (DMSO/$CDCl_3$ 2:1 [14]): δ (ppm) = 2.23 (s, 3H), 2.32 (s, 3H), 3.40 (br s, 1H), 6.07 (s, 1H)].

**1-Amino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 13.** MS: $m/z$ = 163 ($M^{+\cdot}$) for $C_8H_9N_3O$ (163.18). $^1$H NMR ($CDCl_3$): δ (ppm) = 2.33 (s, 3H, $CH_3$), 2.38 (s, 2H, $CH_3$), 6.15 (br s, 4H, $2NH_2$ $D_2O$ exchangeable), 6.31 (s, 1H, pyridyl H-5).

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## REFERENCES AND NOTES

[1] Al-Awadi, N. A.; Ibrahim, Y. A.; Dib, H. H.; Ibrahim, M. R.; George, B. J.; Abdallah, M. R. Tetrahedron 2006, 62, 6214.

[2] Kandari, H.; Al-Kharafi, F. N.; Al-Awadi, A.; El-Dusouqui, O. M. E. S.; Ali, A.; Katrib, A. Appl Catal A: Gen 2005, 295, 1.

[3] Al-Etaibi, A. M.; Abdallah, M. R.; Al-Awadi, N. A.; Ibrahim, Y. A.; Hassan, M. J Phys. Org. Chem 2004, 17, 49.

[4] Alnajjar, A.; Amer, S. A.; Riad, R. M.; Elghamry, I.; Elnagdi, M. H. J Chem Res (S) 1996, 296.

[5] Gilchrist, T. L. Heterocyclic Chemistry, 3rd ed.; Addison Wesely Longman: Harlow, 1997; p 138.

[6] Al-Awadi, N. A.; Elnagdi, M. H.; Mathew, T.; Elghamry, I.; Abdelkhalik, M. M. Int J Chem Kinet 1996, 28, 741.

[7] Al-Awadi, N. A.; Abdelkhalik, M. M.; Patel, M.; Dib, H. H. J Heterocyclic Chem 2007, 44, 989.

[8] Malhas, R. N.; Al-Awadi, N. A.; El-Dusouqui, O. M. E. Int J Chem Kinet 2007, 39, 82.

[9] Martin, D.; Weise, A. Chem Ber 1966, 99, 3367.

[10] Henry, R. M.; Dehn, W. M. J Am Chem Soc 1950, 72, 2280–1.

[11] Wishnok, J. S.; Tannenbaum, S. R. Anal Chem 1977, 49, 715A–6A.

[12] SciFinder, CAS Register Number: 1530–87-6. Source: Integrated Spectral Database System of Organic Compunds. Data were obtained from the National Institute of Advanced Industrial Science and Technology, Japan.

[13] SciFinder, CAS Register Number: 1530–89-8. Source: Integrated Spectral Database System of Organic Compunds. Data were obtained from the National Institute of Advanced Industrial Science and Technology, Japan.

[14] Alberola, A.; Andrés, C.; Ortega, A. G.; Pedross, R.; Vicente, M. J Heterocyclic Chem 1987, 24, 709.

# Synthesis and Crystal Structure Characterization of 3,5-Bis(2-quinolyl)-1,2,4-triazole



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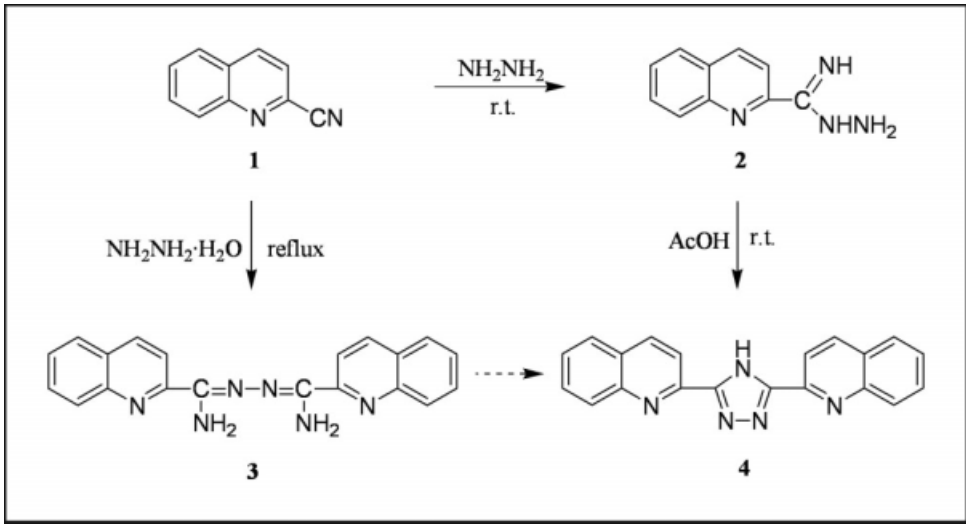


The first quinolyl substituted 1,2,4-triazole, 3,5-bis(2-quinolyl)-1,2,4-triazole (**4**), was synthesized from 2-cyanoquinoline (**1**) through an intermediate 2-quinolylhydrazidine (**2**) with 60.4% yield in a simple way. In the synthetic process of **4**, another new intermediate, 1,4-diamino-1,4-bis(2-quinolyl)-2,3-diaza-1,3-butadiene (**3**) was obtained in a yield of 81.5%. Additionally, the absolute configurations of both **3** and **4** were determined by X-ray crystallography.

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## INTRODUCTION

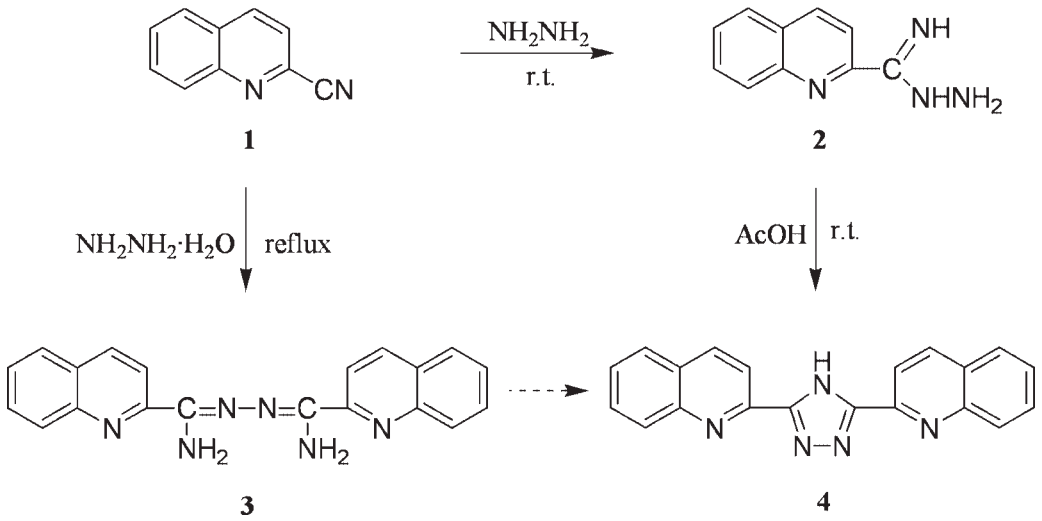
Over recent years, heterocyclic compounds containing 1,2,4-triazole rings have attracted widespread attention because of their broad applications as antifungus, antitumor, fungicide, weedicide, and so on [1]. Moreover, substituted 1,2,4-triazoles are very useful ligands in coordination chemistry [2–4]. This is mainly because of that they can act as bridging ligands between transition metal ions thus providing rich and versatile coordination modes. More interestingly, their ligand strength is in the right region to give iron(II) spin-crossover complexes, which could be used as molecular-based memory devices, displays and switching materials [5,6].

Although a lot of 1,2,4-triazole compounds with substituted alkyl, phenyl or pyridyl groups [3,7] have been synthesized successfully, substituted 1,2,4-triazoles with quinolyl group, an important alkaloid with stronger conjugated system, have never been reported so far. Recently, we have prepared some new triaryltriazole compounds [8,9] and their complexes [10–16]. As a continuation of our investigation on the substituted 1,2,4-triazoles, herein, we present the first synthesis of 3,5-bis(2-quinolyl)-1,2,4-triazole (**4**) through the nucleophilic addition of hydrazine to 2-cyanoquinoline (**1**) (Scheme 1). The product **4** was characterized by UV, FTIR, $^1$H NMR, TOF-MS spectra, elemental analysis and single crystal X-ray diffraction. In addition, another new intermediate, 1,4-diamino-1,4-bis(2-quinolyl)-2,3-diaza-1,3-butadiene (**3**), has also been obtained and its crystal structure was described [17].

## RESULTS AND DISCUSSION

Several methods have been reported for the syntheses of 3,5-diaryl-substituted 1,2,4-triazoles [18–24]. However, following the method (Scheme 2) reported by Geldard and Lions [23] using 2-cyanoquinoline (**1**) instead of 2-cyanopyridine as starting material for the synthesis

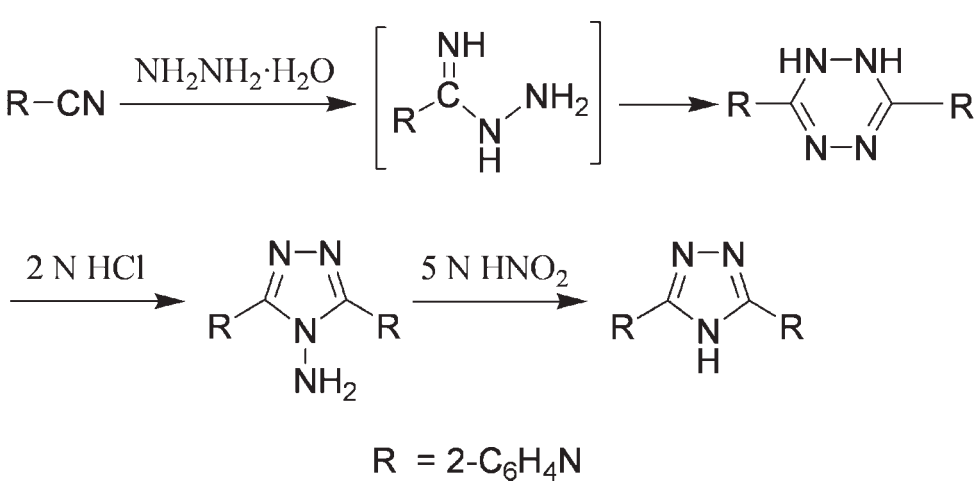
**Scheme 1**




of **4**, we did not obtain the corresponding 1,2,4,5-tetrazine. The corresponding 1,2,4,5-tetrazine was also not obtained, though we changed the reaction conditions such as the molar ratios of the 2-cyanoquinoline and hydrazine hydrate, reaction temperature, and replacing hydrazine hydrate with anhydrous hydrazine. Instead, two different intermediates were identified. One is 1,4-diamino-1,4-bis(2-quinolyl)-2,3-diaza-1,3-butadiene (**3**) with 81.5% yield after refluxing **1** and hydrazine hydrate (molar ratios 1:2) for 2 h at 110°C [24]. The other is 2-quinolylhydrazidine (**2**) in a yield of 94.6% by stirring **1** and anhydrous hydrazine (molar ratios 1:33) in anhydrous ethanol for 3 h at room temperature [25]. The structure of **3** has been determined by X-ray crystallography (Fig. 1). When **3** was heated to 200°C in argon atmosphere, only trace amounts of compound **4** was formed. In contrast, when **2** was mixed in acetic acid at room temperature, **4** was obtained in a yield of 60.4% [26]. To our knowledge, this is the first report to synthesize 3,5-diaryl-substituted 1,2,4-triazoles without involving the corresponding 1,2,4,5-tetrazine and 1,2,4-triazoline intermediates compared with the other methods [23,24].

The molecular structure of **4** was also confirmed by X-ray crystallography. Single crystals of **4** were obtained by slow evaporation of its ethanol solution at ambient temperature. A structural view with atom-numbering scheme is shown in Figure 2 and selected bond lengths and bond angles are listed in Table 1. The X-ray structure analysis indicates that **4** consists of two quinolyl rings and one triazole ring. These rings do not share a common plane. The quinolyl ring with N1 atom makes a dihedral angle of 10.1(4)° with the triazole ring, whereas the quinolyl ring with N5 atom makes a dihedral angle of 35.5(4)° with respect to the triazole plane. The dihedral angle between two quinolyl groups is

**Scheme 2**



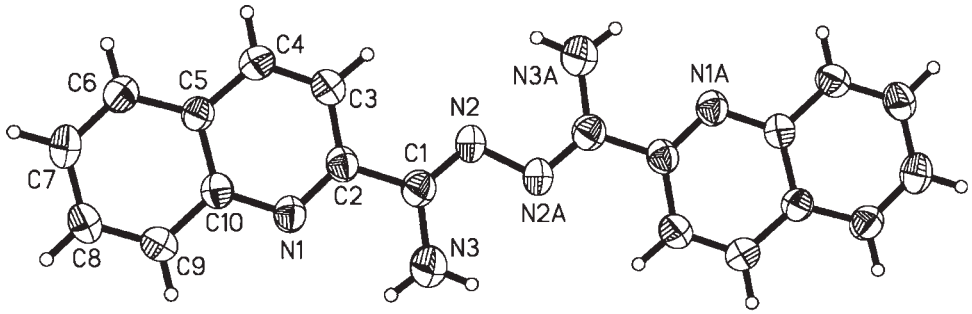



**Figure 1.** A view of **3** showing the atom-numbering scheme. Thermal ellipsoids are shown at the 50% probability level.

37.7(4)°. The bond lengths and bond angles in the structure of **4** are in the usual ranges. In the crystal, the possibility of N—H···N hydrogen bonds is reduced due to the presence of the bulky quinolyl groups. However, the molecules of **4** are further stabilized by C—H···π interactions involving C19-H19 and the phenyl ring at (−1/2 + *x*, 1/2−y, 1/2 + z) [C19···π = 3.588(5) Å and C19-H19···π = 136.6(4)°] [8].

## EXPERIMENTAL

Melting points were determined with an X-4 digital microscope melting-point apparatus (Beijing) and are uncorrected. UV-vis spectra were recorded on a Perkin-Elmer Lambda 35 spectrophotometer at room temperature. FT-IR spectra were recorded on a Nicolet 380 FT-IR instrument using KBr disks. $^1$H NMR spectra were measured on a Bruker AM 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Mass spectra were recorded on an Autoflex II TOF/TOF. Elemental analyses of compounds were performed with an Elementer Varian EL III instrument. Commercial reagents were used without further purification unless otherwise stated. 2-Cyanoquinoline (**1**) was synthesized according to literature method [27].

**2-Quinolylhydrazidine (2).** A mixture of **1** (1.54 g, 10 mmol) and anhydrous hydrazine (10.2 mL, 321 mmol) was stirred in anhydrous ethanol (6.3 mL) at ambient temperature for 2 h. The solid was collected and washed with cold water. Then the crude product was recrystallized from anhydrous ethanol to give yellow needles 1.76 g (94.6%), mp 191–192°C (lit. mp 191–192°C [25]); IR (ν, cm$^{-1}$): 3436, 3290, 3178, 3061, 3012, 1636, 1599, 1561, 1507, 831, 747, 625, 477. $^1$H NMR ($CDCl_3$, ppm): δ 4.74 (s, 2H, NH), 5.38 (s, 2H, $NH_2$), 7.51–7.54 (t, 1H, ArH), 7.68–7.71 (t, 1H, ArH), 7.79–7.81 (d, 1H, ArH), 8.05–8.07 (d, 1H, ArH), 8.10–8.15 (m, 2H, ArH).

**1,4-Diamino-1,4-bis(2-quinolyl)-2,3-diaza-1,3-butadiene (3).** A mixture of **1** (1.2 g, 7.8 mmol) and hydrazine hydrate (1.2 mL) was stirred at 110°C for 2 h. Upon cooling to ambient temperature, the solid was collected and recrystallized from ethyl acetate to give yellow needles 1.08 g (81.5%), mp 178–180°C; UV (EtOH, nm): 209 (1.32), 240 (1.70), 296 (0.53), 308 (0.51), 332 (0.47, sh). IR (ν, cm$^{-1}$): 3436, 3289, 3180, 3058, 1637, 1598, 1561, 1507, 831, 747, 625, 477. $^1$H NMR ($CDCl_3$, ppm): δ 5.47 (s, 2H, $NH_2$), 7.54–7.58 (t, 1H, ArH), 7.62–7.76 (t, 1H, ArH), 7.82–7.85 (d, 1H, ArH), 8.07–8.10 (d, 1H, ArH), 8.16–8.17 (t, 2H, ArH). Anal. Calcd. for $C_{20}H_{16}N_6$: C, 70.57; H, 4.74; N, 24.69. Found: C, 70.68; H, 4.99; N, 24.54.

**3,5-Bis(2-quinolyl)-1,2,4-triazole (4).** At 0°C, **2** (2.44 g, 13.1 mmol) was mixed with glacial acetic acid (7.5 mL, 131 mmol) and then stirred for 3 h at room temperature. After the removal of unreacted acid under vacuum, the crude product was recrystallized from anhydrous ethanol to yield colorless crystals 1.28 g (60.4%), mp 226–227°C; UV (EtOH, nm): 213 (2.04), 248 (2.27), 306 (0.71), 320 (0.83), 335 (1.00). IR (ν, cm$^{-1}$): 3174, 3056, 1698, 1615, 1598, 1567, 1502, 836, 769, 615, 476. $^1$H NMR ($CDCl_3$, ppm): δ 7.66 (s, 1H, ArH), 7.84 (s, 1H, ArH), 7.93 (s, 1H, ArH), 8.36 (s, 1H, ArH), 8.43 (s, 1H, ArH), 8.56 (s, 1H, ArH). MS: m/z 324.1 ($M^+ + 1$), 323.1 ($M^+$), 295.1 ($M^+ + 1 - N_2$), 294.1 ($M^+ - N_2$). Anal. Calcd. for $C_{20}H_{13}N_5$: C, 74.28; H, 4.05; N, 21.66. Found: C, 74.42; H, 4.18; N, 21.52.

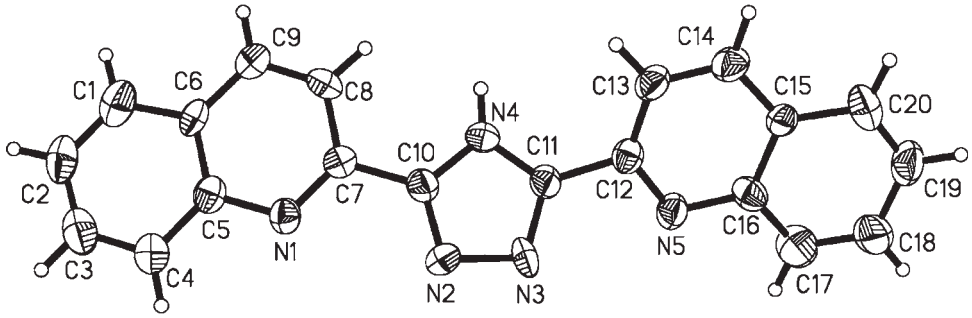



**Figure 2.** A view of **4** showing the atom-numbering scheme. Thermal ellipsoids are shown at the 50% probability level.

**Table 1**

Selected bond lengths and angles for **4.**

| | Bond length (Å) | | Bond angle (°) |
|---|---|---|---|
| N1—C7 | 1.308 (5) | C7—N1—C5 | 118.1 (4) |
| N1—C5 | 1.383 (5) | C10—N2—N3 | 103.6 (3) |
| N2—C10 | 1.321 (5) | C11—N3—N2 | 106.9 (3) |
| N2—N3 | 1.387 (4) | C11—N4—C10 | 104.5 (3) |
| N3—C11 | 1.359 (5) | C12—N5—C16 | 116.1 (4) |
| N4—C10 | 1.330 (5) | N1—C7—C10 | 118.6 (4) |
| N4—C11 | 1.319 (5) | C8—C7—C10 | 118.4 (4) |
| N5—C12 | 1.316 (5) | N5—C12—C11 | 113.2 (4) |
| N5—C16 | 1.385 (5) | C13—C12—C11 | 121.0 (4) |
| C7—C10 | 1.470 (5) | | |
| C11—C12 | 1.482 (6) | | |

**Single-crystal X-ray diffraction analysis of 4.** $C_{20}H_{13}N_5$, $M_r = 323.35$, monoclinic, $P2_1/c$, $a = 14.306(3)$ Å, $b = 7.0990(14)$ Å, $c = 15.372(3)$ Å, $\beta = 95.85(3)°$, $V = 1553.0(5)$ Å$^3$, $Z = 4$, $\rho = 1.383$ mg/m$^3$, $\mu = 0.087$ mm$^{-1}$, $F(000) = 672$, $R_1 = 0.0775$ for 1248 observed ($I > 2\sigma(I)$) reflections and 0.1822 for all 2939 reflections, Goodness-of-fit = 1.003, 226 parameters.

A colorless block crystal of **4** with dimensions 0.06 × 0.10 × 0.10 mm$^3$ was selected for lattice parameter determination and collection of intensity data at 293 K on a FR590 CAD4 four-circle diffractometer with monochromated Mo $K_\alpha$ radiation ($\lambda = 0.71073$ Å) using a $\theta/2\theta$ scan mode. The data was corrected for Lorenz and polarization effects during data reduction. An empirical absorption correction based on $\psi$ scans was applied. The structure was solved by the direct methods and refined on $F^2$ by full-matrix least-squares methods using the SHELXL version 5.10 [28]. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms for C—H and N—H were placed in calculated positions (0.96 Å), assigned fixed isotropic thermal parameters at 1.2 times the equivalent isotropic $U$ of the atoms to which they are attached, and allowed to ride on their respective parent atoms.

CCDC 736135 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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**REFERENCES AND NOTES**

[1] Potts, K. T. Chem Rev 1961, 61, 87.
[2] Haasnoot, J. G. Coord Chem Rev 2000, 200–202, 131.
[3] Klingele, M. H.; Brooker, S. Coord Chem Rev 2003, 241, 119.
[4] Kitchen, J. A.; Brooker, S. Coord Chem Rev 2008, 252, 2072.
[5] van Koningsbruggen, P. J. Top Curr Chem 2004, 233, 123.
[6] Zhu, D. R.; Xu, Y.; Yu, Z.; Guo, Z. J.; Sang, H.; Liu, T.; You, X. Z. Chem Mater 2002, 14, 838.
[7] Al-Masoudi, I. A.; Al-Soud, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. Chem Heterocyl Comp 2006, 42, 1377.
[8] Fun, H. K.; Chinnakali, K.; Shao, S. C.; Zhu, D. R.; You, X. Z. Acta Crystallogr 1999, C55, 770.
[9] Zhu, D. R.; Xu, Y.; Zhang, Y.; Wang, T. W.; You, X. Z. Acta Crystallogr 2000, C56, 895.
[10] Zhu, D. R.; Song, Y.; Xu, Y.; Zhang, Y.; Fun, H. K.; You, X. Z. Polyhedron 2000, 19, 2019.
[11] Zhu, D. R.; Xu, Y.; Mei, Y. H.; Tu, C.; You, X. Z. J Mol Struct 2001, 559, 119.
[12] Zhu, D. R.; Wang, T. W.; Zhong, S. L.; Xu, Y.; You, X. Z. Chin J Inorg Chem 2004, 20, 508.
[13] Zhu, D. R.; Wang, Z. X.; Song, J.; Li, Y. Z.; Lan, D. Y. Chin J Inorg Chem 2005, 21, 128.
[14] Zhou, J.; Yang, J.; Qi, L.; Shen, X.; Zhu, D. R.; Xu, Y.; Song, Y. Transition Met Chem 2007, 32, 711.
[15] Qi, L.; Zhu, D. R.; Xie, D. J.; Wu, Y. F.; Shen, X. Chin J Inorg Chem 2008, 24, 868.
[16] Yang, J.; Bao, W. W.; Ren, X. M.; Xu, Y.; Shen, X.; Zhu, D. R. J Coord Chem 2009, 62, 1809.
[17] Xu, R. H.; Zhou, J.; Xu, Y.; Qi, L.; Shen, X.; Zhu, D. R. Acta Crystallogr 2006, E62, o5234.
[18] Cheng, L.; Zhang, W. X.; Ye, B. H.; Lin, J. B.; Chen, X. M. Inorg Chem 2007, 46, 1135.
[19] Klingsberg, E. J Org Chem 1958, 23, 1086.
[20] Baldwin, J. J.; Kasinger, P. A.; Novello, F. C.; Duggan, D. E. J Med Chem 1975, 18, 895.
[21] Yeung, K. S.; Farkas, M. E.; Kadow, J. F.; Meanwell, N. A. Tetrahedron Lett 2005, 46, 3429.
[22] Kauffmann, T.; Albrecht, J.; Berger, D.; Legler, J. Angew Chem Int Ed 1967, 6, 633.
[23] Geldard, J.; Lions, F. J Org Chem 1965, 30, 318.
[24] Case, F. H. J Heterocycl Chem 1970, 7, 1001.
[25] Case, F. H. J Org Chem 1965, 30, 931.
[26] Bradford, F. E.; Connor, L. P.; Kilner, C. A.; Halcrow, M. A. Polyhedron 2004, 23, 2141.
[27] Langry, K. C. Org Prep Proced Int 1994, 26, 429.
[28] Sheldrick, G. M. SHELXL v5.10; Bruker AXS, Inc.: Wisconsin, USA, 1997.

# Synthesis and Antimicrobial Activity of Some Methyl-2-[*N*-Coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylates

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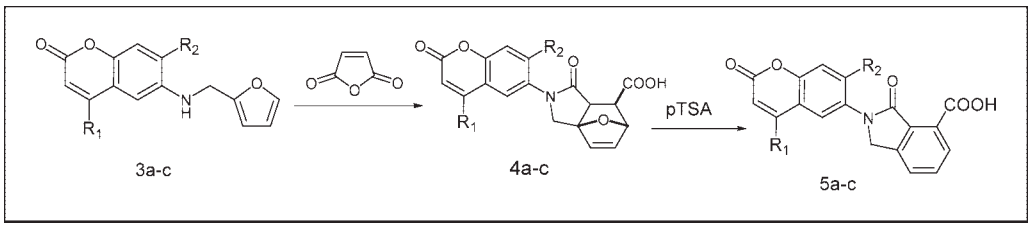


N-substituted furylmethylimines are prepared by condensing 6-aminocoumarins with furfural, these on sodium borohydride reduction afford *N*-[coumarin-6′-yl]-2-furylamines. Intramolecular [4+2] cycloaddition of these amines with maleic anhydride results into 3-[*N*-coumarin-6′-yl]-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]dec-8-ene-6-carboxylic acids **4a–c**. The [4+2] cycloadducts on *p*-toluene sulphonic acid treatment followed by esterification yield the titled compounds. Compound **5a–c** was also reduced to isoindolone alcohol **7a–c** by sodium borohydride in the presence of a base. All the compounds have been tested *in vitro* for their antimicrobial activity against gram-positive bacteria *Bacillus subtilis, Staphylococcus aureus*, one gram-negative bacteria, *Escherichia coli*, and one fungal strain *Candida albicans* at 100 μg/mL concentration.

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## INTRODUCTION

A variety of heterocyclic compounds bearing isoindolone skeleton reported to possess wide range of biological activities, such as antipsychotic [1], antihypertensive [2], antiviral [3], and antileukemic [4]. Furthermore, isoindolones have been widely used as building blocks for the synthesis of various drugs and natural products. Likewise, coumarins have also gained considerable synthetic and pharmacological interest for a long time because of their various biological activities [5–9]. In continuation of our work [10–15], keeping the biological profile of the two class of compounds in view, it appeared of interest to synthesize a molecular entity displaying the structural features of both the class of compounds.

Intramolecular Diels-Alder reaction of furan (IMDAF) methodology offers a facile way of constructing isoindolone moiety on a pre-existing 2-furylmethyl amine system [16]. In this article, we wish to report the synthesis of methyl-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylates using the IMDAF approach.

## RESULTS AND DISCUSSION

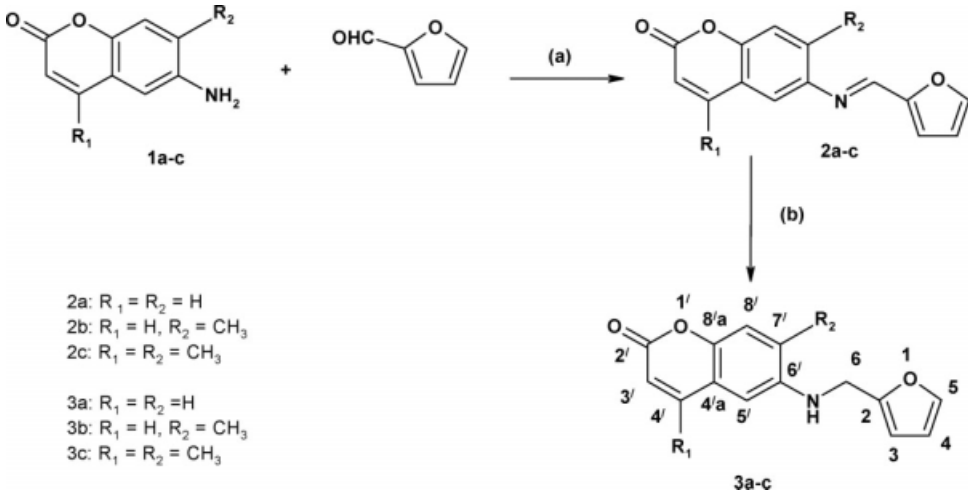
The required N-substituted 2-furylmethyl-amine **3a–c** was obtained by sodium borohydride reduction of the N-substituted 2-furylmethimines (**2a–c**) derived from 6-amino coumarin (**1a–c**) and furfural (Scheme 1). Capitalizing on the reactivity of the furan nucleus to words dienophiles in the Diels-Alder reaction, these furylmethyl amine were subsequently treated with maleic anhydride to afford compound **4a–c**.

The formation of stereochemically defined exo-tricyclic cycloadduct proceeds smoothly *via* initial N-acylation followed by intramolecular Diels-Alder reaction (one-pot reaction) [17–19] Scheme 2.

In the next step, ring opening followed by aromatization of the epoxy isoindolones was accomplished by subjecting the cycloadduct (**4a–c**) to *p*-toluene sulphonic acid (pTSA) in refluxing toluene [16]. The resultant product was characterized as 2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylic acid (**5a–c**). The presence of carboxy function was confirmed by converting (**5a–c**) to their corresponding methyl esters (**6a–c**) and isoindolone alcohol (**7a–c**) Scheme 3.

**Spectral characterization.** Formation of furfural amines **3a–c** was confirmed by the IR spectra, which showed characteristic —NH stretching at 3438 cm$^{-1}$. In its $^1$H NMR in $CDCl_3$, it showed a singlet at δ 4.34 ppm integrating for two methylene protons. The formation of cycloadduct was confirmed by the absence of —NH stretching in IR spectra and the presence of characteristic bands for the vibrations of the amide and carboxylic group in the regions of 1620–1690 and 1710–

**Scheme 1.** Reagents and conditions:(a) toluene, reflux, 5 h and (b) $NaBH_4$, MeOH, 0°C, 3 h.



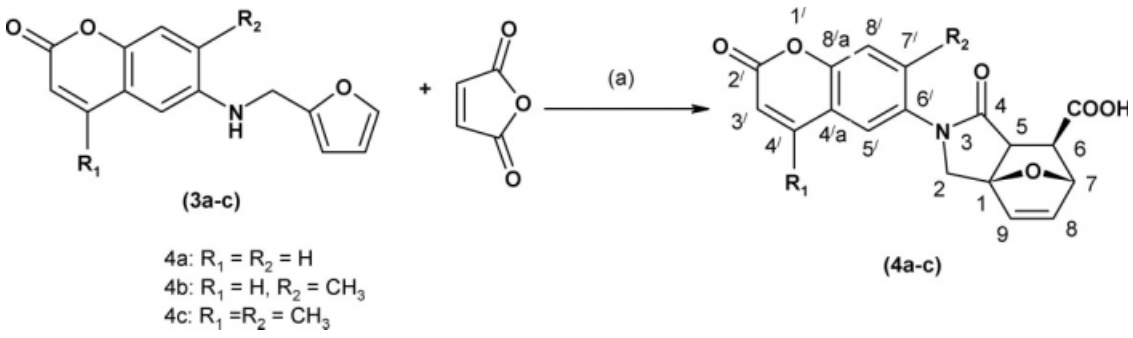

1726 $cm^{-1}$, respectively. The $^1H$ NMR spectra of compound **4c** contain three characteristic signals for mutually interacting protons 7-H, 8-H, and 9-H with chemical shifts of 5.07, 6.50, and 6.65 ppm, respectively, and coupling constants $J_{7,8} = 1.8$ Hz and $J_{8,9} = 5.7$ Hz, respectively. The absence of the $J_{6,7}$ spin–spin coupling constant indicates the endo arrangement of the 5-H and 6-H protons ($J_{5,6} = 9$ Hz) and the exo arrangement of the carboxyl and amide constituents. The C-2 protons of $CH_2$ are magnetically nonequivalent and are observed as an AB quartet at 4.57 and 3.84 ppm ($J_{AB} = 11.4$ Hz), respectively. Compound **5c** shows a singlet at δ 5.13 for the $CH_2$ protons along with other signals. Compounds **5a–c** were independently confirmed by converting them into their corresponding methyl-esters, showing stretching vibration between 1730 and 1735 $cm^{-1}$ for carbonyl group of methyl ester. The $^1H$ NMR of compound **6c** shows an additional singlet at δ 3.83 ppm for three protons of methyl ester. 5-Hydroxymethyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone **7a–c** shows singlet at δ 4.68 for $CH_2$—OH protons along with the other signals.

*In vitro* antimicrobial evaluation of newly synthesized compounds was done against three bacterial and one fungal strain by agar-well diffusion method [20] at 100 μg/mL concentration. Antibacterial activity of the test compounds was evaluated against two gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus,* and one gram-negative bacteria, *Escherichia coli*, using ampicillin as standard drug. Antifungal activity was screened against one fungal strain, *Candida albicans*, using clotrimazole as standard drug. The results are given in Table 1.

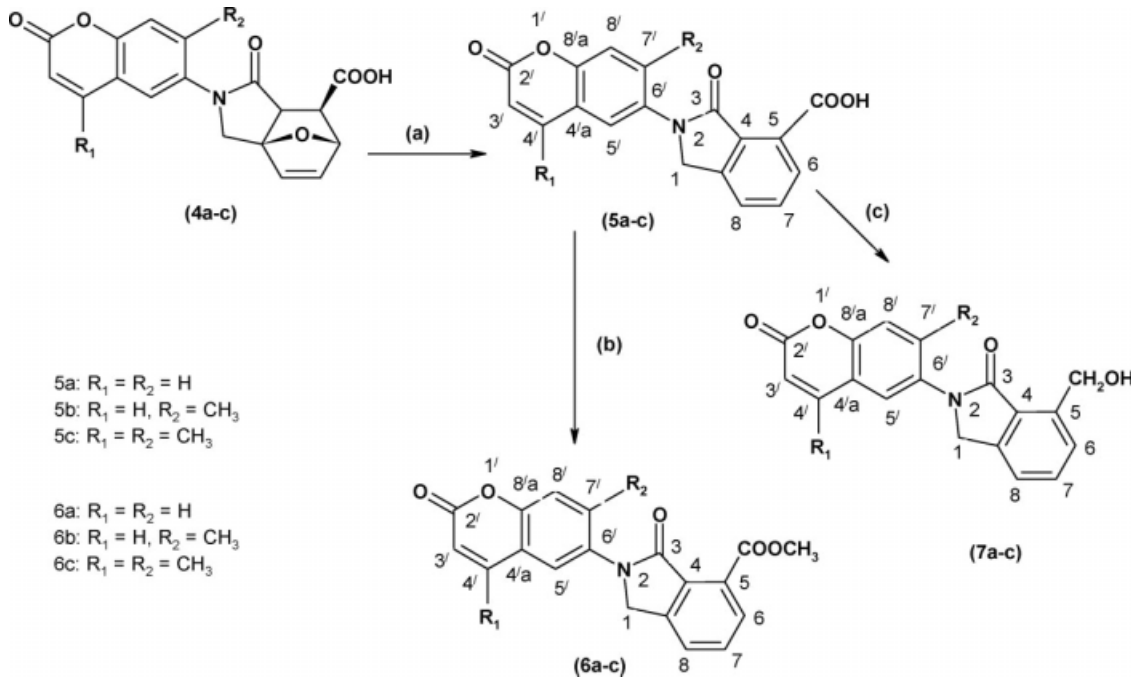
## CONCLUSIONS

In conclusion, a series of novel 2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylic acid (**5a–c**), methyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone-5-carboxylate (**6a–c**), and 5-hydroxymethyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone (**7a–c**) were synthesized by IMDAF, and their antimicrobial activities have been evaluated.

**Scheme 2.** Reagents and conditions: (a) maleic anhydride, benzene.



**Scheme 3.** Reagents and conditions: (a) pTSA, toluene, reflux, (b) MeOH, Conc. $H_2SO_4$, reflux, 8 h, and (c) THF, ethylchloroformate, TEA/$NaBH_4$/MeOH, r.t, 24 h.




Among the tested compounds, compounds **5c**, **6c,** and **7c** with methyl substitution on fourth and seventh positions of benzopyran ring have showed significant activities.

## EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. FTIR spectra ($V_{max}$ in $cm^{-1}$) were recorded on a Perkin Elmer 400 spectrometer using KBr. NMR spectra were recorded on JEOL NMR AL300 (300 MHz) using TMS as standard and mass spectra on a Shimadzu GC-MS QP-2010. Elemental analyses were carried out in IIT, Mumbai. The reactions are followed up and purity of the products is carried out on precoated TLC plates (Silica gel 60 F254, Merck), visualizing the spots in ultraviolet light. All the new compounds gave satisfactory elemental analyses.

**Synthesis of *N*-[coumarin-6′-yl]-2-furylmethinimine (2a–c).** Imines (**2a–c**) were prepared by refluxing a mixture of freshly distilled furfuraldehyde and appropriate 6-amino coumarin in toluene using Dean-Stark apparatus, refluxing was continued for 5 h. Toluene was distilled off on a rotary evaporator and the crude imine was used in the next step without purification.

**Table 1**

Antibacterial and antifungal activities of the compounds as zone of inhibition (mm) (100 μg/mL).

| Comp. | *Bacillus subtilis* | *Staphylococcus aureus* | *Escherichia coli* | *Candida albicans* |
|---|---|---|---|---|
| **5a** | 14 | 14 | 15 | 16 |
| **5b** | 14 | 15 | 14 | 15.5 |
| **5c** | 18 | 19 | 22 | 18 |
| **6a** | 9 | 13 | 13 | 14 |
| **6b** | 11 | 14 | 14 | 15 |
| **6c** | 16 | 17.5 | 18 | 16 |
| **7a** | 8 | 10 | 13 | 13 |
| **7b** | 10 | 12 | 14 | 15.5 |
| **7c** | 15 | 14 | 15 | 16.5 |
| **DMSO** | Control | Control | Control | Control |
| **Ampicillin** | 18 | 19 | 16 | – |
| **Clotrimazole** | – | – | – | 22 |

**Synthesis of *N*-[coumarin-6′-yl]-2-furylmethylamine (3a–c).** Sodiumborohydride was added in small portions to a solution of imine (**2a–c**) in methanol at 0°C for 30 min and there after at room temp for 3 h, and then acidified with 10% HCl to pH 1. The resulting mixture was adjusted to pH 11 with aq $NH_3$ solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated *in vacuo* to give off white solid.

***3a.*** Yield 68%; mp 118–120°C. IR (KBr, $cm^{-1}$): 3438, 2950, 1710; $^1H$ NMR ($CDCl_3$): δ 4.10 (s, 1H, NH, $D_2O$-exchangable), 4.34 (s, 2H, $C_6$—$CH_2$), 6.25 (d, 1H, $J$ = 9 Hz $C_3'$—H), 6.30–6.85 (m, 3H, furfural-H), 6.80 (d, IH, $J$ = 8.7 Hz, $C_8'$—H), 7.12 (d, 1H, $J$ = 8.7 Hz, $C_7'$—H), 7.30 (s, 1H, $C_5'$—H), 7.64 (d, 1H, $J$ = 9 Hz, $C_4'$—H). Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.41; H, 4.68; N, 5.65.

***3b.*** Yield 65%; mp 122–124°C. IR (KBr, $cm^{-1}$): 3435, 2945, 1713; $^1H$ NMR ($CDCl_3$): δ 2.20 (s, 3H, $C_7'$—$CH_3$), 4.05 (s, 1H, NH, $D_2O$-exchangable), 4.28 (s, 2H, $C_6$—$CH_2$), 6.21 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 6.28–6.85 (m, 3H, furfural-H), 7.08 (s, 1H, $C_8'$—H), 7.18 (s, 1H, $C_5'$—H), 7.68 (d, 1H, $J$ = 9 Hz, $C_4'$—H). Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.41; H, 5.20; N, 5.30.

***3c.*** Yield 62%; mp 123–125°C. IR (KBr, $cm^{-1}$): 3431, 2950, 1708; $^1H$ NMR ($CDCl_3$): δ 2.24 (s, 3H, $C_7'$—$CH_3$), 2.35 (s, 3H, $C_4'$—$CH_3$), 3.96 (s, 1H, NH, $D_2O$-exchangable), 4.38 (s, 2H, $C_6$—$CH_2$), 6.19 (s, 1H, $C_3'$—H), 6.30–6.88 (m, 3H, furfural-H), 7.08 (s, 1H, $C_8'$—H), 7.28 (s, 1H, $C_5'$—H); ms: $m/z$ = 269 (35%) [$M^+$], 188 (25%), 160 (20%), 117 (10%), 81 (100%). Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found C, 71.15; H, 5.66; N, 5.31.

**Synthesis of 3-[*N*-coumarin-6′-yl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1.5}$]dec-8-ene-6-carboxylic acid (4a–c).** To a stirred solution of **3a–c** in anhydrous benzene was added maleic anhydride at r.t. The solution was stirred at r.t. for 10 h. The product was filtered and washed with benzene to yield cycloadduct **4a–c**. Recrystallization from hexane-ethyl acetate gave desired acids **4a–c** as colorless solids.

***4a.*** Yield 88%; mp 220–222°C, IR (KBr, $cm^{-1}$): 3076, 1725, 1665; $^1H$ NMR (DMSO-$d_6$): δ 2.87 (d, 1H, $J$ = 9 Hz, $C_6$—H), 3.01 (d, 1H, $J$ = 9 Hz, $C_5$—H), 3.80 (d, 1H, $J$ = 11.4 Hz, $C_{2a}$—H), 4.52 (d, 1H, $J$ = 11.4 Hz, $C_{2b}$—H), 5.05 (d, 1H, $J$ = 1.8 Hz, $C_7$—H), 6.50 (dd, 1H, $J$ = 5.7 and 1.8 Hz, $C_8$—H), 6.65 (d, 1H, $J$ = 5.7 Hz, $C_9$—H), 6.25 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 6.81 (d, 1H, $J$ = 9 Hz, $C_8'$—H), 7.08 (d, 1H, $J$ = 9 Hz, $C_7'$—H), 7.20 (s, 1H, $C_5'$—H), 7.85 (d, 1H, $J$ = 9 Hz, $C_4'$—H), 12.30 (s, 1H, COOH). Anal. Calcd. for $C_{18}H_{13}NO_6$: C, 63.72; H, 3.86; N, 4.13. Found C, 63.51; H, 3.92; N, 4.22.

***4b.*** Yield 86%; mp 225–227°C, IR (KBr, $cm^{-1}$): 3070, 1722, 1672; $^1H$ NMR (DMSO-$d_6$): δ 2.28 (s, 3H, $C_7'$—$CH_3$), 2.86 (d, 1H, $J$ = 9 Hz, $C_6$—H), 3.05 (d, 1H, $J$ = 9 Hz, $C_5$—H), 3.77 (d, 1H, $J$ = 11.4 Hz, $C_{2a}$—H), 4.50 (d, 1H, $J$ = 11.4 Hz, $C_{2b}$—H), 5.09 (d, 1H, $J$ = 1.8 Hz, $C_7$—H), 6.51 (dd, 1H, $J$ = 5.7 and 1.8 Hz, $C_8$—H), 6.62 (d, 1H, $J$ = 5.7 Hz, $C_9$—H), 6.21 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 6.89 (s, 1H, $C_8'$—H), 7.22 (s, 1H, $C_5'$—H), 7.82 (d, 1H, $J$ = 9 Hz, $C_4'$—H), 12.25 (s, 1H, COOH). Anal. Calcd. for $C_{19}H_{15}O_6N$: C, 64.59; H, 4.28; N, 3.96. Found C, 64.29; H, 4.42; N, 4.11.

***4c.*** Yield 82%; mp 221–223°C, IR (KBr, $cm^{-1}$): 3072, 1720, 1671, $^1H$ NMR (DMSO-$d_6$): δ 2.25 (s, 3H, $C_7'$—$CH_3$), 2.40(s, 3H, $C_4'$—$CH_3$), 2.95 (d, 1H, $J$ = 9 Hz, $C_6$—H), 3.02 (d, 1H, $J$ = 9 Hz, $C_5$—H), 3.84 (d, 1H, $J$ = 11.4 Hz, $C_{2a}$—H), 4.57 (d, 1H, $J$ = 11.4 Hz, $C_{2b}$—H), 5.07 (d, 1H, $J$ = 1.8 Hz, $C_7$—H), 6.50 (dd, 1H, $J$ = 5.7 and 1.8 Hz, $C_8$—H), 6.19 (s, 1H, $C_3'$—H), 6.65 (d, 1H, $J$ = 5.7 Hz, $C_9$—H), 7.32 (s, 1H, $C_8'$—H), 7.64 (s, 1H, $C_5'$—H), 12.28 (s, 1H, COOH); $^{13}C$ NMR(DMSO—$d_6$, δ): 17.55 ($C_7'$—$CH_3$), 17.99 ($C_4'$—$CH_4$), 44.88 (C-2), 50.0 (C-6), 51.50 (C-5), 80.26 (C-7), 88.75 (C-1), 113.80 (C-3′), 118.0 (C-8′), 123.41 (C-4′a), 128 (C-5′), 134.10 (C-8), 135.44 (C7′), 136.80 (C-6′), 141.43 (C-9), 151.75 (C-8′a), 153.0 (C-4′), 159.80 (C-2′, C=O), 170.23 (C-4, C=O), 174.0 (COOH); ms: $m/z$ = 367 (45%) [$M^+$], 160 (35), 188 (25), 91(60). Anal. Calcd. for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found C, 65.18; H, 4.77; N, 3.94.

**Synthesis of 2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolene-5-carboxylic acid (5a–c).** A mixture of cycloadduct **4a–c** (1 mmol), toluene, and pTSA (3 mmol) in a flask equipped with reflux condenser was stirred at refluxing temperature. The progress of the reaction was monitored by TLC. When the reaction was complete, toluene was distilled off on a rotary evaporator. The resulting residue was dissolved in $CH_2Cl_2$ and washed thoroughly with water. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo* to give solid mass, which was purified by column chromatography (ethyl acetate–pet ether) to give the desired product.

***5a.*** Yield 50%; mp 280–282°C, IR (KBr, $cm^{-1}$): 2995, 1716, 1675, 1500; $^1H$ NMR (DMSO-$d_6$): δ 5.10 (s, 2H, $C_1$—$CH_2$), 6.30 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 7.15 (d, 1H, $J$ = 9 Hz, $C_7'$—H), 7.20 (d, 1H, $J$ = 9 Hz, $C_8'$—H), 7.38 (s, 1H, $C_5'$—H), 7.75–7.99 (m, 3H, Arom-H), 7.89 (d, 1H, $J$ = 9 Hz, $C_4'$—H), 11.89 (s, 1H, COOH). Anal. Calcd. for $C_{18}H_{11}NO_5$: C, 67.29; H, 3.45; N, 4.36. Found C, 67.12; H, 3.51; N, 4.48.

***5b.*** Yield 48%; mp 284–286°C, IR (KBr, $cm^{-1}$): 2995, 1720, 1670; $^1H$ NMR (DMSO-$d_6$): δ 2.30 (s, 3H, $C_7'$—$CH_3$), 5.15 (s, 2H, $C_1$—$CH_2$), 6.28 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 7.20 (s, 1H, $C_8'$—H), 7.35 (s, 1H, $C_5'$—H), 7.70–7.95 (m, 3H, Arom-H), 7.84 (d, 1H, $J$ = 9 Hz, $C_4'$—H), 11.80 (s, 1H, COOH). Anal. Calcd. for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found C, 67.89; H, 3.96; N, 4.27.

***5c.*** Yield 45%; mp 285–287°C, IR (KBr, $cm^{-1}$): 2991, 1723, 1674; $^1H$ NMR (DMSO-$d_6$): δ 2.26 (s, 3H, $C_7'$—$CH_3$), 2.38 (s, 3H, $C_4'$—$CH_3$), 5.13 (s, 2H, $C_1$—$CH_2$), 6.38 (s, 1H, $C_3'$—H), 7.30 (s, 1H, $C_8'$—H), 7.39 (s, 1H, $C_5'$—H), 7.70–7.99 (m, 3H, Arom-H), 12.05 (s, 1H, COOH); $^{13}C$ NMR (DMSO-$d_6$, δ): 17.70 ($C_7'$—$CH_3$), 18.01 ($C_4'$—$CH_4$), 54.28 (C-1), 114.18 (C-3′), 118.17 (C-8′), 124. 71 (C-4′a), 127.0 (C-5′), 130.10 (C-8), 132.0 (C-7), 133.80 (C-7′), 135.60 (C-4), 136.44 (C-7′), 138.0 (C-5), 138.10 (C-6′), 139.20 (C-6), 152.75 (C-8′a), 154.0 (C-4′), 159.640 (C-2′, C=O), 165.0 (C-3, C=O), 170.20 (COOH); ms. $m/z$ = 349 (65%) [$M^+$], 338(55%), 217(100%), 161 (70%). Anal. Calcd. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found C, 68.52; H, 4.41; N, 4.09.

**Synthesis of methyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolene-5-carboxylate (6a–c).** Mixture of compound (**5a–c**) (1 mmol), conc. $H_2SO_4$ (0.5 mL), and absolute methanol (10 mL) was refluxed for 8 h. Excess methanol was distilled off by rotary evaporation. The resulting mass was diluted with ethyl acetate and washed with aq. $NaHCO_3$. The organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo* to give the corresponding esters (**6a–c**), which were purified by recrystallization using ethyl acetate–pet ether.

***6a.*** Yield 62%; mp 170–172°C, IR (KBr, $cm^{-1}$): 3050, 1730, 1685; $^1H$ NMR (DMSO-$d_6$): 3.80 (s, 3H, $OCH_3$), 4.92 (s, 2H, $C_1$—$CH_2$), 6.32 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 7.21 (d, 1H, $J$ = 9 Hz, $C_7'$—H), 7.28 (d, 1H, $J$ = 9 Hz, $C_8'$—H), 7.50 (s, 1H, $C_5'$—H), 7.65–7.87 (m, 3H, Arom-H), 7.85 (d, 1H, $J$ = 9 Hz, $C_4'$—H). Anal. Calcd. for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found C, 67.89; H, 3.96; N, 4.29.

***6b.*** Yield 58%; mp 175–177°C, IR (KBr, $cm^{-1}$): 3045, 1732, 1689; $^1H$ NMR (DMSO-$d_6$): δ 2.20 (s, 3H, $C_7'$—$CH_3$), 3.78 (s, 3H, $OCH_3$), 4.95 (s, 2H, $C_1$—$CH_2$), 6.30 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 7.32 (s, 1H, $C_8'$—H), 7.50 (s, 1H, $C_5'$—H), 7.62–7.89 (m, 3H, Arom-H), 7.80 (d, 1H, $J$ = 9 Hz, $C_4'$—H). Anal. Calcd. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found C, 68.58; H, 4.39; N, 4.12.

***6c.*** Yield 55%; mp 173–175°C, IR (KBr, $cm^{-1}$): 3045, 1735; $^1H$ NMR (DMSO-$d_6$): δ 2.20 (s, 3H, $C_7'$—$CH_3$), 2.25 (s, 3H, $C_4'$—$CH_3$), 3.82 (s, 3H, $OCH_3$), 4.98 (s, 2H, $C_1$—$CH_2$), 6.36 (s, 1H, $C_3'$—H), 7.40 (s, 1H, $C_8'$—H), 7.60 (s, 1H, $C_5'$—H), 7.72–7.87 (m, 3H, Arom-H); $^{13}C$ NMR (DMSO-$d_6$, δ): 18.20 ($C_7'$—$CH_3$), 18.91 ($C_4'$—$CH_4$), 53.28 ($OCH_3$), 53.63 (C-1), 114.84 (C-3′), 118.83(C-8′), 125. 64 (C-4′a), 126.0 (C-5′), 131.10 (C-8), 133.0 (C-7), 133.90 (C-7′), 135.60 (C-4), 136.44 (C-7′), 136.0 (C-5), 137.10 (C-6′), 138.20 (C-6), 150.75 (C-8′a), 152.0 (C-4′), 158.80 (C-2′, C=O), 160.0 (C-3, C=O), 168.0 (C=O); ms. $m/z$ = 363 (50%) [$M^+$], 304 (30%), 188 (60%), 160 (25%). Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found C, 69.22; H, 4.79; N, 3.98.

**Synthesis of 5-hydroxymethyl-2-[*N*-coumarin-6′-yl]-3-oxo-2,3-dihydro-1*H*-isoindolone (7a–c).** To a suspension of the acid **5a–c** (0.3 mmol) in tetrahydrofuran (THF) (6 mL) at −20°C were added ethyl chloroformate (0.36 mmol) and triethlyamine (TEA) (0.45 mmol), and the reaction mixture was stirred at 0°C for 1 h. To the reaction mixture at 0°C were slowly added solid $NaBH_4$ (0.6 mmol) and MeOH (2 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and washed with $NaHCO_3$. The organic layer was washed with brine solution, dried over $Na_2SO_4$, and concentrated *in vacuo*. Column chromatographic purification gave compound (**7a–c**).

***7a.*** Yield 55%; mp 260–262°C, IR (KBr, $cm^{-1}$): 3372, 2995, 1716; $^1H$ NMR (DMSO-$d_6$): δ 5.12 (s, 2H, $C_1$—$CH_2$), 6.31 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 7.13 (d, 1H, $J$ = 9 Hz, $C_7'$—H), 7.21 (d, 1H, $J$ = 9 Hz, $C_8'$—H), 7.38 (s, 1H, $C_5'$—H), 7.75–7.89 (m, 3H, Arom-H), 7.83 (d, 1H, $J$ = 9 Hz, $C_4'$—H), 4.78 (s, 2H, $CH_2$—OH). Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.36; H, 4.23; N, 4.56. Found C, 70.61; H, 4.35; N, 4.76.

***7b.*** Yield 52%; mp 264–266°C, IR (KBr, $cm^{-1}$): 3378, 2958, 1718; $^1H$ NMR (DMSO-$d_6$): δ 2.33 (s, 3H, $C_7'$—$CH_3$), 5.13 (s, 2H, $C_1$—$CH_2$), 6.21 (d, 1H, $J$ = 9 Hz, $C_3'$—H), 7.25 (s, 1H, $C_8'$—H), 7.32 (s, 1H, $C_5'$—H), 7.70–7.88 (m, 3H, Arom-H), 7.80 (d, 1H, $J$ = 9 Hz, $C_4'$—H), 4.72 (s, 2H, $CH_2$—OH). Anal. Calcd. for $C_{19}H_{15}NO_4$: C, 71.03; H, 4.68; N, 4.36. Found C, 71.25; H, 4.78; N, 4.52.

***7c.*** Yield 50%; mp 268–270°C, IR (KBr, $cm^{-1}$): 3389, 2990, 1721, 1674; $^1H$ NMR (DMSO-$d_6$): δ 2.23 (s, 3H, $C_7'$—$CH_3$), 2.36 (s, 3H, $C_4'$—$CH_3$), 5.10 (s, 2H, $C_1$—$CH_2$), 6.36 (s, 1H, $C_3'$—H), 7.31 (s, 1H, $C_8'$—H), 7.35 (s, 1H, $C_5'$—H), 7.70–7.99 (m, 3H, Arom-H), 4.68 (s, 2H, $CH_2$—OH); $^{13}C$ NMR (DMSO-$d_6$, δ): 17.70 ($C_7'$—$CH_3$), 18.09 ($C_4'$—$CH_4$), 53.28 (C-1), 60.1 ($CH_2OH$) 113.18 (C-3′), 118.17 (C-8′), 124. 71 (C-4′a), 127.0 (C-5′), 131.10 (C-8), 132.0 (C-7), 134.80 (C-7′), 135.60 (C-4), 136.44 (C-7′), 138.0 (C-5), 138.10 (C-6′), 139.20 (C-6), 152.75 (C-8′a), 153.0 (C-4′), 159.6 (C-2′,C=O), 164.0 (C-3, C=O). Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found C, 71.88; H, 5.25; N, 4.40.

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## REFRENCES AND NOTES

[1] Bellioti, T. R.; Brink, W.A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. Bioorg Med Chem Lett 1998, 8, 1499.

[2] Ferland, J. M.; Demerson, C. A.; Humber, L. G. Can J Chem 1985, 63, 361.

[3] Zhuang, Z. P.; Kung, M. P.; Kung, H. F. J Med Chem 1998, 41, 57.

[4] Norman, M. H.; Minick, D. J.; Rigdon, G. C. J Med Chem 1996, 39, 149.

[5] Yun, B. S.; Lee, I. K.; Ryoo, I. J.; Yoo, I. D. J Nat Prod 2001, 64, 1238.

[6] Zhao, H.; Neamati, N.; Hong, H. X.; Mazumder, A.; Wang, S. M.; Pommier, Y. J Med Chem 1997, 40, 242.

[7] El-Sayed, A. M.; Abd-Allah, O. A. Phosphorus Sulfur Silicon Relat Elem 2001, 170, 75.

[8] Nofal, Z. M.; El-Zahar, M. I.; Abd El-Karim, S. S. Molecules 2000, 5, 99.

[9] El-Agrody, A. M.; Abd El-Latif, M. S.; El-Hady, N. A.; Fakery, A. Molecules 2001, 6, 519.

[10] Mulwad, V. V.; Shirodkar, J. M. J Heterocycl Chem 2003, 40, 377.

[11] Mulwad, V. V.; Pawar, R. B.; Chaskar, A. C. J Korean Chem Soc 2008, 52, 249.

[12] Mulwad, V. V.; Mir, A. A. J Chem Res 2008, 5, 292.

[13] Mulwad, V. V.; Satwe, D. S. Indian J Chem B 2004, 43, 2727.

[14] Choudhari, B. P.; Mulwad, V. V. Indian J Chem B 2006, 45, 309.

[15] Mulwad, V. V.; Chaskar, A. C.; Shirodkar, J. M. Indian J Chem B 2005, 44, 1465.

[16] Sarang, P. S.; Yadav, A. A.; Patil, P. S.; Trivedi, G. K. Synthesis 2007, 7, 1091.

[17] Zylber, J.; Tubel, A.; Brun, P. Tetrahedron: Asymmetry 1995, 6, 377.

[18] Prajapati, D.; Borthakur, D. R.; Sandhu, J. S. J Chem Soc Perkin Trans 1993, 1, 1197.

[19] Murli, R.; Surya Prakash Rao, H.; Scheeren, H. W. Tetrahedron 2001, 57, 3165.

[20] Hugo, W. B.; Russel, A. B. Pharmaceutical Microbiology, 4th ed.; Blackwell Scientific Publications: London, 1987; p 26.

# Synthesis and Fungicidal Activity of 2-Substituted-3-(4-Fluorophenyl)-benzofuro [3,2-d] Pyrimidin-4(3H)-ones



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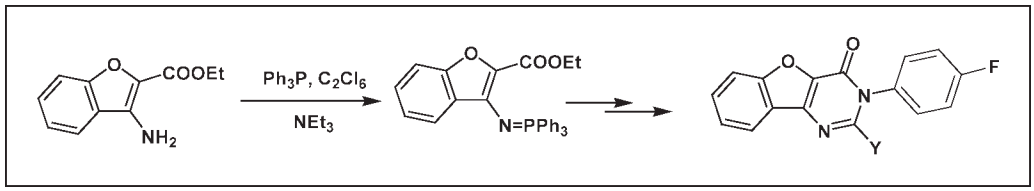


Carbodiimide, obtained from aza-Wittig reaction of iminophosphorane with 4-fluorophenyl isocyanate, reacted with various nucleophiles under mild conditions to give a series of 2-substituted-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones in satisfactory yield. Their structures were confirmed using NMR, EI-Ms, IR, and elementary analysis, and compound **7b** was further analyzed by single-crystal. The preliminary bioassays indicated that these compounds showed moderate fungicidal activities against six kinds of fungi at a concentration of 50 mg/L.

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## INTRODUCTION

Benzofuropyrimidinones are important heterocycles bearing remarkable biological activities. Some of them have shown good analgesic, anti-inflammatory, and antimicrobial activities [1–3], whereas others exhibited good anticoccidial and blood sugar-lowering activities [4,5]. On the other hand, many examples have been demonstrated that incorporation of fluorine atom in molecular structure of heterocyclic compounds often resulted in the improvement of pharmacological properties of the compounds as compared to their non-fluorine analogs [6,7]. The introduction of a fluorine atom to the benzofuropyrimidinone system is expected to influence the biological activities significantly. However, there is no report of a generally useful synthesis of 2-substituted-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones.

The aza-Wittig reactions of functionalized iminophosphoranes with isocyanates have been applied to produce carbodiimides, functional groups consisting of the formula N=C=N, able to undergo a plethora of heterocyclization reactions [8,9]. Here, in continuation of our earlier work [10,11], we wish to report a new method of the previously unreported incorporation of fluorine atom in molecular structure of benzofuropyrimidinones *via* the aza-Wittig reactions of functionalized iminophosphorane with 4-fluorophenyl isocyanate under mild condition, which synthesized 2-substituted-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones.

## RESULT AND DISCUSSION

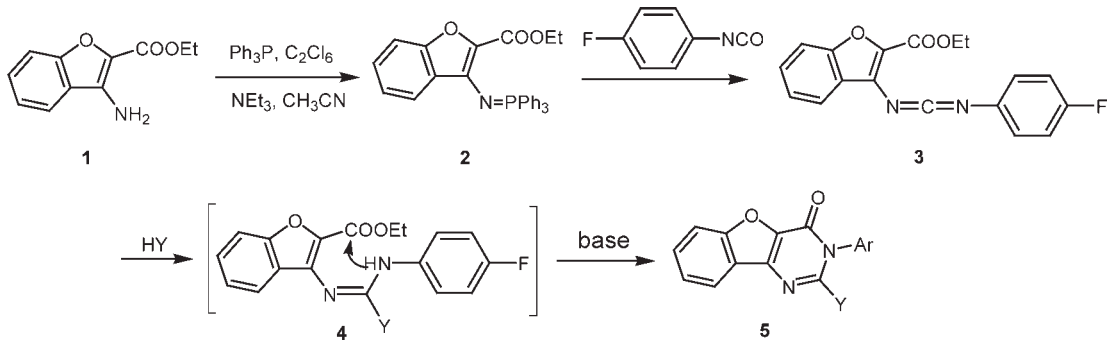
**Synthesis.** The iminophosphorane 2 reacted with *p*-fluorophenyl isocyanate to give carbodiimide 3, which were allowed to react with secondary amines to provide guanidine intermediates 4 ($Y=R_2N$). In the presence of catalytic amount of sodium ethoxide, 4 were converted easily to 2-dialkylamino-3-*p*-fluorophenyl-benzofuro [3,2-d] pyrimidin-4(3H)-ones 5 in satisfactory yields at room temperature (Scheme 1).

The reaction of carbodiimide 3 with phenols produced 2-aryloxy-3-*p*-fluorophenyl-benzofuro [3,2-d] pyrimidin-4(3H)-ones 5 (Y = ArO) in the presence of catalytic amount of potassium carbonate in good yields. The direct reaction of carbodiimide 3 with primary alcohol (ROH) gave 2-alkoxy-3-*p*-fluorophenyl-benzofuro [3,2-d] pyrimidin-4(3H)-ones 5 (Y = RO) in excellent yields in the presence of catalytic amount of $RO^-Na^+$. The results are listed in Table 1.

The reaction of carbodiimide 3 with primary amine $RNH_2$ in the presence of $EtO^-Na^+$ produced only 2-alkylamino-3-*p*-fluorophenyl-benzofuro [3,2-d] pyrimidin-4(3H)-ones 7, and the other isomer 8 was not found (Scheme 2). The same selectivity was also observed in similar cases [11]. The results are also listed in Table 1.

The structures of all products were confirmed using NMR, IR, elemental analysis, and MS. The structure of **7** was deduced from its $^1$H NMR data. Among the possible regioisomers, we obtained only **7** from the reaction mixture after recrystallization; the other isomer **8** was

**Scheme 1**




not found by $^1$H NMR analysis of the reaction mixture. Furthermore, a single crystal of **7b** was obtained from a $CH_2Cl_2$ solution of **7b**. X-ray structure analysis verified again the proposed structure [12] (Fig. 1), which showed that all ring atoms in the benzofuro [3,2-d] pyrimidinone system are essentially coplanar; the C15-C20 phenyl ring is twisted with respect to it, with a dihedral angle of 87.35(3)°. Intermolecular C---H. . .O and N---H. . .O hydrogen bonds link the molecules, helping to stabilize the crystal structure. Further stability the crystal structure is provided by offset π–π stacking interactions involving the fused benzofuro [3,2-d] pyrimidin system moieties.

**Fungicidal activity.** The fungicidal activities of compounds **5** and **7** were screened against six kinds of fungi, *Fusarium oxysporum, Rhizoctonia solani, Botrytis cinerea, Gibberella zeae, Dothiorella gregaria,* and *Colletotrichum gossypii* at a concentration of 50 mg/L according to the reported method [13] and the results are also listed in Table 2. It was found that the compounds showed moderate fungicidal activities when fluorine atom was introduced. As a result, fluorine containing compounds **5i** (79%) displayed better fungicidal activities than non-substituted phenyl compounds **5j** (42%) to *B. cinerea*.

In conclusion, we have developed an efficient synthesis of 2-substituted-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones *via* the aza-Wittig reactions of functionalized iminophosphorane with 4-fluorophenyl isocyanate. Because of the mild reaction condition, good yields, easily accessible starting material, and straightforward product isolation, we think that the versatile synthetic approach discussed here in many cases compares favorably with other existing methods. The preliminary bioassay indicated that all compounds showed moderate fungicidal activities against six kinds of fungi, *F. oxysporum, R. solani, B. cinerea, G. zeae, D. gregaria,* and *C. gossypii* at a concentration of 50 mg/L.

**Table 1**

Yields of compounds **5** and **7**.

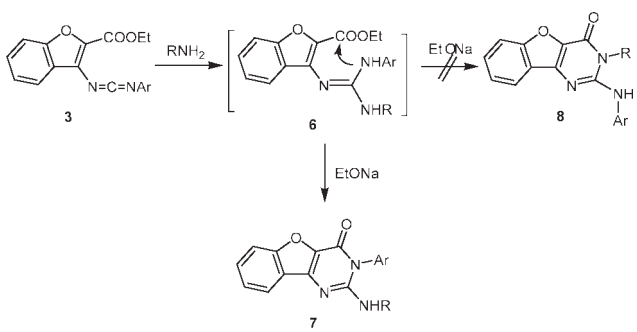
| Compounds | Ar | Y(R) | Yield (%)[a] |
|---|---|---|---|
| **5a** | p-F-Ph |  | 84 |
| **5b** | p-F-Ph |  | 85 |
| **5c** | p-F-Ph | —N($C_2H_5$)$_2$ | 87 |
| **5d** | p-F-Ph | —N(i-$C_3H_7$)$_2$ | 80 |
| **5e** | p-F-Ph | 3,4-dimethylphenoxy | 87 |
| **5f** | p-F-Ph | 4-Chloro-2-methyl-phenoxy | 81 |
| **5g** | p-F-Ph | 4-Methyl-phenoxy | 88 |
| **5h** | p-F-Ph | Methoxy | 87 |
| **5i** | p-F-Ph | Ethoxy | 89 |
| **5j**[b] | Ph | Ethoxy | 82 |
| **7a** | p-F-Ph | *n*-Propyl | 83 |
| **7b** | p-F-Ph | *n*-Butyl | 79 |
| **7c** | p-F-Ph | Cyclohexyl | 88 |
| **7d**[b] | Ph | *n*-Propyl | 83 |

[a] Yields of isolated products based on iminophosphorane **2**.
[b] Ref. 11.

## EXPERIMENTAL

The NMR spectrums ($CDCl_3$) were recorded on Varian XL-400 spectrometer with TMS as an internal standard, and IR spectrum was taken on a Shimadzu IR-408 Infrared spectrometer in KBr Pellets (ν in $cm^{-1}$). The mass spectra were meas-

**Scheme 2**



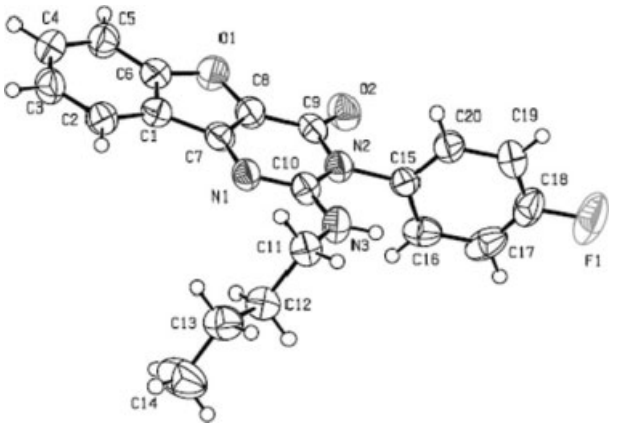



**Figure 1.** X-ray crystal structure of **7b**.

ured on a Finnigan Trace MS spectrometer. Elemental analyses were taken on a Vario EL III elementary analysis instrument. The melting points were determined on X4 microscopic melting apparatus (uncorrected). All the solvents and materials were reagent grade and purified as required.

**General procedure for the preparation of 2-dialkylamino-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones 5a–5d.** To a solution of iminophosphorane **2** (0.93 g, 2 mmol) in dry methylene chloride (15 mL) was added *p*-Fluorophenyl isocyanate (2 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 8–12 h at 0–5°C, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. After filtration, the solvent was removed to give carbodiimide **3**, which was used directly without further purification. To the solution of **3** prepared above in methylene chloride (15 mL) was added dialkylamine (2 mmol). After the reaction mixture was allowed to stand for 0.5–4 h, the solution was condensed and anhydrous ethanol (10 mL) with several drops of $EtO^-Na^+$ in EtOH was added. The mixture was stirred for 1–4 h at room temperature. The solution was concentrated under reduced pressure and the residual was recrystallized from ethanol and dichloromethane (v/v = 1:1) at room temperature to give 2-substituted-benzofuro [3,2-d] pyrimidin-4(3H)-ones **5a–5d.**

***2-(4-Morpholinyl)-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5a).*** White crystals (yield: 0.61 g, 84%), Mp: 233–234°C. $^1$H NMR ($CDCl_3$, 400 MHZ) δ = 3.15 (t, *J* = 4.8, 4H, 2 × $OCH_2$), 3.47 (t, *J* = 4.8, 4H, 2 × $NCH_2$), 7.21–8.03 (m, 8H, Ar-H); IR (KBr): 1701 (C=O), 1538, 1253, 1109 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 365 ($M^+$, 60), 320 (69), 308 (93), 214 (40), 130 (56), 102 (47), 86 (48); Anal. Calcd for $C_{20}H_{16}FN_3O_3$ (365.4): C, 65.75; H, 4.41; N, 11.50; Found: C, 65.83; H, 4.50; N, 11.43.

***2-(1-Piperidinyl)-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5b).*** White crystals (yield: 0.62 g, 85%), Mp: 253–255°C. $^1$H NMR ($CDCl_3$, 400 MHZ) δ =1.27–1.47 (m, 6H, 3 × $CH_2$), 3.11–3.14 (m, 4H, 2 × $NCH_2$), 7.19–8.03 (m, 8H, Ar-H); IR (KBr): 1703 (C=O), 1540, 1248, 1098 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 363 ($M^+$, 100), 320 (27), 254 (32), 223 (24), 178 (89), 130 (21), 102 (69), 84 (51); Anal. Calcd for $C_{21}H_{18}FN_3O_2$ (363.4): C, 69.41; H, 4.99; N, 11.56; Found: C, 69.50; H, 5.12; N, 11.44.

***2-Diethylamino-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5c).*** White crystals (yield: 0.61 g, 87%), Mp: 177–179°C. $^1$H NMR ($CDCl_3$, 400 MHZ) δ = 0.88 (t, *J* = 7.2 Hz, 6H, 2 × $CH_3$), 3.11 (q, *J* = 7.2 Hz, 4H, 2 × $NCH_2$), 7.18–8.03 (m, 8H, Ar-H); IR (KBr): 1704 (C=O), 1537, 1245, 1112 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 351 ($M^+$, 90), 322 (100), 254 (46), 228 (77), 184 (48), 130 (66), 102 (75), 94 (52); Anal. Calcd for $C_{20}H_{18}FN_3O_2$ (351.4): C, 68.36; H, 5.16; N, 11.96; Found: C, 68.43; H, 5.25; N, 11.85.

***2-Diisopropylamino-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5d).*** White crystals (yield: 0.61 g, 80%), Mp: 171–172°C; $^1$H NMR ($CDCl_3$, 400 MHZ) δ = 1.13 (d, *J* = 6.4 Hz, 12H, 4 × $CH_3$), 3.52 (m, 2H, 2 × NCH), 7.17–8.00 (m, 8H, Ar-H); IR (KBr): 1702 (C=O), 1539, 1245, 1098 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 379 ($M^+$, 14), 336 (100), 322 (22), 130 (9.5), 102 (4), 99 (17); Anal. Calcd for

**Table 2**

The fungicidal activities of **5** and **7** (50 mg/L).

| Compounds | Relative inhibition % | | | | | |
|---|---|---|---|---|---|---|
| | *Fusarium oxysporium* | *Rhizoctonia solani* | *Botrytis cinerea* | *Gibberella zeae* | *Dothiorella gregaria* | *Colletotrichum gossypii* |
| **5a** | 21.1 | 30.2 | 45.0 | 41.4 | 50.5 | 31.1 |
| **5b** | 47.5 | 68.5 | 78.0 | 62.9 | 32.8 | 43.3 |
| **5c** | 48.5 | 62.2 | 75.0 | 28.6 | 22.9 | 48.5 |
| **5d** | 42.2 | 17.1 | 25.0 | 38.6 | 37.7 | 28.5 |
| **5e** | 54.3 | 62.4 | 50.0 | 31.4 | 24.7 | 48.5 |
| **5f** | 55.6 | 66.4 | 58.8 | 56.1 | 39.5 | 65.2 |
| **5g** | 31.1 | 12.0 | 30.0 | 42.9 | 34.7 | 64.4 |
| **5h** | 38.5 | 18.1 | 75.0 | 15.7 | 25.9 | 32.2 |
| **5i** | 60.7 | 62.4 | 79.0 | 60.0 | 53.5 | 60.7 |
| **5j** | 39.8 | 53.6 | 42.0 | 31.2 | 26.5 | 47.8 |
| **7a** | 45.9 | 17.1 | 57.0 | 18.6 | 40.6 | 21.1 |
| **7b** | 35.9 | 17.1 | 35.0 | 18.6 | 10.0 | 38.5 |
| **7c** | 32.2 | 42.2 | 55.0 | 21.4 | 15.9 | 38.5 |
| **7d** | 28.5 | 45.1 | 35.0 | 28.6 | 27.9 | 48.5 |

$C_{22}H_{22}FN_3O_2$ (379.4): C, 69.64; H, 5.84; N, 11.07; Found: C, 69.71; H, 5.92; N, 11.00.

**General procedure for the preparation of 2-aroxy-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones 5e–5g.** To the solution of carbodiimide **3** (ca. 2 mmol) prepared above in $CH_3CN$ (15 mL) was added $K_2CO_3$ (0.2 mmol) and ArOH (2 mmol) in anhydrous $CH_3CN$ (10 mL). The mixture was stirred for 6–8 h at 50–60°C. The solution was concentrated under reduced pressure and the residue was recrystallized from dichloromethane and ethanol (v/v = 2:1) at room temperature to give **5e–5g**.

***2-(3,4-Dimethylphenoxy)-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5e).*** White crystals (87% yields), Mp: 172–173°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 2.25 (s, 6H, 2 × $CH_3$), 6.91–7.84 (m, 11H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ = 19.1, 19.8, 112.7, 116.4, 116.6, 118.2, 121.7 (1), 122.3, 123.5, 129.5, 129.8 (2), 130.2, 130.5, 134.3, 135.5, 138.0, 142.0, 149.7, 153.6, 157.2, 161.4, 163.8; IR (KBr): 1698 (C═O), 1536, 1332, 1112 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 400 (47), 262 (100),130 (30),102 (16), 95 (6); Anal. Calcd for $C_{19}H_{16}FN_3O_2$ (400.4): C, 71.99; H, 4.28; N, 7.00. Found: C, 72.05; H, 4.34; N, 6.96.

***2-(4-Chloro-2-methyl-phenoxy)-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5f).*** White crystals (81% yield), Mp: 241–242°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 2.18 (s, 3H, Ar-$CH_3$), 7.16–7.82 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ = 16.5, 112.8, 116.8, 121.8, 122.2, 123.7, 127.5, 127.7, 129.4, 129.8, 130.2, 131.6, 134.1, 135.7, 142.0, 145.1, 151.5, 153.4, 157.3, 161.6, 164.1. IR (KBr): 1701 (C═O), 1543, 1328, 1098 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 420 (M$^+$, 22), 282 (100), 130 (21), 95 (4); Anal. Calcd for $C_{23}H_{14}ClFN_2O_3$ (420.1): C, 65.64; H, 3.35; N, 6.66. Found: C, 65.61; H, 3.37; N, 6.59.

***2-(4-Methyl-phenoxy)-3-(4-fluro-phenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5g).*** White crystals (88% yield), Mp: 170–172°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 2.37 (s, 3H, Ar-$CH_3$), 7.04–7.86 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ = 20.8, 112.8, 116.4, 116.7, 120.9, 121.3, 122.9, 123.2, 129.6, 129.8 (2), 130.5, 135.5, 135.7, 142.0, 149.6, 153.5, 157.3, 161.4, 163.9. IR (KBr): 1705 (C═O), 1539, 1346, 1108 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 386 (M$^+$, 44), 249 (100), 130 (27), 95 (6); Anal. Calcd for $C_{23}H_{15}FN_2O_3$ (386.4): C, 71.50; H, 3.91; N, 7.25. Found: C, 71.42; H, 3.88; N, 7.19.

**General procedure for the preparation of 2-alkoxy-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-ones 5h–5i.** To the solution of carbodiimide **3** (ca. 2 mmol) prepared above in anhydrous ROH (8 mL) was added $RO^-Na^+$ (0.2 mmol, 10% equiv) in ROH. The mixture was stirred for 4–6 h at room temperature. The solution was condensed and the residue was recrystallized from ROH to give **5h–5i**.

***2-Methoxy-3-(4-florophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5h).*** White crystals (yield: 0.54 g, 87%), Mp: 236–237°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 4.04 (s, 3H, $CH_3$), 7.19–8.03 (m, 8H, Ar-H); IR (KBr): 1701 (C═O), 1541, 1340, 1108 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 310 (100), 136 (33), 130 (47), 108 (98), 102 (68), 95 (28), 75 (16); Anal. Calcd for $C_{19}H_{16}FN_3O_2$ (310.3): C, 65.81; H, 3.57; N, 9.03. Found: C, 65.87; H, 3.62; N, 8.98.

***2-Ethoxy-3-(4-florophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (5i).*** White crystals (yield: 0.56 g, 89%), Mp: 202–204°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 1.28 (t, *J* = 7.2, 3H, $CH_3$), 4.50 (d, *J* = 7.2, 2H, $CH_2$), 7.19–8.02 (m, 8H, Ar-H); IR (KBr): 1699 (C═O), 1540, 1339, 1112 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 324 (M$^+$, 96), 295 (46), 185 (68), 158 (100), 130 (20), 102 (70), 95 (10); Anal. Calcd for $C_{18}H_{13}FN_2O_3$ (324.3): C, 66.66; H, 4.04; N, 8.64. Found: C, 66.71; H, 4.10; N, 8.60.

**General procedure for the preparation of 2-alkylamino-benzofuro [3,2-d] pyrimidin-4(3H)-ones 7a–7c.** To the solution of carbodiimide **3** (ca. 2 mmol) prepared above in methylene chloride (15 mL) was added alkylamine (2 mmol). After the reaction mixture was allowed to stand for 0.5–2 h, the solution was condensed and anhydrous ethanol (10 mL) with several drops of $EtO^-Na^+$ in EtOH was added. The mixture was stirred for 1–4 h at room temperature. The solution was concentrated under reduced pressure and the residual was recrystallized from ethanol and dichloromethane (v/v = 1:2) at room temperature to give 2-alkylamino-benzofuro [3,2-d] pyrimidin-4(3H)-ones **7a–7c**.

***3-(4-Fluorophenyl)-2-(n-propylamino)-benzofuro [3,2-d] pyrimidin-4(3H)-one (7a).*** White crystals (yield: 0.56 g, 83%), Mp: 199–200°C; $^1$H NMR (400 MHz, $CDCl_3$) δ = 0.87 (t, *J* = 7.2 Hz, 3H, $CH_3$), 1.54–1.60 (m, 2H, $CH_2$), 3.42–3.47 (m, 2H, $NCH_2$), 4.11 (s, 1H, NH), 7.30–8.02 (m, 8H, Ar-H); IR (KBr): 3341 (N─H), 1699 (C═O), 1540, 1342, 1111 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 337 (M$^+$, 32), 294 (100), 185 (35), 160 (64), 130 (71), 102 (82), 95 (53); Anal. Calcd for $C_{19}H_{16}FN_3O_2$ (337.4): C, 67.65; H, 4.78; N, 12.46. Found: C, 67.71; H, 4.84; N, 12.37.

***3-(4-Fluorophenyl)-2-(n-butylamino)-benzofuro [3,2-d] pyrimidin-4(3H)-one (7b).*** White crystals (yield: 0.56 g, 79%), Mp: 191–192°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 0.89 (t, *J* = 7.2 Hz, 3H, $CH_3$), 1.25–1.54 (m, 4H, 2 × $CH_2$), 3.43–3.47 (m, 2H, $NCH_2$), 4.14 (s, 1H, NH), 7.29–8.01 (m, 8H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ = 13.6, 19.8, 31.0, 41.8, 112.6, 117.6 (2), 121.5, 122.9, 123.0, 129.2, 130.8 (1), 132.9, 144.6, 151.8, 153.6, 157.2, 161.7,164.2. IR (KBr): 3336 (N─H), 1704 (C═O), 1533, 1340, 1115 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 351 (M$^+$, 78), 334 (41),308 (35), 294 (100), 185 (48), 130 (70),102 (82), 95 (52); Anal. Calcd for $C_{20}H_{18}FN_3O_2$ (351.4): C, 68.36; H, 5.16; N, 11.96. Found: C, 68.33; H, 5.20; N, 11.89.

***2-(Cyclohexylamino)-3-(4-fluorophenyl)-benzofuro [3,2-d] pyrimidin-4(3H)-one (7c)*** White crystals (yield: 0.66 g, 88%), Mp: 188–190°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 1.05–1.42 (m, 6H, 3 × $CH_2$), 1.60–1.62 (m, 4H, 2 × $CH_2$), 1.96–1.99 (m, 1H, CH), 4.02–4.05 (m, 1H, NH), 7.19–8.04 (m, 9H, Ar-H); IR (KBr): 1704 (C═O), 1533, 1340, 1115 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 377 (M$^+$, 22), 294 (100), 185 (20), 130 (29),102 (30), 98 (27), 55 (26); Anal. Calcd for $C_{22}H_{20}FN_3O_2$ (377.4): C, 70.01; H, 5.34; N, 11.13. Found: C, 69.97; H, 5.37; N, 11.08.

**Fungicidal testing.** *F. oxysporium, R. solani, B. cinereapers, G. zeae, D. gregaria,* and *C. gossypii* were provided through the courtesy of the Center for bioassay, Central China Normal University. The tested samples were dissolved in 0.5 mL of DMF, added to a drop of emulsifying agent (Tween 80) and sterile water at a concentration of 500 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50°C. The mixtures were poured into Petri dishes. After the dishes were cooled, the solidified plates were incubated with 4 mm mycelium disk, inverted, and incubated at 28°C for 48 h. The mixed medium without

sample was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(C-T)/C] \times 100\%$. Here, $I$ is the growth inhibition rate (%), $C$ is the control settlement radius (mm), and $T$ is the treatment group fungi settlement radius (mm).

**Crystal structure determination.** Single crystal X-ray diffraction data for **7b** at 292 K on a Bruker Smart Apex Area CCD equipped with Mo Ka radiation ($\lambda = 0.71073$ A°). Crystallographic data (excluding structure factors) for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 671114. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ.

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## REFERENCES AND NOTES

[1] Naya, S.; Ohtoshi, H.; Nitta, M. J Org Chem 2006, 71, 176.

[2] Wendt, J. A.; Deeter, S. D.; Bove, S. E.; Knauer, C. S.; Brooker, R. M.; Augelli-Szafran, C. E.; Schwarz, R. D.; Kinsora, J. J.; Kilgore, K. S. Bioorg Med Chem Lett 2007, 17, 5396.

[3] Bodke, Y.; Sangapure, S. S. J Indian Chem Soc 2003, 80, 187.

[4] Glazer, E. A.; McFarland, J. W. US Patent 4,725,599, 2008; Chem Abstr 1989, 110, 231654x.

[5] Ishida, A.; Inage, M.; Akatsuka, H.; Inamasu, M.; Mitsui, T. JP 6,220,059, 1994; Chem Abstr 1995, 122, 81390q.

[6] Elliott, A. J.; Hudlicky, M. In Chemistry of Organic Fluorine Compounds. II. A Critical Review; Avlath, A. E., Ed.; American chemical society: Washington, DC, 1995; pp 1119–1125.

[7] Smart, B. E. J Fluor Chem 2001, 121, 3.

[8] Ulrich, H. Chemistry and Technology of Carbodiimides; John Wiley & Sons, Ltd.: Chichester, 2007.

[9] Li, Q.; Wei, Y.; Hao, J.; Zhu, Y.; Wang, L. J Am Chem Soc 2007, 129, 5810.

[10] Ding, M. W.; Xu, S. Z.; Zhao, J. F. J Org Chem 2004, 69, 8366.

[11] Hu, Y. G.; Liu, M. G.; Ding, M. W. Helv Chim Acta 2008, 91, 862.

[12] Crystal data of **7b**. $C_{20}H_{18}FN_3O_2$, Mr = 351.37; Crystal system: tetragonal; space group: P-42(1)c; unit cell dimensions: $a$ = 11.0922(6), $b$ = 11.0922(6), $c$ = 28.6271(15)Å, $V$ = 3522.2(3) Å3, $Z$ = 8, Dc = 1.325, $F$ (000) = 1472, $\mu = 0.095$ mm$^{-1}$, MoKa radiation ($\lambda = 0.71073$), $R = 0.0498$, wR = 0.1238 for 2336 observed reflections with $I > 2\sigma(I)$.

[13] Ren, Q.; Cui, Z.; He, H.; Gu, Y. J Fluor Chem 2007, 128, 1369.

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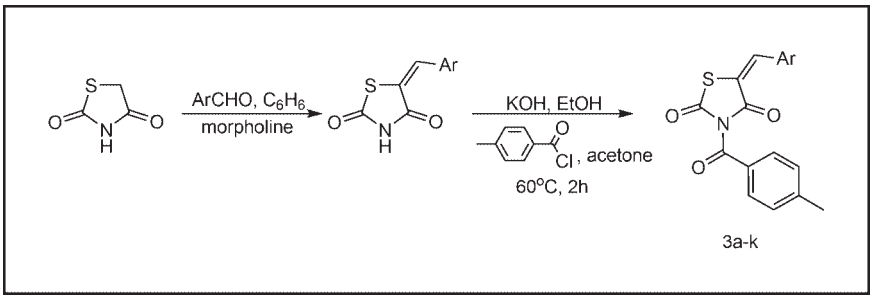


The derivatives of 5-substituted-2,4-thiazolidinedione have a broad spectrum of biological activities. In this article, new 5-(arylidene)-3-(4-methylbenzoyl)thiayolidine-2,4-diones **3a–k,** with arylidene groups such as 4-phenylbenzylidene **3a,** 3,4-dimethoxybenzylidene **3b,** 2-hydroxybenzylidene **3c,** 4-ethoxybenzylidene **3d,** 5-methyl-2-furfurylidene **3e**, 4-dimethylaminobenzylidene **3f,** 1-naphthylidene **3g,** 3,4-methylenedioxybenzylidene **3h,** 4-benzyloxybenzylidene **3i**, benzylidene **3j**, and 4-methoxybenzylidene **3k,** were synthesized by direct acylation of alkali metal salts of 5-arylidene-2,4-thiazolidinediones with 4-methylbenzoylchloride. Their structures were confirmed by elemental analysis, IR, $^1$H NMR and MS spectroscopy. In addition, crystal structure of the compound **3d** was determined using single-crystal X-ray diffraction data.

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## INTRODUCTION

Thiazolidinone derivates are reported to show variety of biological activities. Depending on the substituents, especially thiazolidinediones can produce different pharmacological activities such as antibacterial, antifungal [1], anticonvulsant [2], antidiabetic [3], cyclooxygenase and lipogenase inhibitory [4], antioxidant [5], and antiproliferative [6] activity. Moreover, the importance of 5-substituted-2,4-thiazolidinedione and their derivatives is due to their biological activities including antimicrobial [1] and fungicidal activity [7], as well as their utilization in a variety of therapeutic areas [8–14].

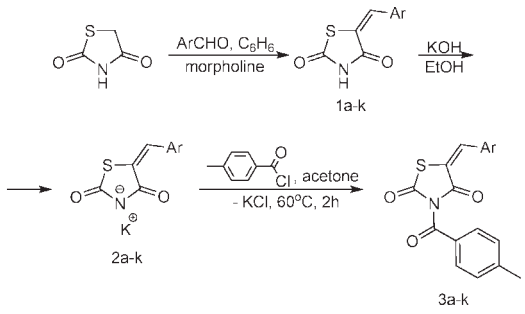
In some heterocyclylbenzenes [15,16] and substituted pyrazoles [17], which have herbicidal and defoliant characteristic, there is a 3-methylbenzoyl substructure. This study is focused on the link of 5-arylidene-2,4-thiazolidinediones and bioactive structural unit, 3-methylbenzoyl group, in order to find novel potential herbicides and defoliants. Crystal structure of the selected compound **3d** was also determined using single-crystal X-ray diffraction data.

## RESULTS AND DISCUSSION

The reactive methylene group of the 2,4-thiazolidinedione has previously been successfully condensed with aldehydes, forming respectively 5-arylidene-2,4-thiazolidinediones **1a–k** [18]. These compounds were later transformed in their potassium salts **2a–k** [19]. By direct acylation of solid alkali metal salts of 5-arylidene-2,4-thiazolidinediones with 4-methylbenzoylchloride in refluxing dry acetone the corresponding 5-(arylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-diones **3a–k** were prepared. The obtained compounds **3a–k** were synthesized as yellow crystals in high yields (56.2–99.4%). The synthesis route is shown in Scheme 1.

All the newly synthesized compounds were characterized by elemental analysis, IR, $^1$H NMR, and MS (see

**Scheme 1**




Ar = $C_{12}H_9$ (a); 3,4-$(MeO)_2C_6H_3$ (b); 2-$OHC_6H_4$ (c); 4-$EtOC_6H_4$ (d); 5-$MeC_4H_2O$ (e); 4-$Me_2NC_6H_4$ (f); 1-$C_{10}H_7$ (g); 3,4-$OCH_2OC_6H_3$ (h); 4-$PhCH_2OC_6H_4$ (i); $C_6H_5$ (j); 4-$MeOC_6H_4$ (k)

''Experimental'' section). The elemental analysis and MS of 5-(arylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-diones **3a–k**, agreed with the molecular formula of these compounds. The structure of synthesized compounds was confirmed by $^1$H NMR and IR spectroscopy. $^1$H NMR spectra 5-(arylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-diones **3a–k,** clearly showed presence of benzoyl protons ($\delta \sim 7.3$ and 7.8 ppm) and methyl protons ($\delta \sim 2.45$ ppm) in comparison with spectra of 5-arylidene-2,4-thiazolidinediones **1a–k** [18]. IR spectra of all newly synthesized compounds **3a–k,** contain characteristic bands attributed to the methyl-benzoyl (C═O, about 1760 $cm^{-1}$) and benzoyl (about 1450 and 1600 $cm^{-1}$) vibrations that are used in the structural characterization of this type of compounds.

**Crystal structure of the compound 3d.** The molecular structure of compound **3d** is shown in Figure 1, and selected bond lengths and bond angles are listed in Table 1. Bond lengths and angles are in well agreement with some parent and similar compounds [20–22]. The main part of molecule, including the side ethoxy group, is almost planar with dihedral angle between benzylidene and thiazolidine-2,4-dione rings of only 5.8°. This is as expected, since practically the same angles (5.4°–5.9°) are found in some similar compounds [20,21]. The slight deviation from planarity can be attributed to the short repulsive S···H14–C14 contact with S···C14 distance of only 3.260(2) Å. On the other hand, dihedral angle between planes of thiazolidine-2,4-dione and methylbenzylidene rings is 67.1°.

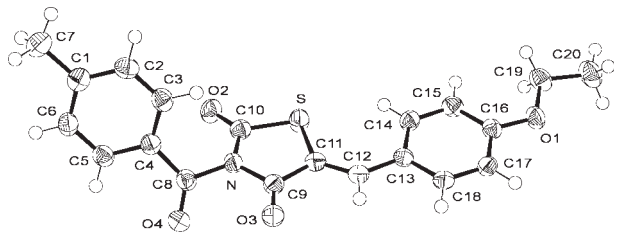



**Figure 1.** The molecular structure of compound **3d.**

The characteristic feature in crystal packing is the stacking of molecules in columns running along *b*-axis (Fig. 2). These columns further make a regular grid parallel to the planes (1 0 1) and (1 0 0) [Fig. 2(a)]. Within the columns there are stacking π−π interactions, which alternatively involve two benzylidene rings or pairs of both benzylidene and thiazolidine-2,4-dione rings [Fig. 2(b)]. As, for example, distances between planes of two benzylidene rings are only 3.32 and 3.33 Å the stacking π–π interactions can be described as very strong. In addition to van der Waals contacts, between the neighboring columns there are several C—H···O interactions involving mainly C atoms from terminal $CH_3$ groups, as well as few C atoms from 4-methylbenzoyl and benzylidene rings. In this way, the columns are only loosely connected to each other.

On the basis of presented crystal structure of **3d** compound it can be assumed that: (a) in all compounds (**3a–k**) the main part of molecule, including benzylidene and thiazolidine-2,4-dione rings, is almost planar; (b) π–π interactions between aromatic rings have a predominant role in molecular packing; (c) in all derivatives the C11—C12 bond is longer than double (C═C) bond, while the C12—C13 bond is shorter than the expected value for a single bond, probably because of delocalization of π-electrons through the whole substructure (C11═CH—$C_{arom}$). This delocalization is a reason why the attempts to carry out some addition reactions, which are inherent for the double bond, were unsuccessful.

## EXPERIMENTAL

**Materials and methods.** The solvent and all reagents used in this study were purchased from commercial suppliers and were used as received. The melting points were obtained with

**Table 1**

Selected bond lengths (Å) and bond angles (°) for **3d**.

| | | | |
|---|---|---|---|
| Bond lenghts (Å) | | | |
| S—C11 | 1.7586(16) | N—C9 | 1.414(2) |
| S—C10 | 1.7620(18) | N—C8 | 1.459(2) |
| O1—C16 | 1.360(2) | C1—C7 | 1.502(3) |
| O1—C19 | 1.450(2) | C4—C8 | 1.471(2) |
| O2—C10 | 1.210(2) | C9—C11 | 1.480(2) |
| O3—C9 | 1.206(2) | C11—C12 | 1.342(2) |
| O4—C8 | 1.200(2) | C12—C13 | 1.450(2) |
| N—C10 | 1.397(2) | C19—C20 | 1.501(3) |
| Bond angles (°) | | | |
| C11—S—C10 | 92.30(18) | O2—C10—N | 125.19(16) |
| C16—O1—C19 | 117.49(13) | O2—C10—S | 123.99(14) |
| C10—N—C9 | 116.01(14) | N—C10—S | 110.78(12) |
| C10—N—C8 | 121.01(14) | C12—C11—C9 | 120.63(15) |
| C9—N—C8 | 122.44(13) | C12—C11—S | 128.61(14) |
| O4—C8—N | 118.55(16) | C9—C11—S | 110.75(12) |
| O4—C8—C4 | 124.94(16) | C11—C12—C13 | 131.73(16) |
| N—C8—C4 | 116.50(15) | O1—C16—C15 | 124.91(15) |
| O3—C9—N | 123.22(16) | O1—C16—C17 | 115.92(15) |
| O3—C9—C11 | 126.70(16) | O1—C19—C20 | 107.02(16) |
| N—C9—C11 | 110.04(14) | | |

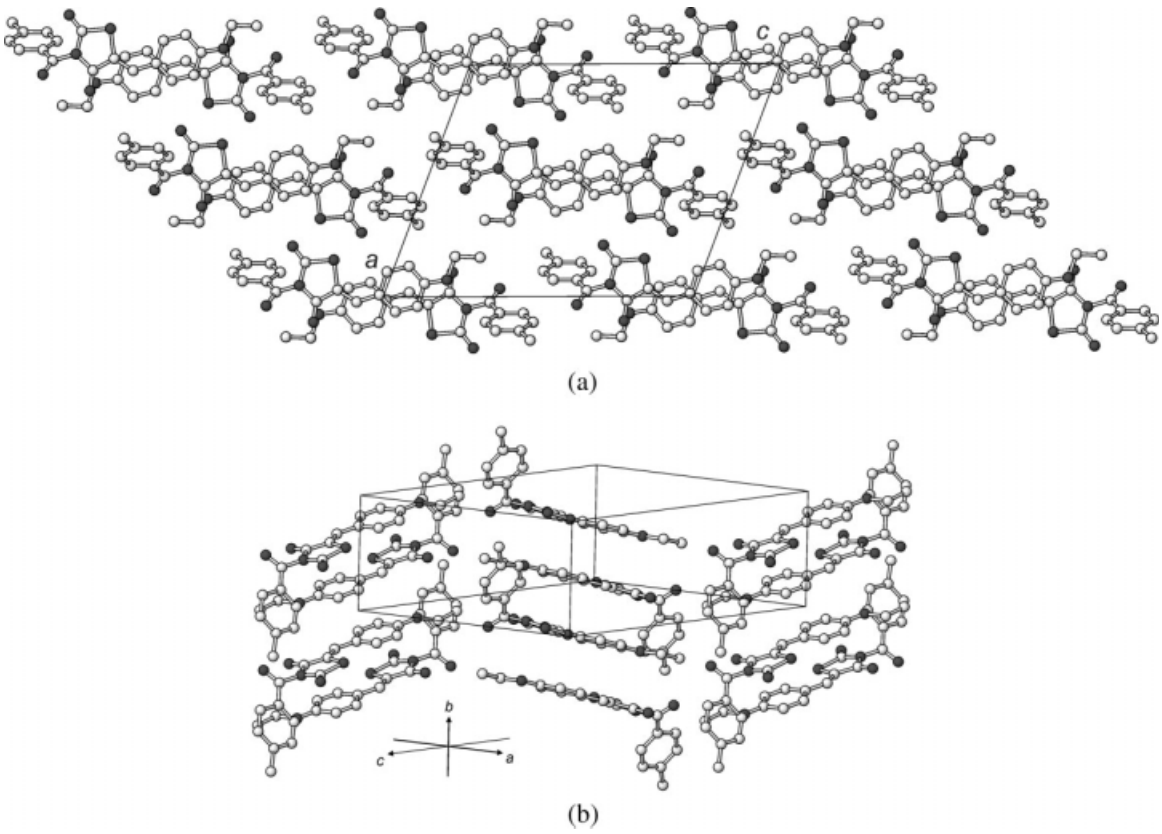



**Figure 2.** The packing of molecules **3d** (heteroatoms are dark, hydrogen atoms are omitted for clarity): (a) projection onto *ac*-plane and (b) projection approximately parallel to the (101) plane.

STUART SMP 10 melting point apparatus. Infrared spectra (ν in $cm^{-1}$) were recorded on a Perkin Elmer FTIR 1725 X spectrophotometer using KBr disks. The $^1H$ NMR spectra were recorded on a Varian Gemini 200 (200 MHz) instrument; chemical shifts (δ) are given relative to tetramethylsilane (TMS). The mass spectra were obtained on Finnigan MAT–8230 BE spectrometer with EI–CI source at 200°C, EI: 70 eV, 0.5 mA; CI: 1 m Torr of isobutane, 150 eV, 0.2 mA.

Single-crystals of the compound **3d** were obtained by recrystallization from EtOH. X-ray diffraction data were collected at 150 K on a Nonius Kappa CCD diffractometer using Mo Kα radiation. The structure was solved by direct methods and refined by a full-matrix least-squares procedure based on $F^2$ using the programs from WinGX suite [23]. All nonhydrogen atoms were refined anisotropically, while the hydrogen atoms were found in Δ$F$ maps and were refined isotropically with no constraints. Selected crystal data and refinement results are listed in Table 2.

**Syntheses.** ***General procedure for the preparation of the 5-(arylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-diones 3a–k.*** 5-Arylidene-2,4-thiazolidinedione potassium salts (1 mmol) were suspended in dry acetone (20 mL) and 4-methylbenzoylchloride (1 mmol) was added at room temperature. The reaction mixtures were stirred at 60°C for 2 h and cooled to room temperature. Finally, the reaction mixtures were filtered and acetone was removed to give the crystalline products. The products were recrystallized from absolute EtOH.

**Table 2**

Crystal data and refinement details for **3d**.

| | |
|---|---|
| Empirical formula | $C_{20}H_{17}NO_4S$ |
| Formula weight | 367.41 |
| Crystal system | monoclinic |
| Space group | $P2_1/n$ |
| $a$ (Å) | 14.4880(5) |
| $b$ (Å) | 6.9780(3) |
| $c$ (Å) | 18.0600(7) |
| α (°) | 90 |
| β (°) | 110.7290(10) |
| γ (°) | 90 |
| $V$ (Å$^3$) | 1707.62(12) |
| Z | 4 |
| Calculated density (g $cm^{-3}$) | 1.429 |
| Absorption coefficient ($mm^{-1}$) | 0.216 mm |
| $F$(000) | 768 |
| Crystal size (mm) | 0.75 × 0.70 × 0.05 |
| Θ range (°) | 3.16–26.37 |
| Limiting indices | $-17 \le h \le 18$, $-8 \le k \le 8$, $-22 \le l \le 22$ |
| Reflections collected/unique | 6383/3453 ($R_{int} = 0.0313$) |
| Data/restraints/parameters | 3453/0/304 |
| Goodness-of-fit on $F^2$ | 1.030 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0378$, $wR_2 = 0.0786$ |
| $R$ indices (all data) | $R_1 = 0.0592$, $wR_2 = 0.0874$ |

***5-(4-Phenylbenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3a).*** This compound was obtained as yellow crystals (ethanol), yield 69.3%, mp 183°C; IR, ν, $cm^{-1}$: 3035 (=C—H), 2925, 2794 (C—H), 1762 (C=O), 1716 (C=O), 1693 (C=O), 1603, 1515, 1448 (C=C), 1408 (C—N), 1258, 1177, 1063, 837, 718, 691; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (s, 3H, $CH_3$), 7.34 (d, $2H_{arom}$, $J = 8.0$), 7.41–7.73 (m, $9H_{arom}$), 7. 87 (d, $2H_{arom}$, $J = 8.4$), 7.99 (s, 1H, =CH); *m/z* (CIMS): 398 ($M^+$). Anal. Calcd. for $C_{24}H_{17}NO_3S$ (399.5): C, 72.16; H, 4.29; N, 3.51; S, 8.03. Found: C, 72.01; H, 4.21; N, 3.59; S, 8.05.

***5-(3,4-Dimethoxybenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3b).*** This compound was obtained as yellow crystals (ethanol), yield 56.2%, mp 228°C; IR, ν, $cm^{-1}$: 3007 (=C—H), 2960, 2838 (C—H), 1751 (C=O), 1712 (C=O), 1686 (C=O), 1591, 1512, 1447 (C=C), 1418 (C—N), 1272, 1242, 1180, 1074 (C—O), 857, 730, 678; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.45 (s, 3H, $CH_3$), 3.95 (s, 6H, 2 $CH_3$), 6.96–7.20 (m, $3H_{arom}$), 7.31 (d, $2H_{arom}$, $J = 8.0$), 7.83 (d, $2H_{arom}$, $J = 8.4$), 7.89 (s, 1H, =CH); *m/z* (CIMS): 383 ($M^+$). Anal. Calcd. for $C_{20}H_{17}NO_5S$ (383.2): C, 62.66; H, 4.74; N, 3.65; S, 8.37. Found: C, 62.50; H, 4.71; N, 3.68; S, 8.57.

***5-(2-Hydroxybenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3c).*** This compound was obtained as yellow crystals (ethanol), yield 83.4%, mp 233°C; IR, ν, $cm^{-1}$: 3415 (O—H), 3043 (=C—H), 2764 (C—H), 1745 (C=O), 1701 (C=O), 1681 (C=O), 1602, 1510, 1455 (C=C), 1412 (C—N), 1293, 1265, 1152 (C—O), 838, 750, 684; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.47 (s, 3H, $CH_3$), 7.33–7.61 (m, $4H_{arom}$), 7.80 (d, 2 $H_{arom}$, $J = 8.2$), 7.99 (s, 1H, =CH), 8.11 (d, 2 $H_{arom}$, $J = 8.0$); *m/z* (CIMS): 339 ($M^+$). Anal. Calcd. for $C_{18}H_{13}NO_4S$ (339.4): C, 63.77; H, 3.86; N, 4.13; S, 9.46. Found: C, 63.47; H, 3.76; N, 3.83; S, 9.55.

***5-(4-Ethoxybenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3d).*** This compound was obtained as yellow crystals (ethanol), yield 97.4%, mp 178°C; IR, ν, $cm^{-1}$: 3041 (=C—H), 2936, 2883 (C—H), 1755 (C=O), 1716 (C=O), 1690 (C=O), 1596, 1509, 1448 (C=C), 1398 (C—N), 1281, 1176, 1143, 1072 (C—O), 840, 729, 690; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.46 (t, 3H, $CH_3$, $J = 7.0$), 2.45 (s, 3H, $CH_3$), 4.11 (q, 2H, $CH_2$, $J = 7.0$), 7.00 (2 $H_{arom}$, *m AA′* $J_1 = 6.8$, $J_2 = 1.99$), 7.32 (d, $2H_{arom}$, $J = 8.0$), 7.47 (2 $H_{arom}$, *m BB′* $J_1 = 6.8$, $J_2 = 1.8$), 7.84 (2 $H_{arom}$, *m BB′* $J_1 = 8.4$, $J_2 = 1.8$), 7.89 (s, 1H, =CH); *m/z* (CIMS): 367 ($M^+$). Anal. Calcd. for $C_{20}H_{17}NO_4S$ (367.4): C, 65.38; H, 4.66; N, 3.81; S, 8.73. Found: C, 65.18; H, 4.62; N, 3.83; S, 8.81.

***5-(5-Methyl-2-furfurylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3e).*** This compound was obtained as yellow crystals (ethanol), yield 95.2%, mp 168°C (decomp.); IR, ν, $cm^{-1}$: 3038 (=C—H), 2920 (C—H), 1758 (C=O), 1711 (C=O), 1681 (C=O), 1611, 1513, 1438 (C=C), 1412 (C—N), 1253, 1159, 1081 (C—O), 864, 731, 690; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.45 (s, 3H, $CH_3$), 6.24 (d, $1H_{furyl}$, $J = 3.5$), 6.78 (d, $1H_{furyl}$, $J = 3.5$), 7.32 (d, 2 $H_{arom}$, $J = 8.0$), 7.60 (s, 1H, =CH), 7.82 (d, $2H_{arom}$, $J = 8.4$); *m/z* (CIMS): 327 ($M^+$). Anal. Calcd. for $C_{17}H_{13}NO_4S$ (327.4): C, 62.37; H, 4.00; N, 4.28; S, 9.79. Found: C, 62.09; H, 3.90; N, 4.25; S, 9.88.

***5-(4-Dimethylaminobenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3f).*** This compound was obtained as yellow crystals (ethanol), yield 91.8%, mp 208°C (decomp.); IR, ν, $cm^{-1}$: 3032 (=C—H), 2911, 2884 (C—H), 1751 (C=O), 1714 (C=O), 1680 (C=O), 1585, 1530, 1441 (C=C), 1379 (C—N), 1296, 1197, 884, 769, 659; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.45 (s, 3H, $CH_3$), 3.09 (s, 6H, N $(CH_3)_2$), 6.75 ($2H_{arom}$, *m AA′* $J_1 = 7.0$, $J_2 = 1.99$), 7.33 ($2H_{arom}$, *m AA′* $J_1 = 7.99$, $J_2 = 0.4$), 7.44 ($2H_{arom}$, *m BB′* $J_1 = 7.2$, $J_2 = 1.99$), 7.83 ($2H_{arom}$, *m BB′* $J_1 = 8.4$, $J_2 = 1.99$), 7.85 (s, 1H, =CH); *m/z* (CIMS): 366 ($M^+$). Anal. Calcd. for $C_{20}H_{18}N_2O_3S$ (366.4): C, 65.49; H, 4.95; N, 7.64; S, 8.75. Found: C, 65.29; H, 4.83; N, 7.59; S, 8.83.

***5-(1-Naphthylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3g).*** This compound was obtained as yellow crystals (ethanol), yield 99.4%, mp 147°C; IR, ν, $cm^{-1}$: 3046 (=C—H), 2909 (C—H), 1762 (C=O), 1717 (C=O), 1690 (C=O), 1603, 1572, 1448 (C=C), 1397 (C—N), 1298, 1181, 891, 736, 641; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.47 (s, 3H, $CH_3$), 7.33 (d, $2H_{arom}$, $J = 8.2$), 7.55–8.15 (m, $9H_{arom}$), 8.69 (s, 1H, =CH); *m/z* (CIMS): 373 ($M^+$). Anal. Calcd. for $C_{22}H_{15}NO_3S$ (373.4): C, 70.76; H, 4.05; N, 3.75; S, 8.59. Found: C, 70.57; H, 4.02; N, 3.77; S, 8.66.

***5-(3,4-Methylenedioxybenzylidene)-3-(4-methylbenzoul)thiazolidine-2,4-dione (3h).*** This compound was obtained as yellow crystals (ethanol), yield 71.2%, mp 152°C; IR, ν, $cm^{-1}$: 3051 (=C—H), 2997, 2908 (C—H), 1752 (C=O), 1713 (C=O), 1689 (C=O), 1607, 1590, 1449 (C=C), 1365 (C—N), 1263, 1066 (C—O), 862, 726, 658; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (s, 3H, $CH_3$), 6.09 (s 2H, —$OCH_2O$—), 7.33 (d, $2H_{arom}$, $J = 8.2$), 6.92–7.12 (m, $3H_{arom}$), 7.81 (d, $2H_{arom}$, $J = 7.8$), 8.85 (s, 1H, =CH); *m/z* (CIMS): 367 ($M^+$). Anal. Calcd. for $C_{19}H_{13}NO_5S$ (367.4): C, 62.12; H, 3.57; N, 3.81; S, 8.73. Found: C, 61.94; H, 3.50; N, 3.77; S, 8.80.

***5-(4-Benzyloxybenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3i).*** This compound was obtained as yellow crystals (ethanol), yield 96.3%, mp 144°C; IR, ν, $cm^{-1}$: 3034 (=C—H), 2923, 2882 (C—H), 1763 (C=O), 1716 (C=O), 1687 (C=O), 1593, 1511, 1453 (C=C), 1386 (C—N), 1292, 1149 (C—O), 831, 783, 698; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.45 (s, 3H, $CH_3$), 5.15 (s, 2H, $CH_2O$), 7.07–7.53 (m, $11H_{arom}$), 7.82 ($2H_{arom}$, *m BB′* $J_1 = 6.6$, $J_2 = 1.6$), 7.89 (s, 1H, =CH); *m/z* (CIMS): 429 ($M^+$). Anal. Calcd. for $C_{25}H_{19}NO_4S$ (429.5): C, 69.91; H, 4.46; N, 3.26; S, 7.47. Found: C, 69.74; H, 4.37; N, 3.23; S, 7.52.

***5-Benzylidene-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3j).*** This compound was obtained as yellow crystals (ethanol), yield 86.3%, mp 118°C; IR, ν, $cm^{-1}$: 3056 (=C—H), 2917 (C—H), 1758 (C=O), 1717 (C=O), 1692 (C=O), 1606, 1492 (C=C), 1373 (C—N), 1254, 1182, 883, 686; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (s, 3H, $CH_3$), 7.33 (d, $2H_{arom}$, $J = 8.0$), 7.48–7.55 (m, $5H_{arom}$), 7.84 ($2H_{arom}$, *m BB′* $J_1 = 6.5$, $J_2 = 1.99$), 7.95 (s, 1H, =CH); *m/z* (CIMS): 323 ($M^+$). Anal. Calcd. for $C_{18}H_{13}NO_3S$ (323.4): C, 66.86; H, 4.05; N, 4.33; S, 9.92. Found: C, 66.66; H, 3.94; N, 4.27; S, 9.98.

***5-(4-Methoxybenzylidene)-3-(4-methylbenzoyl)thiazolidine-2,4-dione (3k).*** This compound was obtained as yellow crystals (ethanol), yield 90.3%, mp 154°C; IR, ν, $cm^{-1}$: 3069 (=C—H), 2844 (C—H), 1766 (C=O), 1720 (C=O), 1689 (C=O), 1594, 1463 (C=C), 1374 (C—N), 1290, 1151 (C—O), 878, 715, 689; $^1$H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 2.45 (s, 3H, $CH_3$), 3.89 (s, 3H, —$OCH_3$), 7.01 ($2H_{arom}$, *m AA′* $J_1 = 6.8$, $J_2 = 1.99$), 7.32 (d, $2H_{arom}$, $J = 8.4$), 7.50 ($2H_{arom}$, *m BB′* $J_1 = 7.0$, $J_2 = 1.99$), 7.83 (d, $2H_{arom}$, $J = 8.2$), 7.89 (s, 1H, =CH); *m/z* (CIMS): 353 ($M^+$). Anal. Calcd. for $C_{19}H_{15}NO4S$ (353.4): C, 64.57; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.29; H, 4.18; N, 3.94; S, 9.108.

## SUPPLEMENTARY DATA

CCDC 733926 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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### REFERENCES AND NOTES

[1] Lima, M. C. A.; Deise, L. B.; Goes, A. J. S.; Suely, L. G.; Pitta, I. R. Pharmazie 1992, 47, 182.

[2] El-Feky, S. A. H. Pharmazie 1992, 48, 894.

[3] Strumvoll, M.; Haring, H. U. Ann Med 2002, 34, 217.

[4] Unangst, P. C.; Connor, W. A.; Sorenson, R. J.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. Bioorg Med Chem Lett 1993, 3, 1729.

[5] Hossain, U.; Bhattacharia, S. Bioorg Med Chem Lett 2007, 17, 1149.

[6] Chandrappa, S.; Benaka Prasad, S. B.; Vinaya, K.; Ananda Kumar, C. S.; Thimmegowda, N. R.; Rangappa, K. S. Invest New Drugs 2008, 26, 437.

[7] Musial, L.; Staniec. J. Roczniki Chemii 1965, 39, 839.

[8] Momose, Y.; Kanji, M.; Hitoshi, I.; Chitoshi, H.; Satoru, O.; Takashi, S. Chem Pharm Bull 1991, 39, 1440.

[9] Takashi, S.; Katsutoshi, M.; Momose, Y.; Hitoshi, I.; Takeshi, F.; Kanji, M. J Med Chem 1992, 35, 2617.

[10] Tomita, M.; Shindo, N.; Hirakatá, K. Kaken Pharm Co Ltd. Patent JO 3077–875–A, 1991.

[11] Kobori, T.; Yamamoto, R.; Fujita, M.; Hiyama, T.; Nagate, T. Taisho Pharm Co Ltd. Patent WO 9207840–$A_1$, 1992.

[12] Brown, F. G. Chem Rev 1961, 61, 463.

[13] Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. Chem Rev 1981, 81, 175.

[14] Tsujie, M.; Nakamori, S.; Okami, J.; Hayashi, N.; Hiraoka, N.; Nagano, H.; Dono, K.; Umeshita, K.; Sakon, M.; Monden, M. Exp Cell Res 2003, 289, 143.

[15] Gupta, S.; Tsukamoto, M.; Pulman, D. A.; Ying, B-P.; Wu, S-Y. Patent WO 9,921,837, 1999.

[16] Gupta, S.; Wu, S–Y.; Tsukamoto, M.; Pulman, D. A.; Ying, B–P. Patent US 6,355,799, 2002.

[17] Yamamoto, T.; Takamatsu, M.; Kawahara, T. Patent JP 63,264,574, 1988.

[18] Popov-Pergal, K.; Čeković, Z.; Pergal, M. Zh Obshch Khim 1991, 61, 2112.

[19] Popov-Pergal, K.; Čeković, Z.; Pergal, M. Sulphur Lett 1989, 9, 95.

[20] Divjaković, V.; Popov-Pergal, K.; Pergal, M.; Klement, U. Acta Crystallogr 1991, C47, 1760.

[21] Drew, M. G. B.; Mok, K. F.; Ang, K. P.; Tan, S. F. Acta Crystallogr 1987, C43, 743.

[22] Form, G. R.; Raper, S.; Downie, T. C. Acta Crystallogr 1975, B31, 2181.

[23] Farrugia, L. J. J Appl Cryst 1999, 32, 837.

# A Convenient Synthesis of Novel *N*-Dichloroacetyl-1,3-oxazolidine



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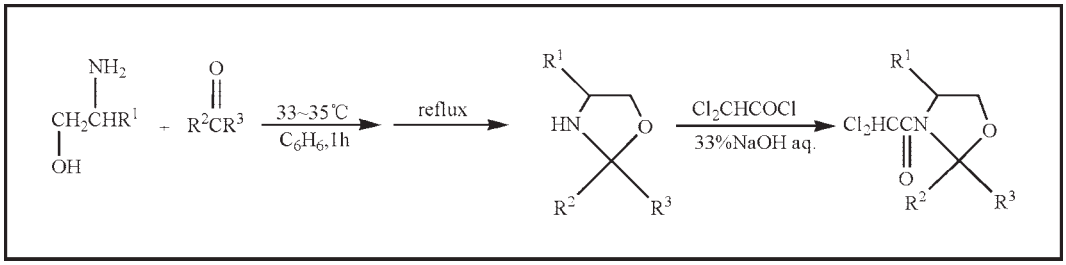


A short and efficient route of synthesis and structural characterization of a series of novel *N*-dichloroacetyl-1,3-oxazolidine derivatives has been developed. These new compounds characterized of the disubstitution at position 2 by alkyl, cycloalkane, and phenyl were synthesized in good yields via a sequential procedure involving condensation and acylation. All the compounds are characterized by IR, $^1$H NMR, $^{13}$C NMR, and element analysis.

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## INTRODUCTION

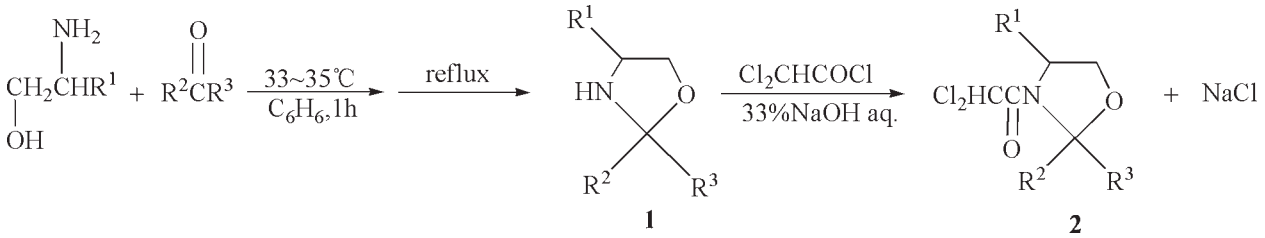
The herbicide safeners are chemicals that increase the tolerance of crop plants to herbicides without affecting the weed control efficacy [1]. Some reports indicate promising results for the development of safeners for postemergence herbicides in many kinds of crops. The discovery of *N*-dichloroacetyl compounds acted as herbicide safener by the mechanism of increasing the activities of glutathione-S-transferase (GST) and some herbicidal target enzyme has drawn widespread attention in agricultural biochemistry [2]. Now many *N*-dichloroacetyl compounds have been commercialized as herbicide safeners, such as benoxacor, dichlormid, furilazole, and so on. *N*-dichloroacetyl oxazolidines are becoming increasingly important for the development of excellent biologically active compounds [3]. According to the theory of structure and activity relationship (SAR), the substituent structure of the oxazolidines will influence the bioactivities. To investigate the relationship between the substituent structure and bioactivity, we designed and synthesized a series of *N*-dichloroacetyl oxazolidines with different substituents on 2 and 4 positions.

Oxazolidines are usually prepared from β-hydroxy amines by a [4+1] ring synthesis [4], and a few examples are reported from the [3+2] cycloaddition of azomethine ylides and carbonyl compounds (mostly benzaldehyde) [5], and in other ways [6]. The acylation of oxazolidines and dichloroacetyl chloride was achieved by using triethylamine as the attaching acid agent and benzene as the reaction medium [7]. Among the commonly used methods, we wished to find a novel and efficient method for the preparation of series of *N*-dichloroacetyl oxazolidine derivatives with different substituents with NaOH aq.acted as the attaching acid agent (Scheme 1). The structure of compounds were listed in Table 1.

## RESULTS AND DISCUSSION

We improved the synthetic route reported in the literatures [6,7] by using different attaching acid agent and reaction temperature without any catalyst. A possible mechanism for the reaction was depicted in Scheme 2. Reaction of an aldehyde or a ketone with β-amino alcohol yielded an open-chain imine, which existed in equilibrium with oxazolidine [8]. As oxazolidine can easily become an imine in the presence of alkaline over 18°C [9], we chose sodium hydroxide solution rather than triethylamine as the attaching acid agent. Triethylamine is soluble in the organic layer and rendered the organic phase where oxazolidine was present as strong alkaline. Under the alkaline condition, oxazolidine quickly became the imine, and hence oxazolidine could not be attained or were hard to be separated. In contrast,

**Scheme 1.** Route for the synthesis N-dichloroacetyl oxazolidines.




sodium hydroxide was insoluble in organic phase, and it not only kept the organic phase weak alkaline, but also reacted quickly with side product HCl. The by-product NaCl could be easily removed from the organic phase. The yields were higher when NaOH aq. acted as attaching acid agent (Table 2).

Another factor controlling the yield was temperature. Under the alkaline condition and with a temperature above 18°C, oxazolidine easily decomposed to imine (Scheme 2). Furthermore, the reaction of oxazolidine with dichloroacetyl chloride was exothermic. Therefore, logically we should employ a low reaction temperature. However, a suboptimal temperature would prolong the time required to add dichloroacetyl chloride and result in superfluous by-products. The reaction temperature was optimized at −5 to 0°C.

We also probed the effect of stirring time on yields. The result showed that the yields were higher when ethanolamine as the reaction agent than that of 2-amino-1-butanol. From the structure of **2h** we found that the ethyl steric hindrance effect hindered the reaction of dichloroacetyl chloride with oxazolidine. Furthermore, the electron donor inductive effect of ethyl (+I) of 2-amine-1-butanol decreased the protonation of amino and hydroxy, which makes it difficult for 2-amine-1-butanol to react with aldehyde or a ketone.

Finally, the single crystal of **2h** was obtained by dissolving it in the solvent of ethyl acetate and light petroleum, followed by slow evaporation. The colorless crystal with a dimension of 0.26 × 0.20 × 0.18 $mm^3$ was selected for X-ray diffraction analysis. The bond lengths and bone angles of the oxazolidine ring were both normal with the average bond length being 1.466 Å (Table 3). The average bond length of cyclopentyl was 1.501 Å, similar to C—C bond length (1.541 Å). The bond lengths of C4—N1 and C4—O1 being close to the typical C—N and C—O bond lengths, respectively (Fig. 1). The C5—O2 bond length of 1.222(3) Å was indicative of a double bond C=O (1.21–1.23 Å). The *p*-π conjunction between N1 and C5—O2 resulted in shorter bond length of C5—N1 [1.336(3) Å] than the typical C—N bond length (1.472 Å; Fig. 1).

In conclusion, we have developed a novel efficient one-pot synthesis of *N*-dichloroacetyl-1,3-oxazolidine derivatives via ring closure and acylation. The advantages of our approach are mild reaction conditions, short reaction time, easy work-up and high yields of products.

## EXPERIMENTAL

**Chemistry.** The infrared (IR) spectra were taken on a KJ-IN-27G infrared spectrophotometer (KBr). The $^1$H NMR spectra and $^{13}$C NMR spectra were recorded on a Bruker AVANVE 300 MHz nuclear magnetic resonance spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. The elemental analysis was performed on FLASH EA1112 elemental analyzer. The melting points were determined on Beijng Taike melting point apparatus (X-4) and uncorrected. All the reagents were of analytical reagents grade.

A total of 0.067 mol ethanolamine (or 2-amino-1-butanol) and 0.067 mol of aldehyde or ketone were mixed with 25 mL of benzene. The reaction mixture was stirred for 1 h at 33–35°C. Then the mixture was heated to reflux and water was stripped off, followed by cooling to 0°C and addition of 7.5 mL of 33% sodium hydroxide solution was added. 7.4 mL (0.08 mol) of dichloroacetyl chloride was added dropwise with stirring and cooling in an ice bath. Then stirring was continued for 2 h. The mixture was rinsed with water until pH = 7. The organic phase was dried over anhydrous magnesium sulfate and the benzene was removed under vacuum. **2d-h** was separated by column chromatography on silica gel. The crude products **2a-c** were recrystallized with ethyl acetate and light petroleum, white crystal was obtained.

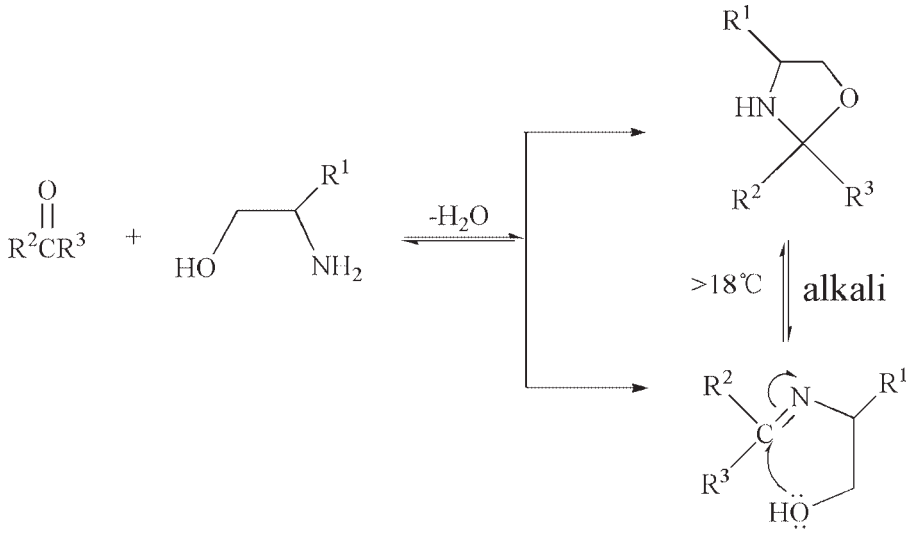
***N-dichloroacetyl-2,2-diethyl-1,3-oxazolidine (2a).*** Yield 68.6%. White crystal, m.p. 55–56°C. Anal. Calcd. for $C_9H_{15}Cl_2NO_2$: C 45.18, H 6.32 N 5.86; found: C 45.16, H 6.42, N 5.84. $^1$H NMR$\delta_H$ ($CDCl_3$) 6.10 (s, 1H, $Cl_2CH$—), 4.09–4.13 (t, $J$ = 6.4 Hz, 2H, C—$CH_2$—O—), 3.85—3.89(t, $J$ = 6.4 Hz, 2H, N—$CH_2$—C), 2.10–2.17 (q, $J$ = 7.2 Hz, 2H,

**Table 1**

Compound structure.

| Compound No. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 2a | H | $CH_2CH_3$ | $CH_2CH_3$ |
| 2b | H | $CH_3$ | $CH_2CH_2CH_3$ |
| 2c | H | $CH_3$ | $CH_2CH(CH_3)_2$ |
| 2d | H | H | $C_6H_5$ |
| 2e | H | $(CH_2)_4$ | |
| 2f | $CH_2CH_3$ | H | H |
| 2g | $CH_2CH_3$ | H | $CH_2CH_2CH_3$ |
| 2h | $CH_2CH_3$ | $(CH_2)_4$ | |

**Scheme 2.** Equilibrium between imine and oxazolidines.




C—$CH_2$—C) 1.88–1.95(q, $J$ = 7.2 Hz, 2H, C—$CH_2$—C) 0.82–0.87(t, $J$ = 7.4 Hz, 6H, 2 × $CH_3$C—) $^{13}$C NMR($CDCl_3$) δ 159.63 101.19 67.06 64.55 46.63 28.04 28.04 7.55 7.55 IR (KBr) ν: 3050–2870 C—H, 1665(C=O), 1410($Cl_2$HC—CO—), 1135 (N—C—O).

***N-dichloroacetyl-2-methyl-2-n-propyl-1,3-oxazolidine (2b).*** Yield 62.4%. White crystal, m.p. 60–62°C. Anal. Calcd. for $C_9H_{15}Cl_2NO_2$: C 45.18, H 6.32 N 5.86; found: C 45.21, H 6.30, N 5.82. $^1$H NMRδ$_H$ ($CDCl_3$) 6.07(s, 1H, $Cl_2$CH—), 4.02–4.12(m, 2H, C—$CH_2$—O—), 3.73–3.90(m, 2H, N—$CH_2$—C), 1.85–2.13 (m, 2H, C—$CH_2$—C) 1.54(s, 3H, $CH_3$C—) 1.22–1.37(m, 2H,C—$CH_2$—C) 0.87–0.92(t, $J$ = 7.4 Hz, 3H, —C—$CH_3$) $^{13}$C NMR($CDCl_3$) δ 159.63 98.23 67.03 63.73 46.15 38.68 22.29 16.61 14.01 IR (KBr) ν: 3000-2850 C—H, 1675(C=O), 1430($Cl_2$HC—CO—),1145 (N—C—O).

***N-dichloroacetyl-2-methyl-2-isobutyl-1,3-oxazolidine (2c).*** Yield 60.5%. White crystal, m.p. 58–59°C. Anal. Calcd. for $C_{10}H_{17}Cl_2NO_2$: C 47.42 H 6.77 N 5.53; found: C 47.42, H 6.66, N 5.62. $^1$H NMRδ$_H$ ($CDCl_3$) 6.06(s, 1H, $Cl_2$CH—), 4.03–4.12(m, 2H, C—$CH_2$—O—), 3.76–3.91(m, 2H, N—$CH_2$—C), 1.88–1.99 (m, 2H, C—$CH_2$—C) 1.67–1.71(m, 1H, C—CH—C) 1.54(s, 3H, $CH_3$C—) 0.93–0.94, (d, $J$ = 6.5 Hz, 3H, —C—$CH_3$) 0.89–0.90, (d, $J$ = 6.5 Hz, 3H, —C—$CH_3$) $^{13}$C NMR($CDCl_3$) δ 159.60 98.62 67.10 63.45 45.83 43.96 24.45 24.13 23.62 22.65 IR (KBr) ν: 3020–2850 C—H, 1660 (C=O), 1420($Cl_2$HC—CO—), 1147 (N—C—O).

***N-dichloroacetyl-2-benzyl-1,3-oxazolidine (2d).*** Yield 58.2%. White crystal, m.p. 101–103°C. Anal. Calcd. for $C_{11}H_{11}Cl_2NO_2$: C 50.79, H 4.26 N 5.38; found: C 50.66 H 4.29, N 5.40. $^1$H NMRδ$_H$ ($CDCl_3$) 7.27–7.46(m, 5H, $C_6H_5$— ), 6.33(s, 1H, $Cl_2$CH—), 6.10(s, 1H, N—CH—O), 4.12–4.26(m, 2H, C—$CH_2$—O—), 3.80–4.10 (m, 2H, N—$CH_2$—C) $^{13}$C NMR($CDCl_3$) δ 160.88, 137.24, 130.41, 129.77, 129.41, 126.53, 90.31, 68.33, 64.63, 45.28 IR (KBr) ν: 3010-2875 C—H, 1675 (C=O), 1425($Cl_2$HC—CO—), 1210 (N—C—O).

***N-Dichloroacetyl-1-oxa-4-aza-spiro-4,4-noncane (2e).*** Yield 52.5%. White crystal, m.p. 85°C–86°C. Anal. Calcd. for $C_9H_{13}Cl_2NO_2$: C 45.56, H 5.53, N 5.91, found: C 45.44 H 5.48 N 5.96. $^1$H NMRδ$_H$ ($CDCl_3$) 6.06(s, 1H, $Cl_2$CH—), 4.00–4.05(t, $J$ = 6.1 Hz, 2H, C—$CH_2$—O—), 3.77–3.81(t, $J$ = 6.1 Hz, 2H, N—$CH_2$—C), 2.30–2.35 (m, 2H, C—$CH_2$—C), 1.88–1.93 (m, 2H, C—$CH_2$—C), 1.66–1.72(m, 4H, C— $(CH_2)_2$—C) $^{13}$C NMR($CDCl_3$) δ 159.65, 105.72, 66.84, 63.83, 45.58 34.80, 34.80, 24.79, 24.79 IR (KBr) ν: 3030–2760 C—H, 1670 (C=O), 1440($Cl_2$HC—CO—), 1141 (N—C—O).

***N-dichloroacetyl-4-ethyl-1,3-oxazolidine (2f).*** Yield 44.4%. Liquid. Anal. Calcd. for $C_7H_{11}Cl_2NO_2$: C 39.64, H 5.23, N 6.60, found: C 39.76 H 5.22 N 6.57. $^1$H NMRδ$_H$ ($CDCl_3$) 5.99 (s, 1H, $Cl_2$CH—), 5.30(s,1H, —N—$CH_2$—O), 5.04 (s,1H, —N—$CH_2$—O), 4.05–4.13 (m, 1H, N—CH—C), 3.80–4.07 (m, 2H, C—$CH_2$—O—), 1.56–1.89 (m, 2H, C—$CH_2$—C) 0.88–1.01 (m,3H, —C—$CH_3$). $^{13}$C NMR($CDCl_3$) δ: 160.50, 79.98, 70.49,

**Table 2**

Comparison of two catalysts for the formation of **2a** and **2f**.

| | Yield (%) | |
|---|---|---|
| Compound no. | $(Et)_3N$ | NaOH aq. |
| 2a | 25.4 | 68.6 |
| 2f | 18.1 | 44.4 |

**Table 3**

Selected bond lengths (Å).

| | | | |
|---|---|---|---|
| C(11)—C(1) | 1.513(5) | C(2)—C(3) | 1.513(4) |
| Cl(1)—C(6) | 1.763(3) | C(2)—C(1) | 1.513(4) |
| Cl(2)—C(6) | 1.770(3) | C(5)—C(6) | 1.525(4) |
| N(1)—C(5) | 1.336(3) | C(4)—C(10) | 1.528(4) |
| N(1)—C(2) | 1.479(3) | C(4)—C(7) | 1.530(5) |
| N(1)—C(4) | 1.489(4) | C(10)—C(9) | 1.522(6) |
| O(2)—C(5) | 1.222(3) | C(7)—C(8) | 1.507(6) |
| O(1)—C(4) | 1.421(3) | C(9)—C(8) | 1.416(6) |
| O(1)—C(3) | 1.429(4) | | |

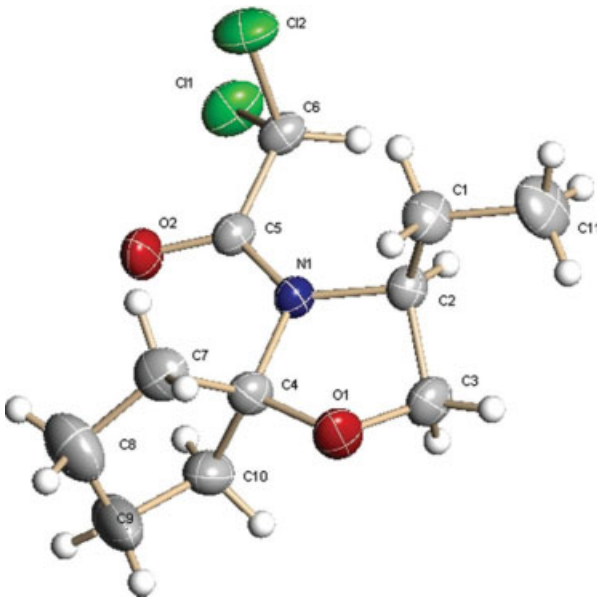



**Figure 1.** Molecular structure for compound **2** h at 30% probability level. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

68.41, 57.58, 24.02, 9.55 IR (KBr) ν: 3095–2878 C—H, 1675 (C=O), 1428($Cl_2HC$—CO), 1145 (N—C—O).

***N-dichloroacetyl-4-ethyl-2-n-propyl-1,3-oxazolidine (2g).*** Yield 40.7%. Liquid. Anal. Calcd. for $C_{10}H_{17}Cl_2NO_2$: C 47.26, H 6.74, N 5.51, found: C 47.34, H 6.63, N 5.47. $^1$H NMR $\delta_H$ ($CDCl_3$) 6.07 (s, 1H, $Cl_2CH$—), 5.17–5.20(m,1H, H—C), 3.89–4.10 (m, 1H, C—CH—N—), 3.81–3.86, (m, 2H, O—$CH_2$—C), 1.44–2.05(m, 6H, C—$CH_2$—C and C—$(CH_2)_2$—C) 0.94–1.01(m, 6H, 2×—C—$CH_3$ $^{13}$C NMR($CDCl_3$) δ 161.56, 91.06, 69.46, 64.97, 60.21, 35.91, 27.06, 18.19, 13.87, 10.77 IR (KBr) ν: 3042–2879 C—H, 1672 (C=O) 1428($Cl_2HC$—CO) 1118(N—C—O).

***N-Dichloroacetyl-3-ethyl-1-oxa-4-aza-spiro-4,4-noncane (2h).*** Yield 46.2%. White crystal, m.p. 74–76°C. Anal. Calcd. for $C_{11}H_{17}Cl_2NO_2$: C 49.64 H 6.44 N 5.26; found: C 49.96, H 6.21, N 5.24. $^1$H NMR$\delta_H$ ($CDCl_3$) 6.08 (s, 1H, $Cl_2CH$—), 3.88–3.89 (m, H, —N—CH—C), 3.78–3.87 (m, 2H, —C—$CH_2$—O—), 2.18–2.47 (m, 2H, C—$CH_2$—C), 1.62–1.91(m, 8H, —$(CH_2)_4$—), 0.94–0.96(t, $J$ =4.5 Hz, 3H, —C—$CH_3$) $^{13}$C NMR($CDCl_3$) δ 160.07, 105.67, 67.06, 65.46, 58.58, 36.34, 33.77, 27.63, 25.10, 24.57, 10.38 IR (KBr) ν: 3010–2950 (C—H) 1660 (C=O) 1435 ($Cl_2HC$—CO—) 1120 (N—C—O).

**Crystal structure determination.**

***Crystal data for compound 2h.*** $C_{11}H_{17}Cl_2NO_2$, monoclinic, space group P2(1)/c, $a$ = 8.9980(15) Å, $b$ = 17.829(3) Å, $c$ = 8.8091(15) Å, α = 90°, β = 109.974(2)°, γ = 90°, $V$ = 1322(4) Å$^3$, $Z$ = 4, $D_c$ = 1.331 g cm$^{-3}$, $V$ = 1328.2(4) Å$^3$, μ = 0.475 mm$^{-1}$, F(000) = 560. Independent reflections were obtained in the range of 2.41° < θ < 28.31°, 3315. The final least-square cycle gave $R_1$ = 0.0603, ω$R_2$ = 0.1231 for 1851 reflections with $I > 2\sigma(I)$. The maximum and minimum differences of peak and hole are 0.322 and −0.277 e/Å$^3$, respectively.

Single-crystal diffraction data was measured on a Brukcr AXSα CCD area-detector diffractometer using graphite monochromated Mo *K*a radiation (λ = 0.071073 nm) at 273(2) K. The structure was solved by direct methods using SHELXS-97 program. All the nonhydrogen atoms were refined an isotropically by the full-matrix least square method on $F^2$ using SHELXS-97 [10]. The atomic scattering factors and anomalous dispersion corrections were taken from the International Table for X-ray Crystallography [11].Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 681329. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: dposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this article.

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## REFERENCES AND NOTES

[1] Hatzios, K. K.; Burgos, N. Weed Sci 2004, 52, 454.

[2] (a) Joanna, D.; John, C. C.; Owen, T. G.; Jones, M. B.; Nicholas, D. P. Pestic Sci 1998, 52, 29; (b) Daniele, D. B.; Luciano, S; Luca, E. Phytochemistry 2007, 68, 2614; (c) Michael, W. P.; Mary, A. S. Plant Physiol 1995, 109, 1483.

[3] (a) Joanna, D.; Caseley, C. J. Pestic Sci 1999, 55, 1043; (b) Aqel, W. A.; Harry, J. D. Chemosphere 2002, 48, 965.

[4] (a) Katarzyna, B.; Dorota, S.; Tadeusz, G. Tetrahedron Lett 2003, 44, 4747; (b) Antonio, G.; Raquel, A.; Jesús Gálvez Tetrahedron Lett 2003, 44, 3809.

[5] (a) Pearson, W. H.; Mi, Y. Tetrahedron Lett 1997, 38, 5441; (b) Alan, R.; Katritzky, D. F.; Ming, Q. Tetrahedron Lett 1998, 39, 6835.

[6] Yli-Kauhaluoma, J. T.; Harwig, C. W.; Wentworth, P., Jr.; Janda, K. D. Tetrahedron Lett 1998, 39, 2269.

[7] (a) Taylor, W. G.; Schreck, C. E. Pestic Sci 1991, 33, 1; (b) Wesley, G. T.; Tse, W. H.; Carl, E. S. Pestic Sci 1996, 46, 307.

[8] Nandkishor, N. K.; Girdharilal, B. T.; Sumit, V. G. Synlett 2007, 12, 1921

[9] Manas, K. G.; Koena, G. Tetrahedron Lett 2007, 48, 3191.

[10] Sheldrick, G. M. SHELXTL97, Program for a Crystal Structure Solution; University of University of Göttingen, Germany, 1997.

[11] Wilson, A. J. International Table for X-ray Crystallography; Kluwer Academic Publisher: Dordrecht, 1992; Vol. C. Tables 6.1.1.4 (p 500) and 4.2.6.8 (p 219).

# One-Pot Three-Component Synthesis of Tetrasubstituted N—H Pyrroles from Secondary Propargylic Alcohols, 1,3-Dicarbonyl Compounds and *tert*-Butyl Carbamate



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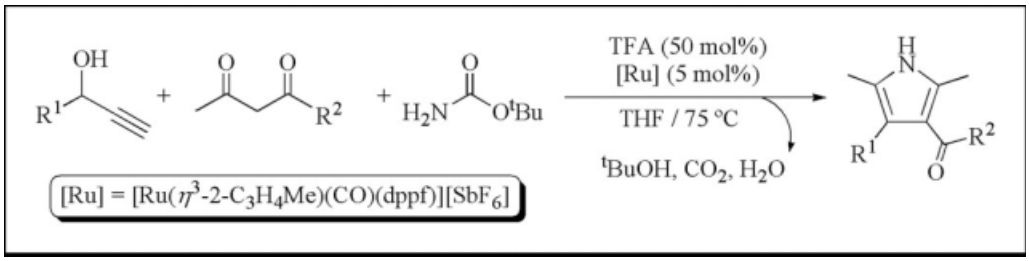


Several tetrasubstituted N—H pyrroles, functionalized with ester or ketone groups at C-3 position, were prepared by one-pot coupling of secondary propargylic alcohols with 1,3-dicarbonyl compounds and *tert*-butyl carbamate, *via in situ* deprotection of the corresponding pentasubstituted N-Boc pyrroles. The three-component coupling process was promoted by the combined use of the 16-electron ruthenium(II) catalyst [Ru($\eta^3$-2-$C_3H_4$Me)(CO)(dppf)][$SbF_6$] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and trifluoroacetic acid (TFA).

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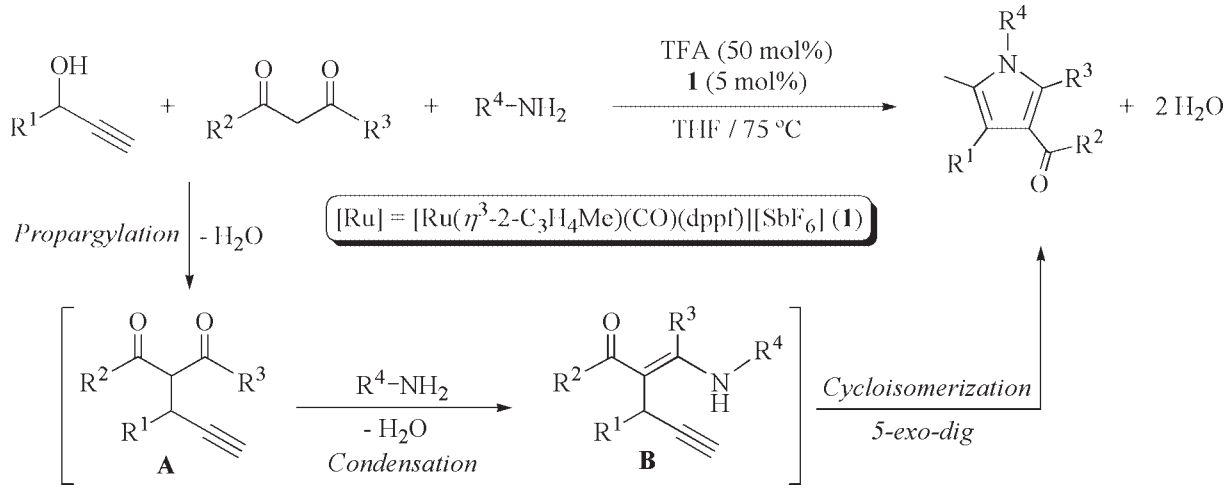
## INTRODUCTION

Pyrroles are one of the most prominent heterocyclic compounds, being present as key structural motifs in several natural products (for reviews, see [1]), conducting organic materials (for reviews, see [2]), and bioactive molecules (for reviews, see [3]). Consequently, a large number of general methods have been developed to construct these five-membered heterocycles, including the well-known Knorr, Paal-Knorr, and Hantzch syntheses, 1,3-dipolar cycloaddition reactions, reductive couplings, and aza-Wittig reactions (see, for example, [4]). However, it is still challenging to prepare polysubstituted pyrroles directly from inexpensive and readily available starting materials. In this sense, important efforts have been made during the last years in the design of multicomponent strategies (for reviews and highlights on pyrrole syntheses through multicomponent reactions, see [5] and for recent examples of multicomponent syntheses of pyrroles, see [6]). Multicomponent reactions (MCR), in which multiple reactants are combined into a single product, offer significant advantages over classical linear syntheses since molecular diversity can be reached from simple precursors in an efficient, economic, and environmentally friendly manner (see, for example, [7]).

In this context, we have recently described an efficient one-pot three-component coupling reaction for the synthesis of fully substituted pyrroles from secondary propargylic alcohols, 1,3-dicarbonyl compounds (β-diketones or β-keto esters), and primary amines (Scheme 1) [8]. The process, which is catalyzed by the 16-electron allyl-ruthenium(II) complex [Ru($\eta^3$-2-$C_3H_4$Me)(CO)(dppf)][$SbF_6$] (**1**; dppf = 1,1′-bis(diphenylphosphino)ferrocene) and trifluoroacetic acid (TFA), involves the initial propargylation of the 1,3-dicarbonyl compound promoted by TFA, subsequent condensation between the resulting γ-keto alkyne **A** and the primary amine to afford a β-enamino ester or ketone **B**, which undergoes a ruthenium-catalyzed 5-*exo-dig* annulation to give the final pyrrole (indium(III) chloride is also able to promote efficiently these propargylation/condensation/cycloisomerization tandem reactions [9]; we note that involvement of propargylic alcohols in multicomponent syntheses of pyrroles is scarcely documented [10]).

Following this route, which allows the direct introduction of carbonyl functionalities onto the pyrrolic skeleton and tolerates the presence of a wide variety of functional groups in the starting materials, a large number of pentasubstituted pyrroles could be synthesized in good to excellent yields [8]. As an extension of these studies, herein, we report on the applicability of this one-pot

**Scheme 1**




three-component reaction for the synthesis of tetrasubstituted N—H pyrroles.

## RESULTS AND DISCUSSION

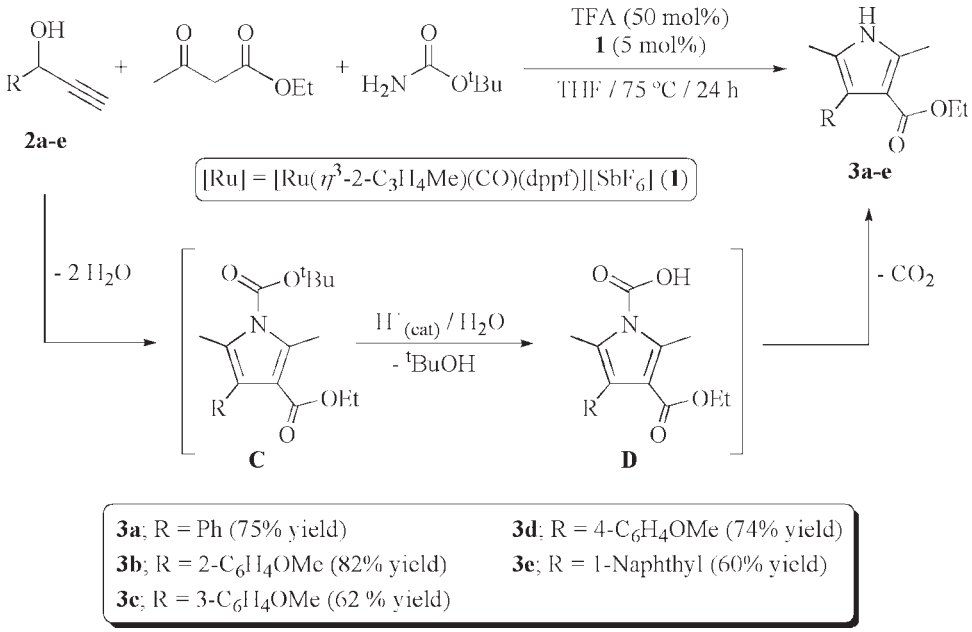
In our first report, we already attempted the preparation of N—H pyrroles by coupling secondary propargylic alcohols with 1,3-dicarbonyl compounds in the presence of simple ammonia sources such as $NH_4OH$ or $NH_4Cl$. Unfortunately, the desired products were not formed using these inexpensive reagents, the reactions leading instead to the major formation of tetrasubtituted furans as the result of the known 5-*exo-dig* annulation of γ-keto alkyne intermediates **A** [11]. Only the use of propargylamine allowed us the preparation of this type of molecules (one example), *via* TFA-promoted scission of the C—N bond on the initially formed pentasubstituted *N*-propargyl pyrrole [8]. However, an extremely long reaction time (4 days) was required reducing considerably the synthetic interest of the process. This fact prompted us to search for a more appropriate NH source compatible with the propargylation/condensation/cycloisomerization sequence outlined in Scheme 1. Thus, our attention turned firstly to ammonium carbamate since it was successfully employed by Zhan and coworkers in related reactions using $InCl_3$ as promoter [9]. However, the reactions, which were performed in the presence of variable amounts of this reagent (1–10 equiv.), led again to the major formation of furans with only traces of the desired NH pyrroles being detected by GC/MS in the crude reaction mixtures. Neither the use of primary silylamines, such as $NH_2SiPh_3$, gave to the desired results. Finally, we were pleased to find that commercially available *tert*-butyl carbamate is compatible with our one-pot three-component reaction. Thus, as shown in Scheme 2, treatment of THF solutions of propargylic alcohols **2a–e** with ethyl acetoacetate and *tert*-butyl carbamate (1:1:1 molar ratio) in the presence of 50 mol % of TFA and 5 mol % of complex **1** led, after 24 h of heating (75°C), to the selective formation of pyrroles **3a–e**, which were isolated in 60–82% yield after appropriate chromatographic workup.

Characterization of **3a–e** was straightforward by following their analytical and spectroscopic data. In particular, the presence of the N—H unit was unambiguously confirmed by the appearance of: (i) an intense absorption band at about 3300 $cm^{-1}$ in their IR spectra, and (ii) a singlet signal at about 8 ppm in their $^1$H-NMR spectra. Pyrroles **3a–e** result from the TFA-mediated hydrolysis of the *tert*-butyl ester (Boc) group in the initially formed pentasubstituted pyrroles **C** (detected monitoring the reactions by GC/MS) and subsequent decarboxylation of the resulting intermediates **D** (The Boc group is a versatile and commonly used protecting group for the pyrrole nitrogen atom, being easily removable in acidic media. See, for example, [12]).

Following the same approach, NH-pyrroles **4a–d** and **5a–b** (Fig. 1) could also be synthesized in 64–79% yield employing methyl acetoacetate and 2,4-pentanedione as the 1,3-dicarbonyl compound, respectively, thus confirming the generality of this transformation.

In summary, an efficient MCR reaction for the preparation of tetrasubstituted N—H pyrroles, functionalized with carbonyl groups at C-3 position, has been developed using the catalytic system [Ru(η$^3$-2-$C_3H_4$Me)(CO)(dppf)][$SbF_6$]/TFA. The results reported herein represent a new example of the utility of the allyl-ruthenium(II) complex **1** in synthetic organic chemistry (for an account on the applications of complex **1** in synthesis, see [13]).

**Scheme 2**




**3a**; R = Ph (75% yield)
**3b**; R = 2-$C_6H_4OMe$ (82% yield)
**3c**; R = 3-$C_6H_4OMe$ (62 % yield)
**3d**; R = 4-$C_6H_4OMe$ (74% yield)
**3e**; R = 1-Naphthyl (60% yield)

## EXPERIMENTAL

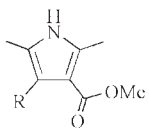
Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were recorded on a Bruker DPX-300 instrument at 300 MHz ($^1$H) or 75 MHz ($^{13}$C). The chemical shift values (δ) are given in parts per million and are referred to the residual peak of the deuterated solvent used ($CDCl_3$). DEPT experiments have been carried out for all the compounds reported. GC/MS measurements were performed on a Agilent 6890N equipment coupled to a 5973 mass detector (70 eV electron impact ionization) using a HP-1MS column. Elemental analyses were acquired with a Perkin-Elmer 2400 microanalyzer. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). All reagents were obtained from commercial suppliers and used without any further purification, with the exception of complex **1** [14] and propargylic alcohols **2b–e** [15] which were prepared by following the methods reported in the literature.

**General procedure for the catalytic reactions.** The appropriate propargylic alcohol **2a–e** (1 mmol), 1,3-dicarbonyl compound (1 mmol), and *tert*-butyl carbamate (1 mmol) were introduced into a sealed tube under a nitrogen atmosphere. THF (0.5 mL), complex **1** (0.049 g, 0.05 mmol), and TFA (37 μL, 0.5 mmol) were then added at room temperature, and the resulting solution was heated at 75°C for 24 h. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using an ethyl acetate/hexane mixture (1:10 v/v) as eluent. $^1$H and $^{13}$C{$^1$H} NMR spectra, as well as melting points, obtained for compounds **3a** [9], **3b** [16], **3d** [8], **3e** [9], **4a** [16], **4c** [16], **5a** [17], and **5b** [18] were in complete accord with those described in the literature. Characterization data for the novel pyrroles **3c** and **4b**,**d** are as follows:

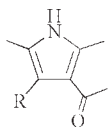
***4-(3-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester (3c)*** Orange solid; Yield: 0.169 g (62%); mp: 144°C; IR (Nujol): 3311 (N—H), 1683 (C=O) cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ 1.08 (t, $J$ = 7.1 Hz, 3H), 2.10, 2.49, and 3.80 (s, 3H each), 4.09 (q, $J$ = 7.1 Hz, 2H), 6.78–6.86 (m, 3H), 7.24 (m, 1H), 8.21 (s, 1H) ppm; $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): δ 11.1, 13.5, 14.0, 55.1, 59.0, 110.5, 111.3, 116.0, 122.1, 123.0, 123.5, 128.1, 133.5, 137.6, 158.7, 165.7 ppm; GC-MS (EI, 70 eV): *m*/*z* 273 (100%, M$^+$), 244 (60), 227 (55), 198 (18), 184 (25), 168 (20), 156 (15), 115 (15); Anal. Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.44; H, 7.19; N, 5.06.

***4-(2-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid methyl ester (4b)*** Orange solid; Yield: 0.205 g (79%); mp: 138°C; IR (Nujol): 3314 (N—H), 1683 (C=O) cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.05, 2.47, 3.59, and 3.75 (s, 3H each), 6.90–6.99 (m, 2H), 7.15 (dd, $J$ = 7.4 and 1.7 Hz, 1H), 7.26 (td, $J$ = 8.0 and 1.7 Hz, 1H), 8.31 (s, 1H) ppm; $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): δ 11.1, 13.4, 50.3, 55.3, 110.3, 111.1, 117.7, 119.9, 123.8, 125.2, 127.6, 131.5, 133.6, 157.4, 166.4 ppm; GC-MS (EI, 70 eV): *m*/*z* 259 (85%, M$^+$), 228 (15), 212 (100), 200 (50), 184 (60), 168 (18), 154 (15), 128 (35), 115 (45), 15 (90); Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.55; H, 6.74; N, 5.52.

***4-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid methyl ester (4d)*** Orange solid; Yield: 0.199 g (77%);



**4a**; R = Ph (68% yield)
**4b**; R = 2-$C_6H_4OMe$ (79% yield)
**4c**; R = 3-$C_6H_4OMe$ (64 % yield)
**4d**; R = 4-$C_6H_4OMe$ (77% yield)



**5a**; R = Ph (70% yield)
**5b**; R = 2-$C_6H_4OMe$ (73% yield)

**Figure 1.** Structures of the NH-pyrroles **4a–d** and **5a–b**.

mp: 140°C; IR (Nujol): 3295 (N—H), 1687 (C=O) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.08, 2.48, 3.64, and 3.82 (s, 3H each), 6.89 and 7.18 (d, $J$ = 8.6 Hz, 2H each), 8.15 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 11.1, 13.7, 50.3, 55.1, 110.1, 112.8, 122.0, 123.4, 128.4, 131.2, 133.9, 157.7, 166.3 ppm; GC-MS (EI, 70 eV): $m/z$ 259 (100%, $M^+$), 244 (20), 228 (20), 198 (18), 184 (23), 168 (24), 156 (30), 115 (40), 42 (60), 15 (80); Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.31; H, 6.78; N, 5.59.

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## REFERENCES AND NOTES

[1] (a) Bellina, F.; Rossi, R. Tetrahedron 2006, 62, 7213; (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. Nat Prod Rep 2006, 23, 517; (c) Fürstner, A. Angew Chem Int Ed 2003, 42, 3582; (d) Hoffmann, H.; Lindel, T. Synthesis 2003, 1753.

[2] (a) Guernion, N. J. L.; Hayes, W. Curr Org Chem 2004, 8, 637; (b) Mac Diarmid, A. G. Synth Met 1997, 84, 27; (c) Deronzier, A.; Moutet, J.-C. Curr Top Electrochem 1994, 3, 159; (d) Curran, D.; Grimshaw, J.; Perera, S. D. Chem Soc Rev 1991, 20, 391.

[3] (a) Huffman, J. W.; Padgett, L. W. Curr Med Chem 2005, 12, 1395; (b) Kidway, M.; Venkataramanan, R.; Mohan, R.; Sapra, P. Curr Med Chem 2002, 9, 1209; (c) Huffman, J. W. Curr Med Chem 1999, 6, 705; (d) Cozzi, P.; Mongelli, N. Curr Pharm Des 1998, 4, 181.

[4] (a) Jones, R. A., Ed. Pyrroles Part II: The Synthesis Reactivity and Physical Properties of Substituted Pyrroles; Wiley: New York, 1992; (b) Black, D. St. C. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; pp 39–117; (c) Sundberg, R. J. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; pp 119–206.

[5] (a) Balme, G. Angew Chem Int Ed 2004, 43, 6238; (b) Patil, N. T.; Yamamoto, Y. ARKIVOC 2007, (x), 121; (c) D'souza, D. M.; Müller, T. J. J. Chem Soc Rev 2007, 36, 1095; (d) Balme. G.; Bouyssi, D.; Monteiro, N. Heterocycles 2007, 73, 87; (e) Cadierno, V.; Crochet, P. Curr Org Synth 2008, 5, 343.

[6] (a) Merkul, E.; Boersch, C.; Frank, T. J. J. Org Lett 2009, 11, 2269; (b) Chen, X.; Hou, L.; Li, X. Synlett 2009, 828; (c) Fontaine, P.; Masson, G.; Zhu, J. Org Lett 2009, 11, 1555; (d) Alizadeh, A.; Babaki, M.; Zohreh, N. Tetrahedron 2009, 65, 1704; (e) Alizadeh, A.; Rezvanian, A.; Bijanzadeh, H. R. Synthesis 2008, 725; (f) Yavari, I.; Kowsari, E. Synlett 2008, 897; (g) Kassaee, M. Z.; Masrouri, H.; Movahedi, F.; Partovi, T. Helv Chim Acta 2008, 91, 227.

[7] (a) Zhu, J.; Bienaymé, H., Eds. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005; (b) Tejedor, D.; García-Tellado, F. Chem Soc Rev 2007, 36, 484 and references cited therein.

[8] Cadierno V.; Gimeno, J.; Nebra, N. Chem Eur J 2007, 13, 9973.

[9] Liu, X.-T.; Huang, L.; Zheng, F.-J.; Zhan, Z.-P. Adv Synth Catal 2008, 350, 2778.

[10] (a) Braun, R. U.; Zeitler, K.; Müller, T. J. J. Org Lett 2001, 3, 3297; (b) Braun, R. U.; Müller, T. J. J. Synthesis 2004, 2391; (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. Angew Chem Int Ed 2003, 42, 2681.

[11] Cadierno, V.; Gimeno, J.; Nebra, N. Adv Synth Catal 2007, 349, 382.

[12] (a) Kocienski, P. J. Protecting Groups; Thieme Verlag: Stuttgart, 2003; (b) Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis; Wiley-Interscience: New York, 1999.

[13] Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. Inorg Chim Acta, to appear (doi:10.1016/j.ica.2009.05.010).

[14] Cadierno, V.; Díez, J.; García-Garrido, S. E.; Gimeno, J. Chem Commun 2004, 2716.

[15] Midland, M. M. J Org Chem 1975, 40, 2250.

[16] Boberg, F.; Garburg, K. H.; Goerlich, K. J.; Pipereit, E.; Ruhr, M. Liebigs Ann Chem 1985, 239.

[17] Alberola, A.; Ortega, A. G.; Sádaba, M. L.; Sañudo, C. Tetrahedron 1999, 55, 6555.

[18] Boberg, F.; Garburg, K. H.; Goerlich, K. J.; Pipereit, E.; Redelfs, E.; Ruhr, M. J Heterocycl Chem 1986, 23, 1853.

# An Efficient One-Pot Synthesis of Some New 2,4-Diaryl Pyrido[3,2-c]coumarins as Potent Antimicrobial Agents



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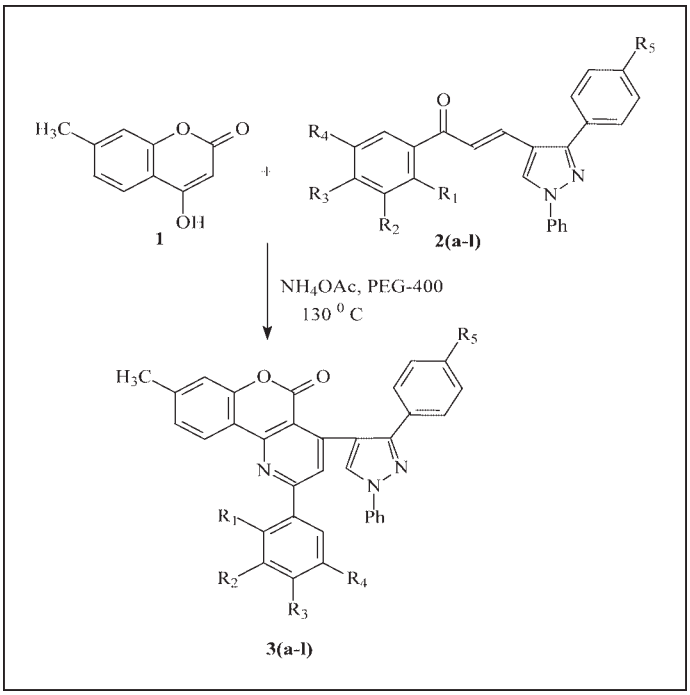


Poly(ethylene glycol) (PEG-400) has been used as sustainable, nonvolatile, and environmental friendly reaction solvent for the synthesis of title compounds. Various diaryl pyrido[3,2-c]coumarins have been synthesized in one step by reacting 4-hydroxy-7-methyl-coumarin with α,β-unsaturated ketones in the presence of ammonium acetate. Further, *in vitro* antimicrobial (antibacterial and antifungal) activities of the compounds were screened against different pathogens. The results revealed that most of them showed potent activity.

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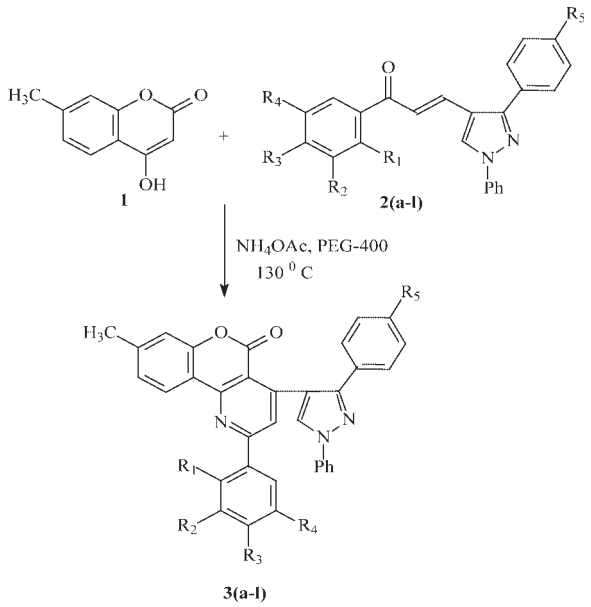
## INTRODUCTION

Coumarins are well-known natural products and may exhibit high level of biological activity [1]. Coumarins are also used as food additives, in cosmetics [2], as optical brightening agents [3], dispersed fluorescent and laser dyes [4]. For instance, coumarin nucleus is present in promising drug candidates as nonpeptidic HIV protease inhibitors [5], topoisomerase II [6], and tyrosine kinase [7] inhibitors. Coumarins fused with pyridines have also been reported to posses antiallergic [8], anticoagulant [9], antidiabetic [10], and analgesic [11] properties, being characterized by a phenanthrene like structure as found in tetrahydrocannabinol. Pyrido[3,2-c]coumarin, the back bone of naturally occurring alkaloid, santiagonamine [12] isolated from Berberis Dawinii (Barberidaca). This alkaloid has interesting wound healing properties [13]. Owing to such interesting properties, synthesis of pyrido-coumarins has remained an active subject of interest. However, a survey of these literatures quotes reveals that the most of the methods are multistep or difficult starting materials. Hence, it

**Scheme 1**




was thought worthwhile to envisage a synthesis of pyrido-fused coumarins.

## RESULTS AND DISCUSSION

In view of the current emphasis on green chemistry [14], our approach is to reduce the use of solvents that are volatile organic compounds (VOCs), which are potentially toxic and hazardous [15]. Recently, liquid polymers or low-melting polymers have emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, nonvolatility, immiscibility with a number of organic solvents, and recyclability. Poly(ethylene glycols) (PEGs) are preferred over other polymers because they are inexpensive, completely nonhalogenated, easily degradable, and of low toxicity [16]. Many organic reactions have been carried out using PEGs as solvent or cosolvent such as Heck reaction [17], asymmetric dihydroxylation [18], Suzuki crosscoupling reaction [19], oxydehydrogenation of alcohols and cyclic dienes, oxidation of sulfides and the Wacker reaction [20], and partial reduction reaction of alkynes [21]. The use of PEG as a recyclable solvent system for the metal mediated radical polymerization of methyl methacrylate and styrene has also been reported [22].

As quoted by Kroehnke [23], reaction of α,β-unsaturated ketones with the active methylene function of phenacyl bromide pyridinium salt of ammonium acetate and acetic acid yields pyridine. This methodology has been successfully utilized by us for the synthesis of variety of pyridyl substituted coumarins. In this article, here, we wish to report the expeditious synthesis of novel pyrido-fused coumarin derivatives (**3a–l**) under benign reaction solvent.

The starting 4-hydroxy-7-methyl-coumarin (**1**) was prepared by the literature procedure using an appropriately *m*-cresol and malonic acid, a Lewis acid ($ZnCl_2$) and as condensing agent phosphorous oxychloride ($POCl_3$), whereas the α,β-unsaturated carbonyl compounds (**2a–l**) were already reported [24]. Thus, various 2,4-diaryl pyrido[3,2-c]coumarins **3**(**a–l**) have been synthesized by reacting 4-hydroxy-7-methyl-coumarin **1** with α,β-unsaturated ketones **2**(**a–l**) in the presence of ammonium acetate in PEG-400 (Scheme 1).

**Mechanism of pyrido-coumarin formation.** The formation of products **3**(**a–l**) involves the Kroehnke's mechanism. Mannich bases provide the required α,β-unsaturated ketones *in situ* during the course of reaction, to which the Micheal addition of coumarioyl methyl pyridinium salts takes place resulting in a 1,5-dionyl pyridinium (not isolated) derivative, which subsequently cyclization in the presence of ammonium acetate afford the 2,4-diaryl pyrido[3,2-c]coumarins (Scheme 2). The

**Scheme 2**

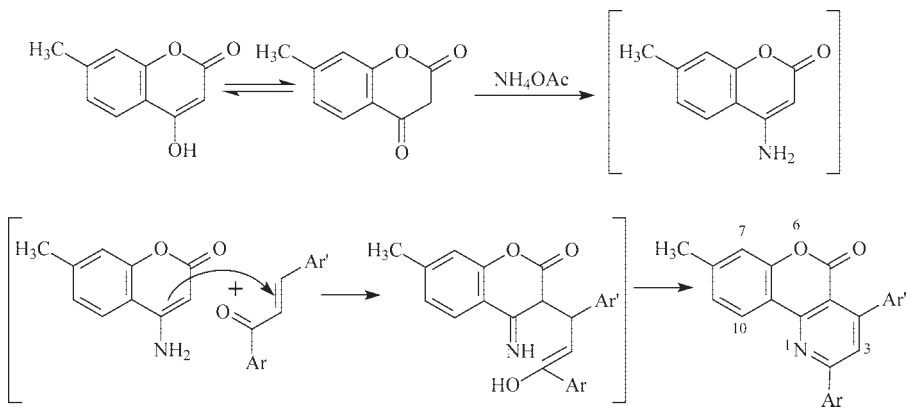


**Table 1**

Physical and analytical data of 2,4-diaryl-pyrido[3,2-c]coumarins.

| Product | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Time[a] | Yield (%)[b] | MP (°C) |
|---|---|---|---|---|---|---|---|---|
| **3a** | H | H | Cl | H | Cl | 2 | 85 | 240 |
| **3b** | OH | H | H | Cl | Cl | 3 | 89 | 266 |
| **3c** | OH | Br | H | Cl | Cl | 2 | 83 | 258 |
| **3d** | OH | I | H | Cl | Cl | 2 | 85 | 230 |
| **3e** | OH | H | OH | H | Cl | 3 | 82 | 172 |
| **3f** | OH | H | Me | Cl | Cl | 3 | 86 | 260 |
| **3g** | OH | Cl | OH | Cl | Cl | 2 | 81 | 243 |
| **3h** | OH | I | Me | Cl | Cl | 3 | 85 | 251 |
| **3i** | OH | H | H | Cl | OH | 2 | 86 | 265 |
| **3j** | OH | Br | H | Cl | OH | 2 | 85 | 170 |
| **3k** | OH | I | H | Cl | OH | 3 | 81 | 255 |
| **3l** | OH | I | H | Me | OH | 3 | 85 | 225 |

[a] Time in hours.
[b] Pure isolated yields of products.

presence of IR absorption bands in the region 1660–1690 $cm^{-1}$ clearly indicates that >C=O group of chalcone has been transformed into coumarin (lactone). $^1H$ NMR revealed that singlet of methyl proton at δ 2.30–2.50 ppm. The multiplet at δ 7.00–8.20 is due to aromatic protons. A singlet of phenolic proton appeared at δ 11.00–12.50 ppm ($D_2O$ exchangeable).

In summary, we have demonstrated an efficient, one-pot method toward the expeditious synthesis of 2,4-diaryl pyrido[3,2-c]coumarins using PEG-400 as an alternative reaction solvent. The advantages of the present protocol are the simplicity of operation, the high yields of products, the recyclability of PEG-400 and preclusion of the usage of volatile organic solvents. Antimicrobial and antifungal activities of the all synthesized compounds were summarized in Table 2. The compounds **3b**, **3d**, **3e**, **3f, 3h**, **3j**, and **3l** showed good antibacterial activity against one or more bacteria. Compounds **3a**, **3c**, **3d**, **3i**, and **3k** were found to be active against *Escherichia coli*. On the other hand, the compounds **3i**, **3k** was found to be active against *Salmonella typhi*. The compounds **3i**, **3j**, and **3k** were also found to be active against *Bacillus subtilis*. Most of the compounds showed inhibitory effect against fungi. The compounds **3a**, **3c**, **3d**, **3g**, **3j**, and **3l** showed most potent activity against all pathogens than other tested compounds. The substitution of hydroxyl group in position 2 and presence of halo groups in 3 and 5 positions of aryl nucleus, which may enhance the antimicrobial activity of the products against various pathogens.

## EXPERIMENTAL

Melting points were determined by open capillary method and were uncorrected. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. $^1H$ NMR spectra were recorded (in DMSO-$d_6$) on Avance-300 MHz spectrometer using TMS as an internal standard. The mass were recorded on EI-Shimazdu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

### Chemistry

***General procedure for the synthesis of α,β-unsaturated carbonyl compounds (2a–l)[24].*** A mixture of substituted 2-hydroxy acetophenone (5 mmol), 1-phenyl-3-(4-sustituted phenyl) pyrazol-4-carboxaldehyde (5 mmol), KOH (1 mmol), and PEG-400 (20 mL) was stirred at 40°C for 1 h. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice cold water (100 mL). Separated product was filtered out. The PEG-400 was recovered from water and utilized to synthesize further chalcones.

***Typical procedure for the synthesis of 2,4-diaryl pyrido[3,2-c]coumarins (3a–l).*** To a well-stirred solution of 4-hydroxy-7-methyl-coumarin **1** (0.528 g; 6 mmol) in PEG-400 (20 mL) was added ammonium acetate (6.0 g) followed by chalcone **2a** (2.514 g; 6 mmol) in PEG-400 (10 mL). The reaction mixture was stirred at room temperature for 30 min and then refluxed gently on oil-bath at 130°C for the period as shown in Table 1. After completion of the reaction (checked by TLC), the reaction mixture was allowed to reach room temperature and was poured into ice cold water (100 mL). The resultant solid was filtered, washed with 2 × 5 mL ice cold water and recrystallized by chloroform to give pure product **3a**.

To check the reusability of the solvent, the filtrate was evaporated to remove water leaving PEG behind in the container and subjected for second run by charging the same substrates. The results of the first and second experiments were almost consistent in yield.

***3-(4-Chloro-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3a).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 1668, 1598 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.35 (s, 3H, $CH_3$), 7.10–8.15 (m, 17H, Ar—H), 8.90 (s, 1H, -5H of pyrazole) ppm; MS (m/z): 574 [$M^+$], 576 [M + 2], 578 [M + 4]; *Anal.* Found for $C_{34}H_{21}O_2N_3Cl_2$: C, 71.02; H, 3.61; N, 7.34 requires: C, 71.19; H, 3.78; N, 7.21%.

***3-(5-Chloro-2-hydroxy-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3b).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3413, 1671, 1605 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.33 (s, 3H, $CH_3$), 7.16–8.24 (m, 16H, Ar—H),

**Table 2**

Antimicrobial activities of synthesized products (**3a–l**).

| | Bacteria[a] | | | | Fungi germination | | | |
|---|---|---|---|---|---|---|---|---|
| Product | *Ec* | *St* | *Sa* | *Bs* | *An* | *Af* | *Pc* | *Fm* |
| **3a** | 21 | 19 | 16 | 19 | RD | RD | −ve | −ve |
| **3b** | 12 | 10 | 08 | 10 | −ve | −ve | RD | RD |
| **3c** | 19 | 22 | 21 | 20 | −ve | −ve | −ve | −ve |
| **3d** | 18 | 14 | 16 | 08 | RD | RD | +ve | +ve |
| **3e** | 19 | 12 | 10 | 14 | RD | −ve | RD | RD |
| **3f** | 08 | 10 | 07 | 14 | +ve | +ve | +ve | +ve |
| **3g** | 22 | 20 | 18 | 22 | −ve | −ve | RD | −ve |
| **3h** | 09 | 12 | 15 | 12 | +ve | +ve | +ve | +ve |
| **3i** | 21 | 20 | 19 | 18 | −ve | −ve | −ve | −ve |
| **3j** | 19 | 12 | 18 | 16 | RD | RD | −ve | RD |
| **3k** | 20 | 16 | 19 | 22 | −ve | −ve | −ve | −ve |
| **3l** | 18 | 12 | 15 | 18 | RD | −ve | −ve | RD |
| Control | – | – | – | – | +ve | +ve | +ve | +ve |
| *Penicillin* | 22 | 22 | 24 | 24 | NA | NA | NA | NA |
| *Nystatin* | NA | NA | NA | NA | −ve | −ve | −ve | −ve |

*Ec*, Escherichia coli; *St*, Salminella typhi; *Sa*, Staphylococcus aureus; *Bs*, Bacillus subtilis; *An*, Aspergillus niger; *Af*, Aspergillus flavus; *Fm*, Fusarium moniliforme, *Pc*, Penicillium chrysogenum. +ve, Growth; −ve, No growth; RD, reduced growth, NA, not applicable.
[a] Zone of inhibition in millimeters.

8.89 (s, 1H, -5H of pyrazole), 11.26 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 590 [$M^+$], 592 [M + 2], 594 [M + 4]; *Anal*. Found for $C_{34}H_{21}O_3N_3Cl_2$: C, 69.16; H, 3.51; N, 7.08 requires: C, 69.21; H, 3.68; N, 7.22%.

***3-(3-Bromo-5-chloro-2-hydroxy-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3c).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3433, 1679, 1606 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.38 (s, 3H, $CH_3$), 7.18–8.25 (m, 15H, Ar—H), 8.90 (s, 1H, -5H of pyrazole), 11.64 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 669 [$M^+$], 671 [M + 2], 673 [M + 4], 675 [M + 6]; *Anal*. Found for $C_{34}H_{20}O_3N_3Cl_2Br$: C, 61.06; H, 3.05; N, 6.21 requires: C, 60.88; H, 3.19; N, 6.34%.

***3-(5-Chloro-2-hydroxy-3-iodo-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3d)*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3421, 1681, 1604 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.43 (s, 3H, $CH_3$), 7.15–8.25 (m, 15H, Ar—H), 8.91 (s, 1H, -5H of pyrazole), 11.68 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 716 [$M^+$], 718 [M + 2], 720 [M + 4]; *Anal*. Found for $C_{34}H_{20}O_3N_3Cl_2I$: C, 57.04; H, 2.81; N, 5.85 requires: C, 57.18; H, 2.72; N, 5.97%.

***3-(2,4-Dihydroxy-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3e).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3398, 3152, 1676, 1602 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.38 (s, 3H, $CH_3$), 5.68 (s, 1H, OH), 7.16–8.22 (m, 16H, Ar—H), 8.90 (s, 1H, -5H of pyrazole), 12.22 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 572 [$M^+$], 574 [M + 2]; *Anal*. Found for $C_{34}H_{22}O_4N_3Cl$: C, 71.36; H, 3.81; N, 7.31 requires: C, 71.49; H, 3.95; N, 7.38%.

***3-(5-Chloro-2-hydroxy-4-methyl-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3f).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3410, 1670, 1602 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.24 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 7.14–8.21 (m, 15H, Ar—H), 8.91 (s, 1H, -5H of pyrazole), 11.31 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 604 [$M^+$], 606 [M + 2], 608 [M + 4]; *Anal*. Found for $C_{35}H_{23}O_3N_3Cl_2$: C, 69.51; H, 3.86; N, 6.91 requires: C, 69.64; H, 3.97; N, 6.85%.

***3-(3,5-Dichloro-2,4-dihydroxy-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3g).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3412, 3168, 1681, 1606 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.38 (s, 3H, $CH_3$), 6.26 (s, 1H, OH), 7.15–8.25 (m, 14H, Ar—H), 8.90 (s, 1H, -5H of pyrazole), 12.28 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 641 [$M^+$], 643 [M + 2], 645 [M + 4], 647 [M + 6]; *Anal*. Found for $C_{34}H_{20}O_4N_3Cl_3$: C, 63.76; H, 3.11; N, 6.58 requires: C, 63.62; H, 3.25; N, 6.65%.

***3-(5-Chloro-2-hydroxy-3-iodo-4-methyl-phenyl)-1-[3-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3h).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3433, 1682, 1605 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), 2.52 (s, 3H, $CH_3$), 7.18–8.26 (m, 14H, Ar—H), 8.90 (s, 1H, -5H of pyrazole), 12.06 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 730 [$M^+$], 732 [M + 2], 734 [M + 4]; *Anal*. Found for $C_{35}H_{22}O_3N_3Cl_2I$: C, 57.61; H, 3.01; N, 5.78 requires: C, 57.56; H, 3.04; N, 5.75%.

***3-(5-Chloro-2-hydroxy-phenyl)-1-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3i).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3398, 3169, 1666, 1599 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.38 (s, 3H, $CH_3$), 7.14–8.18 (m, 16H, Ar—H), 8.86 (s, 1H, -5H of pyrazole), 10.48 (s, 1H, OH), 11.78 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 572 [$M^+$], 574 [M + 2]; *Anal*. Found for $C_{34}H_{22}O_4N_3Cl$: C, 71.36; H, 3.91; N, 7.31 requires: C, 71.51; H, 3.78; N, 7.39%.

***3-(3-Bromo-5-chloro-2-hydroxy-phenyl)-1-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3j).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3405, 3188, 1672, 1602 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), 7.16–8.22 (m, 15H, Ar—H), 8.71 (s, 1H, -5H of pyrazole), 10.61 (s, 1H, OH), 12.23 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 650 [$M^+$], 652 [M + 2], 654 [M + 4]; *Anal*. Found for $C_{34}H_{21}O_4N_3ClBr$: C, 62.72; H, 3.21; N, 6.51 requires: C, 62.84; H, 3.35; N, 6.46%.

***3-(5-Chloro-2-hydroxy-3-iodo-phenyl)-1-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3k).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3416, 3196, 1675, 1608 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.38 (s, 3H, $CH_3$), 7.15–8.26 (m, 15H, Ar—H), 8.84 (s, 1H, -5H of pyrazole), 10.68 (s, 1H, OH), 12.32 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 698 [$M^+$], 700 [M + 2]; *Anal*. Found for $C_{34}H_{21}O_4N_3ClI$: C, 58.54; H, 3.05; N, 6.01 requires: C, 58.62; H, 3.23; N, 6.14%.

***3-(2-Hydroxy-3-iodo-4-methyl-phenyl)-1-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-7-methyl-9-oxa-4-aza-phenanthren-10-one (3l).*** IR (KBr $cm^{-1}/\upsilon_{max}$): 3396, 3159, 1678, 1604 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.24 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$), 7.16–8.25 (m, 15H, Ar—H), 8.88 (s, 1H, -5H of pyrazole), 10.51 (s, 1H, OH), 12.36 (s, 1H, —OH, $D_2O$ exchangeable) ppm; MS (m/z): 677 [$M^+$]; *Anal*. Found for $C_{35}H_{24}O_4N_3I$: C, 62.01; H, 3.59; N, 6.18 requires: C, 62.18; H, 3.68; N, 6.11%.

**Biology.** All the synthesized compounds **3(a-l)** were screened for their *in vitro* antimicrobial activity by agar well diffusion method [25]. Antibacterial activity was checked against bacteria *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis*. The culture strains of bacteria maintained on nutrient agar slant at 37 ± 2°C temperature for 24–48 h. Antifungal activity was studied against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, and *Fusarium moniliforme*. The results were compared with *Penicillin* and *Nystatin*, respectively. All the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27 ± 2°C temperature for 24–28 h, till sporulation. Spore of strains were transferred in 5 mL of sterile water containing 1% Tween-80 (to suspend the spore properly). The spores were counted by Hemocytometer ($10^6$ CFU/mL). Sterile plate PDA was prepared containing 2% agar 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27 ± 2°C temperature for 12 h. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL pyrido coumarin solution of concentration 50, 100, and 250 μg/mL for screening minimum inhibitory concentration (MIC). Dimethyl sulfoxide (DMSO) was used as control without compound.

The plates were kept in refrigerator for 20 min for diffusion and then incubated at 27 ± 2°C temperature for 24–28 h in incubator. After incubation, zone of inhibition of compounds was measured in millimeters, along with control and standard. MIC value of pyrido coumarins was obtained 100 μg/mL for both antibacterial and antifungal activity. Results of the study are shown in Table 2.

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## REFERENCES AND NOTES

[1] Murray, R. D. H.; Mendey, J.; Brown, S. A. The Natural Coumarins; Wiley: New York, 1982, p 147.

[2] Kennedy, R. O.; Tharnes, R. D. Coumarins: Biology, Application and Mode of Action; Wiley: Chichester, 1997, p 1.

[3] Zahradink, M. The Production and Application of Fluorescent Brightening Agents; Wiley: New York, 1992, p 284.

[4] Maeda, M. Laser Dyes; Academic Press: New York, 1984, p 19.

[5] Thaisrivongs, S.; Janakiraman, M. N.; Chong, K. T.; Tomich, P. K.; Dolack, L. A.; Turner, S. R.; Strohbach, J. W.; Lynn, J. C.; Horng, M. M.; Hinshaw, R. R.; Watenpugh, K. D. J Med Chem 1996, 39, 2400.

[6] Rappa, G.; Shyam, K.; Lorico, A.; Fodstad, O.; Sartorelli, A. C. Oncol Res 2000, 12, 113.

[7] Yang, E. D.; Zhao, Y. N.; Zhang, K.; Mack, P. Biochem Biophys Res Commun 1999, 260, 682.

[8] Ukawa, K.; Ishiguro, T.; Wada, Y.; Nohara, A. Heterocycles 1986, 24, 1931.

[9] Brauninger, H.; Plagemann, R.; Schalicke, H. D.; Peseke, K. Naturwiseenschaftliche Reihe 1986, 35, 34.

[10] Heber, D. Arch Pharm 1987, 320, 402.

[11] Heber, D.; Berghaus, T. J Heterocycl Chem 1994, 31, 1353.

[12] Valencia, E.; Patra, A.; Freyer, A. J.; Shamma, M.; Fajardo, V. Tetrahedron Lett 1984, 25, 31.

[13] Lewis, W. H.; Stonard, R. J.; Porras-Reyes, B.; Mustoe, T. A.; Thomas, A. U.S. Pat. 5,156,847 (1992).

[14] Tanaka, K.; Toda, F. Chem Res 2000, 100, 1025; references cited therein.

[15] Anstas, P. T.; Varner, J. C. Green Chemistry: Theory and Practice; Oxford University Press, 1998, p 160.

[16] Heldebrant, D.; Jessop, P. G. J Am Chem Soc 2003, 125, 5600.

[17] Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S.; Reddy, N. R. K. Org Lett 2002, 4, 4399.

[18] (a) Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S.; Reddy, N. R. K. Chem Commun 2003, 1716; (b) Jiang, R.; Kuang, Y.-Q.; Sun, X.-L.; Zhang, S. Y. Tetrahedron: Asymmetry 2004, 15, 743.

[19] Namboodiri, V. V.; Varma, R. S. Green Chem 2001, 3, 146.

[20] Haimov, A.; Neumann, R. Chem Commun 2002, 876.

[21] Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. Tetrahedron Lett 2004, 45, 2421.

[22] Perrier, S.; Gemici, H.; Li, S. Chem Commun 2004, 604.

[23] Kroehnke, F. Synthesis 1976, 1, 1

[24] Dawane, B. S.; Bhosale, R. B.; Pekamwar, S. S. J Pharm Res 2007, 6, 119.

[25] Shrinivasan, D.; Sangeetha, N.; Suresh, T.; Lakshmanaperumalsamy, P. J. Ethnopharmacol 2001, 74, 217.

# 1*H*-Benzimidazole-2-acetonitriles as Synthon in Fused Benzimidazole Synthesis



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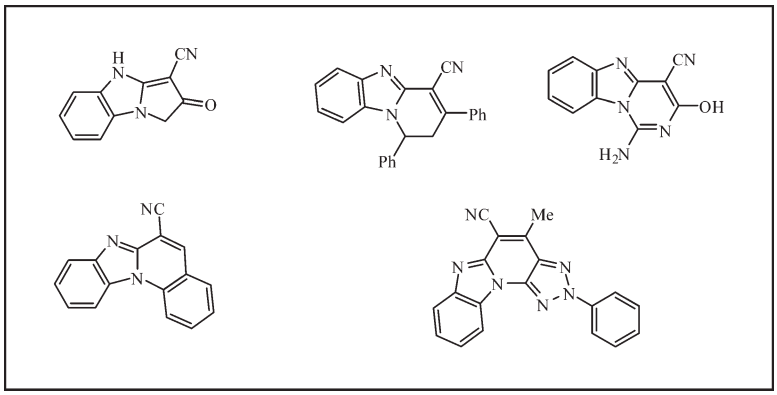

This review summarizes the methods for preparing 1*H*-benzimidazole-2-acetonitriles and their reactions in the past years, some of which have been applied to the synthesis of biologically active molecules. The main reactions are divided into several groups according to some types of the fused benzimidazoles.

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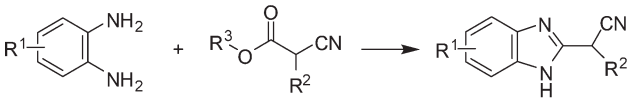
## 1. INTRODUCTION

1*H*-Benzimidazole-2-acetonitriles are convenient precursors which have been extensively utilized in heterocyclic synthesis. Many reactions were developed in the last decades for which the reactivity of 1*H*-benzimidazole-2-acetonitriles towards diverse reagents was utilized for the synthesis of nitrogen bridged heterocycles. From the point of view for biological activities, benzimidazole derivatives are useful intermediates and subunits for the development of molecules having pharmaceutical or biological interests [1,2]. Also, substituted benzimidazole derivatives have found applications in diverse therapeutic areas such as antiulcer drugs, anticancer drugs, antiviral drugs, and antiprotozoan species [3–6]. The main purpose of this review is to present a survey of the literature on the synthesis and reactions of 1*H*-benzimidazole-2-acetonitriles during the last decades.

**Scheme 1**



**1**

## 2. METHODS FOR SYNTHESIS OF 1*H*-BENZIMIDAZOLE-2-ACETONITRILES

Two major approaches have been developed for the synthesis of 1*H*-benzimidazole-2-acetonitriles. The first approach involves the construction of the 1*H*-benzimidazole-2-acetonitriles by cyclization of *o*-phenylenediamine derivatives with reagents such as cyanoacetic acid ester, ethyl 2-cyanoacetimidate, and cyanoacetamide. The second method entails ring transformation of benzodiazepine-3-carbonitrile.

**2.1. From *o*-phenylenediamine derivatives.** 1*H*-Benzimidazole-2-acetonitriles **1** were synthesized by fusion of *o*-phenylenediamines and cyanoacetate at high temperature (Scheme 1) [7–15].

Katsuyama and Kubo have been reported the synthesis of 5-hydroxymethyl-1*H*-benzimidazole-2-acetonitrile **2** starting from 3,4-diaminobenzoic acid (Scheme 2) [16].

Ethyl 2-cyanoacetimidate hydrochloride was converted into 1*H*-benzimidazole-2-acetonitrile **3** by fusion with 1,2-phenylenediamine (Scheme 3) [17].

Compound **3** was prepared by condensation of 1,2-phenylenediamine with cyanoacetamide in an inert organic solvent (Scheme 4) [18].

Cyclocondensation of enaminonitriles (R = $CO_2Et$, Bz) with *o*-pheylenediamine gave 1*H*-benzimidazole-2-acetonitrile **4** (Scheme 5) [19].

**2.2. Ring transformation of benzodiazepine-3-carbonitrile.** Treatment of benzodiazepine-3-carbonitrile **5** with methoxyamine hydrochloride resulted in the ring transformation of oxime **6** whose hydrolysis and neutralization gave the target molecule (Scheme 6) [20,21].

Ring cleavage of benzodiazepines **7** (R = Me, Et) with methylamine provided dihydropyrimidines **8**, which underwent ring transformations and hydrolysis to furnish 2-(1*H*-benzo[*d*]imidazol-2-yl)-3-(methylamino)acrylonitrile **9** (Scheme 7) [22].

## 3. SYNTHESIS OF FUSED BENZIMIDAZOLES

**3.1. Pyrrolobenzimidazoles.** Elwan has reported the synthesis of pyrrolo[1,2-*a*]benzimidazoles **12**. The reaction of 1*H*-benzimidazole-2-acetonitrile **3** with hydrazonoyl halides (**10a**, X = Cl; $R_1$ = Me; $R_2$ = H, Cl, Me; **10b**, X = Br; $R_1$ = Ph; $R_2$ = H, $NO_2$, Me) in the presence of triethylamine led to the formation of pyrrolo[1,2-*a*]benzimidazoles **12**. It has been suggested that the reaction starts from the nucleophilic substitution of the halogen with the benzimidazole carbanion to provide intermediate **11**, which upon dehydration gives the pyrrolobenzimidazoles **12** (Scheme 8) [23].

Awadallah *et al*. revised the structure of **12** into the 3-arylazo-2-methylpyrrolo[1,2-*a*]benzimidazoles (**13**, Ar = 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$) by the X-ray crystallography (Scheme 9) [24].

On the other hand, the reaction of hydrazonoyl chlorides (**14** X = Cl; $R_1$ = Et; $R_2$ = H, Cl, Me, $NO_2$; $R_2$ = H; $R_1$ = Me; $R_2$ = Cl) with 1*H*-benzimidazole-2-acetonitrile **3** in the presence of sodium ethoxide yielded the pyrazolopyrrolobenzimidazole **16** *via* the intermediates **15** (Scheme 10) [23,25].

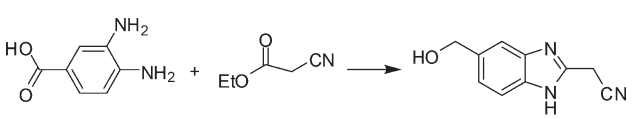
Condensation of the benzimidazoline **17** with the 2-aminothiophene-3-carboxylates **18** [$R_1$ = Ph, $R_2$ = H (**18a**); $R_1R_2 = (CH_2)_4$ (**18b**)] in DMF at 100°C provided the tetrahydropyrrolothienopyrimidinediones **19** in 42–67% yields. The reaction of compound **17** with triethylamine produced pyrrolobenzimidazole **20**. This reactivity was explained in terms of steric factors of **17** in which the substituent shields the heterocyclic nitrogen atom and hinders intramolecular alkylation (Scheme 11) [26].

Reaction of dichloromaleimide with 1*H*-benzimidazole-2-acetonitriles followed by intramolecular cyclization of **21** furnished 1,3-dioxo-1,3-dihydropyrrolo [3′,4′:4,5]pyrrolo[1,2-*a*]benzimidazoles **22** (R = H, Me) [27] (Scheme 12).

The pyrrolo[1,2-*a*]benzimidazole-3-carbonitrile **24** was prepared by reaction of compound **3** with oxalic acid bis(*p*-tolylimidoyl) chloride **23** in the presence of triethylamine (Scheme 13) [28].

Treatment of 1-alkyl-4,5-dichloro-3-nitropyridazin-6-one (**25**, $R_1$ = Et, Me) with ambident nucleophiles (*i.e*., 1*H*-benzimidazole-2-acetonitriles) in the presence of potassium carbonate led to selective substitution of a chorine

**Scheme 2**



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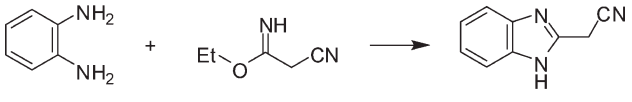
**Scheme 3**



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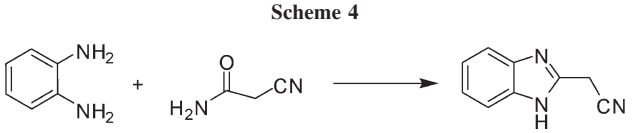
**Scheme 4**



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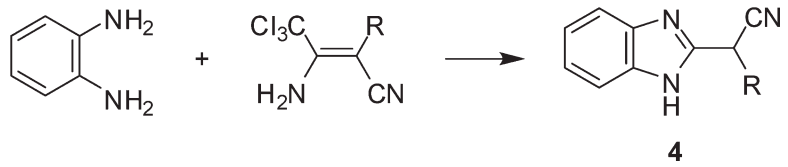
**Scheme 5**



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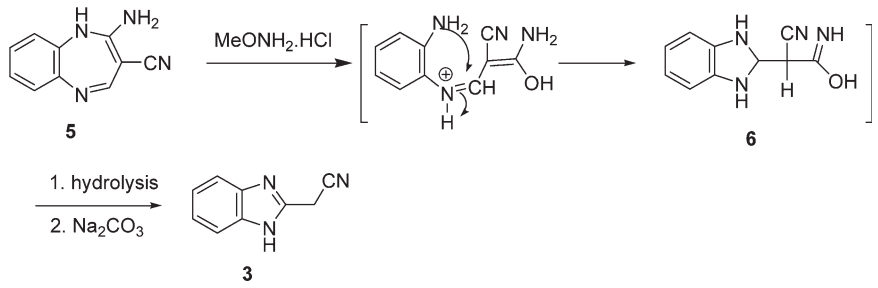
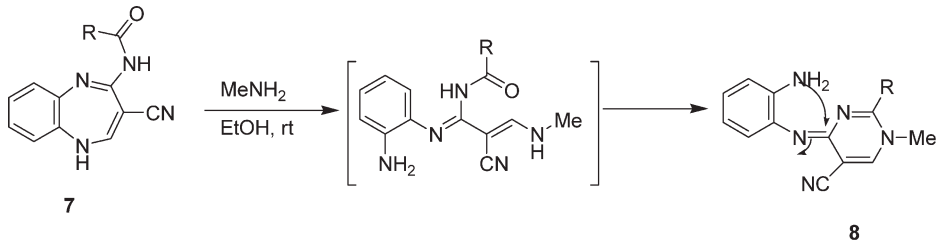
**Scheme 6**

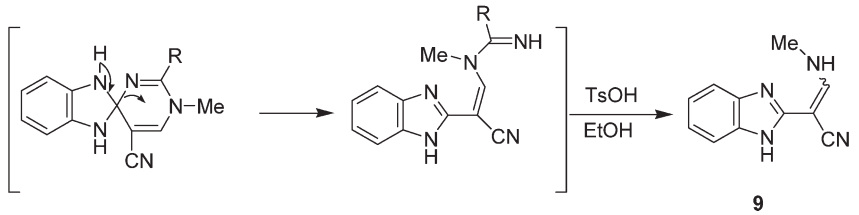


**5** **6** **3**

**Scheme 7**

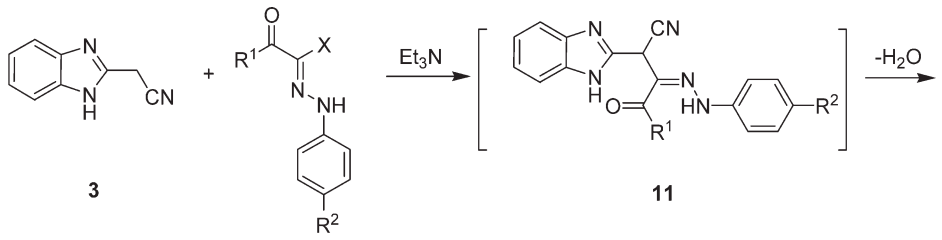


**7** **8**

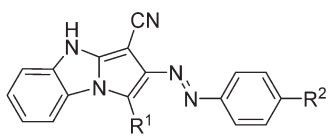


**9**

**Scheme 8**

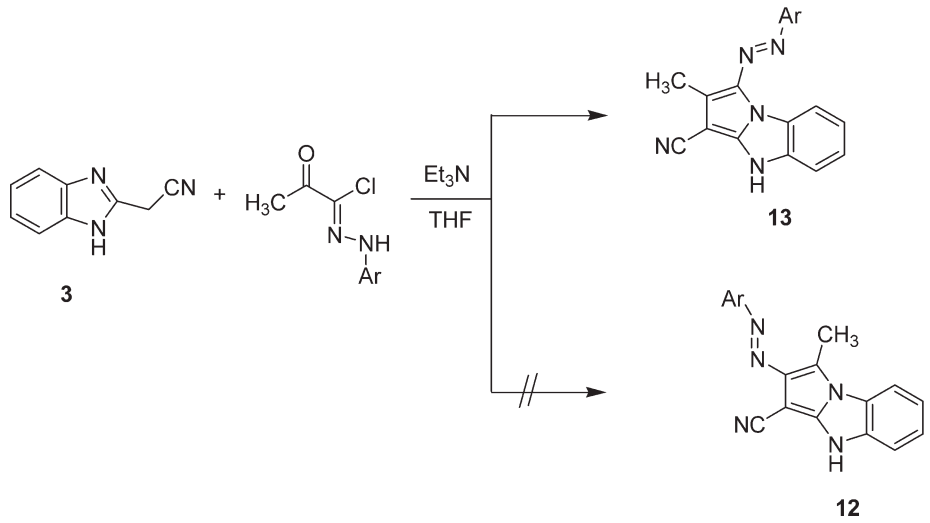


**3** **10** **11**

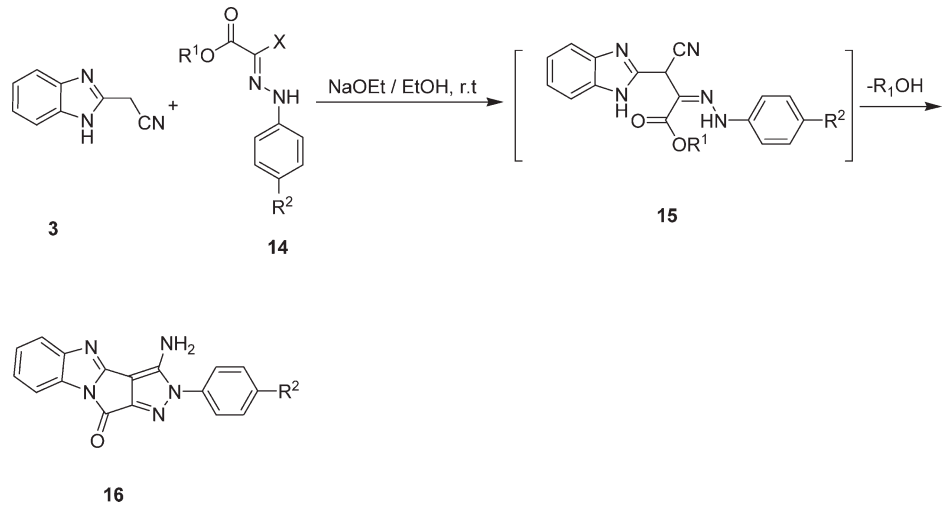


**12**

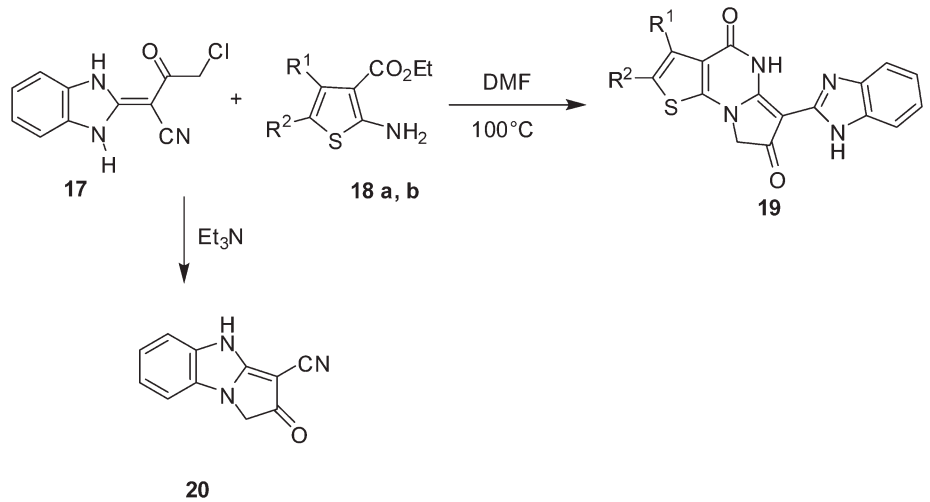
**Scheme 9**



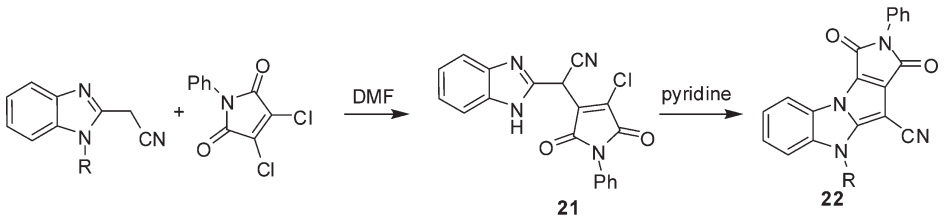

**Scheme 10**



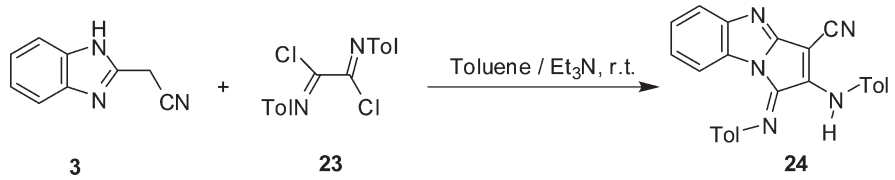

**Scheme 11**



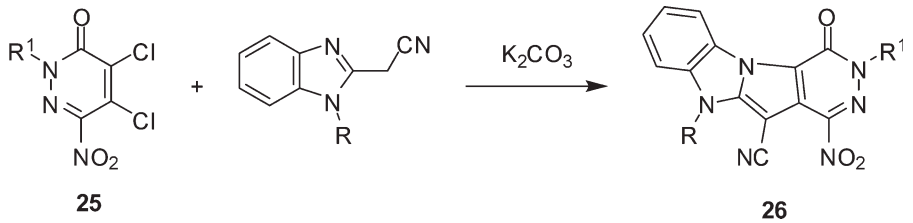
**Scheme 12**



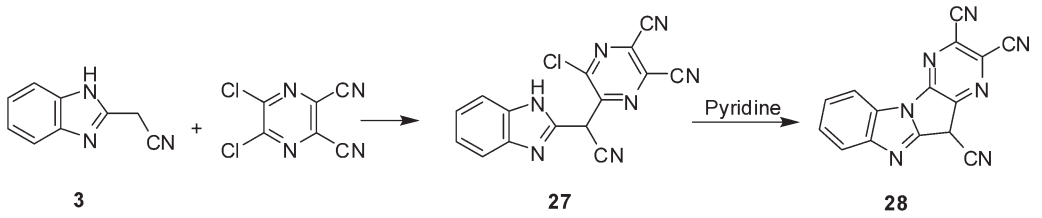

**Scheme 13**




**Scheme 14**




**Scheme 15**

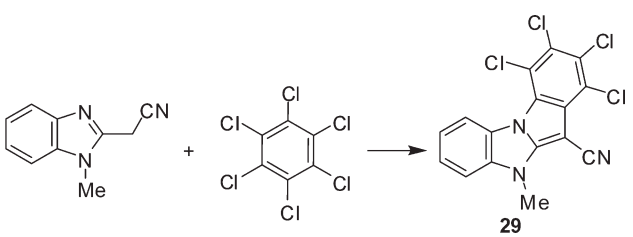



atom by the quaternary carbon atom of the carbanion formed from a substituted acetonitrile **26** (Scheme 14) [29].

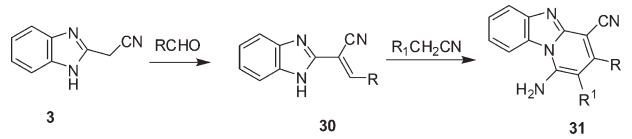
Reaction of 2,3-dichloro-5,6-dicyanopyrazine with **3** led to α-(3-chloro-5,6-dicyanopyrazin-2-yl)-α-(2-azaheteroaryl)acetonitriles **27**. Subsequent heating in pyridine causes an intramolecular cyclization to yield condensed pyrrolo[*b*]pyrazine **28** (Scheme 15) [30].

The nucleophilic substitution reaction of hexachlorobenzene with 1-methyl-1*H*-benzimidazole-2-acetonitrile yielded the condensed indole **29** (Scheme 16) [31].

**Scheme 16**



**Scheme 17**



**3.2. Pyridobenzimidazoles.** Condensation of the pyridine ring with benzimidazole, that is, the passage to pyridobenzimidazoles, extended the spectrum of biological activity [32,33]. The main methods for preparation of pyridobenzimidazoles starting from 2-cyanomethylbenzimidazoles can be occurred *via* Knoevenagel reaction followed by cyclocondensation, Michael addition, reaction with enaminones, and cyclocondensation with β-dicarbonyl compounds.

***3.2.1. Knoevenagel reaction.*** Cyclization of **30** with malononitrile or ethyl cyanoacetate (R = aromatic subs.; $R_1$ = CN, $CO_2Et$) in ethanol in the presence of piperidine produced pyridobenzimidazoles **31**(Scheme 17) [34].

Highly fluorescent 7-(diethylamino)benzimidazo[1,2-*a*]quinoline-3-carbonitrile **33** was prepared by cyclization of 4-(diethylamino)-2-methoxybenzaldehyde **32** with **3** (Scheme 18) [35].

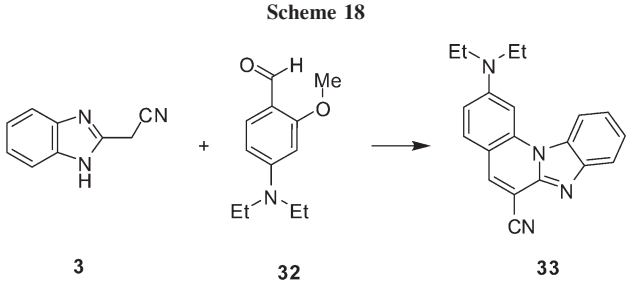
Reaction of the **3** with 2,6-dihalobenzaldehydes (**34**, X = F, Cl, Br) in dioxane led to cinnamonitriles **35** and intramolecular cyclization in DMF benzo[4,5]imidazo[1,2-*a*]quinoline-6-carbonitriles **36** which was obtained directly by refluxing in DMF containing triethylamine (Scheme 19) [36,37].

1-Aryl-3-chloro-4-isoquinolinecarbaldehydes (**37**; R = 4-chlorophenyl, 2,3-dichlorophenyl, 3- and 4-nitrophenyl) were condensed with **3** in DMF to produce diheteroarylpropenenitriles (**38**, same R), which cyclized to yield **39** (same R) [38] (Scheme 20).

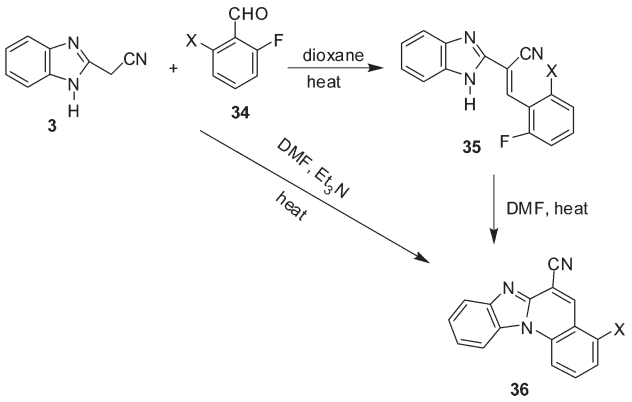
The condensation of 1-phenylpyrazole-4-carboaldehydes (**40**, R = Me, Ph) with benzimidazole-2-acetonitrile **3** led to the formation of fluorescent 3-methyl-1-phenyl-1*H*-pyrazolo[4.3:5,6]pyrido[1,2-*a*]benzimidazole-5-carbonitrile **41**. Similar condensation of 2-chloro-7-methylquinoline-3-carbaldehyde **42** furnished the corresponding 1,2-fused benzimidazo heterocycle **43** (Scheme 21) [39,40].

Chromenes (**44**, R = H, Cl, Br, Me, Et) reacted with **3** in ethylene glycol to yield pyridobenzimidazoles **45** in 65–80% yields (Scheme 22) [41].

**Scheme 18**



**Scheme 19**



Ring transformations of pentose glycals (**46**, $R_1$ = H, $R_2$ = BnO; $R_1$ = BnO, $R_2$ = H) with **3** furnished the pyridiobenzimidazoles **47** (Scheme 23) [42,43].

Vilsmeier-Haack reaction of 3-β-acetoxyandrostan-17-one **48** with phosphorus oxychloride and DMF produced 3-β-acetoxy-17-chloro-16-formyl-5α-androst-16-ene **49**. Reaction of **49** with 1*H*-benzimidazole-2-acetonitrile **3** in refluxing ethanolic solution furnished benzimidazolopyridoandrostane **51** in 82% yield, However, the intermediate **50** was yielded in 70% in the presence of piperidine (Scheme 24) [44].

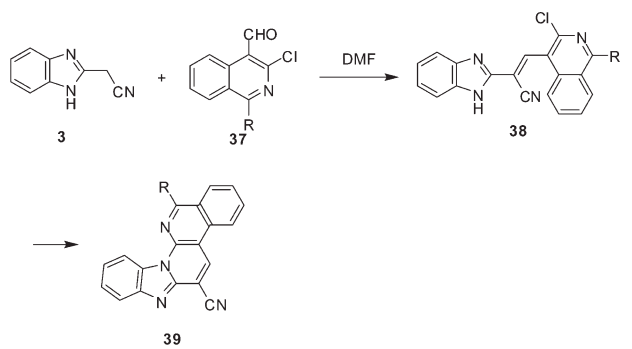
***3.2.2. Michael addition.*** Michael addition of **3** to chalcone in ethanol having a catalytic amount of piperidine led to the formation of pyridobenzimidazole **52** (Scheme 25) [45,46].

Addition of 1*H*-benzimidazole-2-acetonitrile **3** to arylidenemalononitrile **53** produced 1-amino-3-aryl pyrido[1,2-*a*]benzomidazole-2,4-dicarbonitrile **54** (R = aryl). Compounds **54** reacted with formamide yielding 4-amino-5-arylpyrimido[5′,4′:5,6]pyrido[1,2-*a*]benzimidazole-6-carbonitrile **55** (R = aryl) [47,48] (Scheme 26).

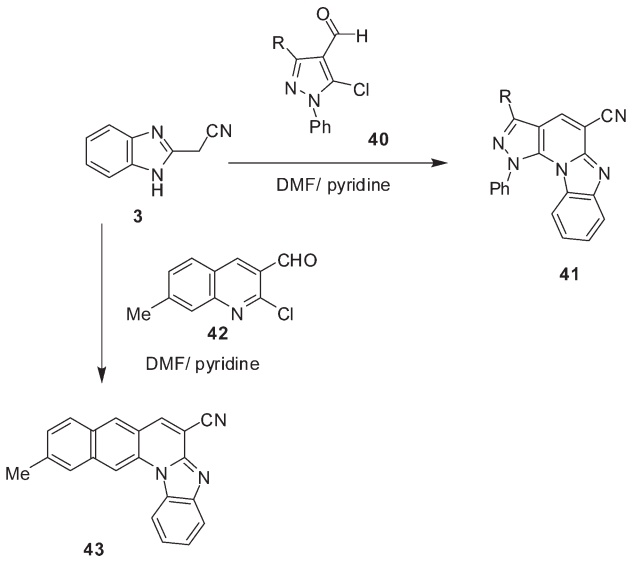
Reaction of arylidene-1*H*-benzimidazol-2-ylacetonitriles **56** with 1*H*-benzimidazole-2-acetonitrile **3** furnished pyrido[1,2-*a*]benzimidazole **57** (Scheme 27) [49].

The formation of pyridobenzimidazole **61** can be achieved by addition of active methylene component **3**

**Scheme 20**



**Scheme 21**




to 4-ethoxymethylene-2-phenyl-5-oxazolone **58** to form the intermediate **59**, which underwent intramolecular acylation at the nitrogen atom of benzimidazole nucleus with cleavage of oxazolone ring to form intermediate **60**. Finally, elimination of ethanol furnished pyridobenzimidazole **61** (Scheme 28) [50].

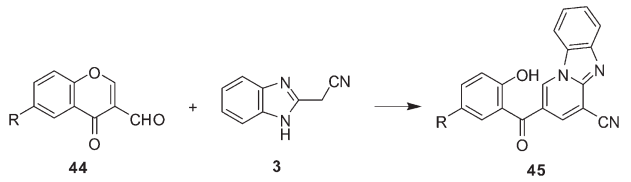
Ethyl 2-cyano-3-(5-chloro-1,3-diphenylpyrazol-4-yl)acrylate **62** underwent Michael addition with **3** to produce pyrido[1,2-*a*]benzimidazole **63** (Scheme 29) [51].

Cyclocondensation of 3-aryl-2-(2-benzimidazolyl)acrylonitrile **64** (R = 1-naphthyl, Ph, 4-$MeOC_6H_4$, 4-$ClC_6H_4$) with ethyl acetoacetate and cyanoacetohydrazide gave pyridobenzimidazolones **65**, and aminopyridobenzimidazoles **66**, respectively (Scheme 30) [52].

Treatment of 1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α,α-*D*-altropyranosid-3-yl)-4-phenyl-but-3-yn-2-one **67** with **3** produced benz[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile derivative **68** (Scheme 31) [53].

***3.2.3. Reaction with enaminones.*** Enaminone derivatives are highly reactive intermediates and are extensively used for the synthesis of heterocyclic compounds. Dawood *et al*., have reported the synthesis of pyrido[1,2-*a*]benzimidazole derivative **70** by reaction of 1-(benzo[d]thiazol-2-yl)-3-(dimethylamino)prop-2-en-1-one **69** with **3** in ethanol in the presence of piperidine (Scheme 32) [54].

**Scheme 22**




The reaction of enaminonitrile **71** with **3** was also conducted in refluxing ethanol in the presence of a catalytic amount of piperidine to afford 3-amino-2-(benzothiazol-2-yl)carbonylpyrido[1,2-*a*]-benzimidazole-4-carbonitrile **72** (Scheme 33) [55].

Also, treatment of enaminonitrile [2-(benzothiazol-2-yl)-3-(*N*,*N*-dimethylamino)-prop-2-enenitrile] **73** with **3** in refluxing ethanol in the presence of catalytic amount of piperidine afforded 3-amino-2-(benzothiazol-2-yl)pyrido[1,2-*a*]benzimidazol-4-carbonitrile **74** (Scheme 34) [56].

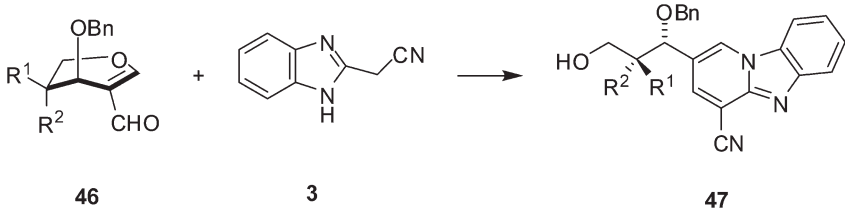
Pyrido[1,2-*a*]benzimidazoles **76** were synthesized by reacting 3-aryl-2-(*N*,*N*-dimethylamino)methylene-3-oxopropanenitriles **75** with **3** [31,55,57]. Elmaati *et al*. in 2002 have been reported the synthesis of pyridobenzimidazole **78**. Reaction of enaminone of acetoacetanilide **77** with **3** yielded the target compound **78** (Scheme 35) [57].

Hassanien in 2005, reported the reaction of methyl 2-benzoyl-3-dimethylaminopropenoate **79** with 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile **3** in refluxing acetic acid in the presence of ammonium acetate to produce methyl 4-cyano-3-phenylbenzimidazo[1,2-*a*]pyridine-2-carboxylate **80**, but not **81** (Scheme 36) [58].

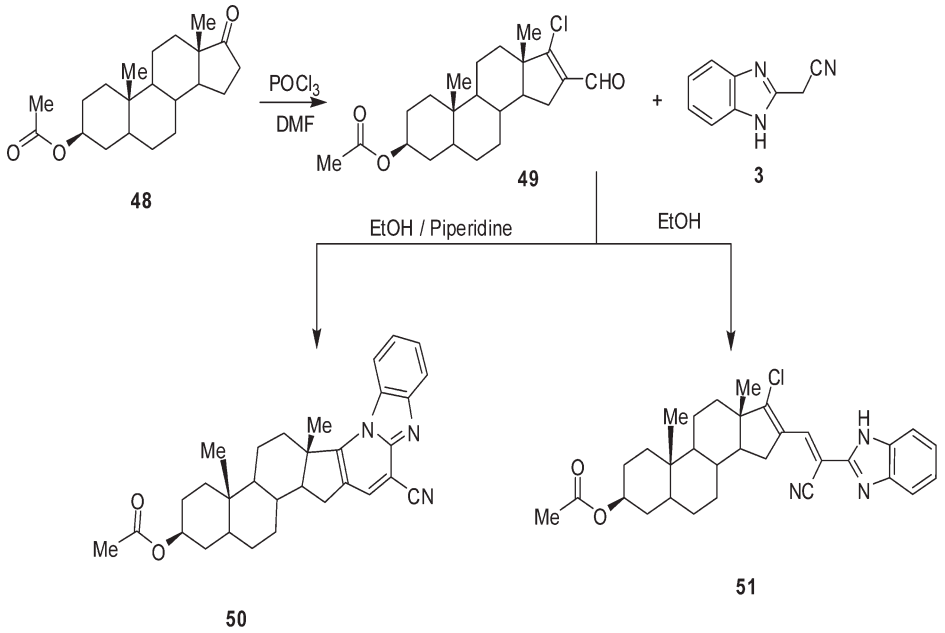
Microwave irradiation of dimedone **82**, dimethylformamidedimethyl acetal and **3** in iso-propanol and a catalytic amount of piperidine led to the formation of tetrahydrobenzo[4,5]imidazo[1,2-*a*]quinolin-6-yl cyanide **83** (Scheme 37) [59].

The enaminone 2-dimethylaminomethylene-1,3-indandione **84** reacted with **3** to produce indenofluorene **85** [33], while its reaction with 2-dimethylaminomethylene-3-(phenylhydrazono)indan-1-one **86** furnished diazaindenofluorene derivative **87** (Scheme 38) [60].

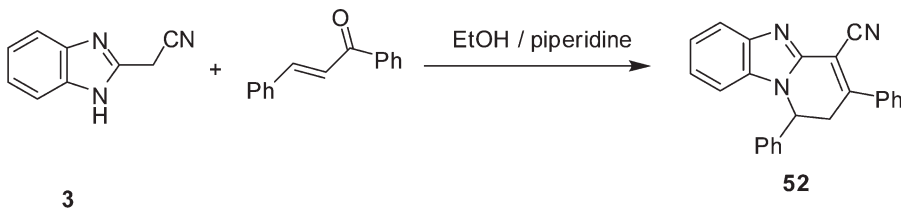
**Scheme 23**



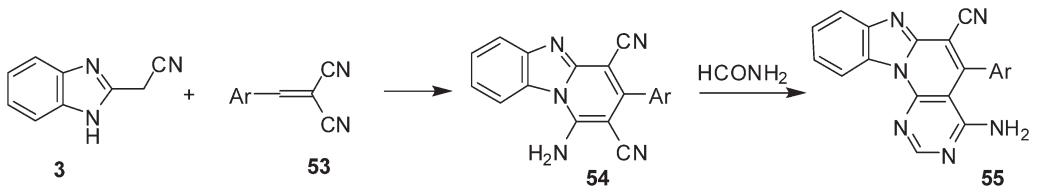
**Scheme 24**



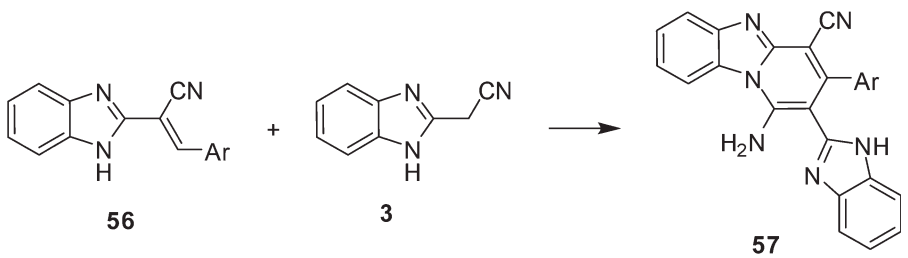

**Scheme 25**



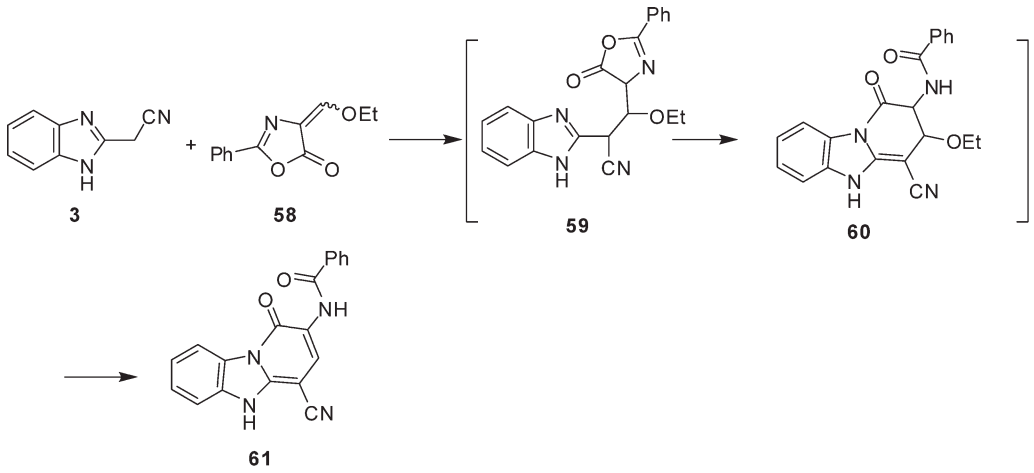

**Scheme 26**



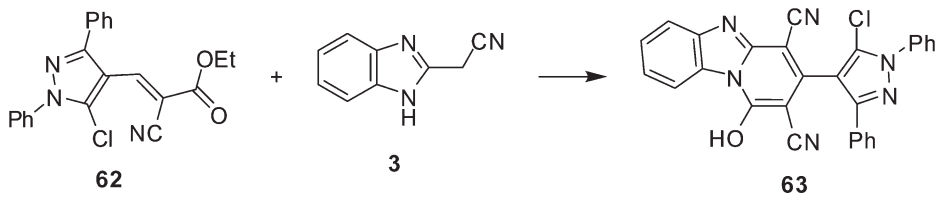

**Scheme 27**



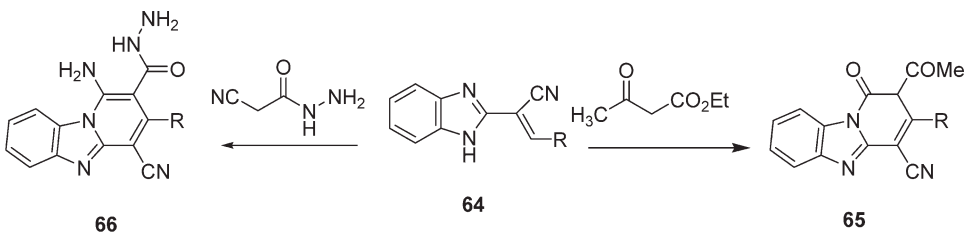
**Scheme 28**



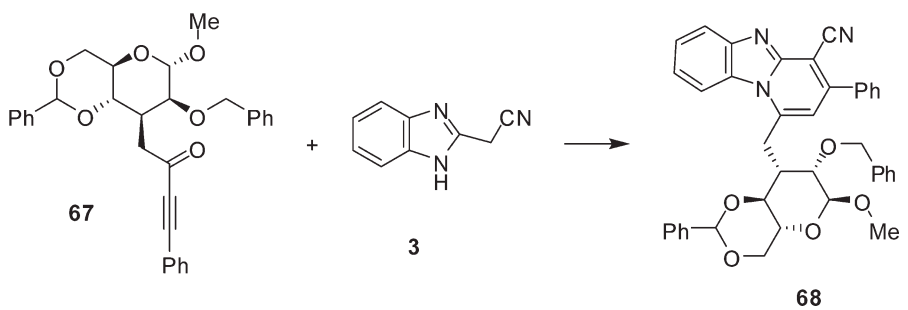
**Scheme 29**



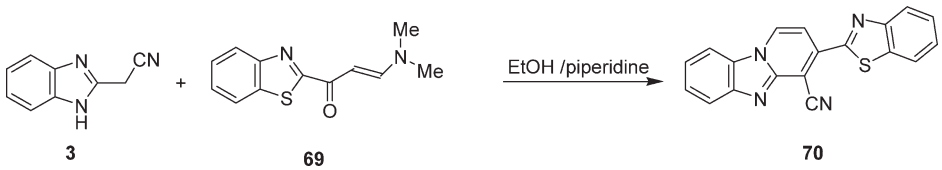
**Scheme 30**



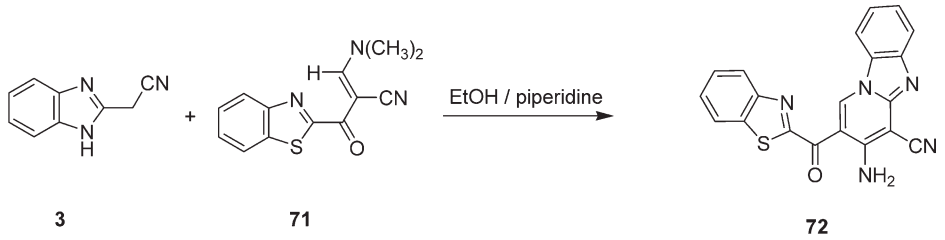
**Scheme 31**



**Scheme 32**

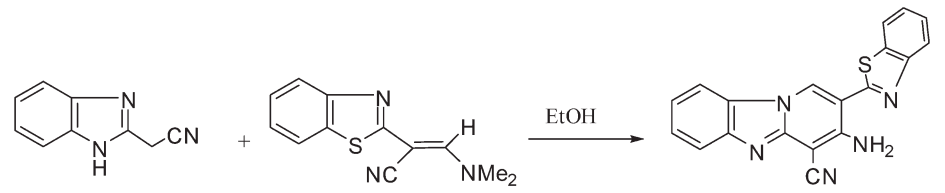


**Scheme 33**




**3** **71** **72**

**Scheme 34**




**3** **73** **74**

Benzo[4,5]imidazo[1,2-*a*]pyridine-2,4-dicarbonitrile **89** was obtained *via* treatment of enaminone **88** with 1*H*-benzimidazole-2-acetonitrile **3** in ethanol and has a catalytic amount of piperidine (Scheme 39) [61,62].

***3.2.4. Reaction with β-dicarbonyl compounds.*** 3-Methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **90** (prepared by the condensation of **3** and ethyl acetoacetate) is formylated with DMF-$POCl_3$ to 2-formyl-3-methylpyrido[1,2-*a*]benzimidazol-4-carbonitrile **91**(Scheme 40) [63].

1-Oxo-*1H,5H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles **94** by fusing **3** with some ethyl acetoacetate **92** in the presence of ammonium acetate or with ethyl β-aminocrotonate **93** (R = H, $R_1$ = Me) [64] (Scheme 41).

Pyrido[1,2-*a*]benzimidazole-4-carboxylic acid **95** was prepared in excellent yield by condensation of **3** with acetyl acetone followed by hydrolysis of the nitrile group by sulfuric acid (Scheme 42) [65,66].

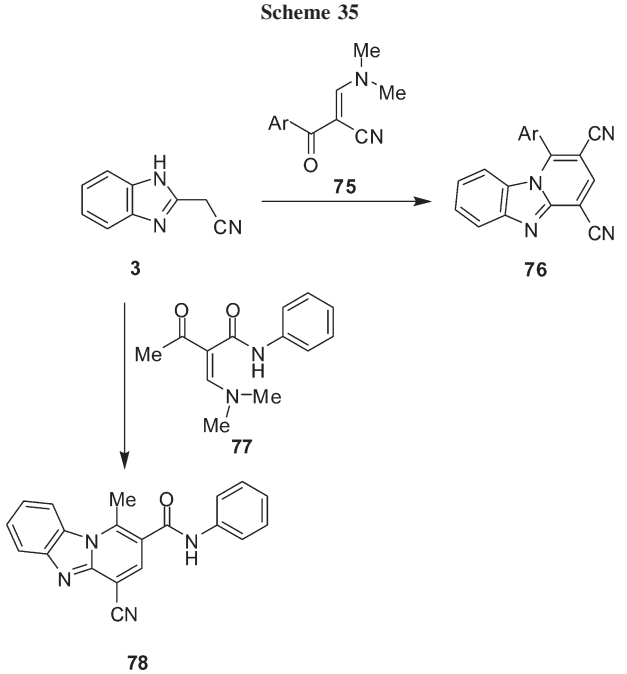
Pyrrolo[3′,4′:3,4]pyrido[1,2-*a*]benzimidazoles **97** [R = Bu, Bn, $MeOCH_2CH_2$, $O(CH_2CH_2)_2NCH_2CH_2$, 2-furyl-$CH_2$, 4-$MeC_6H_4$, 2-$MeC_6H_4$] were prepared in two steps. The condensation of **3** with ethyl 4-chloro-3-oxobutanoate led to the formation of 3-chloromethyl-1,5-dihydro-1-oxopyrido[1,2-*a*]benzimidazole-4-carbonitrile **96**. Amination of **96** with primary amines yielded **97** (Scheme 43) [67].

Condensation of benzimidazole **98** with ethoxymethylenemalonic acid esters (**99**, R = Et, Me) and acetoacetic ester gave the corresponding pyrido[1,2-*a*]benzimidazoles **100**, **101** (Scheme 44) [7].

Cycloalkylpyrido[1,2-*a*]benzimidazoles **102–104** were prepared by reaction of **3** with dimethyl 2-oxocyclopentane-1,3-dicarboxylate, dimethyl 3-oxocyclopentane-1,2-dicarboxylate, or methyl 2-oxocyclohexanecarboxylate in the presence of two equivalent of ammonium acetate at 140°C, these compounds exhibited a good *in vitro* antineoplastic activity especially against most of the leukemia cell lines (Scheme 45) [68–70].

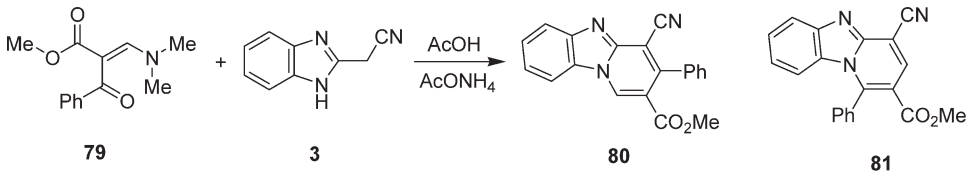
***3.2.5. C-acylation.*** 2-Chloronicotinoyl chloride reacted with 1-methyl-benzimidazole-2-acetonitriles, to give 97% conjugated nitrile **105** which cyclized on heating to give the corresponding 1,8-naphthyridine **106** in high yield (Scheme 46) [71].

**Scheme 35**



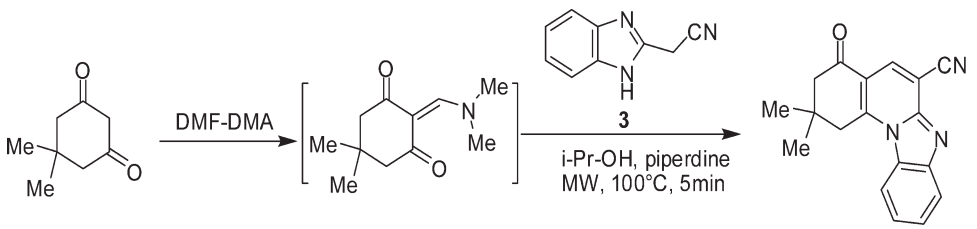

**3** **76** **78**

**Scheme 36**




79 3 80 81

**Scheme 37**




82 83

1-Methyl-benzimidazole-2-acetonitriles condensed with 2-haloaromatic esters (**107**, X = Cl, F; R = H, $O_2N$; $R_1$ = Me, Et) in refluxing acetonitrile containing potassium or cesium carbonate to give condensed isoquinolones **108** (Scheme 47) [72–74].

3-Hydroxy-*1H,5H*-pyrido[1,2-*a*]benzimidazol-1-ones (**110**, R = Et, Bu, $PhCH_2$, Ph) were prepared by cyclization of 1*H*-benzimidazole-2-acetonitrile with the dicarboxylate **109** (Scheme 48) [75,76].

Condensed azine **112** was prepared by cyclization of the corresponding benzothiophene **111** in refluxing ether (Scheme 49) [77].

***3.2.6. Miscellaneous methods.*** A one-step synthesis of benzimidazolo[1,5-*a*]pyridine **114** was reported. The reaction of 2-(2-phenylhydrazono)malononitrile **113** with **3** in refluxing ethanol yielded the target molecule **114** (Scheme 50) [78].

2-Imino-*N*′-*p*-arylpropanehydrazonoyl cyanide (**115**, R = Me, OMe, $NO_2$) were condensed with **3** in acetic acid to give the corresponding 3-methylpyrido[1,2-*a*]benzimidazoles **116** which then oxidized with cuprous acetate in DMF to triazolo[4,5-*b*]pyrido[1′,2′-*a*]benzimidazoles **117** (Scheme 51) [79].

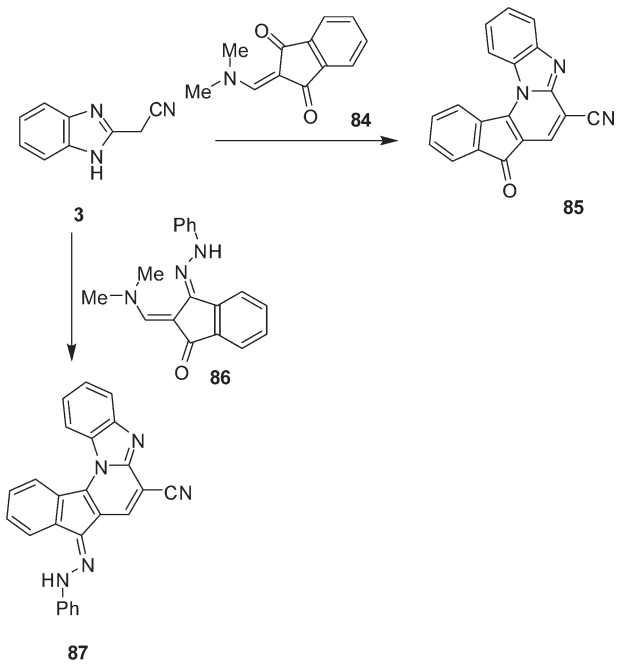
Reaction of **3** with 3-aminobut-2-enenitrile **118** afforded 1-amino-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **119** (Scheme 52) [80].

Compound **3** reacted with sodium salts of 3-hydroxymethylene-2-alkanones (**120**, R = H, Me, $R_1$ = Me, aryl) in piperidine acetate and aqueous ethanol to yield two isomeric structures **121** and **122**. The X-ray analysis confirmed the presence of **121** in the solid state (Scheme 53) [81].

The cycloannulation of dianion **123** derived from **3** with the acyclic ketene dithioacetals (**124**, R = Ph, Me) produced 4-cyano-1-phenyl (or 1-methyl)-3-(methylthio)-pyrido[1,2-*a*]benzimidazoles **125** in good yields *via* the intermediate **124** (Scheme 54) [82].

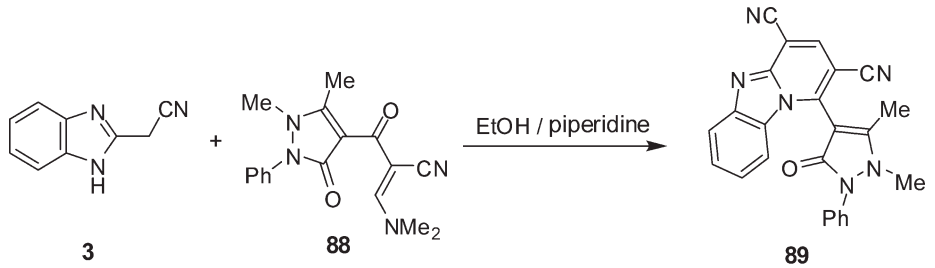
Benzimidazole-2-acetonitriles (R = H, Me) were treated with carbon disulphide and dimethyl sulfate to furnish thioesters **126**. Reactions of (**126**, R = H, Me) with methyl 2-cyano-3,3-bis(methylthio)acrylate (**127a**, X = $CO_2Me$), 2-[bis(methylthio)methylene]malononitrile (**127b**, X = CN), and 2-(ethoxymethylene)malononitrile gave pyridobenzimidazoles (**128**, $R_1$ = SMe, Z = O, NH; $R_1$ = H, Z = NH) (Scheme 55) [83].

**Scheme 38**

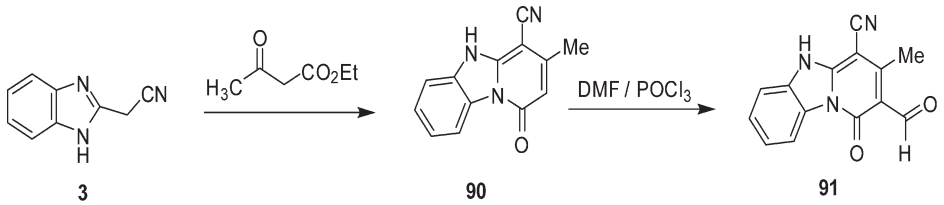



85

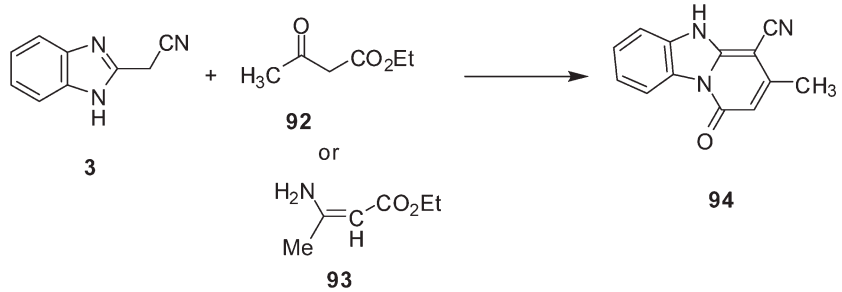
**Scheme 39**



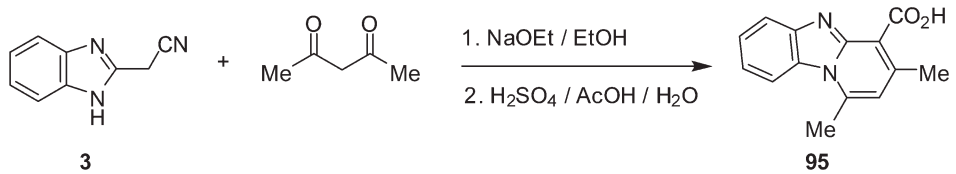

**Scheme 40**



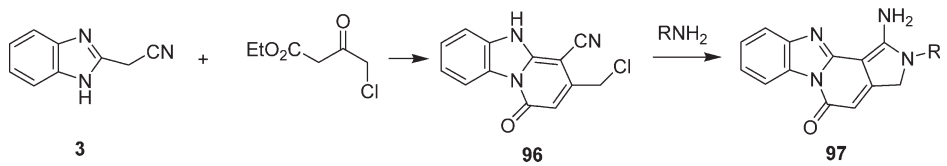

**Scheme 41**



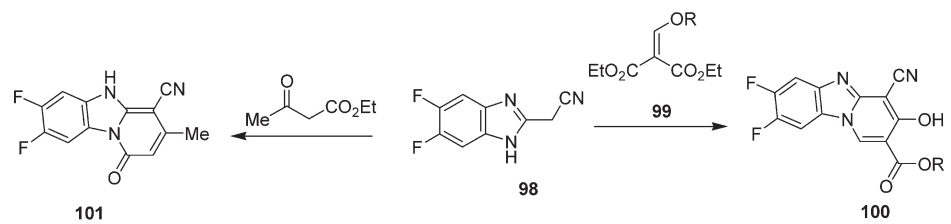

**Scheme 42**



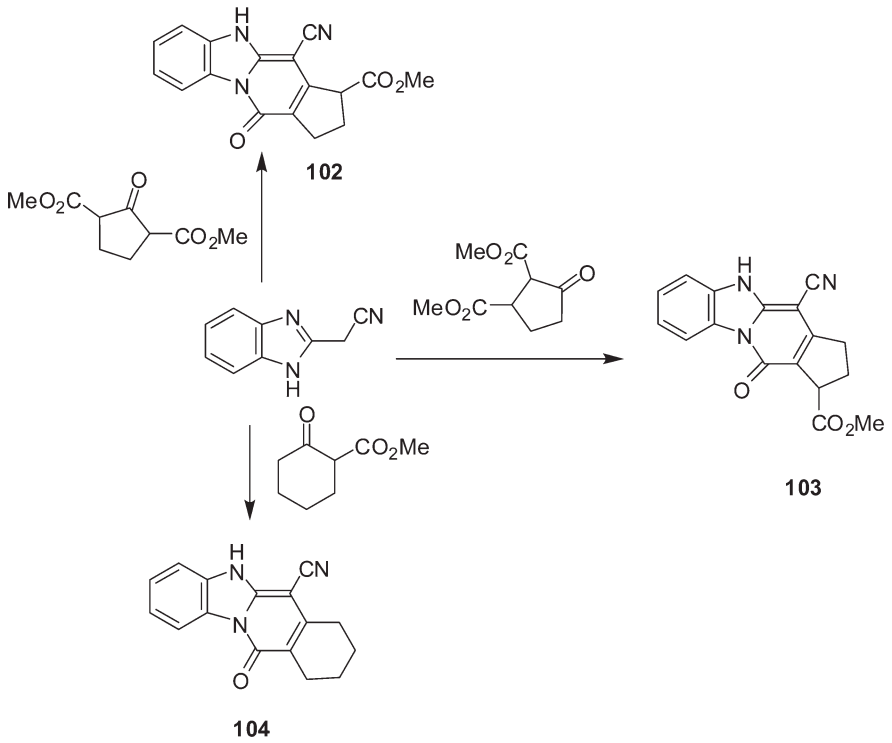

**Scheme 43**




**Scheme 44**



**Scheme 45**



The reaction of **3** with triethyl orthoformate and hippuric acid derivatives in refluxing acetic anhydride afforded pyrido[1,2-*a*]benzimidazole derivatives **131** *via* the intermediates **129** then **130**. The latter cyclizes *via* water elimination to yield pyrido[1,2-*a*]benzimidazole derivatives **131** (Scheme 56) [84].

Thermal condensation of **3** with diethyl ethoxymethylenemalonate in diphenyl ether at 240–250°C gave 75% yield ethyl 4-cyano-3-hydroxypyrido[1,2-*a*]benzimidazole-2-carboxylate **132** (Scheme 57) [33].

Base-catalyzed condensation-cyclization of **3** with 4-(methylthio)-2-oxo-6-aryl-2*H*-pyran-3-carbonitriles (**133**, Ar = aryl, 3-pyridyl, 4-pyridyl) led to the formation of pyrido[1,2-*a*]benzimidazoles **134** as a major product and pyrano[4,3-*d*]pyrido[1,2-*a*]benzimidazoles **135** as a minor one (Scheme 58) [85].

Reactions of 2-chlorobenzonitriles (**136**, R = H, $NO_2$) and 2-chloro-3-quinolinecarbonitrile with 1*H*-benzimidazole-2-acetonitriles ($R_1$ = H, Me, Et) gave condensed isoquinolinimines (**137**; R = H, $NO_2$; X = NH, NMe, NEt) and condensed 1,8-naphthyridinimines (**138**; X = NMe) [86] (Scheme 59).

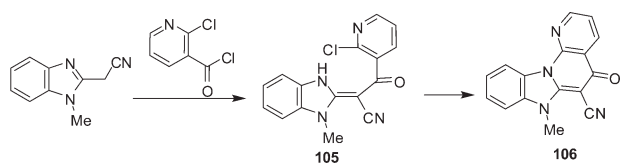
2-(2-Hydroxyethyl)-1-oxo-pyrido[l,2-*a*]benzimidazole-4-carbonitrile **139** was prepared by reacting **3** with 2-acetylbutyrolactone in the presence of ammonium acetate, whereas the 2-benzamido compound **140** was obtained by reacting **3** with 4-ethoxymethylene-2-phenyloxazolin-5-one (Scheme 60) [87].

Cyanamide in the presence of methanol, s-triazine and **3** gave primary product cyanoethene **141** which was stabilized *via* intermediate **142** to give pyridobenzimidazole **143** (Scheme 61) [88].

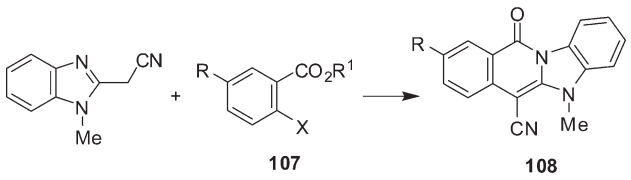
The reaction of 3-methylthio-4-phenyl-1,2-dithiolium perchlorate **144** with **3** in a mixture of acetonitrile/dioxane in the presence of triethylamine gave two products. The major product was cyanopyridobenzimidazole **145** formed by initial reaction of acetonitrile at the unsubstituted 5-position of the dithiole ring, followed by ring opening and recyclization. The other product was dithiole **146** (Scheme 62) [89].

Reactions of **3** with diketene in acetic acid at room temperature gave *C*-acetoacetyl derivative **147** which easily cyclized to give 4-cyano-3-methylpyrido[1,2-*a*]benzimidazole-1(5*H*)-one **148** (Scheme 63) [90].

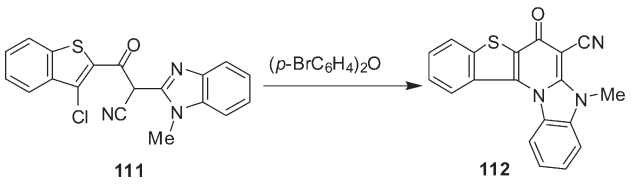
**Scheme 46**



**Scheme 47**



**Scheme 49**



The nucleophilic attack of carbanion of 1*H*-benzimidazole-2-acetonitriles (R = H, Me) at C-4 of pyrimidine ring in **149** led to the formation of the non-isolated intermediate **150**, which underwent intramolecular cyclization through acylation at the nitrogen atom of benzimidazole leading to pyridopyrimidine **151** (Scheme 64) [91].

**3.3. Pyrimidobenzimidazoles.** A one-step synthesis of azolo[5″,1″:3′,4′][1,2,4]triazino[5′,6′:4,5]pyrimido[1,6-*a*]benzimidazoles (**155**, Z = N, CH) has been achieved by the reaction of ethyl 2-cyanomethyl-1*H*-benzimidazole-1-carboxylate **152** with heterocyclic diazonium salts **153** through the formation of the intermediate **154** (Scheme 65) [92].

Acylation of 2-(1*H*-imidazol-2-yl)acetonitriles (R = H, Me) by haloalkyl isocyanates (**156**, Ar = Ph, 4-tolyl, 4-anisyl) followed by heterocyclization of **157** afforded 1,2,3,5-tetrahydrobenzo[4,5]imidazo[1,2-*c*]pyrimidines **158** (Scheme 66) [93].

Compound **3** reacted with ethyl chloroformate in the presence of triethylamine to give *N*- and *C*-acyl derivatives **152** and **159** respectively, which separated by fractional crystallization from dioxane. Reaction of C-acyl derivative **159** with guanidine sulfate in dry pyridine and sodium methoxide gave 1-amino-3-hydroxy-4-cyanopyrimidino[1,6-*a*]benzimidazole **160** (Scheme 67) [94].

Abdelhamid *et al*. have reported the synthesis of benzimidazo[1,2-*c*]pyrimidine-4-carbonitriles **162**. Treatment of 2-(1-ethoxycarbonyl)benzimidazoylacetonitrile **152** with isothiocyanates (R = Me, Ph) in the presence of potassium hydroxide gave the target compounds **162** in good yield *via* the formation of thioanilide intermediate **161** (Scheme 68) [95,96].

The reaction of **3** with sulfur, arylisothiocyanates, and carbon disulfide has been reported by Ivachtchenko *et al*. [97] and Badawy *et al*. [98] to give **163** which underwent methylation to give **164** (Scheme 69).

The mechanism of the reaction has described as follows (Scheme 70):

Five-component condensation of isothiocyanates ($R_1$ = 4-EtO, 3-MeO), sulfur, 1*H*-benzimidazole-2-acetonitrile **3**, triethylamine, and carbon disulfide furnished triethylammonium 3-aryl-[1,3]thiazolo[4′,5′:4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thioxo-5-thiolates **166**, the alkylation of **166** led to 3-aryl-5-R-thio-[1,3]thiazolo[4′,5′:4,5]pyrimidino[1,6-*a*]benzimidazole-2(3*H*)-thiones **167** ($R_2$ = Me, 2-(methyl)-1,3-dioxolane, $CH_2CO_2Et$) [97] (Scheme 71).

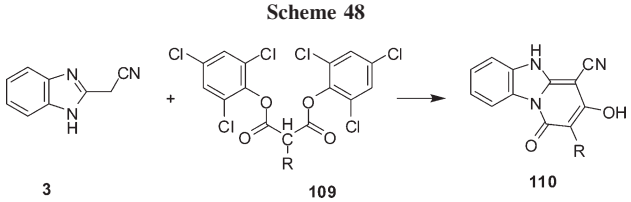
A buffered solution of 1,2,4-triazole-5-diazoium salt **168** was coupled with 1-methylbenzimidazole-2-yl-acetonitrile **3** to yield the corresponding hydrazones **169**, intramolecular cyclization of the latter compound gave triazolo[5,1-*c*]-1,2,4-triazine **170**. Similarly, indazole-3-diazonium chloride **171** also coupled readily with **3** to yield hydrazone **172** which cyclized in refluxing pyridine to produce 1,2,4-triazino[3,4-*b*]indazole **173** in to two tautomeric forms [99] (Scheme 72).

Compound **3** reacted with a variety of *N*-acyl imidates (**174**, $R_1$ = Me, Et; $R_2$ = Me, Et, Ph) under microwave irradiation in open vessels to give the corresponding pyrimido[1,6-*a*]benzimidazoles **175** [100] (Scheme 73).

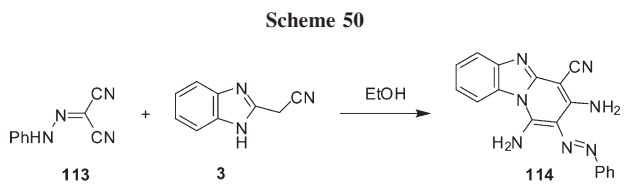
Compound **3** condensed with aminoesters (**176**, $R_1$ = Ph, 4-$EtOC_6H_4$, 2- and 4-$ClC_6H_4$, 2,5-$Cl_2C_6H_3$, 2-naphthyl, PhNMe; $R_2$ = alkyl) to give 60–75% cyanoketones **177**, which underwent acid-catalyzed intramolecular cycloaddition to give 78–87% title compounds (**178**, $R_1$ = Ph, 4-$EtOC_6H_4$, 2-$ClC_6H_4$, PhNMe). Refluxing (**178**, $R_1$ = Ph) with anhydrides or acid chlorides gave 72–98% tetracyclic cyclocondensation products (**179**, $R_3$ = Me, Et, 2-$XC_6H_4$; X = H, F, Cl, Br, iodo) [101] (Scheme 74).

Badawey *et al*. [102] reported that **3** (R = H, Me) was allowed to react with ethoxycarbonylisocyanate at

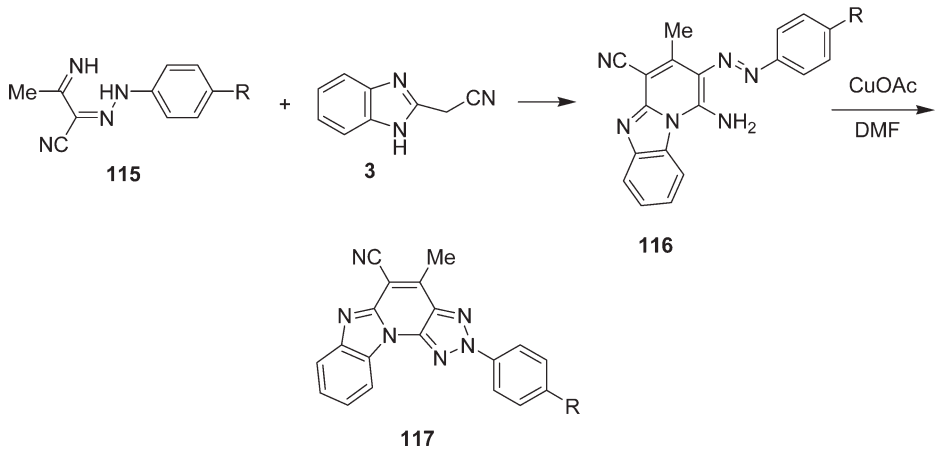
**Scheme 48**



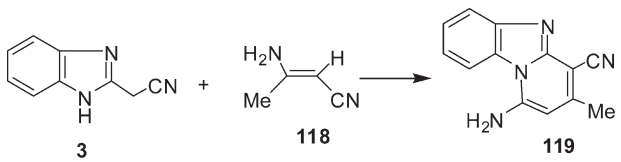
**Scheme 50**



**Scheme 51**



**Scheme 52**

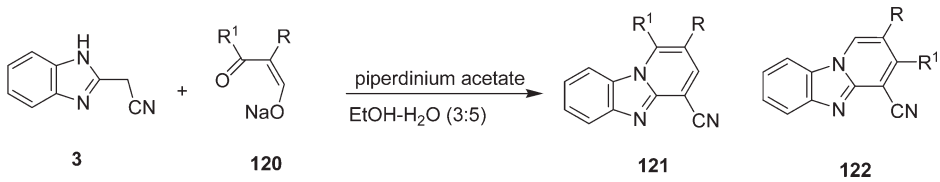


room temperature to afford the intermediate **180**, which was readily cyclized in boiling bromobenzene to the corresponding 7,8-disubstituted-1,3-dioxo-*2H*,*5H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **181** in excellent yield (Scheme 75).

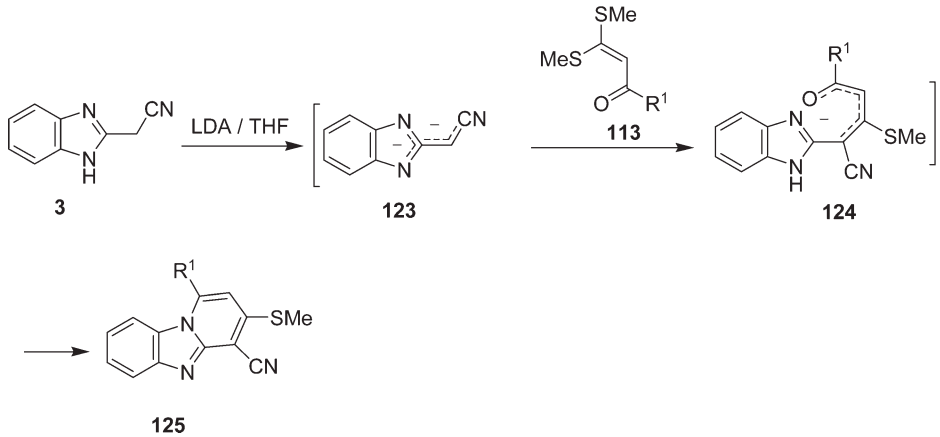
Reaction of **3** with cyanoamide (**182**, R = SMe, $SCH_2Ph$, 4-phenylpiperazino, Me, 4-$MeC_6H_4$, 4-$ClC_6H_4$, 2-furyl, 2-thienyl; $R_1$ = SMe, $SCH_2Ph$, OMe) and β-diketones (**183**, $R_2$ = Me, Ph) gave the pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **184**(Scheme 76) [103].

Compound **3** and 2-(2,2,2-trifluoro-*N*-methylacetamido)benzoyl chloride **185** gave the 1-acylbenzimidazole **186**, which was cyclized with sodium *t*-butoxide in pyridine to give quinolone **187**, which was cyclized with

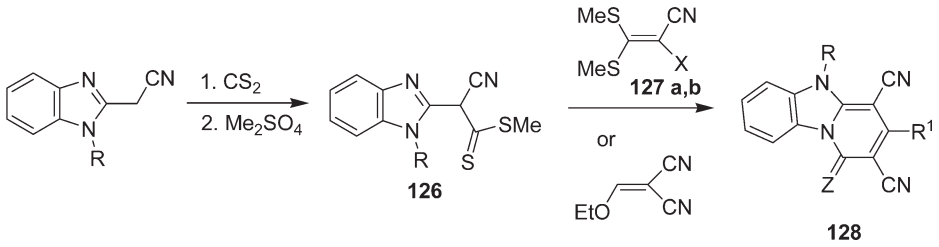
**Scheme 53**



**Scheme 54**



**Scheme 55**



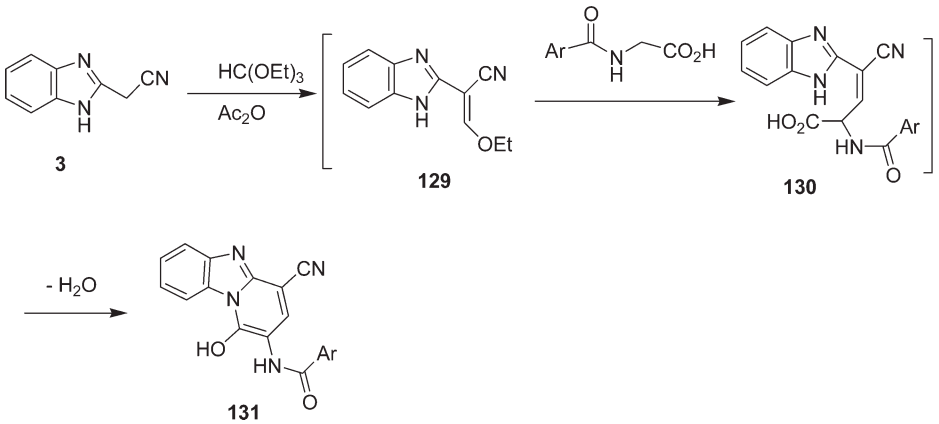
acid chlorides, anhydrides, or triethylorthoformate to give **188** (Scheme 77) [104].

Pyrimido[1,6-*a*]benzimidazole **189** was prepared by heating of **3** with trichloroacetonitrile followed by cyclocondensation with triethylorthoformate (Scheme 78) [105].

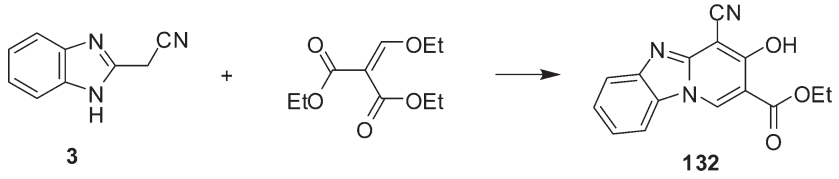
2-Amino-3-(benzimidazol-2-yl)-1,8-naphthyridine **190** was obtained by condensation of 2-aminonicotinaldehyde with **3**. 7-Arylbenzimidazo[1′,2′:1,6]pyrimido[4,5-*b*][1,8]naphthyridines (**192**, R = Ph, 4-$MeC_6H_4$, 2-thienyl, *etc*.) were prepared by oxidation of the 6,7-dihydro derivatives **191**, which were obtained by condensation of benzaldehydes with 2-amino-3-(2-benzimidazolyl)-1,8-naphthyridine **190** (Scheme 79) [106].

Pyrroloquinoline **194** was prepared in good yield by treating 1*H*-benzimidazole-2-acetonitrile **3** with quinoline derivative **193** in refluxing pyridine containing sodium *t*-butoxide. Cyclization of **194** by refluxing acetic anhydride gave 85% **195** (Scheme 80) [107].

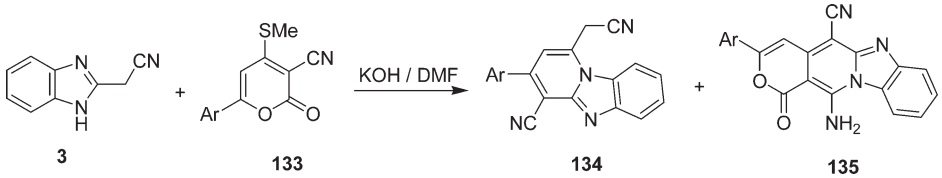
**Scheme 56**



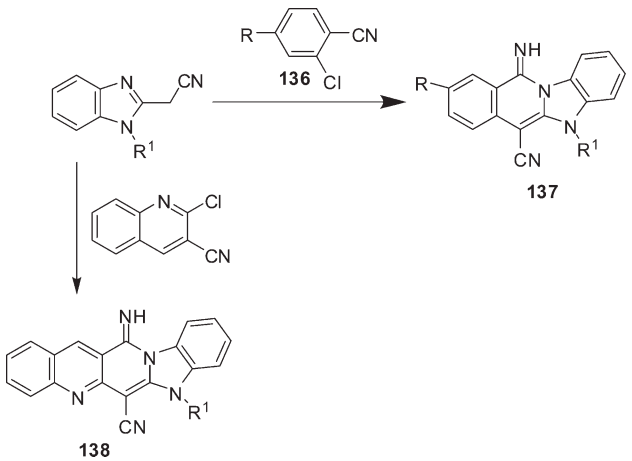
**Scheme 57**



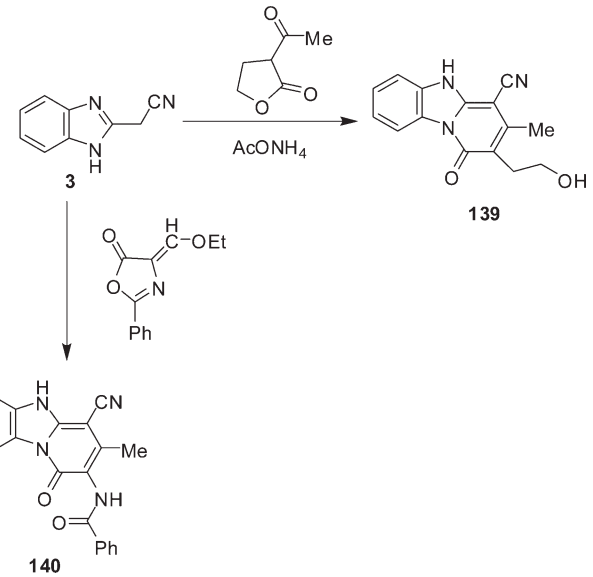
**Scheme 58**



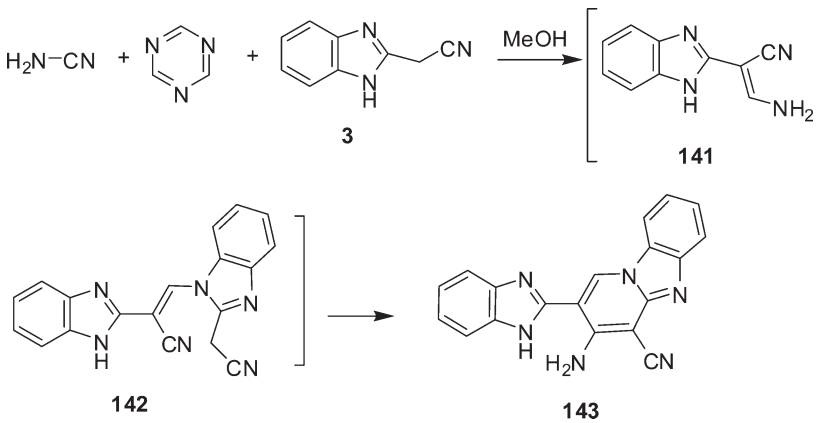
**Scheme 59**



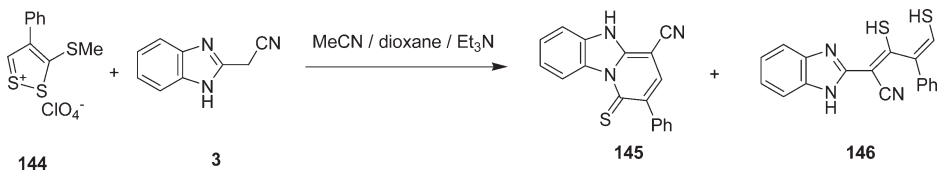
**Scheme 60**



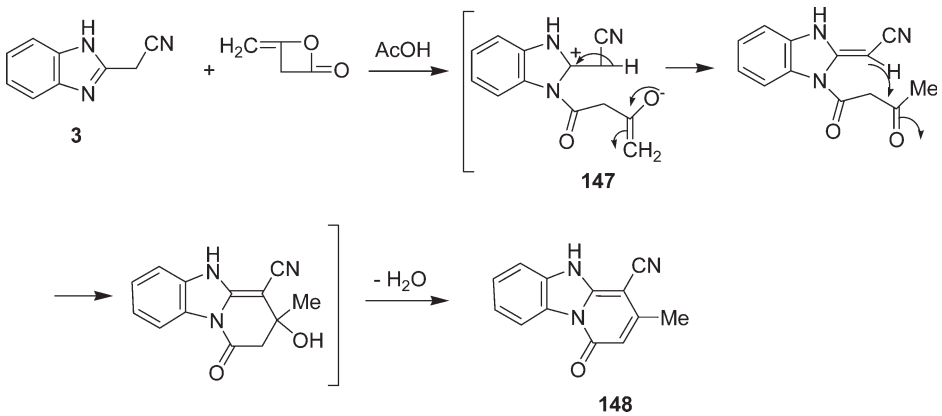
**Scheme 61**



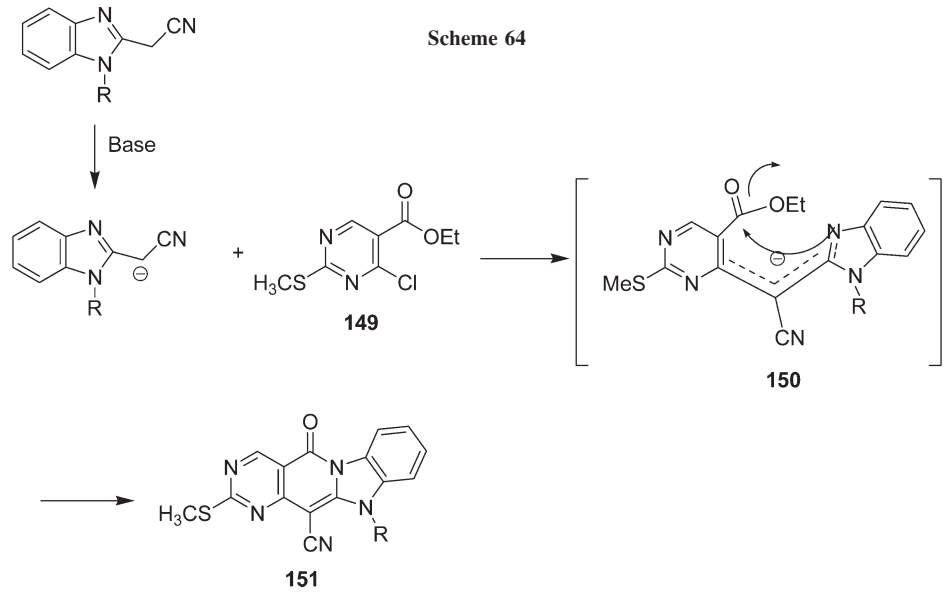
**Scheme 62**



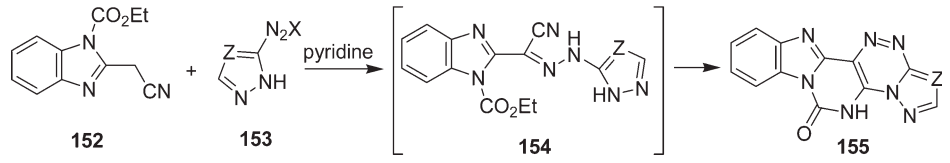
**Scheme 63**



**Scheme 64**



**Scheme 65**

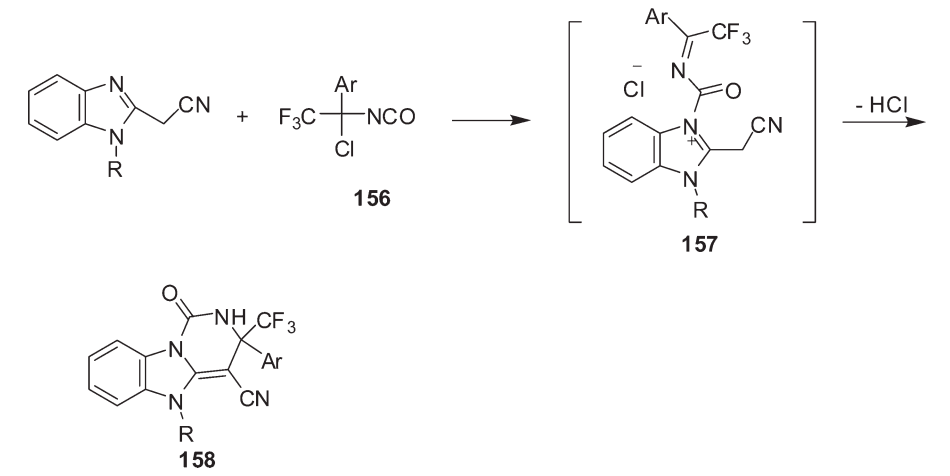


Benzimidazolylchromones (**198**, X = O, S) were prepared in high yields by cyclocondensation of hydroxy aromatic carboxylic acid methyl esters or 2-mercaptomethylbenzoate **197** with **3**. Acylation of **198** with acid chlorides (R = Me, Ph, Pr) gave benzimidazolobenzothiopyranopyrimidine **199** (Scheme 81) [108–110].

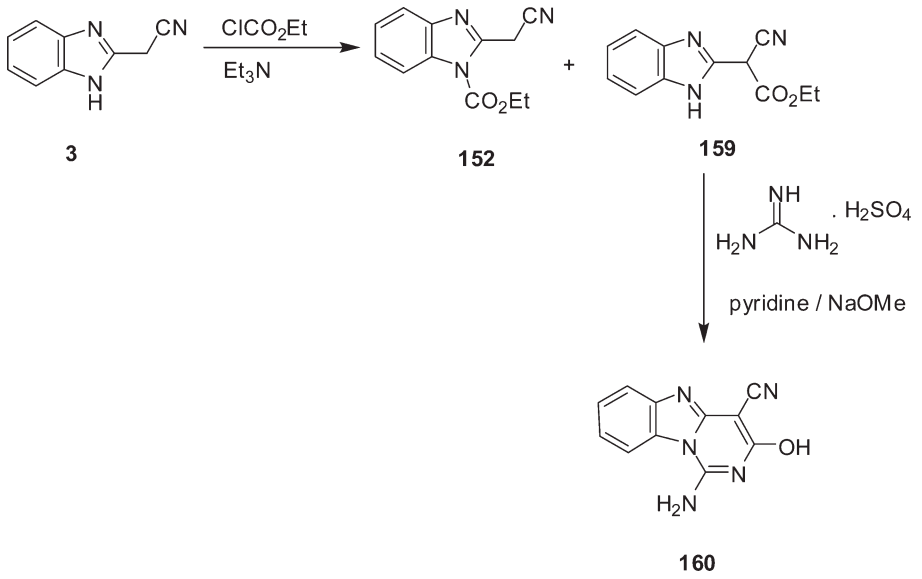
Cyclocondensation of **3** with hydrazones (**200**, $R_1$ = H, 2-, 3-, 4-Me, 4-Br) gave 90–99% **201** which were cyclized by acyl chlorides or anhydrides to give 80–94% **202** [$R_1$ as above, $R_2$ = H, Me, Et, Ph, 3,4,5-$(MeO)_3C_6H_2$] [110,111] (Scheme 82).

Treatment of 2,3,5-trimethyl-1,4-benzoquinone with **3** (R = H, Me) gave 2-amino-3-(benzimidazol-2-yl)benzo[*b*]furans **203** in high yield, respectively. Compound **203** were converted to 87–98% **204** ($R_1$ = $R_2$ = H; $R_1$ = Me, $R_2$ = Ac; $R_1$ = Et, $R_2$ = COEt; $R_1$ = Pr, $R_2$ =

**Scheme 66**

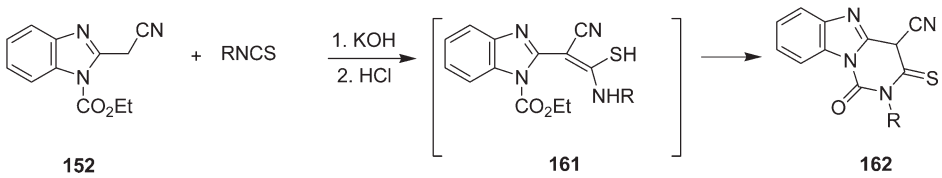


**Scheme 67**



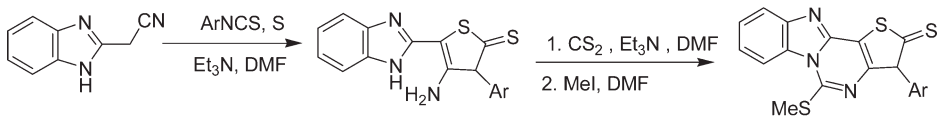

3 152 159 160

**Scheme 68**



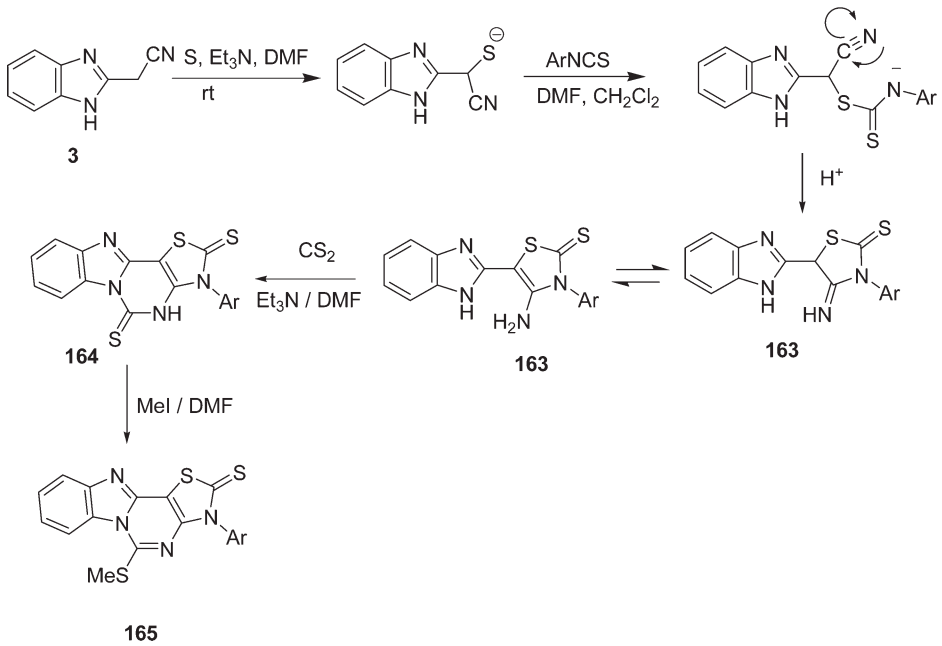

152 161 162

**Scheme 69**



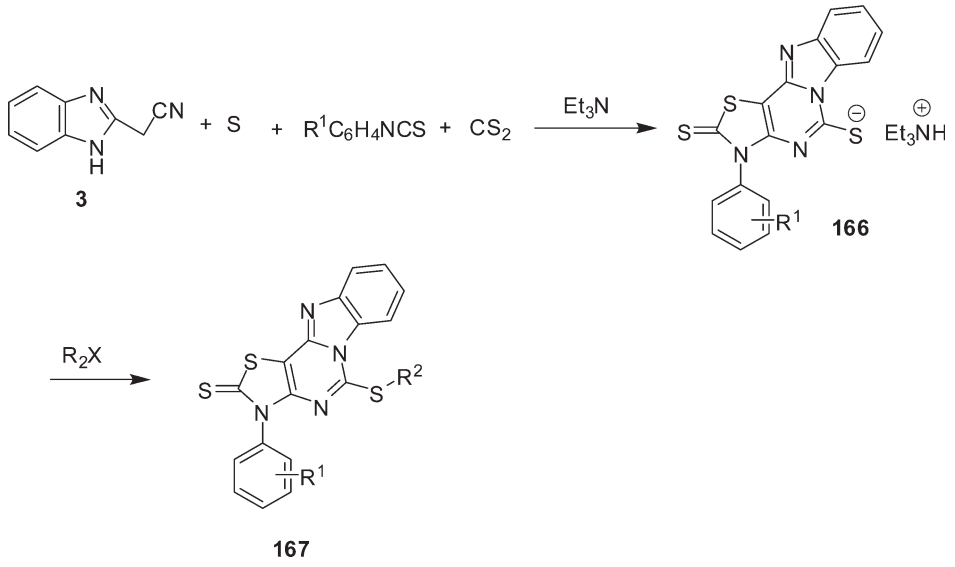

3 163 164

**Scheme 70**

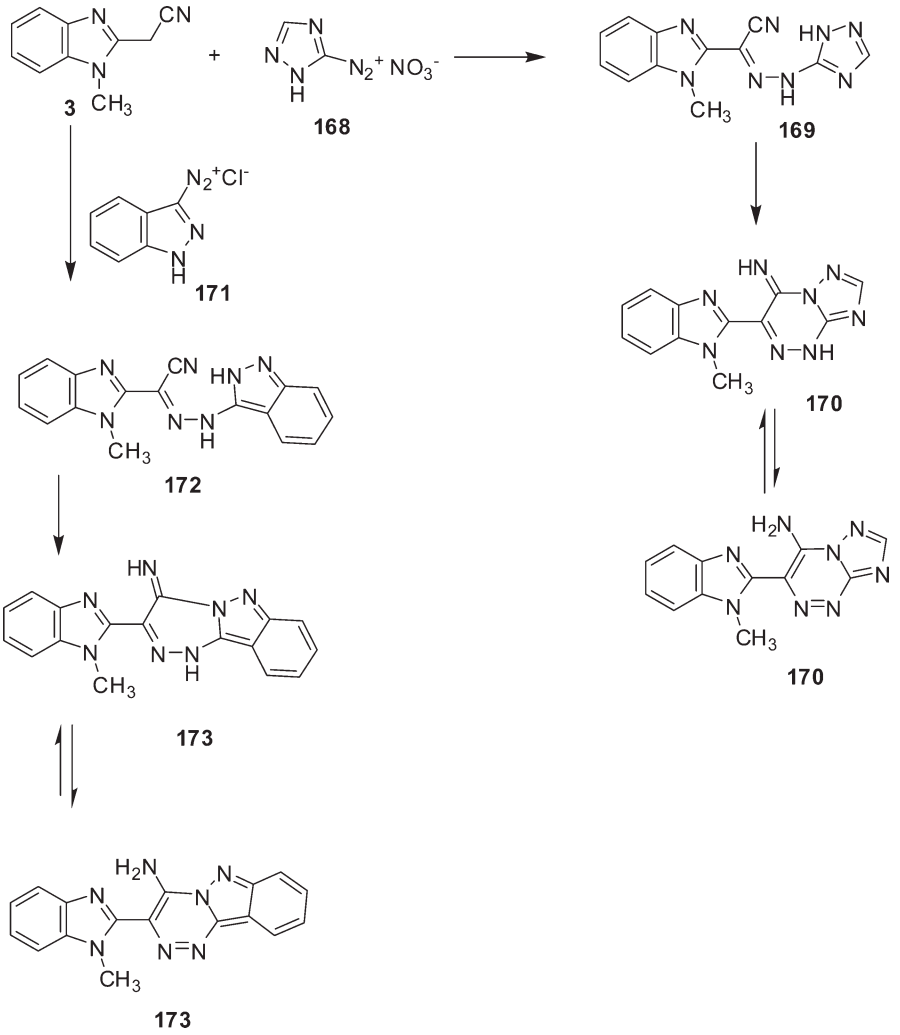



3 163 163 164 165

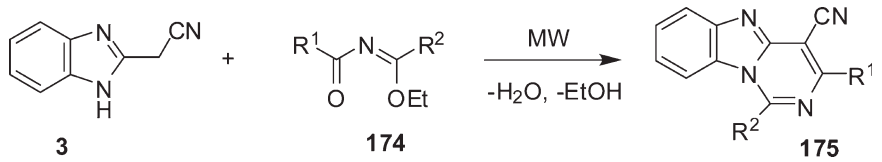
**Scheme 71**




**Scheme 72**

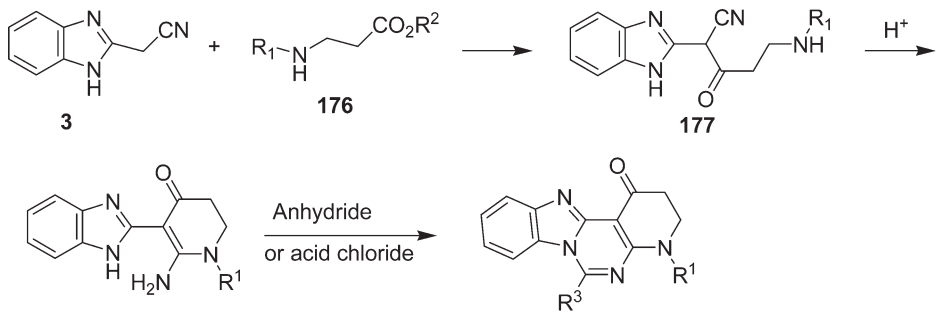


**Scheme 73**



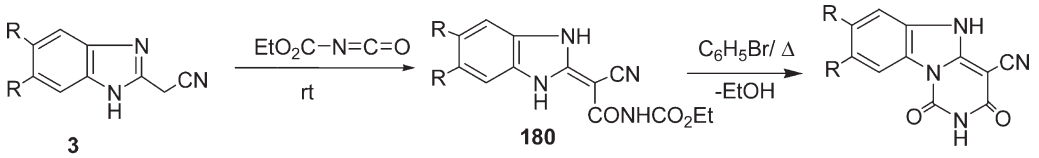

3 174 175

**Scheme 74**



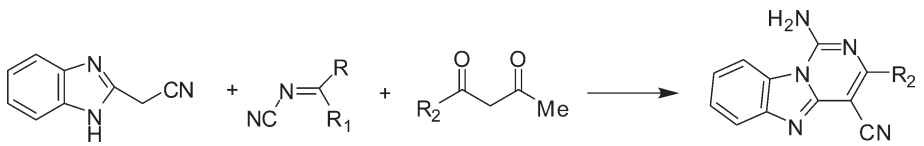

3 176 177 178 179

**Scheme 75**



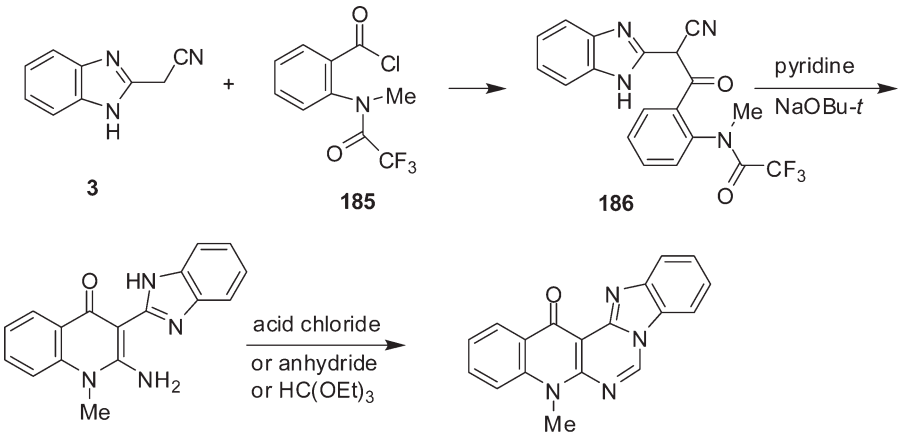

3 180 181

**Scheme 76**



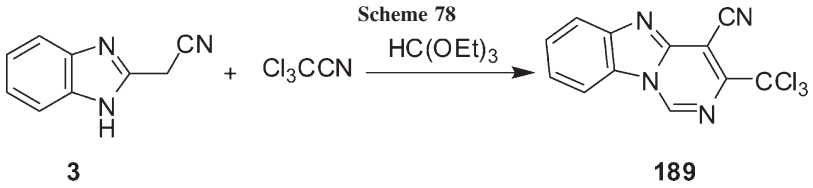
3 182 183 184

**Scheme 77**

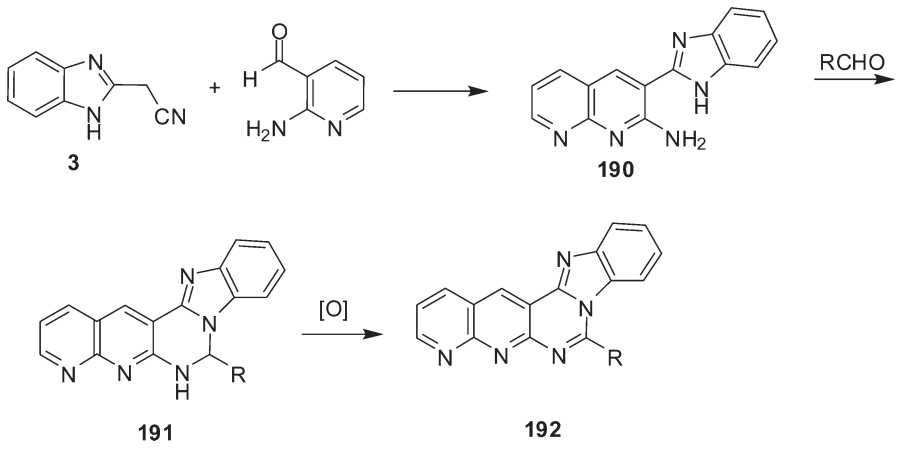



3 185 186 187 188

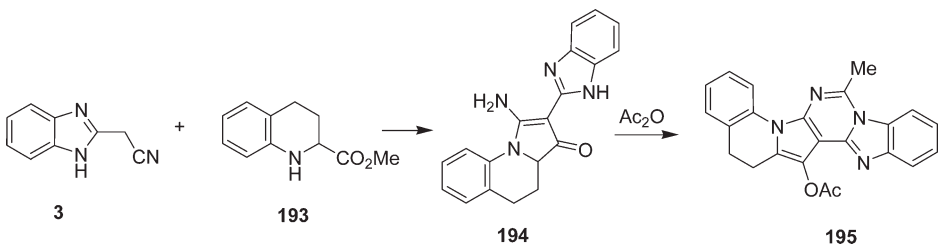
**Scheme 78**



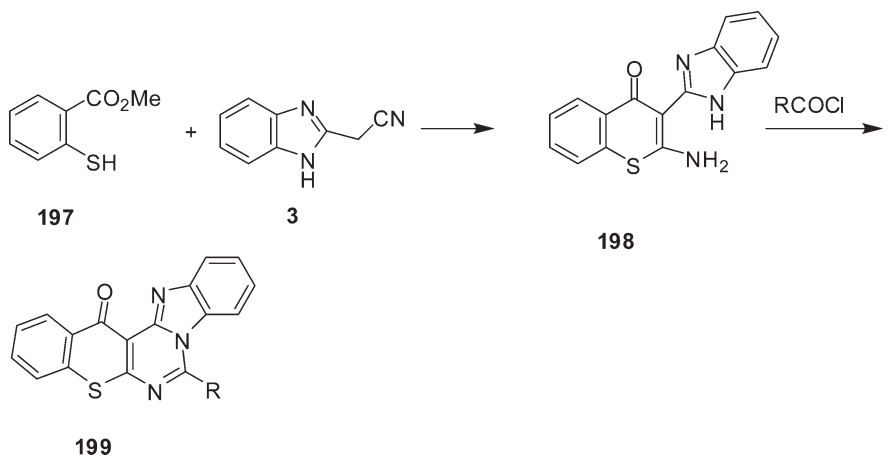

**Scheme 79**



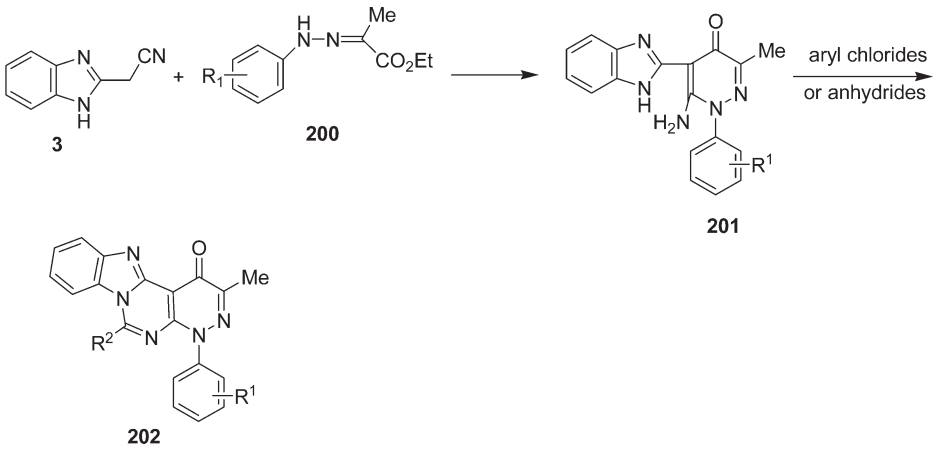

**Scheme 80**



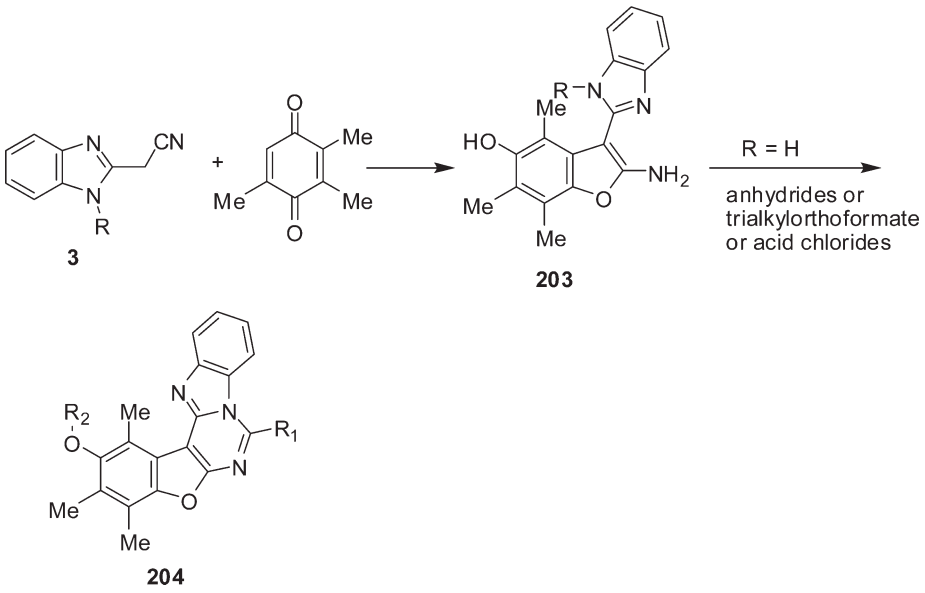

**Scheme 81**



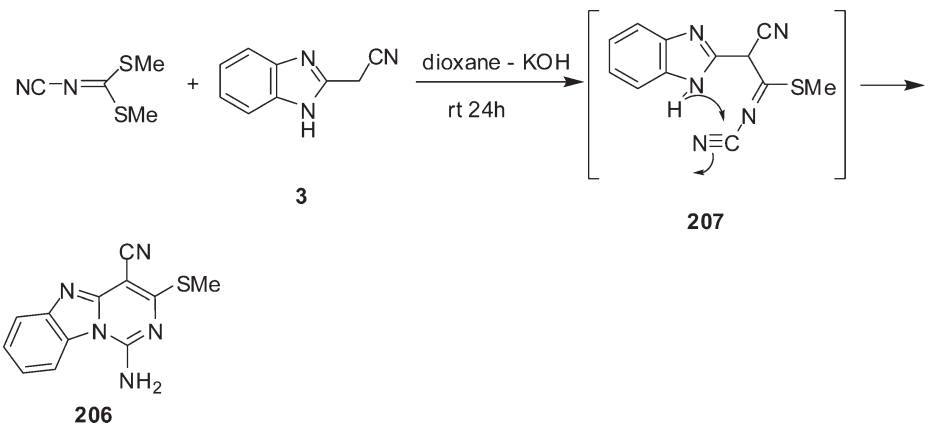
**Scheme 82**




**Scheme 83**




**Scheme 84**



COPr; $R_1$ = Ph, $R_2$ = Bz) by treatment with anhydrides trialkylorthoformate or acid chlorides (Scheme 83) [112].

Reaction of dimethyl *N*-cyanodithioiminocarbonate with **3** can be utilized for the synthesis of 2-amino-5-cyano-4-(methylthio)pyrimidino[1,6-*a*]benzimidazole **206**, by reaction in dioxane containing a catalytic amount of potassium hydroxide at room temperature (Scheme 84) [113].

## REFERENCES AND NOTES


[1] Mavrava, A. T.; Anchina, K. K.; Vuchev, D. I.; Tesnove, J. A.; Kondeva, M. S.; Miteka, K. M. Bioorg Med Chem 2005, 13, 5550.

[2] Yildiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ukarturk, N. Eur J Med Chem 2004, 39, 291.

[3] Kuhler, T. C.; Swanson, M.; Christenson, B.; Klintenberg, A.; Lamm, B.; Fagerhag, J.; Olwegard-Halvarson, M.; Shcherbuchin, V.; Elbrring, T.; Sjstrom, J. J Med Chem 2002, 45, 4282.

[4] Demirayak, S.; Mohsen, U. A.; Karaburun, A. C. Eur J Med Chem 2002, 37, 255.

[5] Kristjan, S. G.; Tidwel, J.; Lippa, N.; Cozalka, G. W.; Dranen, N. V.; Roger, G. P.; Drach, J. C.; Townsend, L. B. J Med Chem 2000, 43, 2464.

[6] Ismail, M. A.; Batista-Parra, A.; Miao, Y.; Wilson, W. D.; Wenzler, T.; Brun, R.; Boykin, D. W. Bioorg Med Chem 2005, 13, 6718.

[7] Kotovskaya, S. K.; Baskakova, Z. M.; Charushin, V. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Balakhnin, S. M.; Serova, O. A. Pharm Chem J 2005, 39, 574.

[8] Song, H.; Ding, S. Ranliao Yu Ranse 2003, 40, 116; Chem Abstr 2005, 144, 214339.

[9] Dietz, E.; Kapaun, G. Eur Pat Appl EP 612732, 1994; (b) Dietz, E.; Kapaun, G. Chem Abstr 1994, 121, 205347.

[10] Tschunarjew, M.; Keil, T. Ger (East) DD 280103, 1990; Chem Abstr 1991, 114, 101997.

[11] Oezden, S.; Atabey, D.; Yildiz, S.; Goeker, H. Bioorg Med Chem 2005, 13, 1587.

[12] Ozden, T.; Ayalp, A.; Ozden, S. FABAD Farmasotik Bilimler Dergisi 1984, 9, 25; Chem Abstr 1984, 101, 110816.

[13] Dost, F. Ger Offen DE 2900506, 1980; Chem Abstr 1980, 93, 239413.

[14] Hansen, G.; Dehnert, J. FR 1361778, 1964; Chem Abstr 1964, 61, 84281.

[15] Buchi, J.; Zwicky, H.; Aebi, A. Arch Pharm 1960, 293, 758; Chem Abstr 1961, 55, 2637.

[16] Katsuyama, I.; Kubo, M. Heterocycles 2007, 71, 2491.

[17] Ben Ammar, H.; Kaddachi, M. T.; Kahn, P. H. Phys Chem News 2003, 9, 137.

[18] Galinowski, S.; Lenartowicz, J. Pol PL 92820, 1977; Chem Abstr 1978, 89, 43425.

[19] Ibrahim, N. S.; Shams, H. Z.; Mohamed, M. H.; Elnagdi, M. H. Chem Ind 1988, 17, 563.

[20] Okamoto, Y.; Takagi, K.; Ueda, T. Chem Pharm Bull 1980, 28, 567.

[21] Okamoto, Y.; Zama, Y.; Itoh, T.; Aotsuka, T.; Kurasawa, Y.; Takagi, K. J Chem Res (S) 1990, 5, 136.

[22] Takagi, K.; Aotsuka, T.; Morita, H.; Okamoto, Y. Synthesis 1987, 4, 379.

[23] Elwan, N. M. Tetrahedron 2004, 60, 1161.

[24] Awadallah, A. M.; Seppelt, K.; Shorafa, H. Tetrahedron 2006, 62, 7744.

[25] Awadallah, A. M.; Zahra, J. A. Molecules 2008, 13, 170.

[26] Volovenko, Y. M.; Resnyanska, E. V.; Tverdokhlebov, A. V. Collect Czech Chem Commun 2002, 67, 365.

[27] Volovenko, Y. M.; Dubinina, G. G. Chem Heterocycl Comp 2001, 37, 122.

[28] Langer, P.; Wuckelt, J.; Doering, M.; Goerls, H. J Org Chem 2000, 65, 3603.

[29] Volovenko, Y. M.; Volovnenko, T. A. Chem Heterocycl Comp 2006, 42, 488.

[30] Volovenko, Y. M.; Dubinina, G. G. Chem Heterocycl Comp 1999, 35, 1089.

[31] Shokol, T. V.; Volovenko, Y. M.; Babichev, F. S. Khim Geterotsikl Soedin 1990, 12, 1696; Chem Abstr 1991, 114, 207131.

[32] Bejan, E.; Haddou, H. A.; Daran, J. C.; Balavoine, G. G. A. Synthesis 1996, 1012.

[33] Badawey, E.; Kappe, T. Eur J Med Chem 1995, 30, 327.

[34] Hammad, M.; Abdel Meguid, S.; El-Anani, M. M.; Shafik, N. Egypt J Chem 1986, 29, 549; Chem Abstr 1989, 111, 7287.

[35] Shenoy, V. U.; Seshadri, S. Dyes Pigm 1989, 11, 137.

[36] Khilya, O. V.; Volovnenko, T. A.; Turov, A. V.; Volovenko, Y. M. Chem Heterocycl Comp 2004, 40, 1063.

[37] Khilya, O. V.; Volovnenko, T. A.; Turov, A. V.; Volovenko, Y. M. Ukrainskii Khim Zh (Russ Ed) 2003, 69, 55; Chem Abstr 2003, 140, 217587.

[38] Volovnenko, T. A.; Tarasov, A. V.; Volovenko, Y. M. Ukrainskii Khim Zh (Russ Ed) 2006, 72, 108; Chem Abstr 2006, 145, 471448.

[39] Gokhale, U. V.; Seshadri, S. Dyes Pigm 1987, 8, 157.

[40] Abd El Latif, F. M.; Barsy, M. A.; Elrady, E. A.; Hassan, M. J Chem Res 1999, 12, 696.

[41] Reddy, K. V. T.; Rao, A. V. S. Org Prep Proc Int 1997, 29, 355; Chem Abstr 1997, 127, 5041.

[42] Bari, A.; Milicevic, S.; Feist, H.; Michalik, D.; Michalik, M.; Peseke, K. Synthesis 2005, 16, 2758.

[43] Montero, A.; Feist, H.; Michalik, M.; Quincoces, J.; Peseke, K. Synthesis 2002, 5, 664.

[44] Elmegeed, G. A. Egypt J Chem 2004, 47, 579; Chem Abstr 2006, 146, 338065.

[45] El-Sayed, A. S. Egypt J Pharm Sci 1999, 40, 129; Chem Abstr 2001, 136, 386069.

[46] Hishmat, O. H.; El-Diwani, H. I.; Melek, F. R.; El-Sahrawi, H. M.; El-Shabrawi, O. Indian J Chem 1996, 35B, 30.

[47] Bogdanowicz-Szwed, K.; Czarny, A. J Prakt Chem 1993, 335, 279.

[48] Elnagdi, M. H.; Sadek, K. U.; El-Maghraby, M. A.; Selim, M. A.; Khalafallah, A. K.; Reaslan, M. A. Phosphorus Sulfur Silicon Relat Elem 1995, 105, 51.

[49] Raslan, M. A. J Chin Chem Soc 2000, 47, 961.

[50] Chiba, T.; Takahashi, T.; Kaneko, C. Chem Pharm Bull 1985, 33, 4002.

[51] Abd El Latif, F. M.; El Rady, E. A.; Dopp, D. J Heterocycl Chem 2003, 40, 57.

[52] Hammad, M. A.; Kamel, M. M.; Abbasi, M. M.; El-Wassimi, M. T.; Hassan, H. N. A. Pharmazie 1986, 41, 141; Chem Abstr 1986, 105, 226445.

[53] Otero, I.; Feist, H.; Michalik, D.; Michalik, M.; Quincoces, J.; Peseke, K. Z Naturforschung B 2005, 60, 1175.

[54] Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. Heteroat Chem 1999, 10, 417.

[55] Dawood, K. M.; Farag, A. M.; Kandeel, Z. E. J Chem Res (S) 1999, 2, 88.

[56] Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. J Chem Res (S) 1998, 208.

[57] Abu Elmaati, T. A.; Said, S.; Elenein, N. A.; Sofan, M. M.; Khodeir, N. Polish J Chem 2002, 76, 945.

[58] Hassanien, A. A.; Mohamed, M. H.; Gohzlan, S. A. S. J Chem Res 2005, 7, 440.

[59] Gorobets, N. Y.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. Tetrahedron 2004, 60, 8633.

[60] Abu Elmaati, T. M.; Said, S. B.; Abu Elenein, N. S.; Khodeir, N. M.; Sofan, M. M. J Heterocycl Chem 2003, 40, 481.

[61] Abu Elmaati, T. M. Acta Chim Slov 2002, 49, 721.

[62] El-Taweel, F. M. A. Phosphorus Sulfur Silicon Relat Elem 2004, 179, 1267.

[63] Rangnekar, D. W.; Rajadhyaksha, D. D. Indian J Technology 1990, 28, 75; Chem Abstr 1990, 113, 134153.

[64] Rida, S. M.; Soliman, F. S. G.; Badawey, E. S. A. M.; Kappe, T. J Heterocycl Chem 1988, 25, 1725.

[65] Mencke, B.; Schmitt, K. Archiv Pharm 1967, 300, 481; Chem Abstr 67, 116846, 1967.

[66] Kuz'menko, V. V.; Komissarov, V. N.; Simonov, A. M. Khim Geterotsikl Soedin 1981, 11, 1497; Chem Abstr 982, 96, 85465.

[67] Tereshchenko, A. D.; Tolmachev, A. A.; Tverdokhlebov, A. V. Synthesis 2004, 373.

[68] Badawey, E. A. M.; Kappe, T. Eur J Med Chem 1999, 34, 663.

[69] Russell, R. K.; van Nievelt, C. E. R. W. J Heterocycl Chem 1995, 32, 299.

[70] Badawey, E. A. M.; Rida, S. M.; Soliman, F. S. G.; Kappe, T. Monatsh Chem 1987, 120, 73.

[71] Volovenko, Y. M.; Nemazanyi, A. G.; Babichev, F. S. Dopovidi Akademii Nauk Ukrains'koi RSR, Seriya B: Geologichni, Khimichni ta Biologichni Nauki, 1984, 3, 33; Chem Abstr 1984, 101, 38376.

[72] Nemazanyi, A. G.; Volovenko, Y. M.; Silaeva, T. A.; Babichev, F. S. Doklady Akademii Nauk SSSR 1990, 310, 1135; Chem Abstr 1990, 113, 78221.

[73] Volovenko, Y. M.; Nemazanyi, A. G.; Ryabokon, I. G.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1988, 54, 295; Chem Abstr 1989, 110, 38921.

[74] Volovenko, Y. M.; Nemazanyi, A. G.; Shevchenko, V. A.; Babichev, F. S. Dopovidi Akademii Nauk Ukrains'koi RSR, Seriya B: Geologichni, Khimichni ta Biologichni Nauki, 1983, 9, 27; Chem Abstr 1984, 100, 6393.

[75] Soliman, F. S. G.; Rida, S. M.; Badawy, E. S. A. M.; Kappe, T. Arch Pharm 1984, 317, 951.

[76] Rida, S. M.; Soliman, F. S. G.; Badawey, E. S. A. M.; El-Ghazzawi, E.; Kader, O.; Kappe, T. J Heterocycl Chem 1988, 25, 1087.

[77] Volovenko, Y. M.; Nemazanyi, A. G.; Vesel'skaya, G. L.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1987, 53, 1085; Chem Abstr 1988, 109, 110333.

[78] Kandeel, Z. E. J Chem Res (S) 1995, 7, 290.

[79] Dhamnaskar, S. V.; Rangnekar, D. W. Dyes Pigm 1988, 9, 467.

[80] Dubey, P. K.; Reddy, P. V.; Prasada, V.; Srinivas, K. ARKIVOC 2007, 15, 192.

[81] Elgemeie, G. H.; Metwally, N. H. Monatsh Chem 2000, 131, 779.

[82] Panda, K.; Suresh, J. R.; Ila, H.; Junjappa, H. J Org Chem 2003, 68, 3498.

[83] Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y. Bunseki Kiki 1977, 15, 413; Chem Abstr 1978, 88, 121047.

[84] Elgemeie, G. H.; Elghandour, A. H.; Hussein, A. M. Synth Commun 2004, 34, 3293.

[85] Babu, V. N. S. R.; Babu, A. N.; Anand, V.; Hanumanthu, P. A. Synth Commun 1998, 28, 4439.

[86] Nath, M.; Srivastava, P.; Goel, A.; Ram, V. J. Eur J Org Chem 1998, 10, 2083.

[87] Volovenko, Y. M.; Volovnenko, T. A.; Kozynchenko, A. P.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1996, 62, 124; Chem Abstr 126, 157445.

[88] Kreutzberger, A.; Kreutzberger, E.; Wiedemann, D. Chemiker-Zeitung 1985, 109, 153; Chem Abstr 1985, 103, 196055.

[89] McKinnon, D. M.; Spevack, P.; Tipples, G. Chem Abstr J Chem 1988, 66, 2339.

[90] Kato, T.; Daneshtalab, M. Chem Pharm Bull 1976, 24, 1640.

[91] Blyumin, E. V.; Volovenko, Y. M.; Neunhoeffer, H.; Shishkina, S. V.; Zubatyuk, R. A.; Shishkin, O. V. Tetrahedron 2002, 58, 5733.

[92] Farag, A. M. J Chem Res (S) 1994, 11, 432.

[93] Vovk, M. V.; Lebed, P. S.; Pirozhenko, V. V.; Tsymbal, I. F. Russ J Org Chem 2004, 40, 1669.

[94] Nawwar, G. A. M.; Zaki, M. M. E. A.; Chabaka, L. M. Phosphorus Sulfur Silicon Relat Elem 1993, 79, 195.

[95] Abdelhamid, A. O.; Elghandour, A. H.; Rateb, N. A.; Awad, A. M. Phosphorus Sulfur Silicon Relat Elem 2006, 181, 1637.

[96] Abdelhamid, A. O.; Zohdi, H. F.; Ziada, M. M. Indian J Chem 2001, 40B, 284; Chem Abstr 2001, 135, 92613.

[97] Ivachtchenko, A.; Kovalenko, S.; Parkhomenko, O.; Chernykh, V. Heterocycl Commun 2002, 8, 329; Chem Abstr 2002, 138, 255190.

[98] Badawey, E. S. A. M.; Hazzaa, A. A.; Rida, S. M.; Fahmy, H. T. Y. Arch Pharm 1992, 325, 565.

[99] Farag, A. M. J Chem Res (S) 1995, 3, 96.

[100] Rahmouni, M.; Derdour, A.; Bazureau, J. P.; Hamelin, J. Tetrahedron Lett 1994, 35, 4563.

[101] Volovenko, Y. M.; Nemazanyi, A. G.; Shokol, T. V.; Kornilov, M. Y.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1990, 56, 390; Chem Abstr 1990, 113, 211933.

[102] Badawey, E. S. A. M.; Rida, S. M.; Soliman, F. S. G.; Kappe, T. J Heterocycl Chem 1989, 26, 405.

[103] Ried, W.; Akyuz, A. Chemiker-Zeitung 1988, 112, 241; Chem Abstr 1989, 110, 114784.

[104] Volovenko, Y. M.; Shokol, T. V.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1986, 52, 742; Chem Abstr 1987, 107, 175932.

[105] Hammad, M. A.; Nawwar, G. A.; Elgemeie, G. H.; Elnagdi, M. H. Heterocycles 1985, 23, 2177.

[106] Reddy, K. V.; Mogilaiah, K.; Sreenivasulu, B. J Indian Chem Soc 1984, 61, 888.

[107] Volovenko, Y. M.; Shokol, T. V.; Dashkovskaya, E. V.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1985, 51, 649; Chem Abstr 1986, 104, 19487.

[108] Litenko, V. A.; Volovenko, Y. M.; Babichev, F. S. Ukrainskii Khim Zh 1983, 49, 1202; Chem Abstr 1984, 101, 72666.

[109] Litenko, V. A.; Volovenko, Y. M.; Babichev, F. S. Ukrainskii Khim Zh (Russ Ed) 1983, 4911, 1202; Chem Abstr 1984, 100, 121001.

[110] Babichev, F. S.; Volovenko, Y. M.; Pereshivana, L. M. Ukrainskii Khim Zh (Russ Ed) 1983, 49, 1095; Chem Abstr 1984, 100, 51533.

[111] Volovenko, Y. M.; Pereshivana, L. M.; Babichev, F. S. Dopovidi Akademii Nauk Ukrains'koi RSR, Seriya B: Geologichni, Khimichni ta Biologichni Nauki, 1979, 3, 193; Chem Abstr 1979, 90, 204004.

[112] Makovetskii, V. P.; Dzvinchuk, I. B.; Volovenko, Y. M.; Svishchuk, A. A. Khim Geterotsikl Soedin 1980, 2, 164; Chem Abstr 1980, 93, 26340.

[113] Elgemeie, G. H.; Sood, S. A. J Chem Res (S) 2001, 10, 439.

# On the Purity of 2-[*ortho*-Anilinyl]-1,3-benzoxazole Derived from 2*H*-3,1-Benzoxazine-2,4(1*H*)dione (*Isatoic Anhydride*) [1,2]



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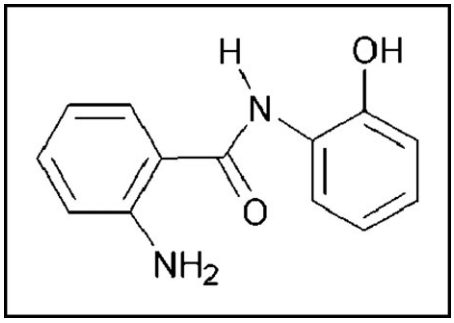


The Lewis acid catalyzed synthesis and chromatographic purification of isatoic anhydride-derived 2-(2′-anilinyl)-1,3-benzoxazole (**2**) can result in the co-isolation of **2** and a light pink colored impurity (<5%). This latter species has been identified (NMR, single crystal X-ray diffraction, mp) as 2′-hydroxy-2-aminobenzanilide (**3**), which represents a predictable intermediate in the formation of **2**. Compound **3** crystallizes in an orthorhombic crystal system of space group $P2_12_12_1$ with four molecules in the unit cell ($\alpha = \beta = \gamma = 90°$; $a = 6.715$ (2) Å, $b = 12.100$ (4) Å, $c = 13.321$ (4) Å; $V = 1082.2$ (6) Å$^3$). Pure **2** is characterized as a colorless, high-melting solid; unlike the dark colored oil that is isolated if **2** contains traces of **3**.

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## INTRODUCTION

Oxazoles, 2-oxazolines (*i.e.*, 4,5-dihydro-1,3-oxazoles) and 1,3-benzoxazoles represent an important group of organic heterocyclic compounds. These materials have found widespread applications as ligands in transition metal and main group coordination chemistry and as important monomers in polymer science. In addition, these heterocycles are used in medicinal chemistry and in regio-selective and enantio-selective synthesis [3–12]. Our own interests lie in the design and application of novel oxazoles for metal-mediated catalysis and in fundamental studies of inorganic structural chemistry [13–18]. Several years ago, Gajare *et al*. demonstrated that isatoic anhydride (*i.e.*, 2*H*-3,1-benzoxazine-2,4(1*H*) dione: **1**; Scheme 1) [19–21] can be used as a useful synthon for the production of *o*-anilinyl-oxazolines, -oxazines, and -benzoxazoles [22]. Their coupling strategy involved the application of kaolinitic clay as a Lewis acid promoter of decarboxylative coupling and subsequent dehydrative ring formation reactions between **1** and ω-aminoalcohols (Scheme 1; E = —$(CRR')_n$— ($n$ = 2 or 3), *o*—$C_6H_4$). Our independent study of this reaction using $ZnCl_2$ [23] or $ZnBr_2$ [24,25] as catalyst had revealed that the desired product of the above reaction between **1** and *o*-aminophenol, *viz*. 2-(1,3-benzoxazol-2-yl)aniline (**2**: *i.e.*, 2-[*o*-anilinyl]-1,3-benzoxazole: Scheme 1), can be problematic to isolate in pure form by these reaction protocols [22,23]. Details of this investigation are reported herein.

## RESULTS AND DISCUSSION

We were perplexed by the earlier disclosure (and indeed in our own synthesis and purification by similar means) [23,24] that compound **2**, following chromatographic isolation, often takes the form of a dark colored analytically pure oil. Compared with the variety of other structurally analogous materials that we had made, it seemed unusual that this compound should exist as a liquid under ambient conditions. A thorough search of the literature reveals that compound **2** has in fact been previously reported by several different synthetic

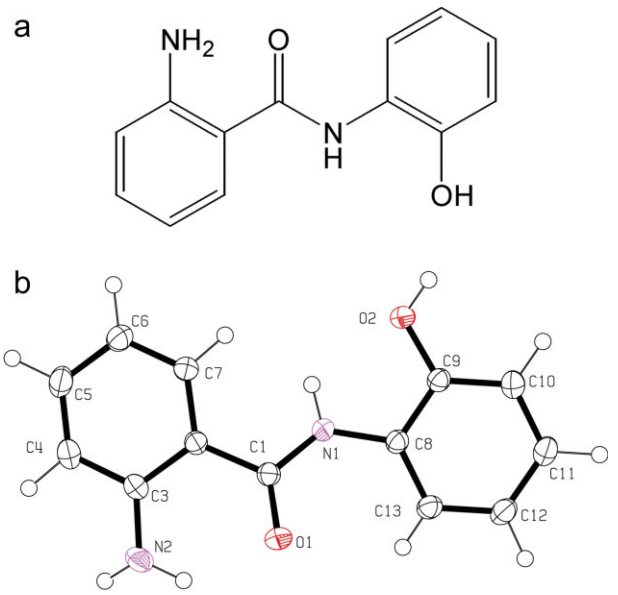



**Figure 1.** (a) A molecular representation of **3**. (b) An ORTEP diagram of a molecule of **3** found in the unit cell. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

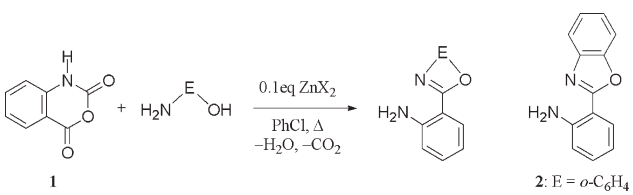
methodologies and in all cases reported as a colorless solid. However, there is considerable discrepancy as to the exact mp of **2** (reported mps: 126°C [26]; 113–115°C [27]; 105–105.5°C [28]; 105°C [29]). On one occasion in our own laboratories, we also obtained the said material as an off-white solid with a mp of 103–105°C (which we likewise reported in 2003 [23]), a property consistent with that reported independently by both Culbertson et al. [29] and Igeta and coworkers [28]. These conflicting observations promoted us to re-examine both **2** and the ''oil'' material more closely, and we have thus found that flash chromatographic isolation of **2** using EtOAc/hexanes (v/v: 50/50 or 25/75) mixtures often leads [22,23] to the contamination of **2** with a small amount of a second light pink-colored compound (**3**). When this impurity is present, impure **2** does indeed take the form of a viscous tar-like oil which is typically dark in color. This material is usually isolated when the accompanying solvent is removed expeditiously by, for example, rotary evaporation. An interesting facet of this oil is the acceptable level of analytical purity (calculated for $C_{13}H_{10}N_2O$: C 74.28, H 4.76, N 13.33; found [22]: C 74.48, H 4.26, N 13.61%). We have succeeded in isolating **2** that is free of **3** by careful fractional crystallization of the resulting mixture dissolved in EtOAc/hexanes. Slow solvent removal by evaporation under ambient conditions (in open test tubes) leads to the gradual precipitation of a white material in the form of needles (identified as **2**) and a second crystalline light pink-colored solid (**3**), which is present in quite small amounts relative to that of **2**. Investigation of this latter material isolated in this way *via* $^1$H NMR spectroscopy and mp measurements (mp: 136–136.5°C) reveals very similar properties to those reported [30] some 40 years ago for 2′-hydroxy-2-aminobenzanilide (lit. mp: 139–140°C: Fig. 1). This compound is an obvious and predictable intermediate [19–21,23] in the synthesis of **2** from **1**. To obtain unequivocal evidence on the nature of **3**, a single crystal X-ray diffraction study was carried out. Compound **3**, 2′-hydroxy-2-aminobenzanilide (Fig. 1), crystallizes in the $P2_12_12_1$ space group with four molecules in the unit cell (see Table 1). The molecules contain virtually co-planar aromatic groupings and intra-molecular *H*-bonding between the amide oxygen atom (O1) and the $NH_2$ group (O1···H—N2 = 2.024 Å) and the amide *H*-atom and the *O*-atom of the phenolic —OH functionality (O2···H1—N1 = 2.132 Å). In addition, a close inter-molecular contact is found between the *H* of this —OH group (*i.e.*, H2C) and O1 (O1···H2C = 1.773 Å). An ORTEP representation of a molecule of **3** from the unit cell is shown in Figure 1.

**Table 1**

Selected bond distances (Å), bond angles (deg), and dihedral angles (deg) for compound **3** with estimated standard deviations in parentheses (see Fig. 1).

| | |
|---|---|
| Bond distances | |
| O1–C1 | 1.235 (2) |
| O2–C9 | 1.364 (2) |
| N1–C1 | 1.349 (2) |
| N1–C8 | 1.410 (2) |
| N2–C3 | 1.371 (2) |
| Bond angles | |
| C8–N1–C1 | 129.68 (11) |
| O1–C1–N1 | 121.86 (11) |
| Dihedral angle | |
| C8–N1–C1–C2 | 173.11 (11) |

**Scheme 1**




The off-white needle form of **2** (mp: 103–105°C) isolated above was subjected to recrystallization from boiling pet. spirit (60–80°C bp range) to yield initially a cream colored material in the form of very thin needles (mp: 106–108°C). This crop was subsequently recrystallized a second time from the same solvent to give colorless needles (mp: 109–111°C). The variability in mp behavior of **2** may be due to its sensitivity to gradual yellowing (presumably oxidation) under ambient

conditions. We have been unable to recrystallize **2** from hydrocarbon media to a point in which the measured mp mimics that disclosed by Padmaja *et al*. (126°C: to our knowledge the highest mp reported for **2**) [26]. Their method used glacial acetic acid for recrystallization. Using this solvent gave white material of mp 113–114°C. It should also be noted that the analytical purity of **2**, as described in [22], could contain traces of **3**. For example, the contamination of a sample of **2** by 1% by weight of **3** (corresponding to 9.3 molecules of **3** per 100 that of **2**) gives a calculated elemental analysis (calc.: C 74.16; H 4.79; N 13.38%) consistent with **2** (*vide supra*) and this concentration of impurity makes it unlikely that **3** would be easily spotted by NMR spectroscopy. Despite these facts, it does appear as if all these levels of purity of **2** are still of sufficient quality for the use of this material in subsequent syntheses [23,31,32].

## EXPERIMENTAL

**Isolation of 2-(1,3-benzoxazol-2-yl)aniline (2) and 2′-hydroxy-2-aminobenzanilide (3).** The synthesis of compounds **2** and **3** was carried out as described in reference [23]. Purification of the reaction mixture *via* flash chromatography (1/1 v/v hexanes/EtOAc) using ~50 g of silica on a column of 2 cm diameter yielded ~40 fractions (~15 mL each in test tubes). These extractions were left to evaporate in open air (fumehood) of which the first 15 contained solid pure (NMR) **2** (yield 36% [23]); fractions 16–18, which were slightly pink in color, yielded about 50 mg of **3** (0.4%) and a small amount of **2**. Compounds **2** and **3** were then separated manually from these fractions. The latter fractions contained species which could not be unequivocally identified (NMR). Properties of **2**: mp 113–114°C (AcOH; lit.: see text); pmr (δ, 400 MHz, deuterochloroform): data was consistent to within experimental error to that reported (lit. [28]). Properties of **3**: mp: 136–136.5°C (1/1 v/v hexanes/EtOAc; lit. [30] 139–140°C); pmr (δ, 600 MHz, deuterochloroform containing ~10% hexadeutero-dmso), 9.11 (s, br, 1H, N*H*), 8.75 (s, br, 1H, O*H*), 7.71 (dd, 1H, $J$ = 1.7, 7.8, Ar*H*), 7.34 (dd, 1H, $J$ = 1.5, 7.9, Ar*H*), 7.00 (td, 1H, $J$ = 1.2, 7.2, Ar*H*), 6.75 (m, 1H, Ar*H*), 6.72 (dd, 1H, $J$ = 1.8, 7.8, Ar*H*), 6.63 (m, 2H, Ar*H*), 6.52 (dd, 1H, $J$ = 1.2, 7.8, Ar*H*), 6.46 (td, 1H, $J$ = 1.2, 7.2, Ar*H*), 2.60 (s, v. br, N$H_2$); cmr (δ, 150 MHz, deuterochloroform containing ~10% hexadeutero-dmso), 167.5 (*C*=O), 148.7, 147.1, 132.1, 127.6, 126.3, 124.4, 121.0, 119.3, 117.0, 116.0, 115.9, 115.5.

**Crystal data for 3.** The structure of complex **3** was solved using previously described methods [33]. Formula $C_{13}H_{12}N_2O_2$, MW: 229.24, orthorhombic, space group $P2_12_12_1$, $a$ = 6.715 (2) Å, $b$ = 12.100 (4) Å, $c$ = 13.320 (4) Å, α = β = γ = 90°, $V$ = 1082.2 (6) Å$^3$, $D_c$ = 1.401 g/cm$^3$, $Z$ = 4. Crystal size: 0.80 × 0.71 × 0.56 mm$^3$, light pink. Temperature = 173 (2) K, λ(MoKα) = 0.71073 Å, Absolute coefficient = 0.097 mm$^{-1}$, $F$(000) = 480, θ range for data collection: 2.27–32.46°, *hkl* range: –4 to 10, –17 to 18, –20 to 18. Reflexions collected: 16,294, Independent reflexions: 3893 [$R$(int) = 0.0581], Completeness to θ = 32.46°: 99.9%, Absorption corr.: numerical, max. and min. transmission: 0.9479, 0.9265, refinement method: full-matrix least-squares on $F^2$, data/restraints/parameters: 3893/0/202, GOF on $F^2$: 1.042, final $R$ indices [$I > 2\sigma(I)$] $R1$ = 0.0446, w$R2$ = 0.1126, $R$ indices (all data): $R1$ = 0.0544, w$R2$ = 0.1193, absolute structure parameter: 0.7 (10), largest diff. peak and hole: 0.241–0.272 eÅ$^{-3}$. The molecular representation found in Figure 1 was drawn using ORTEP-III for Windows [34]. CCDC #747662 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

## CONCLUSIONS

This investigation has demonstrated that compound **2** (*i.e*., 2-[1,3-benzoxazol-2-yl]aniline) can be problematic to isolate in very pure form under the reaction conditions described independently by us and Gajare *et al*. Contamination of **2** by its ring opened precursor (2′-hydroxy-2-aminobenzanilide: **3**) can lead to the isolation of analytically ''pure'' material in an oil-like form. Caution is likewise advised as to the measurement of the purity of solid **2** by mp determination although lower melting point material appears to be of sufficient purity for later synthetic applications. Material with the most pronounced mp behavior is that which has been recrystallized from glacial acetic acid as described previously [26]. The contaminant of **2**, *viz*. **3**, has been fully characterized (mp, NMR, X-ray diffraction).

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## REFERENCES AND NOTES

[1] 2-[*ortho*-Anilinyl]-1,3-benzoxazole is also referred to as 2-(1,3-benzoxazol-2-yl)aniline.

[2] Oxazoles XXIV. Part XXIII. See Deshpande et al. [13].

[3] Desimoni, G.; Faita, G.; Jørgensen, K. A. Chem Rev 2006, 106, 3561.

[4] Hargaden, G. C.; Guiry, P. J. Chem Rev 2009, 109, 2505.

[5] Meyers, A. I. J Org Chem 2005, 70, 6137.

[6] Pfaltz, A. Acta Chem Scand 1996, 50, 189.

[7] Rasappan, R.; Laventine, D.; Reiser, O. Coord Chem Rev 2008, 252, 702.

[8] Gade, L. H.; Bellemin-Laponnaz, S. Coord Chem Rev 2007, 251, 718.

[9] Fraile, J. M.; García, J. I.; Mayoral, J. A. Coord Chem Rev 2008, 252, 624.

[10] Lorcy, D.; Bellec, N.; Fourmigué, M.; Avarvari, N. Coord Chem Rev 2009, 253, 1398.

[11] Maggini, S. Coord Chem Rev 2009, 253, 1793.

[12] Culbertson, B. M. Prog Polym Sci 2002, 27, 579.

[13] Deshpande, A. A.; Gossage, R. A.; Jackson, S. M.; Quail, J. W.; Sadowy, A. L.; Yadav, P. N. Z Naturforsch 2009, 64b, 1046.

[14] Gossage, R. A.; Yadav, P. N.; MacInnis, T. D.; Quail, J. W.; Decken, A. Can J Chem 2009, 87, 368.

[15] Gossage, R. A.; Jenkins, H. A.; Jones, N. D.; Jones, R. C.; Yates, B. F. Dalton Trans 2008, 3115.

[16] Cabeza, J. A.; da Silva, I.; del Río, I.; Gossage, R. A.; Miguel, D.; Suarez, M. Dalton Trans 2006, 2450.

[17] Decken, A.; Eisnor, C. R.; Gossage, R. A.; Jackson, S. M. Inorg Chim Acta 2006, 359, 1743.

[18] del Río, I.; Gossage, R. A. Acta Crystallogr 2009, E65, m103.

[19] (a) Shvekhgeimer, M.-G. Khim Geterosiklicheskikh Soed 2001, 435; (b) Shvekhgeimer, M.-G. Chem Heterocycl Compd 2001, 37, 385.

[20] Coppola, G. M. Synthesis 1980, 505.

[21] Kappe, T.; Stadlbauer, W. Adv Heterocycl Chem 1981, 28, 127.

[22] Gajare, A. S.; Shaikh, N. S.; Jnansehwara, G. K.; Deshpande, V. H.; Ravindranathan, T.; Bedekar, A. V. J Chem Soc Perkin Trans 1 2000, 999.

[23] Button, K. M.; Gossage, R. A. J Heterocycl Chem 2003, 40, 513.

[24] Gossage, R. A. Curr Org Chem 2006, 10, 923.

[25] Gossage, R. A. In Experiments in Green and Sustainable Chemistry; Roesky, H. W., Kennepohl, D., Eds.; Wiley-VCH: Weinheim, 2009; Chapter 4, p 19.

[26] Padmaja, J.; Satyanarayana Reddy, M.; Ratnam, C. V. Indian J Chem 1987, 26B, 951.

[27] Kini, S. G.; Saraswat, G.; Gandhi, A. M. Indian J Heterocycl Chem 2005, 15, 99.

[28] Ohsawa, A.; Kawaguchi, T.; Igeta, H. Chem Pharm Bull 1982, 30, 4352.

[29] Haskell, T. H.; Peterson, F. E.; Watson, D.; Plessas, N. R.; Culbertson, T. J Med Chem 1970, 13, 697.

[30] Sam, J.; Richmond, C. W. J Heterocycl Chem 1964, 1, 245.

[31] Dubey, S. K.; Sharma, S.; Iyer, R. N. Z Naturforsch 1979, 34b, 99.

[32] Barni, E.; Pasquino, S.; Savarino, P.; Di Modica, G. Dyes Pigm 1985, 6, 1.

[33] Gossage, R. A.; Jenkins, H. A. Acta Chim Slov 2009, 56, 329.

[34] Farrugia, L. J. J Appl Crystallogr 1997, 30, 565.

# A Novel Three-Component One-Pot Reaction Involving β-Naphthol, Aldehydes, and Urea Promoted by TMSCl/NaI

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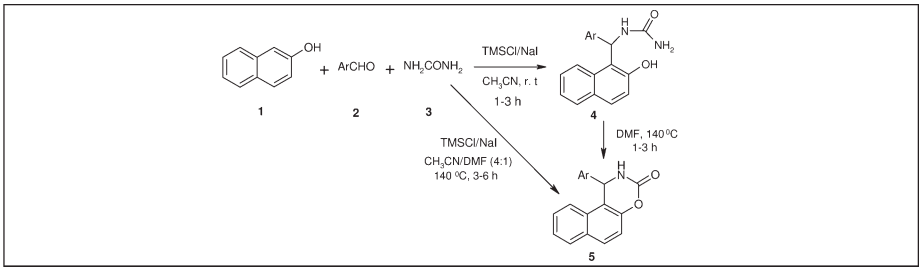


Amidoalkyl naphthol derivatives have been synthesized in good yields in a one-pot condensation of β-naphthol, aromatic aldehydes and urea in presence of TMSCl/NaI at room temperature. Ring closure of amidoalkyl naphthol derivatives occurred at 140°C to afford 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazin-3-one derivatives.

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## INTRODUCTION

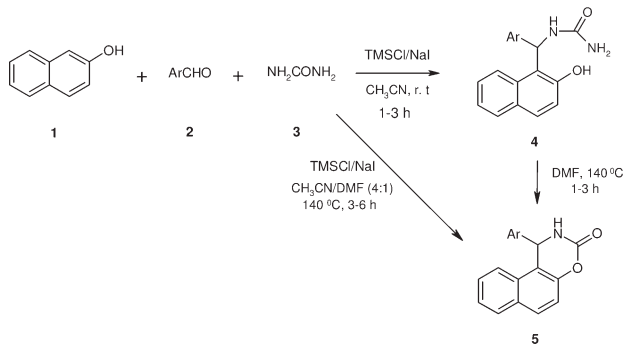
Multicomponent reactions have emerged as powerful strategies with the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules, which provide maximum diversity are encouraging on economy and environmental grounds [1]. One such example is the reaction of β-naphthol and aldehydes with urea to produce amidoalkyl naphthols or oxazinone derivatives. Benzoxazin-4-one derivatives are an important class of heterocyclic compounds [2–5], which exibit many industrial, research, and clinical applications. Naphthalene condensed oxazinone derivatives are known to possess interesting pharmacological and reported as antibacterial agents [6]. These compounds have also been used in the preparation of chiral amino phosphine ligands for asymmetric catalysis [7]. Even though a large number of methods [8–15] were reported for the preparation of intermediate compounds (amidoalkyl naphthols), ring closure reactions to give naphthalene condensed oxazinone derivatives have not been thoroughly investigated [16–19]. This has stimulated significant interest and there is always considerable demand in exploring more milder, convenient, practical, and efficient reagents for their synthesis using multicomponent reactions. Therefore, the development of simple, convenient, and practical procedures for the synthesis of naphtho[1,2-e][1,3]oxazin-3-one derivatives continue to be a challenging endeavor in synthetic organic chemistry.

## RESULTS AND DISCUSSION

TMSCl/NaI combination has been explored in various organic transformations [19]. In continuation of our efforts to explore the synthetic utility of TMSCl/NaI combination [20], herein we report a three-component approach for the one-pot synthesis of a series of amidoalkyl naphthols and naphthoxazinones under different reaction conditions using TMSCl/NaI (Scheme 1).

Initially, we examined the reaction of naphthol (**1**), benzaldehyde (**2**), and urea (**3**) in the presence of TMSCl/NaI in $CH_3CN$ at room temperature and found to give the corresponding intermediate amidoalkyl naphthol derivative **4a** in 81% yield. The structure of the product was confirmed by spectral data and compared with the authentic sample. Similarly, other aromatic aldehydes were also reacted to give the intermediate compounds in good yields at room temperature (Scheme 2) and the results are presented in Table 1. Under present conditions, formation of side products, such as, dibenzoxanthenes was not observed. When an intermediate amidoalkyl naphthol derivative **4a** was heated in DMF at 140°C for 1.2 h cyclization occurred to produce the naphthoxazinone **5a**. Encouraged by this result, the reaction of β-naphthol (**1**), benzaldehyde (**2**), and urea (**3**) in the presence of TMSCl/NaI in $CH_3CN$/DMF (4:1) was directly heated at 140°C and found to give the cyclized product, naphthoxazinone **5a** exclusively within 1 h, without isolating the intermediate **4a**. To find out the scope and generality of this reaction, we turned our attention to various substituted aldehydes.

**Scheme 1**




The aromatic aldehydes containing both electron-donating and electron-withdrawing groups afforded the desired products. All the reactions were clean at 140°C and the corresponding cyclized products **5b–m** were obtained in good yields without isolating intermediate compounds **4**. The results are summarized in Table 2. The products were characterized by spectral data and known compounds were compared with the authentic samples data.

In summary, we have demonstrated an efficient protocol for the synthesis of amidoalkyl naphthols and naphthoxazinone derivatives using TMSCl/NaI as promoter. The notable features of this method are mild reaction conditions, greater selectivity, simplicity in operation, which make it an attractive and very useful process for the synthesis of amidoalkyl naphthol and naphthoxazinone derivatives of biological importance.

## EXPERIMENTAL

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FTIR 240-c spectrophotometer using KBr optics. $^1$H NMR spectra were recorded onVarian-unity 300 spectrometer in CDCl3 using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

**General procedure for the synthesis of amidoalkyl naphthol derivatives 4 and naphthoxazinones 5.** To a mixture of 1 equiv. of β-naphthol, 1 equiv. of aromatic aldehyde and 1.5 equiv. of urea in acetonitrile (10 mL) was added 1.5 equiv. of TMSCl and 1.5 equiv. of NaI at 0°C and stirred at room temperature (see Table 1). After completion, followed by TLC, acetonitrile was removed and ethyl acetate was added to the residue. Ethyl acetate was washed with water, sodium thiosulfate, and brine solution, dried, and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford the pure product **4**.

**Scheme 2**

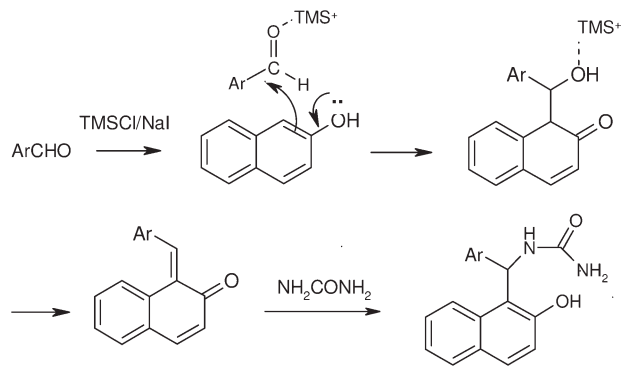
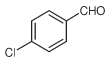
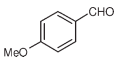
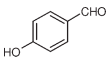
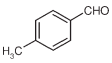



**Table 1**

TMSCl/NaI catalyzed synthesis of amidoalkyl naphthols (**4**).[a,b]

| Entry | Aldehyde | Time (h) | Yield (%) | mp (°C) |
|---|---|---|---|---|
| **4a** |  | 1.5 | 81 | 212 |
| **4b** |  | 1.8 | 79 | 208 |
| **4c** |  | 1.2 | 78 | 193 |
| **4d** |  | 3 | 78 | 198 |
| **4e** |  | 2.3 | 81 | 179 |

[a] All products were confirmed by their spectral data and compared with authentic samples.
[b] Isolated yields after purification.

A mixture of intermediate amidoalkyl naphthol derivative **4** in DMF was heated at 140°C for 1–3 h. After completion of cyclization reaction, followed by TLC, water was added and extracted with ether. The organic layer was washed with water and brine solution, dried, and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford naphthoxazinone product **5**.

**General procedure for the one-pot synthesis of naphthoxazinones 5.** To a mixture of 1 equiv. of β-naphthol, 1 equiv. of aromatic aldehyde and 1.5 equiv. of urea in acetonitrile/dimethyl formamide (6 mL:1.5 mL; 4:1) was added 1.5 equiv. of TMSCl and 1.5 equiv. of NaI at 0°C and stirred at 140°C (see Table 2). After completion, followed by TLC, solvent mixture was removed by rotary evaporation and ethyl acetate was added to the residue. Ethyl acetate was washed with water, sodium thiosulfate, and brine solution, dried, and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford the pure product **5**.

**Spectral data of amidoalkyl naphthol derivatives 4.**

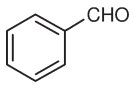
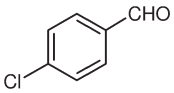
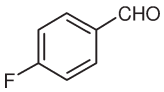
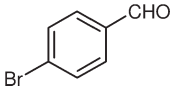
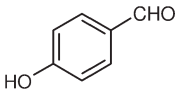
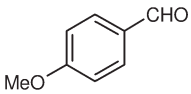
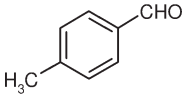
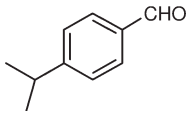
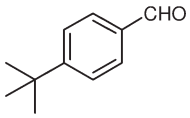
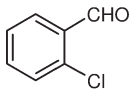
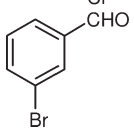
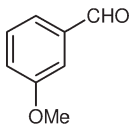
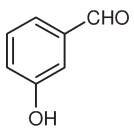
***Compound 4a.*** mp 212°C; $^1$H NMR (300 MHz, DMSO): 5.55 (s, 2H), 7.22.7.51 (m, 9H), 7.63–7.81 (m, 2H), 7.94–8.20 (d, $J$ = 7.8 Hz, 2H), 9.80 (s, 1H). IR (KBr): 3450, 3210, 1640, 1575, 1510, 1425, 1360, 1242, 816 cm$^{-1}$. ESI MS: $m/z$ 292 ($M^+$).

***Compound 4b.*** mp 208°C; $^1$H NMR (200 MHz, DMSO): 5.61 (s, 2H), 7.05–7.42 (m, 8H), 7.65–7.83 (d, $J$ = 11.2 Hz, 1H), 8.23 (d, $J$ = 8.2 Hz, 1H), 9.95 (s, 1H). IR (KBr): 3420, 3320, 1651, 1570, 1520, 1420, 1362, 1242, 815 cm$^{-1}$. ESI MS: $m/z$ 326 ($M^+$).

***Compound 4c.*** mp 193°C; $^1$H NMR (300 MHz, DMSO): 3.75 (s, 3H), 5.53 (s, 2H), 7.52–7.81 (m, 8H), 7.95–8.12 (m, 2H), 8.24 (d, $J$ = 8.2 Hz, 2H), 9.65 (s, 1H). IR (KBr): 3410, 3320, 1650, 1578, 1523, 1425, 1362, 1240, 780 cm$^{-1}$. ESI MS: $m/z$ 322 ($M^+$).

**Table 2**

TMSCI/NaI catalyzed synthesis of naphtho[1,2-e][ ] benzoxazinones (**5**).[a,b]

| Entry | Aldehyde | Time (h) | Yield (%) | mp (°C) |
|---|---|---|---|---|
| **5a** |  | 2 | 78 | 219 |
| **5b** |  | 2.6 | 86 | 208 |
| **5c** |  | 1.5 | 86 | 203 |
| **5d** |  | 1.9 | 79 | 221 |
| **5e** |  | 2.4 | 89 | 182 |
| **5f** |  | 1.6 | 78 | 187 |
| **5g** |  | 2.4 | 86 | 166 |
| **5h** |  | 3 | 81 | 172 |
| **5i** |  | 2.5 | 80 | 178 |
| **5j** |  | 4 | 62 | 199 |
| **5k** |  | 3.2 | 68 | 222 |
| **5l** |  | 4.9 | 66 | 172 |
| **5m** |  | 5 | 71 | 189 |

[a] All products were characterized by spectral data and compared with the authentic samples.
[b] Isolated pure products.

***Compound 4d.*** mp 198°C; $^1$H NMR (300 MHz DMSO): 5.65 (s, 2H), 7.52–7.65 (m, 8H), 7.72–7.96 (m, 2H), 8.34 (d, $J$ = 8.3 Hz, 2H), 9.73 (s, 1H). IR (KBr): 3445, 3322, 1646, 1575, 1530, 1415, 1360, 1242, 816, 780 cm$^{-1}$. ESI MS: $m/z$ 308 ($M^+$).

***Compound 4e.*** mp 179°C; $^1$H NMR (200 MHz, DMSO): 2.13 (s, 3H), 5.56 (s, 2H), 6.92–7.85 (m, 8H), 7.93–8.13 (m, 2H), 8.34 (d, $J$ = 8.3 Hz, 2H), 9.63 (s, 1H). IR (KBr): 3420, 3326, 1652, 1572, 1475, 1365, 1241, 860, 781 cm$^{-1}$. ESI MS: $m/z$ (%) 306 ($M^+$+1).

**Spectral data of naphthoxazines 5.**

***Compound 5a.*** mp 219°C; $^1$H NMR (300 MHz, DMSO): 6.12 (d, $J$ = 2.26 Hz, 1H), 7.24–8.12 (m, 3H), 8.88 (brs, 1H). IR (KBr): 3296, 1721, 1517, 720 cm$^{-1}$. ESI MS: $m/z$ 275 ($M^+$).

***Compound 5b.*** mp 208°C; $^1$H NMR (300 MHz, DMSO): 6.21 (s, 1H), 7.26–8.10 (m, 10H), 8.92 (brs, 1H). IR (KBr): 3229, 3142, 1734, 1517, 747 cm$^{-1}$. ESI MS: $m/z$ 310 ($M^+$+1).

***Compound 5c.*** mp 203°C; $^1$H NMR (200 MHz, $CDCl_3$): 6.23 (s, 1H), 7.31–8.02 (m, 10H), 8.94 (brs, 1H). IR (KBr): 3126, 1751, 1509, 736 cm$^{-1}$. ESI MS: $m/z$ (%) 293 ($M^+$).

***Compound 5d.*** mp 221°C; $^1$H NMR (200 MHz, DMSO): 6.21 (s, 1H), 7.20–8.13 (m, 10H), 8.90 (brs, 1H). IR (KBr): 3229, 3146, 1730, 1515, 723 cm$^{-1}$. ESI MS: $m/z$ 377 ($M^+$+Na).

***Compound 5e.*** mp 182°C; $^1$H NMR (300 MHz, DMSO): 5.6 (s, 1H), 7.32–8.20 (m, 10H), 8.55 (brs, 1H), 11.10 (s, 1H). IR (KBr): 3673, 3215, 1701, 1551, 746 cm$^{-1}$. ESI MS: $m/z$ 291 ($M^+$).

***Compound 5f.*** mp 187°C; $^1$H NMR (200 MHz, DMSO): 3.76 (s, 3H), 6.24 (s, 1H), 7.20–8.01 (m, 10H), 8.65 (brs, 1H). IR (KBr): 3149, 2942, 1733, 1607, 1510, 842, 723 cm$^{-1}$. ESI MS: $m/z$ 305($M^+$).

***Compound 5g.*** mp 166°C; $^1$H NMR (300 MHz, DMSO): 2.03 (s, 3H), 6.26 (s, 1H), 7.26–8.05 (m, 10H), 8.86 (brs, 1H). IR (KBr): 3148, 2921, 1735, 1512, 723 cm$^{-1}$. ESI MS: $m/z$ 289 ($M^+$).

***Compound 5h.*** mp 172°C; $^1$H NMR (300 MHz DMSO): 1.25 (s, 6H), 2.56 (m, 1H), 6.01 (d, $J$ = 2.86 Hz, 1H), 7.24–8.08 (m, 10H), 8.82 (brs, 1H). IR (KBr): 3281, 2924, 1729, 1513, 830 cm$^{-1}$. ESI MS: $m/z$ 317 ($M^+$).

***Compound 5i.*** mp 178°C; $^1$H NMR (200 MHz, DMSO): 1.24 (s, 6H), 1.31 (s, 3H), 6.30 (s, 1H), 7.40–8.19 (m, 10H), 8.92 (brs, 1H). IR (KBr): 3203, 2959, 1727, 1515, 828, 740 cm$^{-1}$. ESI MS: $m/z$ (%) 332 ($M^+$+1).

***Compound 5j.*** mp 199°C; $^1$H NMR (300 MHz, DMSO): 6.13 (s, 1H), 7.21–8.06 (m, 10H), 8.92 (brs, 1H). IR (KBr): 3220, 3142, 1729, 1513, 820, 748 cm$^{-1}$. ESI MS: $m/z$ 309 ($M^+$).

***Compound 5k.*** mp 222°C; $^1$H NMR (200 MHz, DMSO): 6.20 (s, 1H), 7.18–8.06 (m, 10H), 8.91 (brs, 1H). IR (KBr): 3252, 3140, 1730, 1512, 823, 758 cm$^{-1}$. ESI MS: $m/z$ 355 ($M^+$+1).

***Compound 5l.*** mp 172°C; $^1$H NMR (200 MHz, $CDCl_3$): 3.78 (s, 3H), 6.12 (s, 1H), 7.03–8.06 (m, 10H), 8.93 (s, 1H). IR (KBr): 3149, 1733, 1510, 814, 743 cm$^{-1}$. ESI MS: $m/z$ 306 ($M^+$+1).

***Compound 5m.*** mp 191°C; $^1$H NMR (200 MHz, DMSO): 6.01 (d, $J$ = 3.38 Hz, 1H), 6.98–8.01 (m, 10H), 8.56 (brs, 1H). IR (KBr): 3423, 3299, 1730, 1515, 812, 743 cm$^{-1}$. ESI MS: $m/z$ 292 ($M^+$+1).

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## REFERENCES AND NOTES

[1] (a) Dömling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168; (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Acc Chem Res 1996, 29, 123; (c) Ugi, I. Pure Appl Chem 2001, 73, 187.

[2] Peet, N. P.; Sunder, S. U.S. Pat. 4, 419, 357 (1983).

[3] Wiker, P., Jr.; Wilson, A. J Am Chem Soc 1955, 77, 5598.

[4] Drummond, G. I.; Severson, D. L. Circ Res 1979, 44, 1945.

[5] Belluci, C.; Gualtieri, F.; Chiarine, A. Eur J Med Chem 1987, 22, 473.

[6] Latif, N.; Mishriky, N.; Assad, F. M. Aust J Chem 1982, 35, 1037.

[7] Wang, Y.; Li, X.; Ding, K. Tetrahedron: Asymmetry 2002, 13, 1291.

[8] Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. Tetrahedron 2008, 64, 1263.

[9] Srihari, G.; Nagaraju, M.; Murthy, M. M. Helv Chim Acta 2007, 90, 1497.

[10] Rahul, N. R.; Devanand, S. B. Chin J Chem 2007, 25, 1710.

[11] Das, B.; Laxminarayana, K.; Ravikanth, B.; Rama Rao, B. J Mol Catal 2007, 261, 180.

[12] Kantevari, S.; Vuppalapati, S. V. N.; Nagaraju, L. Catal Commun 2007, 8, 1857.

[13] Khodaei, M. M.; Khosropour, A. R.; Moghanian, H. Synlett 2006, 916.

[14] Selvam, N. P.; Perumal, P. T. Tetrahedron Lett 2006, 47, 7481.

[15] Nagawade, R. R.; Shinde, D. Acta Chim Slov 2007, 54, 642.

[16] Szatmari, I.; Hetenyi, A.; Lazar, L.; Fulop, F. J Heterocycl Chem 2004, 41, 361.

[17] Cimarelli, C.; Palmieri, G.; Volpini, E. Can J Chem 2004, 82, 1314.

[18] Dabiri, M.; Delbari, A. S.; Bazgir, A. Synlett 2007, 821.

[19] Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543.

[20] (a) Olah, G. A.; Narang, S. C. Tetrahedron 1982, 38, 2225; (b) Jian, L.; Xiaoxia, W.; Yongmin, Z. Synlett 2005, 1039; (c) Xiufang, Z.; Xiaolei, W.; Junbiao, C.; Kang, Z. Synlett 2006, 3277; (d) Kamal, A.; Laxman, E.; Laxman, N.; Rao, N. V. Bioorg Med Chem Lett 2000, 10, 2311; (e) Uli, K.; Stefanie, A. Org Biomol Chem 2005, 3, 3184.

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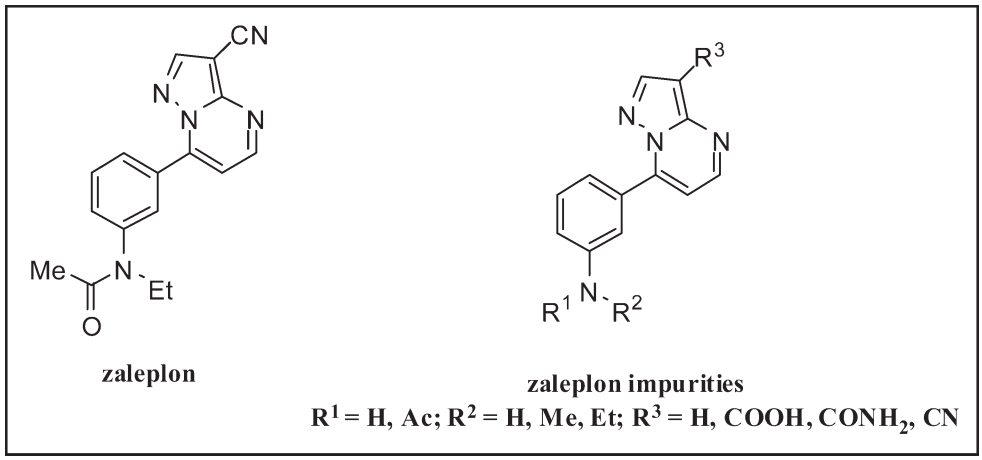


Synthesis of several potential impurities and/or degradation products of zaleplon is identified. All the prepared compounds were unambiguously identified by NMR techniques. Spectral characteristics (IR, UV, MS) of these compounds are also given.

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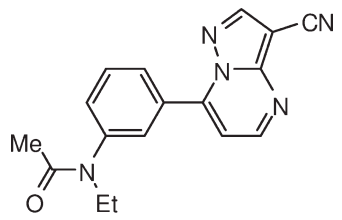
## INTRODUCTION

Zaleplon (**1**) is a nonbenzodiazepine hypnotic belonging with zolpidem and zopiclon to the so-called Z-hypnotic class [1,2]. Clinical results have shown that zaleplon is efficacious in the treatment of insomnia where difficulty in falling asleep is the primary problem. Zaleplon unlike many other hypnotic drugs does not interfere with sleep architecture and can be administered for up to 5 weeks without the risk of dependence or rebound insomnia upon discontinuation [3].



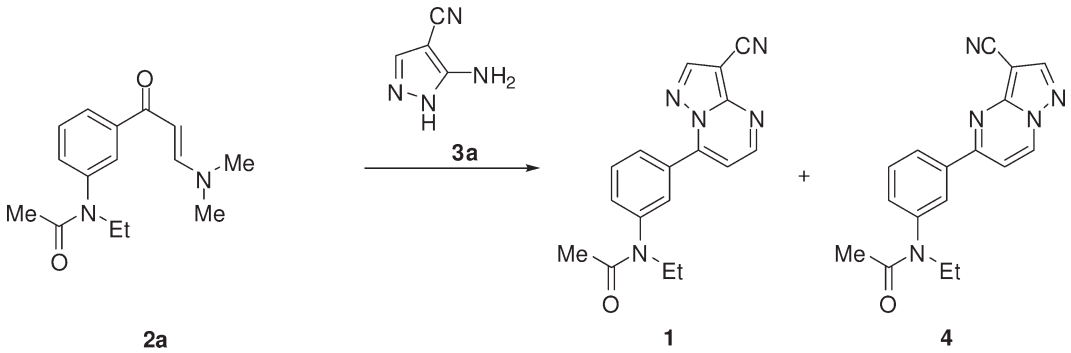

**zaleplon (1)**

Most of the described methods [4–7] of preparation of zaleplon are based on reaction of *N*-[3-[(2*E*)-3-(dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylacetamide (**2a**) with 5-amino-1*H*-pyrazol-4-carbonitrile (**3a**) under acidic conditions. The original patent [4] describes the reaction in anhydrous acetic acid, but under these conditions considerable amounts of the corresponding isomer **4** is formed. Much better results are achieved using aqueous acetic [5] or formic [6] acids. Probably the best results regarding purity and yields are obtained when the reaction is done in aqueous alcohols in the presence of hydrochloric acid [7,8] (Scheme 1).

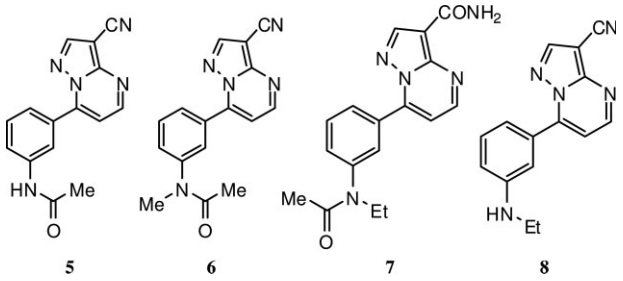
One of the principal parts of documentation of any active pharmaceutical ingredient (API) is description of impurities and/or degradation products which can be present. Identified impurities should be included in the specification when they are present at a level higher than the identification threshold, which is usually 0.10%. These impurities must be not only identified but also either isolated or independently synthesized.

Several impurities of zaleplon, including regioisomer **4** and compounds **5–8**, have recently been isolated and identified [9]. We have recently reported synthesis of zaleplon regioisomer **4** based on the Suzuki-Miyaura coupling [10]. To the best of our knowledge, no report on the synthesis of compounds **5–8** has been published

**Scheme 1.** Formation of zaleplon (**1**) and its regioisomer **4**.




and therefore we decided to synthesize these and other potential impurities as standards.

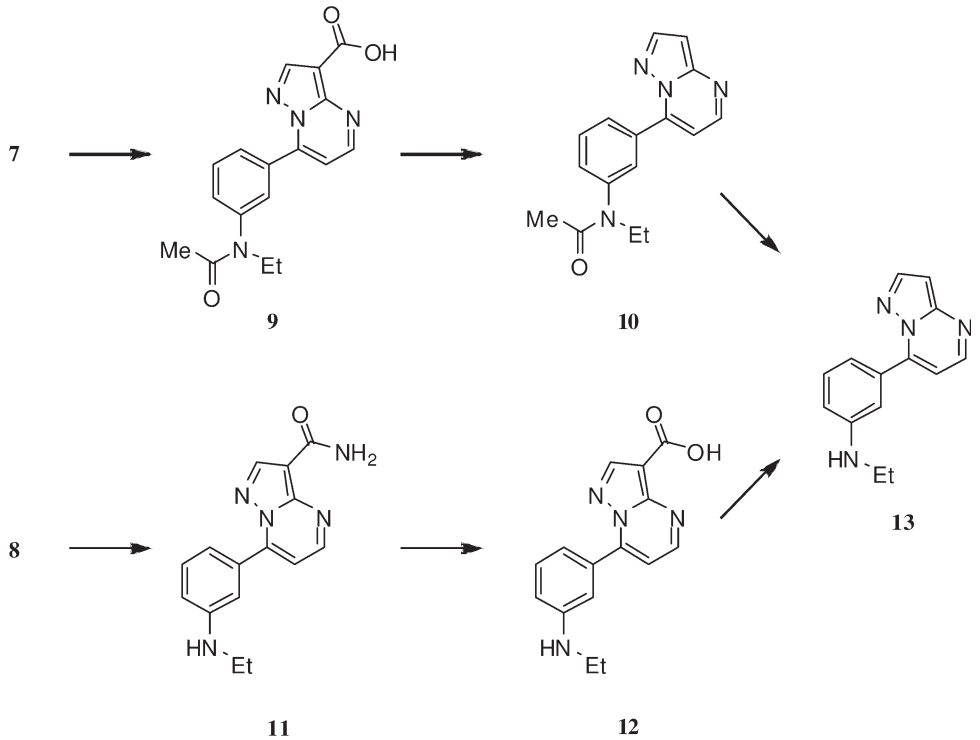



From the structures, it is evident that compounds **5** and **6** are process-related impurities formed by reaction of the corresponding impurities in **2** with **3a**. On the other hand, compounds **7** and **8** are products of hydrolysis of zaleplon leading to the nitrile group hydrolysis and anilide group hydrolysis, respectively. Our initial stress tests of zaleplon envisaged also formation of other similar impurities, as shown in Scheme 2, and therefore we decided to synthesise them.

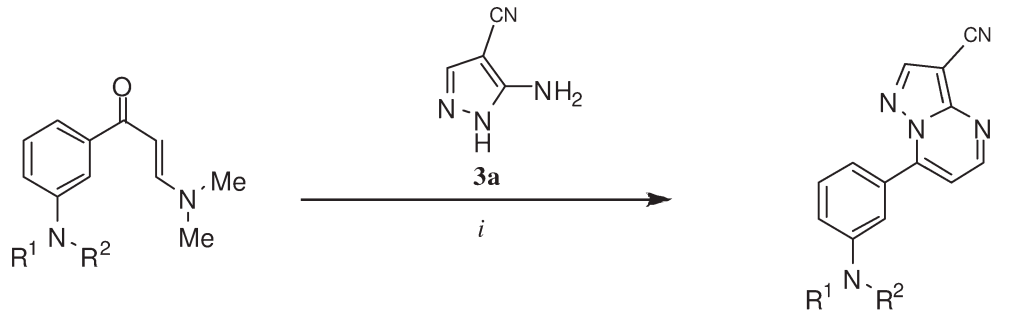
## RESULTS AND DISCUSSION

During our development of generic zaleplon, we decided to prepare compounds **5–13** as standards. Compounds **5** and **6** were prepared analogously as zaleplon starting from commercially available compound **2b** and compound **2c**, respectively. Compound **2c** was prepared

**Scheme 2.** Possible degradation pathways of zaleplon under stress tests conditions.



**Scheme 3.** Preparation of process-related impurities **5** and **6** and impurity **8**.




**2b** $R^1$ = Ac, $R^2$ = H
**2c** $R^1$ = Ac, $R^2$ = Me
**2d** $R^1$ = CHO, $R^2$ = H
**2e** $R^1$ = CHO, $R^2$ = Et

*i;* HCl, EtOH, reflux

**5** $R^1$ = Ac, $R^2$ = H
**6** $R^1$ = Ac, $R^2$ = Me
**8** $R^1$ = H, $R^2$ = Et
**14** $R^1$ = CHO, $R^2$ = Et

from **2b** using sodium hydride/iodomethane. For the synthesis of compounds **8**, **11**–**13**, we decided to start from **2d** ($R^1$ = CHO, $R^2$ = H), which was easily obtained from 3-aminoacetophenone by subsequent formylation, folowed by treatment with DMFDMA. Compound **2d** then provided **2e** using NaH/DMF and EtI.

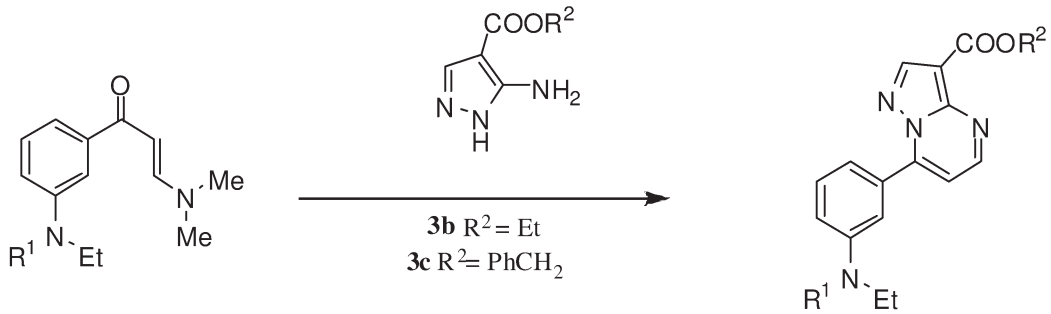
$^1$H NMR spectra of all of the compounds **2** showed that the methyl groups are nonequivalent as a result of the hindered rotation of dimethylamino group.

Compounds **2b** and **2c** heated with pyrazole **3a** in EtOH or MeOH and small amounts of concentrated hydrochloric acid provided good yields of the corresponding products **5** and **6**. Formyl derivative **2e** under the same conditions, was completely deprotected to give compound **8**. When the reaction was done with anhydrous solution of HCl in EtOH or in formic acid, the corresponding formyl derivative **14** was obtained (Scheme 3).

We intended to prepare amide impurity **7** by aminolysis of the corresponding ethyl ester and we also hoped that hydrolysis of this ester can provide acid **9**. For this purpose we prepared pyrazolecarboxylate **3b** using a modification of the literature procedure [11]. Similarly, also the corresponding benzyl ester **3c** was prepared [12]. Using general procedure described above, starting from compounds **2a** and **2e**, esters **15-18** were prepared (Scheme 4).

Aminolysis of both esters **15** and **16** to the corresponding amides **19** and **20** was very sluggish even using saturated ethanolic ammonia at 100°C under pressure; the mixtures after five days still contain about 10% of the starting compounds. Compound **19** was also

**Scheme 4.** Preparation of esters **15–18**.

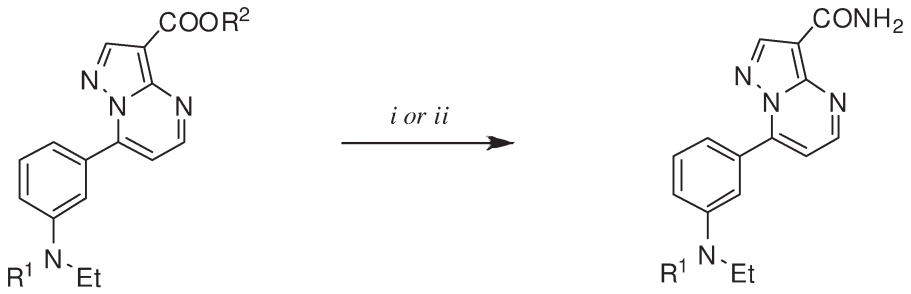



**2a** $R^1$ = Ac
**2e** $R^1$ = CHO

*i;* HCl, EtOH, reflux

**15** $R^1$ = Ac, $R^2$ = Et
**16** $R^1$ = H, $R^2$ = Et
**17** $R^1$ = Ac, $R^2$ = $PhCH_2$
**18** $R^1$ = H $R^2$ = $PhCH_2$

**Scheme 5.** Aminolysis of esters **15** and **16**.




**15** $R^1$ = Ac, $R^2$ = Et
**16** $R^1$ = H, $R^2$ = Et

**19** $R^1$ = Ac
**20** $R^1$ = H

*i;* $NH_3$, EtOH, 100 °C, 5 d; *ii,* $NH_3$, EtOH, $MgBr_2$, 100 °C, 1 d

obtained using catalysis [13] with $MgBr_2$, which shortened the reaction time but the crude mixture contained several impurities not present in case the reaction was done without the catalyst (Scheme 5).

Our initial attempts to synthesize acid **9** by hydrolysis of the corresponding ester **15** led under all conditions used to complex mixtures. Therefore the benzyl esters **17** and **18** were prepared and their hydrogenolytic debenzylation provided the corresponding acids **9** and **12** (Scheme 6). However, prolongation of the reaction time led to partial overreduction providing compounds having molecular weight higher by 4H (LC-MS).

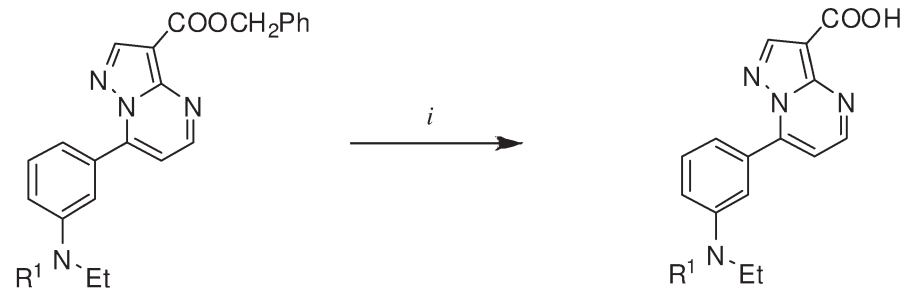
Initially we tried to avoid direct condensation of compounds **2a** and **2e** with 3-amino-4-pyrazol carboxylic acid (**3d**) and its amide (**3e**) since we expected partial hydrolysis and decarboxylation during the reaction. When we tried to do the reaction of **2a** with **3d** in a mixture of ethanol and hydrochloric acid, a mixture of the required acid **9** and its ethyl ester **15** was formed. However, we found that at 50°C in acetic acid the reaction is clean to give the required product **9** in good yield. Similarly, using formic acid and the following hydrolysis with aqueous hydrochloric acid, unsubstituted compound **12** was obtained (Scheme 7).

## EXPERIMENTAL

Reagents used in the synthesis were purchased from Sigma-Aldrich and were used without purification.

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Nicolet Nexus FTIR instrument (Thermo) by accumulation of 64 scans with 4 $cm^{-1}$ resolution using the ATR technique (ZnSe crystal); wavenumbers are given in $cm^{-1}$. The UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer (ethanol) in the range 190–400 nm. NMR experiments were carried out on a Bruker Avance 250. The Mass spectra [MS/MS; ionization mode APCI(+)] were measured on an API 3000 PE machine (Sciex Instruments, Applied Biosystems).

**Scheme 6.** Debenzylation of benzyl esters **17** and **18**.

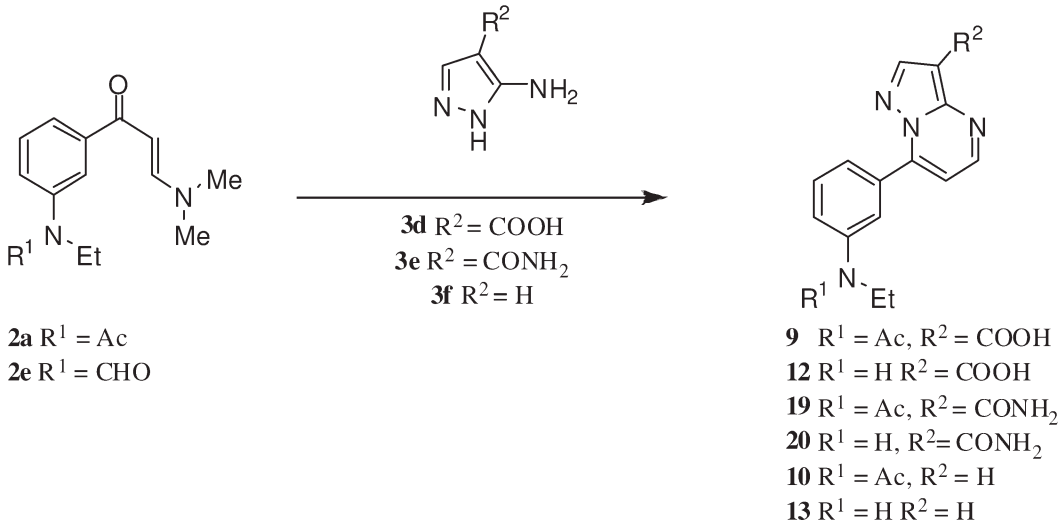



**17** $R^1$ = Ac
**18** $R^1$ = H

**9** $R^1$ = Ac
**12** $R^1$ = H

*i;* $H_2$, EtOH, Pd/C

**Scheme 7.** Preparation of amides and acids by direct condensation.




**2a** $R^1$ = Ac
**2e** $R^1$ = CHO

**9** $R^1$ = Ac, $R^2$ = COOH
**12** $R^1$ = H $R^2$ = COOH
**19** $R^1$ = Ac, $R^2$ = $CONH_2$
**20** $R^1$ = H, $R^2$ = $CONH_2$
**10** $R^1$ = Ac, $R^2$ = H
**13** $R^1$ = H $R^2$ = H

The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Centrifugally accelerated axial chromatography was done using Cyclograph™ instrument (Analtech) with silica gel prescraped rotors.

***N*-[3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]phenyl]-*N*-methylacetamide (2c).** *N*-[3-[(2*E*)-(3-(Dimethylamino)prop-2-enoyl]phenyl]acetamide (**2b**, 5.8 g, 25 mmol) was added to a stirred 50% suspension of NaH (1.5 g) in DMF (80 mL) and the mixture was stirred under nitrogen for 1 h. Then a solution of iodomethane (5 g, 35 mmol) in DMF (10 mL) was added dropwise to the mixture and stirred at ambient temperature for 2.5 hrs. The mixture was poured into water (300 mL), washed with hexane and then the aqueous layer was extracted with $CH_2Cl_2$ (5 × 50 mL, 5 × 20 mL). The extract was washed with brine and dried with $MgSO_4$. Crystallization of the residue after evaporation from ethyl acetate provided 5.2 g of yellow crystals (91%), mp 140–144°C. IR: CH 2815, C=O 1637, C=C 1585, 1538, CH 1367 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.89 (s, 3H, $CH_3CO$), 2.88 (s, 3H, $NCH_3$), 3.17 (s, 3H, $NCH_3$), 3.29 (s, 3H, $NCH_3$), 5.65 (d, $J$ = 12.5, 1H, =CHCO), 7.26-7.87 (m, 5H, Ar—H, =CH—N); $^{13}C$ NMR ($CDCl_3$): 22.45, 37.10, 45.15, 91.66, 126.07, 126.62, 129.29, 129.43, 142.32, 144.56, 154.65, 170.46, 186.96. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C 68.27; H 7.37; N 11.37. Found: C 68.22; H 6.94; N 11.06. HRMS Calcd. for $C_{14}H_{19}N_2O_2$ $(M+H)^+$ 247.14465. Found: 247.14406.

***N*-(3-Acetylphenyl)formamide.** A mixture of 3-aminoacetophenone (10 g, 0.07 mol) and formic acid (100 mL) was refluxed for 10 hrs. Residue after evaporation was then crystallized from toluene (charcoal) to provide 10.5 g of beige crystals (87%); mp 92–94°C [ref. 14 mp 93–94°C ($Et_2O$)]. IR: NH 3256, 3194, 3139, CH 3076, 3021, C=O 1667, C=C 1591, 1556, 1477 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.61 (s, 3H, $CH_3$), 7.27-8.07 (m, 4H, Ar—H), 8.44 (s, 1H, CHO). Anal. Calcd. for $C_9H_9NO_2$: C 66.25; H 5.56; N 12.06. Found: C 66.38; H 5.78; N 12.34. HRMS Calcd. for $C_9H_{10}NO_2$ $(M+H)^+$ 164.07116. Found: 164.07104.

***N*-[3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]phenyl]formamide (2d).** A solution of *N*-(3-acetylphenyl)formamide (3.25 g, 20 mmol) and DMFDMA (4.5 g, 37.8 mmol) in DMF (8 mL) was refluxed for 8 hrs and then stirred overnight. The formed yellow crystals were filtered off; yield 2.5 g (66%), mp 162–165°C. IR: NH 3229, 3184, CH 3066, 2846, 2767, C=O 1698, 1636, C=C 1595, 1516 $cm^{-1}$. $^1H$ NMR ($DMSO_{d6}$): δ 2.91 (s, 3H, $NCH_3$), 3.14 (s, 3H, $NCH_3$), 5.73 (d, 1H, $J$ = 12.5, [dnond]CHCO), 7.37-8.01 (m, 5H, Ar—H, =CH—N), 8,30 (s, 1H, CHO), 10.23 (bs, 1H, NH). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 66.21; H 6.67; N 13.01. HRMS Calcd. for $C_{12}H_{15}N_2O_2$ $(M+H)^+$ 219.11335. Found: 219.11310.

***N*-[3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylformamide (2e).** Compound **2d** (2.52 g, 11.6 mmol) was added to a stirred 50% suspension of NaH (0.7 g, 14.6 mmol) in DMF (40 mL), and the mixture was stirred under nitrogen for 1 h. The mixture was cooled with ice-water and a solution of iodoethane (2.3 g, 15 mmol) in DMF (5 mL) was added dropwise and stirred at ambient temperature for 4 hrs. After that the mixture was poured into water and extracted with $CH_2Cl_2$. The extract was washed with brine and dried with $MgSO_4$. Crystallization of the residue after evaporation from ethyl acetate provided 0.63 g of yellow crystals (22%), mp 69–73°C. IR: CH 2922, 2809, C=O 1667, 1634, C=C 1548, 1482 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.17 (t, 3H, $J$ = 7.2, $CH_3$), 2.96 (s, 3H, $NCH_3$), 3.17 (s, 3H, $NCH_3$), 3.85 (q, 2H, $J$ = 7.2, $NCH_2$), 5.71 (d, 1H, $J$ = 12.3, =CHCO), 7.23-7.86 (m, 5H, Ar—H, =CH—N), 8.38 (s, 1H, CHO). Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C 68.27; H 7.37; N 11.37. Found: C 68.21; H 7.52; N 11.51. HRMS Calcd. for $C_{14}H_{19}N_2O_2$ $(M+H)^+$ 247.14465. Found: 247.14392.

**General procedure for the synthesis of compounds 5, 6, 15, 17.** Typically, a mixture of 3-(dimethylamino)-1-phenylprop-2-en-1-one **2** (10 mmol) and pyrazole **3** (10 mmol), ethanol (50 mL) and hydrochloric acid (1 mL) was refluxed for 1 h. The mixture was cooled down, the formed precipitate was filtered off to give the crude product, which was then crystallized from an appropriate solvent.

**N-*[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]acetamide (5).*** This compound was obtained after crystallization from *i*-PrOH in 77% yield according to the above general procedure; mp 257–261°C (ref. 15 mp 254–255°C). IR: NH 3314, CH 3092, CN 2235, C=O 1687, C=C + C=N 1615, 1583, 1538, 1478 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 204 (4.30), 234 (4.60), 338 (3.91). $^1H$ NMR ($CDCl_3$): δ 2.09 (s, 3H, $CH_3CO$), 7.50-8.34 (m, 5H, Ar—H), 8.86 (s, 1H, H-2), 8.90 (d, 1H, $J$ = 5.0, H-5), 10.23 (bs, 1H, NH). $^{13}C$ NMR ($CDCl_3$): 23.94, 81.34, 110.62, 113.37, 119.89, 122.01, 124.27, 129.05, 129.82, 139.41, 147.20, 147.51, 151.05, 153.71, 168.65. Anal. Calcd. for $C_{15}H_{11}N_5O$: C 64.97; H 4.00; N 25.26. Found: C 65.22; H 3.94; N 12.26. HRMS Calcd. for $C_{15}H_{12}N_5O$ $(M+H)^+$ 278.10419. Found: 278.10364.

**N-*[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]*-N-*methylacetamide (6).*** This compound was obtained after crystallization from *i*-PrOH in 60% yield according to the above general procedure; mp 202–205°C. IR: CH 3075, C≡N 2231, C=O 1645, C=C + C=N 1613, 1549, 1479 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 204 (4.40), 232 (4.58), 338 (3.85). $^1H$ NMR ($CDCl_3$): δ 2.01 (s, 3H, $CH_3CO$), 3.36 (s, 3H, $CH_3N$), 7.21-7.51 (m, 2H, Ar—H), 7.68 (t, 1H, $J$ = 10.0, H-14), 7.94-7.99 (m, 2H, Ar—H), 8.44 (s, 1H, H-2), 8.81 (d, 1H, $J$ = 5.0, H-5). $^{13}C$ NMR ($CDCl_3$): 22.63, 35.76, 83.73, 109.87, 112.51, 128.41, 129.57, 130.35, 131.03, 131.65, 143.47, 146.94, 147.11, 151.32, 152.61, 169.63. Anal. Calcd. for $C_{16}H_{13}N_5O$: C 65.97; H 4.50; N 24.04. Found: C 66.12; H 4.65; N 24.36. HRMS Calcd. for $C_{16}H_{14}N_5O$ $(M+H)^+$ 292.11983. Found: 292.11948.

***Ethyl 7-[3-[acetyl(ethyl)amino]phenyl]pyrazolo[1,5-a]pyrimidin-3-carboxylate (15).*** This compound was obtained after crystallization from EtOH in 93% yield according to the above general procedure; mp 127–132°C. IR: OH 3390, CH 2971, C=O 1688, 1651, C=C + C=N 1602, 1547, 1489 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 206 (4.36), 234 (4.42), 340 (3.79). $^1H$ NMR ($CDCl_3$): δ 1.18 (t, 3H, $J$ = 7.1, $NCH_2C\mathbf{H}_3$), 1.41 (t, 3H, $J$ = 7.1, $OCH_2C\mathbf{H}_3$), 1.95 (s, 3H, $CH_3CO$), 3.81 (q, 2H, $J$ = 7.1, $NCH_2$), 4.45 (q, 2H, $J$ = 7.1, $OCH_2$), 7.14 (d, 1H, $J$ = 2.7, H-6), 7.29-8.01 (m, 4H, Ar—H), 8.61 (s, 1H, H-2), 8.89 (d, 1H, $J$ = 2.7, H-5). $^{13}C$ NMR ($CDCl_3$): 13.11, 14.51, 23.00, 44.09, 60.47, 103.33, 109.11, 128.72, 129.60, 130.20, 131.11, 131.67, 143.30, 146.48, 147.41, 148.91, 152.44, 162.47, 169.87. Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C 64.76; H 5.72; N 15.90. Found: C 64.36; H 5.93; N 16.17. HRMS Calcd. for $C_{19}H_{21}N_4O_3$ $(M+H)^+$ 353.16137. Found: 353.16077.

***Benzyl 7-(3-(N-ethylacetamido)phenyl)pyrazolo[1,5-a]pyrimidin-3-carboxylate (17).*** This compound was obtained after flash chromatography (hexane–acetone 6 : 4) and following crystallization from EtOH in 62% yield according to the above general procedure (reaction time 4 hrs); mp 112–114°C. IR: CH 2968, 2930, C=O 1694, 1652, C=C + C=N 1610, 1545, 1480. UV $\lambda_{max}$ (log ε): 206 (4.54), 234 (4.52), 340 (3.95). $^1H$ NMR ($CDCl_3$): δ 1.17 (t, 3H, $J$ = 7.2, $CH_3$), 1.94 (s, 3H, $CH_3CO$), 3.82 (q, 2H, $J$ = 7.2, $NCH_2$), 5.46 (s, 2H, $OCH_2$), 7.12-8.00 (m, 10H, Ar—H), 8.62 (s, 1H, H-2), 8.82 (d, 1H, $J$ = 5.0, H-5). $^{13}C$ NMR ($CDCl_3$): 13.12, 22.99, 44.07, 65.94, 103.08, 109.12, 128.05, 128.18, 128.50, 128.67, 129.61, 130.19, 131.12, 131.66, 136.42, 143.38, 146.47, 147.47, 149.15, 152.37, 162.10, 169.75. Anal. Calcd. for $C_{24}H_{22}N_4O_3$: C 69.55; H 5.35; N 13.52. Found: C 69.44; H 5.39; N 11.67. HRMS Calcd. for $C_{24}H_{23}N_4O_3$ $(M+H)^+$ 415.17702. Found: 415.17682.

***N*-[3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl]-*N*-ethylformamide (14).** A mixture of **2e** (0.62 g, 2.5 mmol) and pyrazole **3a** (0.3 g, 2.7 mmol) was dissolved in ethanol (10 mL) and then a saturated solution of HCl in ethanol (1 mL) was added. The mixture was refluxed for 3–4 hrs, evaporated and the residue was crystallized from MeOH provided 0.45 g (62%) of yellow crystals; mp 125–128°C. IR: CH 3089, 2974, C≡N 2230, C=O 1678, C=C + C=N 1611, 1552, 1493 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 204 (4.41), 234 (4.63), 338 (3.89). $^1H$ NMR ($CDCl_3$): δ 1.24 (t, 3H, $J$ = 7.5, $CH_3$), 3.95 (q, 2H, $J$ = 7.5 $CH_2$), 7.14-8.65 (m, 8H, Ar—H, NCHO). $^{13}C$ NMR ($CDCl_3$): 13.09, 40.15, 83.51, 109.90, 111.09, 112.48, 124.83, 126.98, 127.46, 130.36, 131.01, 141.54, 146.60, 147.17, 151.07, 152.60, 161.69. Anal. Calcd. for $C_{16}H_{13}N_5O$: C 65.97; H 4.50; N 24.04. Found: C 66.23; H 4.72; N 24.24. HRMS Calcd. for $C_{16}H_{14}N_5O$ $(M+H)^+$ 292.11984. Found: 292.11935.

**General procedure for the synthesis of compounds 8, 16, 18, 10, 13.** Typically, a mixture of 3-(dimethylamino)-1-phenylprop-2-en-1-one **2** (10 mmol), pyrazole **3** (10 mmol), ethanol (50 mL) and 10% hydrochloric acid (10 mL) was refluxed for 1 h. The mixture was evaporated, the residue was triturated with 10% $Na_2CO_3$, the insoluble portion was filtered off to give the crude product, which was then crystallized from an appropriate solvent.

***7-[3-(Ethylamino)phenyl]pyrazolo[1,5-a]pyrimidin-3-carbonitrile (8).*** This compound was obtained after crystallization from EtOH in 95% yield according to the above general procedure; mp 172–179°C. IR: CH 3071, 2707, 2662, 2478, C≡N 2227, C=C + C—N 1612, 1544, 1495 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 206 (4.15), 234 (4.32), 338 (3.68). $^1H$ NMR (DMSO): δ 1.24 (t, 3H, $J$ = 7.5, $CH_3$), 3.26 (q, 2H, $J$ = 7.5, $CH_2$), 7.26-8.91 (m, 7H, Ar—H). $^{13}C$ NMR (DMSO): 12.75, 81.32, 110.65, 113.37, 129.60, 130.39, 147.20, 147.50, 151.05, 153.69. Anal. Calcd. for $C_{15}H_{13}N_5$: C 68.42; H 4.98; N 26.60. Found: C 68.18; H 4.73; N 26.86. HRMS Calcd. for $C_{15}H_{14}N_5$ $(M+H)^+$ 264.12492. Found: 264.12436.

***Ethyl 7-[3-(ethylamino)phenyl]pyrazolo[1,5-a]pyrimidin-3-carboxylate (16).*** This compound was obtained after crystallization from EtOH in 84% yield according to the above general procedure; mp 189–202°C. IR: CH 3072, 2664, 2485, C=O 1705, C=C + C=N 1611, 1581, 1548, 1494 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 208 (4.31), 244 (4.44), 340 (3.84). $^1H$ NMR (DMSO): δ 1.25 (t, 3H, $J$ = 7.2, $NCH_2C\mathbf{H}_3$), 1.33 (t, 3H, $J$ = 7.2, $OCH_2C\mathbf{H}_3$), 3.29 (q, 2H, $J$ = 7.5, $NCH_2$), 4.34 (q, 2H $J$ = 7.2, $OCH_2$), 7.33-7.90 (m, 5H, Ar—H), 8.66 (s, 1H, H-2), 8.89 (d, 1H, $J$ = 5.0, H-5). $^{13}C$ NMR (DMSO): 12.53, 14.40, 44.09, 59.55, 101.97, 109.88, 128.55, 129.61, 130.22, 130.98, 131.09, 131.76, 143.33, 146.68, 146.85, 148.16, 153.01, 161.69. Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C 65.79; H 5.85; N 18.05. Found: C 65.47; H 6.04; N 18.25. HRMS Calcd. for $C_{17}H_{19}N_4O_2$ $(M+H)^+$ 311.15080. Found: 311.15021.

***Benzyl 7-[3-(ethylamino)phenyl]pyrazolo[1,5-a]pyrimidin-3-carboxylate (18).*** This compound was obtained after flash chromatography (hexane–acetone 7 : 3 to hexane–acetone–methanol 7 : 3 : 1) followed by crystallization from EtOH in 60% yield according to the above general procedure; mp 145–157°C. IR: CH 3051, 2964, 2518, 2378, C=O 1695, C=C + C=N 1608, 1588, 1544, 1492 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 210 (4.35), 246 (4.46), 338 (3.88). $^1H$ NMR ($CDCl_3$): δ 1.47 (t, 3H, $J$ = 7.2, $CH_3$), 3.50 (q, 2H, $J$ = 7.5, $NCH_2$), 5.44 (s, 2H, $OCH_2$), 7.13-8.86 (m, 12H, Ar—H), 11.50 (bs, NH). $^{13}C$ NMR

($CDCl_3$): 11.00, 48.21, 66.01, 103.06, 109.51, 124.77, 126.43, 128.07, 128.14, 128.50, 130.44, 131.97, 135.93, 136.31, 145.58, 147.39, 148.99, 152.64, 162.13. Anal. Calcd. for $C_{22}H_{20}N_4O_2$: C 70.95; H 5.41; N 15.04. Found: C 70.68; H 5.33; N 15.22. HRMS Calcd. for $C_{22}H_{21}N_4O_2$ $(M+H)^+$ 373.16645. Found: 373.16605.

***N*-Ethyl-*N*-(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide (10).** This compound was obtained after crystallization from EtOH in 72% yield according to the above general procedure; mp 105–108°C. IR: CH 3051, 2973, C=O 1646, C=C + C=N 1600, 1537, 1393 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 204 (4.33), 234 (4.61), 350 (3.55). $^1H$ NMR (DMSO): δ 1.04 (t, 3H, $J$ = 7.1, $CH_3$), 1.82 (s, 3H, $CH_3CO$), 3.70 (q, 2H, $J$ =7.1, $NCH_2$), 6.84 (d, 1H, $J$ = 2.2, H-3), 7.31 (d, 1H, $J$ = 4.3, H-6), 7.53 (d, 1H, $J$ = 7.9, H-4′ or H-6′), 7.67 (t, 1H, $J$ = 7.9, H-5′), 8.07 (m, 1H, H-2′), 8.13 (d, 1H, $J$ = 7.9, H-4′ or H-6′), 8.27 (d, 1H, $J$ = 2.2, H-2), 8.62 (d, 1H, $J$ = 4.3, H-5). $^{13}C$ NMR (DMSO): 12.90, 22.64, 43.07, 96.61, 107.85, 129.16, 129.67, 130.61, 131.79, 142.56, 144.46, 144.50, 149.34, 149.48, 170.03. Anal. Calcd. for $C_{16}H_{16}N_4O$: C 68.55; H 5.75; N 19.99. Found: C 68.46; H 5.90; N 20.16. HRMS Calcd. for $C_{16}H_{17}N_4O$ $(M+H)^+$ 281.14024. Found: 281.13962.

**N-*Ethyl*-N-*(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)amine (13).** This compound was obtained after crystallization from EtOH in 66% yield according to the above general procedure; mp 185–190°C. IR: CH 3062, 2913, 2661, 2483, C=C + C=N 1606, 1580, 1538, 1452 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 204 (4.08), 232 (4.53), 352 (3.62). $^1H$ NMR (DMSO): δ 1.27 (t, 3H, $J$ = 7.2, $CH_3$), 3.37 (q, 2H, $J$ = 7.2, $CH_2$), 6.85 (d, 1H, $J$ = 2.4, H-3), 7.25 (d, 1H, $J$ = 4.4, H-6), 7.46 (d, 1H, $J$ = 7.3, H-4′ or H-6′), 7.61 (t, 1H, $J$ = 7.9, H-5′), 7.85 (d, 1H, $J$ = 7.3, H-4′ or H-6′), 7.97 (m, 1H, H-2′), 8,28 (d, 1H, $J$ = 2.4, H-2), 8.64 (d, 1H, $J$ = 4.4, H-5), 11.75 (bs, NH). $^{13}C$ NMR (DMSO): 12.07, 42.96, 96.60, 107.75, 128.33, 129.24, 129.70, 130.33, 131.72, 142.72, 144.50, 144.94, 149.30, 149.54. Anal. Calcd. for $C_{14}H_{14}N_4$: C 70.57; H 5.92; N 23.51. Found: C 70.21; H 5.66; N 23.04. HRMS Calcd. for $C_{14}H_{15}N_4$ $(M+H)^+$ 239.12967. Found: 239.12918.

**7-(3-(*N*-Ethylacetamido)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (19).**

***Method A.*** A mixture of compound **15** (1 g, 2.8 mmol) and ethanol saturated with ammonia (10 mL) was heated in a pressure tube at 100°C for 5 days (TLC; toluene–ethanol–dioxane–ammonia 5 : 2 : 4 : 1). The residue after evaporation was purified by flash chromatography (hexane–acetone, 7 : 3) to give 0.65 g of crude compound **19** and its crystallization (EtOH) provided 0.45 g (50%) of yellowish crystals; mp 233–237°C. IR: NH 3394, 3121, CH 2984, C=O 1652, C=C + C=N 1622, 1597, 1544, 1482 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 206 (4.49), 234 (4.51), 350 (3.82). $^1H$ NMR (DMSO): δ 1.06 (t, 3H, $J$ = 7.2, $NCH_2C\mathbf{H}_3$), 1.85 (s, 3H, $C\mathbf{H}_3CO$), 3.72 (q, 2H, $J$ = 7.2, $CH_2$), 7.54-8.20 (m, 7H, 5 × Ar—H, 1 × $CONH_2$), 8.61 (s, 1H, H-2), 8.86 (d, 1H, $J$ = 4.5, H-5). $^{13}C$ NMR (DMSO): 12.91, 22.67, 43.37, 105.49, 109.32, 128.81, 129.43, 129.75, 130.11, 131.12, 142.63, 145.73, 146.09, 147.53, 151.86, 162.54, 169.70. UV $\lambda_{max}$ (log ε): 206 (4.49), 234 (4.51), 350 (3.82). Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C 63.15; H 5.30; N 21.66. Found: C 63.38; H 5.48; N 21.99. HRMS Calcd. for $C_{17}H_{18}N_5O_2$ $(M+H)^+$ 324.14605. Found: 324.14551.

***Method B.*** The procedure is similar as Method (A), only 0.2 g of $MgBr_2$ was added and the mixture was heated for 1 day to provide after chromatography 38% of **19**.

***Method C.*** A mixture of **2a** (0.2 g, 0.8 mmol), 3-amino-4-pyrazol carboxamide (**3e**; 0.1 g, 0.8 mmol), and ethanol (3.8 mL) with concentrated HCl (0. 1 mL) was heated in a vial at 50°C for 24 hrs. A solid precipitated during the heating. The mixture was cooled down, the precipitate was filtered off to give 0.17 g of yellow crystals (66%); mp 233–237°C.

**7-[3-(Ethylamino)phenyl]pyrazolo[1,5-*a*]pyrimidin-3-carboxamide (20).** Using Method A described for the preparation of 7-[3-[acetyl(ethyl)amino]phenyl]pyrazolo[1,5-*a*]pyrimidin-3-carboxamide (**19**), compound **20** was obtained in 60% yield; mp 193–203°C. IR: NH 3366, 3305, 3116, CH 2950, C=O 1666, C=C + C=N 1626, 1543, 1513, 1472 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 206 (4.07), 246 (4.15), 350 (3.81). $^1H$ NMR (DMSO): δ 1.20 (t, 3H, $J$ = 7.1, $CH_3$), 3.10 (q, 2H, $J$ = 7.1, $CH_2$), 5.90 (t, 1H, $J$ = 5.3, NH), 6.80-7.38 (m, 5H, Ar—H), 7.50 (s, 1H, $CONH_2$), 7.63 (s, 1H, $CONH_2$), 8.59 (s, 1H, H-2), 8.81 (d, 1H, $J$ = 4.5, H-5). $^{13}C$ NMR (DMSO): 14.21, 37.22, 105.17, 108.77, 112.55, 114.79, 116.61, 129.06, 130.45, 145.60, 146.80, 148.18, 148.88, 151.77, 162.64. Anal. Calcd. for $C_{15}H_{15}N_5O$: C 64.04; H 5.37; N 24.90. Found: C 63.87; H 5.22; N 25.34. HRMS Calcd. for $C_{15}H_{16}N_5O$ $(M+H)^+$ 282.13549. Found: 282.13510.

**7-(3-(*N*-Ethylacetamido)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (9).** A mixture of *N*-[(2*E*)-3-[3-(dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylacetamide (**2a**, 1 g, 4 mmol), 3-amino-4-pyrazolecarboxylic acid (**3d**; 0.5 g, 4 mmol), acetic acid (20 mL) was stirred at 50°C for 24 hrs. The mixture was evaporated, the residue was dissolved in $CH_2Cl_2$ and extracted with 10% solution of $Na_2CO_3$ (5 × 8 mL). Insoluble particles were filtered off from the collected aqueous portions and the clear solution was acidified with acetic acid. Then the solution was extracted with $CH_2Cl_2$ (10 × 15 mL) and the extract was dried with $MgSO_4$. The residue after evaporation was triturated with water and the insoluble portion was filtered off to give 0.3 g (48%); mp 195–200°C (decomp.). IR: NH 3293, CH 2973, 2934, C=O 1652, 1575, 1544, C=C + C=N 1402, CO 1299 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 206 (4.11), 236 (4.33), 352 (3.56). $^1H$ NMR (250 MHz, DMSO): 1.05 (t, 3H, $J$ = 7.1, $NCH_2C\mathbf{H}_3$), 2.08 (s, 3H, $COCH_3$), 3.72 (q, 2H, $J$ = 7.1, $CH_2$), 7.31 (d, 1H, $J$ = 4.4, H-6), 7.54 (d, 1H, $J$ = 7.6, H-4′ or H-6′), 7.67 (d, 1H, $J$ = 7.6, H-5′), 8.01 (m, 1H, H-2′), 8.11 (d, 1H, $J$ = 7.6, H-4′ or H-6′), 8.34 (s, 1H, H-2), 8.65 (d, 1H, $J$ = 4.4, H-5). $^{13}C$ NMR (DMSO): 12.93, 22.65, 43.55, 107.78, 111.84, 128.59, 129.17, 129.67, 130.67, 131.81, 142.60, 145.00, 146.92, 147.06, 150.34, 165.72, 174.69. HRMS Calcd. for $C_{17}H_{17}N_4O_3$ $(M+H)^+$ 325.13007. Found: 325.129469.

**7-(3-(*N*-Ethylamino)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (12).** A mixture of *N*-[(2*E*)-3-[3-(dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylformamide (**2a**) (**2e,** 0.25 g, 1 mmol), 3-amino-4-pyrazolecarboxylic acid (**3d**; 0.13 g, 1 mmol), formic acid (4 mL) was stirred at 75°C for 16 hrs. The mixture was evaporated and the residue was stirred with concentrated hydrochloric acid (3 mL) at 50°C for 15 min. The residue after evaporation was dissolved in water (10 mL), alkalized with 10% NaOH and extracted with diethyl ether (2 × 5 mL). The extract was dried with $MgSO_4$ and the residue after evaporation containing according to TLC pure product of decarboxylation **13** (50 mg, 21%). The aqueous layer was neutralized with acetic acid and extracted with dichloromethane (3 × 10 mL). The extract was washed with water and dried with $MgSO_4$. The residue after evaporation was triturated with water and the insoluble

portion was filtered off to provide 0.19 g (64%) of yellowish crystals; mp 198–206°C (decomp.). IR: CH 2981, 2941, C=O 1667, 1652, NH 1538, CO 1231 $cm^{-1}$. UV $\lambda_{max}$ (log ε): 204 (4.35), 236 (4.43), 352 (3.40). $^1$H NMR (250 MHz, DMSO): 1.18 (t, 3H, $J = 7.2$, $NCH_2C\mathbf{H}_3$), 3.07 (q, 2H, $J = 7.2$, $CH_2$), 6.78 (d, 1H, $J = 4.4$, H-6), 7.14-7.35 (m, 4H, arom. H), 8.57 (s, 1H, H-2), 8.78 (d, 1H, $J = 4.4$, H-5). $^{13}$C NMR (DMSO): 14.23, 37.99, 109.22, 112.57, 114.69, 114.97, 116.62, 129.02, 130.17, 130.61, 147.01, 147.97, 152.40, 163.23, 173.05. HRMS Calcd. for $C_{15}H_{14}N_4O_3$ $(M+H)^+$ 298.106590. Found: 298.11893.

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## REFERENCES AND NOTES

[1] Anon. Drugs Future 1996, 21, 37.

[2] Doplet, M.; Plosker, G. L. Drugs,2000, 60, 413.

[3] Walsh, J. K.; Pollak, C. P.; Scharf, M. B.; Schweitzer, P. K.; Vogel, G. W. Clin Neuropharmacol 2000, 23, 17.

[4] Dusza, J. P.; Tomcufcik, A. S.; Albright, J. D.; (American Cyanamide), US 4,626,538 (1985); Chem Abstr 1986, 105, 72777.

[5] Thurajrajan, P.; (American Cyanamide), US 5,714,607 (1995); Chem Abstr 1998, 128, 154095.

[6] Korycinska, M.; Stawinski, T.; Wieczorek, M.; (Adamed), WO 95,456 (2003); Chem Abstr 2003, 139, 381506.

[7] Korodi, F.; Fehér, E.; Magyar, E.; (TEVA Pharmaceuticals), WO 100828 (2002); Chem Abstr 2002, 138, 24725.

[8] Rádl, S. (Zentiva), WO 37,824 (2004); Chem Abstr 2004, 143, 43894.

[9] Bharathi, C.; Prabahar, K. J.; Prasad, C. S.; Karavana, K. M.; Magesh, S.; Handa, V. K.; Nadala, R.; Naidu, A. J Pharm Biomed Anal 2007, 44, 101.

[10] Rádl, S.; Blahovcová, M.; Tkadlecová, M.; Havlíček, J. Heterocycles, to appear.

[11] Howe, R. K.; Bolluyt, S. C. J Org Chem 1969, 34, 1713.

[12] Cusack, N. J.; Shaw, G.; Litchfield, G. J. J Chem Soc C 1971, 1501.

[13] Guo, Z.; Dowdy, E. D.; Li, W.-S.; Polniaszek, R.; Delaney, E. Tetrahedron Lett 2001, 42, 1843.

[14] Zhang, M. Q.; Haemers, A.; Vanden Berghe, D.; Pattyn, S. R.; Bollaert, W.; Levshin, I. J Heterocycl Chem 1991, 28, 673.

[15] Shaikh, A. C.;Chen C. J Labelled Compd Radiopharm 2008, 51, 72.

# Cerium (IV) Ammonium Nitrate as an Efficient Lewis Acid for the One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Their Corresponding 2-(1*H*) Thiones

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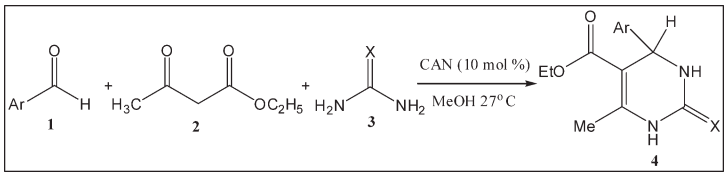


A simple and highly efficient procedure for the Biginelli condensation reaction of aldehydes, β-ketoesters, urea, or thiourea catalyzed by Ceric ammonium nitrate (CAN) as a Lewis-acid at ambient temperature is described. The procedure proved to be simple and of high yield.

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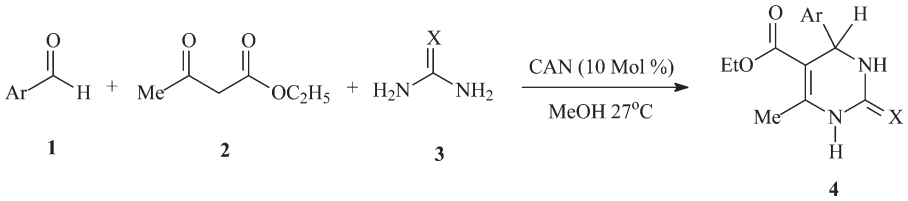
## INTRODUCTION

Dihydropyrimidines (DHPMs) and their derivatives are class of heterocycles that posses a wide range of biological and therapeutic properties. They act as calcium channel blockers, antihypertensive agents, and α-la-antagonists and neuropeptide Y (NPY) antagonists [1–3]. Furthermore, several bioactive isolated marine alkaloids, in particular, the batzelladine alkaloids were found to contain 2-amino-1,4-dihydropyrimidine carboxylate core that have been found to be potent HIV gp-120-CD4 inhibitors [4–6]. They also have known to posses antibacterial, antiviral, antitumor and anti-inflammatory activities [7,8]. Thus, a synthesis of these heterocyclic molecules has been of much importance in current years.

The most simple and direct method for their synthesis was first reported by Biginelli [9] since more than 100 years ago; it involves a three one-pot condensation of benzaldehyde, ethyl acetoacetate, and urea under strong acidic conditions with a low yield. In the past 10 years, several one-pot methodologies for the synthesis of DHPM derivatives were developed. This involves the use of several catalysts such as lanthanide triflates [10], $ZrCl_4$ [11], $VCl_3$ [12], $PPh_3$ [13], $InBr_3$ [14], $GaX_3$ [15], $H_3BO_3$ [16], $KAl(SO_4)_2{\cdot}12H_2O$ supported on silica [17], $Y(NO_3)_3{\cdot}6H_2O$ [18], $Ce(NO_3)_3{\cdot}6H_2O$ [19], $CeCl_3$ and InCl3 [20], Nafion-H [21]. Microwave heating [22], ultrasound irradiation [23], and ionic liquids [24] were also performed as green techniques for their synthesis. Very recently, an efficient synthesis of DHPMs utilizing $CaF_2$ in refluxing EtOH [25], $Cu(NH_2SO_3)_2$ in refluxing acetic acid [26] and the use of etidronic acid catalyst [27] were reported. However, many drawbacks were associated with such synthesis such as the use of expensive reagents, strong acidic conditions, long reaction times, and low to moderate yields. Consequently, there is a need to develop a new efficient and simple method using inexpensive and environmentally benign catalyst. Ceric ammonium nitrate (CAN) was tested as an alternative catalyst. It is worth mentioning that the $CeCl_3{\cdot}7H_2O$ or $Ce(NO_3)_3{\cdot}6H_2O$ catalyzed synthesis of DHMPs suffers from some drawbacks such as the use of fairly high amounts of catalysts (100–20 mol %) or heating at 80°C.

Ceric ammonium nitrate (CAN) is a convenient and widely used reagent for affecting a broad spectrum of synthetic transformations due to its many advantages such as solubility in water and various organic solvents, inexpensiveness, ecofriendly nature, uncomplicated handling, fast conversions, and convenient work-up procedure which make CAN a potent catalyst in organic synthesis. Although DHMPs has been previously synthesized utilizing CAN as one electron oxidant [28] under ultrasound irradiation, we found that there is no need for sonification as the reaction proceeds smoothly at ambient temperature. Also, we do believe that CAN acts as a Lewis acid catalyst because of the applicability of our protocol for the synthesis of DHMP thiones. The use of CAN as a Lewis-acid catalyst in C—N bond formation

**Scheme 1**




in heterocyclic chemistry is somehow limited [29]. Thus, in continuation to our efforts in the synthesis of azoles and azines [30,31] *via* simple and high-yielding protocol, we report herein and for the first time a novel three component one-pot synthesis of Biginelli 3,4-dihydropyrimidine-2(1H)-ones and 2-(1H)-thiones in high yields *via* the reaction of aromatic aldehydes, ethyl acetoacetate, urea, or thiourea using CAN as catalyst at ambient temperature.

## RESULTS AND DISCUSSION

When aryl aldehydes **1** was treated with ethyl acetoacetate **2** and urea or thiourea **3** in MeOH (10 mL) in the presence of CAN (10 mol %) at ambient temperature (27°C), and the reaction mixture was left overnight, the dihydropyrimidinones/thiones **4** were obtained in a high yield (cf. Scheme 1). The optimization of the reaction was investigated. For this goal, we explored the effect of catalyst molar ratio and solvent effect on the overall yield. Our investigation clearly revealed that addition of (10 mol %) of CAN to the reaction mixture containing 1:1:1.2 molar ratio of 1:2:3 at ambient temperature was optimal for the formation of the condensation products. In addition, MeOH was found to be the best solvent among those tested ($H_2O$, EtOH, THF).

To study the scope of the procedure, a variety of aromatic, heteroaromatic, and α,β-unsaturated aldehydes were utilized. In all cases, the reaction proceeds smoothly in a high yield with a slight decrease in the yield when the aryl substituent involves a strong electron donating group. However, attempts to apply this to simple aliphatic aldehydes were unsuccessful (Table 1).

A proposed mechanism to account for the formation of 4 is demonstrated in Scheme 2.

**Table 1**

CAN catalyzed one-pot synthesis of Biginelli 3,4-dihydropyridin-2(1*H*)-ones and their corresponding 2-(1*H*)-thiones.

| Entry | Ar | X | Yield (%) | mp (°C) Found | mp (°C) Lit. |
|---|---|---|---|---|---|
| **4a** | $C_6H_5$ | O | 95 | 202–203 | 201–204 [26] |
| **4b** | 4-$CH_3OC_6H_4$ | O | 93 | 203–205 | 204–206 [26] |
| **4c** | 4-$CH_3C_6H_4$ | O | 94 | 213–215 | 212–213 [26] |
| **4d** | 3-$NO_2C_6H_4$ | O | 96 | 225–227 | 226–228 [26] |
| **4e** | 4-$ClC_6H_4$ | O | 93 | 212–214 | 212–214 [5] |
| **4f** | 2-Furyl | O | 88 | 204–206 | 205–207 [5] |
| **4g** | $C_6H_5CH{=}CH$ | O | 84 | 241–242 | 241–243 [28] |
| **4h** | $C_6H_5$ | S | 94 | 207–209 | 207–209 [26] |
| **4i** | 4-$CH_3OC_6H_4$ | S | 92 | 150–152 | 150–152 [32] |
| **4j** | 4-$NO_2C_6H_4$ | S | 93 | 108–110 | 109–111 [32] |

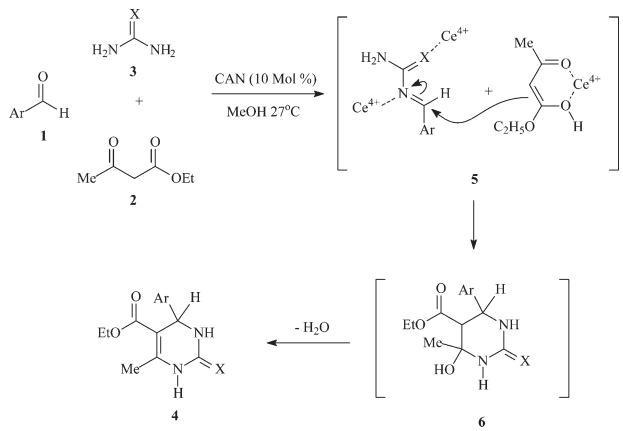
## CONCLUSIONS

In conclusion, a catalytic amount of ceric ammonium nitrate (CAN) efficiently catalyzes the three component one-pot synthesis of Biginelli condensation product in MeOH at ambient temperature. The procedure proved to be simple, highly efficient, produces excellent yields which make it a useful and important addition to the well-known Biginelli reaction.

## EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analyses were obtained on a LECO CHNS-932 Elemental Analyzer. Infrared spectra were recorded in KBr on a Perkin-Elmer 2000 FTIR system. $^1$H-NMR and $^{13}$C-NMR (DMSO-$d_6$) spectra were determined on a Bruker DPX spectrometer operating at 400 MHz for $^1$H-NMR and 100 MHz for $^{13}$C-NMR in DMSO-$d_6$ as solvents and TMS as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI 70 eV.

**Scheme 2**



**General procedure for the synthesis of compounds 4a–j.** To a mixture of each of aldehyde 2a–i (10 mmol), ethylacetoacetate (10 mmol), urea or thiourea (12 mmol) dissolved in MeOH (20 mL), was added cerium IV ammonium nitrate (10 mol %). The reaction mixture was stirred at room temperature (27°C) overnight. Brine solution was then added to the mixture and the salt formed was collected by filtration and recrystallized from EtOH to afford pure samples of compounds **4a–j**.

***Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 4a.*** Mp 201–203°C. IR (KBr): 3230 and 3200 (2NH), 1685 and 1664 (CO) $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO): δ = 1.12 (t, 3H, *J* = 7.2 Hz, $CH_3$), 2.32 (s, 3H, $CH_3$), 4.02 (q, 2H, *J* = 7.2 Hz, $CH_2$), 5.09 (d, 1H, *J* = 4 Hz, pyrimidyl 4-H), 6.87 (t, 1H, *J* = 7.3 Hz, Ar-H), 7.30 (t, 2H, *J* = 7.5 Hz, Ar-H), **6.35** (**t**, 2H, *J* = 7.5 Hz, Ar-H), 9.66 (**s**, 1H, NH), 10.44 (**s**, 1H, NH). ms (EI, 70 eV): m/z = **278** ($M^+$, 100). Anal. Calcd for $C_{14}H_{16}O_3N_2$ (260.29): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.62; H, 6.22; N, 10.78.

***Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 4b.*** Mp 203–205°C. IR (KBr): 3230 and 3204 (2NH), 1688 and 1664 (CO) $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO): δ = 1.10 (t, 3H, *J* = 7.2 Hz, $CH_3$), 2.24 (s, 3H, $CH_3$), 3.72 (s, 3H, $OCH_3$), 4.00 (q, 2H, *J* = 7.2 Hz, $CH_2$), 5.09 (d, 1H, *J* = 3.2 Hz, pyrimidyl 4-H), 6.87 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.14 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.68 (**s**, 1H, NH), 9.15 (**s**, 1H, NH). ms (EI, 70 eV): m/z = 290 ($M^+$,100).Anal. Calcd for $C_{15}H_{18}O_4N_2$ (290.31): C, 62.05; H, 6.24; N, 9.64. Found: C, 61.85; H, 6.28; N, 9.66.

***Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 4h.*** Mp 150–152°C. IR (KBr): 3230 and 3204 (2NH), 1688 and 1664 (CO) $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO): δ = 1.12 (t, 3H, *J* = 7.1 Hz, $CH_3$), 2.29 (s, 3H, $CH_3$), 3.73 (s, 3H, $OCH_3$), 4.00 (q, 2H, *J* = 7.1 Hz, $CH_2$), 5.08 (d, 1H, *J* = 3.5 Hz, pyrimidyl 4-H), 6.93 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.13 (d, 2H, *J* = 8.5 Hz, Ar-H), 9.26 (**s**, 1H, NH), 10.3 (**s**, 1H, NH). ms (EI, 70 eV): m/z = 306 ($M^+$, 100). Anal. Calcd for $C_{15}H_{18}O_3N_2S$ (306.38): C, 58.80; H, 5.92; N, 9.14; S, 10.47. Found: C, 58.78; H, 5.88; N, 9.12; S, 10.44.

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## REFERENCES AND NOTES

[1] Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, D. Z.; Schewartz, J.; Smillie, K. M.; Malley, M. F. J Med Chem 1990, 33, 2629.

[2] Nagarathnam, D.; Miao, S. W.; Lagu, B.; Chiu, G.; Fang, J.; Murali Dhar, T. G.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F.; Wong, W. C.; Sun, W.; Tian, D.; Zhang, J.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Ransom, R. W.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Gluchowski, C. J Med Chem 1999, 42, 4764.

[3] Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J. Z.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. 1995, 38, 119.

[4] Snider, B. B.; Jinsheng, C.; Patil, A. D.; Freyer, A. J. Tetrahedron Lett 1966, 37, 6977.

[5] Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brossi, C. D.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westly, J. W.; Potts, B. C. M. J Org Chem 1995, 60, 1182.

[6] Snider, B. B.; Shi, Z. J Org Chem 1993, 58, 3828.

[7] Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. Tetrahedron 1997, 53, 2803.

[8] Kappe, C. O. Acc Chem Res 2000, 33, 879.

[9] Biginelli, P. Gazz Chim Ital 1893, 23, 360.

[10] Su, W. K.; Li, J. J.; Zheng, Z. G.; Shen, Y. C. Tetrahedron Lett 2005, 46, 6037.

[11] Reddy, Ch. V.; Mahesh, M.; Raju, P. V. K.; Rajua, T.; Babua, R.; Reddy, V. V. N. Tetrahedron Lett 2002, 43. 2657.

[12] Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. Tetrahedron Lett 2003, 44, 6497.

[13] Debache, A.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. A. Tetrahedron Lett 2008, 49, 6119.

[14] Fua, N.; Yuana, Y.; Caoa, Z.; Wanga, S.; Wanga, J.; Peppe, C. Tetrahedron Lett 2002, 58, 4801.

[15] Saini, A.; Kumar, S.; Sandhu, J. S. Indian J Chem Sect B 2007, 46, 1886.

[16] Tu, S. J.; Fang, F.; Miao, C. B.; Jiang, H.; Feng, Y. J.; Shi, D. Q.; Wang, X. S. Tetrahedron Lett 2003, 44, 6153.

[17] Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. Appl Catal A Gen 2006, 300, 85.

[18] Ghosh, R.; Maiti, S.; Chakraborty, A. J Mol Catal A Chem 2004, 217, 47.

[19] Adib, M.; Ghanbary, K.; Mostofi, M.; Ganjali, M. R. Molecules 2006, 11, 649.

[20] Muñoz-Muñiz, O.; Juaristi, E. ARKIVOC 2003, XI, 16.

[21] Lin, H. X.; Zhao, Q. J.; Xu, B.; Wang, X. H. Chin Chem Lett 2007, 18, 502.

[22] Banik, B. K.; Reddy, A. T.; Datta, A.; Mukhopadhyay, C. Tetrahedron Lett 2007, 48, 7392.

[23] Li, J. T.; Han, J. F.; Yang, J. H.; Li, T. S. Ultrason Sonochem 2003, 10, 119.

[24] Peng, J. J.; Deng, Y. Q. Ionic Tetrahedron Lett 2001, 42, 5917.

[25] Chitraa, S.; Pandiarajan, K. Tetrahedron Lett 2009, 50, 2222.

[26] Liu, C. J.; Wang, J. D. Molecules 2009, 14, 763.

[27] Pansuriya, A. M.; Savant, M. M.; Bhuva, C. V.; Singh, J.; Naliapara, Y. T. ARKIVOC 2009, vii, 79.

[28] Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. J Chem Soc Perkin Trans 1 2001, 1939.

[29] Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. Synlett 2003, 156.

[30] Al-Qalaf, F.; Mekheimer, R. A.; Sadek, K. U. Molecules 2008, 13, 2908.

[31] Alnajjar, A.-A.; Abdelkhalik, M.; Al-Enezi, A.; Elnagdi, M. Molecules 2009, 14, 68.

[32] Zhan, H. W.; Wang, J.-X.; Wang, X. T. Chin Chem Lett 2008, 19, 1183.

# Synthesis of Pyrazolopyridine 3-Carboxylates by Friedlander Condensation



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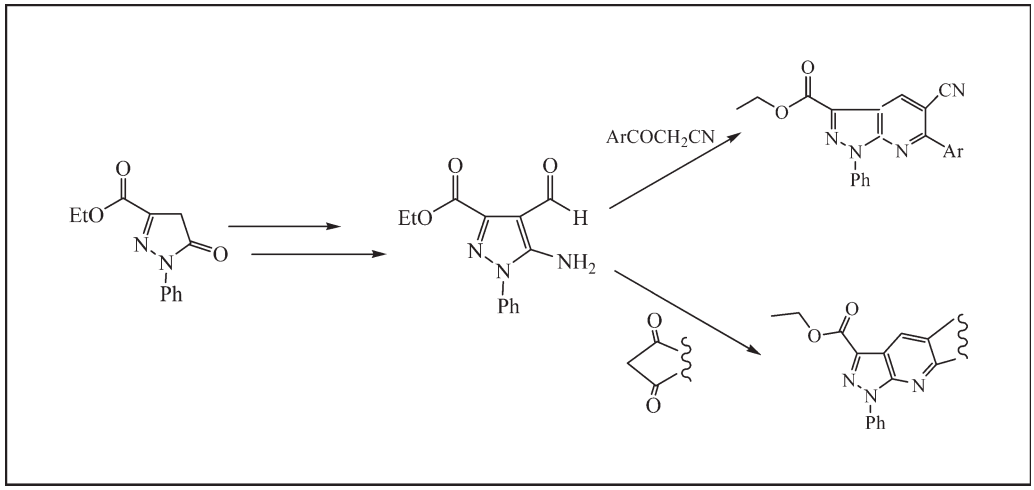


A series of 1,3,6-trisubstituted and 1,3,5,6-tetrasubstituted pyrazolo [3,4-*b*] pyridines **5** have been synthesized by series of reactions on 1-phenyl-3-carboxylate pyrazolone to obtain *o*-aminoaldehyde, which undergo facile condensation with various α-methylene ketones, nitriles, and esters, furnish fused pyridine derivative in good yield.

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## INTRODUCTION

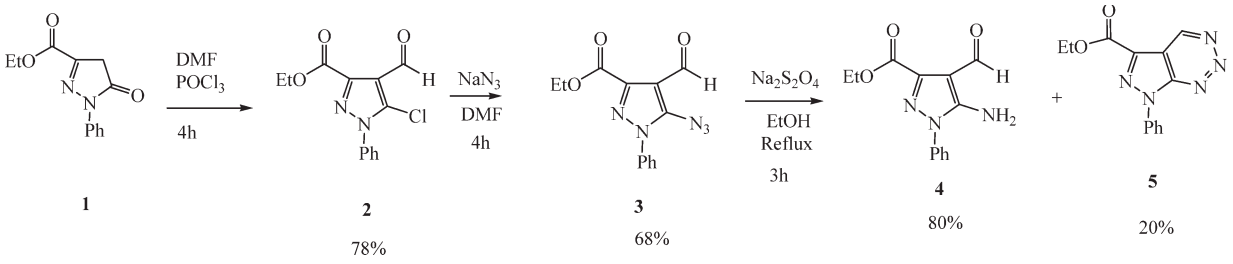
Pyrazolo[3,4-*b*]pyridines as aza-analogues of indazoles are attractive targets in organic synthesis because of their significant biological activities, such as hypoglycemic [1], psychotropic [2], cytotoxic [3], antiviral [4], fungicidal [5], antiasthmatic [6], antiallergic [7], antitumor [8], and antibacterial [9]. These compounds were also used in coronary of neurodegenerative diseases [10,11]. A number of pyrazolo[3,4-*b*]pyridines display interesting anxiolytic activity (*e.g.*, tracazolate), which are potentially biologically active compounds as new inhibitors of xantine oxidases [12]. They have proved to be active against gram-positive and gram-negative bacteria [13] and also as compounds for inhibition of cholesterol formation [14].

*o*-Aminoaldehydes are the key intermediates for the synthesis of various biologically active heterocycles, *e.g.*, [15,16]. The Friedlander condensation of *o*-aminoaldehyde with ketones furnished required tri/tetra cyclic pyrazolo[3,4-*b*]pyridine. The required starting compound *i.e.*, ethyl 4,5-dihydro-5-oxo-1-phenyl-1*H*-carboxylate **1** is prepared by esterification of ethyl 4,5-dihydro-5-oxo-1-phenyl-1*H*-carboxylicacid [17].

*o*-Aminoaldehyde **4,** the key starting compound, was obtained by series of reactions including Vilsmeir-Haack formylation of **1** to furnish *o*-chloroaldehyde **2**, which on $S_N2$ displacement of chloride ($Cl^-$) by azide ($-N_3$) yield **3** in 68% yield. Compound **3** on reductions with sodium dithionate $Na_2S_2O_4$ yields two products *o*-aminoaldehyde **4** in 80% and triazine-5-carboxylate **5** in 20%. The formation of compound **5** can be rationalized by condensation of carbonyl with electronegative nitrogen of azide.

Compounds **4** and **5** were separated on column and were characterized by spectroscopic and analytical methods (Scheme 1), *e.g.*, IR spectra of **4** and **5** both showed ester carbonyl stretching at 1760 $cm^{-1}$, whereas only **4** showed doublet at 3451 and 3347 $cm^{-1}$ for $NH_2$ and 2712 and 1716 $cm^{-1}$for CHO groups. The peaks due to $NH_2$ and CHO are absent in IR spectra of **5**. The $^1$H-NMR of **4** and **5** also help lot to distinguish between **4** and **5**. The $NH_2$ and CHO protons were observed at δ 5.91 and 10.26 in compound **4** and both of these signals

**Scheme 1**

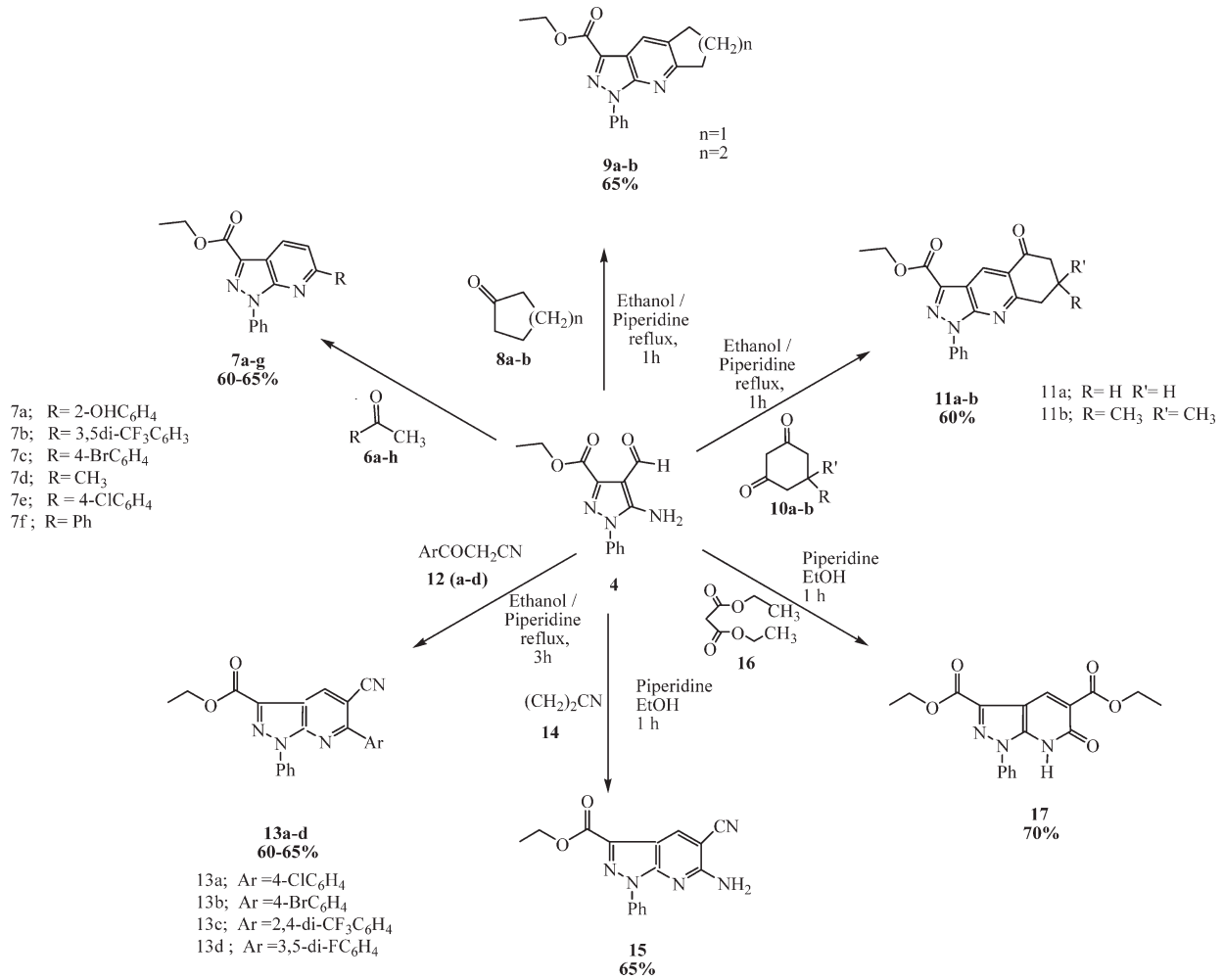



are absent in **5**. While compound **5** showed a sharp singlet at δ 8.31 for $C_4H$. The elemental analyses were also in agreement with the proposed structures of **4** and **5**.

The novel Friedlander condensation of *o*-aminoaldehyde **4** with α-methylene ketones, nitriles, and esters containing active methylene groups was carried out in the presence of piperidine offered fused pyridines in good yields. Thus, the condensation of aromatic methyl ketones **6** and **4** under ethanol reflux furnishes **7** in 60–65% yields. The cyclic ketones **8** on condensation with **4** yield tricyclic pyridines **9** in 60–65% yield.

Similarly, *o*-aminoaldehyde **4** on condensation with dimedone or cyclohexane 1,2-dione **10** offered **11** in 60% yield. Compound **11** is α-methylene ketones functionality, which has potential to generate new heterocycles (Scheme 2). All the obtained compounds were well characterized by IR, $^1$H-, $^{13}$C-NMR, and mass

**Scheme 2**



spectroscopy given in the Experimental section. In all above reaction, the ester group remains intact in the product. The reactions reported here provide a versatile method for synthesis of various substituted 3-ethycarboxy pyrazolo[3,4-*b*]pyridines. We have extended Friedlander condensation using nitriles and esters having reactive methylene group to generate libraries of new heterocycles having multifunctional groups. Reactions with reactive methylene such as aroylacetonitrile **12** and malanonitrile **14** with **4** furnished 6-aryl 5-cyanopyrazloyridines **13** and 6-amino-5-cyanopyrazloyridines **15** in 60–65% yield. Another multifunctional heterocycle **17** was obtained by condensation of diethylmalonate with *o*-aminopyrazole **4** (Scheme 2). The IR, $^1$H-NMR, $^{13}$C-NMR, Mass, and elemental analysis confirm all structures of these synthesized compounds.

## EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Schimadzu FFTIR-408 spectrophotometer. $^1$H, $^{13}$C-NMR spectra were recorded on a Varian XL-300 (300 MHz, 75 MHz) spectrometer in DMSO-$d_6$ or $CDCl_3$ using TMS as an internal standard, and chemical shifts are expressed in δ (ppm) unit. Elemental analyses were carried out on Hosli CH-Analyzer and are within ±0.3 of the theoretical percentages. All reactions were monitored by thin-layer chromatography carried out on 0.2-mm silica gel (sd Fine Chemicals, 60–120 mesh powder). Common reagent grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

**Ethyl-5-chloro-4-formyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate (2).** To a solution of ethyl-4,5 dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate **1** (0.1 mol, 23.2 g) in dimethyl formamide (0.5 mol, 37 mL) was added phosphorous oxychloride (0.3 mol, 46 mL) in small portions at 10–15°C with stirring. The reaction mixture was stirred at 65–70°C for 4 h and poured into ice-cold water (900 mL). The precipitated product was filtered by suction, washed with water, and recrystallized. Colorless prism (ethanol), mp. 135–136°C, yield 24.5 g (78%), IR: 3417m, 2720, 1739s, 1671m, 1597w cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.34 (t, 3H, $J$ = 6.8 Hz, $CH_3$), 4.41 (q, 2H, $J$ = 6.8 Hz, $OCH_2$), 7.54–7.61 (m, 5H, Ar-H), 10.31 (S, 1H, CHO). Anal. Calcd. for $C_{13}H_{11}Cl\ N_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.25; H, 3.70; N, 10.23.

**Ethyl-5-azido-4-formyl-4,5-dihydro-1-phenyl-1*H*-pyrazole-3-carboxylate (3).** To the solution of ethyl-5-chloro-4-formyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate **2** (27.869 g, 0.1 mol) in dimethylformamide (150 mL), sodium azide (7.15 g, 0.109 mol) was slowly added for 30 min. The reaction mixture was stirred for 4 h (TLC check, toluene/acetone 8:2) and poured in ice-cold water (1000 mL). The precipitated solid was filtered on suction pump and dried to give colorless prism (ethanol), mp. 75–76°C. Yield 19.38 g (68%), IR: 3419m, 3390m, 2164m, 1720s, 1668m, 1597w cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.33 (t, $J$ = 6.8 Hz, 3H, $CH_3$); 4.46 (q, $J$ = 6.8 Hz, 2H, —$OCH_2$); 7.50–7.60 (m, 5H, Ar-H), 10.26 (s, 1H CHO). Anal. Cacld. for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.67; H, 3.78; N, 24.38. *m*/*z* (70 eV): 285.

**General procedure for the synthesis of ethyl-5-amino-4-formyl-4,5-dihydro-1-phenyl-1*H*-pyrazole-3-carboxylate (4) and ethyl-7-phenyl-7*H*-pyrazolo[3,4-d][1,2,3]triazene-5-carboxylate (5).** A mixture of ethyl-5-azido-4-formyl-4,5-dihydro-1-phenyl-1*H*-pyrazole-3-carboxylate (25 g, 0.089 mol) and sodium dithionate (0.1 mol, 17.4 g) in ethanol (275 mL) was refluxed for 3 h (TLC check, toluene/acetone, 8:2). The mixture was then poured into ice-cold water (800 mL). The precipitated solid was filtered by suction, washed with water, and dried. The obtained solid was separated by column chromatography using silica 60–120 mesh powder and eluting with toluene/acetone as 9:1. mp. 183–184°C, yield 18.44 g (80%), pale-yellow-color needles (ethanol) IR: 3451m, 3347m, 2712s, 1716m, 1677s, 1597w cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.41 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 4.49 (q, $J$ = 7.2 Hz, 2H, $OCH_2$), 5.91 (bs, 2H, exchange with $D_2O$, $NH_2$), 7.47–7.48 (m, 5H, Ar-H), 10.26 (s, 1H, CHO). $^{13}$C-NMR (75 MHz DMSO-$d_6$) 15.0, 61.9, 105.6, 125.5, 129.7 (2C'S), 130.6 (2C'S), 137.4, 143.0, 151.4, 162.2, 186.3. Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N,16.21. Found: C, 60.34; H, 5.23; N, 16.46.

**Ethyl-7-phenyl-7*H*-pyrazolo[3,4-d][1,2,3]triazene-5-carboxylate (5).** Yellow needle (ethanol) mp. 216–217°C, yield 4.61 g (20%), IR: 2980m, 1760s, 1710s, 1610m, 1510s cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.44 (t, $J$ = 6.2 Hz, 3H, $CH_3$), 4.45 (q, $J$ = 6.2 Hz, 2H, —$OCH_2$), 7.43–7.48 (m, 5H, Ar-H), 8.31 (s, 1H, CH). Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.82; H, 4.20; N, 26.18.

**General procedure for the synthesis of 1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxylate (7a–g).** A mixture of 4 (0.2 g, 7.0 mmol) and substituted acetophenone 6 (0.12 g, 8.0 mmol) in ethanol (15–20 mL) with catalytic amount of piperedine (0.5 mL) was refluxed for 3 h (TLC check. toluene/acetone, 8:2). The reaction mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized.

**Ethyl-6-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazolo-[3,4-b]pyridine-3-carboxylate (7a).** Colorless prism (methanol) mp. 140–141°C, yield 1.5 g (60%), IR: 3450m, 1835s, 1730s, 1668m cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$): δ 1.43 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.45 (q, $J$ = 6.8 Hz, 2H, $OCH_2$), 7.0 (t, $J$ = 7.1 Hz, 2H Ar-H), 7.2 (t, $J$ = 7.1 Hz, 2H, Ar-H), 7.6 (d, 1H, $J$ = 6.8 Hz, Ar-H), 8.0–8.1 (m, 5H, Ar-H), 8.3 (d, $J$ = 6.8 Hz,1H, Ar-H), 11.90 (bs, 1H —OH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) 15.1, 62.0, 115.2, 118.4, 119.6, 120.4, 122.2, 123.6 (2C), 128.9, 130.3, 130.5 (2C), 132.8, 133.1, 136.3, 138.7, 149.4, 157.9, 158.6, 162.0. Anal. Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N,11.69. Found: C, 70.24; H, 4.58; N,11.87. *m*/*z* (70 eV): 359 [M + 1].

**Ethyl-6-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (7b).** Colorless needle (ethanol/water, 8:2), mp. 168–170°C, yield 1.94 g (58%), IR: 3280m, 1710s, 1640w cm$^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.42 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.46 (q, 2H, $J$ = 6.8 Hz, —$OCH_2$), 7.45 (d, $J$ = 8.1 Hz, 2H, Ar-H), 7.56 (d, $J$ = 8.1 Hz, 2H, Ar-H), 8.14 (s, 1H, Ar-H), 8.25 (d, $J$ = 7.6 Hz, 2H, Ar-H), 8.48 (d, $J$ = 7.6 Hz, 2H, Ar-H), 8.70 (s, 1H, Ar-H). Anal. Calcd. for $C_{23}H_{15}F_6N_3O_2$: C, 57.63; H, 3.15; N, 8.77. Found: C, 57.48; H, 3.29; N, 8.84; *m*/*z* (70 eV) = 482 [M + 1, 90%], 481 [M + 1, 60%], 480, 439, 338, 254.

**Ethyl-6-(4-bromophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (7c).** Colourless needles (ethanol/water, 8:2), mp. 170–172°C, yield 1.76 g (60%), IR: 1760w, 1620m, 1091w $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$): δ 1.50 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.60 (q, $J$ = 6.8 Hz, 2H, $OCH_2$), 8.31 (dd, $J$ = 8.2 and 2.3 Hz 2H, Ar-H), 7.92 (dd, $J$ = 8.2 and 2.3 Hz, 2H, Ar-H), 7.23–7.7 (m, 5H, Ar-H), 9.01 (d, 1H, $J$ = 8.60 Hz, Ar-H); 9.21 (d, 1H, $J$ = 8.60 Hz Ar-H). Anal. Calcd. for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found C, 59.68; H, 3.79; N, 9.90.

**Ethyl-6-methyl-1-phenyl-1*H*-pyrazolo [3,4-*b*]pyridine-3-carboxylate (7d).** Colorless needles (ethanol/water, 8:2) mp. 136–137°C, yield 1.21 g (62%), IR: 2350s, 1668m, 1610s, 1540w, 1410w $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.41 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.40 (q, $J$ = 6.8 Hz, 2H, $CH_2$), 2.67 (s, $J$ = 6.6 Hz, 3H, $CH_3$), 7.22 (t, $J$ = 6.3 Hz, 2H, Ar-H), 7.61 (t, $J$ = 6.3 Hz, 1H, Ar-H), 8.0–8.1 (m, 2H, Ar-H), 8.32 (d, $J$ = 7.3 Hz, 1H, Ar-H), 8.60 (d, $J$ = 7.2 Hz, 1H, Ar-H). Anal. Calcd. for: $C_{16}H_{15}N_3O_2$ Calcd: C, 68.34, H, 5.37, N,14.94. Found: C, 68.33, H, 5.36, N, 14.90.

**Ethyl-6-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-b]pyridine-3-carboxylate (7e).** Colorless needles (ethanol: water, 8:2) mp. 186–187°C, yield 1.45 g (55%). IR: 2339m, 1668s, 1630w, 1576s $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.70 (t, $J$ = 6.4 Hz, 3H, $CH_3$), 4.41 (q, $J$ = 6.4 Hz, 2H, $OCH_2$), 7.23–7.70 (m, 5H, Ar-H), 7.75 (d, $J$ = 8.2 Hz, 2H, Ar-H), 7.99 (d, $J$ = 8.2 Hz, 2H Ar-H), 8.11 (d, $J$ = 8.2 Hz, 1H, Ar-H), 8.32 (d, $J$ = 8.3 Hz, 1H, Ar-H). Anal. Calcd. for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 59.54; H, 3.98; N, 11.32.

**Ethyl-1,6 diphenyl-1*H*-pyrazolo [3,4-*b*] pyridine-3-carboxylate (7f).** Colorless needles (ethylacetate), mp.176–177°C, yield 1.44 g (60%). IR: 2339m, 1587w $cm^{-1}$ $^1$H-NMR ($CDCl_3$): δ 1.70 (t, $J$ = 6.4 Hz, 3H, $CH_3$), 4.45 (q, $J$ = 6.4 Hz, 2H, $OCH_2$), 7.23–7.70 (m, 10H, Ar-H), 7.75 (d, $J$ = 8.1 Hz, 1H, Ar-H), 8.11 (d, $J$ = 8.1 Hz, 1H, Ar-H). Anal. Calcd. for: $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.26; H, 4.75; N, 12.42.

**General procedure for the synthesis of pyrazolo-[4,3-*e*]pyridine-3-carboxylate (9a, b).** The mixture of 4 (0.2 g, 7.0 mmol) and aromatic ketones 8 (7.0 mmol) with catalytic amount of piperedine (0.2 mL) was dissolved in ethanol (15 mL). The reaction mixture was then refluxed for 4 h (TLC check, toluene/acetone, 8:2). The reaction mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized to furnish compound 9.

**Ethyl-1-phenyl-1,5,6,7-tetrahydrocyclopenta[*b*]pyrazolo [4,3-*e*]pyridine-3-carboxylate (9a).** Colorless needles (ethanol/DMF, 5:1), mp.160–161°C, yield 1.39 g (65%). IR: 1740m, 1605s, 1510 w $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): δ 1.43 (t, 3H, $J$ = 6.8 Hz, $CH_3$), 2.21 (t, 2H, $J$ = 6.4 Hz, $CH_2$), 3.21 (t, $J$ = 6.4 Hz, $CH_2$), 3.45 (t, 2H, $J$ = 6.4 Hz, $CH_2$), 4.51 (q, 2H, $J$ = 6.8 Hz, $OCH_2$), 7.17–8.32 (m, 5H, Ar-H), 8.44 (s, 1H, $C_4$H). $m/z$ (70 eV): 307 (M + 1, 90%). $^{13}$C-NMR (75 MHz, DMSO-$d_6$). 144.2, 160.4, 60.9, 14.1, 110.3,147.8, 134.0, 33.1, 135.5, 165.1, 34.9, 25.3, 139.7, 120.2, 129.4, 126.3, 129.4, 120.2. Anal. Cacld. for $C_{18}H_{16}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.30; H, 5.62; N, 13.60.

**Ethyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo-[3,4-b] quinoline-3-carboxylate (9b).** Colorless needles (ethanol/DMF, 5:1), mp. 163–164°C, yield 1.33 g (62%), IR: 1742w, 1605s, 1510 w $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.52 (t, $J$ = 6.4 Hz, 3H, $CH_3$), 2.10 (t, $J$ = 6.4 Hz, 4H, 2 ($CH_2$), 2.90 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 3.01 (t, 2H, $J$ = 6.4 Hz, $CH_2$), 4.60 (q, $J$ = 7.1 Hz, 2H, $OCH_3$), 7.5–8.10 (m, 5H, Ar-H), 8.20 (s, 1H. $C_4$—H). Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.11; H, 5.98; N, 13.11.

**General procedure for the synthesis of pyrazolo [3,4-b]quinoline-3-carboxylate (11a, b).** The mixture of 4 (0.2 g, 7.0 mmol) and dimedone 10 (7.0 mmol) with catalytic amount of piperedine (0.2 mL) was refluxed in ethanol (15 mL) for 4 h (TLC check). The reaction mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized to afford compound 11.

**Ethyl-5,6,7,8-tetrahydro-5-oxo-1-phenyl-1*H*-pyrazolo [3,4-*b*]quinoline-3-carboxylate (11a).** Colorless needles (ethanol/DMF, 8:2), mp. 201–202°C, yield 1.31 g (56%). IR: 2990w, 1740s, 1640s, 1620s, 1590w, 1410w $cm^{-1}$. $^1$H-NMR ($CDCl_3$): 1.40 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 2.10 (t, 4H, $J$ = 6.3 Hz, $2CH_2$), 2.72 (t, 2H, $J$ = 6.8 Hz, $CH_2$), 3.24 (t, $J$ = 6.3 Hz, 2H, $CH_2$), 4.51 (q, 2H, $J$ = 6.8 Hz, $CH_2$), 7.5–8.20 (m, 5H, Ar-H), 8.90 (s, 1H, Ar-H). $m/z$ (70 eV): 335 (M + 1, 80%). Anal. Calcd. for: $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.11; H, 5.06; N, 12.48.

**Ethyl-5,6,7,8-tetrahydro-7,7-dimemehtyl-5-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline-3-carboxylate (11b).** Colorless needles (ethanol/DMF, 8:2), mp. 204–206°C, yield 1.40 g (60%), IR: 2980m, 1750m, 1700, 1640, 1410 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): δ 1.42 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 2.47 (s, 2H, $CH_2$), 2.62 (s, 3H, $CH_3$), 3.20 (s, 3H, $CH_3$), 3.28 (s, 2H, $OCH_2$), 7.45 (t, 1H, Ar-H), 7.62 (t, $J$ = 7.1 Hz, 2H, Ar-H), 8.21 (d, $J$= 7.1 Hz 1H, Ar-H), 8.90 (s,1H, $C_4$—H). $m/z$ (70 eV): 363[M + 1]. $^{13}$C-NMR(75 MHz, DMSO-$d_6$), 144.2, 160.4, 60.9, 14.2, 110.3, 147.8, 135.9, 133.1, 168.1, 52.3, 33.2, 53.2, 196.9,26.7, 26.7, 139.7, 120.2, 129.4, 126.3, 129.3, 120.2. Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.43; H, 5.78; N, 11.52.

**General procedure for the synthesis of pyrazolo-[3,4-b]pyridine-3-carboxylate (13a–d).** The mixture of **4** (0.2 g, 7.0 mmol), benzoylacetonitrile **12** (7.0 mmol), and catalytic amount of piperedine (0.5 mL) were dissolved in ethanol (15 mL). The reaction mixture was then refluxed for 4 h (TLC check, toluene/acetone, 8:2). The mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized to afford compound **13**.

**Ethyl-6-(4-chlorophenyl)-5-cyano-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxylate (13a).** Colorless solid (ethanol/DMF, 8:2), mp. 246–247°C, yield 1.74 g (62%), IR: 3000w, 2240w, 1740m, 1680m, 1620s, 1510, 1420w $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): δ 1.62 (t, 3H, $J$ = 6.8 Hz, $CH_3$), 4.70 (q, $J$ = 6.8 Hz, 2H, —$OCH_2$), 7.1–7.82 (m, 5H, ArH), 7.92 (d, $J$ = 6.8 Hz, 2H, $CH_2$), 8.15 (d, $J$ = 8 Hz, 2H, $CH_2$), 9.01 (s, 1H, $C_4$H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$), 110.3, 147.8, 163.9, 108.7, 141.3, 134.4, 144.2, 160.4, 60.9, 14.1, 129.0, 129.4, 132.9, 129.4, 129.0, 139.7, 120.2, 129.4, 126.3, 129.4, 120.2, 117.0. Anal. Calcd. for $C_{22}H_{15}ClN_4O_2$: C, 65.59; H, 3.75; N, 13.91. Found: C, 65.59; H, 3.75; N, 13.91.

**Ethyl-6-(4-bromophenyl)-5-cyano-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (13b).** Pale-yellow-color solid (ethanol/DMF, 8:2), mp. 261–262°C, yield 1.87 g (55–58%), IR: 2240s, 1780s, 1680w, 1620s, 1510w, 1420w $cm^{-1}$. $^1$H-

NMR ($CDCl_3$): δ 1.60 (t, $J$ = 6.74 Hz, 3H, $CH_3$), 4.70 (q, $J$ = 6.74 Hz, 2H, $OCH_2$), 7.20–7.80 (m, 5H, Ar-H), 7.92 (d, $J$= 8.2 Hz, 2H, $CH_2$), 8.18 (d, $J$ = 8.2 Hz, 2H, $CH_2$), 9.03 (s, 1H, Ar-H). Anal. Calcd. for $C_{22}H_{15}BrN_4O_2$: C, 59.08; H, 3.38; N,12.53. Found: C, 59.13; H, 3.35; N, 12.48.

**Ethyl-6-(2,4-bis(trifluoromethyl)phenyl)-5-cyano-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (13c).** Pale-yellow-color solid (ethanol/DMF, 8:2), mp. 190–192°C, yield 2.10 g (60%), IR: 3100s, 2250s, 1710m, 1610m, 1540w, 1410w $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.51 (t, 3H, $J$ = 6.8 Hz, $CH_3$), 4.60 (q, 2H, $J$ = 6.8 Hz, $CH_2$), 7.58–7.61 (m, 5H, Ar-H), 8.08 (s, 1H, Ar-H), 8.82 (s, 1H, Ar-H), 8.46 (s, 1H, Ar-H), 9.11 (s, 1H, $C_4H$). Anal. Calcd. for $C_{24}H_{14}F_6N_4O_2$: C, 57.15; H, 2.80; N, 11.11. Found: C, 57.10; H, 2.83; N, 11.08.

**Ethyl-5-cyano-6-(3,5-difluorophenyl)-1-phenyl-1*H*-pyrazolo [3,4-*b*] pyridine-3-carboxylate (13d).** Colorless needles (ethanol/DMF, 8:2), mp. 204–206°C. Yield 1.64 g (58–60%), IR: 3080w, 2240s, 1745m, 1620s, 1540m, 1420w $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.55 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.60 (q, $J$ = 6.8 Hz, 2H, —$OCH_2$), 7.10 (dd, $J$ = 8.3 and 2.3 Hz, 1H, Ar-H), 7.40 (d, $J$ = 8 Hz, 1H, Ar-H), 7.50 (d, $J$ = 2.3 Hz, 1H, Ar-H), 7.55–7.85 (m, 5H, Ar-H), 9.10 (s, 1H, Ar-H). Anal. Calcd. for $C_{22}H_{14}F_2N_4O_2$: C, 65.35; H, 3.49; N, 13.86. Found: C, 65.31; H, 3.46; N, 13.84.

**Ethyl-6-amino-5-cyano-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (15).** To the reaction mixture of **4** (0.2 g, 7.0 mmol) and malononitrile **14** (0.05 g, 8.0 mmol) in ethanol (15 mL), catalytic amount of piperedine (0.5 mL) was added. The reaction mixture was refluxed for 4 h (TLC check, toluene/acetone, 8:2) and then cooled to room temperature. The separated solid was filtered by suction to afford colorless needles (ethanol/DMF, 8:2), mp. 206–207°C, yield 1.40 g (65%), IR: 3476w, 2240s, 1610s, 1590w, 1554w $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): δ 1.55 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.60 (q, $J$ = 6.8 Hz, 2H, $OCH_2$), 5.40 (bs, 2H, $NH_2$, $D_2O$ exchange), 7.20–8.10 (m, 5H, Ar-H), 8.6 (s, 1H, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 15.0 (2C), 62.1 (2C), 91.9, 108.6, 117.5, 122.8, 128.2, 130.1, 139.1, 140.0, 152.4, 159.8,161.7. Anal. Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.51; H, 4.26; N, 22.79. Found: C, 62.53; H, 4.23; N, 22.75.

**Diethyl 6,7-dihydro-6-oxo-1-phenyl-1*H*-pyrazolo [3,4-*b*]pyridine-3,5-dicarboxylate (17).** A mixture of **4** (0.2 g, 7.0 mmol) and diethylmalonate **16** (0.14 g, 9.0 mmol) in ethanol (15 mL) with catalytic amount of piperedine (0.5 mL) was refluxed for 4 h (TLC check, toluene/acetone, 8:2). The reaction mixture was cooled at room temperature. The separated solid was filtered by suction to afford pale-yellow solid (ethanol/DMF, 8:2), mp. 142–143°C, yield 1.73 g (70%), IR: 3450w, 1710s, 1674s, 1610s, 1595w $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): δ 1.20 (t, $J$ = 6.4 Hz, 3H, $CH_3$), 1.42 (t, $J$ = 6.8 Hz, 3H, $CH_3$), 4.11 (q, $J$ = 6.3 Hz, 2H, $OCH_2$), 4.39 (q, $J$ = 6.3 Hz, 2H, —$OCH_2$); 7.25–8.30 (m, 5H, Ar-H), 8.40 (s, 1H, $C_4H$); 12.60 (bs, 1H, NH). $m/z$ (70 eV): 354 [M − 1]. $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 14.1 (2C), 61.0 (2C), 139.7, 120.2, 129.4, 126.3, 129.4, 120.2, 143.4, 97.0, 136.6, 161.2, 120.9, 135.8, 165.0, 160.4. Anal. Calcd. for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.83; H, 4.85; N, 11.80.

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## REFERENCES AND NOTES

[1] Anton-Fos, G. M.; Garcia-Domenech, R.; Perez-Gimenez, F.; Peris-Ribera, J. E.; Garcia-March, F. J.; Salabert-Salvador, M. T. Arzneimittel-Forschung 1994, 44, 821.

[2] (a) Feurer, A.; Luithle, J.; Wirtz, S.-N.; Koenig, G.; Stasch, J. P.; Stahl, E.; Schreiber, R.; Wunder, F.; Lang, D. PCT. Int. Appl. (Bayer Healthcare AG, Germany), 2004, WO2004009589; Feurer, A.; Luithle, J.; Wirtz, S.-N.; Koenig, G.; Stasch, J. P.; Stahl, E.; Schreiber, R.; Wunder, F.; Lang, D. Chem Abstr 2004, 140, 146157; (b) Ehlert, J.; Ragan, P.; Chen, A.; Roeske, W. R.; Yamamura, H. I. Eur J Pharmacol 1982, 78, 249; (c) Patel, J. B.; Malick, J. B.; Salama, A. I.; Goldberg, M. E. Pharmacol Biochem Behav 1985, 23, 675; (d) Young, R.; Glennon, R. A.; Dewey, W. L. Psychopharm (Berlin) 1987, 93, 494.

[3] Sanghvi, Y. S.; Larson, S. B.; Willis, R. C.; Robins, R. K.; Ravankar, G. R. J Med Chem 1989, 32, 945.

[4] (a) Ludwig, S.; Planz, O.; Sedlack, H. H.; Pleschka, S. PCT. Int. Appl. (Medinnova Ges.m.b. H., Germany), WO2004009589, 2004; Ludwig, S.; Planz, O.; Sedlack, H. H.; Pleschka, S. Chem Abstr 2004, 141, 307497; (b) Ludwig, S.; Planz, O.; Sedlack, H. H.; Pleschka S. Ger. Offen. DE 10138912, 2003; Ludwig, S.; Planz, O.; Sedlack, H. H.; Pleschka S. Chem Abstr 2003, 138, 198569.

[5] Mitsubishi Chem Corp. Eur. Pat. 658547-A1 (1996) (week 9622).

[6] (a)Tamaoki, J.; Isono, K.; Sakai, N.; Chiyotani, A.; Konno, K. Res Commun Chem Pathol Pharnacol 1992, 77, 65; Tamaoki, J.; Isono, K.; Sakai, N.; Chiyotani, A.; Konno, K. Chem Abstr 1992, 117, 1846304.

[7] (a) Okada, S.; Asano, M.; Kimura, K.; Iijima, H.; Inone, H.; Takishina, T. Kokyu 1990, **9**, 1140; Okada, S.; Asano, M.; Kimura, K.; Iijima, H.; Inone, H.; Takishina, T. Chem Abstr 1991, 114, 1569285.

[8] (a) Ooe, T.; Kobayashi, H. Jpn Kokai Tokkyo Koho Jpn. Pat. 14, 05331168, 1993; Ooe, T.; Kobayashi, H. Chem Abstr 1994, 121, 108778r.

[9] Joshi, K. C.; Dubey, K.; Dandia, A. Pharmazie 1981, 36, 336.

[10] (a) Bischoff, H.; Stasch, J. PCT. Int. Appl. WO 2003015770, 2003; Bischoff, H.; Stasch, J. Chem Abstr 2003, 138, 180718.

[11] (a) Aiet, I. A.; Resink, A.; Schweighoffer, F. U.S. Pat. 2004219552, 2004 (Exonhit Therapeutics S.A., France); Aiet, I. A.; Resink, A.; Schweighoffer, F. Chem Abstr 2004, 141, 388737; (b) Aiet, I. A.; Resink, A.; Schweighoffer, F. PCT. Int. Appl. 2003, WO2003016563; Aiet, I. A.; Resink, A.; Schweighoffer, F. Chem Abstr 2003, 138, 203092.

[12] Lynck, B.; Khan, M.; Teo, H.; Pedrotti, F. Can J Chem 1988, 66, 420.

[13] EI-Dean, A. M.; Aralla, A. A.; Mohammad, T. A.; Geies, A. A. Z Naturforsch Teil B 1991, 46, 541.

[14] (a) Fujikawa, Y.; Suzuki, M.; Iwasaki, H.; Sakashita, M.; Kitahara, M. Eur. Pat. Appl. EP 339,358, 1989; Fujikawa, Y.; Suzuki, M.; Iwasaki, H.; Sakashita, M.; Kitahara, M. Chem Abstr 1990, 113, 23903.

[15] Hawes, E.; Gorecki, D. K. J. J Heterocycl Chem 1972, 9, 703.

[16] Reddy, K.; Moglilaiah, K.; Sreenivasulu, B. J Ind Chem Soc 1984, 63, 443.

[17] (a) Cheng, C. C.; Yan, S. Y. In Organic Reactions; Wiley: New York, 1982; Vol. 28, p 37; (b) Mundy, B. P.; Ellerd, M. G. In Name Reactions and Reagents in Organic Synthesis; Wiley: New York, 1988; p 86; (c) Hassner, A.; Stumer, C. In Organic Synthesis Based on Named and Unnamed Reactions (Tetrahedron Organic Chemistry Series); Baldwin, J. E., Magnus, P. D., Eds.; Elsevier Science: Oxford; 1994; Vol. 11, p 132; (d) Dias-Ortiz, A.; de la Hoz, A.; Langa, F. Green Chem 2000, 2, 165; (e) Karthikeyan, G.; Perumal, P. T. J. Heterocycl Chem 2004, 41, 1039.

# Silica-Bonded *S*-Sulfonic Acid as Recyclable Catalyst for the Synthesis of 1,8-Dioxo-decahydroacridines and 1,8-Dioxo-octahydroxanthenes

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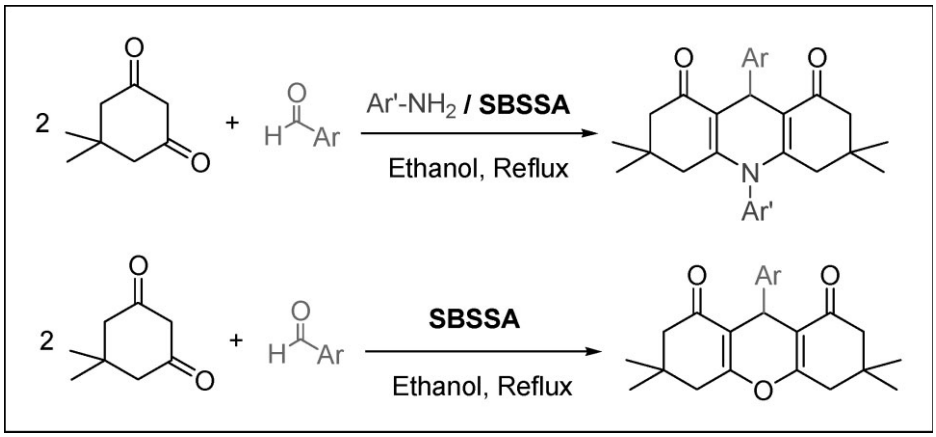


Silica-bonded *S*-sulfonic acid (SBSSA) has been found to be an efficient catalyst for the synthesis of 1,8-dioxo-decahydroacridines and 1,8-dioxo-octahydroxanthenes in excellent yields. The former have been synthesized from aromatic aldehydes, amines, and 5,5-dimethyl-1,3-cyclohexanedione, whereas the latter from this mixture without amines. The method is an easy access to functionalized acridine and xanthene derivatives. The catalyst can be reused.

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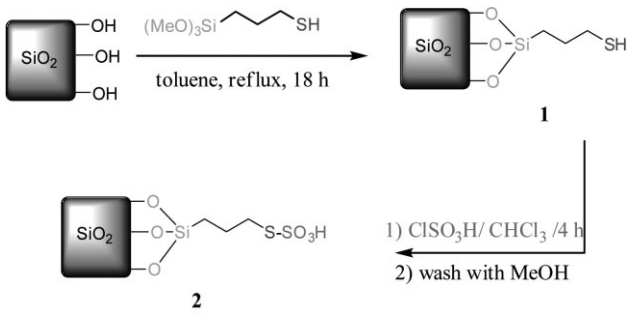
## INTRODUCTION

The development of heterogeneous catalysts for fine chemical synthesis has become a major area of research. The potential advantages of these materials over homogeneous systems (simplified recovery and reusability, the potential for incorporation in continuous reactors and micro reactors) can lead to novel and environmentally benign chemical procedures for academia and industry [1]. From this viewpoint, catalytic reactions lead to valuable processes, because the use of stoichiometric reagents that are often toxic poses inherent limitations from both an economical and an environmental viewpoint and in specific relation to product purification and waste management [2]. It is clear that green chemistry not only requires the use of environmentally benign reagents and solvents but also it is very crucial to recover and reuse the catalyst. One way to overcome the problem of recyclability of the traditional acid catalyst is to chemically anchor their reactive center onto a large surface area inorganic solid carrier to create new organic–inorganic hybrid catalyst [3]. In these types of solids, the reactive centers are highly mobile similar to homogeneous catalysts and at the same time these species have the advantage of being recyclable in the same fashion as heterogeneous catalysts. In view of this, several types of solid sulfonic acid functionalized silica (both amorphous and ordered) have been synthesized and applied as an alternative to traditional sulfonic acid resins and homogeneous acids in catalyzing chemical transformations [4,5]. Application of solid acids in organic transformation has an important role, because these species have many advantages, such as, simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal [4–10].

1,8-Dioxo-9-aryl-10-aryl-decahydroacridines and their derivatives are polyfunctionalized 1,4-dihydropyridine derivatives. In recent years, 1,4-dihydropyridines and their derivatives have attracted strong interest for the treatment of cardiovascular diseases, such as, angina pectoris [11] and hypertension [12]. Acridine derivatives have been used to synthesize labeled conjugates with medicinals, peptides, proteins, and nucleic acids [13–15] that exhibit antitumor and DNA-binding properties. Multicomponent reactions (MCRs) constitute, an

**Scheme 1.** Preparation of silica bonded *S*-sulfonic acid.




especially attractive synthetic strategy, for rapid and efficient library generation because the products are formed in a single step and diversity can be achieved simply by varying the reaction components [16]. Thus, new routes utilizing a MCR protocol for the synthesis of these molecules can attract considerable attention in the search for rapid-entry methods to these heterocycles.

Reportedly, the conventional synthesis of acridines and their derivatives has been performed in an organic acid, such as, HOAc [17]. Recently, few methodologies have been reported in the literature for the synthesis of decahydroacridines [18]. Each of these methods has limitations, such as, poor yields, cumbersome work up procedure, and generation of polluting effluents [17].

Xanthenes are an important class of organic compounds that find use as dyes, fluorescent material for visualization of biomolecules, and in laser technologies due to their useful spectroscopic properties [19]. Xanthenes have also received significant attention from many pharmaceutical and organic chemists essentially because of the broad spectrum of their biological and pharmaceutical properties, such as, antiviral [20], antibacterial [21], antinociceptive activities [22] as well as efficiency in photodynamic therapy [23] and anti-inflammatory activities [24]. There are several reports in the literature for the synthesis of 1,8-dioxooctahydroxanthene derivatives using aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione, these include $InCl_3{\cdot}4H_2O$ in ionic liquid [25], solid-state condensation by grinding at room temperature [26], diammonium hydrogen phosphate [27], *p*-dodecylbenzenesulfonic acid in water [28], $Fe^{3+}$-montmorilonite [29], $NaHSO_4$-$SiO_2$ or silica chloride [30], amberlyst-15 [18d], silica sulfuric acid [31], tetrabutylammonium hydrogen sulfate [32], trimethylsilylchloride [33], 1-butyl-3-methylimidazolium hydrogen sulfate [34], montmorillonite K-10-supported [35], and covalently anchored sulfonic acid on silica gel [36]. Each of these methods have their own advantages but also some of them often suffer from one or more disadvantages, such as, prolonged reaction time, tedious work-up processes, low yield [37], expensive reagents [18d,25], and hazardous organic solvents [37]. Consequently, there is scope for further innovation of methods with milder reaction conditions, short reaction times, increase in variation of the substituents in the components, and better yields in the synthesis of 1,8-dioxodecahydroacridines and 1,8-dioxo-octahydroxanthenes, which can be possibly achieved by choosing silica-bonded *S*-sulfonic acid (SBSSA) as a catalyst for this MCR.

## RESULTS AND DISCUSSION

Recently, we have reported the preparation of SBSSA and its application as catalyst for the synthesis of 1,1-diacetates [5a], quinoxaline [5b], and coumarin derivatives [5c] (Scheme 1).

In our continued interest in the development of a highly expedient methodology for the synthesis of fine chemicals and heterocyclic compounds of biological importance [38], we report here the synthesis of 1,8-dioxo-9-aryl-10-aryl-decahydroacridines and 1,8-dioxo-octahydroxanthenes in the presence of SBSSA as a heterogeneous solid acid (Scheme 2).

To determine the scope of the designed protocol, a number of commercially available aromatic aldehydes have condensed with dimedone and aryl amines under optimized reaction conditions, and the results are summarized in Table 1. We investigated further the electronic effect of different substituents present on the aldehyde component. It was observed that a wide range of aldehydes having both electron-donating and electron-withdrawing groups were equally facile for the reaction, resulting in the formation of decahydroacridine derivatives in very good yields. We also observed that various aniline derivatives reacted smoothly under the reaction conditions.

**Scheme 2.** Synthesis of 1,8-dioxo-9-aryl-10-aryl-decahydroacridines and 1,8-dioxo-octahydroxanthene using SBSSA as catalyst.

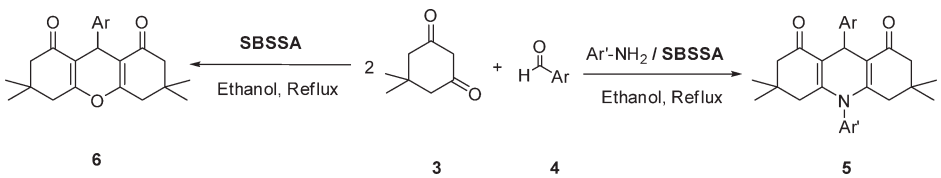
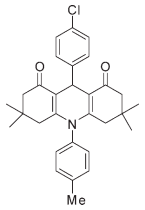
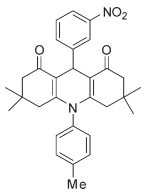
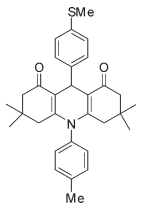
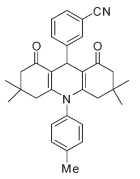
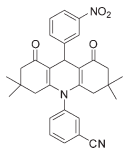
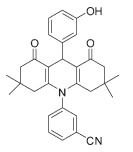
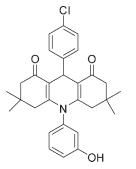
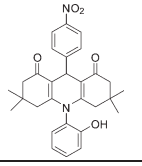


**Table 1**

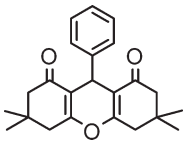
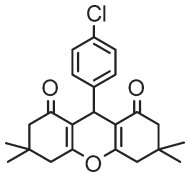
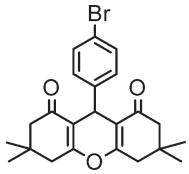
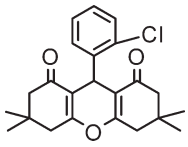
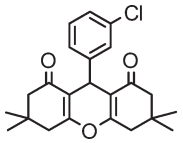
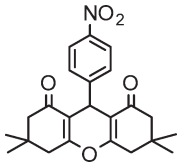
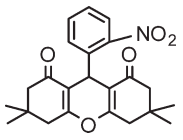
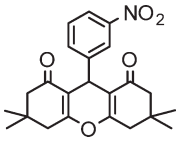
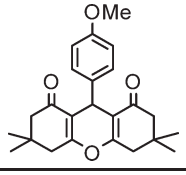
Synthesis of 1,8-dioxo-9-aryl-10-aryl-decahydroacridines derivatives in the presence of SBSSA under reflux conditions.[a]

| Entry | Ar | Ar′ | Product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 4-Cl—$C_6H_4$ | 4-Me—$C_6H_4$ |  **5a** | 1.0 | 96 |
| 2 | 3-$NO_2$—$C_6H_4$ | 4-Me—$C_6H_4$ |  **5b** | 2.5 | 85 |
| 3 | 4-MeS—$C_6H_4$ | 4-Me—$C_6H_4$ |  **5c** | 3.0 | 93 |
| 4 | 3-CN—$C_6H_4$ | 4-Me—$C_6H_4$ |  **5d** | 4.5 | 89 |
| 5 | 3-$NO_2$—$C_6H_4$ | 3-CN—$C_6H_4$ |  **5e** | 3.0 | 84 |
| 6 | 3-HO—$C_6H_4$ | 3-CN—$C_6H_4$ |  **5f** | 3.0 | 92 |
| 7 | 4-Cl—$C_6H_4$ | 3-HO—$C_6H_4$ |  **5g** | 2.5 | 95 |
| 8 | 4-$NO_2$—$C_6H_4$ | 2-HO—$C_6H_4$ |  **5h** | 1.5 | 96 |

[a] Reaction conditions: Dimedone (2 mmol), aldehyde (1 mmol), aniline derivative (1 mmol), catalyst (0.03 g) in refluxing ethanol.
[b] Isolated yield.

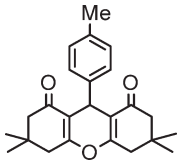
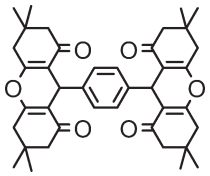
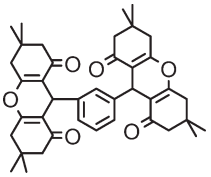
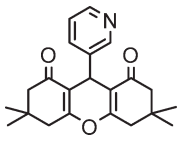
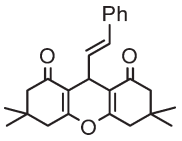
**Table 2**

Synthesis of 1,8-dioxo-octahydroxanthenes derivatives in the presence of SBSSA in ethanol under reflux conditions.[a]

| Entry | Ar | Product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ |  **6a** | 10.0 | 98 |
| 2 | 4-Cl—$C_6H_4$ |  **6b** | 4.0, 4.0, 4.5, 5.0, 5.0 | 92, 91, 89, 91, 90 |
| 3 | 4-Br—$C_6H_4$ |  **6c** | 3.0 | 96 |
| 4 | 2-Cl—$C_6H_4$ |  **6d** | 5.0 | 90 |
| 5 | 3-Cl—$C_6H_4$ |  **6e** | 5.0 | 90 |
| 6 | 4-$NO_2$—$C_6H_4$ |  **6f** | 2.0 | 95 |
| 7 | 2-$NO_2$—$C_6H_4$ |  **6g** | 3.0 | 87 |
| 8 | 3-$NO_2$—$C_6H_4$ |  **6h** | 3.0 | 94 |
| 9 | 4-MeO—$C_6H_4$ |  **6i** | 6.0 | 91 |

(*Continued*)

**Table 2**
(*Continued*)

| Entry | Ar | Product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 10 | 4-Me—$C_6H_4$ |  **6j** | 9.0 | 91 |
| 11 | 4-OHC—$C_6H_4$ |  **6k** | 5.0 | 64 |
| 12 | 3-OHC—$C_6H_4$ |  **6l** | 7.0 | 65 |
| 13 | 3-Pyridyl |  **6m** | 6.0 | 71 |
| 14 | $C_6H_5$—CH=CH— |  **6n** | 3.0 | 94 |

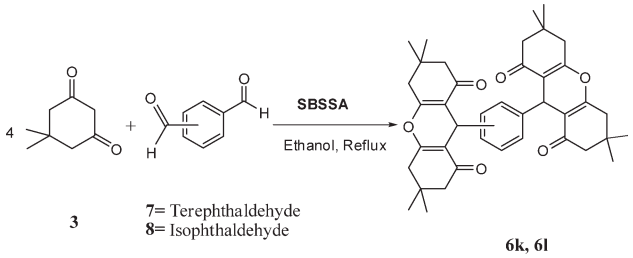
[a] Reaction conditions: Dimedone (2 mmol), aldehyde (1 mmol), catalyst (0.03 g) in refluxing ethanol.
[b] Isolated yield.

Encouraged by these results, we carried out reaction of 5,5-dimethyl-1,3-cyclohexanedione (**3**) and aromatic aldehydes (**4**) in the presence of SBSSA (0.03 g) in refluxing ethanol, which afforded 1,8-dioxo-octahydroxanthene derivatives **6a–n** in excellent yields within a short period of time (Scheme 2, Table 2). Here also the aromatic aldehydes containing both electron-donating and electron-withdrawing groups afforded the products in high yields.

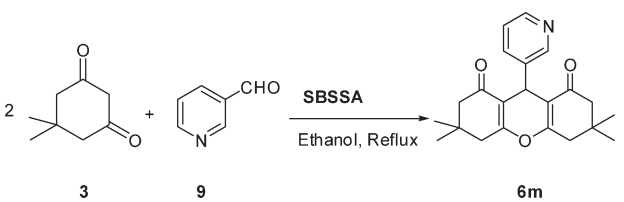
The practical synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde (**7**) and isophthaldehyde (**8**) with dimedone (**3**) to give structurally complex xanthenone derivatives (**6k** and **6l**), Scheme 3.

An important feature of this method is that the heterocyclic functionality present in the molecule remains

**Scheme 3.** Synthesis of bis(1,8-dioxo-octahydroxanthenes).




**Scheme 4.** Synthesis of 9-(pyridine-3-yl)-1,8-dioxo-octahydroxanthene.



unaffected. This fact was amply demonstrated by the reaction of pyridine-3-caboxaldehyde (**9**) with dimedone (**3**), which gave 9-(pyridine-3-yl)-1,8-dioxo-octahydroxanthene (**6m**) in excellent yield (Scheme 4).

The possibility of recycling the catalyst was examined using the condensation reaction of 5,5-dimethyl-1,3-cyclohexanedione and 4-chlorobenzaldehyde in ethanol under the optimized conditions. When the reaction was complete, the mixture was filtered and the remaining was washed with warm ethanol, and the catalyst reused in the next reaction. The recycled catalyst could be reused four times without any additional treatment. No observation of any appreciable loss in the catalytic activity of SBSSA was observed (Table 2, entry 2).

In conclusion, we have developed an efficient method for the synthesis of 1,8-dioxo-9-aryl-10-aryl-decahydroacridines and 1,8-dioxo-octahydroxanthenes in high yields using SBSSA as a catalyst. The catalyst was recovered and reused without any noticeable loss of reactivity. The mild reaction conditions and simplicity of the procedure offers improvements over many existing methods.

## EXPERIMENTAL

**General.** Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies. All of the products are known, except **5c**–**5h**, and characterized by comparison of their spectral (IR, $^1$H NMR) and physical data with those reported in literature. SBSSA was prepared according to our previous reported procedure [5].

**General procedure for the synthesis of 1,8-dioxo-9-aryl-10-aryl-decahydroacridines derivatives.** To a solution of an aromatic aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) and aryl amine (1 mmol) in ethanol (2 mL) in a round-bottom flask, SBSSA (0.03 g) was added. The mixture was heated under reflux conditions and the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the remaining was washed with warm ethanol in order to separate catalyst. Then, water (20 mL) was added to the filtrate and was allowed to stand at room temperature for 1 h. During this time, crystals of the pure product were formed, which were collected by filtration and dried. For further purification, if needed, the products were recrystalized from hot ethanol. The spectral data are given below.

***9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-10-p-tolylacridine-1,8-(2H,5H,9H,10H)-dione (5a).*** mp 273–275°C, (ref. 18e, 270–271°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.82 (s, 6H), 0.97 (s, 6H), 1.87 (d, 2H, $J$ = 17.4 Hz), 2.08–2.15 (m, 4H), 2.22 (d, 2H, $J$ = 16.2 Hz), 2.51 (s, 3H), 5.26 (s, 1H), 7.12 (d, 2H, $J$ = 8.2 Hz), 7.23 (d, 2H, $J$ = 8.3 Hz), 7.36–7.40 (m, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 21.73, 27.15, 30.15, 32.80, 32.87, 42.18, 50.60, 114.56, 128.56, 129.13, 129.74, 130.05, 131.84, 136.60, 140.06, 145.34, 150.64, 196.21.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-10-p-tolylacridine-1,8-(2H,5H,9H,10H)-dione (5b).*** mp 289–291°C, (ref. 18e. 285–287°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.81 (s, 6H), 0.99 (s, 6H), 1.92 (dd, 2H, $J_1$ = 17.5 Hz, $J_2$ = 0.9 Hz), 2.15 (d, 4H, $J$ = 16.6 Hz), 2.24 (d, 2H, $J$ = 16.2 Hz), 2.52 (s, 3H), 5.38 (s, 1H), 7.14–7.23 (m, 2H), 7.40–7.45 (m, 3H), 7.97–8.01 (m, 2H), 8.25 (t, 1H, $J$ = 1.9 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 21.71, 27.05, 30.10, 32.87, 33.31, 42.13, 50.53, 114.21, 121.53, 122.37, 129.22, 129.95, 130.93, 131.79, 135.70, 136.38, 140.22, 148.85, 151.26, 196.11.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-(methylthio)-phenyl)-10-p-tolyl-acridine-1,8-(2H,5H,9H,10H)-dione (5c).*** mp 239°C; IR (KBr): 3080, 2960, 2880, 1639, 1570, 1505, 1360, 1220, 882, 838, 730, 562, 520 ($cm^{-1}$); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.84 (s, 6H), 0.97 (s, 6H), 1.87 (d, 2H, $J$ = 17.5 Hz), 2.10 (d, 2H, $J$ = 17.5 Hz), 2.15 (d, 2H, $J$ = 16.2 Hz), 2.22 (d, 2H, $J$ = 16.2 Hz), 2.46 (s, 3H), 2.52 (s, 3H), 5.26 (s, 1H), 7.12 (d, 2H, $J$ = 7.7 Hz), 7.19 (d, 2H, $J$ = 8.1 Hz), 7.36–7.40 (m, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 16.59, 21.71, 27.23, 30.15, 32.76, 32.80, 42.20, 50.64, 114.85, 127.26, 128.86, 135.52, 136.79, 139.92, 144.06, 150.38, 196.23; Anal. Calc. C, 76.66; H, 7.26; N, 2.88; S, 6.60; Found C, 76.49; H, 7.09; N, 2.67.

***3-(1,2,3,4,5,6,7,8,9,10-Decahydro-3,3,6,6-tetramethyl-1,8-dioxo-10-p-tolylacridin-9-yl)benzonitrile (5d).*** mp 256–257°C; IR (KBr): 3080, 2960, 2880, 2320, 1638, 1590, 1558, 1480, 1450, 1360, 1308, 1220, 1140, 998, 930, 842, 830, 720 ($cm^{-1}$); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.80 (s, 6H), 0.94 (s, 6H), 1.86 (d, 2H, $J$ = 17.5 Hz), 2.09 (d, 2H, $J$ = 14.6 Hz), 2.12 (d, 2H, $J$ = 12.5 Hz), 2.19 (d, 2H, $J$ = 16.2 Hz), 2.47 (s, 3H), 5.24 (s, 1H), 7.05 (d, 1H, $J$ = 7.9 Hz), 7.10 (d, 2H, $J$ = 8.3 Hz), 7.15 (t, 1H, $J$ = 7.8 Hz), 7.33–7.36 (m, 3H), 7.39 (d, 1H, $J$ = 1.7 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 21.68, 27.13, 30.09, 32.77, 33.00, 42.13, 50.60, 114.36, 126.46, 126.65, 128.42, 128.98, 129.66, 130.06, 134.13, 136.50, 140.06, 148.68, 150.83, 196.09; Anal. Calc. C, 80.14; H, 6.94; N, 6.03; Found C, 79.97; H, 6.77; N, 5.87.

***3-(1,2,3,4,5,6,7,8-Octahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-1,8-dioxo-acridin-10(9H)-yl)benzonitrile (5e).*** mp 266–268°C; IR (KBr): 3080, 2960, 2880, 2203, 1643, 1635, 1595, 1578, 1440, 1362, 1240, 1220, 1140, 879, 801, 699 ($cm^{-1}$); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.83 (s, 6H), 1.01 (s, 6H), 1.83 (d, 2H, $J$ = 17.4 Hz), 2.13 (d, 2H, $J$ = 17.5 Hz), 2.17 (d, 2H, $J$ = 16.4 Hz), 2.26 (d, 2H, $J$ = 16.3 Hz), 5.37 (s, 1H), 7.46 (t, 1H, $J$ = 7.9 Hz), 7.63–7.68 (m, 2H), 7.82 (t, 1H, $J$ = 7.8 Hz), 7.91–7.95 (m, 2H), 8.00 (dd, 1H, $J_1$ = 8.2 Hz, $J_2$ = 1.4 Hz), 8.21 (s, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 27.15, 30.04, 33.03, 33.23, 42.35, 50.39, 114.91, 117.53, 121.77, 122.26, 129.47, 133.82, 135.62, 140.17, 148.26, 148.81, 149.80, 195.90; Anal. Calc. C, 72.71; H, 5.90; N, 8.48; Found C, 72.57; H, 5.76; N, 8.32.

***3-(1,2,3,4,5,6,7,8-Octahydro-9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-acridin-10(9H)-yl)benzonitrile (5f).*** mp >300°C decomp.; IR (KBr): 3250, 3080, 2960, 2880, 2320, 1610, 1590, 1555, 1500, 1460, 1410, 1340, 1260, 1240, 1142, 1110, 838, 710 ($cm^{-1}$); $^1$H NMR [$CDCl_3$-DMSO-$d_6$ (2%), 500 MHz], δ: 0.72 (s, 6H), 0.85 (s, 6H), 1.63 (d, 2H, $J$ = 17.3 Hz), 1.94 (d, 2H, $J$ = 17.3 Hz), 2.01 (d, 2H, $J$ = 16.2 Hz), 2.08 (d, 2H, $J$ = 16.2 Hz), 5.06 (s, 1H), 6.47 (dd, 1H, $J_1$ = 7.8 Hz, $J_2$ = 2.0 Hz), 6.75–6.78 (m, 4H), 6.93 (t, 1H, $J$ = 7.8 Hz), 7.48 (d, 1H, $J$ = 7.3 Hz), 7.62 (t, 2H, 7.8 Hz), 7.76 (d, 1H, $J$ = 7.8 Hz), 8.5 (brs, 1H); $^{13}$C NMR [$CDCl_3$-DMSO-$d_6$ (2%), 125 MHz], δ: 27.05, 29.86, 32.31, 32.64, 41.99, 50.39,

113.56, 114.84, 114.94, 117.68, 119.27, 129.10, 133.47, 135.01, 140.06, 147.30, 149.16, 157.50, 195.72; Anal. Calc. C, 77.23; H, 6.48; N, 6.00; Found C, 77.09; H, 6.33; N, 5.81.

***9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-10-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-acridine-1,8-(2H,5H,9H,10H)-dione (5g).*** mp 267–269°C; IR (KBr): 3390, 3120, 2960, 2880, 1639, 1595, 1560, 1480, 1443, 1360, 1305, 1220, 1140, 998, 935, 840, 720, 560 ($cm^{-1}$); $^1H$ NMR [$CDCl_3$-DMSO-$d_6$ (2%), 500 MHz], δ: 0.68 (s, 6H), 0.83 (s, 6H), 1.82 (d, 2H, $J$ = 17.5 Hz), 1.97–2.09 (m, 6H), 5.07 (s, 1H), 6.54–6.58 (m, 2H), 6.90 (d, 1H, $J$ = 5.0 Hz), 7.07 (d, 2H, $J$ = 8.3 Hz), 7.20–7.24 (m, 3H), 9.52 (brs, 1H); $^{13}C$ NMR [$CDCl_3$-DMSO-$d_6$ (2%), 125 MHz], δ: 26.93, 30.03, 32.66, 41.73, 50.52, 114.12, 128.39, 128.62, 131.63, 139.76, 145.27, 150.96, 195.40; Anal. Calc. C, 73.17; H, 6.35; Cl, 7.45; N, 2.94; Found C, 73.01; H, 6.19; N, 2.81.

***3,4,6,7-Tetrahydro-10-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-9-(4-nitrophenyl)-acridine-1,8-(2H,5H,9H,10H)-dione (5h).*** mp >300°C decomp.; IR (KBr): 3380, 3120, 2960, 2880, 1638, 1595, 1520, 1360, 1340, 1220, 1140, 998, 860, 827 ($cm^{-1}$); $^1H$ NMR [$CDCl_3$-DMSO-$d_6$ (2%), 500 MHz], δ: 0.67 (s, 6H), 0.84 (s, 6H), 1.84 (d, 2H, $J$ = 17.5 Hz), 1.98 (d, 2H, $J$ = 16.3 Hz), 2.04–2.10 (m, 4H), 5.18 (s, 1H), 6.55–6.59 (m, 2H), 6.92 (d, 2H, $J$ = 7.9 Hz), 7.21–7.24 (m, 1H), 7.47 (d, 2H, $J$ = 8.7 Hz), 7.98 (d, 2H, 8.7 Hz), 9.48 (brs, 1H); $^{13}C$ NMR [$CDCl_3$-DMSO-$d_6$ (2%), 125 MHz], δ: 26.95, 29.98, 32.68, 41.73, 50.44, 113.44, 123.69, 129.14, 139.58, 146.38, 154.10, 196.09; Anal. Calc. C, 71.59; H, 6.21; N, 5.76; Found C, 71.43; H, 6.09; N, 5.29.

**General procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives.** To a solution of an aromatic aldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) in ethanol (2 mL) in a round-bottom flask, SBSSA (0.03 g) was added. The mixture was heated under reflux conditions and the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the remaining was washed with warm ethanol in order to separate catalyst. Then, water (20 mL) was added to the filtrate and was allowed to stand at room temperature for 1 h. During this time, crystals of the pure product were formed, which were collected by filtration and dried. For further purification if needed, the products recrystalized from hot ethanol. The NMR data are given below.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2H-xanthene-1,8-(5H,9H)-dione (6a).*** mp 203–204°C, (ref. 32, 204–206°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 1.02 (s, 6H), 1.13 (s, 6H), 2.19 (d, 2H, $J$ = 16.2 Hz), 2.26 (d, 2H, $J$ = 16.2 Hz), 2.50 (s, 4H), 4.78 (s, 1H), 7.12 (t, 1H, $J$ = 7.2 Hz), 7.24 (t, 2H, $J$ = 7.5 Hz), 7.32 (d, 2H, $J$ = 7.6 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.75, 29.69, 32.26, 32.61, 41.29, 51.18, 116.07, 126.76, 128.45, 128.80, 144.54, 162.70, 196.76.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-chlorophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6b).*** mp 230–232°C, (ref. 33, 230–232°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 1.03 (s, 6H), 1.14 (s, 6H), 2.20 (d, 2H, $J$ = 16.3 Hz), 2.27 (d, 2H, $J$ = 16.3 Hz), 2.50 (s, 4H), 4.75 (s, 1H), 7.22 (d, 2H, $J$ = 8.5 Hz), 7.27 (d, 2H, $J$ = 8.5 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.72, 29.68, 31.89, 32.61, 41.28, 51.13, 115.69, 128.63, 130.19, 132.45, 143.13, 162.83, 196.71.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-bromophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6c).*** mp 240–241°C, (ref. 33, 240–242°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 1.03 (s, 6H), 1.14 (s, 6H), 2.20 (d, 2H, $J$ = 16.3 Hz), 2.27 (d, 2H, $J$ = 16.3 Hz), 2.50 (s, 4H), 4.74 (s, 1H), 7.21 (d, 2H, $J$ = 8.4 Hz), 7.37 (d, 2H, $J$ = 8.4 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.73, 29.69, 31.98, 32.62, 41.28, 51.12, 115.63, 120.66, 130.60, 131.57, 143.64, 162.82, 196.69.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(2-chlorophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6d).*** mp 225–227°C, (ref. 32, 225–227°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 1.05 (s, 6H), 1.13 (s, 6H), 2.19 (d, 2H, $J$ = 16.2 Hz), 2.26 (d, 2H, $J$ = 16.2 Hz), 2.48 (s, 4H), 5.03 (s, 1H), 7.09 (dt, 1H, $J_1$ = 7.6 Hz, $J_2$ = 1.6 Hz), 7.19 (dt, 1H, $J_1$ = 7.6 Hz, $J_2$ = 1.1 Hz), 7.26 (dd, 1H, $J_1$ = 7.9 Hz, $J_2$ = 1.0 Hz),), 7.46 (d, 1H, $J$ = 7.3 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.79, 29.69, 32.28, 32.43, 41.25, 51.14, 114.13, 126.74, 128.20, 130.56, 133.34, 133.88, 140.32, 163.37, 196.84.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(3-chlorophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6e).*** mp 184–186°C, (ref. 32, 182–184°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 0.99 (s, 6H), 1.09 (s, 6H), 2.17 (d, 2H, $J$ = 16.2 Hz), 2.22 (d, 2H, $J$ = 16.2 Hz), 2.46 (s, 4H), 4.71 (s, 1H), 7.06 (dt, 1H, $J_1$ = 9.1 Hz, $J_2$ = 1.5 Hz), 7.13 (t, 1H, $J$ = 7.9 Hz), 7.21 (d, 1H, $J$ = 1.2 Hz),), 7.23 (t, 1H, $J$ = 1.3 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.79, 29.62, 32.16, 32.63, 41.27, 51.13, 115.51, 127.05, 127.40, 128.75, 129.65, 134.28, 146.54, 162.99, 196.67.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-nitrophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6f).*** mp 222–223°C, (ref. 32, 221–223°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 1.02 (s, 6H), 1.15 (s, 6H), 2.20 (d, 2H, $J$ = 16.3 Hz), 2.29 (d, 2H, $J$ = 16.3 Hz), 2.53 (s, 4H), 4.86 (s, 1H), 7.51 (dd, 2H, $J_1$ = 7.0 Hz, $J_2$ = 1.7 Hz), 8.12 (dd, 2H, $J_1$ = 7.0 Hz, $J_2$ = 1.7 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.70, 29.64, 32.64, 32.79, 41.27, 51.03, 114.96, 123.83, 129.78, 146.92, 151.94, 163.36, 196.63.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(2-nitrophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6g).*** mp 252–254°C, (ref. 32, 248–249°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 0.98 (s, 6H), 1.07 (s, 6H), 2.13 (d, 2H, $J$ = 16.2 Hz), 2.21 (d, 2H, $J$ = 16.2 Hz), 2.45 (s, 4H), 5.51 (s, 1H), 7.21 (dt, 1H, $J_1$ = 7.7 Hz, $J_2$ = 1.4 Hz), 7.34 (d, 1H, $J$ = 7.5 Hz), 7.41 (dt, 1H, $J_1$ = 7.5 Hz, $J_2$ = 1.2 Hz),), 7.73 (d, 1H, $J$ = 8.1 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 28.00, 29.16, 29.36, 32.48, 41.26, 51.04, 114.60, 125.03, 127.59, 131.46, 132.40, 138.46, 150.27, 163.44, 196.73.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-2H-xanthene-1,8-(5H,9H)-dione (6h).*** mp 170–172°C, (ref. 32, 170–172°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 0.98 (s, 6H), 1.10 (s, 6H), 2.15 (d, 2H, $J$ = 16.3 Hz), 2.24 (d, 2H, $J$ = 16.3 Hz), 2.49 (s, 4H), 4.82 (s, 1H), 7.38 (t, 1H, $J$ = 7.9 Hz), 7.79 (d, 1H, $J$ = 7.7 Hz), 7.96 (dd, 1H, $J_1$ = 8.0 Hz, $J_2$ = 1.9 Hz),), 8.02 (t, 1H, $J$ = 1.9 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.72, 29.61, 32.52, 32.66, 41.23, 51.06, 114.96, 122.06, 123.02, 129.21, 136.07, 146.74, 148.73, 163.46, 196.76.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-methoxyphenyl)-2H-xanthene-1,8-(5H,9H)-dione (6i).*** mp 242–244°C, (ref. 32, 240–242°C); $^1H$ NMR ($CDCl_3$, 500 MHz), δ: 0.98 (s, 6H), 1.08 (s, 6H), 2.15 (d, 2H, $J$ = 16.3 Hz), 2.21 (d, 2H, $J$ = 16.3 Hz), 2.44 (s, 4H), 3.71 (s, 3H), 4.68 (s, 1H), 6.74 (dd, 2H, $J_1$ = 6.8 Hz, $J_2$ = 1.9 Hz), 7.19 (dd, 2H, $J_1$ = 6.8 Hz, $J_2$ = 1.9 Hz). $^{13}C$ NMR ($CDCl_3$, 125 MHz), δ: 27.76, 29.69, 31.38, 32.61, 41.29, 51.20, 55.52, 113.89, 116.21, 129.73, 136.98, 158.38, 162.48, 196.86.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-p-tolyl-2H-xanthene-1,8-(5H,9H)-dione (6j).*** mp 215–217°C, (ref. 32, 217–218°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.98 (s, 6H), 1.09 (s, 6H), 2.15 (d, 2H, $J$ = 16.3 Hz), 2.20–2.23 (m, 5H), 2.45 (s, 4H), 4.70 (s, 1H), 7.00 (d, 2H, $J$ = 8.0 Hz), 7.17 (d, 2H, $J$ = 8.0 Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 21.47, 27.80, 29.69, 31.86, 32.62, 41.30, 51.20, 116.19, 128.66, 129.20, 136.17, 141.63, 162.51, 196.80.

***3,4,6,7-Tetrahydro-9-(4-(2,3,4,5,6,7,8,9-octahydro-3,3,6,6-tetramethyl-1,8-dioxo-1H-xanthen-9-yl)phenyl)-3,3,6,6-tetramethyl-2H-xanthene-1,8(5H,9H)-dione (6k).*** mp >300°C (dec.), (ref. 34, >300°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 0.87 (s, 12H), 0.99 (s, 12H), 2.07 (d, 4H, $J$ = 16.2 Hz), 2.11 (d, 4H, $J$ = 16.2 Hz), 2.33 (d, 4H, $J$ = 17.6 Hz), 2.39 (d, 4H, $J$ = 17.6 Hz), 4.59 (s, 2H), 6.99 (s, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 27.80, 29.41, 31.03, 32.57, 41.12, 51.10, 115.91, 128.16, 142.15, 162.93, 196.73.

***3,4,6,7-Tetrahydro-9-(3-(2,3,4,5,6,7,8,9-octahydro-3,3,6,6-tetramethyl-1,8-dioxo-1H-xanthen-9-yl)phenyl)-3,3,6,6-tetramethyl-2H-xanthene-1,8(5H,9H)-dione (6l).*** mp 238–240°C, (ref. 32, 236–238°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 1.03 (s, 12H), 1.11 (s, 12H), 2.16 (d, 4H, $J$ = 16.2 Hz), 2.21 (d, 4H, $J$ = 16.2 Hz), 2.46 (d, 4H, $J$ = 17.4 Hz), 2.56 (d, 4H, $J$ = 17.4 Hz), 4.72 (s, 2H), 7.07–7.09 (m, 3H), 7.15 (s, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 28.02, 29.57, 31.76, 32.56, 41.27, 51.27, 116.01, 126.84, 128.18, 128.66, 144.04, 162.72, 196.66.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(pyridin-3-yl)-2H-xanthene-1,8(5H,9H)-dione (6m).*** mp 184–186°C, (ref. 34, 184–186°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 1.01 (s, 6H), 1.12 (s, 6H), 2.18 (d, 2H, $J$ = 16.3 Hz), 2.26 (d, 2H, $J$ = 16.3 Hz), 2.50 (s, 4H), 4.73 (s, 1H), 7.16–7.18 (m, 1H), 7.72–7.75 (dt, 1H, $J_1$ = 7.8 Hz, $J_2$ = 1.9 Hz), 8.36 (dd, 1H, $J_1$ = 4.7 Hz, $J_2$ = 1.5 Hz), 8.45 (d, 1H, $J$ = 1.9 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 27.79, 29.58, 32.63, 41.20, 51.03, 115.11, 123.44, 136.96, 140.07, 148.04, 149.90, 163.24, 196.73.

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-styryl-2H-xanthene-1,8-(5H,9H)-dione (6n).*** mp 174–176°C, (ref. 32, 176–178°C); $^1$H NMR ($CDCl_3$, 500 MHz), δ: 1.16 (s, 12H), 2.31 (d, 2H, $J$ = 16.3 Hz), 2.35 (d, 2H, $J$ = 16.3 Hz), 2.45 (d, 2H, $J$ = 18.7 Hz), 2.50 (d, 2H, $J$ = 17.8 Hz), 4.44 (d, 1H, $J$ = 6.0 Hz), 6.30 (d, 1H, $J$ = 16.0 Hz), 6.36 (dd, 1H, $J_1$ = 16.0 Hz, $J_2$ = 6.0 Hz), 7.17–7.20 (m, 1H), 7.26 (t, 2H, $J$ = 7.5 Hz), 7.31 (dd, 2H, $J_1$ = 7.1 Hz, $J_2$ = 1.4 Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz), δ: 28.02, 28.32, 29.66, 32.62, 41.38, 51.28, 114.95, 126.77, 127.51, 128.70, 130.84, 131.76, 137.69, 163.44, 196.91.

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## REFERENCES AND NOTES

[1] Choudhary, D.; Paul, S.; Gupta, R.; Clark, J. H. Green Chem 2006, 8, 479.

[2] Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S.-C. Appl Catal B 2005, 61, 206.

[3] Melero, J. A.; van Grieken, R.; Morales, G. Chem Rev 2006, 106, 3790.

[4] (a) Karimi, B.; Khalkhali, M. J Mol Catal A Chem 2005, 232, 113; (b) Karimi, B.; Abedi, S.; Clark, J. H.; Budarin, V. Angew Chem Int Ed Engl 2006, 45, 4776.

[5] (a) Niknam, K.; Saberi, D.; Nouri Sefat, M. Tetrahedron Lett 2009, 50, 4058; (b) Niknam, K.; Saberi, D.; Mohagheghnejad, M. Molecules 2009, 14, 1915; (c) Niknam, K.; Saberi, D.; Baghernejad, M. Chin Chem Lett 2009, 20, 1444; (d) Niknam, K.; Saberi, D. Tetrahedron Lett 2009, 50, 5210; (e) Niknam, K.; Saberi, D. Appl Catal A 2009, 366, 220.

[6] Niknam, K.; Zolfigol, M. A.; Razavian, S. M.; Mohammahpoor-Baltork, I. J Heterocycl Chem 2006, 43, 199.

[7] Niknam, K.; Zolfigol, M. A.; Khorramabadi-Zad, A.; Zare, R.; Shayegh, M. Catal Commun 2006, 7, 494.

[8] Niknam, K.; Karami, B.; Zolfigol, M. A. Catal Commun 2007, 8, 1427.

[9] Niknam, K.; Zolfigol, M. A.; Sadabadi, T. J Iran Chem Soc 2007, 4, 199.

[10] Niknam, K.; Zolfigol, M. A.; Dehghani, A. Heterocycles 2008, 75, 2513.

[11] Antman, E.; Muller, J.; Goldberg, S.; Macalpin, R.; Rubenfire, M.; Tabatznik, B.; Liang, C.; Heupler, F.; Achuff, S.; Reichek, N.; Geltman, E.; Kerin, N. Z.; Neff, R. K.; Raunwald, E. N Engl J Med 1980, 302, 1269.

[12] (a) Guazzi, M.; Olivari, M.; Polese, A.; Fiorentini, C.; Margrini, F.; Moruzzi, P. Clin Pharmacol Ther 1977, 22, 528; (b) Hornung, R. S.; Gould, B. A.; Jones, R. I.; Sonecha, T. N.; Raferty, E. B. Am J Cardiol 1983, 51, 1323.

[13] Delfourne, E.; Roubin, C.; Bastide, J. J Org Chem 2000, 65, 5476.

[14] Antonini, J.; Polucci, P.; Magnano, A.; Martelli, S. J Med Chem 2001, 44, 3329.

[15] Ferlin, M. G.; Marzano, C.; Chiarelotto, G.; Baccichetti, F.; Bordin, F. Eur J Med Chem 2000, 827.

[16] Weber, L. Curr Med Chem 2002, 9, 2085.

[17] (a) Chorvat, R. J.; Rorig, K. J. J Org Chem 1988, 53, 5779; (b) Martin, N.; Quinteiro, M.; Seoane, C.; Soto, L.; Mora, A.; Suarez, M.; Ockoa, E.; Morals, A. J Heterocycl Chem 1995, 32, 235; (c) Suarez, M.; Loupy, A.; Salfran, E.; Moran, L.; Rolando, E. Heterocycles 1999, 51, 21.

[18] (a) Venkatesan, K.; Pujari, S. S.; Srinivasan, K. V. Synth Commun 2009, 39, 228; (b) Chandrasekhar, S.; Rao, Y. S.; Sreelakshmi, L.; Mahipal, B.; Reddy, C. R. Synthesis 2008, 1737; (c) Dabiri, M.; Baghbanzadeh, M.; Arzroomchilar, E. Catal Commun 2008, 9, 939; (d) Das, B.; Thirupathi, P.; Mahender, I.; Reddy, V. S.; Rao, Y. K. J Mol Catal A: Chem 2006, 247, 233; (e) Jin, T. S.; Zhang, J. S.; Guo, T. T.; Wang, A. Q.; Li, T. S. Synthesis 2004, 2001; (f) Wang, X. S.; Shi, D. Q.; Wang, S. H.; Tu, S. J. Chin J Org Chem 2003, 23, 1291; (g) Schekotikhin, Y. M.; Getmanenko, Y. A.; Nickolaeva, T. G.; Kriven'ko, A. P. Khim Geterotsikl Soedin 2001, 10, 1344.

[19] (a) Menchen, S. M.; Benson, S. C.; Lam, J. Y. L.; Zhen, W.; Sun, D.; Rosenblum, B. B.; Khan, S. H.; Taing, M. U.S. Pat. 6,583,168 (2003); Chem Abstr 2003, 139, p54287f; (b) Hunter, R. C.; Beveridge, T. J. Appl Environ Microbiol 2005, 71, 2501; (c) Ahmad, M.; King, T. A.; Ko, D.-K.; Cha, B. H.; Lee, J. J Phys D: Appl Phys 2002, 35, 1473.

[20] Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J. PCT 9,706,178 (1997); Chem Abstr 1997, 126, p212377y.

[21] Hideo, T. Jpn Kokai Tokkyo Koho 56,005,480 (1981); Chem Abstr 1981, 95, 80922b.

[22] Llama, E. F.; Campo, C. D.; Capo, M.; Anadon, M. Eur J Med Chem 1989, 24, 391.

[23] Ion, R. M.; Frackowiak, D.; Planner, A.; Wiktorowicz, K. Acta Biochim Pol 1998, 45, 833.

[24] Poupelin, J. P.; Saint-Rut, G.; Foussard-Blanpin, O.; Narcisse, G.; Uchida-Ernouf, G.; Lacroix, R. Eur J Med Chem 1978, 13, 67.

[25] Fan, X.; Hu, X.; Zhang, X.; Wang, J. Can J Chem 2005, 83, 16.

[26] Jin, T. S.; Zhang, J.-S.; Wang, A.-Q.; Li, T.-S. Synth Commun 2005, 35, 2339.

[27] Darviche, F.; Balalaie, S.; Chadegani, F.; Salehi, P. Synth Commun 2007, 37, 1059.

[28] Jin, T. S.; Zhang, J. S.; Xiao, J. C.; Wang, A. Q.; Li, T. S. Synlett 2004, 866.

[29] Song, G.; Wang, B.; Luo, H.; Yang, L. Catal Commun 2007, 8, 673.

[30] Das, B.; Thirupathi, P.; Mahender, I.; Reddy, K. R.; Ravikanth, B.; Nagarapu, L. Catal Commun 2007, 8, 535.

[31] Seyyedhamzeh, M.; Mirzaei, P.; Bazgir, A. Dyes Pigm 2008, 76, 836.

[32] Karade, H. N.; Sathe, M.; Kaushik, M. P. ARKIVOC 2007, 13, 252.

[33] Kantevari, S.; Bantu, R.; Nagarapu, L. ARKIVOC 2006, 16, 136–148.

[34] Niknam, K.; Damya, M. J Chin Chem Soc 2009, 56, 659.

[35] Sharifi, A.; Abaee, M. S.; Tavakkoli, A.; Mirzaei, M.; Zolfaghari, A. Synth Commun 2008, 38, 2958.

[36] Mahdavi, G. H.; Bigdeli, M. A.; Saeidi Hayeniaz, Y. Chin Chem Lett 2009, 20, 539.

[37] Horning, E. C.; Horning, M. G. J Org Chem 1946, 11, 95.

[38] (a) Niknam, K.; Zolfigol, M. A. J Iran Chem Soc 2006, 3, 59; (b) Niknam, K.; Zolfigol, M. A.; Sadabadi, T.; Nejati, A. J Iran Chem Soc 2006, 3, 318; (c) Niknam, K.; Zolfigol, M. A.; Hossieninejad, Z.; Daneshvar, N. Chin J Catal 2007, 28, 591; (d) Niknam, K.; Fatehi-Raviz, A. J Iran Chem Soc 2007, 4, 438; (e) Niknam, K.; Daneshvar, N. Heterocycles 2007, 71, 373; (f) Niknam, K.; Zolfigol, M. A.; Safikhani, N. Synth Commun 2008, 38, 2919.

# Straightforward Microwave-Assisted Synthesis of 1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles under Solvent-Free Conditions

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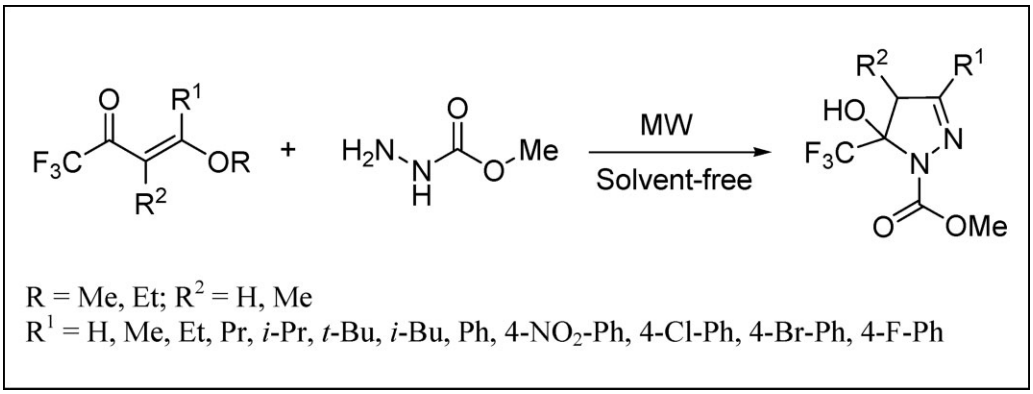


An efficient microwave-assisted synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles from the cyclocondensation reaction between enones [$CF_3C(O)C(R^2) = C(R^1)(OR)$, where $R^2$ = H, Me; $R^1$ = H, Me, Et, Pr, *i*-Pr, *t*-Bu, *i*-Bu, Ph, 4-$NO_2$-Ph, 4-Cl-Ph, 4-Br-Ph, 4-F-Ph and R = Me, Et] and methyl hydrazinocarboxylate under solvent-free conditions is reported. This process is an efficient alternative to the traditional thermal heating and furnishes the heterocyclic compounds in good to excellent yields in a short reaction time. To show the versatility of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles, dehydration reactions of these compounds are also demonstrated.

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## INTRODUCTION

In recent years, the progress in the field of solvent-free reactions has gained significance because of the high efficiency, operational simplicity and environmentally benign processes. The use of microwave energy to heat chemical reactions on a laboratory scale is growing at a rapid rate. In many instances, controlled microwave heating under sealed vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions when compared to conventional synthetic methods [1,2]. The advantages of this useful technology have more recently also been exploited in the context of multistep total synthesis [3] and medicinal chemistry/drug discovery [4] and have additionally penetrated other important fields [5–8]. The use of microwave irradiation in chemistry has thus become such a popular technique in the scientific community that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale [9]. In this context, the use of microwave-assisted organic synthesis (MAOS) has emerged as an alternative and efficient tool, especially in heterocyclic synthesis [10]. 4,5-Dihydropyrazoles are important nitrogen-containing five-membered heterocyclic compounds, with an extensive application in the agrochemical [11] and pharmaceutical fields [12–15]. 4,5-Dihydropyrazoles are quite stable, and have inspired chemists to utilize this fragment in bioactive moieties to synthesize new compounds possessing biological activities. In addition, the presence of fluorine at strategic positions in the molecules can alter the course of the reaction as well as the biological properties of the product [16]. Several 4,5-dihydropyrazoles have played a crucial role in the development of theoretical studies in heterocyclic chemistry and are also extensively used building blocks in organic chemistry [11]. The introduction of halogens and halogenated groups into organic molecules often confers significant and useful changes in their chemical and physical properties.

Therefore, methods for the synthesis of halogenated compounds have received considerable interest in recent years, in particular, fluorinated compounds [17a,b]. The presence of a trifluoromethyl group into cyclic compounds especially at a strategic position of drug molecules has become an important aspect of pharmaceutical research owing to the unique physical and biological properties of fluorine [17c]. The steric requirement of the fluorine atom resembles that of hydrogen (Van der Waals radii: $CF_3$ = 1.35 Å versus $CH_3$ = 1.29 Å). Thus substitution of a methyl by a trifluoromethyl group in a drug candidate usually allows the trifluoromethylated analog to be comparable in size and follow similar drug-protein interactions of parent methyl compound. However, the strong covalent bonding of C—F bond (116 kcal $mol^{-1}$) versus that of the C—H bond (100 kcal $mol^{-1}$) [17d] can often avoid unwanted metabolic transformations. The high electronegativity of fluorine enables a trifluoromethyl group to decrease the electron density and the basicity or enhance the electrophilicity of the neighboring functional groups within a molecule. In many systems, the substitution of the methyl group by a trifluoromethyl group results in added lipophilicity ($\pi_{CF3}$ = 1.07 versus $\pi_{CH3}$ = 0.50) [17e], which may lead to easier absorption and transportation of the molecules within biological systems and thereby improve the overall pharmacokinetic properties of drug candidates.

General methods for the preparation of these compounds involve reactions of hydrazine derivatives with trifluoromethylated precursors such as 1-trifluoromethylated 1,3-diketones [18], β-alkoxyvinyl trifluoromethyl ketones [19], β-trifluoromethyl enaminones [20], and others [21–25]. 1,3-Dipolar cycloaddition reactions of diazoalkanes or nitrilimines with olefins or alkynes have also been carried out, but this procedure has been little used in pyrazole synthesis because 1,3-dipoles are often difficult to prepare and are potentially explosive [26]. In recent years, we have developed a general synthesis of 1,1,1-trihalo-4-methoxy-3-alken-2-ones [27], important halogen-containing building blocks, and shown their usefulness in heterocyclic preparations, such as isoxazoles, pyrazoles, pyrrolidinones, pyrimidines, pyridines, thiazines, and diazepines [27]. Our research group is continuously interested in a more environmentally benign synthesis, which can be demonstrated by our recent articles that focus on solvent-free synthesis [28] and the use of ionic liquids as reaction media [29], associated to efficient techniques such as microwave [30] and ultrasound irradiation [31]. In our sustained interest on the study of heterocyclic synthesis, herein, we wish to report a mild and efficient microwave-assisted method for the preparation of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles and their derivatives, 5-trifluoromethylpyrazoles, under solvent-free conditions.

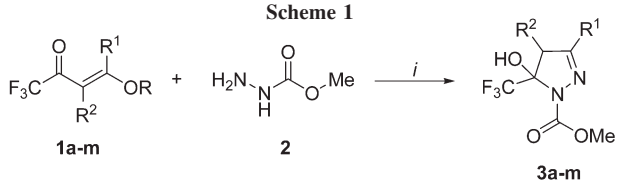
## RESULTS AND DISCUSSION

The enones **1a–m** were obtained from the acylation reaction of enol ether or acetal with trifluoroacetic anhydride in accordance with the methodology developed in our laboratory [27]. Methyl hydrazinocarboxylate **2** was obtained commercially.

The synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles **3a–m** was performed in a microwave equipment specially designed for organic synthesis. The reaction was carried out under solvent-free conditions by the mixture of enones **1a–m** with methyl hydrazinocarboxylate **2**, in a molar ratio of 1:1.25, respectively, under solvent-free conditions in a range of time between 6 and 8 min and at temperatures indicated in Scheme 1. Under these reaction conditions, the products 4,5-dihydro-1*H*-pyrazoles **3a–m** were obtained in good to high yields and in short reaction times (Scheme 1).

The scope of this microwave-assisted method developed for 4,5-dihydropyrazoles was demonstrated by using enones with various substituents ($R^1$). The results obtained show that the presence of a substituent $R^1$ in the 4-position of the enone **1** influenced the reaction conditions. Enones containing 4-alkyl and 4-aryl substituents were more reactive and presented shorter reaction times, while the non-substituted enone **1a** ($R^1$ = H) required a longer reaction time. This behavior can be explained by the inductive and hyperconjugative/mesomeric effects of the alkyl and aryl substituents, which make the C-β of the enone more

**Scheme 1**




*i:* Solvent-free, MW

| Reactant[a] | R | $R^2$ | $R^1$ | Product | *T* (°C) | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| **1a** | Et | H | H | **3a** | 100 | 8 | 78 |
| **1b** | Me | H | Me | **3b** | 100 | 6 | 90 |
| **1c** | Me | H | Et | **3c** | 100 | 6 | 92 |
| **1d** | Me | H | Pr | **3d** | 100 | 6 | 89 |
| **1e** | Me | H | *i*-Pr | **3e** | 100 | 6 | 90 |
| **1f** | Me | H | *t*-Bu | **3f** | 100 | 6 | 80 |
| **1g** | Me | H | *i*-Bu | **3g** | 100 | 6 | 87 |
| **1h** | Me | H | Ph | **3h** | 50 | 6 | 82 |
| **1i** | Me | H | 4-$NO_2$-Ph | **3i** | 50 | 6 | 73 |
| **1j** | Me | H | 4-Cl-Ph | **3j** | 50 | 6 | 90 |
| **1k** | Me | H | 4-Br-Ph | **3k** | 50 | 6 | 85 |
| **1l** | Me | H | 4-F-Ph | **3l** | 50 | 6 | 80 |
| **1m** | Et | Me | H | **3m** | 100 | 6 | 50 |

[a] Molar ratio of reactants **1**:**2** was of 1:1.25.
[b] Yields of isolated products.

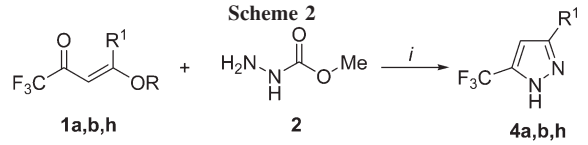
reactive. It is also possible to note that aryl substituted enones (**1h–l**) furnished the products at lower temperatures.

Although the 4,5-dihydropyrazoles **3b,m** have been reported in the literature, their synthesis and spectral characterization have not yet been reported. 4,5-Dihydropyrazoles **3** showed sets of $^{1}H$ and $^{13}C$ NMR data that correspond to the proposed structures. Compounds **3** showed $^{1}H$ NMR chemical shifts of the diastereotopic methylene protons (H-4a and H-4b) as a characteristic AB-system and as a doublet at the range of 3.10–3.74 ppm, respectively, with a geminal coupling constant at the range of $^{2}J$ 18–20 Hz. Previous studies have demonstrated that the doublet in the low field is correspondent to the hydrogen ''cis'' in relation to the hydroxyl group [32]. The same compounds showed $^{13}C$ NMR spectra with typical chemical shifts of 4,5-dihydropyrazole rings at the ranges of 144.3–153.9 (C-3), 38.5–45.6 (C-4), 89.3–92.0 (C-5), 122.5–124.3 ($CF_3$).

The efficiency of this synthetic route was more apparent when the same reaction was performed using conventional thermal heating. Under these conditions of heating, the addition of a solvent was necessary. Ethanol was the solvent chosen due to its polarity and environmental properties that make it a good solvent for cyclocondensation reactions. The reaction of enone **1m** with methyl hydrazinocarboxylate **2** was performed in a molar ratio of 1:1.25, respectively. After 20 h, at room temperature the product **3m** was isolated in moderate yield (70%).

Many studies have shown that the presence of the trifluoromethyl group in 4,5-dihydro-1*H*-pyrazoles is one of the important factors involved in their stability [27]. Thus, it is extremely important to investigate the possibility of dehydrating 4,5-dihydropyrazoles to obtain the aromatic 1-carboxymethyl-pyrazoles. In a strategy to obtain the dehydrated products using microwave irradiation, the reaction of enones **1** with methyl hydrazinocarboxylate **2** was carried out in a molar ratio of 1:1.2 under solvent-free conditions at 200°C. However, the 1-carboxy-5-trifluoromethylpyrazole was not obtained, and the formation of 5-dehydropyrazoles **4a,b,h** was observed, as a result of dehydration with simultaneous loss of the carboxylate group (Scheme 2). Product **4h** was obtained after only 12 min of irradiation at 200°C, demonstrating that the dehydration reaction under MW conditions was sensitive to the substituent effect, and that the phenyl substituent stabilized the products 1-carboxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles.

**Scheme 2**




**1a,b,h** **2** **4a,b,h**

*i:* Solvent-free, MW

| Enone | R | $R^1$ | *T* (°C) | Time (min) | Product[a] | Yield[b] (%) |
|---|---|---|---|---|---|---|
| **1**[a] | Et | H | 200 | 8 | **4a** | 74 |
| **1b** | Me | Me | 200 | 6 | **4b** | 94 |
| **1h** | Me | Ph | 200 | 12 | **4h** | 80 |

[a] Molar ratio of reactants **1**:**2** was 1:1.2.
[b] Yield of isolated products.

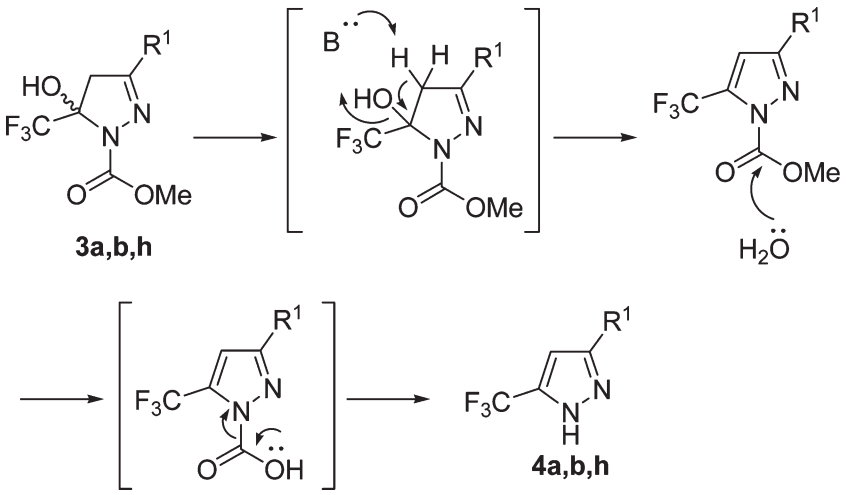
This failure to obtain dehydrated 5-trifluoromethyl-1*H*-pyrazole was a surprise, considering that in previous studies [33], we obtained similar trihalomethylated 4,5-dihydropyrazoles containing a strong electron-withdrawing group attached to the N1-atom, where it was possible to eliminate a water molecule and to obtain the aromatic pyrazole without the loss of the N1-group, by stirring the reaction mixture in ethanol, for 24 hours, at 45°C, followed by reflux in the presence of sulfuric acid for 4 hours. However, we also observed that some 4,5-dihydropyrazoles with an electron-withdrawing group attached to the N1-atom underwent dehydration when heated, with the simultaneous loss of the methyl carboxylate group leading to the formation of 5-trifluoromethylpyrazole [34]. Scheme 3 shows the mechanistic pathway for the formation of products **4a,b,h** [35]. Firstly, the base removes the acid hydrogen leading to water elimination. Then, ester hydrolysis occurs by nucleophilic attack of water on the carboxyl carbon of the ester and subsequent decarboxylation, leading to NH-pyrazole formation.

In summary, we have developed a simple and fast microwave-assisted and solvent-free method to obtain both 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles and their 5-dehydropyrazoles derivatives. This method furnished the products in high to excellent yields through the employment of an environmentally benign approach.

## EXPERIMENTAL

Unless otherwise indicated, all common reactants and solvents were used as obtained from commercial suppliers without further purifications. Reactions were performed using a CEM Discover (300 W) microwave mono Mode for Synthesis controlled by Synergis Version 3.5.9 software. The irradiation power was established at a maximum level of 200 W, the internal vessel pressure at a maximum level of 250 psi. The exact power and pressure was different for each reaction and depended on the reaction temperature, as shown in Figures 1 and 2. The reaction temperatures were constant and recorded by an infrared probe provided by the instrument manufacturer for direct monitoring of the internal temperature, as shown in Figures 1 and 2. Reactions to obtain **3a–m** were performed in simultaneous cooling mode (Power On) and with maximum stirring, while the reactions to obtain **4a,b,h** were performed in Power Off mode.

**Scheme 3**




$^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 400 ($^1$H at 400.13 MHz and $^{13}$C at 100.62 MHz) in 5 ppm sample tubes at 298 K (digital resolution ± 0.01 ppm) in $CDCl_3$/TMS solutions. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked to a HP-5 capillary column (30 m 0.32 mm of internal diameter), and helium was used as the carrier gas. All melting points were determined on a Reichert Thermovar apparatus.

**Conventional method typical procedure for the synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles (3m).** Enones **1m** (1 mmol), methyl hydrazinocarboxylate **2** (1.2 mmol) and ethanol (3 mL) were placed into a round-bottom flask equipped with a stir bar. The mixture was stirred at room temperature during 20 h. After the completion of the reaction, ethanol was removed, dichloromethane (10 mL) was added and the solution was washed with water (3 × 10 mL). The organic layer was dried with $Na_2SO_4$ and the solvent was removed under reduced pressure. The product **3m** was obtained in their pure form without further purification.

**Microwave irradiation typical procedure for the synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles (3a–m).** Enones **1a–m** (1 mmol) and methyl hydrazinocarboxylate **2** (1.25 mmol) were placed into a 10 mL reaction vessel equipped with a stir bar. The mixture was irradiated at 50 or 100°C (Scheme 1), the power irradiated during the reaction was in the range of 45–80 W, where the internal pressure was of 31–34 psi. The reaction was performed in simultaneous cooling mode (Power On) with high magnetic stirring, during the times and temperatures described in Scheme 1. After completion of the reaction, dichloromethane (10 mL) was added and the solution was washed with water (3 × 10 mL). The organic layer was dried with $Na_2SO_4$ and the solvent was removed under reduced pressure. The products **3a-m** were obtained in their pure form without further purification.

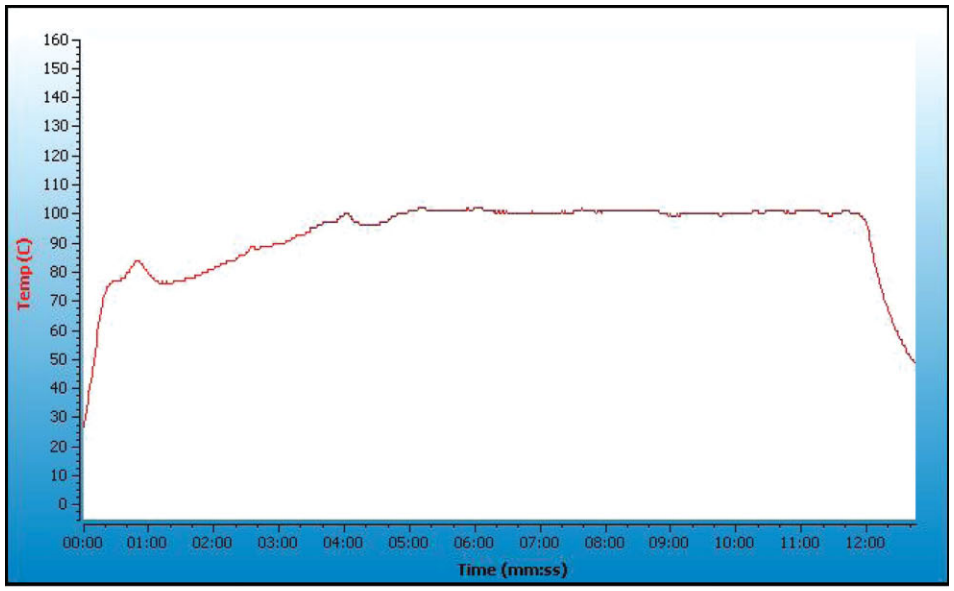
**Typical procedure for the synthesis of 5-trifluoromethyl-1*H*-pyrazoles (4a,b,h).** Enones **1a,b,h** (1 mmol) and methyl hydrazinocarboxylate **2** (1.2 mmol) were placed into a 10 mL reaction vessel equipped with a stir bar. The mixture was irradiated at 200°C, the power irradiated during the reaction was in the range of 25–200 W, where the internal pressure was of 54–86 psi. The reaction was performed without simultaneous cooling (Power Off) at high magnetic stirring, during the times and temperatures described in Scheme 2. After the completion of the reaction, dichloromethane (10 mL) was added and the solution was washed with water (3 × 10 mL). The organic layer was dried with $Na_2SO_4$ and the solvent was removed under reduced pressure. The products **4a,b,h** were obtained in their pure form without further purification.

**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3a).** Oil; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.17 (d, 1H, $^2J$ = 19 Hz, H4b), 3.36 (d, 1H, $^2J$ = 19 Hz, H4a), 3.89 (s, 3H, OMe), 6.95 (s, 1H, H3). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 44.8 (C4), 53.5 (OMe), 89.3 (q, $^2J$ = 33 Hz, C5), 122.85 (q, $^1J$ = 286 Hz, $CF_3$), 144.3 (C3), 153.5 (C=O). GC/MS (m/z, %) 212 ($M^+$, 8), 181 (5), 143 (100), 69 (25).

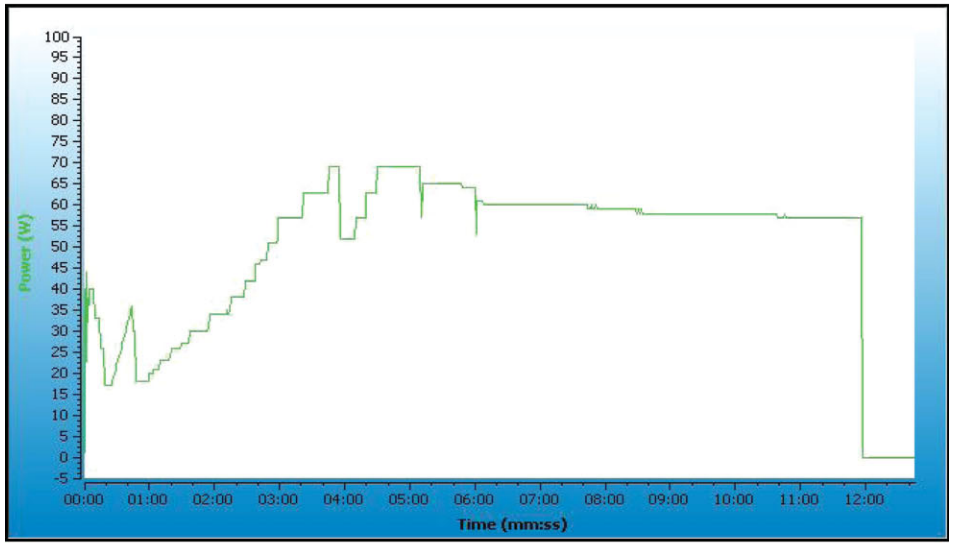
**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazole (3b).** M.p. 54-56°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.07 (t, 3H, $CH_3$, H9), 3.13 (d, 1H, $^2J$ = 19 Hz, H4b), 3.38 (d, 1H, $^2J$ = 19 Hz, H4a), 3.88 (s, 3H, OMe). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 15.1 ($CH_3$), 44.8 (C4), 53.3 (OMe), 90.6 (q, $^2J$ = 34 Hz, C5), 122.9 (q, $^1J$ = 286 Hz, $CF_3$), 153.4 (C3), 153.9 (C=O). GC/MS (m/z, %) 226 ($M^+$, 23), 195 (5), 157 (100), 126 (5) 98 (10), 81 (18).

**1-Carboxymethyl-3-ethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3c).** M.p. 82–84°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.17 (t, 3H, $CH_3$, H10), 2.43 (q, 2H, $CH_2$, H9), 3.07 (d, 1H, $^2J$ = 19 Hz, H4b), 3.23 (d, 1H, $^2J$ = 19, H4a), 3.85 (s, 3H, OMe). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.3 ($CH_3$), 22.9 ($CH_2$), 44.7 (C4), 53.4 (OMe), 90.4 (q, $^2J$ = 34 Hz, C5), 122.9 (q, $^1J$ = 286 Hz, $CF_3$), 153.7 (C3), 158.5 (C=O). GC/MS (m/z, %) 240 ($M^+$, 15), 209 (5), 171 (100), 112 (10), 95 (18).

**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-propyl-4,5-dihydro-1*H*-pyrazole (3d).** M.p. 49–53°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.94 (t, 3H, $CH_3$, H11), 1.60 (q, 2H, $CH_2$, H10), 2.35 (t, 2H, $CH_2$, H9), 3.08 (d, 1H, $^2J$ = 19 Hz, H4b), 3.24 (d, 1H, $^2J$ = 19 Hz, H4a), 3.87 (s, 3H, OMe). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.2 ($CH_3$), 19.5 ($CH_2$),




(1)



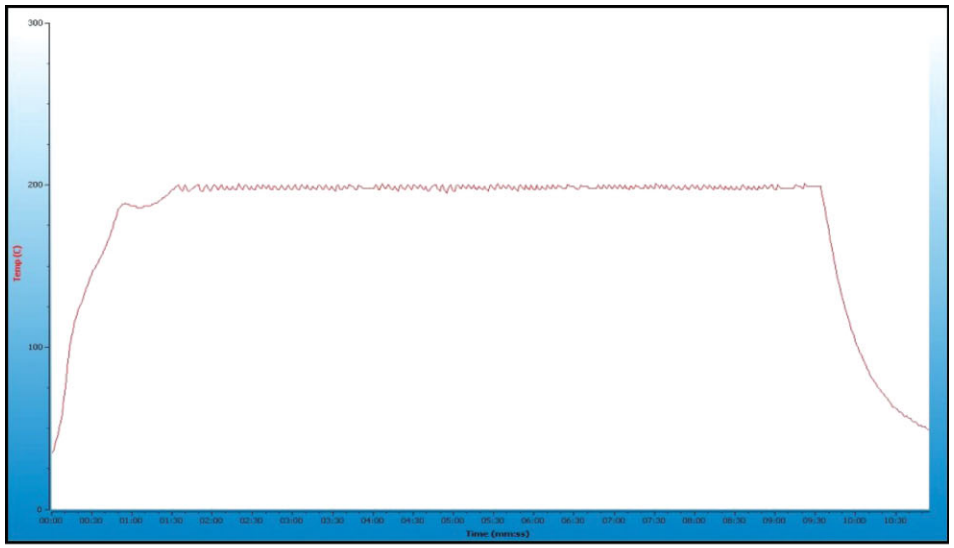

(2)

**Figure 1.** Range of temperature (1) and power (2) furnished by MW for obtaining compound **3a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

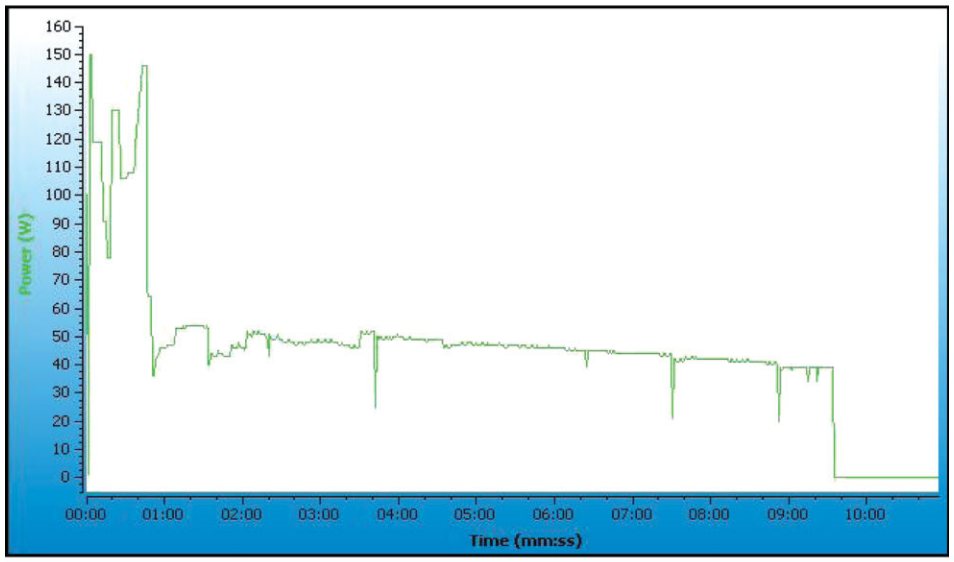
31.4 ($CH_2$), 44.9 (C4), 53.4 (OMe), 90.4 (q, $^2J$ = 34 Hz, C5), 122.9 (q,$^1J$ = 286 Hz, $CF_3$), 153.8 (C3), 157.5 (C=O). GC/MS (m/z, %) 254 ($M^+$, 19), 185 (100), 153 (38), 142 (10), 125 (10).

**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-(1-methylethyl)-4,5-dihydro-1*H*-pyrazole (3e).** M.p. 69–71°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.18 (s, 6H, $2CH_3$, H10), 2.76 (d, 1H, CH, H9), 3.10 (d, 1H, $^2J$ = 18 Hz, H4b), 3.27 (d, 1H, $^2J$ = 18 Hz, H4a), 3.88 (s, 3H, OMe); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.4 ($CH_3$), 21.9 ($CH_3$), 22.3 (CH), 38.5 (C4), 53.5 (OMe), 90.4 (q, $^2J$ = 34 Hz, C5), 153.6 (C3), 157.0 (C=O), 123.2 (q,$^1J$ = 286 Hz, $CF_3$); GC/MS (m/z, %) 254 ($M^+$, 30), 211 (5), 185 (100), 153 (38), 126 (8.5).

**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-(1,1-dimethylethyl)-4,5-dihydro-1*H*-pyrazole (3f).** M.p. 97–99°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (s, 9H, $3CH_3$, H10), 3.13 (d, 1H, $^2J$ = 18 Hz, H4b), 3.29 (d, 1H, $^2J$ = 18 Hz, H4a), 3.88 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.6 (3 $CH_3$), 42.5 (C4), 58.0 (OMe), 90.9 (q, $^2J$ = 34 Hz, C5), 123.1 (q, $^1J$ = 286 Hz, $CF_3$), 153.9 (C3), 164.2 (C=O); GC/MS (m/z, %) 268 ($M^+$, 19), 199 (100), 167 (19), 140 (10).




(1)




(2)

**Figure 2.** Range of temperature (1) and power (2) furnished by MW for obtaining compound **4a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-(2-methylpropyl)-4,5-dihydro-1*H*-pyrazole (3g).** M.p. 41–43°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.99 (2s, 6H, $2CH_3$, H11), 1.94 (q, 1H, CH, H10), 2.30 (t, 2H, $CH_2$, H9), 3.12 (d, 1H, $^2J$ = 19 Hz, H4b), 3.28 (d, 1H, $^2J$ = 19 Hz, H4a), 3.91 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.1 ($CH_3$), 29.0 ($CH_2$), 28.0 ($CH_2$), 21.8 ($CH_2$), 45.06 (C4), 57.38 (OMe), 90.8 (q, $^2J$ = 34 Hz, C5), 122.7 (q,$^1J$ = 286 Hz, $CF_3$), 153.17 (C3), 157.35 (C=O); GC/MS (m/z, %) 268 ($M^+$, 33), 251 (4.5), 199 (100), 167 (40).

**1-Carboxymethyl-3-phenyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3h).** M.p. 153–155°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.55 (d, 1H, $^2J$ = 18 Hz, H4a), 3.69 (d, 1H, $^2J$ = 18 Hz, H4b), 3.94 (s, 3H, $OCH_3$), 7.43–7.45 (m, 3H, H-Ar), 7.69–7.73 (m, 2H, H-Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.3 (C4), 53.8 (OMe), 91.6 (q, $^2J$ = 34 Hz, C5), 123.5 (q, $^1J$ = 286 Hz, $CF_3$), 130.9, 129.7, 128.7, 126.6 (C-Ar), 152.9 (C3), 158.2 (C=O); GC/MS (m/z, %) 288 ($M^+$, 85), 257 (2), 229 (2), 219 (100).

**1-Carboxymethyl-3-(4-nitrophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3i).** M.p. 180–182°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.59 (d, 1H, $^2J$ = 18 Hz, H4b), 3.74 (d, 1H, $^2J$ = 18 Hz, H4a), 3.97 (s, 3H, $OCH_3$), 8.20–8.31 (m, 4H, H-Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.1 (C4), 54.1 (OMe), 92.0 (q, $^2J$ = 34 Hz, C5), 122.85 (q, $^1J$ = 286 Hz, $CF_3$), 150.5, 135.7, 127.5, 124.0 (C-

Ar), 148.9 (C3), 153.7 (C=O); GC/MS (m/z, %) 333 ($M^+$, 28), 316 (1), 274 (1), 264 (100).

**1-Carboxymethyl-3-(4-chlorophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3j).** M.p. 107–109°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.61 (d, 1H, $^2J$ = 19 Hz, H4a), 3.66 (d, 1H, $^2J$ = 19 Hz, H4b), 3.94 (s, 3H, $OCH_3$), 7.40 (d, 2H, H-Ar), 7.69 (d, 2H, H-Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.2 (C4), 55.9 (OMe), 91.4 (q, $^2J$ = 34 Hz, C5), 124.3 (q, $^1J$ = 286 Hz, $CF_3$), 137.1, 129.1, 128.4, 127.6 (C-Ar), 151.8 (C3), 153.9 (C=O); GC/MS (m/z, %) 323 ($M^+ + H^+$, 30), 322 (90), 253 (100), 209 (70), 137 (60).

**1-Carboxymethyl-3-(4-bromophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3k).** M.p. 148–151°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.51 (d, 1H, $^2J$ = 18 Hz, H4a), 3.65 (d, 1H, $^2J$ = 18 Hz, H4b), 3.94 (s, 3H, $OCH_3$), 7.56 (s, 4H, H-Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.1 (C4), 53.8 (OMe), 90.4 (q, $^2J$ = 32 Hz, C5), 122.9 (q, $^1J$ = 287 Hz, $CF_3$), 132.1, 128.8, 128.1, 125.5 (C-Ar), 151.8 (C3), 153.8 (C=O); GC/MS (m/z, %) 367 ($M^+$, 82), 297 (100), 280 (1).

**1-Carboxymethyl-3-(4-fluorophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3l).** M.p. 145–147°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.52 (d, 1H, $^2J$ = 18 Hz, H4a), 3.66 (d, 1H, $^2J$ = 18 Hz, H4b), 3.94 (s, 3H, $OCH_3$), 7.11 (d, 2H, H-Ar), 7.72 (d, 2H, H-Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.3 (C4), 53.8 ($OCH_3$), 91.3 (q, $^2J$ = 34 Hz, C5), 122.5 (q,$^1J$ = 286 Hz, $CF_3$), 165.6, 163.1, 128.8, 115.9 (C-Ar), 151.8 (C3), 153.9 (C=O); GC/MS (m/z, %) 306 ($M^+$, 75), 237 (100), 218 (6).

**1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-4-methyl-4,5-dihydro-1*H*-pyrazole (3m).** M.p. 68–71°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (d, 1H, $CH_3$), 1.43 (q, 1H, CH), 3.92 (s, 3H, $OCH_3$), 6.87 (s, 1H, CH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 9.9 ($CH_3$), 47.7 (C4), 53.7 (OMe), 89.4 (q, $^2J$ = 34 Hz, C5), 123.2 (q, $^1J$ = 286 Hz, $CF_3$), 149.7 (C3), 154.1 (C=O); GC/MS (m/z, %) 227 ($M^+ + H^+$, 13), 209 (27), 157 (100), 113 (24).

**5-Trifluoromethyl-1*H*-pyrazole (4a).** Oil; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.60 (d, 1H, $^3J$ = 2.0 Hz, H4), 7.86 (d, 1H, $^3J$ = 2.0 Hz, H3), 13.57 (s, 1H, NH). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.3 (q, $^2J$ = 36.7 Hz, C5), 130.5 (C3), 122.1 (q, $^1J$ = 267.7 Hz, $CF_3$), 103.2 (C4). GC/MS (m/z, %) 136 ($M^+$, 100), 117 (49), 69 (65).

**5-Trifluoromethyl-3-methyl-1*H*-pyrazole (4b).** M.p. 89–90°C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 3H, Me), 6.30 (s, 1H, H4), 12.89 (s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.3 (Me), 102.8 (C4), 121.5 (q, $^1J$ = 287 Hz, $CF_3$), 141.4 (C3), 142.8 (q, $^2J$ = 34 Hz, C5); GC/MS (m/z, %) 150 ($M^+$, 100), 131 (45), 101 (40), 81 (40), 51 (22).

**5-Trifluoromethyl-3-phenyl-1*H*-pyrazole (4h).** Oil; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.80 (s, 1H, H4), 7.26–7.59 (m, 5H, H-Ar). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.1 (C3), 143.5 (q, $^2J$ = 38.1 Hz, C5), 121.1 (q, $^1J$ = 268.6 Hz, $CF_3$), 100.9 (C4), 125.6, 127.9, 129.1, 129.3 (C-Ar). GC/MS (m/z, %) 212 ($M^+$, 100), 193 (9), 143 (25), 77 (27).

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## REFERENCES AND NOTES

[1] (a) Loupy, A., Ed. Microwaves in Organic Synthesis, 2nd ed., Wiley-VCH: Weinheim, 2006; (b) Kappe, C. O.; Stadler, A. Microwaves in Organic and Medicinal Chemistry, Wiley-VCH: Weinheim, 2005.

[2] (a) Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250; (b) Roberts, B. A.; Strauss, C. R. Acc Chem Res 2005, 38, 653; (c) Kappe, C. O.; Dallinger, D. Nature Rev Drug Discov 2006, 5, 51; (d) Collins, J. M.; Leadbeater, N. E. Org Biomol Chem 2007, 5, 1141; (e) Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563; (f) Appukkuttan, P.; Van der Eycken, E. Eur J Org Chem 2008, 1133.

[3] (a) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. Tetrahedron 2002, 58, 6285; (b) Artman, D. D.; Grubbs, A. W.; Williams, R. M. J Am Chem Soc 2007, 129, 6336; (c) Appukkuttan, P.; Van der Eycken, E. In Microwave Methods in Organic Synthesis; Larhed, M., Olofsson, K., Eds.; Springer: Berlin, 2006; Chapter 1, pp 1–47.

[4] (a) Larhed, M.; Hallberg, A. Drug Disc Today 2001, 6, 406; (b) Wathey, B.; Tierney, J.; Lidström, P.; Westman, J. Drug Disc Today 2002, 7, 373; (c) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. Mini-Rev Med Chem 2003, 3, 449; (d) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. Drug Disc Today: Technol 2005, 2, 155; (e) Kappe, C. O.; Dallinger, D. Nat Rev Drug Discov 2006, 5, 51.

[5] (a) Bogdal, D.; Penczek, P.; Pielichowski, J.; Prociak, A. Adv Polym Sci 2003, 163, 193; (b) Wiesbrock, F.; Hoogenboom, R.; Schubert, U. S. Macromol Rapid Commun 2004, 25, 1739; (c) Hoogenboom, R.; Schubert, U. S. Macromol Rapid Commun 2007, 28, 368; (d) Bogdal, D.; Prociak, A. Microwave-Enhanced Polymer Chemistry and Technology; Blackwell Publishing: Oxford, 2007.

[6] (a) Barlow, S.; Marder, S. R. Adv Funct Mater 2003, 13, 517; (b) Zhu, Y.-J.; Wang, W. W.; Qi, R.-J.; Hu, X.-L. Angew Chem Int Ed 2004, 43, 1410; (c) Perelaer, J.; de Gans, B.-J.; Schubert, U. S. Adv Mater 2006, 18, 2101; (d) Jhung, S. H.; Jin, T.; Hwang, Y. K.; Chang, J.-S. Chem Eur J 2007, 13, 4410.

[7] Tsuji, M.; Hashimoto, M.; Nishizawa, Y.; Kubokawa, M.; Tsuji, T. Chem Eur J 2005, 11, 440.

[8] (a) Collins, J. M.; Leadbeater, N. E. Org Biomol Chem 2007, 5, 1141; (b) Lill, J. R.; Ingle, E. S.; Liu, P. S.; Pham, V.; Sandoval, W. N. Mass Spectrom Rev 2007, 26, 657.

[9] (a) Kremsner, J. M.; Stadler, A.; Kappe, C. O. Top Curr Chem 2006, 266, 233; (b) Glasnov, T. N.; Kappe, C. O.; Macromol Rapid Commun 2007, 28, 395; (c) Ondruschka, B.; Bonrath, W.; Stuerga, D. In Microwaves in Organic Synthesis, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006, Chapter 2, p 62.

[10] Bougrin, K.; Loupy, A.; Soufiaoui, M. J Photochem Photobiol C: Photochem Rev 2005, 6, 139.

[11] (a) Mulder, R.; Wellinga, K.; Van Daalen, J. J. Naturwissenschaften 1975, 62, 531; (b) Katritzky, A. R.; Rees, C. W.; Scriven; E. F. V. Comprehensive Heterocyclic Chemistry II, Elsevier: New York, 1996; Vol. 3.

[12] Taylor, E. C.; Patel, H.; Kumar, H. Tetrahedron 1992, 48, 8089.

[13] (a) Bansal, E.; Srivatsava, V. K.; Kumar, A. Eur J Med Chem 2001, 36, 81; (b) Souza, F. R.; Souza, V. T.; Ratzlaff, V.; Borges, L. P.; Oliveira, M. R.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P.; Mello, C. F. Eur J Pharmcol 2002, 451, 141.

[14] Ahn, J. H.; Kim, H. M.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Yang, S. D.; Cheon, H. G.; Kim, S. S. Bioorg Med Chem Lett 2004, 14, 4461.

[15] Rajendera, P. Y.; Lakshmana, R. A.; Prasoona, L.; Murali, K.; Ravi, K. P. Bioorg Med Chem Lett 2005, 15, 5030.

[16] (a) Strunecka, J.; Patocka, P.; Connett, J. Appl Biomed 2004, 2, 141; (b) Kevin, B.; Park, N. R.; Kitteringham, P. M. Annu Rev Pharmacol Toxicol 2001, 41, 443.

[17] (a) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. Eds. Fluorine in Bioorganic Chemistry; Elsevier: Amsterdam, 1993; (b) Hudlicky, M. Chemistry of Organic Fluorine Compounds; Ellis Horwood: Chichester, 1992; (c) Lin, P.; Jiang, J. Tetrahedron 2000, 56, 3635; (d) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. J Org Chem 1998, 63, 2161; (e) Arnone, A.; Bernardi, R.; Blasco, F.; Cardillo, R.; Resnati, G.; Gerus, I. I.; Kukhar, V. P. Tetrahedron 1998, 54, 2809.

[18] (a) Song, L.-P.; Zhu, S.-Z. J Fluorine Chem 2001, 111, 201; (b) Singh, S. P.; Kumar, D.; Jones, B. G.; Threadgill, M. D. J Fluorine Chem 1999, 94, 199.

[19] (a) Braibante, M. E. F.; Colla, G. C.; Martins, M. A. P. J Heterocycl Chem 1993, 30, 1159; (b) Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. J Fluorine Chem 1998, 92, 23; (c) Yu, H.-B.,Huang, W.-Y. J Fluorine Chem 1997, 84, 65.

[20] Jeong, I. H.; Jeon, S. L.; Min, Y. K.; Kim, B. T. Tetrahedron Lett 2002, 43, 7171.

[21] Hamper, B. C. J Fluorine Chem 1990, 48, 123.

[22] Tang, X.-Q.; Hu, C.-M. J Fluorine Chem 1995, 73, 129.

[23] Linderman, R. J.; Kirollos, K. S. Tetrahedron Lett 1989, 30, 2049.

[24] Tang, X.-Q.; Hu, C.-M. Chem Commun 1994, 631.

[25] Guan, H.-P.; Tang, X.-Q.; Luo, B.-H.; Hu, C.-M. Synthesis 1997, 1489.

[26] (a) Padwa, A. 1,3-Dipolar Cycloaddition Chemistry, Wiley: New York, 1984; Vol.1; (b) Aggarwal, V. K.; Vicente, J.; Bonnert, R. V. J Org Chem 2003, 68, 5381; (c) Foti, F.; Grassi, G.; Risitano, F. Tetrahedron Lett 1999, 40, 2605.

[27] (a) Martins, M. A. P.; Guarda, E. A.; Frizzo, C. P.; Moreira, D. N.; Marzari, M. R. B.; Zanatta, N.; Bonacorso, H. G. Catal Lett DOI 10.1007/s10562-009–9873-6; (b) Martins, M. A. P.; Guarda, E. A.; Frizzo, C. P.; Scapin, E.; Beck, P.; da Costa, A. C.; Zanatta, N.; Bonacorso, H. G. J Mol Catal A: Chem 2007, 266, 100; (c) Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. Curr Org Synth 2004, 1, 391; (d) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. Tetrahedron 2007, 63, 7753.

[28] (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. Chem Rev 2009, 109, 4140; (b) Martins, M. A. P.; Peres, R. L.; Fiss, G. F.; Dimer, F. A.; Mayer, R.; Frizzo, C. P.; Marzari, M. R. B.; Zanatta, N.; Bonacorso, H. G. J Braz Chem Soc 2007, 18, 1486.

[29] (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. Chem Rev 2008, 108, 2015; (b) Moreira, D. N.; Frizzo, C. P.; Longhi, K.; Zanatta, N.; Bonacorso, H. G.; Martins, M. A. P. Monatsh Chem 2008, 139, 1049; (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Rosa, F. A.; Marzari, M. R. B.; Zanatta, N.; Bonacorso, H. G. Catal Commun 2008, 9, 1375; (d) Martins, M. A. P.; Guarda, E. A.; Frizzo, C. P.; Marzari, M. R. B.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. Monatsh Chem 2008, 139, 1321.

[30] (a) Martins, M. A. P.; Pereira, C. M. P.; Moura, S.; Frizzo, C. P.; Beck, P.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C. J Heterocycl Chem 2007, 44, 1195; (b) Martins, M. A. P.; Beck, P.; Machado, P.; Brondani, S.; Moura, S.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C. J Braz Chem Soc 2006, 17, 408.

[31] (a) Sant'Anna, G. S.; Machado, P.; Sauzem, P. D.; Rosa, F. A.; Rubin, M. A.; Ferreira, J.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. Bioorg Med Chem Lett 2009, 19, 546; (b) Martins, M. A. P.; Pereira, C. M. P.; Cunico, W.; Moura, S.; Rosa, F. A.; Peres, R. L.; Machado, P.; Zanatta, N.; Bonacorso, H. G. Ultrasonics Sonochem 2006, 13, 364.

[32] Martins, M. A. P.; Zoch, A. N.; Zanatta, N.; Flores, A. F. C. Spectrosc Lett 1998, 31, 621.

[33] (a) Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; Drekener, R. L.; da Silva, L. B.; Zanatta, N.; Martins, M. A. P. Heteroat Chem 2006, 17, 132; (b) Moura, S.; Flores, A. F. C.; Paula, F. R.; Pinto, E.; Machado, P.; Martins, M. A. P. Lett Org Chem 2008, 5, 91.

[34] Martins, M. A. P.; Moreira, D. N.; Frizzo, C. P.; Longhi, K.; Zanatta, N.; Bonacorso, H. G. J Braz Chem Soc 2008, 19, 1361.

[35] Curran, D. P.; Zhang, Q. Adv Synth Catal 2003, 345, 329.

# Furan Ring Recyclization in 2-Furfurylthieno[2,3-*b*]pyridines: An Intramolecular N-alkylation of Pyrrole Ring under Acid Conditions



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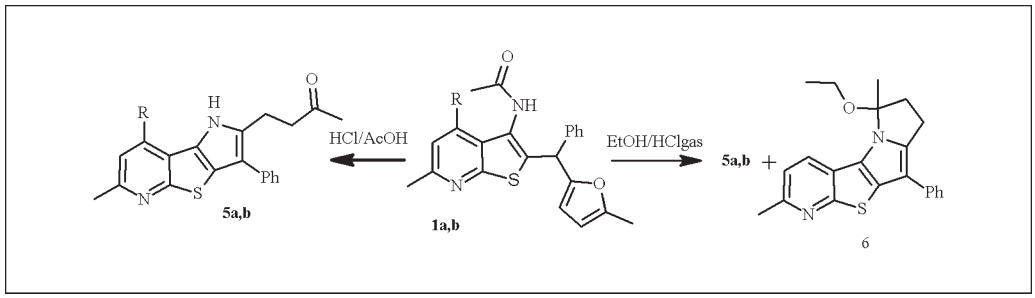


The preparation of new 3-amino-2-furfurylthieno[2,3-*b*]pyridines (**1a,b**, 69–80%) is described. Subsequent acidic rearrangement of **1a,b** afforded two new annulated heterocyclic products, **5a,b**, pyrrolothieno[2,3-*b*]pyridines (45–74%), and **6**, pyridothieno[2,3-*b*]pyrrolizine (22%), depending on reaction conditions.

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## INTRODUCTION

Thieno[2,3-*b*]pyridine derivatives are well known to possess varied biological and pharmacological activities, and hence, their synthesis has been of interest to chemists [1–7]. We have successively used different thieno[2,3-*b*]pyridine derivatives as intermediates for synthesis of some interesting conjugated and annulated heterocyclic systems [8–11].

Thus, continuing our investigation along this line, we herein wish to report the synthesis and acid catalyzed transformations of *N*-{2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-*b*]pyridin-3-yl}acetamides.

## RESULTS AND DISCUSSION

The preparation and transformations of 3-amino-2-furfurylthieno[2,3-*b*]pyridines (e.g. 1, Scheme 1) under acid conditions have attracted our attention because these substances could be considered as heteroanalogues of *ortho*-aminobenzylfurans, which were converted into indole derivatives *via* the furan ring recyclization under acid conditions [12–14] (Scheme 1).

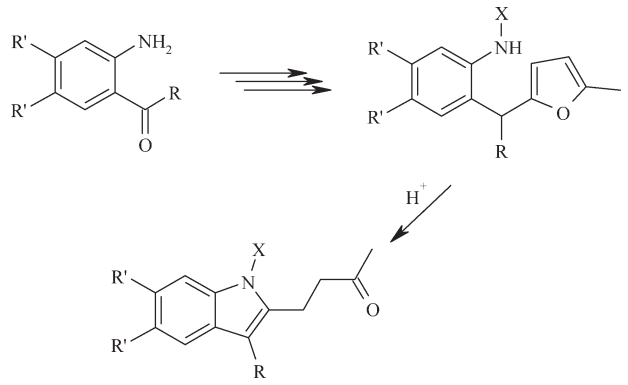
The 3-amino-2-furfurylthieno[2,3-*b*]pyridines **1** were prepared easily from 3-amino-2-benzoylthieno[2,3-*b*]pyridines **2** according to Scheme 2. This approach included an acetylation of aminoketones **2** with acetyl chloride followed by reduction of carbonyl group and alkylation of 2-methylfuran with the alcohols obtained. A mixture of 70% $HClO_4$, acetic anhydride, and acetic acid ($HClO_4$:$Ac_2O$:AcOH = 5.6:3.3:5.2 mmoles) was used as a catalyst for the last stage. The application of the catalyst allowed to decrease undesired side-transformations of alcohols **4a,b** and 2-methylfuran during the reaction [15].

A new heterocyclic system—pyridothienopyrrole **5**—was made from **1** by successive treatment with concentrated HCl in acetic acid under heating (Scheme 3). A cleavage of the protective acetyl group was observed during the reaction.

An attempt to recyclize **1** on heating in ethanolic HCl solution gave the unusual results: if **1b** (R = Me) was smoothly converted into the corresponding pyridothienopyrrole **5b** (64%), **1a** (R = H) gave two substances. We found that in addition to the expected **5a** (45%) another product—a compound **6** (22%)—was isolated from the reaction mixture (Scheme 3).

The structure of **6** is assigned by X-ray analysis [Fig.(1)] [16]. The crystal was grown from $CH_2Cl_2$-petroleum ether mixture. Pyrrolidine moiety of the molecule is practically planar: the angle between planes C(7)-N(2)-C(10)-C(6) and C(7)-C(8)-C(9) is 176.1°. H(8b)-C(8)-C(7)-C(19), H(8a)-C(8)-C(7)-H(9a), H(9b)-C(9)-C(8)-H(8b), and H(9a)-C(9)-C(8)-H(8a) torsion

**Scheme 1**

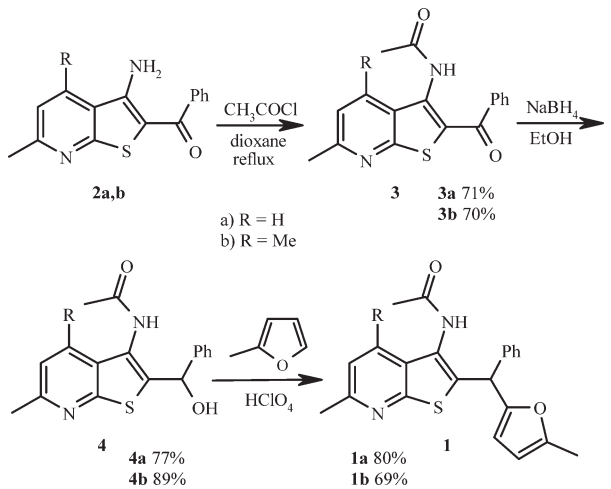


angles equals 4.6, 2.4, 2.1, and 4.7°, correspondingly. Phenyl substituent is located in a plane forming an angle of 3.4° with the heterocyclic core.

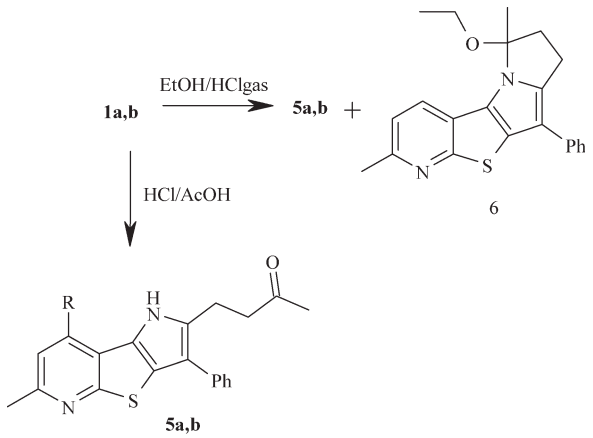
We suppose that the formation of **5a** and **6** proceeds as follows: the furan ring opening leads to a diketone, which in turn reacts with amino group to afford **A** (Scheme 4). The aromatization of **A** leads to pyrrole ring formation as observed earlier for benzylfurans [11–13] to give compound **5a** (Path ***a***). Another route—pyrrolizine **6** formation—is a concurrent process. Probably, compound **6** is provided by ring closure of dihydropyrrolothienopyridine **A** with side chain carbonyl group to produce a cyclic semiaminal **B** (Path ***b***). The interaction between the semiaminal **B** and EtOH molecule allows fixing the pyrrolizine ring as ethoxy derivative which then converts into **6**.

We found that all efforts to furnish the pyrrolizine **6** by heating of the ketone **5a** under identical conditions failed. In our opinion, this result confirms the proposed mechanism: the alkylation occurs before the aromatization of the pyrrole ring. On treating **1a,b** with HCl/

**Scheme 2**




**Scheme 3**




AcOH mixture only **5a,b** (74%, 61%) were formed. In this case the Path ***a*** is predominant because of the equilibrium between cyclic seminal **B** and **A**.

As to the recyclization of **1b**, we suppose that the Me-substituent in position 4 of the pyridine ring prevents the pyrrolidine ring closure, probably, due to steric factors. So in this case, the Path ***a*** is the only possible way for the reaction.

In conclusion, acid-catalyzed transformations of 2-furfurylthieno[2,3-*b*]pyridines have been studied, and the unusual intramolecular N-alkylation of pyrrole ring under acid condition has been disclosed. Possible mechanism of the reaction has been proposed.

## EXPERIMENTAL

Melting points are uncorrected. $^1$H-NMR spectra were measured in DMSO-$d_6$ on Bruker AM 300 spectrometer using TMS as an internal standard. Coupling constant ($J$) values are given in Hz. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV impact ionization. IR spectra were recorded

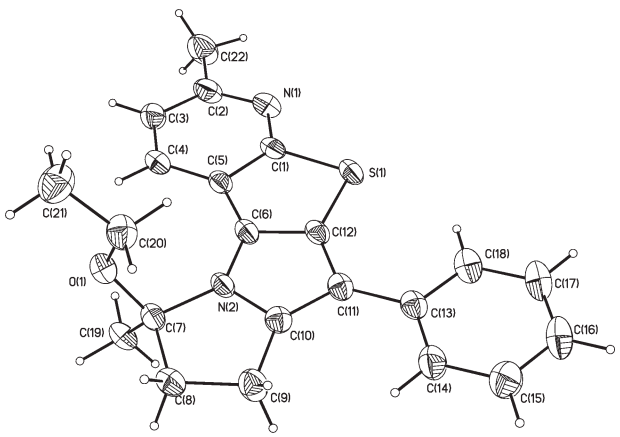
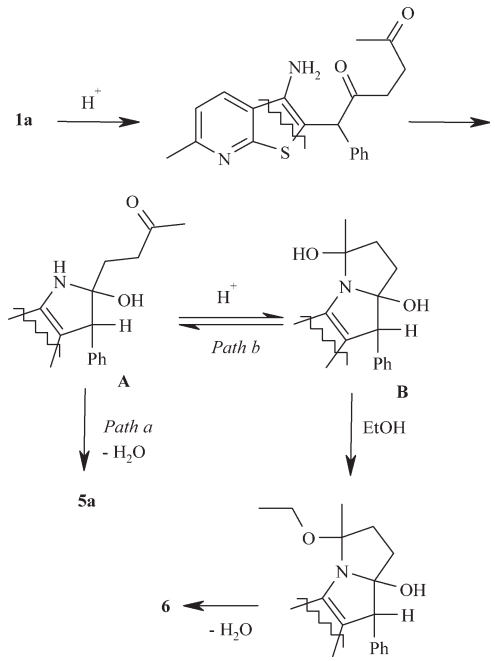



**Figure 1.** ORTEP of the molecular structure of compound **6.**

**Scheme 4**




on an InfraLUM FT-02 spectrometer, and absorptions are given in wavenumbers ($cm^{-1}$). Column chromatography was carried out using KSK silica gel (5–40 μm) manufactured by Sorbpolymer Ltd.

**General procedure for acetylation of amines 2a,b.** A mixture of amine (**2a,b**) (10 mmoles) and AcCl (20 mmoles) in 1,4-dioxane (60 mL) was refluxed until the complete conversion of the compounds **2** (TLC). To the cooled stirred mixture, water (10–15 mL) was added drop by drop, and the resulted mixture was left at RT for crystallization of a product. The precipitate thus obtained was separated with suction, washed with aq solution of sodium hydrocarbonate, water, and air-dried. Recrystallization of the solid from DMF yielded compounds **3a,b** as colorless crystals.

***N-(2-Benzoyl-4,6-dimethylthieno[2,3-b]pyridin-3-yl)acetamide (3a).*** This compound was obtained as colorless crystals in 71% yield, mp 161–162°C; IR: NH 3245, CO 1662, CO 1645 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 1.50 (s, 3H, $COCH_3$), 2.57 (s, 3H, 4-$CH_3$), 2.62 (s, 3H, 6-$CH_3$), 7.19 (s, 1H, H-5), 7.52 (t, 2H, $H_{Ph}$, $J$ = 7.3 Hz), 7.62–7.74 (m, 3H, phenyl protons), 9.76 ppm (s, 1H, NH), ms: *m/z* 324 (29), 281 (100), 121 (11), 105 (13), 59 (25), 43 (49). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.80; H, 5.09; N, 8.70.

***N-(2-Benzoyl-6-methylthieno[2,3-b]pyridin-3-yl)acetamide (3b).*** This compound was obtained as colorless crystals in 70% yield, mp 187–188°C; IR: NH 3213, 3192, CO 1705, CO 1635 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 1.65 (s, 3H, $COCH_3$), 2.65 (s, 3H, 6-$CH_3$), 7.42–7.55 (m, 3H, phenyl protons), 7.60–7.67 (m, 2H, phenyl protons), 7.72 (d, 1H, $J$ = 7.3 Hz, H-5), 8.33 (d, 1H, $J$ = 8.1 Hz, H-4), 10.51 ppm (s, 1H, NH); ms: *m/z* 310 (21), 269 (12), 268 (82), 267 (94), 105 (17), 101 (13), 77 (100), 69 (12), 59 (35), 57 (17), 55 (14), 51 (18), 45 (22). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.91; H, 4.68; N, 8.91.

**General procedure for the reduction of acylaminoketones 3a,b.** To a vigorously stirred suspension of acylaminoketone (**3a,b**) (5 mmoles) in ethanol (40 mL), $NaBH_4$ (0.23 g, 6 mmoles) was added portion wise, and the mixture was kept at 50–60°C for 2 h. After that the mixture was diluted with water (200 mL) and a precipitate formed was separated by filtration. The solid was recrystallized from ethanol yielding alcohols **4a,b**.

***N-{2-[Hydroxy(phenyl)methyl]-4,6-dimethylthieno[2,3-b]pyridin-3-yl}acetamide (4a).*** This compound was obtained as white powder in 77% yield, mp 178–179 °C; IR: OH 3280, NH 3225, 3120, CO 1652 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 2.03 (s, 3H, $COCH_3$), 3.35 (s, 6H, 4-,6-$CH_3$), 5.98 (d, 1H, *CH*—OH, $J$ = 3.7 Hz), 6.36 (d, 1H, CH—*OH*, $J$ = 3.7 Hz), 7.00 (s, 1H, H-5), 7.20–7.41 (m, 5H, phenyl protons), 9.51 ppm (s, 1H, NH), ms: *m/z* 326 (0.7), 308 (20), 293 (40), 267 (100), 265 (98), 251 (12), 105 (21), 101 (10), 80 (38), 76 (17), 59 (24), 43 (59). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.32; H, 5.60; N, 8.69.

***N-{2-[Hydroxy(phenyl)methyl]-6-methylthieno[2,3-b]pyridin-3-yl}acetamide (4b).*** This compound was obtained as white powder in 89% yield, mp 197–198°C; IR: OH 3259, NH 3230, 3158, CO 1656 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 2.06 (s, 3H, $COCH_3$), 2.50 (c, 3H, 6-$CH_3$), 6.12 (d, 1H, *CH*—OH, $J$ = 4.4 Hz), 6.37 (d, 1H, CH—*OH*, $J$ = 4.4 Hz), 7.19–7.43 (m, 6H, phenyl protons, H-5), 7.75 (d, 1H, H-4, $J$ = 8.8 Hz), 9.67 ppm (s, 1H, NH); ms: *m/z* 253 (32), 252 (20), 251 (100), 134 (26), 105 (30), 91 (15), 90 (19), 77 (41), 65 (12), 63 (11), 59 (15), 43 (28). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.46; H, 5.24; N, 8.89.

***Preparation of N-{2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-b]pyridin-3-yl}acetamide (1a,b).*** To a solution of **4a,b** (8.3 mmoles) in 1,4-dioxane (20 mL), 2-methylfuran (1.12 mL, 12.5 mmoles) and a catalyst (0.4 mL), which was a mixture of 70% $HClO_4$ (2 mL), $Ac_2O$ (5.3 mL) and AcOH (3 mL), was added [15]. The mixture was refluxed for 5 h until no initial compound remained (TLC control), then it was poured into of cold water (100 mL), neutralized with sodium hydrocarbonate to pH ∼ 6–7. The crude product was filtered with suction and recrystallized from ethanol with charcoal.

***N-{6-Methyl-2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-b]pyridin-3-yl}acetamide (1a).*** This compound was obtained as white powder in 80% yield, mp 186–187°C; IR: NH 3247, CO 1659 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 2.05 (s, 3H, $COCH_3$), 2.22 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 5.90 (s, 1H, CH), 6.00 (d, 1H, $H_{Fur}$, $J$ = 3.2 Hz), 6.08 (d, 1H, $H_{Fur}$, $J$ = 3.2 Hz), 7.26 (s, 5H, phenyl protons), 7.77 (s, 2H, H-5, H-4), 9.68 ppm (s, 1H, NH). Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44. Found: C, 70.21; H, 5.32; N, 7.41.

***N-{4,6-Dimethyl-2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-b]pyridin-3-yl}acetamide (1b).*** This compound was obtained as colorless crystals in 69% yield, mp 187–188°C; IR: NH 3272, CO 1654 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 2.04 (s, 6H, 2× $CH_3$), 2.23 (s, 6H, 2× $CH_3$), 5.77 (s, 1H, CH), 6.02 (d, 1H, $H_{Fur}$, $J$ = 3.2 Hz), 6.04 (d, 1H, $H_{Fur}$, $J$ = 3.2 Hz), 7.03 (s, 1H, H-5), 7.21–7.38 (m, 5H, phenyl protons), 9.57 ppm (s, 1H, NH); ms: *m/z* 390 (82), 374 (12), 332 (88), 305 (49), 303 (18), 291 (28), 289 (18), 271 (11), 265 (19), 229 (12), 184 (17), 178 (20), 171 (37), 165 (11), 155 (12), 141 (32), 127 (15), 105 (25), 101 (16), 76 (14), 59 (21), 44 (29), 43 (54). Anal. Calcd.

for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17. Found: C, 70.65; H, 5.78; N, 7.24.

**General procedure for the reaction of thieno[2,3-*b*]pyridines 1a,b with HCl/AcOH mixture.** A solution of **1a,b** (2 mmoles) in a mixture of glacial acetic acid (20 mL) and hydrochloric acid (5 mL) was refluxed until no initial compounds remained (TLC) and then was poured into cold water (100 mL) and neutralized with sodium hydrocarbonate to pH ~ 6–7. A precipitate was collected, washed with water, and air-dried. A hot solution of the solid in dichloromethane-petroleum ether mixture was filtered through a pad of silica gel to give desired compounds **5a,b**.

***4-(6-Methyl-3-phenyl-1H-pyrrolo[2′,3′:4,5]thieno[2,3-b]pyridin-2-yl)butan-2-one (5a).*** This compound was obtained as white powder in 74% yield; mp 98–99°C; IR: NH 3360, CO 1709 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 2.12 (s, 3H, $COCH_3$), 2.57 (s, 3H, $CH_3$), 2.92 (t, 2H, $CH_2CH_2COCH_3$, $J$ = 8.1 Hz), 3.10 (t, 2H, $CH_2CH_2COCH_3$, $J$ = 8.1 Hz), 7.28 (d, 1H, H-5, $J$ = 8.1 Hz), 7.43–7.58 (m, 5H, phenyl protons), 8.04 (d, 1H, H-4 $J$ = 7.3 Hz), 11.87 ppm (s, 1H, NH); ms: *m*/*z* 334 (54), 314 (12), 289 (12), 279 (16), 278 (30), 277 (100), 275 (19), 59 (13), 58 (15), 55 (11), 43 (26), 42 (13), 41 (12). Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.86; H, 5.40; N, 8.35.

***4-(4,6-Dimethyl-3-phenyl-1H-pyrrolo[2′,3′:4,5]thieno[2,3-b]pyridin-2-yl)butan-2-one (5b).*** This compound was obtained as white powder in 61% yield; mp 178–179°C; IR: NH 3262, CO 1715 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 2.11 (s, 3H, $COCH_3$), 2.70 (s, 6H, 2× $CH_3$), 2.92 (t, 2H, $CH_2CH_2COCH_3$, $J$ = 7.3 Hz), 3.12 (t, 2H, $CH_2CH_2COCH_3$, $J$ = 7.3 Hz), 7.06 (s, 1H, H-5), 7.25–7.29 (m, 2H, phenyl protons), 7.43–7.57 (m, 3H, phenyl protons), 11.46 ppm (s, 1H, NH); ms: *m*/*z* 348 (44), 291 (100), 151 (15), 128 (29), 115 (30), 101 (26), 89 (11), 76 (26), 66 (11), 59 (16), 58 (40), 51 (24), 45 (14). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: C, 72.38; H, 5.91; N, 7.94.

**General procedure for the interaction of thieno[2,3-*b*]pyridines 1a,b with EtOH/HCl(gas).** A solution of **1a,b** (2 mmoles) in EtOH saturated with dry HCl (gas) (20 mL) was refluxed for 50 min. Then the mixture was poured into cold water (100 mL), and neutralized with sodium hydrocarbonate to pH ~ 6–7. The solid formed was filtered off, washed with water, and air-dried. For **1b**—the precipitate was purified as described above yielding **5b** in 64% yield.

In case of **1a,** the solid was separated by column chromatography (silica gel, petroleum ether : ethyl acetate 1:2) to afford **5a** and **6** as colorless crystals in 45 and 22% yield, respectively.

***9-Ethoxy-3,9-dimethyl-6-phenyl-8,9-dihydro-7H-pyrido[3′,2′:4,5]thieno[2,3-b]pyrrolizine (6).*** This compound was obtained as colorless crystals in 22% yield, mp 166–167°C; IR: 3053, 2984, 2921, 2881, 1603, 1559, 1540, 1453, 1420, 1338, 1212, 1132, 1101, 1065, 976, 813, 761, 723, 688, 510 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 1.05 (t, 3H, $OCH_2CH_3$, $J$ = 6.6 Hz), 1.80 (s, 3H, $CH_3$), 2.60 (c, 3H, $CH_3$-Py), 2.98 (t, 2H, $CH_2$, $J$ = 7.3 Hz), 3.35 (q, 2H, $OCH_2CH_3$, $J$ = 6.6 Hz), 3.59 (t, 2H, $CH_2$, $J$ = 7.3 Hz), 7.23 (t, 1H, 4-$H_{Ph}$, $J$ = 7.3 Hz), 7.37 (d, 1H, $H_{Py}$, $J$ = 8.1 Hz,), 7.48 (t, 2H, $J$ = 7.3 Hz, 3-, 5-$H_{Ph}$), 7.56 (d, 2H, 2-, 6-$H_{Ph}$, $J$ = 7.3 Hz), 8.14 ppm (d, 1H, $H_{Py}$, $J$ = 8.1 Hz); ms: *m*/*z* 362 (37), 317 (12.8), 315 (11), 301 (24), 277 (25), 96 (14), 95 (100), 43 (23). Anal. Calcd for $C_{22}H_{22}N_2OS$: C, 72.89; H, 6.12; N, 7.73. Found: C, 72.91; H, 6.10; N, 7.74.

## REFERENCES AND NOTES

[1] Dave, Ch. G.; Shah, A. B.; Shah H. C. J Heterocycl Chem 1997, 34, 937.

[2] Bakhite, E. A.; Al-Sehemi, A. G.; Yamada, Y. J Heterocycl Chem 2005, 42, 1069.

[3] Abdelkhalik, M. M.; Eltoukhy, A. M.; Agamy, S. M.; Elnagdi, M. H. J Heterocycl Chem 2004, 41, 431.

[4] Al-Huniti, M. H.; El-Ababdelah, M. M.; Zahra, J. A.; Sabri, S. S.; Ingendoh, A. Molecules 2007, 12, 497.

[5] Broggini, G.; Chiesa, K.; De Marchi, I.; Martinelli, M.; Pilati, T.; Zecchi, G. Tetrahedron 2005, 61, 3525.

[6] Yuh Wen Ho. Dyes Pigments 2005, 66, 223.

[7] Bakhite, E. A.; Abdel-Rahman, A. E.; Al-Taifi, E. A. Phosphorus, Sulfur, Silicon Relat Elem 2004, 179, 513.

[8] Stroganova, T. A.; Butin, A. V.; Vasilin, V. K.; Nevolina, T. A.; Krapivin G. D. Synlett 2007, 1106.

[9] Abdel-Moneim Makhmud, M.; Vasilin, V. K.; Krapivin, G. D. Khim Geterotsikl Soedin 2006, 1801 (Chem Heterocycl Comp (Engl Ed.) 2006, 42, 1501).

[10] Vasilin, V. K.; Kaigorodova, E. A.; Firgang, S. I.; Krapivin, G. D. Khim Geterotsikl Soedin 2004, 462 (Chem Heterocycl Comp (Engl Ed.) 2004, 40, 377).

[11] Vasilin, V. K.; Lipunov, M. M.; Konyushkin, L. D.; Krapivin, G. D. Khim Geterotsikl Soedin 2006, 1582 (Chem Heterocycl Comp(Engl. Ed.) 2006, 42, 1368).

[12] Butin, A. V.; Stroganova, T. A.; Lodina, I. V.; Krapivin, G. D. Tetrahedron Lett 2001, 42, 2031.

[13] Butin, A. V.; Smirnov, S. K.; Stroganova, T. A. J Heterocycl Chem 2006, 43, 623.

[14] Butin, A. V.; Smirnov, S. K.; Stroganova, T. A.; Bender, W.; Krapivin, G. D. Tetrahedron 2007, 63, 474.

[15] Kosulina, D.Yu.; Vasilin, V. K.; Stroganova, T. A.; Sbitneva, E. A.; Krapivin, G.D. Pat. (RU) 2346947, 2009.

[16] CCDC 693220 for **6** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; Available at: deposit@ccdc.cam.ac.uk.

# An Efficient One-Pot Three Component Synthesis of 1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones Using Montmorillonite K10 under Solvent Free Conditions

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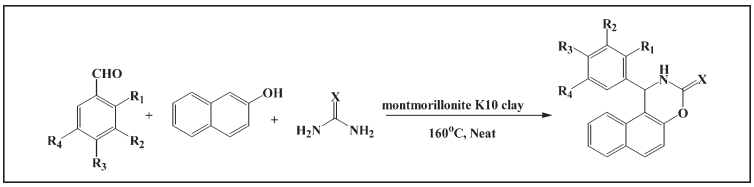


An efficient green protocol for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones employing a three-component one-pot condensation reaction of β-naphthol, aromatic aldehyde, urea or thiourea in the presence of montmorillonite K10 clay under solvent free conditions has been described. The present procedure offers advantages such as shorter reaction time (<90 min), simple workup, excellent yields, recovery and reusability of catalyst.

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## INTRODUCTION

Recently, benzoxazinone derivatisation has attained considerable significance in potential antiviral target compounds [1]. The prime driving force in this area is the fight against HIV by developing more efficacious drugs than Efavirenz (Sustiva), a benzoxazinone derivative which is presently in clinical use for the treatment of AIDS.

The construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Due to their broad spectrum of biological activities naphthalene-condensed 1,3-oxazin-3-ones have been reported to act as antibacterial agents [2]. Heterogeneous organic reactions have proven useful to chemists both in academia and in industry. Clay-catalyzed organic transformations have generated considerable interest because of their inexpensive nature and special catalytic attributes under heterogeneous reaction conditions [3].

In this context, a recent report [4] and related publications [5] on one pot three component synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones by the condensation of aldehydes, urea or thiourea with β-naphthol in the presence of acid *p*-TSA attracted our attention. This method suffers from the drawbacks of green chemistry such as prolonged reaction times, recovery and reusability of catalyst. The demand for environmentally benign procedure with reusable catalyst necessitated us to develop an alternate method for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones. In continuation of our work on the use of heterogeneous solid acid catalysts [6], we describe in this report a general and efficient green protocol for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones, employing a one-pot three-component condensation of β-naphthol, aromatic aldehydes urea or thiourea in the presence of montmorillonite K10 clay under solvent free conditions. This method is superior to the reported methods in all aspects such as short reaction times and excellent yields.

## RESULTS AND DISCUSSION

Initially to determine the most appropriate reaction conditions and to evaluate the catalytic activity of Lewis/protic acid catalysts, a model study was carried out on the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3] oxazine-3-one **4a** (Table 1) by the condensation of benzaldehyde **1a** with β-naphthol **2** and urea **3a** in different sets of reaction conditions. Among all the tested catalysts such as Silica sulfuric acid, *p*-TSA, AcOH, LiCl, $CuCl_2$, $HClO_4$-$SiO_2$, Amberlist-15, and IR-120 under solvent free conditions we found that the best results were obtained with the condensation in the presence of montmorillonite K10 catalyst (Table 1, entry **1**).

The condensation of mixture of benzaldehyde **1a** (1 mmol) with β-naphthol **2** (1 mmol) and urea **3a** (1.5 mmol) in the presence of montmorillonite K10 (0. 3 mmol) was carried out at 160°C for 0.5 h under solvent free conditions (Scheme 1). The reaction proceeded

**Table 1**

Synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine -3-one 4a using different catalysts under solvent free conditions.

| Entry | Catalyst | Yield (%)[b] | Ref |
|---|---|---|---|
| 1 | Montmorillonite K10 clay | 89 | – |
| 2 | Silica sulfuric acid | 65 | – |
| 3 | *p*-TSA | 58 | 4 |
| 4 | AcOH | 45 | 4 |
| 5 | LiCl | 38 | 4 |
| 6 | $CuCl_2$ | 30 | 4 |
| 7 | $HClO_4$-$SiO_2$ | 64 | – |
| 8 | Amberlist-15 | 48 | – |
| 9 | IR120 | 44 | – |

[a] Benzaldehyde (1 mmol), urea (1.5 mmol), β-napthol (1 mmol), catalyst (0.3 mmol).
[b] Isolated yields.

smoothly and gave the corresponding 1,2-dihydro-1-aryl naphtho[1,2-e][1,3]oxazine-3-one **4a** as the sole product in 89% isolated yield. Ethyl acetate was added to the reaction mixture and simply filtering the mixture and evaporating the solvent from the filtrate gave the crude product, which was purified by crystallization in ethyl acetate: hexane (1:3) to obtain **4a** as white solid.

To evaluate the generality of the process, several examples illustrating the present method for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones **4** was studied (Table 2). The reaction of β-naphthol **2** with various aromatic aldehydes bearing electron withdrawing groups (such as nitro, halide), electron releasing groups (such as methoxy, methyl or hydroxyl groups), and urea or thiourea was carried out in the presence of Montmorillonite K 10 as a catalyst.

The heterocyclic aldehydes such as furfural (entry m, Table 2) and 2-Chloroquinoline-3-aldehyde (entry n, Table 2) on reaction with β-naphthol **2** and urea **3** in the presence of montmorillonite K10 clay under solvent free conditions was sluggish and the corresponding products were isolated only in 10–15% yields. The poor reaction of heterocyclic aldehydes (entry m & n Table 2) with β-naphthol **2** can be explained by considering the possibility of binding of basic hetero atom (m & n) on the surface of Montmorillonite K10 clay. The results obtained in the current method are illustrated in Table 2. All products obtained were fully characterized by spectroscopic methods such as IR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy and also by comparison with the reported spectral data [4].

On the basis of all our experimental results, together with the literature reports [4], we have proposed the plausible mechanism for the formation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones **4** in the presence of Montmorillonite K10 clay (Scheme 2). The reaction is believed to proceed through the formation of an *N*-acylimine intermediate **5** formed *in situ* by the reaction of aldehyde **1** with urea or thiourea **3**. The subsequent addition of the β-naphthol to the *N*-acylimine, followed by cyclization affords the corresponding products **4**(a-p) and ammonia.

The simplicity, together with the use of inexpensive, non-toxic, and environmentally benign catalyst under solvent free condition is other remarkable features of the procedure. The catalyst was recovered by filtration, washed several times with methanol, dried at 120°C for 72 h and reused with out significant loss of catalyst activity.

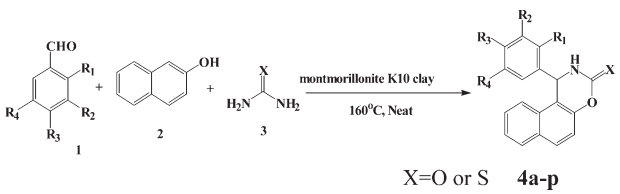
In conclusion, we have reported herein a novel and ecofriendly method for the synthesis of 1,2-dihydro-1-aryl naphtho[1,2-e][1,3]oxazine-3-ones using Montmorillonite K10 clay under solvent free conditions. The advantages of the present protocol are mild heterogeneous reaction conditions, shorter reaction times, and easy work up. The inexpensive, ready availability, recyclablity of the catalyst make the procedure an attractive alternative to the existing methods for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones.

## EXPERIMENTAL

**General procedure.** A mixture of β-naphthol (1 mmol), aldehyde (1 mmol), urea or thiourea (1.5 mmol) and Montmorillonite K10 clay (0.3 mmol) was rapidly stirred and heated at 160°C for the specified time (Table 2). After TLC indicates the disappearance of starting material, reaction was cooled to room temperature, ethyl acetate (25 mL) was added and the insoluble material was filtered to separate the catalyst. The filtrate was concentrated under vacuum and the crude residue was purified by crystallization in ethyl acetate: hexane (1:3) to afford pure product **4** in excellent yields as specified in Table 2. The catalyst filtered was washed with methanol (3 × 10 mL), dried at 120°C for 72 h and reused. The isolated product yields after each cycle is 78%. All products obtained were fully characterized by spectroscopic methods such as IR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy and have been identified by the comparison of the spectral data with those reported.

***1-Phenyl-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (4a).*** m.p. 210–212°C, IR (KBr) $\nu_{max}$ 3281, 2928, 1727, 1627, 1514, 1458, 1435, 1396, 1338, 1289, 1221, 1165, 1111, 981, 925, 828, 745 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ

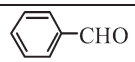
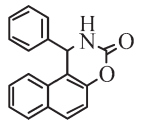
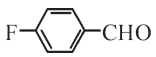
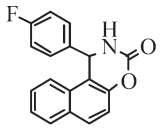
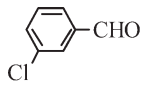
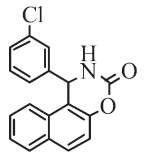
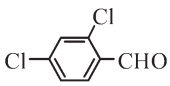
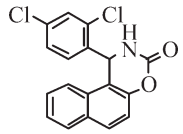
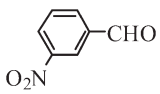
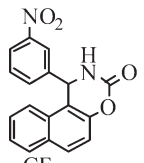
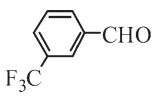
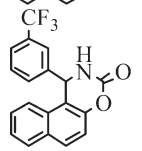
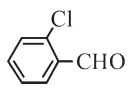
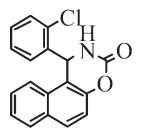
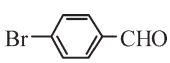
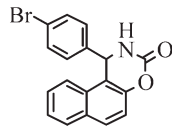
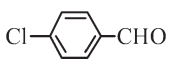
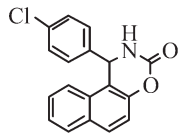
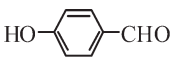
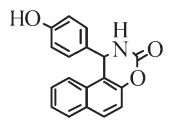
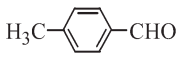
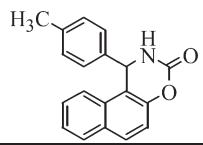
**Scheme 1.** X = O or S **4a-p.**




X=O or S **4a-p**

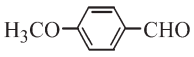
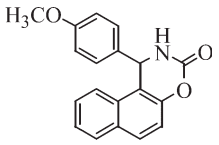
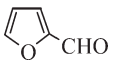
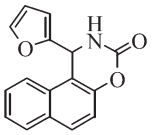
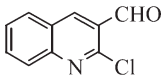
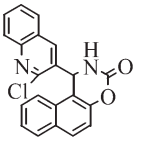
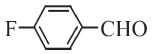
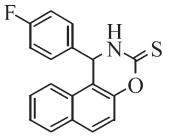
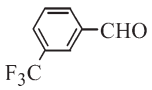
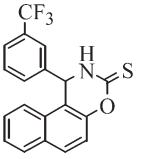
**Table 2**

Reaction of β-naphthol with various aldehydes and urea or thiourea.

| Entry | Aldehyde **1** | Urea/Thiourea **3** | Product **4** | Reaction Time (min) | Yield[a] (%) |
|---|---|---|---|---|---|
| a |  | $NH_2CONH_2$ |  | 30 | 89 |
| b |  | $NH_2CONH_2$ |  | 30 | 84 |
| c |  | $NH_2CONH_2$ |  | 55 | 85 |
| d |  | $NH_2CONH_2$ |  | 50 | 90 |
| e |  | $NH_2CONH_2$ |  | 30 | 79 |
| f |  | $NH_2CONH_2$ |  | 30 | 85 |
| g |  | $NH_2CONH_2$ |  | 45 | 84 |
| h |  | $NH_2CONH_2$ |  | 60 | 75 |
| i |  | $NH_2CONH_2$ |  | 45 | 72 |
| j |  | $NH_2CONH_2$ |  | 90 | 70 |
| k |  | $NH_2CONH_2$ |  | 90 | 72 |

(*Continued*)

**Table 2**
(*Continued*)

| Entry | Aldehyde **1** | Urea/Thiourea **3** | Product **4** | Reaction Time (min) | Yield[a] (%) |
|---|---|---|---|---|---|
| l |  | $NH_2CONH_2$ |  | 90 | 70 |
| m |  | $NH_2CONH_2$ |  | 90 | 15 |
| n |  | $NH_2CONH_2$ |  | 90 | 10 |
| o |  | $NH_2CONH_2$ |  | 45 | 64 |
| p |  | $NH_2CONH_2$ |  | 45 | 65 |

[a] Field of isolated products.

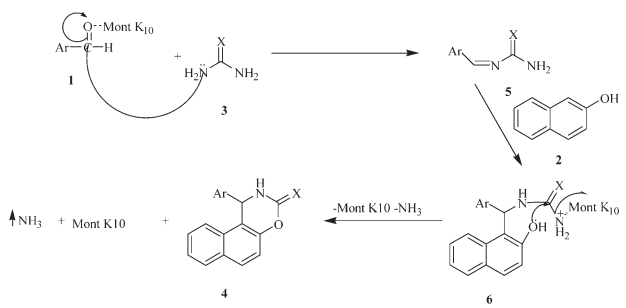
6.04 (d, $J$ = 3.12 Hz, 1H), 7.26–7.40 (m, 7H), 7.56–7.64 (m, 2H), 7.78–7.86 (m, 2H), 8.56 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 56.4, 113.8, 117.6, 123.4, 125.0, 127.4, 127.8, 127.9, 129.2, 129.5, 129.9, 131.0, 131.3, 142.0, 148.1, 150.1. MS (ESI) m/z 276 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.53; H, 4.75; N, 5.09.

***1-(4-Fluorophenyl)-1,2-dihydronaphtho[1,2-e][1,3] oxazin-3-one (4b).*** m.p. 199–200°C. IR (KBr) $\nu_{max}$ 3427, 3215, 3127, 2955, 1750, 1627, 1509, 1396, 1224, 1180, 808, 736 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.02 (d, $J$ = 2.29 Hz, 1H), 6.93–7.01 (m, 2H), 7.22–7.54 (m, 6H), 7.79–7.86 (m, 2H), 8.54 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 52.9, 112.0, 114.3, 114.8, 115.7, 121.5, 123.9, 126.2, 127.5, 127.8, 127.9, 129.1, 129.5, 137.2, 146.6, 148.7, 158.4, 163.3. MS (ESI) m/z 294 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{12}FNO_2$: C, 73.71; H, 4.12; N, 4.78. Found: C, 73.72; H, 4.11; N, 4.77.

***1-(3-Chlorophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (4c).*** m.p.192–195°C. IR (KBr) $\nu_{max}$ 3433, 3348, 2923, 1752, 1678, 1623, 1464, 1384, 1222, 1177 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.07 (d, $J$ = 2.93 Hz, 1H), 7.22–7.56 (m, 7H), 7.78–7.90 (m, 3H), 8.72 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 52.8, 111.4, 115.4, 121.2, 123.7, 124.1, 125.7, 126.1, 126.8, 127.3, 127.6, 129.1, 132.8, 143.1, 146.4, 148.3, 154.5. MS (ESI) m/z 310 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.79; H, 3.91; N, 4.52.

***1-(2,4-Dichlorophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (4d).*** m.p.239–242°C. IR (KBr) $\nu_{max}$ 3244, 3141, 1737, 1627, 1623, 1586, 1468, 1393, 1287, 1225, 1117, 748 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.48 (d, $J$ = 3.12 Hz, 1H), 6.96–7.08 (m, 2H), 7.28–7.52 (m, 5H), 7.81–7.89 (m, 2H) 8.29 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 50.2, 111.0, 115.7, 121.1, 124.1, 126.6, 127.2, 127.7, 127.9, 128.4, 129.3, 129.7, 132.0, 133.3, 137.0, 147.0, 148.4. MS (ESI) m/z 344 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{11}Cl_2NO_2$: C, 62.81; H, 3.22; N, 4.07. Found: C, 62.82; H, 3.22; N, 4.06.

**Scheme 2.** Plausible mechanism for the formation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones 4.



***1-(3-Nitrophenyl)-1,2-dihydronaphtho[1,2-e][1,3] oxazin-3-one (4e).*** m.p. 228–230°C, IR (KBr) $\nu_{max}$ 3380, 3065, 2924, 1727, 1627, 1594, 1527, 1346, 1221, 1176, 810, 744 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.42 (d, $J$ = 2.34 Hz, 1H), 7.31–7.95 (m, 8H), 8.32–8.35 (m, 2H), 8.86 (s, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 52.3, 110.9, 115.6, 120.9, 121.2, 121.7, 123.9, 126.3, 127.4, 127.6, 128.9, 129.3, 129.4, 132.0, 143.0, 146.9, 148.2. MS (ESI) m/z 321 ($[M + H]^+$). Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.49; H, 3.78; N, 8.76.

***1-(3-Trifluoromethylphenyl)-1,2-dihydronaphtho [1,2-e][1,3] oxazin-3-one (4f).*** m.p. 251–253°C, IR (KBr) $\nu_{max}$ 3446, 3248, 2924, 1752, 1705, 1631, 1592, 1517, 1395, 1321, 1223, 1171, 1113, 1064, 920, 813, 738 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.15 (d, $J$ = 2.93 Hz, 1H), 7.28–7.55 (m, 7H), 7.72 (s, 1H), 7.82–7.90 (m, 2H), 8.76 (s, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 53.0, 111.4, 115.7, 120.0, 121.3, 122.9, 123.7, 124.0, 126.4, 127.6, 127.9, 128.6, 129.5, 142.2, 146.8, 148.6. MS (ESI) m/z 344 ($[M + H]^+$). Anal. Calcd for $C_{19}H_{12}F_3NO_2$: C, 66.47; H, 3.52; N, 4.08. Found: C, 66.48; H, 3.52; N, 4.08.

***1-(2-Chlorophenyl)-1,2-dihydronaphtho[1,2-e][1,3] oxazin-3-one (4g).*** m.p. 222–224°C, IR (KBr) $\nu_{max}$ 3393, 3059, 2925, 1741, 1583, 1438, 1372, 1231, 1123, 1042, 976, 784, 746 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.54 (d, $J$ = 1.46 Hz, 1H), 7.12–7.52 (m, 8H), 7.83–7.88 (m, 2H), 8.10 (s, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 50.4, 111.4, 115.6, 121.2, 123.9, 126.4, 126.8, 127.5, 127.9, 128.1, 128.5, 128.6, 129.3, 131.0, 138.2, 146.8, 148.4. MS (ESI) m/z 310($[M + H]^+$). Anal. Calcd for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.79; H, 3.90; N, 4.51.

***1-(4-Fluorophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazine-3-thione (4o).*** Thick syrup; IR (KBr) $\nu_{max}$ 3060, 2923, 1628, 1600, 1508, 1460, 1390, 1267, 1216, 1162, 1016, 843, 811, 750 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 4.37 (s, 1H), 6.84–7.82 (m, 10H), 9.22 (brs, 1H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 29.7, 109.4, 115.0, 115.2, 117.7, 123.1, 123.5, 126.3, 126.4, 126.6, 127.6, 128.5, 129.4, 129.5, 129.7, 151.0, 153.3. MS (ESI) m/z 360 ($[M + H]^+$). Anal. Calcd for $C_{18}H_{12}FNOS$: C, 69.88; H, 3.91; N, 4.53. Found: C, 69.88; H, 3.91; N, 4.54.

***1-(3-Trifluoromethylphenyl)-1,2-dihydronaphtho [1,2-e][1,3] oxazine-3-thione (4p).*** Thick syrup; IR (KBr) $\nu_{max}$ 3240, 3052, 2923, 1627, 1512, 1443, 1327, 1263, 1165, 1121, 1071, 845, 742 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$): δ 4.45 (s, 1H), 7.02–7.86 (m, 10H), 9.10 (brs, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$ + DMSO-$d_6$): δ 30.0, 108.7, 116.8, 117.9, 118.2, 122.4, 122.5, 124.6, 125.7, 127.2, 127.8, 128.2, 128.8, 131.6, 133.1, 134.4, 142.2, 152.5, 154.8. MS (ESI) m/z 360 ($[M + H]^+$). Anal. Calcd for $C_{19}H_{12}F_3NOS$: C, 63.50; H, 3.37; N, 3.90. Found: C, 63.51; H, 3.37; N, 3.91.

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## REFERENCES AND NOTES

[1] (a) Patel, M.; Ko, S. S.; McHugh, R. J., Jr.; Markwalder, J. A.; Srivastava, A. S.Cordova, B. C; Kable, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Seitz, S. P. Bioorg Med Chem Lett 1999, 9, 2805; (b) Patel, M.; McHugh, R. J., Jr.; Cordova, B. C.; Kable, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Koo, S. S. Bioorg Med Chem Lett 1999, 9, 3221; (c) Waxman, L.; Darke, P. L. Antiviral Chem Chemother 2000, 11, 1; (d) Klasek, A.; Koristek, K.; Polis, J.; Kosmrlj, J. Tetrahedron 2000, 56, 1551; (e) Girgis, A. S. Pharmazie 2000, 426; (f) Mindl, J.; hrabik, O.; Sterba, V.; Kavalek, J. Collect Czech Chem Commun 2000, 65, 1262.

[2] Latif, N.; Mishriky, N.; Assad, F. M. Aust J Chem 1982, 35, 1037.

[3] (a) Balogh, M.; Laszlo, P.Organic Chemistry Using Clays; Springer: Berlin, 1993; (b) Chisem, J.; Chisem, I. C.; Rafelt, J. S.; Macquararrie, D. J.; Clark, J. H. Chem Commun 1997, 2203; (c) Meshram, H. M.; Shekar, K. C.; Ganesh, Y. S. S.; Yadav, J. S. Synlett 2000, 1273.

[4] Minoo, D.; Akram, S. D.; Ayoob, B. Synlett 2007, 5, 821.

[5] (a) Lal Dhar, S. Y.; Beerendra, S. Y.; Suman, D. Tetrahedron 2004, 60, 131; (b) Thomas, K. Tetrahedron 2005, 61, 3091. (c) Myriam, O.; Christian, A.; Daniele, C.; Alain, C.; Pascal, D.; Martine, D. Bioorg Med Chem Lett 2006, 16, 4641.

[6] (a) Pardhasaradhi, M.; Srinivas, K.; Nair, C. K. S.; Kumar, P. N. Tetrahedron Lett 1998, 39, 7411. (b) Mereyala, H. B.; Chary, M. V.; Kantevari, S. Synthesis 2007, 187; (c) Srinivas, K.; Rajashaker, B.; Lingaiah, N. ARKIVOC 2006, xvi, 136; (d) Srinivas, K.; Srinivasu, V. N. V.; Dhanraj, O. B.; Lingaiah, N. J Mol Catal A: Chem 2007, 266, 109; (e) Srinivas, K.; Rajashaker, B.; Lingaiah, N. J Mol Catal A: Chem 2007, 269, 53; (f) Kantevari, S.; Chary, M. V.; Srinivasu, V. N. V. Tetrahedron 2007, 63, 13024.

# Synthesis of Tetrahetrocyclic Systems Including Pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine Fused with Pyrazole Derivatives and Isolated with 1,3,4-Oxa-, Thiadiazole, and 1,2,4-Tetrazole Derivatives

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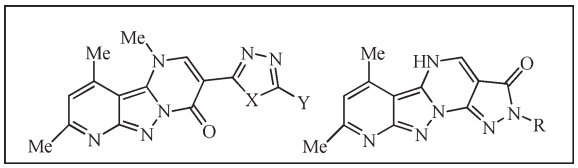


A series of isolated and fused tetracyclic compounds, containing pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine linked with 1,3,4-oxa-, thiadiazole, 1,2,4-tetrazole, and pyrazole derivatives were prepared by the reaction of 1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate and some common reagents to provide the product in satisfactory yields.

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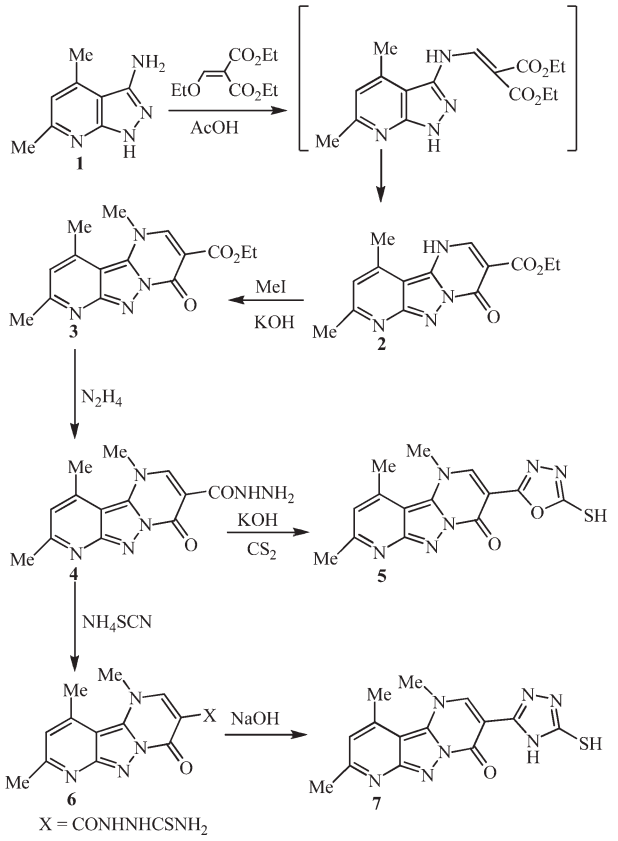
## INTRODUCTION

1*H*-Pyrazolo[3,4-*b*]pyridines comprise a very interesting class of compounds because of their significant and versatile biological and pharmacological activities, such as antimalarial [1], antiproliferative [2], antimicrobial [3–5] inhibition of cyclin-dependent kinases [6] and cardiovascular [7–9] antiviral [10–12] and antileishmanial [13] activities. In general, the pyrazolopyridines are found to be active antitubercular agents [14,15] active against gram positive and negative bacteria [16]. As well as pyrazolopyrimidines [17,18] are selective inhibitors of cyclic 3′,5′-adenosine mono-phosphat (cAMP) phosphodiesterases *in vitro*, and some of them possess anxiolytic properties comparable to those of benzodiazepines.[19]. Moreover, pyridopyrazolopyrimidines revaled antiproliferative activity [20] and are used as potent kinase inhibitors [21]. To enhance the activity of pyrazolopyridines and pyrazolopyrimidines, several approaches were followed to construct another ring over those ring systems described in the literature [22–26] are available on preparation of pyridopyrazolopyrimidines which left much scope for further study. Furthermore, it has been reported that certain compounds bearing 1,3,4-oxa-, thiadiazole, and 1,2,4-triazole nucleus possess significant anti-inflammatory activity [27–37]. In view of these reports, we reported herein the synthesis of some newer heterocyclic systems containing pyridopyrazolopyrimidine system isolated with 1,2,4-triazoles, 1,3,4-oxa-, and thiadiazoles, and fused with pyrazoles derivative.

## RESULTS AND DISCUSSION

4,6-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-amine was prepared according to the reported method [38,39] which undergo the cyclocondensation reaction with diethyl ethoxymethylenemalonate yielded directly the 8,10-dimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidine-3-carboxylate (**2**) without the isolation of the enamine intermediate [40], the structure of **2** was confirmed by the correctly positioned and coupled $^1$H NMR spectrum, which presents signals as triplet at δ 1.29, quartet at 4.32 ppm because of the ester group and as singlet at δ 8.68, 12.24 ppm due to the H-2 and NH protons, respectively. The $^{13}$C NMR spectrum of **2** showed a characteristic signals, for the ester group, at δ 24.2, 62.0 ($CH_2CH_3$), 166.0 (*C*OOEt), and 154.5 (C-4) ppm. The latter compound **2** was alkylated, by its reaction with methyl iodide in presence of KOH to afford 1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**), to increase its solubility during its reactions, which was elucidated by the appearance of the new signals in the $^1$H NMR spectrum as singlet at δ 3.96 ppm due to N—$CH_3$. The alkylated derivative **3** was subjected to react with hydrazine hydrate to give the corresponding carbohydrazide derivative **4** which was confirmed by its IR spectrum showed a characteristic C=O absorptions at 1640 and 1677 cm$^{-1}$, and its $^1$H NMR spectrum agree with the structure which showed a characteristic a broad singlet band for CONHN$H_2$ at δ 4.78 ppm. Hydrazide derivative (**4**) is versatile synthetic intermediate for the

**Scheme 1**

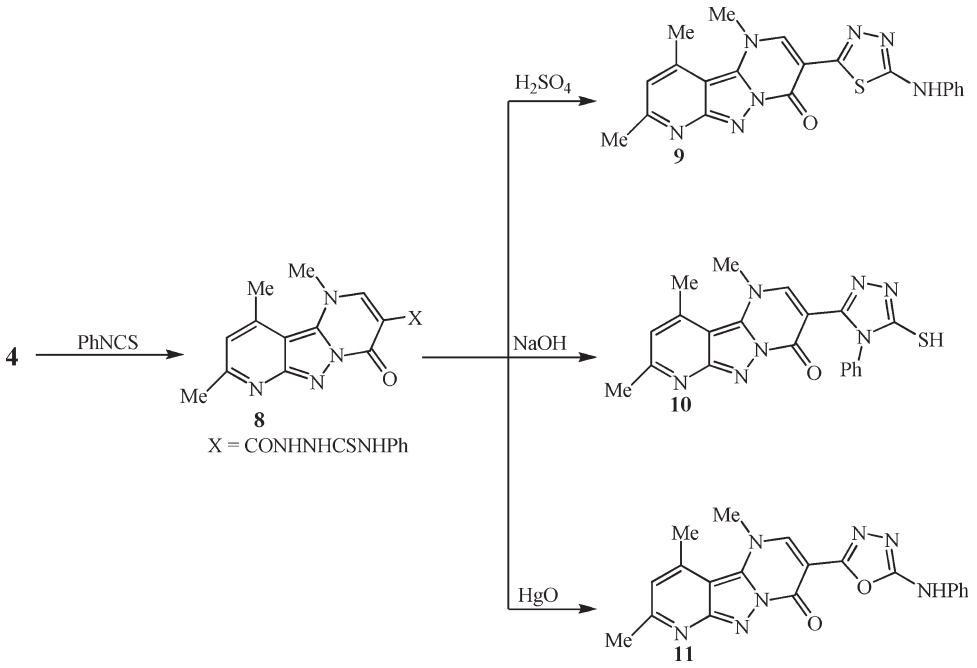


preparation of many heterocyclic moieties. In view of this report, we report herein some reactions of this hydrazide **4** to obtain new heterocyclic rings attached and/or fused to the pyridopyrazolopyridine moiety. Reaction of hydrazide **4** with $CS_2$ in alc. KOH at reflux temperature afforded the corresponding 1,8,10-trimethyl-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**5**) which was elucidated, besides the elemental analysis, $^1$H NMR spectrum represented the presence of the characteristic broad singlet due to the SH group at δ 13.12 ppm and its mass spectrum revealed the molecular ion peak at *m*/*z* 328 indicated the molecular weight of **5**. The $^{13}$C NMR spectrum showed a characteristic isooxazole signals at δ 162.0 and 171.3 ppm. Also the reaction of **4** with ammonium thiocyanate in absolute ethanol gave the corresponding thiosemicarbazide **6** which undergo the cyclization reaction through its treatment with sodium hydroxide giving 1,8,10-trimethyl-3-(5-sulfanyl-4*H*-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**7**) which was confirmed by $^1$H NMR spectrum which showed the presence of signals as a broad bands at δ 10.92 and 12.55 ppm due to the NH and SH groups, respectively, its mass spectrum presents peaks corresponding to peaks at *m*/*z* 327 and 328 corresponding to $M^+$ and $M^+$+1, respectively (Scheme 1).

On treatment of the hydrazide **4** with phenylisothiocyanate, in the way like its reaction with ammonium thiocyanate, afforded the corresponding the thiosemicarbazide **8** which was considered the key intermediate to prepare the 1,8,10-trimethyl-3-[5-(phenylamino)-1,3,4-thiadiazol-2-yl]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**9**), 1,8,10-trimethyl-3-(4-phenyl-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**10**), and 1,8,10-trimethyl-3-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]pyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidin-4(1*H*)-one (**11**), in about 66–74% yields, after its treatment with sulfuric acid, 2*N* sodium hydroxide, and mercuric oxide, respectively. The preferred formation of the 1,3,4-thiadiazole derivative **9** under such acidic conditions can be due to the loss of nucleophilicity of *N*-4 as a result of its protonation leading to an increase in the nucleophilicity of the sulfur atom toward the attack of the carbonyl carbon. On the other hand, the cyclization of **4** was carried out under alkaline conditions, the nucleophilicity of N-4 is enhanced and leads to cyclization with carbonyl carbon atom to afford the 1,2,4-triazole derivative **10**. 1,3,4-Oxadiazole derivative **11** was performed by mercuric oxide, the mode of cyclization includes desulfurization, which introduces the oxygen atom in the cyclization process. The structure assignment of these derivatives were based on the $^1$H NMR spectra showed signals due to the N*H*Ph present in **9** and **11** at δ 9.86, 9.46 ppm, as a broad singlet, but in derivative **10** showed the broad singlet at δ 13.06 ppm due to the SH group. All the other aromatic and aliphatic protons were observed at the expected regions. Mass spectra of these derivatives showed a [$M^+$+1] peak, in agreement with their molecular formula, also the elemental analysis are consistent with the structure of these derivatives **9**, **10**, and **11** (Scheme 2).

The starting material, pyridopyrazolopyrimidine carboxylate **2** was transformed into ethyl 4-chloro-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate by phosphorous oxychloride at boiling temperature thus providing intermediate precursor **12** for all four new final compounds. They furnished fused tetracyclic compounds **13a–d** by reaction with various purchased hydrazines in boiling xylene. The previously reported method, consisting of a nucleophylic substitution of the chlorine atom with the hydrazine derivative followed by cyclization [41], again showed itself to be useful and profitable for the aims proposed. 6,8-dimethyl-2,3-dihydro-3*H*-pyrazolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-one derivatives **13a–d** were elucidated by the IR spectra which presented strong peaks at 1640–1620, 3466–3409,

**Scheme 2**




and 2210 $cm^{-1}$ which were attributed to the carbonyl (C═O) and ─NH groups on the pyrazole and pyrimidine, respectively. The mass spectra of these compounds **13a–d** indicated that the molecular ion peaks were observed as $M^+$ and $M^+$+H. From their $^1H$ NMR spectra, it is possible to observe the presence of signals corresponding to the NH of pyrimidine at the range δ 10.99–11.15 ppm, the absence of the ester group and presence the new signals in aliphatic region such as in compound **13a** at δ 4.18 ppm due to the N─$CH_3$ and the increase of signals in the aromatic part because the presence of phenyl derivatives in compounds **13b–d**. In addition, the elemental analysis is consistent with the structure of theses compounds **13a–d** (Scheme 3).

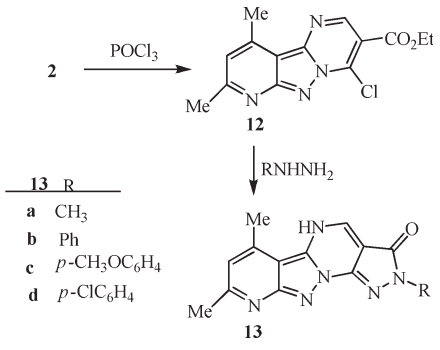
## EXPERIMENTAL

Melting points were determined using Kofter block instrument. The progresses of reactions were monitored by TLC (analytical silica gel plates 60 $F_{254}$). NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 300 MHz for $^1H$ NMR and at 75.5 MHz for $^{13}C$ NMR with TMS as an internal standard, chemical shifts are reported in ppm (δ) and coupling constants (*J*) are given in Hz. IR spectra were recorded on Perkin-Elmer 1430 sectrpphotometer using KBr disc technique. Mass spectra were measured on a Kratos 50 tc spectrometers. Elemental analyses were performed at the Chemistry Institute, Copenhagen University.

**Ethyl 8,10-dimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4] pyrazolo[1,5-a]pyrimidine-3-carboxylate (2).** A mixture of 1.94 g of aminopyrazolopyridine **1** (12 mmol) and 2.59 g of diethyl ethoxymethylenemalonate (12 mmol) was dissolved in 20-mL glacial acetic acid and the reaction mixture was refluxed for 10 h cooling to room temperature and poured into ice/water. The solid product was collected by filtration, washed with water, dried, and recerystalization from methanol to afford the yellow crystals of **2**, 3.12 g (91%), mp 222–223°C; $^1H$ NMR (DMSO-$d_6$): δ 1.29 (t, 3H, $J$ = 7 Hz, $CH_3CH_2$), 2.66 (s, 3H, $CH_3$), 2.91 (s, 3H, $CH_3$), 4.32 (q, 2H, $J$ = 7.0 Hz $CH_3CH_2$), 7.03 (s, 1H, ArH), 8.68 (s, 1H, ArH), 12.24 (bs, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$): δ 14.3, 19.2, 24.2, 62.0, 91.2, 116.8, 122.2, 145.8, 148.2, 151.2, 153.6, 154.5, 158.3, 166.0; ms (EI): *m/z* 287 ($M^+$+1, 5), 286 ($M^+$, 26), 241 (23), 240 (100). Anal. Cacld. for $C_{14}H_{14}N_4O_3$ (286.29): C, 58.73; H, 4.93, N, 19.57. Found: C, 58.60; H, 4.75; N, 19.35.

**1,8,10-Trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo [1,5-a]pyrimidine-3-carboxylate (3).** A solution of 1.77 g (6.2 mmol) of **2** in 20 mL of acetone, cooled by immersion in a water/ice bath, was added to 1.74 g (31.0 mmol) of powdered KOH. On vigorous stirring, 1.76 g of methyl iodide (12.4 mmol) was added and the mixture was stirred for 30 min at room temperature. After the addition of 90 mL of toluene, a precipitate of inorganic salt had formed, which was filtered

**Scheme 3**



off. The organic mixture was treated with 20 mL of saturated NaCl solution, dried with anhydrous $Na_2SO_4$, and evaporated under reduced pressure. The residue was triturated with ethanol and the solid product was collected by filtration, and recrystalization from ethanol to afford the white powder of **3**, 1.52 g (82%); mp 150–152°C; IR (KBr) ν $cm^{-1}$ 1745 ($CO_2Et$), 1633 (CO); $^1H$ NMR ($CDCl_3$): δ 1.26 (t, 3H, $J = 7$ Hz, $CH_3CH_2$), 2.56 (s, 3H, $CH_3$), 2.83 (s, 3H, $CH_3$), 3.96 (s, 3H, N—$CH_3$), 4.29 (q, 2H, $J = 7$ Hz, $CH_3CH_2$), 7.00 (s, 1H, ArH), 8.68 (s, 1H, ArH); (EI): *m/z* 301 ($M^+$+1, 20), 300 ($M^+$, 100),, 255 (25), 227 (30), 184 (8), 131 (60), 115 (16). Anal. Cacld. for $C_{15}H_{16}N_4O_3$ (300.31): C, 59.99; H, 5.37, N, 18.66. Found: C, 59.76; H, 5.25; N, 18.45.

**1,8,10-Trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4] pyrazolo [1,5-a]pyrimidine-3-carbohydrazide (4).** A mixture of 3.0 g of **3** (10 mmol) and 1.25 g of hydrazine hydrate (25 mmol) in 30 mL ethanol was heated under reflux for 4 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from methanol to give colorless of **4**, 2.51 g (88%); mp 266–267°C; IR (KBr) ν $cm^{-1}$: 3310–3212 ($NHNH_2$), 1640, 1677 (2 CO); $^1H$ NMR (DMSO-$d_6$): δ 2.54 (s, 3H, $CH_3$), 2.81 (s, 3H, $CH_3$), 3.86 (s, 3H, N—$CH_3$), 4.78 (bs, 2H, $NH_2$), 7.22 (s, 1H, ArH), 8.78 (s, 1H, ArH), 9.45 (bs, 1H, NH); ms (EI): *m/z* 287 ($M^+$+1, 55), 286 ($M^+$, 20), 257 (15), 228 (100), 199 (23), 175 (12), 147 (36). Anal. Cacld. for $C_{13}H_{14}N_6O_2$ (286.29): C, 54.54; H, 4.93, N, 29.35. Found: C, 54.33; H, 4.65; N, 29.15.

**1,8,10-Trimethyl-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)pyrido [2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (5).** A mixture of 2.86 g of hydrazide **4** (10 mmol) and 0.6 mL of carbon disulfide (10 mmol) was added to a solution of 0.56 g KOH (10 mmol) in 50 mL water and 50 mL ethanol. The reaction mixture was refluxed for 4 h. After evaporating it to dryness under reduced pressure, a solid product was obtained. This was dissolved in 50 mL water and acidified with conc. HCl. The precipitate was filtered off, washed with water, and recrystallized from ethanol to afford the whit crystals of **5**, 2.25 g (69%); mp 210–212°C; $^1H$ NMR (DMSO-$d_6$): δ 2.55 (s, 3H, $CH_3$), 2.86 (s, 3H, $CH_3$), 3.88 (s, 3H, N—$CH_3$), 7.32 (s, 1H, ArH), 8.95 (s, 1H, ArH), 13.12 (bs, 1H, SH); $^{13}C$ NMR (DMSO-$d_6$): δ 14.3, 19.2, 24.2, 90.2, 116.7, 121.6, 145.5, 148.4, 151.1, 152.4, 155.3, 157.5, 162.0, 171.3; ms (EI): *m/z* 329 ($M^+$+1, 10), 328 ($M^+$, 65), 294 (100), 239 (20), 201 (23), 151 (12), 77 (11). Anal. Cacld. for $C_{14}H_{12}N_6O_2S$ (328.35): C, 51.21; H, 3.68, N, 25.59. Found: C, 51.12; H, 3.55; N, 25.43.

***N′*-[(Amino-sulfanylidyne)methyl]-1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-carbohydrazide (6).** To a mixture 0.29 g of hydrazide **4** (1 mmol) and 0.23 g of ammonium thiocyanate (3 mmol), 4 mL of hydrochloric acid (36%) was added, in 50 mL ethanol. The reaction mixture was refluxed for 12 h, cooled, and the mixture poured into ice/water with stirring. The solid formed was collected by filtration, dried, and recrystallized from ethanol to afford a pale yellow crystals of **6**, 0.31 g (89%), mp 225–226°C; IR (KBr) ν $cm^{-1}$: NH 3300–3200, ($NH_2$, NH), 1655–1640 (CO) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.43 (s, 3H, $CH_3$), 2.67 (s, 3H, $CH_3$), 3.89 (s, 3H, N—$CH_3$), 5.03 (bs, 2H, $NH_2$), 7.22 (s, 1H, ArH), 8.65 (s, 1H, ArH), 9.71 (bs, 1H, CSNH), 10.17 (bs, 1H, CONH); ms (EI): *m/z* 346 ($M^+$+1, 35), 345 ($M^+$, 10), 330 (5), 286 (100), 245 (24), 217 (12), 152 (30). Anal. Cacld. for $C_{14}H_{15}N_7O_2S$ (345.38): C, 48.69; H, 4.38, N, 28.39. Found: C, 48.30; H, 4.22; N, 28.26.

**1,8,10-Trimethyl-3-(5-sulfanyl-4H-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (7).** A mixture of 0.69 g thiosemicarbazid **6** (2 mmol) and 50-mL sodium hydroxide (2*N*) was heated under reflux for 2 h. The reaction mixture was cooled, the precipitate formed was collected by filtration, dried, and recrystallized from methanol to afford the yellow crystals of **7**, 0.52 g (80%); mp 239–240°C; IR (KBr) ν $cm^{-1}$: (NH) 3320,1645 (CO), 2786 (SH); $^1H$ NMR (DMSO-$d_6$): δ 2.70 (s, 3H, $CH_3$), 2.77 (s, 3H, $CH_3$), 3.93 (s, 3H, N—$CH_3$), 7.15 (s, 1H, ArH), 8.50 (s, 1H, ArH), 10.92 (bs, 1H, NH), 12.55 (bs, 1H, SH); ms (EI): *m/z* 328 ($M^+$+1, 60), 327 ($M^+$, 100), 294 (15), 227 (60), 246 (13), 201 (11), 184 (8). Anal. Cacld. for $C_{14}H_{13}N_7OS$ (327.36): C, 51.36; H, 4.00, N, 29.95. Found: C, 51.22; H, 3.97; N, 29.86.

***N′*-{[Imino(phenyl)-sulfanylidyne]methyl}-1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-carbohydrazide (8).** To a solution of 2.86 g hydrazide **4** (10 mmol) in 10 mL ethanol, 1.35 g phenylisothocyanate (10 mmol) were added. The reaction mixture was heated under reflux for 2 h. The product that separated on cooling was filtered off, washed with ethanol, and dried well to give white crystals of **8**, 3.86 g (92%); mp 173–175°C; $^1H$ NMR (DMSO-$d_6$): δ 2.65 (s, 3H, $CH_3$), 2.87 (s, 3H, $CH_3$), 3.95 (s, 3H, N—$CH_3$), 7.13–7.79 (m, 6H, ArH), 8.81 (s, 1H, ArH), 9.50 (bs, 1H, ArNH), 9.81 (bs, 1H, CSNH), 10.18 (bs, 1H, CONH); ms (EI): *m/z* 421 ($M^+$, 60), 344 (100), 256 (35), 227 (9), 194 (16), 166 (25), 121 (23), 109 (10). Anal. Cacld. for $C_{20}H_{19}N_7O_2S$ (422.48): C, 56.99; H, 4.54, N, 23.26. Found: C, 56.62; H, 4.33; N, 23.14.

**1,8,10-Trimethyl-3-[5-(phenylamino)-1,3,4-thiadiazol-2-yl] pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (9).** A solution of 2.11 g thiosemicarbazide **8** (5 mmol) in 10 mL cold conc. sulfuric acid was stirred until dissolution and the left at room temperature for 2 h with stirring. The reaction mixture was poured onto crushed ice and the precipitate product was filtered off, washed with water, and recrystallized from ethanol to give pale yellow crystals of **9**, 1.50 g (74%); mp 207–208°C; $^1H$ NMR (DMSO-$d_6$): δ 2.64 (s, 3H, $CH_3$), 2.82 (s, 3H, $CH_3$), 3.96 (s, 3H, N—$CH_3$), 7.14–7.65 (m, 6H, ArH), 8.65 (s, 1H, ArH), 9.86 (bs, 1H, ArNH); $^{13}C$ NMR (DMSO-$d_6$): δ 15.6, 19.4, 23.5, 93.0, 116.7, 117.3, 117.8, 122.4, 125.1, 129.5, 140.5, 145.9, 148.4, 151.1, 155.0, 152.2, 155.6, 158.9, 159.0, 160.1; ms (EI): *m/z* 404 ($M^+$+1, 30), 403 ($M^+$, 100), 326 (21), 271 (15), 240 (24), 174 (12), 145 (22). Anal. Cacld. for $C_{20}H_{17}N_7OS$ (403.46): C, 59.54; H, 4.25, N, 24.30. Found: C, 59.35; H, 4.13; N, 24.17.

**1,8,10-Trimethyl-3-(4-phenyl-5-sulfanyl-4H-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (10).** A solution of 2.11 g thiosemicarbazide **8** (5 mmol) in 50 mL sodium hydroxide (2*N*) was heated under reflux for 4 h. The reaction mixture was cooled and acidified with hydrochloric acid (2*N*). The resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to afford the yellow crystals of **10**, 1.40 g (69%), mp 210–211°C; $^1H$ NMR (DMSO-$d_6$): δ 2.66 (s, 3H, $CH_3$), 2.85 (s, 3H, $CH_3$), 3.96 (s, 3H, N—$CH_3$), 7.16–7.76 (m, 6H, ArH), 8.33 (s, 1H, ArH), 13.06 (bs, 1H, SH); ms (EI): *m/z* 404 ($M^+$+1, 30), 403 ($M^+$, 60), 326 (11), 293 (33), 227 (50), 193 (100), 166 (33), 119 (20), 106 (10). Anal. Cacld. for $C_{20}H_{17}N_7OS$ (403.46): C, 59.54; H, 4.25, N, 24.30. Found: C, 59.44; H, 4.17; N, 24.14.

**1,8,10-Trimethyl-3-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (11).** Mercuric oxide 2.37 g (11 mmol) was added to a solution of 4.21 g thiosemicarbazide **8** (10 mmol) in 20 mL methanol and the resulting mixture was refluxed for 4 h. The precipitated mercuric sulfide was filtered off and washed with hot methanol. The filtrate on cooling gave a precipitate which was recrystallized from ethanol to afford the white crystals of **11**, 2.55 g (66%), mp 183–184°C; $^1$H NMR (DMSO-$d_6$): δ 2.69 (s, 3H, $CH_3$), 2.83 (s, 3H, $CH_3$), 3.94 (s, 3H, N—$CH_3$), 7.12–7.66 (m, 6H, ArH), 8.78 (s, 1H, ArH), 9.46 (bs, 1H, ArNH); ms (EI): *m/z* 387 ($M^+$, 100), 310 (30), 283 (15), 227 (30), 174 (40), 117 (10). Anal. Cacld. for $C_{20}H_{17}N_7O_2$ (387.39): C, 62.01; H, 4.42, N, 25.31. Found: C, 61.94; H, 4.31; N, 25.14.

**4-Chloro-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-carboxylate (12).** A mixture of 2.86 g of ethylcarboxylate **2** (10 mmol) and 7.75 g of phosphorous oxychloride (50 mmol) was refluxed for 3 h. After cooling, the suspension was then added to ice/water. Then, with stirring, it was carefully made alkaline with aqueous sodium hydroxide (28%) and the resulting precipitate was collected, washed many times with water, dried, and recrystallized from ethanol to afford a pale yellow powder of **12**, 2.81 g (92%), mp 150–152°C; $^1$H NMR (DMSO-$d_6$): δ 1.31 (t, 3H, $J$ = 7 Hz, C$H_3$CH$_2$), 2.68 (s, 3H, $CH_3$), 2.95 (s, 3H, $CH_3$), 4.41 (q, 2H, $J$ = 7.0 Hz $CH_3$C$H_2$), 7.11 (s, 1H, ArH), 8.77 (s, 1H, ArH); ms (EI): *m/z* 305 ($M^+$+1, 12), 304 ($M^+$, 72), 267 (30),240 (100), 223 (15), 195 (15). Anal. Cacld. for $C_{14}H_{13}ClN_4O_2$ (304.73): C, 55.18; H, 4.30; N, 18.39. Found: C, 55.10; H, 4.22; N, 18.20.

**Synthesis of the N-substituted 6,8-Dimethyl-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one derivatives (13a–d).** 4-Chloro-pyridopyrazolopyrimidine 0.30 g (1 mmol) was dispersed in 20 mL of xylene and the suspension was heated to refluxing until complete dissolution. Then, a slight excess of hydrazine compound (1.5 mmol) was added with 0.16 g of triethylamin (1.5 mmol) and the reaction mixture was refluxed for the required time (9–12 h). A precipitate had formed was collected, washed many times with ethanol, dried under vacuum, and finally recrystallized with absolute ethanol giving **13a–d**: **13a**, 0.17 g (65%); **13b**, 029 g (88%); **13c**, 0.23 g (64%); and **13d**, 0.31 g (86%).

***2,6,8-Trimethyl-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13a)*** White crystals, mp 280–282°C; $^1$H NMR (DMSO-$d_6$): δ 2.55 (s, 3H, $CH_3$), 2.72 (s, 3H, $CH_3$), 4.18 (s, 3H, N—$CH_3$), 7.05 (s, 1H, ArH), 8.66 (s, 1H, ArH), 10.99 (bs, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 18.3, 24.1, 40.5, 99.3, 109.5, 122.2, 136.3, 145.6, 148.0, 153.3, 155.2, 158.3, 166.4; ms (EI): *m/z* 269 ($M^+$+1, 20), 268 ($M^+$, 100), 253 (30), 224 (40), 197 (15). Anal. Cacld. for $C_{13}H_{12}N_6O$ (268.27): C, 58.20; H, 4.51; N, 31.33. Found: C, 58.12; H, 4.23; N, 31.21.

***6,8-Dimethyl-2-phenyl-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13b)*** White powder, mp 310–312°C; $^1$H NMR (DMSO-$d_6$): δ 2.60 (s, 3H, $CH_3$), 2.75 (s, 3H, $CH_3$), 7.06–7.55 (m, 6H, ArH), 8.91 (s, 1H, ArH), 11.10 (bs, 1H, NH); ms (EI): *m/z* 331 ($M^+$+1, 40), 330 ($M^+$, 100), 253 (20), 224 (11), 197 (12), 160 (41), 118 (33) 77 (5). Anal. Cacld. for $C_{18}H_{14}N_6O$ (330.34): C, 65.44; H, 4.27; N, 25.44. Found: C, 65.22; H, 4.20; N, 25.31.

***6,8-Dimethyl-2-(4-methoxy-phenyl)-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13c)*** Yellow powder, mp 270–271°C; $^1$H NMR (DMSO-$d_6$): δ 2.63 (s, 3H, $CH_3$), 2.78 (s, 3H, $CH_3$), 3.79 (s, 3H, $OCH_3$), 7.16–7.56 (m, 5H, ArH), 8.96 (s, 1H, ArH), 11.12 (bs, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 19.6, 24.3, 55.4, 101.3, 109.5, 114.2, 121.6, 122.4, 127.6, 136.7, 132.8, 145.7, 148.6, 150.5, 153.5, 154.9, 155.4, 158.7, 165.1; ms (EI): *m/z* 361 ($M^+$+1, 39), 360 ($M^+$, 60), 329 (100), 252 (21), 197 (12), 121 (10), 107 (41). Anal. Cacld. for $C_{19}H_{16}N_6O_2$ (360.37): C, 63.32; H, 4.48; N, 23.32. Found: C, 63.19; H, 4.30; N, 23.20.

***6,8-Dimethyl-2-(4-chloro-phenyl)-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13d)*** White powder, mp 240–241°C; $^1$H NMR (DMSO-$d_6$): δ 2.67 (s, 3H, $CH_3$), 2.79 (s, 3H, $CH_3$), 7.19–7.87 (m, 5H, ArH), 8.98 (s, 1H, ArH), 11.15 (bs, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 19.7, 24.5, 99.3, 110.6, 113.4, 119.5, 126.5, 135.7, 131.7, 143.5, 145.7, 149.5, 151.6, 156.8, 157.4, 159.3, 160.5, 164.5; ms (EI): *m/z* 365 ($M^+$+1, 80), 364 ($M^+$, 100), 328 (30), 300 (18), 284 (15), 257 (13), 231 (18), 201 (55), 146 (16), 131 (22), 112 (13). Anal. Cacld. for $C_{18}H_{13}ClN_6O$ (364.79): C, 59.27; H, 3.59; N, 23.04. Found: C, 59.18; H, 3.41; N, 22.88.

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## REFERENCES AND NOTES

[1] Menezes, C. M. S.; SantáAnna, C. M. R.; Rodrigues, C. R.; Barreiro, E. J. J Mol Struct (Theochem) 2002, 579, 31.

[2] Poreba, K.; Oplski, A.; Wietrezyk, J. Acta Pol Pharm 2002, 59, 215.

[3] Goda, F. E.; Abedl-Aziz, A. A. M.; Attef. O. A. Bioorg Med Chem 2004, 12, 1845.

[4] Attaby, F. A.; Abdel-Fattah, A. M. Phosphorus Sulfur Silicon Relat Elem 1999, 155, 253.

[5] Eleairy, M. A. A.; Attaby, F. A.; Elsayed, M. S. Phosphorus Sulfur Silicon Relat Elem 2000, 167, 161.

[6] Misra, R. N.; Xiao, H. Y.; Rawlins, D. B.; Shan, W.; Kellar, K. A.; Mulheron, J. G.; Sack, J. S.; Tokarski, J. S.; Kimball, S. D.; Webster, K. R. Biorg Med Chem Lett 2003, 13, 2405.

[7] Stasch, J. P.; Dembowsky, K.; Perzborn, E.; Stahl, E.; Schramm, M. Br J Pharmacol 2002, 135, 344.

[8] Boerrigter, G.; Costello-Boerrigter, L. C.; Cataliotti, A.; Tsuruda, T.; Harty, G. J.; Lapp, H.; Stasch, J. P.; Burnett, J. C. Circulation 2003, 107, 686.

[9] Bawankule, D. U.; Stathishkumar, K.; Sardar, K. K.; Chanda, D.; Krishna, A. V.; Prakash, V. R.; Mishra, S. K. J Pharmacol Exp Ther 2005, 314, 207.

[10] Attaby, F. A.; Elghandour, A. H. H.; Ali, M. A.; Ibrahim, Y. M. Phosphorus Sulfur Silicon Relat Elem 2006, 181, 1087.

[11] Attaby, F. A.; Elghandour, A. H. H.; Ali, M. A.; Ibrahim, Y. M. Phosphorus Sulfur Silicon Relat Elem 2007, 182, 133.

[12] Azevedo, A. R.; Ferreira, V. F.; de Mello, H.; Leao-Ferreira, L. R.; Jabor, A. V.; Frugulhetti, I. C. P. P.; Pereira, H. S.; Moussatche, N.; Bernardino, A. M. R. Heterocycl Commun 2002, 8, 427.

[13] De Mello, H.; Echevarria, A.; Bernardino, A. M.; Canto-Cavalheiro, M.; Leon, L. L. J Med Chem 2004, 47, 5427.

[14] Sekikawa, I.; Nishie, J.; Tono-Oka, S.; Tanaka, Y.; Kakimoto, S. J Heterocycl Chem 1973, 10, 931.

[15] Kukzynski, L.; Mrizikiewiez, A.; Banaszkiewicz, W.; Poreba, K. Pol J Pharmacol Pharm 1979, 31, 217.

[16] Kamal, A. M.; Atalla, A. A.; Mohamed, T. A.; Gies, A. A. Z Naturforsch B: Chem Sci 1991, 46, 541.

[17] Novinson, T.; Hanson, R.; Dimmitt, M. K.; Simon, L. N.; Robins, R. K.; O'Brien, D. E. J Med Chem 1974, 17, 645.

[18] Novinson, T.; Miller, J. P.; Scholten, M.; Robins, R. K.; Simon, L. N.; Obrien, D. E.; Meyer, R. B. J Med Chem 1975, 18, 460.

[19] Kirkpatrich, W. E.; Okabe, T.; Hillyard, I. W.; Robins, R. K.; Dren, A. T.; Novinson, T. J Med Chem 1977, 20, 386.

[20] Poeba, K.; Opolski, A.; Wietrzyk, J.; Kowalska, M. Arch Pharm 2001, 334, 219.

[21] Alberti, M. J.; Auten, E. P.; Lackey, K. E.; McDonald, O. B.; Wood, E. R.; Preugschat, F.; Cutler, G. J.; Kane-Carson, L.; Liu, W.; Jung, D. K. Med Chem Lett 2005, 15, 3778.

[22] Chandra, A. S. R.; Narsaiah, B.; Venkataratnam, R. V. J Flourine Chem 1997, 86, 127.

[23] Krishanaiah, A.; Narsaiah, B. J Flourine Chem 2001, 109, 183.

[24] Kanth, R. S.; Reddy, G. V.; Maitraie, D.; Narsaiah, B.; Shanthan, R. P.; Kumar, K. R.; Sridhar, B. J Flourine Chem 2006, 127, 1211.

[25] Mohamed, A. M. G.; Azza, M.; Mohamed, A. A. E. Can J Chem 2007, 85, 592.

[26] El-Essawy, A. F. Synth Commun, to appear.

[27] Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R. J Med Chem 1993, 36, 1090.

[28] Tozcoparan, B.; Gokhan, N.; Aktay, G.; Yesilada, E.; Ertan, M. Eur J Med Chem 2000, 35, 743.

[29] Amir, M.; Khan, M. S. Y.; Zaman, M. S. Indian J Chem 2004, 43B, 2189.

[30] Tozcoparan, B.; Kupeli, E.; Aktay, G.; Yesilada, E.; Ertan, M. Biorg Med Chem 2007, 15, 1808.

[31] Henichart, J. P.; Houssin, R.; Berier, J. L. J Heterocycl Chem 1986, 23, 1531.

[32] Awad, L. F.; El Ashry, E. S. H. Carbohydr Res 1998, 312, 9.

[33] Varvarasou, A.; Sistra-Papastaikoud, T.; Tsantili-Kakoulidou, A.; Vamvakides, A. Farmaco 1998, 53, 320.

[34] Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altmok, G. Farmaco 2002, 57, 101.

[35] Holla, B. S.; Poorjary, K. N.; Roa, B. S.; Shivananda, M. K. Eur J Med Chem 2002, 37, 511.

[36] Amir, M.; Shikha, K. Eur J Med Chem 2004, 39, 535.

[37] Demirbas, N.; Alpay Karaoglu, S.; Demirbas, A.; Sancak, K. Eur J Med Chem 2004, 39, 793.

[38] Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. Chem Lett 1976, 499.

[39] Hojo, M.; Masuda, R.; Okada, E. A. Synthesis 1990, 347.

[40] Krishnaiah, A.; Narsaiah, B. J Fluorine Chem 2001, 109, 183.

[41] Yokoyama, N.; Ritter, B.; Neubert, A. D. J Med Chem 1982, 25, 337.

# One Pot Synthesis of Spiro Pyrimidinethiones/Spiro Pyrimidinones, Quinazolinethiones/Quinazolinones, and Pyrimidopyrimidines

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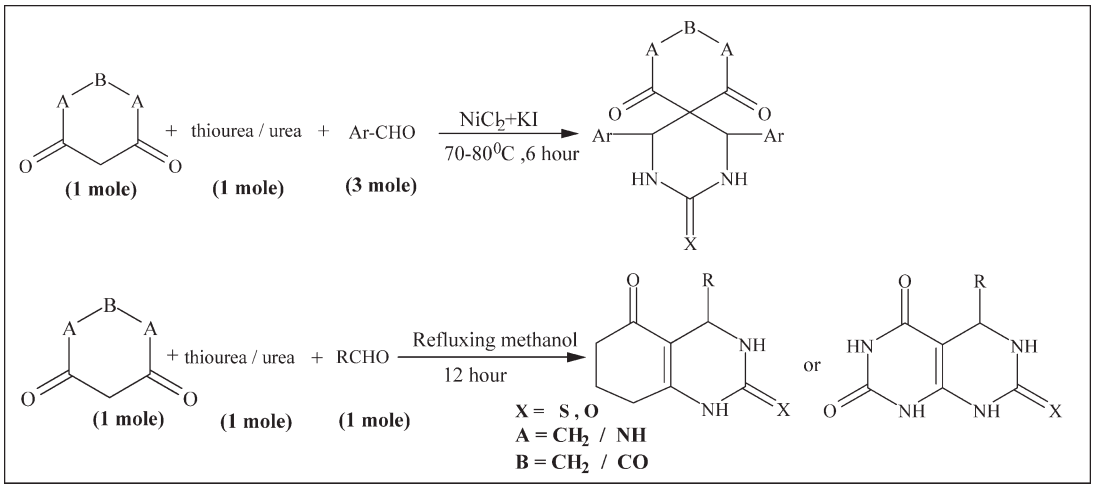


Condensation of cyclohexane-1,3-dione/barbituric acid, thiourea/urea, and aromatic aldehyde in the mole ratio of 1:1:3 in solventless reaction in presence of $NiCl_2$/KI afforded 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione analogues and 7,11-diaryl-9-thioxo-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,-trione/7,11-diaryl-2,4,8,10-tetraazaspiro[5.5] undecane-1,3,5,9-tetraone analogues, respectively. The similar condensation of cyclohexane-1,3-dione/ cyclohexanone, thiourea/urea, and aromatic aldehyde/heteroaromatic aldehyde in the mole ratio of 1:1:1 in refluxing methanol afforded 4-aryl/heteroaryl-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one, 4-aryl/heteroaryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione analogues and 4-aryl/heteroaryl-1,2,3,4,5, 6,7,8-octahydroquinazoline-2-thione, 4-aryl/heteroaryl-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one analogues, respectively. Condensation of heterocyclic active methylene compound, barbituric acid, thiourea/ urea, and aromatic aldehydes under similar set of conditions in 1:1:1 mole ratio was carried which afforded 5-aryl-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione/5-aryl-1,2,3,4,5, 6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione analogues. Similar condensation of an active methine compound, 2-acetylcyclohexanone, thiourea/urea, and aromatic aldehydes in the mole ratio of 1:1:1 produced 5-aryl-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one/5-aryl-1-methyl-2, 4-diazaspiro[5.5]undec-1-ene-3, 7-dione analogues, the spiro compounds of entirely different kind. All these identifications and characterizations have been based on the elemental analysis and spectral data.

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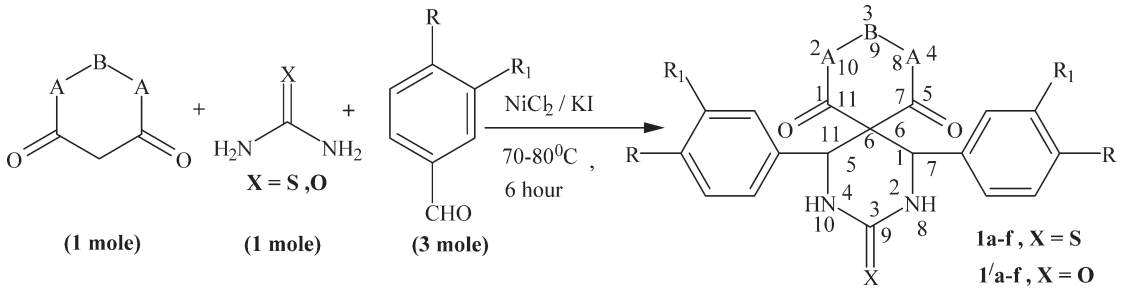
## INTRODUCTION

The synthesis of spiro compounds has been a subject of great interest to research workers. Spiro derivatives based on heteropolycyclics have antibacterial, anticonvulsant, antitumor, and anticancer activities. Similarly, condensed heterocyclics containing quinazoline moiety are ranked among the most versatile biologically active compounds possessing pharmacological properties like being anticonvulsant [1, 2], anticoagulant [3], antifibrillatory [4], cardiac stimulant [5], diuretic [6], antibacterial [7], antiviral [8], antifungal [9], antiasthematic, antiallergic [10], and antitubercular [11a]. In addition to its diverse biological activity, the quinazoline nucleus is also a key component in a relatively varied range of colored products [11b]. Compounds possessing pyrimidopyrimidine nucleus show potent biological activities including inhibition of angiogenesis, tumor inhibition [12], and tyrosine kinase inhibitors [13]. Some of the pyrimidopyrimidine derivatives, particularly 3-(2-methylphenyl)-10-phenyl-2-thioxothiazolo[4,5-d]pyrimido[2,1-

**Scheme 1**




**1a , 1′a ;** R = $CH_3$ , $R^1$ = H , A = B = $CH_2$

**1b , 1′b ;** R = $OCH_3$ , $R^1$ = H , A = B = $CH_2$

**1c , 1′c ;** R = $R^1$ = $OCH_3$ , A = B = $CH_2$

( Internal Numbering )

**1d , 1′d ;** R = $CH_3$ , $R^1$ = H , A = NH , B = CO

**1e , 1′e ;** R = $OCH_3$ , $R^1$ = H, A= NH , B = CO

**1f , 1′f ;** R = $R^1$ = $OCH_3$ , A = NH , B = CO

( External Numbering )

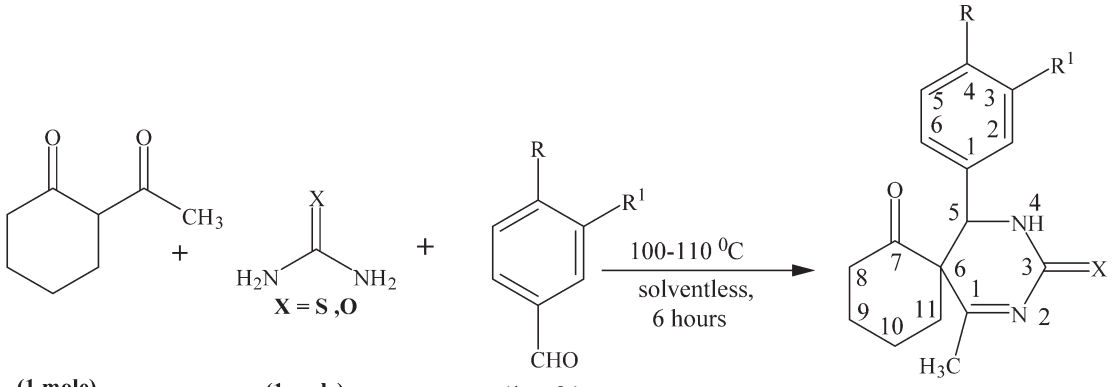
b]pyrimidine [14] have been screened for antifungal activity against *Aspergillus niger* and *Penicillium citrinum*. These promising biological activities encouraged us to prepare some new heterocyclic derivatives.

In the past decade, dihydropyrimidinones and their derivatives have attracted considerable interest because they exhibit promising activities as calcium channel blockers, antihypertensive agents, α-1a-antagonists [15], and neuropeptide Y (NPY) antagonists. Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties [16], most notably among these are the batzellandine alkaloids, which were found to be potent HIV group-120-CD4 inhibitors [17]. The synthesis of the core heterocyclic nucleus of dihydropyrimidinones, tetrahydropyrimidinones, partially reduced quinazolines, and their thio analogues is of much current importance. The most simple and straightforward procedure, first reported by Biginelli in 1893, involves three-component, one pot condensation of a ethyl acetoacetate with an aldehyde and urea under strongly acidic conditions [18]. This procedure is known as the Biginelli reaction. The major drawback associated with this protocol is the low yield, particularly for substituted aromatic and aliphatic aldehydes [19]. Recently, many synthetic methods for preparing dihydropyrimidinones have been reported including classical conditions, with microwave and ultrasound irradiation and by using Lewis acids as well as protic acid promoters such as; $H_2SO_4$ [20], $BF_3$ $Et_2O$/CuCl [21], $InCl_3$ [22], $BiCl_3$ [23], $LiClO_4$ [24], $Ag_3PW_{12}O_{40}$ [25], and $FeCl_3$ $6H_2O$/HCl [26]. Acidic ionic liquids as effective catalysts for this transformation were also utilized [27]. However, some of the reported methods also suffer from drawbacks such as nonrecyclability, harsh reaction conditions, long reaction times, the need of an additive, tedious work-up, and environmental pollution. Moreover, some of the methods are only practical for aromatic aldehydes especially the unsubstituted ones. Therefore, a need still exists for versatile, simple and environment-friendly processes wehereby DHPMs as single ring compounds, as a component in condensed heterocycles and as moieties in spiro heterocyclic systems can be formed under milder and practical conditions. In recent years, multicomponent coupling reactions [28] for the synthesis of the title and closely related compounds have received considerable attention. It is a major attraction to chemists because two or more steps in the synthetic sequence can be carried out without the isolation of intermediates. Thus, the synthesis of compounds containing heterocyclic nucleus is of current interest under this strategy. We, herein, report three component coupling reaction (Biginelli type of reaction), which provides an easy access to spiro and condensed/fused heterocycles in fairly good yield. It is worthwhile to mention here, that we proposed a new one pot method for synthesizing novel spiro pyrimidinethiones/spiro pyrimidinones; varied substituted and reduced quinazolinethiones/quinazolinones and condensed pyrimidopyrimidines. In this work, we describe a general and practical route for the Biginelli type cyclocondensation reactions using $NiCl_2$ + KI as the catalyst. This can serve as a general method which provides an easy access to spiro and condensed systems in excellent yield.

## RESULTS AND DISCUSSION

A facile and one pot combination that not only preserves the simplicity of Biginelli's one pot reaction but also consistently produces excellent yields of the spiro

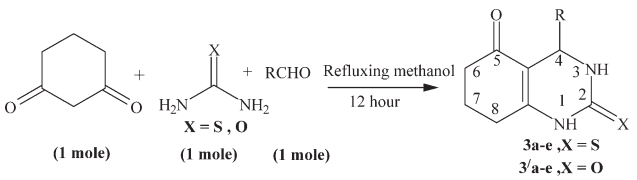
**Scheme 2**



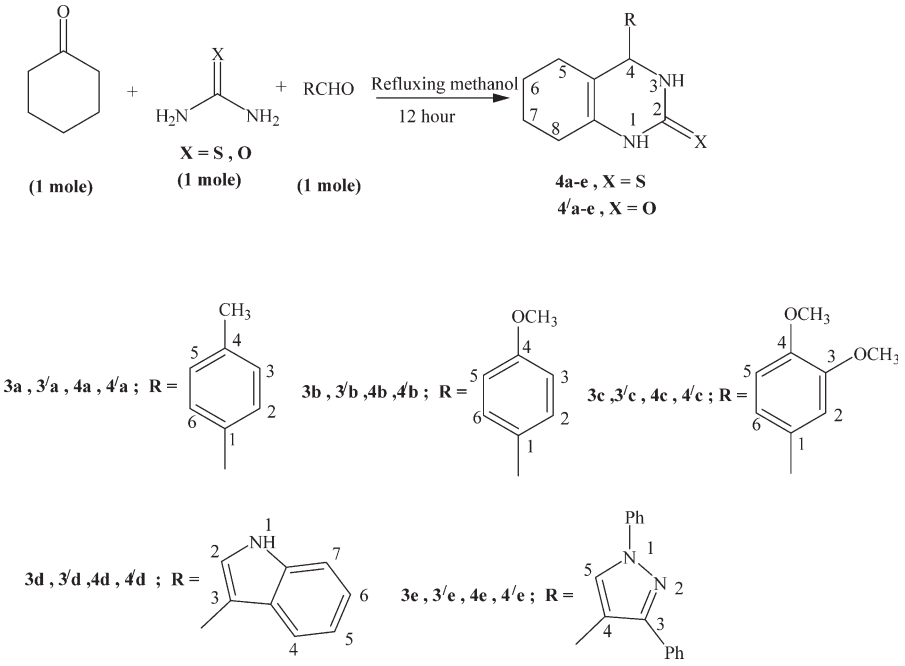

**2a , 2′a ;** R = R$^1$ = H
**2b , 2′b ;** R = $CH_3$ , R$^1$ = H
**2c , 2′c ;** R = $OCH_3$ , R$^1$ = H
**2d , 2′d ;** R = R$^1$ = $OCH_3$
**2e , 2′e ;** R = Cl , R$^1$ = H

pyrimidinethiones/spiro pyrimidinones (**1a-f/1′a-f**) has been developed as shown in Scheme 1. In a typical general experimental procedure by using highly exceptional conditions, a melt of the mixture of 1,3-dicarbonyl compound (cyclohexane-1,3-dione or barbituric acid), thiourea/urea, an aromatic aldehyde in the mole ratio of 1:1:3 was stirred without using any solvent at 70–80°C in the presence of catalytic amount of $NiCl_2$ + KI for a certain period of time required to complete the reaction (TLC), resulting in the formation of spiro pyrimidinethiones/spiro pyrimidinones. To study the generality of this process, many transformations illustrating this novel and general method for the synthesis of spiro pyrimidinethiones/spiro pyrimidinones were studied and the physical data including elemental analysis of the products is summarized in experimental section. A variety of substituted aromatic aldehydes and the cyclic dicarbonyl compounds afforded high yields of products in high purity. These reactions leading to the formation of spiro pyrimidinethiones/spiro pyrimidinones were confounded from the green perspectives, by the requirements for extractive isolation followed by recrystallization to afford material of a suitable quality. The solvent free approach afforded good yields of products examined during the course of this study. In majority of instances, solvent free approach generated pyrimidinethiones/pyrimidinones of exceptionally good purity. For comparison, condensation of an active methine compound, 2-acetylcyclohexanone (a cyclic β -diketone), thiourea/urea, and aromatic aldehyde in the mole ratio of 1:1:1 produced altogether an unexpected and a novel spiro compound instead of a normal condensed product (a quinazoline analogue), which was characterized as 5-aryl-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one/5-aryl-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione analogue (**2a-e/2′a-e**) as shown in Scheme 2. In another general experimental procedure, condensation of cyclohexane-1,3-dione, thiourea/urea, and aromatic aldehyde/heteroaromatic aldehyde in the mole ratio of 1:1:1 in refluxing methanol for 10–12 h resulted in the formation of 4-aryl/heteroaryl-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one/4-aryl/heteroaryl-1, 2,3,4,5,6,7,8-octahydro quinazoline-2,5-dione derivatives (**3a-e/3′a-e**) as shown in Scheme 3. Similarly, condensation of cyclohexanone, thiourea/urea, and aromatic or heteroaromatic aldehydes produces 4-aryl/heteroaryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione/4-aryl/heteroaryl-1,2,3,4,5,6,7,8 octahydroquinazolin-2-one analogues (**4a-e/4′a-e**) as shown in Scheme 4. Condensation of active methylene heterocyclic compound, barbituric acid, thiourea/urea, and aromatic aldehyde under similar set of conditions afforded 5-aryl-7-thioxo-1,2,3,4,5,6,7,8-pyrimidine-2,4,7-trione derivatives (**5a-d/5′a-d**) as shown in Scheme 5. The physical data of the products of all these reactions has been included in the experimental section. In conclusion, three-component condensation provides an efficient and improved method for the synthesis of spiro and condensed heterocycles. Moreover, this method offers

**Scheme 3**



**Scheme 4**




several advantages including high yield, simple work-up procedure and is free from pollution. The structures of all these compounds were established by elemental analysis and spectral studies (IR, $^1$H NMR, and $^{13}$C NMR spectra of some compounds).

A characteristic multiplet at δ 2.0–2.35 due to six protons of the trimethylene chain of the cyclohexane component of the spiro system; a sharp singlet signal due to two similar benzylic methyl protons corresponding to six protons at δ 2.40 and a downfield singlet around δ 5.0 due to two identical protons at positions 1 and 5 of the spiro system along with the usual appearance of aromatic protons in the $^1$H NMR spectrum speaks unequivocally of the characterized 1,5-bis(*p*-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione structure of the thioxo compound **1a**. The prominent absence of appearance of methylene chain protons, presence of two closely located sharp singlet signals of three protons of each of the two methoxyl groups, one at δ 3.68 and the other at δ 3.72 and more downfield appearance of a signal of two protons due to H-7 and H-11 of the spiro system at δ 5.25 in the $^1$H NMR spectra of **1f** not only confirmed but distinguished this tetrazaspiro system from the diazaspiro system. Disappearance of a triplet signal due to methine proton of 2-acetylcyclohexanone and appearance of a slightly upfield singlet at δ 1.22 due to methyl group as compared with that of 2-acetylcyclohexanone (δ 2.68); a multiplet due to eight protons of tetramethylene chain at δ 1.79–2.25; a signal at δ 3.70 due to methoxyl protons and a highly downfield singlet at δ 5.18 due to one proton, H-5 in $^1$H NMR spectrum of **2c** confirmed the generation of a substituted and functionalized cyclohexanespiropyrimidine system, characterized for this compound. The only characteristic difference in the $^1$H NMR spectra of quinazoline compounds **3** and **4** is that in former we have a slightly downfield multiplet due to six protons of the trimethylene chain and in the latter a slightly up field multiplet due to eight protons of the tetramethylene chain. In compounds **5**, where in the $^1$H NMR spectra there is a dearth of protons on the carbon atoms of the heterocyclic system, the only prominent singlet characterizing the system is due to a single proton at δ 4.70, supplemented by the elemental analysis data and characteristic IR peaks data as detailed in the experimental part of individual compounds.

In products **1a-f** and **1′a-f**, besides the stereochemistry involved due to spiro system of the 2 six-membered heterocyclic and carbocyclic ring, there are two similar chiral centers on one of the rings of the spiro system. So,

**Scheme 5**

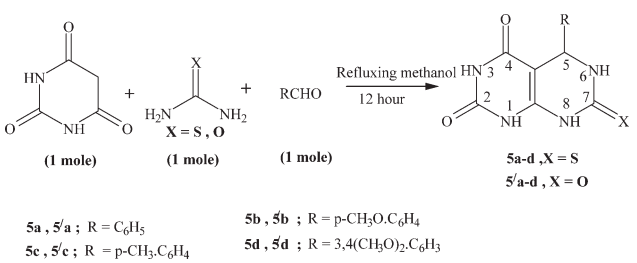


**Table 1**

Antimicrobial activity of 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione (**1a-c/1′a-c**) and 7,11-diaryl-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione/7,11-diaryl-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9 tetraone (**1d-e/1′d-e**).

| | Antibacterial activity | | | Antifungal activity | | |
|---|---|---|---|---|---|---|
| Compd No. | *Escherichia coli* | *Bacillus subtilis* | *Bacillus cereus* | *Aspergillus niger* | *Penicillium* species | *Cladosporium* species |
| **1a** | 10 | – | – | – | – | 13 |
| **1b** | 11 | – | – | – | – | 14 |
| **1c** | 14 | – | – | – | – | 16 |
| **1d** | 15 | – | – | – | – | 17 |
| **1e** | 17 | – | – | – | – | 20 |
| **1f** | 19 | – | – | – | – | 20 |
| **1′a** | 12 | – | – | – | – | 14 |
| **1′b** | 10 | – | – | – | – | 13 |
| **1′c** | 16 | – | – | – | – | 17 |
| **1′d** | 17 | – | – | – | – | 16 |
| **1′e** | 19 | – | – | – | – | 19 |
| **1′f** | 17 | – | – | – | – | 18 |

Standard norfloxacin: *Escherichia coli* 28, *Bacillus subtills* 26, *Bacillus cereus* 28; standard fluconazol: *Aspergillus niger* 32, *Penicillium* species 25, *Cladosporium* species 23.

theoretically three distereoisomers (not four distereoisomers and a pair of racemates) should exist including a pair of enantiomers and a meso (optically inactive) stereomer for all these compounds. In this study, it could not be established whether entirely the meso stereomer is formed or one of the optically active enantiomers or a mixture of all the stereomers is formed. However, from the almost zero specific optical rotation values observed for these compounds, it could be summarized that either the only meso stereoisomer or almost a 50:50 racemic mixture is formed. The resolution into enantiomers in this study could not be carried on successfully and is under active study presently. The compounds **2a-e**, **2′a-e**, **3a-e**, **3′a-e**, **4a-e**, **4′a-e**, **5a-d**, and **5′a-d** were all obtained also as racemates.

**Antimicrobial activity.** Some of the compounds were screened for their antibacterial activity against *Escherichia coli*, *Bacillus sublitis*, and *Bacillus cereus* at concentration of 1000 μg and for antifungal activity against *Aspergillus niger*, Penicillium *species*, and *Cladosporium species* at the same concentration by well diffusion technique [16,17,29–33]. Standard antibacterial norfloxacin and antifungal fluconazole were also screened under similar conditions for a comparison. The zones of inhibition formed were measured [34] in millimeters and are shown in Table 1.

Antimicrobial activity of 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione (**1a-c/1′a-c)** and 7,11-diaryl-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3, 5-trione/7,11-diaryl-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9 tetraone (**1d-e/1′d-e)**.

It was interesting to observe summarily that all the compounds **1a-f** and **1′a-f** were highly effective against *E. coli* for antibacterial and *Cladosporium* species for antifungal activity and noneffective against other species.

## EXPERIMENTAL

**General.** Melting points were measured in open capillaries on perfit melting point apparatus and are incorrect. IR spectra on KBr were recorded on Brucker-4800 infrared spectrometer. NMR and EIMS/HRMS spectra were recorded on Brucker AC-400 (400 MHz and 100 MHz) and JEOL D-300 mass spectrometer, respectively. Elemental analysis was carried out on simple CHNS analyzer (CHNS-932, LECO Corporation, USA). $^{1}H$ and $^{13}C$ chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as internal standard. All experiments were performed in oven dried glass apparatus. SISCO silica was used as adsorbent for TLC (0.5 mm thick plates) and TLC plates were eluted with 1:9 ratios of ethyl acetate and *n*-hexane. The column chromatography was performed over silica gel (60–120 mesh) with graded solvent systems of ethyl acetate-pet. ether (60–80).

**General procedure for the synthesis of 1,5-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1a-f/1′a-f).** To a magnetically stirred melt of aromatic aldehyde (3 moles) and cyclic active methylene compound (cyclohexane-1,3-dione or barbituric acid) (1 mole) at (70–80°C); thiourea/urea (1 mole) and $NiCl_2$ + KI (0.1 mole) were added at this temperature. The mixture was stirred at 110°C for 6–8 h. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled at room temperature and poured onto crushed ice and again stirred for 10–20 min. The solid thus separated was filtered, washed with cold water and crystallized from ethanol to get **1a-f/1′a-f.**

***1,5-Bis-(p-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5] undecane-7,11-dione (1a).*** Yield 78%; Mp 210–212°C; IR (KBR, v, $cm^{-1}$): 1185 (C=S), 1650–1710 (C=O), 3360–3430 (NH); $^{1}H$ NMR ($CDCl_3$) δ: 2.00–2.35 (m, 6H, 3 × $CH_2$), 2.40 (s, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$, 4.99 (s, 2H, 1,5–Hs), 7.00–7.05 (m, 8H, ArHs), and 7.90–8.20 (bs, 2H, NH, $D_2O$ exchangable).

*Anal*. Calcd. for $C_{23}H_{24}N_2O_2S$: C, 70.40; H, 6.12; N, 7.14; S, 8.16. Found: C, 70.23; H, 6.14; N, 7.16; S, 8.19.

***1,5-Bis-(4-methoxyphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione (1b).*** Yield 75%; Mp 204–206°C; IR (KBR, v, $cm^{-1}$): 1180 (C=S), 1620–1700 (C=O), 3350–3420 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.90–2.30 (m, 6H, 3 × $CH_2$), 3.70 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 4.90 (s, 2H, 1,5–Hs), 6.75–7.05 (m, 8H, ArHs), and 7.88–8.00 (bs, 2H, NH); $^{13}C$ NMR δ: 16.2, 38.5, 47.8, 56.1, 90.5, 114.0, 129.1, 131.0, 159.2, 163.1, 211.1. *Anal*. Calcd. for $C_{23}H_{24}N_2O_4S$: C, 65.09; H, 5.66; N, 6.60; S, 7.54. Found: C, 64.91; H, 5.68; N, 6.53; S, 7.59.

***1,5-Bis-(3,4-dimethoxyphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7,11-dione (1c).*** Yield 75%; Mp 230–232°C; IR (KBR, v, $cm^{-1}$): 1178 (C=S), 1670–1705 (C=O), 3290–3430 (NH); $^1H$ NMR($CDCl_3$) δ: 1.95–2.35 (m, 6H, 3 × $CH_2$), 3.65 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.75 (s, 3H,$OCH_3$), 4.87 (s, 2H, 1,5-H), 6.60–6.90 (m, 6H, ArHs) and 7.82–8.01 (bs, 2H, NH); $^{13}C$ NMR δ: 16.4, 38.3, 48.9, 56.1, 90.0, 114.8, 123.5, 130.8, 152.5, 170.1, 211.4. *Anal*. Calcd. for $C_{25}H_{28}N_2O_6S$: C, 61.98; H, 5.78; N, 5.78; S, 6.61. Found: C, 61.80; H, 5.80; N, 5.82; S, 6.55.

***7,11-Bis-(p-methylphenyl)-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione (1d).*** Yield 77%; Mp 240–242°C; IR (KBR, v, $cm^{-1}$): 1175 (C=S), 1670–1705 (C=O), 3290–3430 (NH); $^1H$ NMR ($CDCl_3$) δ: 2.25 (s, 3H, CH3), 2.30 (s, 3H, CH3), 5.29 (s, 2H, 7, 11–Hs), 7.10–7.20 (m, 8H, ArHs), and 7.89–8.20 (bs, 4H, NH). *Anal*. Calcd. for $C_{21}H_{20}N_4O_3S$: C, 61.76; H, 4.90; N, 13.72; S, 7.84. Found: C, 61.58; H, 4.91; N, 13.75; S, 7.73.

***7,11-Bis-(4-methoxyphenyl)-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione (1e).*** Yield 82%; Mp 234–236°C; IR (KBR, v, $cm^{-1}$): 1182 (C=S), 1660–1700 (C=O), 3280–3425 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.72 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 5.27 (s, 2H, 7, 11–Hs), 6.90–7.10 (m, 8H, ArHs), and 7.87–8.22 (bs, 4H, NH); $^{13}C$ NMR δ: 52.2, 56.8, 72.5, 114.3, 122.8, 132.4, 140.5, 146.0, 150.2, 151.7, 163.0, 176.8. *Anal*. Calcd. for $C_{21}H_{20}N_4O_5S$: C, 57.27; H, 4.54; N, 12.72; S, 7.27. Found: C, 57.09; H, 4.55; N, 12.75; S, 7.23.

***7,11-Bis-(3,4-dimethoxyphenyl)-9-thioxo-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5-trione (1f).*** Yield 86%; Mp 244–246°C; IR (KBR, v, $cm^{-1}$): 1180 (C=S), 1665–1700 (C=O), 3270–3420 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.68 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 5.25 (s, 2H, 7,11-H), 6.67–6.90 (m, 6H, ArHs), and 7.89–8.90 (bs,4H,NH); $^{13}C$ NMR δ: 52.4, 56.2, 71.4, 114.7, 115.0, 121.8, 132.2, 139.2, 144.7, 147.5, 163.1, 176.1. *Anal*. Calcd. for $C_{23}H_{24}N_4O_7S$: C, 55.20; H, 4.8; N, 11.2; S, 6.4. Found: C, 55.01; H, 5.0; N, 11.5; S, 6.9.

***1,5-Bis-(p-methylphenyl)-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1′a).*** Yield 90%; Mp 212–214°C; IR (KBR, v, $cm^{-1}$): 1660–1700 (C=O), 3382–3470 (NH). $^1H$ NMR ($CDCl_3$) δ: 2.10–2.25 (m, 6H, 3 × $CH_2$), 2.43 (s, 3H, CH3), 2.45 (s, 3H, $CH_3$), 4.87–5.01 (s, 2H, 1,5–Hs), 6.95–7.10 (m, 8H, ArHs), and 7.80–8.15 (bs, 2H, NH). *Anal*. Calcd. for $C_{23}H_{24}N_2O_3$: C, 73.40; H, 6.38; N, 7.44. Found: C, 73.21; H, 6.40; N, 7.38.

***1,5-Bis-(4-methoxyphenyl)-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1′b).*** Yield 80%; Mp 210–211°C; IR (KBR, v, $cm^{-1}$): 1675–1710 (C=O), 3370–3430 (NH); $^1H$ NMR ($CDCl_3$) δ: 2.15–2.30 (m, 6H, 3 × $CH_2$), 3.55 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.97 (s, 2H, 1,5–Hs), 6.90–7.15 (m, 8H, ArHs), and 7.85–8.20 (bs, 2H, NH); $^{13}C$ NMR δ: 15.5, 40.5, 44.8, 59.7, 92.4, 119.7, 139.3, 142.0, 165.2, 167.6, 218.9. *Anal*. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.64; H, 5.88; N, 6.86. Found: C, 67.46; H, 5.90; N, 6.74.

***1,5-Bis-(3,4-dimethoxyphenyl)-2,4-diazaspiro[5.5]undecane-3,7,11-trione (1′c).*** Yield 87%; Mp 232–234°C; IR (KBR, v, $cm^{-1}$): 1670–1705 (C=O), 3390–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 2.00–2.10 (m, 6H, 3 × $CH_2$), 3.60 (s, 3H, $OCH_3$), 3.64 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 4.83 (s, 2H, 1,5-H), 6.82–7.10 (m, 6H, ArHs), and 7.80–8.15 (bs, 2H, NH); $^{13}C$ NMR δ: 16.2, 38.5, 49.1, 56.3, 90.3, 115.2, 122.5, 131.4, 147.8, 154.3, 211.2. *Anal*. Calcd. for $C_{25}H_{28}N_2O_7$: C, 64.10; H, 5.98; N, 5.98. Found: C, 63.92; H, 5.96; N, 5.91.

***7,11-Bis-(p-methylphenyl)-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9-tetraone (1′d).*** Yield 80%; Mp 246–248°C; IR (KBR, v, $cm^{-1}$): 1672–1710 (C=O), 3380–3460 (NH); $^1H$ NMR ($CDCl_3$) δ: 2.20 (s, 3H, CH3), 2.25 (s, 3H, CH3), 5.15 (s, 2H, 7, 11–Hs), 7.00–7.10 (m, 8H, ArHs), and 7.80–8.15 (bs, 4H, NH). *Anal*. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.10; N, 14.28. Found: C, 64.10; H, 5.12; N, 14.25.

***7,11-Bis-(4-methoxyphenyl)-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9-tetraone (1′e).*** Yield 90%; Mp 240–242°C; IR (KBR, v, $cm^{-1}$): 1680–1720 (C=O), 3270–3420 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.70 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 5.20 (s, 2H, 7, 11–Hs), 6.80–7.20 (m, 8H, ArHs), and 7.82–8.20 (bs, 4H, NH). *Anal*. Calcd. for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.71; N, 13.20. Found: C, 59.25; H, 4.72; N, 13.14.

***7,11-Bis-(3,4-dimethoxyphenyl)-2,4,8,10-tetrazaspiro[5.5]undecane-1,3,5,9-tetraone (1′f).*** Yield 87%; Mp 250–252°C; IR (KBR, v, $cm^{-1}$): 1675–1710 (C=O), 3280–3450 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.65 (s, 3H, $OCH_3$), 3.68 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 5.15 (s, 2H, 7,11-H), 6.87–7.10 (m, 6H, ArHs), and 7.60–8.40 (bs, 4H, NH); $^{13}C$ NMR δ: 55.6, 59.8, 86.4, 118.2, 120.0, 128.8, 138.9, 140.7, 148.8, 150.8, 163.9, 180.1. *Anal*. Calcd. for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.95; N, 11.57. Found: C, 56.84; H, 4.97; N, 11.61.

**General procedure for the synthesis of 5-aryl-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one/5-aryl-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2a-e/2′a-e).** These heterocycles were prepared by following the same procedure as mentioned for (**1a-f/1′a-f**) by condensing appropriate aromatic aldehyde, thiourea/urea, and 2-acetylcyclohexanone in the mole ratio of 1:1:1 simply by stirring at 100–110°C for 6 h without using any solvent and catalyst. The work of the reaction was done as usual by pouring ice cold water on to the reaction mixture residue. The spectral characterizations of the synthesized compounds are as follows:

***1-Methyl-5-phenyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2a).*** Yield 77%; Mp 170–172°C; IR (KBR, v, $cm^{-1}$): 1180 (C=S), 1680–1700 (C=O), 3420 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.32 (s, 3H, CH3), 1.95–2.30 (m, 8H, 4 × $CH_2$), 5.26 (s, 1H, 5-H), 7.01–7.03 (m, 5H, ArHs), and 9.01 (bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.13; H, 6.29; N, 9.79; S, 11.18. Found: C, 66.92; H, 6.30; N, 9.84; S, 11.23.

***1-Methyl-5-(p-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2b).*** Yield 74%; Mp 178–180°C; IR (KBR, v, $cm^{-1}$): 1175 (C=S), 1670–1690 (C=O), 3410 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.30 (s, 3H, CH3), 1.90–2.30 (m, 8H, 4 × $CH_2$), 5.20 (s, 1H, H-5), 7.01–7.01 (m, 4H, ArHs), and 9.01

(bs, 1H, NH);$^{13}$C NMR δ: 12.2, 20.6, 22.1, 27.4, 36.9, 38.2, 45.1, 62.0, 128.0, 129.2, 134.7, 136.2, 164.4, 175.0, 211.2. *Anal*. Calcd. for $C_{17}H_{20}N_2OS$: C, 68.0; H, 6.66; N, 9.33; S, 10.66. Found: C, 67.79; H, 6.68; N, 9.35; S, 10.69.

***5-(4-Methoxyphenyl)-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2c).*** Yield 70%; Mp 184–186°C; IR (KBR, v, $cm^{-1}$): 1182 (C=S), 1665–1695 (C=O), 3415 (NH); $^1$H NMR ($CDCl_3$) δ: 1.22 (s, 3H, $CH_3$), 1.79–2.25 (m, 8H, 4 × $CH_2$), 3.70 (s, 3H, $OCH_3$), 5.18 (s, 1H, H-5), 6.98–7.01 (m, 4H, ArHs), and 8.90 (bs, 1H, NH). *Anal*. Calcd. for $C_{17}H_{20}N_2O_2S$: C, 64.55; H, 6.32; N, 8.86; S, 10.12. Found: C, 64.36; H, 6.34; N, 8.89; S, 10.15.

***5-(3,4-Dimethoxyphenyl)-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2d).*** Yield 72%; Mp 192–193°C; IR (KBR, v, $cm^{-1}$): 1178 (C=S), 1680–1700 (C=O), 3400 (NH); $^1$H NMR ($CDCl_3$) δ: 1.15 (s, 3H, $CH_3$), 1.74–2.29 (m, 8H, 4 × $CH_2$), 3.62 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 5.15 (s, 1H, H-5), 6.98–7.00 (m, 3H, ArHs), and 8.75 (bs, 1H, NH). *Anal*. Calcd. for $C_{18}H_{22}N_2O_3S$: C, 62.42; H, 6.35; N, 8.09; S, 9.24. Found: C, 62.24; H, 6.37; N, 8.14; S, 9.28.

***5-(p-Chlorophenyl)-1-methyl-3-thioxo-2,4-diazaspiro[5.5]undec-1-en-7-one (2e).*** Yield 74%; Mp 220–222°C; IR (KBR, v, $cm^{-1}$): 1180 (C=S), 1650–1690 (C=O), 3380 (NH); $^1$H NMR ($CDCl_3$) δ: 1.25 (s, 3H, CH3), 1.80–2.20 (m, 8H, 4 × $CH_2$), 5.29 (s, 1H, H-5), 7.05–7.25 (m, 4H, ArHs), and 9.05 (bs, 1H, NH);$^{13}$C NMR δ: 12.8, 22.2, 27.8, 38.6, 39.2, 45.2, 50.2, 128.7, 131.0, 137.5, 164.4, 173.8, 211.5. *Anal*. Calcd. for $C_{16}H_{17}N_2OSCl$: C, 59.90; H, 5.30; N, 8.73; S, 9.98. Found: C, 59.71; H, 5.32; N, 8.79; S, 9.95.

***1-Methyl-5-phenyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′a).*** Yield 77%; Mp 172–174°C; IR (KBR, v, $cm^{-1}$): 1660–1705 (C=O), 3470 (NH); $^1$H NMR ($CDCl_3$) δ: 1.32 (s, 3H, $CH_3$), 1.80–2.05 (m, 8H, 4 × $CH_2$), 5.76 (s, 1H, 5-H), 7.41–7.83 (m, 5H, ArHs), and 9.11 (bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.66; N, 10.37. Found: C, 71.19; H, 6.62; N, 10.40.

***1-Methyl-5-(p-methylphenyl)-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′b).*** Yield 76%; Mp 180–182°C; IR (KBR, v, $cm^{-1}$): 1670–1700 (C=O), 3466 (NH); $^1$H NMR ($CDCl_3$) δ: 1.20 (s, 3H, $CH_3$), 1.95–2.20 (m, 8H, 4 × $CH_2$), 4.90 (s, 1H, H-5), 6.90–7.21 (m, 4H, ArHs), and 9.28 (bs, 1H, NH); $^{13}$C NMR δ: 15.2, 22.8, 27.8, 30.4, 34.8, 38.9, 46.2, 60.2, 126.0, 128.1, 139.5, 149.8, 169.8, 185.8, 230.2**.** *Anal*. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.85. Found: C, 71.64; H, 7.06; N, 9.80.

***5-(4-Methoxyphenyl)-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′c).*** Yield 74%; Mp 189–191°C; IR (KBR, v, $cm^{-1}$): 1675–1692 (C=O), 3410 (NH); $^1$H NMR ($CDCl_3$) δ: 1.32 (s, 3H, $CH_3$), 2.10–2.25 (m, 8H, 4 × $CH_2$), 3.72 (s, 3H, $OCH_3$), 4.95 (s, 1H, H-5), 6.90–7.00 (m, 4H, ArHs), and 8.72 (bs, 1H, NH). *Anal*. Calcd. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.6; N, 9.33. Found: C, 67.82; H, 6.8; N, 9.38.

***5-(3,4-Dimethoxyphenyl)-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′d).*** Yield 76%; Mp 191–201°C; IR (KBR, v, $cm^{-1}$): 1690–1710 (C=O), 3410 (NH); $^1$H NMR ($CDCl_3$) δ: 1.15 (s, 3H, $CH_3$), 2.05–2.29 (m, 8H, 4 × $CH_2$), 3.7 0 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 5.05 (s, 1H, H-5), 6.88–7.10 (m, 3H, ArHs), and 8.76 (bs, 1H, NH). *Anal*. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.45; H, 6.66; N, 8.48. Found: C, 65.27; H, 6.68; N, 8.54.

***5-(p-Chlorophenyl)-1-methyl-2,4-diazaspiro[5.5]undec-1-ene-3,7-dione (2′e).*** Yield 72%; Mp 221–223°C; IR (KBR, v, $cm^{-1}$): 1670–1700 (C=O), 3420 (NH); $^1$H NMR ($CDCl_3$) δ: 1.30 (s, 3H, $CH_3$), 1.70–2.10 (m, 8H, 4 × $CH_2$), 4.99 (s, 1H, H-5), 7.00–7.25 (m, 4H, ArHs), and 8.90 (bs, 1H, NH); $^{13}$C NMR δ: 15.7, 25.8, 28.9, 39.9, 40.5, 50.8, 54.8, 130.2, 134.6, 150.3, 168.4, 178.8, 220.4. Anal. Calcd. for $C_{16}H_{17}N_2O_2Cl$: C, 63.05; H, 5.58; N, 9.19. Found: C, 62.87; H, 5.59; N, 9.24.

**General procedure for the synthesis of reduced 4-aryl/heteroaryl-2-thioxo-quinazolin-5-one, 4-aryl/heteroaryl-quinazoline-2,5-dione (3a-e/3′a-e), 4-aryl/heteroaryl quinazoline-2-thione/4-aryl/heteroaryl-quinazolin-2-one (4a-e/4′a-e), and 5-aryl-7-thioxo pyrimidopyrimidine-2,4-dione/5-aryl-pyrimidopyrimidine-2,4,7-trione (5a–d/5′a-d).** A highly grinded and finally powdered homogeneous trinary mixture of appropriate aromatic/hetero aromatic aldehyde (1 mole), thiourea/urea (1 mole), and cyclohexane-1,3-dione/cyclohexanone/barbituric acid (1 mole) in 70–80 mL of methanol was refluxed for 10–12 h. After the completion of reaction as monitored by TLC, the reaction mixture was concentrated to one-third of its volume and was then poured onto ice cold water. The precipitate separated out, filtered, washed, dried, and further recrystallized from ethanol to get the required product.

***4-(p-Methylphenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3a).*** Yield 80%; Mp 225–227°C; IR (KBR, v, $cm^{-1}$): 1172 (C=S), 1692 (C=O), 3430–3442 (NH); $^1$H NMR ($CDCl_3$) δ: 1.60–2.38 (m, 6H, 3 × $CH_2$), 2.30 (s, 3H, CH3), 4.89 (s, 1H, 4–H), 7.02–7.24 (m, 4H, ArHs), 7.80 (bs, 1H, NH), and 9.60 (bs, 1H, NH); $^{13}$C NMR δ: 16.8, 22.4, 26.8, 34.6, 50.2, 115.3, 116.8, 118.2, 118.9, 124.6, 130.4, 135.3, 144.8, 160.6, 197.2. *Anal*. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.66; H, 5.88; N, 10.29; S, 11.76. Found: C, 66.48; H, 5.85; N, 10.29; S, 11.73.

***4-(4-Methoxyphenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3b).*** Yield 78%; Mp 249–251°C; IR (KBR, v, $cm^{-1}$): 1190 (C=S), 1620 (C=O), 3435–3445 (NH); $^1$H NMR ($CDCl_3$) δ: 1.45–2.30 (m, 6H, 3 × $CH_2$), 3.73 (s, 3H, $OCH_3$), 4.74 (s, 1H, 4–H), 6.90–7.21 (m, 4H, ArHs), 7.72 (bs, 1H, NH), and 9.56 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.50; H, 5.55; N, 9.72; S, 11.11. Found: C, 62.34; H, 5.59; N, 9.69; S, 11.08.

***4-(3,4-Dimethoxyphenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3c).*** Yield 76%; Mp 240–242°C; IR (KBR, v, $cm^{-1}$): 1178 (C=S), 1620 (C=O), 3435–3445 (NH); $^1$H NMR ($CDCl_3$) δ: 1.40–2.20 (m, 6H, 3 × $CH_2$), 3.70 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.70 (s, 1H, 4–H), 6.90–7.25 (m, 3H, ArHs), 7.72 (bs, 1H, NH), 9.55 (s, 1H, NH); $^{13}$C NMRδ: 16.8, 34.6, 40.6, 48.1, 56.1, 113.4, 114.2, 114.7, 120.6, 135.5, 142.2, 145.4, 147.2, 156.6, 197.4. *Anal*. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.37; H, 5.6; N, 8.58; S, 10.06. Found: C, 60.19; H, 5.7; N, 8.55; S, 10.03.

***4-(Indol-3-yl)-2-thioxo–1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3d).*** Yield 74%; Mp 253–257°C; IR (KBR, v, $cm^{-1}$): 1180 (C=S), 1680 (C=O), 3390–3445 (NH); $^1$H NMR ($CDCl_3$) δ: 1.70–2.46 (m, 6H, 3 × $CH_2$), 5.65 (s, 1H, 4–H), 7.04–8.29 (m, 5H, ArHs), 8.59 (s, 1H, exch. NH), 9.41 (s, 1H, NH), and 10.92 (s, 1H, exch. NH); $^{13}$C NMR δ: 19.8, 34.6, 40.2, 52.6, 111.0, 111.2, 112.3, 119.2, 120.2, 121.3, 122.5,

131.4, 136.2, 155.8, 178.0, and 198.0. *Anal*. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.64; H, 5.0; N, 14.14; S, 10.77. Found: C, 64.46; H, 5.2; N, 14.16; S, 10.74.

***4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (3e).*** Yield 72%; Mp 255–257°C; IR (KBR, v, $cm^{-1}$): 1182 (C=S), 1680 (C=O), 3435–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.85–2.45 (m, 6H, 3 × $CH_2$), 5.52 (s, 1H, 4–H), 7.01–7.80 (m, 10H, ArHs), 7.84 (s, 1H, 5′H), 7.90 (s, 1H, NH), 10.80 (s, 1H, NH); $^{13}C$ NMR δ: 20.0, 35.6, 40.9, 45.2, 111.6, 117.8, 126.0, 128.4, 129.2, 139.8, 155.4, 157.2, 178.4, 197.7. *Anal*. Calcd. for $C_{23}H_{20}N_4OS$: C, 69.0; H, 5.0; N, 14.0; S, 8.0. Found: C, 68.83; H, 5.2; N, 13.96; S, 8.5.

***4-(p-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2 5-dione (3′a).*** Yield 82%; Mp 222–223°C; IR (KBR, v, $cm^{-1}$): 1660 (C=O), 3430–3442 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.48–2.20 (m, 6H, 3 × $CH_2$), 2.35 (s, 3H, CH3), 4.89 (s, 1H, 4–H), 6.98–7.40 (m, 4H, ArHs), 7.70 (bs, 1H, NH), and 9.55 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.93. Found: C, 70.12; H, 6.23; N, 10.91.

***4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′b).*** Yield 74%; Mp 230–232°C; IR (KBR, v, $cm^{-1}$): 16,700 (C=O), 3432–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.40–2.15 (m, 6H, 3 × $CH_2$), 3.71 (s, 3H, $OCH_3$), 4.80 (s, 1H, 4–H), 6.92–7.20 (m, 4H, ArHs), 7.70 (bs, 1H, NH), and 9.58 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.17; H, 5.8; N, 10.29. Found: C, 65.98; H, 5.6; N, 10.26.

***4-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′c).*** Yield 80%; Mp 241–243°C; IR (KBR, v, $cm^{-1}$): 1675 (C=O), 3460–3442 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.60–2.40 (m, 6H, 3 × $CH_2$), 3.72 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 5.05 (s, 1H, 4–H), 7.05–7.15 (m, 3H, ArHs), 7.70 (bs, 1H, NH), 9.45 (s, 1H, NH); $^{13}C$ NMR δ: 15.2, 38.6, 44.8, 50.1, 58.2, 115.7, 120.7, 122.8, 130.6, 140.5, 148.2, 150.5, 155.2, 158.9, 200.7. *Anal*. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.38; H, 5.98; N, 9.24.

***4-(Indol-3-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′d).*** Yield 76%; Mp 256–258°C; IR (KBR, v, $cm^{-1}$): 1685 (C=O), 3370–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.90–2.30 (m, 6H, 3 × $CH_2$), 5.25 (s, 1H, 4–H), 7.10–7.25 (m, 5H, ArHs), 7.92 (s, 1H, exch. NH), 9.42 (s, 1H, NH), and 10.82 (s, 1H, exch. NH); $^{13}C$ NMR δ: 18.9, 38.9, 42.5, 55.6, 118.0, 120.2, 126.9, 129.2, 130.5, 132.3, 136.5, 139.4, 140.2, 158.8, 188.0, 200.8. *Anal*. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.33; N, 14.94. Found: C, 68.14; H, 5.31; N, 14.90.

***4-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (3′e).*** Yield 72%; Mp 256–258°C; IR (KBR, v, $cm^{-1}$): 1620 (C=O), 3435–3445 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.95–2.40 (m, 6H, 3 × $CH_2$), 5.25 (s, 1H, 4–H), 7.00–7.60 (m, 10H, ArHs), 7.65 (s, 1H, 5′H), 9.80 (s, 1H, NH), 10.65 (s, 1H, NH); $^{13}C$ NMR δ: 20.8, 34.2, 42.9, 45.8, 115.6, 118.5, 122.0, 125.4, 130.2, 135.8, 145.4, 155.2, 180.7, 199.8. *Anal*. Calcd. for $C_{23}H_{20}N_4O_2$: C, 71.87; H, 5.20; N, 14.58. Found: C, 71.79; H, 5.21; N, 14.53.

***4-(p-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4a).*** Yield 75%; Mp 228–230°C; IR (KBR, v, $cm^{-1}$): 1181 (C=S), 3438–3445 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.62–2.32 (m, 8H, 4 × $CH_2$), 2.35 (s, 3H, $CH_3$), 4.86 (s, 1H, 4–H), 7.02–7.20 (m, 4H, ArHs), 7.90 (bs, 1H, NH), and 10.7 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2S$: C, 69.76; H, 6.9; N, 10.85; S, 12.40. Found: C, 69.68; H, 7.1; N, 10.81; S, 12.20.

***4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4b).*** Yield 77%; Mp 256–258°C; IR (KBR, v, $cm^{-1}$): 1168 (C=S), 3398–3442 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.42–2.32 (m, 8H, 4 × $CH_2$), 3.71 (s, 3H, $OCH_3$), 4.70 (s, 1H, 4–H), 6.92–7.23 (m, 4H, ArHs), 7.70 (bs, 1H, NH), and 9.52 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2OS$: C, 65.69; H, 6.56; N, 10.21; S, 11.67. Found: C, 65.51; H, 6.55; N, 10.23; S, 11.70.

***4-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4c).*** Yield 78%; Mp 256–258°C; IR (KBR, v, $cm^{-1}$): 1175 (C=S), 3435–3445 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.40–2.20 (m, 8H, 4 × $CH_2$), 3.70 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.70 (s, 1H, 4–H), 6.90–7.25 (m, 3H, ArHs), 7.72 (bs, 1H, NH), and 9.55 (bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.15; H, 6.57; N, 9.2; S, 10.52. Found: C, 62.96; H, 6.59; N, 9.0; S, 10.59.

***4-(Indol-3-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4d).*** Yield 72%; Mp 254–256°C; IR (KBR, v, $cm^{-1}$): 1172 (C=S), 3367–3445 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.72–2.41 (m, 8H, 4 × $CH_2$), 5.60 (s, 1H, 4–H), 7.8–8.20 (m, 5H, ArHs), 8.50 (s, 1H, exch. NH), 9.31 (s, 1H, NH), and 10.23 (s, 1H, exch. NH). *Anal*. Calcd. for $C_{16}H_{17}N_3S$: C, 67.84; H, 6.0; N, 14.84; S, 11.30. Found: C, 67.66; H, 6.2; N, 14.89; S, 11.35.

***4-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (4e).*** Yield 76%; Mp 260–262°C; IR (KBR, v, $cm^{-1}$): 1185 (C=S), 3440–3445 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.92–2.43 (m, 8H, 4 × $CH_2$), 5.56 (s, 1H, 4–H), 7.02–7.82 (m, 11H, ArHs and 5′H),7.92 (s, 1H, exch. NH), and 10.83 (s, 1H, exch. NH); $^{13}C$ NMR δ: 21.3, 25.8, 32.2, 38.4, 46.3, 112.2, 115.7, 126.3, 128.3, 129.8, 139.3, 152.8, 157.1, 178.3. *Anal*. Calcd. for $C_{23}H_{22}N_4S$: C, 74.09; H, 5.69; N, 14.50; S, 8.29. Found: C, 73.92; H, 5.7; N, 14.59; S, 8.24.

***4-(p-Methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′a).*** Yield 78%; Mp 225–227°C; IR (KBR, v, $cm^{-1}$): 1678 (C=O), 3338–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.72–2.30 (m, 8H, 4 × $CH_2$), 2.30 (s, 3H, $CH_3$), 4.96 (s, 1H, 4–H), 7.00–7.10 (m, 4H, ArHs), 7.95 (bs, 1H, NH), and 10.2 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2O$: C, 74.38; H, 7.43; N, 11.57. Found: C, 74.18; H, 7.45; N, 10.62.

***4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′b).*** Yield 75%; Mp 251–253°C; IR (KBR, v, $cm^{-1}$): 1670 (C=O), 3394–3435 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.70–2.31 (m, 8H, 4 × $CH_2$), 3.73 (s, 3H, $OCH_3$), 4.85 (s, 1H, 4–H), 7.00–7.23 (m, 4H, ArHs), 7.85 (bs, 1H, NH), and 10.5 (bs, 1H, NH). *Anal*. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.76; H, 6.97; N, 1 0.85. Found: C, 69.68; H, 6.99; N, 10.92.

***4-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′c).*** Yield 80%; Mp 252–254°C; IR (KBR, v, $cm^{-1}$): 1675 (C=O), 3490–3443 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.70–2.25 (m, 8H, 4 × $CH_2$), 3.72 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 4.90 (s, 1H, 4–H), 7.10–7.25 (m, 3H, ArHs), 7.82 (bs, 1H, NH), and 10.2(bs, 1H, NH). *Anal*. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.66; H, 6.94; N, 9.72. Found: C, 66.48; H, 6.96; N, 9.68.

***4-(Indol-3-yl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′d).*** Yield 78%; Mp 255–257°C; IR (KBR, v, $cm^{-1}$): 1670 (C=O), 3490–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.72–2.21 (m, 8H, 4 × $CH_2$), 5.70 (s, 1H, 4–H), 7.7–8.10 (m, 5H, ArHs), 8.65 (s, 1H, exch. NH), 9.85 (s, 1H, NH), and 10.82 (s, 1H, exch. NH). *Anal*. Calcd. for $C_{16}H_{17}N_3O$: C, 71.91; H, 6.36; N, 15.73. Found: C, 71.72; H, 6.38; N, 15.79.

***4-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,2,3,4,5,6,7,8-octahydroquinazolin-2-one (4′e).*** Yield 78%; Mp 264–266°C; IR (KBR, v, $cm^{-1}$): 1676 (C=O), 3480–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 1.70–2.25 (m, 8H, 4 × $CH_2$), 5.85 (s, 1H, 4–H), 7.10–8.20 (m, 11H, ArHs and 5′H), 8.50 (s, 1H, exch. NH), and 10.70 (s, 1H, exch. NH). *Anal*. Calcd. for $C_{23}H_{22}N_4O$: C, 74.59; H, 5.94; N, 15.13. Found: C, 72.78; H, 5.95; N, 15.15.

***5-Phenyl-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5a).*** Yield 72%; Mp 228–230°C; IR (KBR, v, $cm^{-1}$): 1178 (C=S), 1665–1710 (C=O), 3310–3450 (NH); $^1H$ NMR ($CDCl_3$) δ: 5.20 (s, 1H, 5–H), 7.10–7.21 (m, 5H, ArHs), 8.82–8.98 (bs, 2H, NH at 1, 8), 9.56 (bs, 1H, NH at 3), and 10.54 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.64; N, 20.43; S, 11.67. Found: C, 52.38; H, 3.60; N, 20.36; S, 11.61.

***5-(4-Methoxyphenyl)-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5b).*** Yield 77%; Mp 232–234°C; IR (KBR, v, $cm^{-1}$): 1182 (C=S), 1670–1708 (C=O), 3410–3452 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.73 (s, 3H, $OCH_3$), 5.30 (s, 1H, 5–H), 6.70–7.20 (m, 4H, ArHs), 8.72–9.12 (bs, 2H, NH at 1, 8), 9.62 (bs, 1H, NH at 3), and 10.55 (bs, 1H, NH at 6); $^{13}C$ NMR δ: 47.4, 56.1, 85.7, 113.7, 126.4, 130.6, 142.6, 153.5, 155.8, 162.0, 165.5. *Anal*. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.94; N, 18.42; S, 10.52. Found: C, 51.12; H, 3.96; N, 18.33; S, 11.02.

***5-(4-Methylphenyl)-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5c).*** Yield 82%; Mp 254–256°C; IR (KBR, v, $cm^{-1}$): 1187 (C=S), 1675–1700 (C=O), 3380–3410 (NH); $^1H$ NMR ($CDCl_3$) δ: 2.22 (s, 3H, CH3), 4.93 (s, 1H, 5–H), 6.98–7.42 (m, 4H, ArHs), 8.80–9.00 (bs, 2H, NH at 1, 8), 9.51 (bs, 1H, NH at 3), and 10.58 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.16; H, 4.16; N, 19.44; S, 11.11. Found: C, 53.98; H, 4.18; N, 19.38; S, 11.07.

***5-(3,4-Dimethoxyphenyl)-7-thioxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4-dione (5d).*** Yield 74%; Mp 271–273°C; IR (KBR, v, $cm^{-1}$): 1185 (C=S), 1660–1700 (C=O), 3320–3450 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.68 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 4.79 (s, 1H, 5–H), 6.87–7.35 (m, 3H, ArHs), 8.90–9.20 (bs, 2H, NH at 1, 8), 9.68 (bs, 1H, NH at 3), and 11.96 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.19; N, 16.76; S, 9.58. Found: C, 50.11; H, 4.21; N, 16.79; S, 9.64.

***5-Phenyl-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione (5′a).*** Yield 75%; Mp 241–243°C; IR (KBR, v, $cm^{-1}$): 1685–1710 (C=O), 3330–3440 (NH); $^1H$ NMR ($CDCl_3$) δ: 5.26 (s, 1H, 5–H), 7.05–7.25 (m, 5H, ArHs), 8.85–8.96 (bs, 2H, NH at 1, 8), 9.90 (bs, 1H, NH at 3), and 10.25 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.87; N, 21.70. Found: C, 55.62; H, 3.89; N, 7.10; S, 21.66.

***5-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydro pyrimido[4,5-d] pyrimidine-2,4,7-trione (5′b).*** Yield 80%; Mp 260–262°C; IR (KBR, v, $cm^{-1}$): 1680–1700 (C=O), 3460–3420 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.70 (s, 3H, $OCH_3$), 4.85 (s, 1H, 5–H), 6.90–7.30 (m, 4H, ArHs), 8.72–9.12 (bs, 2H, NH at 1, 8), 9.60 (bs, 1H, NH at 3) and 10.58 (bs, 1H, NH at 6); $^{13}C$ NMR δ: 45.4, 58.2, 90.7, 115.8, 128.9, 132.5, 140.5, 152.8, 156.9, 160.5, 166.8. *Anal*. Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.16; H, 4.16; N, 19.44. Found: C, 53.98; H, 4.18; N, 19.38.

***5-(4-Methylphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione (5′c).*** Yield 77%; Mp 252–254°C; IR (KBR, v, $cm^{-1}$): 1685–1700 (C=O), 3385–3420 (NH); $^1H$ NMR ($CDCl_3$) δ: 2.20 (s, 3H, $CH_3$), 4.95 (s, 1H, 5–H), 6.90–7.52 (m, 4H, ArHs), 8.85–9.00 (bs, 2H, NH at 1, 8), 9.58 (bs, 1H, NH at 3), and 10.50 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.58. Found: C, 57.17; H, 4.42; N, 20.52.

***5-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione (5′d).*** Yield 76%; Mp 270–272°C; IR (KBR, v, $cm^{-1}$): 1670–1705 (C=O), 3330–3470 (NH); $^1H$ NMR ($CDCl_3$) δ: 3.72 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 4.90 (s, 1H, 5–H), 6.85–7.30 (m, 3H, ArHs), 8.98–9.30 (bs, 2H, NH at 1, 8), 9.58 (bs, 1H, NH at 3), and 10.58 (bs, 1H, NH at 6). *Anal*. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.40; N, 16.66. Found: C, 52.65; H, 4.42; N, 16.61.

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## REFERENCES AND NOTES

[1] Zelberminto, L. G.; Estestr Nauch, B. V. Insti Permsk Univ 1964, 67, 141; Chem Abstr 1966, 64, 122220.

[2] Seth, P. K.; Parmar, S. S. Can J Pharmacol 1965, 43, 1019.

[3] Umio, S.; Kariyone, K.; Zenno, H.; Kamya, T. Jap Pat 1970, 12, 670; Chem Abstr 1968, 68, 2195.

[4] Shetty, B. V. US Pat 1970, 2, 549, 634; Chem Abstr 1971, 75, 5940.

[5] Otto, H.; Houlohan, W. W. Swiss Pat 1971, 3, 54, 499; Chem Abstr 1971, 75, 5930.

[6] Handymann, G. E. US Pat 1971, 3, 563, 990; Chem Abstr 1971, 75, 5930.

[7] Pandey, V. K.; Lolani, H. C.; Shanker, K.; Dovel, D. C. Indian Drugs 1983, 20, 315.

[8] Pandey, V. K.; Misra, D.; Shukla, S. Indian Drugs 1994, 31, 532.

[9] Pandey, V. K. Indian Drugs 1988, 26, 168.

[10] Pandey, V. K.; Pathak, L. P.; Misra, S. K. Ind J Chem 2005, 44B, 1940.

[11] (a) Shashikant, R. P.; Krishana, V. V.; Manvi, F. V.; Desai, B. G.; Bhat, A. R. Ind J Chem B 2006, 45, 1778; (b) Bhatti, H. S.; Seshadri, S. Colour Technol 2004, 120, 1019.

[12] Rossman, P.; Roche, H. L.; Nutley, N. J. The 37th Middle Atlantic Regional Meeting of the American Chemical Society, New Brunswick, NJ, 2005.

[13] Falvio, F. S.; van Meel, C. A. J. Pharmacol Exp Therap 2004, 311, 502.

[14] Nizamuddin-Mishra, M.; Srivastava, M. K.; Khan, M. H. Ind J Chem B 2001, 40, 66.

[15] Revnvak, G. G.; Kunball, S. D.; Beyer, B. G.; Di Marco, J. D.; Cucinotta-Gougoutar, J.; Malley, A. J. P.; Mecarthy, M.; Zhang, R.; Morel, S. J Med Chem 1995, 38, 119.

[16] Snider, B. B.; Shi, Z. J Org Chem B 1993, 58, 3828.

[17] Patil, A. D.; Mai, S.; Trunch, A.; Faulkner, D. J.; Carte, B.; Breen, A. L. B.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Patts, B. C. M. J Org Chem 1995, 60, 1182.

[18] Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. Tetrahedron 2000, 56, 1859.

[19] Biginelli, P. Gazz Chim Ital 1893, 23, 360.
[20] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.
[21] Hu, E. H.; Sidler, D. R.; Dolling, U. H. J Org Chem 1998, 63, 3454.
[22] Ranu, B. C.; Hajra, A.; Jana, U. J Org Chem 2000, 65, 6270.
[23] Ramalinga, K.; Vijayalakshmi, P.; Kaimala, T. N. B. Synlett 2000, 863.
[24] Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. Synthesis 2001, 9, 1341.
[25] Yadav, J. S.; Reddy, B. V. S.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. Eur J Org Chem 2004, 41, 552.
[26] Lu, J.; Ma, H. Synlett 2000, 63.
[27] (a) Arfan, A.; Paquin, L.; Bazureau, J. P. Russian J Org Chem 2007, 43, 1058; (b) Legeay, J. C.; Eynde, J. J. V.; Bazureau, J. P. Tetrahedron 2005, 61, 12386.
[28] Saini, A.; Kumar, S.; Sandhu, J. S. Ind J Chem B 2004, 43, 2482.
[29] Anonymous. Phytopathology 1943, 33, 627.
[30] Horsfall, J. G.; Rich, S. Ind Phytopath 1953, 6, 1.
[31] Vincent, J. C.; Vincent, H. W. Proc Soc Expt Bio Med 1944, 55, 162.
[32] Wooley, R. E.; Blue, J. L. J Med Microbiol 1975, 8, 189.
[33] Gould, J. C. Br Med Bull 1960, 16, 29.
[34] Thornberry, H. H. Phyto-Pathol 1950, 40, 419.

# Facile and One Pot Synthetic Routes for Various Novel, Differently Fused and Promising Heteropolycycles

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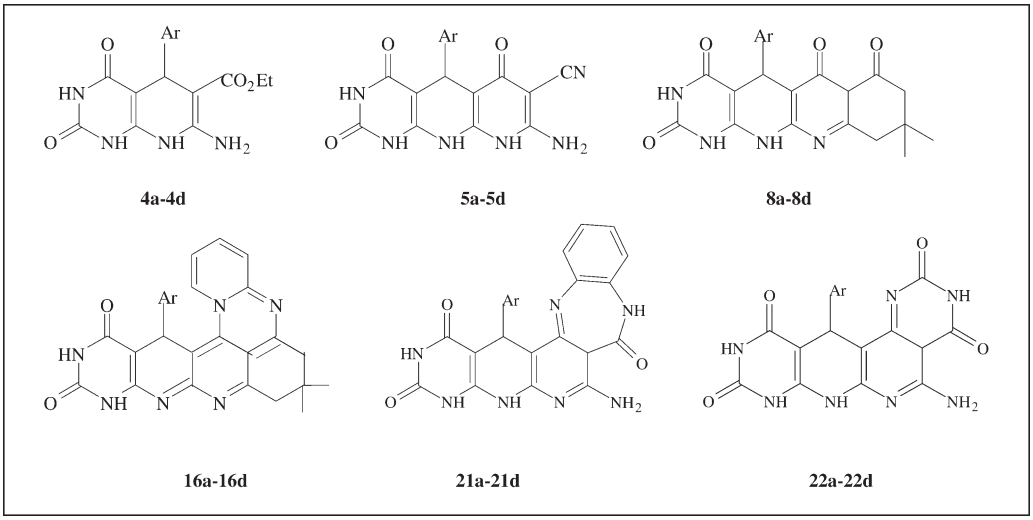


Four-component one pot cyclocondensation of aromatic aldehydes 1, ethyl cyanoacetate 2, barbituric acid 3 and ammonium acetate in methanol gave substituted and functionalised pyrido[2,3-d]pyrimidine derivatives 4 and 4′ after initial Knoevenagel, subsequent Micheal and final heterocyclization reactions. Compounds 4 on reaction with different active methylene compounds resulted in the formation of again functionalized and diversly substituted pyrimidonaphthyridines 5-7, 9 and benzo[b] pyrimidonaphthyridines 8. The various compounds of systems 7 and 8 on further condensation with the reactive and mostly the bifunctional moieties like urea/thiourea, and 2-aminopyridine generated the novel and differently fused dipyrimidonaphthyridines 10/11 and pyrimidonaphthyridinoquinazolines 13/14, and pyrido-pyrimido- pyrimido[1,8]naphthyridines 15 and pyrimidonaphthyridino- pyridoquinazolines 16, respectively, hitherto unknown in literature. Compounds 7 on condensation with *o*-phenylenediamine produced novel pyrimidonaphthyridinobenzodiazepines 12. Other novel systems like pyrido[2,3-d;6,5-d′]dipyrimidines 17, dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines 18, 1,3,4,6,7,8,9,11-octazabenzo[de]-naphthacenes 19, dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines 20, pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3-b][1,5]benzodiazepines 21, dipyrimido[4,5-b:4′,5′-f][1,8]naphthyridines 22 and dipyrimido [4,5-b:5′,4′-g][1,8] naphthyridines 23 have also been generated in this study.

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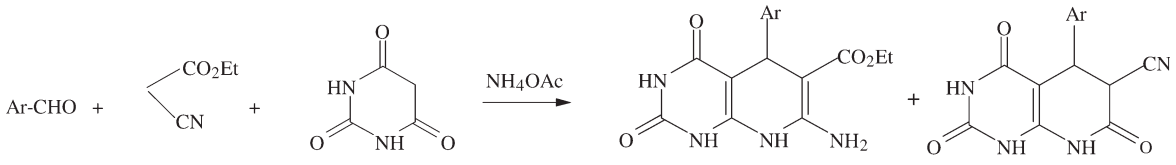
## INTRODUCTION

The benzodiazepines are a class of drugs with hypnotic [1], anxiolytic, anticonvulsant, amnestic, and muscle relaxant properties. They serve as cholecystokinin A and B antagonists [2], opioid receptor ligands [3], platelet-activating factor antagonists [4], HIV inhibitors [5], and farnesyltransferase inhibitors [6]. Benzodiazepines [7] can be used in anxiety disorders, insomnia, involuntary movement disorders, and in detoxification from alcohol and other substances. The pyridopyrimidines are very popularly and widely known compounds as a consequence of their activity against a variety of pathogenic bacteria and have potential activity such as antipyretic, diuretic, bacteriostatic, sedative, and coronary dilating agents [8]. The chemical transformations of the pyridopyrimidine ring system by the introduction and assemblage of different substituents and heterocyclic rings in fused form have allowed expansion of the research to the structure activity relationship to afford new insight into the molecular interactions at the receptor level. Many heterocyclic compounds having pyrido-pyrimidine nucleus are also known to have a wide range of biological activities [9]. Condensed system having 1,8-naphthyridine and a pyrimidine nucleus constitutes a

**Scheme 1**




**1** **2** **3** **4a-4d** **4′a-4′d**

**a;** Ar = 4-CH $_3$O-$C_6H_4$
**b;** Ar = 3,4-(CH $_3$O)$_2$-$C_6H_3$
**c;** Ar = 4-CH $_3$-$C_6H_4$
**d;** Ar = 3,4-OCH $_2$O-$C_6H_3$

group of important compounds because of their vital pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used to have antibacterial [10], antithrombic [11], and anticonvulsant behavior [12]. The quinazoline ring system is a commonly encountered structural core in a number of natural and synthetic molecules with a wide range of biological activities [13]. Many of the quinazoline derivatives are known to exhibit anti-inflammatory [14], anthelmentic [15], analgesic [16], CNS-depressant [17], and anticonvulsive activities [18]. Metolazone and quinethazone are two quinazoline-based drugs that are used currently as diuretics in medicines [19]. Vasicine and related naturally occurring quinazoline alkaloids, and other quinazoline bearing natural metabolites including a number of tryptoquivalines are the famous broncodilators [20], oxytocics, and antifungals being used since time immemorial. The bacterial and bacteriolytic activities have not been extensively studied in pyrimidine, quinazoline, naphthyridine, and benzo[b]diazepine systems in both isolation and in fused assemblages. Literature survey reveals that a fair amount of work has been published in the condensation reactions of barbituric acid, dimedone, and other active methylene carbocyclic and heterocyclic compounds. Because of long standing interest in our laboratory in the condensation reactions of active methylene compounds [21–23] and generation of new fused (''ortho'' and ''ortho and peri''), bridged [23], spiro [24], ring assembly and cyclophane [25] heterocyclic compounds, we have extended our synthetic activity along these lines to include the synthesis of some pyridopyrimidine, pyrimidonaphthyridine, benzo[b]pyrimidonaphthyridine, dipyrimidonaphthyridine, pyrimidonaphthyridinoquinazoline, pyrimidonaphthyridinobenzodiazepine, pyridopyrimido- pyrimido- naphthyridine, pyrimidonaphthyridino-pyridoquinazoline, and 1,3,4,6,7,8,9,11-octazabenzo[de]naphthacene systems.

It was interesting to study these di- and tri- and unknown and unreported tetra-, penta-, and hexa- cyclic heterocyclic systems containing various vital nitrogen heterocyclic moieties, expectedly enriched with potential antimicrobial, antifungal, and other important biological activities. To prepare these novel classes of compounds, we synthesized and used ethyl 7-amino-2,4-diketo-5-aryl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate **4** as the key intermediate synthon.

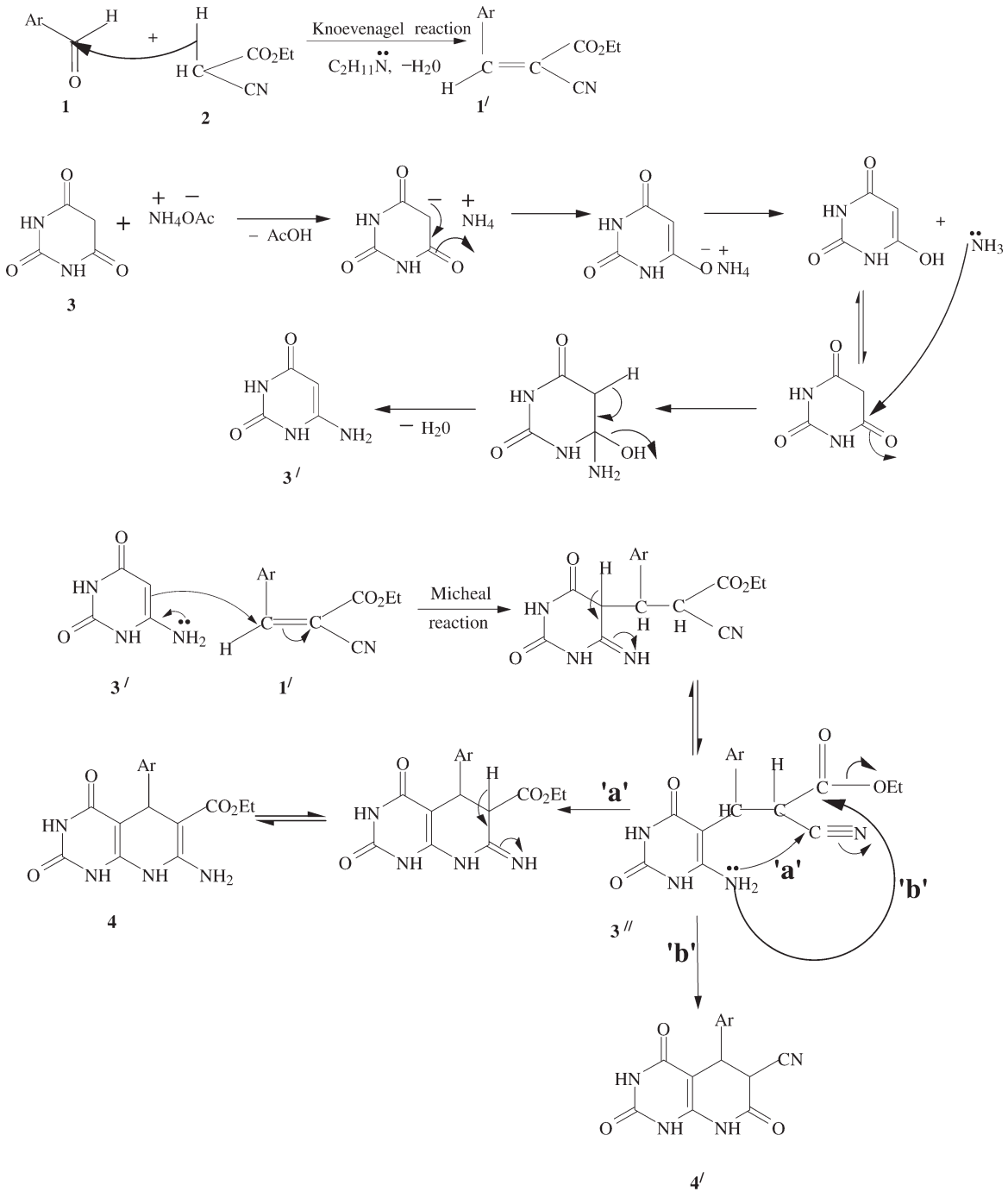
## RESULTS AND DISCUSSION

The key intermediates **4a–4d** used as starting materials [26] have been prepared in better yields by refluxing the aromatic aldehydes **1**, ethyl cyanoacetate **2**, barbituric acid, **3** and excess of ammonium acetate in methanol though some traces of compound **4′** in each case were formed. The main product **4** was separated by fractional crystallization and from the mother liquor a pale yellow colored side product **4′** was isolated in each case that was characterized as 6-cyano-5-aryl-1,2,3,4,5,6,7,8-octahydropyrido[2,3-d]pyrimidine-2,4,7-trione. The formation of these key intermediates **4** and mechanism of their formation have been exhibited (Scheme 1 and 2 respectively).

The reaction sequence in the formation of **4** may be proceeding via initial formation of ethyl arylidenecyanoacetate **1′** by reaction of aromatic aldehyde **1** and ethyl cyanoacetate **2** through typical Knoevenagel condensation. Subsequently, the intermediate **1′** reacts with 6-amino uracil **3′** obtained through the aminodehydration of barbituric acid **3** to produce another intermediate **3″** which on cyclocondensation results in the formation of **4** and **4′** (Scheme 2).

The structure of **4a** was established on the basis of elemental analysis, IR and $^1$H NMR spectral data. The IR spectrum of compound **4a** showed strong absorption bands at υ 3333 and 3423 cm$^{-1}$ for amino group and at υ 1675, 1682, 1690 cm$^{-1}$ for (C=O) group. Its $^1$H NMR spectrum showed as usual a quartet and a triplet

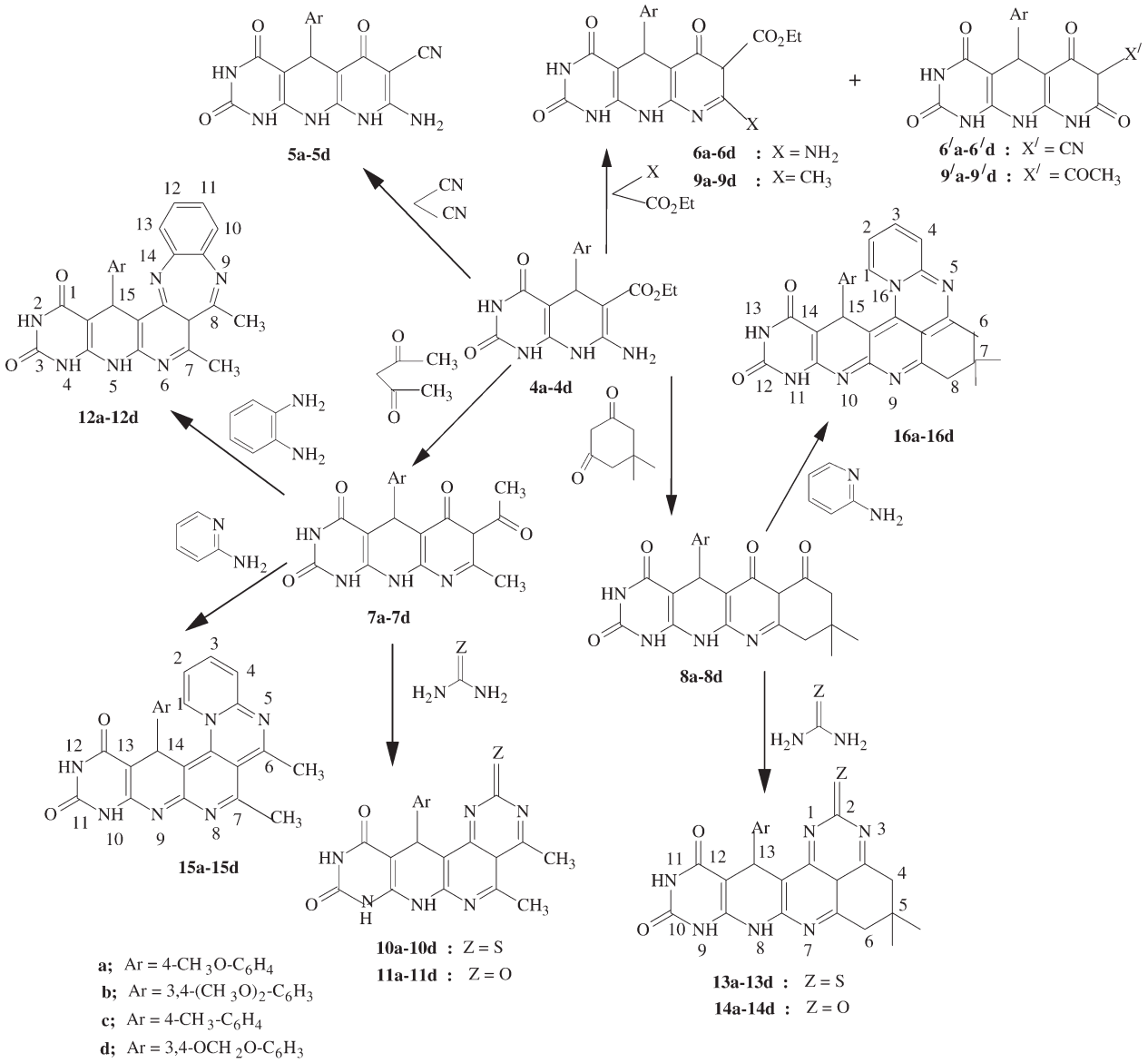
**Scheme 2**



due to $CH_2$ and $CH_3$ protons respectively of the ethyl ester functionality besides other protons including a multiplet of aromatic proton, a singlet of chiral proton, a singlet at δ 3.75 due to $OCH_3$ group and $D_2O$ exchangeable protons. Treatment of compounds **4a–4d** with malononitrile under refluxing in DMF in the presence of catalytic amount of piperidine gave products identified as 8-amino-7-cyano-5-aryl-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones **5a–5d** (Scheme 3). The structures of these products were established on the basis of their analytical and spectral data.

Condensation of compounds **4a–4d** with ethyl cyanoacetate under similar conditions gave major products identified as 8-amino-7-ethoxycarbonyl-5-aryl-1,2,3,4,5,6, 7,10-octahydro-pyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones

**Scheme 3**




**6a–6d** and minor products identified as 7-cyano-5-aryl-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6,8-tetraones **6′a–6′d**. Their structures were established as usual on the basis of elemental and spectral data. Similar condensation of compounds **4a–4d** with acetylacetone [27] under refluxing in DMSO in the presence of catalytic amount of $P_2O_5$ gave the enamine ketones in good yields. The enamine ketones were then cyclized in presence of $K_2CO_3$ and copper powder in refluxing dry acetone giving substituted pyrimidonaphthyridine derivatives **7a–7d**. Condensation of compounds **4a–4d** with other active methylene compounds like dimedone and ethyl acetoacetate resulted in the formation of substituted benzo[b] pyrimidonaphthyridine **8a–8d** and substituted pyrimidonaphthyridine compounds **9a–9d** and **9′a–9′d**, respectively. The structures of all these compounds were established as usual by elemental analysis and spectral studies, details of which are given in the experimental section. Cyclocondensation of compounds **7a–7d** with urea/thiourea separately resulted in the formation of substituted dipyrimidonaphthyridines **10a–10d** and **11a–11d** and similar treatment of **8a–8d** resulting in the formation of pyrimidonaphthyridinoquinazoline derivatives **13a–13d** and **14a–14d**. On condensation with *o*-phenylenediamine, compounds **7a–7d** resulted in the formation of substituted pyrimidonaphthyridinobenzodiazepine compounds **12a–12d**. The $^1$H NMR data of compound **12b** showed two singlets at δ 3.73 and 3.78 indicating the presence of two methoxyl groups, a singlet at δ 4.74 indicating the presence of chiral CH proton, peaks at δ 8.79, 8.95 and 9.74 due to three $D_2O$

exchangeable (NH) protons. The three aromatic protons of 3,4-dimethoxyphenyl group appeared at δ 6.64–6.95 as a multiplet and another multiplet was located at δ 7.13–7.32 due to four aromatic protons of the benzodiazepine moiety. A singlet at δ 2.47 due to methyl group attached to diazepine ring and another very highly downfield singlet at δ 2.83 revealed the presence of methyl group attached to pyridine ring. These assignments richly characterized the compound **12b** as 7,8-dimethyl-15-(3,4-dimethoxy phenyl)-2,3,4,5,7a,15-hexahydro-1*H*-pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3-b][1,5]benzo- diazepine-1,3-dione. Further, compounds **7a–7d** and **8a–8d** on similar cyclocondensations with 2-aminopyridine were attributed to generate substituted pyrido[2′,1′:2,3]pyrimido[4,5-f] pyrimido[4,5-b][1,8]naphthyridine-11,13-diones **15a–15d** and substituted pyrimido [5′,4′:6,7] [1,8]naphthyridino[4,3,2-de] pyrido[2,1-b]quinazolines **16a–16d**, respectively, on the grounds that the $^1$H NMR data of compound **15c** revealed the presence of two $D_2O$ exchangeable (NH) protons at δ 8.96 and 9.74, a singlet at δ 2.22 due to methyl group of *p*-methylphenyl ring, a singlet at δ 4.74 indicating the presence of chiral CH proton, a double doublet at δ 6.80–6.95 and 6.65–6.67 with ortho coupling indicating the presence of *p*-methylphenyl ring, a multiplet at δ 6.39–6.62 showing the presence of another set of four aromatic protons and two sharp singlets at δ 2.29 and 2.72 due to other two methyl groups in the compound; and $^1$H NMR data of compound **16d** showing peaks due to two $D_2O$ exchangeable (NH) protons at δ 8.97 and 9.79, two singlet at δ 1.88 and 2.12 due to two methylene groups, a singlet at δ 1.11 due to six protons of two gem dimethyl groups, a singlet at δ 4.74 due to chiral CH proton, a multiplet at δ 6.49–6.62 showing the presence of four protons of Nitrogen bridged pyrimidine ring, a sharp singlet at δ 5.87 due to two methylenedioxy protons and a multiplet at δ 6.47–6.89 due to three aromatic protons of the methylenedioxyphenyl group.

Compounds **4, 5** and **6** on condensation with formamide could close the recurring generation of the COOR/CN group at adjacent position to $NH_2$ group in the same ring resulting in the production of pyrido[2,3-d;6,5-d′]dipyrimidines **17**, dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines **18** which subsequently generated 1,3,4,6,7,8,9,11-octaza benzo[de]naphthacenes **19** with more of formamide and dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridines **20**, respectively. In addition, compound **6** on treatment with *o*-phenylenediamine produced a novel pentacyclic heterocyclic system, pyrimido [5′,4′:6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepines **21**, and on heating with thiourea, it produced dipyrimido[4,5-b:4′,5′-f][1,8]naphthyridine **22** and dipyrimido[4,5-b:5′,4′-g][1,8]naphthyridine **23** the two differently fused systems (Scheme 4). The compounds **22** and **23** have been distinguished on the basis of analytical and spectral data. In the $^1$H NMR spectra, the singlet at δ 2.26 ppm due to the proton on the fused tertiary carbon atom (C-4a) of the structure **22** (experimental data given for **22b**) does not appear as downfield as the singlet at δ 3.92 ppm due to the proton on the fused tertiary carbon atom (C-6a) of the structure **23** (experimental details given for **23a**), latter is flanked on either side by C═O groups. There is a marked $D_2O$ exchangeable singlet at δ 3.85 ppm for **22b** due to $NH_2$ group in the $^1$H NMR spectrum. Such chemical shift value is absent in $^1$H NMR spectrum of **23a**. Analytical data of **22a** and **23a** (with same aryl substituents) have revealed their molecular formulae to be $C_{19}H_{15}N_7O_4S$ and $C_{19}H_{14}N_6O_5S$, respectively, which are same as calculated for their proposed structures. So, structure **22** is a $H_{15}N_7O_4$ compound without aryl groups, whereas structure **23** is a $H_{14}N_6O_5$ compound without aryl groups. The observed % of Nitrogen in former is 22.54 and in latter 19.19. Same is true for the other pairs, i.e., **22b** and **23b**, **22c** and **23c**, and **22d** and **23d**. The m/z for the parent peak ($M^+$) could also speak for different molecular masses of the two structures **22** and **23**.

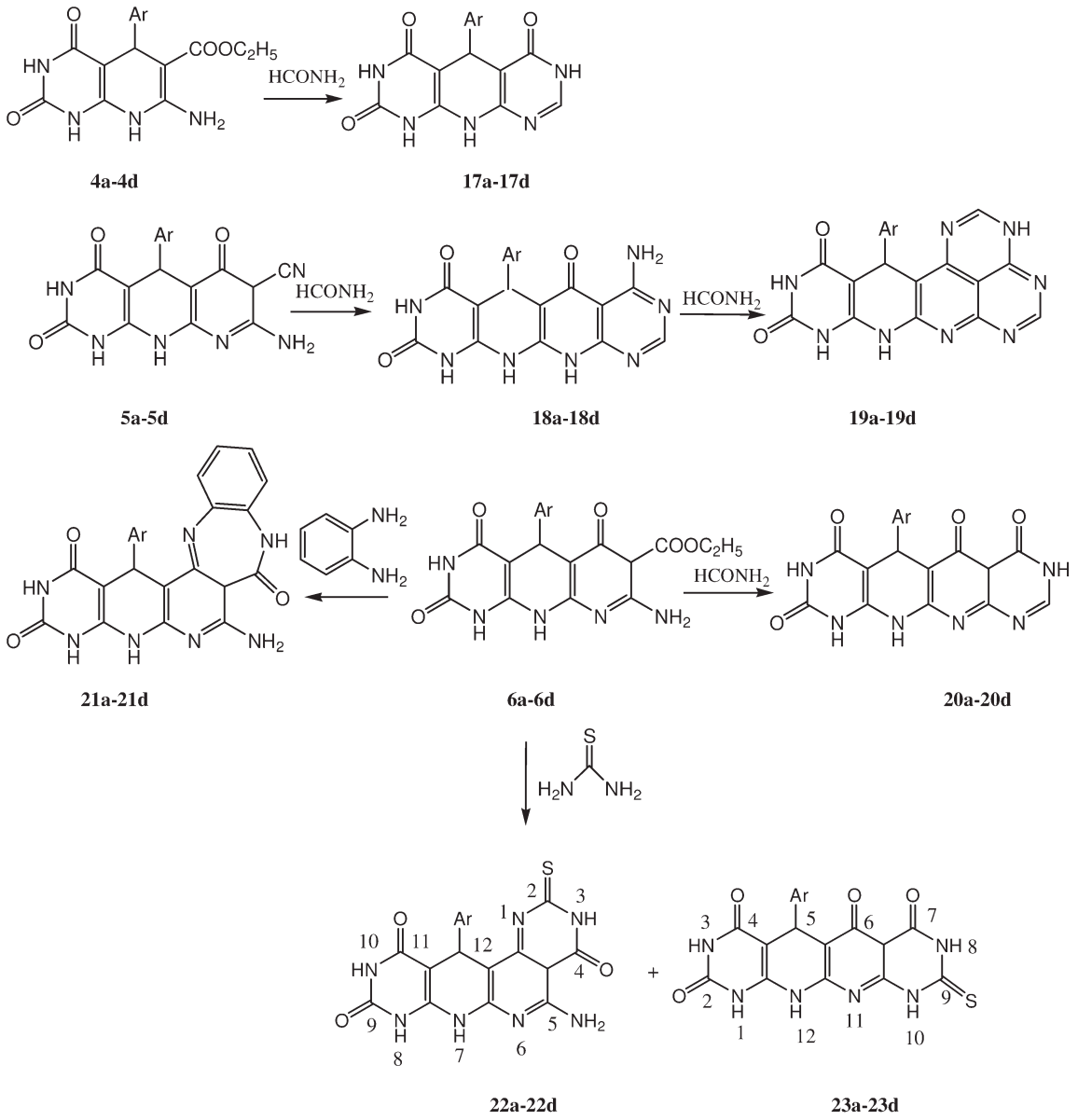
In compound **23a**, the pure ketonic group on Carbon-6 shows C═O stretching frequency 1715 $cm^{-1}$, higher than the other carbonyl stretching frequencies (1660–1680$cm^{-1}$) of lactam and thiolactam rings present in structures **22** and **23**. This higher valued carbonyl stretching frequency is absent in the IR spectrum of structure **22b**. The free amino group on the unsaturated carbon atom shows marked N—H stretching frequency (3200–3500$cm^{-1}$) in structures **22** and this is lacking in IR spectrum of structure **23a**.

The preliminary tests of the keto compound like formation of 2,4-dinitrophenyl hydrazone, phenylhydrazone, semicarbazone, and oxime could be confirmed only for structure **23** (keto group at C-6). Structure **22** could not respond to these tests as it contains carbonyl groups only in the form of lactam and thiolactam functionalities. Similarly, Structures **22** give all the preliminary tests of free amino group.

All the other products were similarly characterized by $^1$H NMR and $^{13}$C NMR data, and their elemental analysis data was also in complete agreement with the assigned structures. The structural formulae, m.ps, yield, molecular formulae, and elemental analysis for these compounds are shown in tabular form (Table 1).

The novel fused heterocyclic systems belonging to compounds **8a–8d**, **10a–10d**, **12a–12d**, **13a–13d**, **15a–15d**, **16a–16d**, **18a–18d**, and **19a–19d** are highly fascinating and interesting and are being reported for the first time in literature especially as regards their generation. The heterocyclic compounds **8** and **18** with linear, ''ortho'' fused structures; **10, 12**, and **15** with angular ''ortho'' fused structures; and compounds **13, 16**, and **19**

**Scheme 4**




**a;** Ar = 4-$CH_3O$-$C_6H_4$
**b;** Ar = 3,4-$(CH_3O)_2$-$C_6H_3$
**c;** Ar = 4-$CH_3$-$C_6H_4$
**d;** Ar = 3,4-$OCH_2O$-$C_6H_3$

with ''ortho'' and ''ortho and peri'' fused structures contain various component heterocyclic moieties like pyrimidine, pyridine, quinazoline, quinoline, [1,8]naphthyridine, and benzodiazepine present in different modes of combinations and all known for their remarkable, varied, and highly useful physiological activities.

From the study of the key reactions discussed in the present exposition for transformation of an active methylene cyclic compound into a polycyclic ring system containing one six-membered ring more than the substrate, it can be summarily concluded that a reaction of an active methylene compound like malononitrile, ethyl cyanoacetate, and ethyl acetoacetate with a cyclic system having $NH_2$ and groups like CN/COOH/COOR in adjacent position to each other can serve as a recurring contributor for the transformation of a linear system into another linear system having one more ring till the reaction gets stopped due to very high cyclicity (7,8,9. . .membered) and molecular weight or availability of very small amount of substrates to proceed further

**Table 1**

Differently substituted compounds with mp's, yields, and molecular formulae.

| Compound | Ar | Mp's (°C) | Yield (%) | Mol. formulae ($M^+$) | Calcd. formula% / Obsd. formula% C | H | N | S |
|---|---|---|---|---|---|---|---|---|
| **4a** | 4-$CH_3O.C_6H_4$ | 294 | 83 | $C_{17}H_{18}N_4O_5$ | 56.97 | 5.06 | 15.63 | – |
| | | | | | 56.92 | 5.02 | 15.75 | |
| **4b** | 3,4-$(CH_3O)_2.C_6H_3$ | 275 | 86 | $C_{18}H_{20}N_4O_6$ | 55.66 | 5.19 | 14.42 | – |
| | | | | | 55.58 | 5.17 | 14.50 | |
| **4c** | 4-$CH_3.C_6H_4$ | 210 | 84 | $C_{17}H_{18}N_4O_4$ | 59.64 | 5.29 | 16.36 | – |
| | | | | | 59.60 | 5.32 | 16.42 | |
| **4d** | 3,4-$OCH_2O.C_6H_3$ | 298 | 85 | $C_{17}H_{16}N_4O_6$ | 54.83 | 4.33 | 15.04 | – |
| | | | | | 54.88 | 4.35 | 15.12 | |
| **4′a** | 4-$CH_3O.C_6H_4$ | 205 | 70 | $C_{15}H_{12}N_4O_4$ | 57.69 | 3.87 | 17.94 | – |
| | | | | | 57.75 | 3.89 | 17.87 | |
| **4′b** | 3,4-$(CH_3O)_2.C_6H_3$ | 202 | 69 | $C_{16}H_{14}N_4O_5$ | 56.14 | 4.12 | 16.36 | – |
| | | | | | 56.10 | 4.09 | 16.48 | |
| **4′c** | 4-$CH_3.C_6H_4$ | 218 | 72 | $C_{15}H_{12}N_4O_3$ | 60.80 | 4.08 | 18.91 | – |
| | | | | | 60.76 | 4.09 | 18.98 | |
| **4′d** | 3,4-$OCH_2O.C_6H_3$ | 220 | 74 | $C_{15}H_{10}N_4O_5$ | 55.22 | 3.08 | 17.17 | – |
| | | | | | 55.17 | 3.12 | 17.25 | |
| **5a** | 4-$CH_3O.C_6H_4$ | 145 | 70 | $C_{18}H_{14}N_6O_4$ | 57.14 | 3.73 | 22.21 | – |
| | | | | | 57.12 | 3.72 | 22.28 | |
| **5b** | 3,4-$(CH_3O)_2.C_6H_3$ | 149 | 72 | $C_{19}H_{16}N_6O_5$ | 55.88 | 3.94 | 20.57 | – |
| | | | | | 55.85 | 3.97 | 20.65 | |
| **5c** | 4-$CH_3.C_6H_4$ | 135 | 69 | $C_{18}H_{14}N_6O_3$ | 59.66 | 3.89 | 23.19 | – |
| | | | | | 59.60 | 3.86 | 23.25 | |
| **5d** | 3,4-$OCH_2O.C_6H_3$ | 141 | 71 | $C_{18}H_{12}N_6O_5$ | 55.10 | 3.08 | 21.42 | – |
| | | | | | 55.07 | 3.09 | 21.47 | |
| **6a** | 4-$CH_3O.C_6H_4$ | 187 | 70 | $C_{20}H_{19}N_5O_6$ | 56.46 | 4.50 | 16.46 | – |
| | | | | | 56.43 | 4.52 | 16.54 | |
| **6b** | 3,4-$(CH_3O)_2.C_6H_3$ | 188 | 68 | $C_{21}H_{21}N_5O_7$ | 55.38 | 4.64 | 15.37 | – |
| | | | | | 55.32 | 4.62 | 15.43 | |
| **6c** | 4-$CH_3.C_6H_4$ | 189 | 65 | $C_{20}H_{19}N_5O_5$ | 58.67 | 4.67 | 17.10 | – |
| | | | | | 58.62 | 4.69 | 17.16 | |
| **6d** | 3,4-$OCH_2O.C_6H_3$ | 182 | 63 | $C_{20}H_{17}N_5O_7$ | 54.67 | 3.90 | 15.93 | – |
| | | | | | 54.63 | 3.92 | 15.97 | |
| **6′a** | 4-$CH_3O.C_6H_4$ | 201 | 68 | $C_{18}H_{13}N_5O_5$ | 56.99 | 3.45 | 18.46 | – |
| | | | | | 56.93 | 3.42 | 18.55 | |
| **6′b** | 3,4-$(CH_3O)_2.C_6H_3$ | 206 | 69 | $C_{19}H_{15}N_5O_6$ | 55.74 | 3.69 | 17.10 | – |
| | | | | | 55.73 | 3.61 | 17.13 | |
| **6′c** | 4-$CH_3.C_6H_4$ | 209 | 71 | $C_{18}H_{13}N_5O_4$ | 59.50 | 3.60 | 19.27 | – |
| | | | | | 59.46 | 3.64 | 19.32 | |
| **6′d** | 3,4-$OCH_2O.C_6H_3$ | 205 | 73 | $C_{18}H_{11}N_5O_6$ | 54.96 | 2.81 | 17.80 | – |
| | | | | | 54.93 | 2.79 | 17.85 | |
| **7a** | 4-$CH_3O.C_6H_4$ | 188 | 68 | $C_{20}H_{18}N_4O_5$ | 60.91 | 4.60 | 14.20 | – |
| | | | | | 60.84 | 4.65 | 14.25 | |
| **7b** | 3,4-$(CH_3O)_2.C_6H_3$ | 172 | 70 | $C_{21}H_{20}N_4O_6$ | 59.43 | 4.75 | 13.20 | – |
| | | | | | 59.40 | 4.78 | 13.24 | |
| **7c** | 4-$CH_3.C_6H_4$ | 174 | 71 | $C_{20}H_{18}N_4O_4$ | 63.48 | 4.79 | 14.80 | – |
| | | | | | 63.56 | 4.77 | 14.82 | |
| **7d** | 3,4-$OCH_2O.C_6H_3$ | 179 | 73 | $C_{20}H_{16}N_4O_6$ | 58.82 | 3.94 | 13.72 | – |
| | | | | | 58.85 | 3.92 | 13.70 | |
| **7′a** | 4-$CH_3O.C_6H_4$ | 215 | 62 | $C_{23}H_{22}N_4O_5$ | 63.58 | 5.10 | 12.89 | – |
| | | | | | 63.63 | 5.08 | 12.92 | |
| **7′b** | 3,4-$(CH_3O)_2.C_6H_3$ | 211 | 64 | $C_{24}H_{24}N_4O_6$ | 62.06 | 5.20 | 12.06 | – |
| | | | | | 62.08 | 5.23 | 12.14 | |
| **7′c** | 4-$CH_3.C_6H_4$ | 203 | 61 | $C_{23}H_{22}N_4O_4$ | 66.01 | 5.29 | 13.38 | – |
| | | | | | 66.08 | 5.25 | 13.41 | |
| **7′d** | 3,4-$OCH_2O.C_6H_3$ | 245 | 62 | $C_{23}H_{20}N_4O_6$ | 61.60 | 4.49 | 12.49 | – |
| | | | | | 61.58 | 4.51 | 12.48 | |
| **9a** | 4-$CH_3O.C_6H_4$ | 218 | 59 | $C_{21}H_{20}N_4O_6$ | 59.43 | 4.75 | 13.20 | – |
| | | | | | 59.39 | 4.76 | 13.28 | |

(*Continued*)

**Table 1**
(*Continued*)

| Compound | Ar | Mp's (°C) | Yield (%) | Mol. formulae ($M^+$) | Calcd. formula% / Obsd. formula% C | H | N | S |
|---|---|---|---|---|---|---|---|---|
| **9b** | 3,4-$(CH_3O)_2.C_6H_3$ | 202 | 57 | $C_{22}H_{22}N_4O_7$ | 58.14 | 4.88 | 12.32 | – |
| | | | | | 58.17 | 4.89 | 12.38 | |
| **9c** | 4-$CH_3.C_6H_4$ | 206 | 58 | $C_{21}H_{20}N_4O_5$ | 61.75 | 4.93 | 13.71 | – |
| | | | | | 61.83 | 4.94 | 13.68 | |
| **9d** | 3,4-$OCH_2O.C_6H_3$ | 228 | 56 | $C_{21}H_{18}N_4O_7$ | 57.53 | 4.13 | 12.78 | – |
| | | | | | 57.65 | 4.11 | 12.77 | |
| **9′a** | 4-$CH_3O.C_6H_4$ | 249 | 53 | $C_{19}H_{16}N_4O_6$ | 57.57 | 4.06 | 14.13 | – |
| | | | | | 57.58 | 4.08 | 14.25 | |
| **9′b** | 3,4-$(CH_3O)_2.C_6H_3$ | 245 | 52 | $C_{20}H_{18}N_4O_7$ | 56.33 | 4.25 | 13.14 | – |
| | | | | | 56.42 | 4.22 | 13.15 | |
| **9′c** | 4-$CH_3.C_6H_4$ | 221 | 56 | $C_{19}H_{16}N_4O_5$ | 59.99 | 4.24 | 14.73 | – |
| | | | | | 59.95 | 4.22 | 14.78 | |
| **9′d** | 3,4-$OCH_2O.C_6H_3$ | 233 | 51 | $C_{19}H_{14}N_4O_7$ | 55.61 | 3.43 | 13.65 | – |
| | | | | | 55.65 | 3.41 | 13.74 | |
| **10a** | 4-$CH_3O.C_6H_4$ | 295 | 55 | $C_{21}H_{18}N_6O_3S$ | 58.05 | 4.17 | 19.34 | 7.38 |
| | | | | | 58.09 | 4.14 | 19.28 | 7.44 |
| **10b** | 3,4-$(CH_3O)_2.C_6H_3$ | >300 | 52 | $C_{22}H_{20}N_6O_4S$ | 56.88 | 4.34 | 18.09 | 6.90 |
| | | | | | 56.83 | 4.30 | 18.15 | 6.94 |
| **10c** | 4-$CH_3.C_6H_4$ | >300 | 54 | $C_{21}H_{18}N_6O_2S$ | 60.27 | 4.33 | 20.08 | 7.66 |
| | | | | | 60.23 | 4.30 | 20.16 | 7.69 |
| **10d** | 3,4-$OCH_2O.C_6H_3$ | >300 | 55 | $C_{21}H_{16}N_6O_4S$ | 56.24 | 3.59 | 18.74 | 7.15 |
| | | | | | 56.21 | 3.62 | 18.79 | 7.18 |
| **11a** | 4-$CH_3O.C_6H_4$ | 284 | 54 | $C_{21}H_{18}N_6O_4$ | 60.28 | 4.33 | 20.08 | – |
| | | | | | 60.23 | 4.30 | 20.15 | |
| **11b** | 3,4-$(CH_3O)_2.C_6H_3$ | 296 | 51 | $C_{22}H_{20}N_6O_5$ | 58.92 | 4.49 | 18.74 | – |
| | | | | | 58.98 | 4.55 | 18.70 | |
| **11c** | 4-$CH_3.C_6H_4$ | 299 | 49 | $C_{21}H_{18}N_6O_3$ | 62.68 | 4.50 | 20.88 | – |
| | | | | | 62.73 | 4.46 | 20.92 | |
| **11d** | 3,4-$OCH_2O.C_6H_3$ | >300 | 47 | $C_{21}H_{16}N_6O_5$ | 58.33 | 3.73 | 19.43 | – |
| | | | | | 58.36 | 3.76 | 19.38 | |
| **12a** | 4-$CH_3O.C_6H_4$ | >300 | 48 | $C_{26}H_{22}N_6O_3$ | 66.94 | 4.75 | 18.01 | – |
| | | | | | 66.98 | 4.77 | 18.10 | |
| **12b** | 3,4-$(CH_3O)_2.C_6H_3$ | 310 | 46 | $C_{27}H_{24}N_6O_4$ | 65.31 | 4.87 | 16.92 | – |
| | | | | | 65.36 | 4.86 | 16.96 | |
| **12c** | 4-$CH_3.C_6H_4$ | 306 | 46 | $C_{26}H_{22}N_6O_2$ | 69.32 | 4.92 | 18.65 | – |
| | | | | | 69.34 | 4.96 | 18.69 | |
| **12d** | 3,4-$OCH_2O.C_6H_3$ | 298 | 48 | $C_{26}H_{20}N_6O_4$ | 64.99 | 4.19 | 17.49 | – |
| | | | | | 64.93 | 4.23 | 17.56 | |
| **13a** | 4-$CH_3O.C_6H_4$ | 290 | 45 | $C_{24}H_{22}N_6O_3S$ | 60.74 | 4.67 | 17.71 | 6.75 |
| | | | | | 60.70 | 4.65 | 17.76 | 6.79 |
| **13b** | 3,4-$(CH_3O)_2.C_6H_3$ | 285 | 47 | $C_{25}H_{24}N_6O_4S$ | 59.51 | 4.79 | 16.65 | 6.35 |
| | | | | | 59.62 | 4.76 | 16.63 | 6.37 |
| **13c** | 4-$CH_3.C_6H_4$ | 288 | 47 | $C_{24}H_{22}N_6O_2S$ | 62.86 | 4.83 | 18.32 | 6.99 |
| | | | | | 62.87 | 4.81 | 18.34 | 6.97 |
| **13d** | 3,4-$OCH_2O.C_6H_3$ | 296 | 48 | $C_{24}H_{20}N_6O_4S$ | 59.00 | 4.12 | 17.20 | 6.56 |
| | | | | | 59.04 | 4.14 | 17.26 | 6.58 |
| **14a** | 4-$CH_3O.C_6H_4$ | 276 | 43 | $C_{24}H_{22}N_6O_4$ | 62.87 | 4.83 | 18.33 | – |
| | | | | | 62.85 | 4.85 | 18.42 | |
| **14b** | 3,4-$(CH_3O)_2.C_6H_3$ | 279 | 45 | $C_{25}H_{24}N_6O_5$ | 61.46 | 4.95 | 17.20 | – |
| | | | | | 61.43 | 4.97 | 17.29 | |
| **14c** | 4-$CH_3.C_6H_4$ | 288 | 44 | $C_{24}H_{22}N_6O_3$ | 65.14 | 5.01 | 18.99 | – |
| | | | | | 65.19 | 5.05 | 18.97 | |
| **14d** | 3,4-$OCH_2O.C_6H_3$ | >300 | 45 | $C_{24}H_{20}N_6O_5$ | 61.01 | 4.26 | 17.78 | – |
| | | | | | 61.05 | 4.29 | 17.87 | |
| **15a** | 4-$CH_3O.C_6H_4$ | >300 | 44 | $C_{25}H_{20}N_6O_3$ | 66.36 | 4.45 | 18.57 | – |
| | | | | | 66.32 | 4.49 | 18.63 | |
| **15b** | 3,4-$(CH_3O)_2.C_6H_3$ | >300 | 42 | $C_{26}H_{22}N_6O_4$ | 64.72 | 4.59 | 17.41 | – |
| | | | | | 64.74 | 4.52 | 17.53 | |

(*Continued*)

**Table 1**
(*Continued*)

| Compound | Ar | Mp's (°C) | Yield (%) | Mol. formulae ($M^+$) | Calcd. formula% / Obsd. formula% C | H | N | S |
|---|---|---|---|---|---|---|---|---|
| **15c** | 4-$CH_3$.$C_6H_4$ | >300 | 44 | $C_{25}H_{20}N_6O_2$ | 68.79 | 4.61 | 19.25 | – |
| | | | | | 68.76 | 4.64 | 19.32 | |
| **15d** | 3,4-$OCH_2O$.$C_6H_3$ | >300 | 46 | $C_{25}H_{18}N_6O_4$ | 64.37 | 3.89 | 18.01 | – |
| | | | | | 64.31 | 3.83 | 18.09 | |
| **16a** | 4-$CH_3O$.$C_6H_4$ | >300 | 38 | $C_{28}H_{24}N_6O_3$ | 68.28 | 4.91 | 17.06 | – |
| | | | | | 68.20 | 4.87 | 17.09 | |
| **16b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | >300 | 39 | $C_{29}H_{26}N_6O_4$ | 66.65 | 5.01 | 16.08 | – |
| | | | | | 66.63 | 5.03 | 16.14 | |
| **16c** | 4-$CH_3$.$C_6H_4$ | >300 | 43 | $C_{28}H_{24}N_6O_2$ | 70.57 | 5.07 | 17.63 | – |
| | | | | | 70.61 | 5.09 | 17.67 | |
| **16d** | 3,4-$OCH_2O$.$C_6H_3$ | >300 | 45 | $C_{28}H_{22}N_6O_4$ | 66.39 | 4.37 | 16.59 | – |
| | | | | | 66.36 | 4.35 | 16.61 | |
| **17a** | 4-$CH_3O$.$C_6H_4$ | 198 | 55 | $C_{16}H_{13}N_5O_4$ | 56.63 | 3.86 | 20.64 | – |
| | | | | | 56.58 | 3.89 | 20.70 | |
| **17b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | 206 | 58 | $C_{17}H_{15}N_5O_5$ | 55.28 | 4.09 | 18.96 | – |
| | | | | | 55.20 | 4.07 | 18.99 | |
| **17c** | 4-$CH_3$.$C_6H_4$ | 215 | 52 | $C_{16}H_{13}N_5O_3$ | 59.44 | 4.05 | 21.66 | – |
| | | | | | 59.40 | 4.08 | 21.68 | |
| **17d** | 3,4-$OCH_2O$.$C_6H_3$ | 195 | 54 | $C_{16}H_{11}N_5O_5$ | 54.39 | 3.13 | 19.82 | – |
| | | | | | 54.25 | 3.14 | 19.87 | |
| **18a** | 4-$CH_3O$.$C_6H_4$ | 267 | 51 | $C_{19}H_{15}N_7O_4$ | 56.29 | 3.73 | 24.18 | – |
| | | | | | 56.23 | 3.74 | 24.15 | |
| **18b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | 251 | 53 | $C_{20}H_{17}N_7O_5$ | 55.17 | 3.93 | 22.51 | – |
| | | | | | 55.15 | 3.90 | 22.48 | |
| **18c** | 4-$CH_3$.$C_6H_4$ | 276 | 50 | $C_{19}H_{15}N_7O_3$ | 58.60 | 3.88 | 25.18 | – |
| | | | | | 58.57 | 3.85 | 25.26 | |
| **18d** | 3,4-$OCH_2O$.$C_6H_3$ | 289 | 52 | $C_{19}H_{13}N_7O_5$ | 54.41 | 3.12 | 23.38 | – |
| | | | | | 54.37 | 3.10 | 23.45 | |
| **19a** | 4-$CH_3O$.$C_6H_4$ | 284 | 48 | $C_{20}H_{14}N_8O_3$ | 57.97 | 3.40 | 27.04 | – |
| | | | | | 57.92 | 3.38 | 27.09 | |
| **19b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | 298 | 47 | $C_{21}H_{16}N_8O_4$ | 56.75 | 3.62 | 25.21 | – |
| | | | | | 56.78 | 3.60 | 25.28 | |
| **19c** | 4-$CH_3$.$C_6H_4$ | >300 | 44 | $C_{20}H_{14}N_8O_2$ | 60.29 | 3.54 | 28.12 | – |
| | | | | | 60.32 | 3.51 | 28.17 | |
| **19d** | 3,4-$OCH_2O$.$C_6H_3$ | >300 | 46 | $C_{20}H_{12}N_8O_4$ | 56.07 | 2.82 | 26.15 | – |
| | | | | | 56.03 | 2.80 | 26.23 | |
| **20a** | 4-$CH_3O$.$C_6H_4$ | 290 | 44 | $C_{19}H_{14}N_6O_5$ | 56.16 | 3.47 | 20.68 | – |
| | | | | | 56.11 | 3.44 | 20.72 | |
| **20b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | >300 | 42 | $C_{20}H_{16}N_6O_6$ | 55.04 | 3.69 | 19.25 | – |
| | | | | | 55.00 | 3.68 | 19.32 | |
| **20c** | 4-$CH_3$.$C_6H_4$ | 287 | 45 | $C_{19}H_{14}N_6O_4$ | 58.46 | 3.61 | 21.52 | – |
| | | | | | 58.41 | 3.58 | 21.57 | |
| **20d** | 3,4-$OCH_2O$.$C_6H_3$ | >300 | 42 | $C_{19}H_{12}N_6O_6$ | 54.29 | 2.87 | 19.99 | – |
| | | | | | 54.24 | 2.84 | 20.23 | |
| **21a** | 4-$CH_3O$.$C_6H_4$ | 298 | 46 | $C_{24}H_{19}N_7O_4$ | 61.40 | 4.07 | 20.88 | – |
| | | | | | 61.48 | 4.10 | 20.94 | |
| **21b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | 292 | 41 | $C_{25}H_{21}N_7O_5$ | 60.11 | 4.23 | 19.63 | – |
| | | | | | 60.15 | 4.19 | 19.69 | |
| **21c** | 4-$CH_3$.$C_6H_4$ | >300 | 43 | $C_{24}H_{19}N_7O_3$ | 63.57 | 4.22 | 21.62 | – |
| | | | | | 63.62 | 4.20 | 21.65 | |
| **21d** | 3,4-$OCH_2O$.$C_6H_3$ | >300 | 45 | $C_{24}H_{17}N_7O_5$ | 59.62 | 3.54 | 20.28 | – |
| | | | | | 59.65 | 3.55 | 20.33 | |
| **22a** | 4-$CH_3O$.$C_6H_4$ | 274 | 41 | $C_{19}H_{15}N_7O_4S$ | 52.16 | 3.45 | 22.41 | 7.33 |
| | | | | | 52.07 | 3.48 | 22.54 | 7.30 |
| **22b** | 3,4-$(CH_3O)_2$.$C_6H_3$ | 289 | 42 | $C_{20}H_{17}N_7O_5S$ | 51.38 | 3.66 | 20.97 | 6.86 |
| | | | | | 51.41 | 3.60 | 20.98 | 6.92 |
| **22c** | 4-$CH_3$.$C_6H_4$ | >300 | 42 | $C_{19}H_{15}N_7O_3S$ | 54.15 | 3.58 | 23.26 | 7.60 |
| | | | | | 54.19 | 3.60 | 23.29 | 7.64 |

(*Continued*)

**Table 1**
(*Continued*)

| Compound | Ar | Mp's (°C) | Yield (%) | Mol. formulae ($M^+$) | Calcd. formula% Obsd. formula% C | H | N | S |
|---|---|---|---|---|---|---|---|---|
| **22d** | 3,4-$OCH_2O.C_6H_3$ | >300 | 44 | $C_{19}H_{13}N_7O_5S$ | 50.55 | 2.90 | 21.71 | 7.10 |
| | | | | | 50.60 | 2.94 | 21.70 | 7.14 |
| **23a** | 4-$CH_3O.C_6H_4$ | >300 | 40 | $C_{19}H_{14}N_6O_5S$ | 52.05 | 3.21 | 19.16 | 7.31 |
| | | | | | 52.09 | 3.28 | 19.19 | 7.35 |
| **23b** | 3,4-$(CH_3O)_2.C_6H_3$ | >300 | 41 | $C_{20}H_{16}N_6O_6S$ | 51.28 | 3.44 | 17.94 | 6.84 |
| | | | | | 51.32 | 3.46 | 17.95 | 6.87 |
| **23c** | 4-$CH_3.C_6H_4$ | >300 | 44 | $C_{19}H_{14}N_6O_4S$ | 54.02 | 3.34 | 19.89 | 7.59 |
| | | | | | 54.08 | 3.36 | 19.86 | 7.66 |
| **23d** | 3,4-$OCH_2O.C_6H_3$ | >300 | 42 | $C_{19}H_{12}N_6O_6S$ | 50.44 | 2.67 | 18.57 | 7.08 |
| | | | | | 50.47 | 2.68 | 18.59 | 7.04 |

due to large number of steps having occurred till then or the reaction is terminated intentionally according to desirability of the required cyclicity by closing the reaction by condensation of the product with formamide and finally generating another terminal pyrimidine ring (Scheme 4).

All the compounds under various heterocyclic systems discussed herein were obtained either as a racemic mixture of a pair of enantiomers or as a mixture of two racemates or as only enantiomer or a diastereomer of unknown stereochemistry. The resolution of the racemic mixtures into the chiral enantiomers could not be carried in this study, and the compounds were used and characterized as obtained.

**Pharmacology.** One compound each from the systems synthesized in this study was subjected to bactericidal and bacteriolytic activity against *Escherichia coli*. The clinical syndromes associated with human beings are urinary track infections, neonatal meningitis, and gastroenteritis.

**The bactericidal and bacteriolytic activity.** The compounds under study (20mg) were dissolved in 500 IL of DMSO. Five microlitres (0.2 mg approx) of the stock solution was taken and 95 IL bacterial suspension in Tris buffer saline (0.8 OD at 580 nm) was added to it. The mixture was incubated at 14°C for 14 h. After incubation, it was subjected to plating in TCBS agar (Thiosulphate, Citric, Bile salt, Sucrose agar). After 12 h, the culture plate was observed for bacterial growth.

For bacteriolytic activity, bacterial suspension in TBS was prepared with an optical density of 0.8 OD at 580 nm (double beam UV spectrometer). TBS (Tris buffer saline) served as the blank. The test compound (10mg) was dissolved in 150 L of DMSO and 2850 IL of bacterial suspension in TBS was added to it. The initial OD of the sample was recorded. The mixture was incubated for 90 min at 23°C. Final OD of the mixture was recorded. The initial OD minus the final OD gives the bacteriolytic activity. The —NH— group and the —O— group on the given moieties may bind with the negatively charged phosphate group on phospholipids present on the wall of bacteria. This causes inhibition of the activities of lysosomal phospholipases because of the neutralization of the negative charges of phospholipid bilayer, leading to potential antibacterial activity.

**Observations.** The active compounds exhibited a range between mild to strong bactericidal activity against gram-negative bacteria *Escherichia coli* (Table 2). The compounds were also subjected to bacteriolytic activity against *E. coli*. The compounds **4d**, **5d**, **6d**, **8d**, **11d**, **18d**, **20d**, **21d**, and **22d** showed mild bacteriolytic activity; compounds **9d**, **10d**, **13d**, **14d**, **15d**, **17d**, **19d**, and **23d** exhibited moderate bacteriolytic activity; and compounds **7d**, **12d**, and **16d** showed strong bacteriolytic activity against *E. coli* (Table 3). Ciprofloxacin was used as standard antibiotic in this study.

## EXPERIMENTAL

**General.** The melting points were determined in open capillary tubes in Perfit melting point apparatus and are uncorrected. The purity of the products was checked on TLC plates coated with silica gel-G and detected by iodine vapors. The IR spectra were recorded on Perkin Elmer Infrared model S99-B and on Shimdzu IR-435 spectrophotometer ($\upsilon_{max}$ in $cm^{-1}$). $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a varian unity 200 MHz NMR spectrophotometer using ppm on δ scale). Elemental analysis was performed on a simple CHNS analyzer (model: CHNS-932, LECO Corporation, USA; IR Technology Services).

**General procedure for the synthesis of ethyl 7-amino-2,4-diketo-5-aryl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylates 4a–4d and 6-cyano-5-aryl-1,2,3,4,5, 6,7, 8-octahydropyrido[2,3-d]pyrimidine-2,4,7-trione 4′a–4′d.** A mixture of equimolar amounts (0.01 moles) of aromatic aldehydes **1**, ethyl cyanoacetate **2**, and barbituric acid **3** along with

**Table 2**

*In vitro* screening of bactericidal activity of compounds against *E. coli*.

| Entry | Compounds | B.A. against *E.coli* |
|---|---|---|
| 1 | **4d** | + |
| 2 | **5d** | + |
| 3 | **6d** | + |
| 4 | **7d** | + |
| 5 | **8d** | ++ |
| 6 | **9d** | + |
| 7 | **10d** | ++ |
| 8 | **11d** | ++ |
| 9 | **12d** | +++ |
| 10 | **13d** | ++ |
| 11 | **14d** | ++ |
| 12 | **15d** | +++ |
| 13 | **16d** | +++ |
| 14 | **17d** | + |
| 15 | **18d** | + |
| 16 | **19d** | +++ |
| 17 | **20d** | ++ |
| 18 | **21d** | +++ |
| 19 | **22d** | ++ |
| 20 | **23d** | ++ |
| 21 | **Ciprofloxacin** | +++ |

Bacterial activity: B.A.
Concentration is 2 mg/mL.
(+): mild bacterial activity was observed.
(++): moderate bacterial activity was observed.
(+++): strong bacterial activity was observed.

excess of ammonium acetate in methanol was refluxed on water bath for 8–10 h. After the reaction is over as monitored on TLC, the reaction mixture was concentrated and cooled at room temperature. The solid products **4** was separated by fractional crystallization as a major product and from the mother liquor a pale yellow colored solid product **4′** was isolated on prolonged cooling as a minor product. The spectral data along with IUPAC names of the products and names of the starting materials for some of the compounds is mentioned below:

***Ethyl 7-amino-2,4-diketo-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,8-hexahydropyrido[2,3-d] pyrimidine-6-carboxylate (4b).*** It was obtained using veratraldehyde. IR(KBr,υ,$cm^{-1}$): 1605 (C=C), 1675, 1682, 1695 (C=O), 3254 ($NH_2$), 3334–3410 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.37 (t, 3H, $CH_3$), 2.94 (q, 2H, $OCH_2$), 3.73 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 4.72 (s, 1H, 5-CH), 5.58 (s, 2H, $NH_2$), 6.74–6.96 (m, 3H, ArH's), 8.76–9.86 (br.s, 3H, NH).

***Ethyl 7-amino-2,4-diketo-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6-carboxylate (4d).*** It was obtained using piperonal. IR(KBr,υ,$cm^{-1}$): 1605 (C=C), 1675, 1680, 1695 (C=O), 3256 ($NH_2$), 3334–3412 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.37 (t, 3H, $CH_3$), 2.94 (q, 2H, $OCH_2$), 4.72 (s, 1H, 5-CH), 5.58 (s, 2H, $NH_2$), 5.79 (s, 2H, $O_2CH_2$), 6.57–6.67 (m, 3H, ArH's), 8.78–9.89 (br.s, 3H, NH).

***6-Cyano-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrido [2,3-d]pyrimidine-2,4,7-trione (4′a).*** It was obtained using anisaldehyde as a minor product along with **4a** as major product. IR(KBr,υ,$cm^{-1}$): 1605 (C=C), 1670, 1680, 1692 (C=O), 2195 (C=N), 3333–3405 (NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$) : δ 3.74 (s, 3H, $OCH_3$), 4.25 (s, 1H, CH), 4.42 (s, 1H, 5-CH), 6.83–6.95 (d, 2H, ArH's), 6.64–6.69 (d, 2H, ArH's), 8.75–9.85 (br.s, 3H, NH, $D_2O$ exchangeable).

***6-Cyano-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrido[2,3-d]pyrimidine-2,4,7-trione (4′b).*** It was obtained using veratraldehyde as a minor product along with **4b** as major product. IR(KBr,υ,$cm^{-1}$): 1605 (C=C) 1670, 1682, 1690 (C=O), 2194 (C=N), 3333–3405 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$) : δ 3.73 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.25 (s, 1H, CH), 4.52 (s, 1H, 5-CH), 6.46–6.54 (m, 3H, ArH's), 8.71–9.83 (br.s, 3H, NH).

**General procedure for the synthesis of 8-amino-7-cyano-5-aryl-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones 5a–5d.** A mixture of **4** (10 mmoles) and malononitrile (10 mmoles) in DMF (20 mL) containing piperidine (0.1 mL) was refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product **5** so formed was collected by filtration and crystallized from acetic acid as brown crystals.

***8-Amino-7-cyano-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6-trione (5b).*** It was obtained from **4b**. IR(KBr,υ,$cm^{-1}$): 1605 (C=C), 1610, 1635, 1674 (C=O), 2223 (C=N), 3430 ($NH_2$), 3445–3538 (4NH),$cm^{-1}$; $^1$H NMR($CDCl_3$): δ 3.73 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.74 (s, 1H, 5-CH), 6.78–6.95 (m, 3H, ArH's), 7.98 (s, 2H, $NH_2$), 8.82–9.89 (br.s, 4H, NH).

***8-Amino-7-cyano-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,9,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-trione (5d).*** It was obtained from **4d**. IR(KBr,υ,$cm^{-1}$): 1605 (C=C), 1612, 1625, 1674 (C=O), 2198 (C=N), 3423 ($NH_2$), 3425–3536 (4NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.74 (s, 1H, 5-CH), 5.86 (s, 2H, $O_2CH_2$), 6.54–6.68 (m, 3H, ArH's), 7.95 (s, 2H, $NH_2$), 8.83–9.87 (br.s, 4H, NH).

**General procedure for the synthesis of substituted pyrimido[4,5-b][1,8]naphthyridines 6a–6d, 6′a–6′d, 9a–9d, and 9′a–9′d.** A mixture of **4** (10 mmoles) and ethyl cyanoacetate/ethyl acetoacetate (10 mmoles) in DMF (20 mL) containing piperidine (0.1 mL) was refluxed for 6–8 h yielding **6, 6′** and **9, 9′**, respectively. The reaction was left to cool at room temperature and then poured on to ice-cold water. The solid product so formed was collected by filtration and crystallized from acetic acid. Using ethyl cyanoacetate, the main product **6** separated out first and from the mother liquor another minor product **6′** separated on keeping in refrigerator. Similarly, **9** and **9′** were separated as major and minor products, respectively, while using ethyl acetoacetate.

***8-Amino-7-ethoxycarbonyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-trione (6a).*** It was obtained from **4a** as a major product. IR(KBr,υ,$cm^{-1}$): 1076 (C—O—C), 1528 (C⋯⋯C of aromatic ring), 1645, 1658, 1672, 1695 (C=O), 2926 (C—H, aliphatic), 3047 (C—H, aromatic ), 3336–3486 (3NH), 3428 ($NH_2$) $cm^{-1}$; $^1$H NMR($CDCl_3$): δ 1.37 (t, 3H, $CH_3$), 2.92 (q, 2H, $OCH_2$), 3.73 (s, 3H, $OCH_3$), 4.21 (s, 1H, CH), 4.42 (s, 1H, 5-CH), 6.65–6.67 (d, 2H, ArH's), 6.70–6.93 (d, 2H, ArH's), 7.89 (s, 2H, $NH_2$), 8.80–9.86 (br.s, 3H, NH).

***8-Amino-7-ethoxycarbonyl-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido [4,5-b][1,8]naphthyridine-2,4,6-trione (6b).*** It was obtained from **4b** as a major product. IR(KBr,υ,$cm^{-1}$): 1078 (C—O—C), 1527 (C⋯⋯C of aromatic ring), 1647, 1662, 1680, 1690 (C=O), 2928 (C—H, aliphatic), 3048 (C—H, aromatic ), 3425 ($NH_2$), 3436–3538 (3NH)$cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.35 (t, 3H, $CH_3$), 2.92 (q, 2H, $OCH_2$),

**Table 3**

*In vitro* screening of bacteriolytic activity of compounds against *E. coli*.

| Entry | Compounds | Bacterial suspension in optical density (OD) | Bacteriolytic test | | | B.A. |
|---|---|---|---|---|---|---|
| | | | Initial (OD) | Final (OD) | Activity (OD) | |
| 1 | **4d** | 0.8 | 0.833 | 0.787 | 0.046 | + |
| 2 | **5d** | 0.8 | 0.833 | 0.788 | 0.045 | + |
| 3 | **6d** | 0.8 | 0.833 | 0.786 | 0.047 | + |
| 4 | **7d** | **0.8** | **0.833** | **0.770** | **0.063** | +++ |
| 5 | **8d** | 0.8 | 0.833 | 0.788 | 0.045 | + |
| 6 | **9d** | **0.8** | **0.833** | **0.778** | **0.055** | ++ |
| 7 | **10d** | **0.8** | **0.833** | **0.780** | **0.053** | ++ |
| 8 | **11d** | 0.8 | 0.833 | 0.788 | 0.045 | + |
| 9 | **12d** | **0.8** | **0.833** | **0.773** | **0.060** | ++ |
| 10 | **13d** | **0.8** | **0.833** | **0.775** | **0.058** | ++ |
| 11 | **14d** | **0.8** | **0.833** | **0.776** | **0.057** | ++ |
| 12 | **15d** | **0.8** | **0.833** | **0.777** | **0.056** | ++ |
| 13 | **16d** | **0.8** | **0.833** | **0.770** | **0.063** | +++ |
| 14 | **17d** | **0.8** | **0.833** | **0.775** | **0.058** | ++ |
| 15 | **18d** | 0.8 | 0.833 | 0.788 | 0.045 | + |
| 16 | **19d** | **0.8** | **0.833** | **0.774** | **0.059** | ++ |
| 17 | **20d** | 0.8 | 0.833 | 0.788 | 0.045 | + |
| 18 | **21d** | 0.8 | 0.833 | 0.786 | 0.047 | + |
| 19 | **22d** | 0.8 | 0.833 | 0.788 | 0.045 | + |
| 20 | **23d** | **0.8** | **0.833** | **0.778** | **0.055** | ++ |

Bacterial activity: B.A.
Concentration is 2 mg/mL.
(+): mild bacterial activity was observed.
(++): moderate bacterial activity was observed.
(+++): strong bacterial activity was observed.

3.74 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 4.18 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.67–6.90 (m, 3H, ArH's), 8.12 (s, 2H, $NH_2$), 8.87–9.87 (br.s, 3H, NH).

***7-Cyano-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6,8–tetraone (6′a).*** It was obtained from **4a** as a minor product along with **6a**. IR(KBr,υ,$cm^{-1}$): 1527 (C⋯C of aromatic ring), 1627, 1640, 1675, 1694 (C=O), 2198 (C=N), 2926 (C—H, aliphatic), 3045 (C=H, aromatic ), 3448–3535 (4NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 3.73 (s, 3H, $OCH_3$), 4.25 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.65–6.69 (d, 2H, ArH's), 6.70–6.72 (d, 2H, ArH's), 8.73–11.93 (br.s, 4H, NH).

***7-Cyano-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6,8–tetraone (6′d).*** It was obtained from **4d** as a minor product along with **6d**. IR(KBr,υ,$cm^{-1}$): 1598 (C=C), 1605, 1635, 1672, 1695 (C=O), 2198 (C=N), 2829 (C—H, aliphatic), 3048 (C—H, aromatic ), 3448–3535 (4NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 4.25 (s, 1H, CH), 4.68 (s, 1H, 5-CH), 5.89 (s, 2H, $O_2CH_2$), 6.49–6.57 (m, 3H, ArH's), 9.89–11.98 (br.s, 4H, NH).

***7-Ethoxycarbonyl-8-methyl-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido [4,5-b][1,8]naphthyridine-2,4,6-trione (9b).*** It was obtained from **4b** as a major product. IR(KBr,υ,$cm^{-1}$): 1078 (C—O—C), 1525 (C⋯C of aromatic ring), 1627, 1657, 1672, 1694 (C=O), 2928 (C—H, aliphatic), 3048 (C—H, aromatic ), 3428 ($NH_2$), 3435–3536 (3NH)$cm^{-1}$; $^1$H NMR ($CDCl_3$): δ1.36 (t, 3H, $CH_3$), 2.95 (q, 2H, $OCH_2$), 3.73 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 4.58 (s, 1H, CH), 4.72 (s, 1H, 5-CH), 6.70–6.74 (m, 3H, ArH's), 8.88–9.85 (br.s, 3H, NH).

***7-Ethoxycarbonyl-8-methyl-5-(4-methylphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido[4,5-b][1,8]naphthyridine-2,4,6-trione (9c).*** It was obtained from **4c** as a major product. IR(KBr,υ,$cm^{-1}$): 1079 (C—O—C), 1525 (C⋯C of aromatic ring), 1605, 1625, 1635, 1674 (C=O), 2935 (C—H, aliphatic), 3045 (C—H, aromatic ), 3424 ($NH_2$), 3435–3537 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.23 (s, 3H, $CH_3$), 1.38 (t, 3H, $CH_3$), 2.74 (q, 2H, $OCH_2$), 4.52 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.64–6.68 (d, 2H, ArH's), 6.72–6.74 (d, 2H, ArH's), 8.89–9.75 (br.s, 3H, NH).

***7-Aceto-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6,8–tetraone (9′a).*** It was obtained from **4a** as a minor product along with **9a**. IR(KBr,υ,$cm^{-1}$): 1527 (C⋯C of aromatic ring), 1647, 1659, 1678, 1694 (C=O), 2926 (C—H, aliphatic), 3045 (C—H, aromatic ), 3425 ($NH_2$), 3448–3535 (4NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.24 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 4.22 (s, 1H, CH), 4.72 (s, 1H, 5-CH), 6.65–6.67 (d, 2H, ArH's), 6.70–6.73 (d, 2H, ArH's), 8.89–11.95 (br.s, 4H, NH).

***7-Aceto-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b] [1,8]naphthyridine-2,4,6,8–tetraone (9′d).*** It was obtained from **4d** as a minor product along with **9d**. IR(KBr,υ,$cm^{-1}$): 1528 (C⋯C of aromatic ring), 1647, 1662, 1678, 1694 (C=O), 2928 (C—H, aliphatic), 3048 (C—H, aromatic ), 3458–3538 (4NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.27

(s, 3H, $CH_3$), 4.24 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 5.78 (s, 2H, $O_2CH_2$), 6.70–6.76 (m, 3H, ArH's), 8.86–11.95 (br.s, 4H, NH).

**General procedure for the synthesis of substituted pyrimido[4,5-b][1,8]naphthyridine-2,4,6-triones 7a–7d and substituted benzo[b]pyrimido[5,4-g][1,8]naphthyridine-2,4,6,7-tetraones 8a–8d.** A suspension of **4** (0.02 mole), the appropriate active methylene compounds, i.e., acetylacetone/dimedone (0.02 mole) and $P_2O_5$ (0.10 g) in dry toluene 20 mL was refluxed for 4 h, and the water was collected in a Dean Stark trap. After cooling, the reaction mixture was filtered. The filtrate was evaporated to dryness. The resulting residue (enamine ketone) was crystallized from ethyl acetate. To (0.03 mole) of the residue was added $K_2CO_3$ (2.0 mmole) and copper powder (0.03 mole) in dry acetone (10 mL) and refluxed for 5–6 h. After completion of reaction, the warm reaction solution was filtered. The filtrate was evaporated to dryness and crystallized from hot ethanol to get **7** and **8**, respectively.

***7-Aceto-8-methyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido[4,5-b][1,8] naphthyridine-2,4,6-trione (7a).*** It was obtained from **4a**. IR(KBr,υ,$cm^{-1}$): 1625 (C⋯C of aromatic ring), 1638, 1675, 1680, 1695 (C=O), 2932 (C—H, aliphatic), 3048 (C—H, aromatic ), 3335–3485 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.68 (s, 3H, $CH_3$), 2.95 (s, 3H, $CH_3$), 3.72 (s, 3H, $OCH_3$), 3.76 (s, 1H, CH), 4.71 (s, 1H, 5-CH), 6.62–6.65 (d, 2H, ArH's), 6.73–6.94 (d, 2H, ArH's), 8.80–9.83 (br.s, 3H, NH).

***7-Aceto-8-methyl-5-(3,4-methylenedioxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrimido [4,5-b][1,8] naphthyridine-2,4,6-trione (7d).*** It was obtained from **4d**. IR(KBr,υ,$cm^{-1}$): 1595 (C⋯C of aromatic ring), 1657, 1675, 1685, 1694 (C=O), 2898 (C—H, aliphatic), 3045 (C—H, aromatic ), 3338–3483 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.32 (s, 3H, $CH_3$), 2.98 (s, 3H, $CH_3$), 3.76 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 5.75 (s, 2H, $O_2CH_2$), 6.64–6.67 (m, 3H, ArH's), 8.92–9.85 (br.s, 3H, NH).

***9,9-Dimethyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,6a,7,8,9,10,12-dodecahydrobenzo[b] pyrimido[5,4-g][1,8]naphthyridine-2,4,6,7-tetraone (8a).*** It was obtained from **4a**. IR(KBr,υ,$cm^{-1}$): 1625 (C⋯C of aromatic ring), 1657, 1663, 1675, 1690 (C=O), 2928 (C—H, aliphatic), 3025 (C—H, aromatic ), 3330–3484 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.54 (d, 2H, $CH_2$), 2.98 (d, 2H, $CH_2$), 3.74 (s, 3H, $OCH_3$), 3.83 (s, 1H, CH), 4.74 (s, 1H, 5-CH), 6.64–6.67 (d, 2H, ArH's), 6.73–6.98 (d, 2H, ArH's), 8.83–9.53 (br.s, 3H, NH).

***9,9-Dimethyl-5-(4-methylphenyl)-1,2,3,4,5,6,6a,7,8,9,10,12-dodecahydrobenzo[b] pyrimido[5,4-g][1,8]naphthyridine-2,4,6,7-tetraone (8c).*** It was obtained from **4c**. IR(KBr,υ,$cm^{-1}$): 1625 (C⋯C of aromatic ring), 1645, 1669, 1680, 1695 (C=O), 2925 (C—H, aliphatic), 3048 (C—H, aromatic), 3338–3480 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.12 (s, 6H, $2CH_3$), 2.52 (s, 3H, $CH_3$), 2.56 (d, 2H, $CH_2$), 2.96 (d, 2H, $CH_2$), 3.85 (s, 1H, CH), 4.72 (s, 1H, 5-CH), 6.62–6.67 (d, 2H, ArH's), 6.72–6.95 (d, 2H, ArH's), 8.87–9.58 (br.s, 3H, NH).

**General procedure for the synthesis of substituted dipyrimido[4,5-b;4′,5′-f] [1,8]naphthyridines 10a–10d and 11a–11d.** A mixture of **7** (10 mmoles) and thiourea/urea (10 mmoles) in DMF (20 mL) was melted and refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products so formed, **10** and **11**, respectively, were collected by filtration and crystallized from ethanol as light brown crystals.

***4,5-Dimethyl-12-(4-methoxyphenyl)-2-thioxo-2,4a,7,8,9,10,11,12-octahydrodipyrimido [4,5-b;4′,5′-f] [1,8]naphthyridine-9,11-dione (10a).*** It was obtained from **7a** using thiourea. IR(KBr,υ,$cm^{-1}$): 1605 (C⋯C of aromatic ring), 1640, 1670 (C=O), 2925 (C—H, aliphatic), 3052 (C—H, aromatic ), 3334–3485 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.20 (s, 3H, $CH_3$), 2.24 (s, 1H, CH), 2.52 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 4.74 (s, 1H, 12-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.96 (d, 2H, ArH's), 8.78–9.84 (br.s, 3H, NH).

***4,5-Dimethyl-12-(3,4-methylenedioxyphenyl)-2-thioxo-2,4a,7,8,9,10,11,12-octahydrodi pyrimido[4,5-b;4′,5′-f] [1,8]naphthyridine-9,11-dione (10d).*** It was obtained from **7d** using thiourea. IR(KBr,υ,$cm^{-1}$): 1645, 1670 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3048 (C—H, aromatic ), 3333–3484 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.21 (s, 3H, $CH_3$), 2.26 (s, 1H, CH), 2.53 (s, 3H, $CH_3$), 4.74 (s, 1H, 12CH), 5.79 (s, 2H, $O_2CH_2$), 6.65–6.69 (m, 3H, ArH's), 8.78–9.76 (br.s, 3H, NH).

***4,5-Dimethyl-12-(3,4-dimethoxyphenyl)-2,4a,7,8,9,10,11,12-octahydrodipyrimido[4,5-b; 4′,5′-f][1,8]naphthyridine-2,9,11-trione (11b).*** It was obtained from **7b** using urea. IR(KBr,υ,$cm^{-1}$): 1595, 1605, 1648 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3042 (C—H, aromatic ), 3330–3488 (3NH) $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.21 (s, 3H, $CH_3$), 2.26 (s, 1H, CH), 2.54 (s, 3H, $CH_3$), 3.71 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.75 (s, 1H, 12-CH), 6.67–6.72 (m, 3H, ArH's), 8.78–9.76 (br.s, 3H, NH). $^{13}$C NMR ($CDCl_3$):16.1, 24.7, 30.1, 56.3, 79.7, 94.8, 115.0, 115.8, 122.6, 130.0, 140.5, 144.6, 145.2, 147.5, 151.6, 161.0, 162.2, 164.1, 164.6, 165.1, 194.5.

***4,5-Dimethyl-12-(4-methylphenyl)-2,4a,7,8,9,10,11,12-octahydrodipyrimido[4,5-b;4′,5′-f] [1,8]naphthyridine-2,9,11-trione (11c).*** It was obtained from **7c** using urea. IR(KBr,υ,$cm^{-1}$): 1605 (C⋯C of aromatic ring), 1594, 1645, 1670 (C=O), 2926 (C—H, aliphatic), 3054 (C—H, aromatic ), 3334–3487 (3NH)$cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.20 (s, 3H, $CH_3$), 2.24 (s, 1H, CH), 2.36 (s, 3H, $CH_3$), 2.52 (s, 3H, $CH_3$), 4.73 (s, 1H, 12-CH), 6.62–6.67 (d, 2H, ArH's), 6.74–6.98 (d, 2H, ArH's), 8.76–9.86 (br.s, 3H, NH).

**General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepine-1,3-diones 12a–12d.** A mixture of **7** (10 mmoles) and *o*-phenylenediamine (10 mmoles) in DMF (20 mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product **12** so formed was collected by filtration and crystallized from ethanol.

***7,8-Dimethyl-15-(4-methoxyphenyl)-2,3,4,5,7a,15-hexahydro-1H-pyrimido[5′,4′:6,7][1,8] naphthyridino[4,3-b][1,5]benzodiazepine-1,3-dione (12a).*** It was obtained from **7a**. IR(KBr,υ,$cm^{-1}$): 1595 (C⋯C of aromatic ring), 1675, 1690 (C=O), 2923 (C—H, aliphatic), 3059 (C—H, aromatic ), 3328–3484 (3NH)$cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.57 (s, 1H, CH), 2.47 (s, 3H, $CH_3$), 2.83 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 4.71 (s, 1H, 15-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.95 (d, 2H, ArH's), 7.13–7.35 (m, 4H, ArH's), 8.88–9.76 (br.s, 3H, NH). $^{13}$C NMR ($CDCl_3$): 16.1, 16.5, 24.7, 26.2, 28.3, 56.0, 79.7, 95.0, 114.0, 123.3, 128.3, 129.6, 130.3, 142.5, 143.0, 145.2, 151.5, 159.1, 164.1, 164.6.

***7,8-Dimethyl-15-(3,4-methylenedioxyphenyl)-2,3,4,5,7a,15-hexahydro-1H-pyrimido[5′,4′: 6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepine-1,3-dione (12d).*** It was obtained from

**7d**. IR(KBr,υ,cm$^{-1}$): 1640, 1695 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3048 (C—H, aromatic ), 3333–3485 (3NH) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.52 (s, 1H, CH), 2.47 (s, 3H, $CH_3$), 2.84 (s, 3H, $CH_3$), 4.74 (s, 1H, 15-CH), 5.76 (s, 2H, $O_2CH_2$), 6.68–6.72 (m, 3H, ArH's), 7.13–7.32 (m, 4H, ArH's), 8.86–9.78 (br.s, 3H, NH).

**General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3,2-de]quinazolines 13a–13d and 14a–14d.** A mixture of **8** (10 mmoles) and thiourea/urea (10 mmoles) in DMF (20 mL) was refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products **13** and **14**, respectively, so formed were collected by filtration and crystallized from ethanol as light brown crystal.

***5,5-Dimethyl-13-(4-methoxyphenyl)-2-thioxo-4,5,6,8,9,10, 11,12,13,13c-decahydro-2H-pyrimido[5′,4′:6,7][1,8]naphthyridino [4,3,2-de]quinazoline-10,12-dione (13a).*** It was obtained from **8a** using thiourea. IR(KBr,υ,cm$^{-1}$): 1605 (C⋯C of aromatic ring), 1672, 1685 (C=O), 2925 (C—H, aliphatic), 3052 (C—H, aromatic ), 3334–3485 (3NH)cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.48 (s, 2H, $CH_2$), 2.81 (s, 2H, $CH_2$), 2.86 (s, 1H, CH), 3.74 (s, 3H, $OCH_3$), 4.74 (s, 1H, 13-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.96 (d, 2H, ArH's), 8.75–9.87 (br.s, 3H, NH).

***5,5-Dimethyl-13-(4-methylphenyl)-2-thioxo-4,5,6,8,9,10,11,12, 13,13c-decahydro-2H-pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3,2-de]quinazoline-10,12-dione (13c).*** It was obtained from **8c** using thiourea. IR(KBr,υ,cm$^{-1}$): 1598 (C⋯C of aromatic ring), 1645–1680 (C=O), 2928 (C—H, aliphatic), 3047 (C—H, aromatic ), 3336–3483 (3NH) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.34 (s, 3H, $CH_3$), 2.48 (s, 2H, $CH_2$), 2.81 (s, 2H, $CH_2$), 2.86 (s, 1H, CH), 4.74 (s, 1H, 13-CH), 6.67–6.68 (d, 2H, ArH's), 6.74–6.98 (d, 2H, ArH's), 8.79–9.88 (br.s, 3H, NH). $^{13}$C NMR ($CDCl_3$): 19.6, 20.9, 27.1, 27.9, 45.1, 45.9, 79.7, 94.8, 128.6, 129.4, 134.7, 141.8, 145.2, 151.6, 164.4, 164.9, 235.8.

***5,5-Dimethyl-13-(3,4-dimethoxyphenyl)-4,5,6,8,9,10,11,12, 13,13c-decahydro-2H-pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3,2-de]quinazoline-2,10,12-trione (14b).*** It was obtained from **8b** using urea. IR(KBr,υ,cm$^{-1}$): 1595, 1638, 1658 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3044 (C—H, aromatic ), 3330–3486 (3NH)cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.27 (s, 2H, $CH_2$), 2.43 (s, 2H, $CH_2$), 2.88 (s, 1H, CH), 3.74 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.75 (s, 1H, 13-CH), 6.87–6.96 (m, 3H, ArH's), 8.78–9.76 (br.s, 3H, NH).

***5,5-Dimethyl-13-(3,4-methylenedioxyphenyl)-4,5,6,8,9,10,11,12, 13,13c-decahydro-2H-pyrimido[5′,4′:6,7][1,8]naphthyridino[4,3,2-de]quinazoline-2,10,12-trione (14d).*** It was obtained from **8d** using urea. IR(KBr,υ,cm$^{-1}$): 1595, 1635, 1648 (C=O), 1605 (C⋯C of aromatic ring), 2850 (C—H, aliphatic), 3333–3484 (3NH) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.23 (s, 2H, $CH_2$), 2.53 (s, 2H, $CH_2$), 2.86 (s, 1H, CH), 4.74 (s, 1H, 13-CH), 5.74 (s, 2H, $O_2CH_2$), 6.68–6.82 (m, 3H, ArH's), 8.81–9.82 (br.s, 3H, NH).

**General procedure for the synthesis of substituted pyrido[2′,1′:2,3]pyrimido[4,5-f] pyrimido[4,5-b][1,8]naphthyridine-11,13-diones 15a–15d.** A mixture of **7** (10 mmoles) and 2-aminopyridine (10 mmoles) in DMF (20 mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products so formed, **15** were collected by filtration and crystallized from ethanol.

***6,7-Dimethyl-14-(4-methoxyphenyl)-11,12,13,14-tetrahydro-10H-pyrido[2′,1′:2,3] pyrimido[4,5-f]pyrimido[4,5-b][1,8]naphthyridine-11,13-dione (15a).*** It was obtained from **7a**. IR(KBr,υ,cm$^{-1}$): 1595 (C⋯C of aromatic ring), 1675, 1695 (C=O), 2923 (C—H, aliphatic), 3059 (C—H, aromatic ), 3329–3481 (2NH) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.32 (s, 3H, $CH_3$), 2.71 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 4.45 (s, 1H, 14-CH), 6.47–6.62 (m, 4H, ArH's), 6.64–6.67 (d, 2H, ArH's), 6.74–6.95 (d, 2H, ArH's), 8.88–9.78 (br.s, 2H, NH). $^{13}$C NMR ($CDCl_3$): 26.9, 27.7, 48.1, 48.8, 56.6, 81.7, 115.0, 115.8, 116.7, 120.6, 122.4, 130.1, 144.6, 147.5, 151.3, 155.6, 157.0, 157.2, 159.1, 161.6, 164.4, 168.9.

***6,7-Dimethyl-14-(4-methylphenyl)-11,12,13,14-tetrahydro-10H-pyrido[2′,1′:2,3]pyrimido [4,5-f]pyrimido[4,5-b][1,8]naphthyridine-11,13-dione (15c).*** It was obtained from **7c**. IR(KBr,υ,cm$^{-1}$): 1590 (C⋯C of aromatic ring), 1670, 1695 (C=O), 2926 (C—H, aliphatic), 3054 (C—H, aromatic ), 3333–3480 (2NH)cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.22 (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$), 2.72 (s, 3H, $CH_3$), 4.74 (s, 1H, 14-CH), 6.39–6.62 (m, 4H, ArH's), 6.65–6.67 (d, 2H, ArH's), 6.80–6.95 (d, 2H, ArH's), 8.96–9.74 (br.s, 2H, NH). $^{13}$C NMR ($CDCl_3$): 16.2, 18.2, 20.9, 96.5, 100.4, 106.9, 116.8, 121.6, 126.7, 128.5, 129.0, 129.4, 134.7, 137.5, 140.3, 141.6, 149.5, 151.5, 159.1, 164.0, 164.6.

**General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3,2-de]pyrido[2,1-b]quinazoline-10,12-diones 16a–16d.** A mixture of **8** (10 mmoles) and 2-aminopyridine (10 mmoles) in DMF (20 mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid products **16** so formed were collected by filtration and crystallized from ethanol.

***7,7-Dimethyl-15-(4-methoxyphenyl)-6,7,8,11,12,13,14,15-octahydropyrimido[5′,4′:6,7][1,8]naphthyridino[4,3,2-de]pyrido[[2,1-b]quinazoline-12,14-dione (16a).*** It was obtained from **8a**. IR(KBr,υ,cm$^{-1}$): 1595 (C⋯C of aromatic ring), 1665, 1685 (C=O), 2927 (C—H, aliphatic), 3058 (C—H, aromatic ), 3336–3487 (2NH) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.48 (s, 2H, $CH_2$), 2.81 (s, 2H, $CH_2$), 3.42 (s, 3H, $OCH_3$), 4.74 (s, 1H, 15-CH), 6.47–6.62 (m, 4H, ArH's), 6.64–6.67 (d, 2H, ArH's), 6.74–6.96 (d, 2H, ArH's), 8.75–9.87 (br.s, 2H, NH).

***7,7-Dimethyl-15-(3,4-methylenedioxyphenyl)-6,7,8,11,12,13,14, 15-octahydropyrimido [5′,4′:6,7][1,8]naphthyridino[4,3,2-de]pyrido[[2,1-b]quinazoline-12,14-dione (16d).*** It was obtained from **8d**. IR(KBr,υ,cm$^{-1}$): 1595 (C⋯C of aromatic ring), 1638, 1680 (C=O), 2890 (C—H, aliphatic), 3049 (C—H, aromatic ), 3333–3485 (2NH)cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 1.88 (s, 2H, $CH_2$), 2.12 (s, 2H, $CH_2$), 4.74 (s, 1H, 15-CH), 5.87 (s, 2H, $O_2CH_2$), 6.17–6.59 (m, 3H, ArH's), 6.49–6.62 (m, 4H, ArH's), 8.97–9.79 (br.s, 2H, NH). $^{13}$C NMR ($CDCl_3$): 21.1, 27.1, 45.6, 47.8, 91.3, 100.4, 106.9, 115.0, 115.8, 116.9, 120.1, 122.7, 126.6, 131.4, 138.5, 140.2, 143.1, 144.6, 147.5, 149.6, 151.5, 161.2, 163.6, 164.0, 164.8.

**General procedure for the synthesis of substituted pyrido[2,3-d;6,5-d′]dipyrimidine-2,4,6-triones 17a–17d.** A mixture of equimolar quantity of **4** (0.01 moles) and formamide (0.01 moles) was refluxed on a water bath for 6 h. After the completion of the reaction, the reaction mixture was poured into

ice-cold water with stirring. The solid product was collected by filtration and crystallized from hot methanol to afford **17**.

***5-(4-methoxyphenyl)-1,2,3,4,5,6,7,10-octahydropyrido[2,3-d;6,5-d′]dipyrimidine-2,4,6-trione (17a).*** It was obtained from **4a**. $^1$H NMR ($CDCl_3$): δ 3.73 (s, 3H, $OCH_3$), 4.74 (s, 1H, 5-CH), 6.63–6.65 (d, 2H, ArH's), 6.85–6.95 (d, 2H, ArH's), 7.48 (s, 1H, CH), 8.50–11.95 (br.s, 4H, NH). $^{13}$C NMR ($CDCl_3$): 39.1, 55.9, 79.7, 100.9, 114.2, 114.9, 129.1, 130.1, 134.5, 150.1, 150.5, 151.2, 157.0, 157.7, 162.5, 163.8.

**General procedure for the synthesis of substituted dipyrimido[4,5-b:5′,4′-g] [1,8]naphthyridine-2,4,6-trione 18a–18d.** A mixture of equimolar quantity of **5** (0.01 moles) and formamide (0.01 moles) was refluxed on a water bath for 6 h. After the completion of the reaction, the reaction mixture was poured into ice-cold water. The solid product was collected by filtration and crystallized from hot methanol to produce **18**. On the other hand, a mixture of **5** and formamide (1:2 ratios) was refluxed on a water bath for 6–8 h. After the completion of the reaction, the reaction mixture was poured into the ice-cold water. The solid product was collected by filtration and crystallized from hot methanol to produce **19** as the main product. From the mother liquor a minor product was also separated on cooling which was exactly identical with **18**.

***7-Amino-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,11,12-octahydrodipyrimido[4,5-b;5′,4′-g] [1,8]naphthyridine-2,4,6-trione (18b).*** It was obtained from **5b**. $^1$H NMR ($CDCl_3$): δ 3.72 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.74 (s, 1H, 5-CH), 5.92 (s, 2H, $NH_2$), 6.52–6.58 (m, 3H, ArH's), 7.85 (s, 1H, CH), 8.85–11.92 (br.s, 4H, NH). $^{13}$C NMR ($CDCl_3$): 36.5, 56.2, 56.8, 79.5, 85.6, 99.3, 114.5, 115.2, 122.6, 135.5, 146.7, 150.2, 150.9, 151.5, 154.5, 155.9, 163.8, 172.6, 183.5.

***13-(3,4-Methylenedioxyphenyl)-8,9,10,11,12,13-hexahydro-3H-1,3,4,6,7,8,9,11-octaza- benzo[de]naphthacene-10,12-diones (19d).*** It was obtained from **5d**. $^1$H NMR ($CDCl_3$): δ 4.72 (s, 1H, 13-CH), 5.82 (s, 2H, $O_2CH_2$), 6.48–6.59 (m, 3H, ArH's), 7.50 (s, 1H, 5-CH), 8.37 (s, 1H, 2-CH), 8.71–11.92 (br.s, 4H, NH). $^{13}$C NMR ($CDCl_3$): 32.8, 81.7, 100.2, 101.4, 111.4, 114.1, 115.2, 122.4, 128.4, 145.8, 146.3, 148.7, 150.5, 155.2, 155.9, 156.0, 156.9, 158.0, 158.7, 163.8.

**General procedure for the synthesis of substituted dipyrimido[4,5-b:5′,4′-g] [1,8]naphthyridines 20a–20d.** A mixture of equimolar quantity of **6** (0.01 moles) and formamide (0.01 moles) was refluxed on a water bath for 6 h. After the completion of the reaction, the reaction mixture was poured into ice-cold water with stirring. The solid product was collected by filtration and crystallized from hot methanol to produce **20**.

***5-(4-Methoxyphenyl)-1,2,3,4,5,6,6a,7,8,12-decahydrodipyrimido[4,5-b;5′,4′-g][1,8]naphthyridine-2,4,6,7-tetraone (20b).*** It was obtained from **6b**. $^1$H NMR ($CDCl_3$): δ 3.78 (s, 3H, $OCH_3$), 3.98 (s, 1H, 6a-CH), 4.48 (s, 1H, 5-CH), 6.63–6.65 (d, 2H, ArH's), 6.85–6.95 (d, 2H, ArH's), 7.89 (s, 1H, 9-CH), 8.59–11.72 (br.s, 4H, NH). $^{13}$C NMR ($CDCl_3$): 36.5, 55.1, 55.9, 79.5, 107.5, 114.2, 114.8, 130.0, 130.6, 134.5, 150.2, 150.5, 150.9, 155.9, 157.8, 163.8, 164.2, 170.5, 196.5.

**General procedure for the synthesis of substituted pyrimido[5′,4′:6,7] [1,8]naphthyridino[4,3-b][1,5]benzodiazepine-1,3,8-triones 21a–21d.** A mixture of 6 (10 mmoles) and *o*-phenylenediamine (10 mmoles) in DMF (20mL) was refluxed for 8–10 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product 21 so formed was collected by filtration and crystallized from ethanol.

***7-Amino-15-(4-methoxyphenyl)-2,3,4,5,7a,8,9,15-octahydro-1H-pyrimido[5′,4′:6,7][1,8] naphthyridino[4,3-b[1,5]benzodiazepine-1,3,8-trione (21a).*** It was obtained from **6a**. $^1$H NMR($CDCl_3$): δ 1.59 (s, 1H, 7a-CH), 3.74 (s, 3H, $OCH_3$), 3.89 (s, 2H, $NH_2$), 4.72 (s, 1H, 15-CH), 6.64–6.67 (d, 2H, ArH's), 6.74–6.95 (d, 2H, ArH's), 7.23–7.58 (m, 4H, ArH's), 8.85–11.90 (br.s, 4H, NH). $^{13}$C NMR ($CDCl_3$) : 37.5, 39.2, 55.9, 79.5, 93.0, 114.8, 114.1, 122.5, 122.9, 125.6, 127.4, 130.1, 130.6, 132.5, 134.7, 142.6, 150.4, 151.2, 151.6, 157.7, 163.8, 164.0, 164.8, 168.2.

**General procedure for the synthesis of substituted dipyrimido[4,5-b;4′,5′-f] [1,8]naphthyridines 22a–22d and substituted dipyrimido[4,5-b;5′,4′-g] [1,8]naphthyridines 23a–23d.** A mixture of **6** (10 mmoles) and thiourea (10 mmoles) in DMF (20 mL) was refluxed for 5–6 h. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product so formed, a mixture of **22** and **23** was collected by filtration and separated by column chromatography (eluant:Pet ether:Methanol::90:10; Pet ether: Methanol::85:15).

***5-Amino-12-(3,4-dimethoxyphenyl)-2-thioxo-2,3,4,4a,7,8,9,10, 11,12-decahydro dipyrimido[4,5-b; 4′,5′-f][1,8]naphthyridine-4,9,11-trione (22b).*** It was obtained from **6a** using thiourea. IR(KBr,υ,$cm^{-1}$): 1625 (C⋯⋯C of aromatic ring), 1660, 1670, 1675 (C═O), 2890 (C—H, aliphatic), 3049 (C—H, aromatic ), 3235 ($NH_2$), 3330–3400 (4NH)$cm^{-1}$; $^1$H NMR($CDCl_3$): δ 2.26 (s, 1H, 4a-CH), 3.71 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.85 (s, 2H, $NH_2$), 4.74 (s, 1H, 12-CH), 6.67–6.72 (m, 3H, ArH's), 8.85–11.92 (br.s, 4H, NH). $^{13}$C NMR ($CDCl_3$): 36.5, 38.9, 55.6, 79.6, 93.2, 114.2, 114.8, 130.1, 130.6, 134.5, 150.6, 151.0, 151.8, 157.6, 159.8, 163.8, 164.0, 164.8, 170.7. MS: m/z, 467 ($M^+$).

***5-(4-Methoxyphenyl)-9-thioxo-1,2,3,4,5,6,6a,7,8,9,10,12-dodecahydrodipyrimido[4,5-b; 5′,4′-g][1,8]naphthyridine-2,4,6,7-tetraone (23a).*** It was obtained from **6a** using thiourea. IR(KBr,υ,$cm^{-1}$): 1605 (C⋯⋯C of aromatic ring), 1657, 1665, 1678, 1715 (C═O), 2895 (C—H, aliphatic), 3042 (C—H, aromatic ), 3330–3470 (5NH)$cm^{-1}$; $^1$H NMR($CDCl_3$): δ 3.92 (s, 1H, 6a-CH), 4.43 (s, 1H, 5-CH), 6.63–6.67 (d, 2H, ArH's), 6.85–6.95 (d, 2H, ArH's), 8.69–11.92 (br.s, 5H, NH). $^{13}$C NMR ($CDCl_3$): 36.5, 55.8, 56.9, 79.5, 107.5, 114.2, 114.8, 130.0, 131.6, 134.5, 150.5, 151.2, 152.9, 155.8, 157.6, 163.8, 164.2, 170.7, 196.5. MS: m/z, 438 ($M^+$).

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## REFERENCES AND NOTES

[1] Schutz, H. Benzodiazepines; Springer: Heidelberg, 1982.

[2] Randall, L. O.; Kappel, B.; Garattini, S.; Mussini, E., Eds. Benzodiazepines, Vol. 27; Raven Press: NewYork, 1973.

[3] Bock, M. G.; Dipardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Friedinger, R. M. J Med Chem 1989, 32, 13.

[4] Romer, D.; Buschler, H. H.; Hill, R. C.; Maurer, R.; Petcher, T. J.; Zeugner, H.; Benson, W.; Finner, E.; Milkowski, W.; Thies, P. W. Nature 1982, 298, 759.

[5] Korneki, E.; Erlich, Y. H.; Lenox, R. H. Science 1984, 226, 1454.

[6] (a) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Mirands, M.; Rodgers, J. D.; Sherrill, R. G.; Clercq, E.

D.; Pauwels, R.; Anderies, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. J Med Chem 1991, 34, 3187; (b) Parker, K. A.; Coburn, C. A. J Org Chem 1992, 57, 97.

[7] Chakrabarti, J. K; David, E. T. Ger. Pat. 2552403, 1976; Chem Abstr 86, 29893e.

[8] Neunhoeffer, H. In Comprehensive Heterocyclic Chemistry. Katritzky, A. R., Rees, C. W. Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p.385.

[9] Bhalerao, U. T.; Krishnaiah, A. Indian J Chem 1995, 34B, 587.

[10] Albrecht, R. Prog Drug Res 1977, 21, 9.

[11] Tonetti, I.; Bertini, D.; Ferrarini, P. L.; Livi, O.; DelTacca, M. Farmaco Ed Sci 1976, 31, 175.

[12] Carboni, S.; DaSettimo, A.; Bertini, D.; Ferrarini, P. L.; Livi, O.; Tonetti, I. Farmaco Ed Sci 1976, 31, 175.

[13] (a) Armarego, W. L. F. Adv Heterocycl Chem 1963, 1, 253; (b) Armarego, W. L. F. Adv Heterocycl Chem 1979, 24, 1.

[14] Saxena, S.; Verma, M.; Saxena, A. K.; Shanker, K. Indian J Pharm Sci 1991, 53, 48.

[15] Srivastava, B.; Shukla, J. S. Indian J Chem Sect B 1991, 30B, 332.

[16] Fisnerova, L.; Brunova, B.; Kocfeldova, Z.; Tikalova, J.; Maturova, E.; Grimova, J. Collect Czech Chem Commun 1991, 56, 2373.

[17] Abdel-Rahman, M. M.; Mangoura, S. A.; El-Bitar, H. I. Chem Abstr 1992, 116, 185c; Bull Pharm Sci Assitu Univ 1990, 13, 137.

[18] Hori, M.; Lemura, R.; Hara, H.; Ozaki, A.; Sukamoto, T.; Ohtaka, H. Chem Pharm Bull 1990, 38, 1286.

[19] Brown, D. J. In Comprehensive Heterocyclic Chemistry. Katritzky, A.R., Ed.; Pergamon Press: Oxford, 1984; Vol. 3, p.153.

[20] Buchi, G.; Luk, K. C.; Kobbe, B.; Townsend, J. M. J Org Chem 1977, 42, 244.

[21] Singh, J.; Koul, S.; Pannu, A. P. S.; Sharma, R. L.; Razdan, T. K. J Heterocycl Chem 2008, 45, 349.

[22] Sachar, A.; Sharma, R. L. Indian J Heterocycl Chem 2007, 16, 415.

[23] Sachar, A.; Sharma, R. L.; Kumar, S.; Kour, D.; Singh.J. J Heterocycl Chem 2006, 43, 1177.

[24] Sharma, R. L.; Kour, D.; Singh, J.; Kumar, S.; Gupta, P.; Gupta, S.; Kour, B.; Sachar, A. J Heterocycl Chem 2008, 45, 1775.

[25] Sharma, R. L.; Singh, J.; Kumar, S.; Kour, D.; Sachar, A.; Gupta, S.; Gupta, P.; Sharma, B. J Heterocycl Chem 2007, 44, 1501.

[26] Tu, S.; Zhang, J.; Zhu, X.; Zhang, Y.; Wang, Q.; Xu, J.; Jiang, B.; Jia, R.; Zhang, J.; Shi, F. J Heterocycl Chem 2006, 43, 985.

[27] Song, Y.-H.; Seo, J. J Heterocycl Chem 2007, 44, 1439.

# A Zeolite Promoted Expeditious One-Pot Synthesis of 1-Arylmethyl-4,5-dihydro-2-aryl-1H-imidazole



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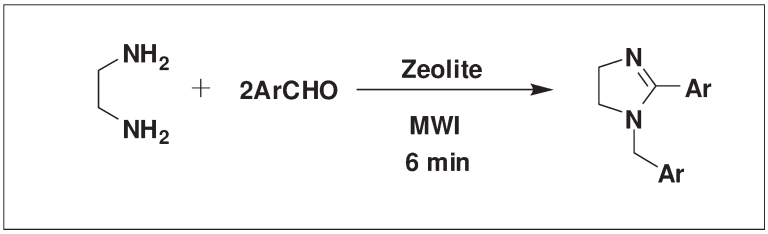


A series of 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles were synthesized expeditiously in good yields from 1,2-diaminoethane and aromatic aldehydes in the presence of zeolite under microwave irradiation in the absence of solvent. The resulting substituted imidazoles are characterized by $^{1}H$ and $^{13}C$ NMR, elemental analysis, and mass spectral data.

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## INTRODUCTION

The use of microwave (MW) irradiation as a non-conventional energy source has become of considerable interest in organic chemistry. This novel method has proved to be very efficient in various reactions, especially in organic synthesis [1–5], which has several advantages over classical thermal conditions in providing increased reaction rates, simplicity, and improved yields. The development of one-pot reaction has been of great interest in organic synthesis because this methodology provides easy access to highly complex molecules from relatively simple reagents under economically favorable reaction conditions. Thus, the combination of the one-pot strategy with the use of eco-friendly zeolite catalysts becomes a powerful means of preparation for specific target compounds to minimize pollutants and to reduce production cost [6–9]. MW irradiation has been used to effect organic reactions, such as cyclization [10], aromatic substitution [11], oxidation [12], alkylation [13], decarboxylation [14], radical reactions [15], condensation [16], peptide synthesis [17], etc.

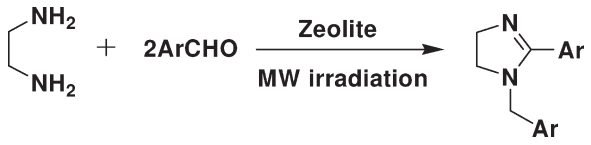
Imidazole chemistry currently attracts considerable attention, where the imidazole derivatives are extensively applied as *N*-ligands coordinating transition metals [18,19]. The application of imidazoles in medicinal chemistry [20], chemistry of natural products/alkaloids [21], and 1,3-disubstituted imidazole salts as ionic liquids [22] are well known. Several methods are reported in the literature for the synthesis of imidazoles, such as: (a) synthesis *via* hetero-Cope rearrangement [23]; (b) four-component condensation of arylglyoxals, primary amines, carboxylic acids, and iso-cyanides on Wang resin [24,25]; (c) reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate [26]. Compounds with an imidazole ring system have many pharmacological properties and play important roles in biochemical processes [27]. Organic chemists have been making extensive efforts to produce heterocyclic compounds by developing new and efficient synthetic transformations [28]. Recently, palladium and copper-catalyzed strategies have been successfully applied to the assembly of various heterocyclic compounds *via* one-pot synthesis [29].

Many of the synthetic protocols for imidazoles reported so far suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous, and often expensive acid catalysts. We have employed to achieve simple and environmentally compatible synthetic methodology for the synthesis of substituted imidazoles in the presence of zeolite under MW irradiation.

## RESULTS AND DISCUSSION

Reactions were carried out simply by mixing 1,2-diaminoethane with different substituted aromatic aldehydes in the presence of zeolite under solvent-free condition

**Scheme 1.** MW assisted synthesis of substituted imidazoles.



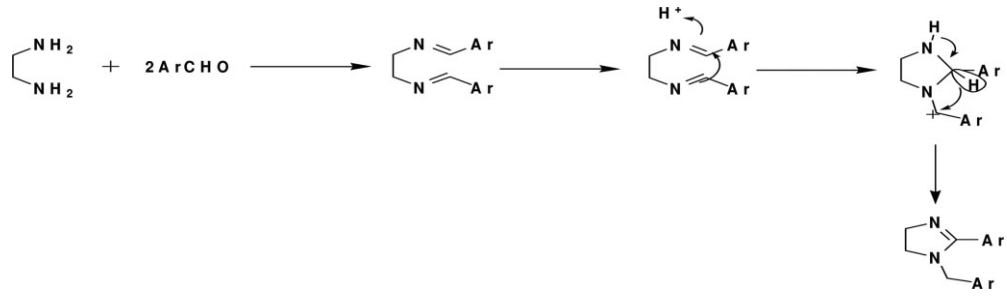

(Scheme 1). All the 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles derivatives were obtained in excellent yields.

This study describes a successful approach for the synthesis of substituted imidazoles using a laboratory MW reactor. This MW technology does not require linking-cleaving chemistry and afford the products immediately. In a solvent-free cyclization reaction of imidazoles is developed, which requires MW irradiation of 1,2-diaminoethane and aromatic aldehydes in the presence of zeolite. This support allows for easy separation of the solid catalyst and product by simple filtration, and in optimal conditions the supported catalyst can be reused multiple times. The readily and exclusive formation of cyclized imidazoles occurs in good yields.

The same reaction under thermal conditions (Scheme 2) affords lower yields (Table 1). Hence, it is clear from the yield comparison plot (Fig. 1) of classical and MW assisted synthesis of the substituted imidazoles that MW irradiation has been found to be easier, convenient, eco-friendly, and yield of all the products are more than good as compared with the classical method. In general, synthesis of substituted imidazole under thermal conditions may occur in two steps, formation of Schiff base and its cyclization.

The reaction may tentatively be visualized to occur *via* a tandem sequence of reactions depicted in reaction mechanism (Mechanism 1) involving (i) formation of *N*,*N*′–bis(aryl)ethylenediimine, (ii) protonation of the *N*,*N*′–bis(aryl)ethylenediimine by zeolite and ring closure leading to a five membered ring in either a sequential or a concerted manner, (iii) 1,3-hydride transfer, and (iv) deprotonation. While the aryl groups/nitrogen atom could stabilize the positively charged intermediates involved in the intermediate steps, the aromatic stabilization of the resulting imidazoles could provide the impetus for the transformation. The reaction under MW condition goes to completion in 6 min. Physical properties of the substituted imidazoles are given in Table 2.

**Mechanism 1:** The possible reaction mechanism.




## EXPERIMENTAL

**General.** All the chemicals and solvents were obtained from Merck (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. The MW assisted synthesis of titled compounds were carried out in a CEM – 908010, bench mate model, 300 watts laboratory MW reactor. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. $^{1}$H NMR and $^{13}$C NMR spectra of the imidazoles were recorded on a Bruker-Avance (300 MHz), Varian-Gemini (200 MHz) spectrophotometer using DMSO solvent and TMS as the internal standard. EI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an EI source.

**Synthesis of 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles.** 1,2-diaminoethane (0.108 g, 1 mmol), benzaldehyde (0.212 g, 2 mmol), and zeolite (montmorillonite K-10) (0.1 g) was thoroughly mixed. The reaction mixture was irradiated for 6 min with 100 W MWs at 110°C in MW oven in the temperature control mode. The completion of the reaction was monitored by TLC. After the irradiation was over, the reaction mixture was cooled and added into water and extracted with diethyl

**Scheme 2.** Synthesis of substituted imidazole under thermal condition.

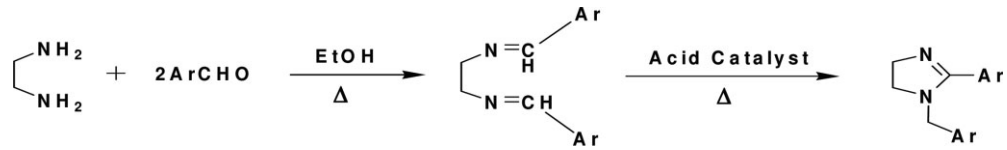


**Table 1**

Time and yield comparison between classical and MW irradiation.

| | | Microwave method | | Classical method | |
|---|---|---|---|---|---|
| Compound | Formula weight | Reaction time (min) | Yield (%)[a] | Reaction time (h) | Yield (%)[a] |
| **1** | 268 | 6 | 91 | 4 | 65 |
| **2** | 326 | 6 | 90 | 4 | 61 |
| **3** | 356 | 6 | 85 | 4 | 58 |
| **4** | 322 | 6 | 92 | 4 | 61 |
| **5** | 272 | 6 | 86 | 4 | 56 |
| **6** | 326 | 6 | 82 | 4 | 60 |
| **7** | 216 | 6 | 80 | 4 | 59 |

[a] Isolated yields

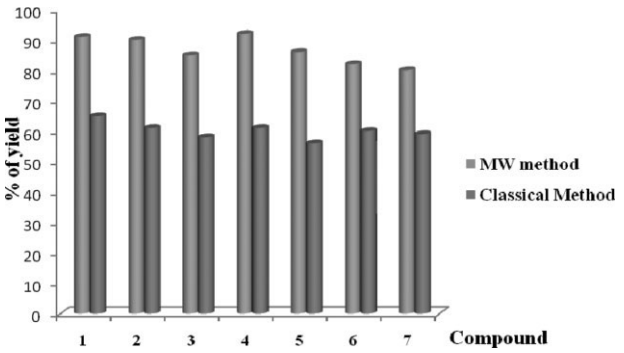



**Figure 1.** Graphical representation of yield comparison between classical and MW Irradiation.

ether. After filtering the zeolite particles, the ethereal layer was washed with water, dried with anhydrous sodium sulphate, and the solvent removed. The crude product was recrystallized from methanol.

**Synthesis of 1-arylmethyl-4,5-dihydro-2-aryl-1H-imidazoles by classical method.** A mixture of Schiff base (0.7 mmol), catalytic amount of $H_2SO_4$ and ethanol (50 mL) were refluxed for ~4 h. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set on one side to cool. Solid deposit was collected by the filtration. The crude product was recrystallized from methanol.

***1-(2-Hydroxybenzyl)-4,5-dihydro-2(2-hydroxyp henyl)-1H-imidazoles (1).*** $^1$H NMR: δ 8.36 (s, 2H, —OH); 6.82–7.33 (m, 8H, Ar-CH); 4.0 (s, 2H, $CH_2$); 3.94 (t, $J$ = 7.7 Hz, 2H, $CH_2$); 3.09 (t, $J$ = 7.6 Hz, 2H, $CH_2$); $^{13}$C NMR: δ 163.0, 160.8, 154.9, 131.2, 129.7, 129.2, 128.1, 122.4, 120.6, 114.3, 111.2, 50.4, 48.1, 40.9; Mass spectra, m/z = 268 (100%).

***1-(3-Nitrobenzyl)-4,5-dihydro-2(3-nitrophenyl)-1H-imidazoles (2).*** $^1$H NMR: δ 7.52-8.53 (m, 8H, Ar-CH); 4.04 (s, 2H, $CH_2$); 3.81 (t, $J$ = 7.6 Hz, 2H, $CH_2$); 3.05 (t, $J$ = 7.6 Hz, 2H, $CH_2$); $^{13}$C NMR: δ 162.8, 147.7, 147.2, 136.2, 133.1, 132.4, 132.1, 127.9, 122.8, 122.5, 117.8, 52.3, 49.9, 49.7; Mass spectra, $m/z$ = 326 (100%).

***1-(3,4-Dimethoxybenzyl)-4,5-dihydro-2(3,4-dimethoxyphenyl)-1H-imidazoles (3).*** $^1$H NMR: δ 6.39–7.02 (m, 6H, Ar-CH); 3.90 (s, 2H, $CH_2$); 3.69 (s, 12H, $CH_3$); 3.59 (t, $J$ = 7.6 Hz, 2H, $CH_2$); 2.88 (t, $J$ = 7.7 Hz, 2H, $CH_2$); $^{13}$C NMR: δ 162.4, 150.9, 148.8, 148.5, 147.3, 129.1, 125.2, 122.0, 120.4, 114.7, 114.4, 112.1, 54.9, 50.0, 49.1, 47.9; Mass spectra, $m/z$ = 356 (100%).

***1-(4-Dimethylaminobenzyl)-4,5-dihydro-2(4-di methylaminophenyl)-1H-imidazoles (4).*** $^1$H NMR: δ 7.56 (d, $J$ = 9 and 2 Hz, 2H, Ar-CH); 7.30 (d, $J$ = 8 and 1 Hz, 2H, Ar-CH); 6.98 (d, $J$ = 9 Hz, 2H, Ar-CH); 6.64 (d, $J$ = 9 Hz, 2H, Ar-CH); 3.88 (s, 2H, $CH_2$); 3.72 (t, $J$ = 7.6 Hz, 2H, $CH_2$); 3.06 (t, $J$ = 7.5 Hz, 2H, $CH_2$); 2.98 (s, 12H, $CH_3$); $^{13}$C NMR: δ 162.7, 152.3, 152.1, 148.1, 129.9, 124.9, 112.0, 78.1, 77.5, 76.9, 62.5, 40.6; Mass spectra, $m/z$ = 322 (100%).

***1-(4-Florobenzyl)-4,5-dihydro-2(4-florophenyl)-1H-imidazoles (5).*** $^1$H NMR: δ 7.64 (d, $J$ = 8 Hz, 2H, Ar-CH); 7.24 (d, $J$ = 8 Hz, 2H, Ar-CH); 7.09 (d, $J$ = 9 Hz, 2H, Ar-CH); 6.98 (d, $J$ = 9 Hz, 2H, Ar-CH); 3.86 (s, 2H, $CH_2$); 3.69 (t, $J$ = 7.6 Hz, 2H, $CH_2$); 3.01 (t, $J$ = 7.6 Hz, 2H, $CH_2$); $^{13}$C NMR: δ 164.7, 162.7, 160.0, 130.9, 129.8, 128.2, 126.9, 113.8, 113.6, 50.6, 49.1, 48.2; Mass spectra, $m/z$ = 272 (100%).

***1-(2-Nitrobenzyl)-4,5-dihydro-2(2-nitrophenyl)-1H-imidazoles (6).*** $^1$H NMR: δ 7.41–8.51 (m, 8H, Ar-CH); 3.97 (s, 2H, $CH_2$); 3.74 (t, $J$ = 7.7 Hz, 2H, $CH_2$); 2.99 (t, $J$ = 7.6 Hz, 2H, $CH_2$); $^{13}$C NMR: δ 162.9, 147.7, 147.4, 134.2, 131.3, 128.9, 127.8, 127.0, 120.2, 50.7, 47.9, 40.1; Mass spectra, $m/z$ = 326 (100%).

***1-(Furyl)-4,5-dihydro-2(furyl)-1H-imidazoles (7).*** $^1$H NMR: δ 7.84 (d, $J$ = 2 Hz, 1H,); 7.43 (d, $J$ = 2 Hz, 1H); 6.41–6.67 (m, 3H); 6.21 (d, $J$ = 3 Hz, 1H); 4.59 (s, 2H, $CH_2$); 3.45 (t, $J$ = 7.5 Hz, 2H, $CH_2$); 2.91 (t, $J$ = 7.6 Hz, 2H, $CH_2$); $^{13}$C NMR: δ 163.1, 147.3, 142.8, 142.1, 141.0, 109.8, 109.6, 109.2, 105.2, 45.6, 44.2, 37.8; Mass spectra, $m/z$ = 216 (100%).

**Table 2**

Physical and analytical data of substituted imidazoles.

| | | | | % Calcd (Found) | | |
|---|---|---|---|---|---|---|
| Compound | Ar | Formula | mp (°C) | C | H | N |
| **1** | *o*-$OHC_6H_4$ | $C_{16}H_{16}N_2O_2$ | 90 | 71.62 (71.60) | 6.01 (6.04) | 10.44 (10.42) |
| **2** | *m*-$NO_2C_6H_4$ | $C_{16}H_{14}N_4O_4$ | 119 | 58.89 (59.03) | 4.32 (4.26) | 17.17 (17.24) |
| **3** | *m, p*-$(OCH_3)_2C_6H_4$ | $C_{20}H_{24}N_2O_4$ | 115 | 67.40 (67.62) | 6.79 (6.83) | 07.86 (07.81) |
| **4** | *p*-$(CH_3)_2NC_6H_4$ | $C_{20}H_{26}N_4$ | 127 | 74.50 (74.31) | 8.13 (8.09) | 17.38 (17.30) |
| **5** | *p*-$FC_6H_4$ | $C_{16}H_{14}N_2F_2$ | 97 | 70.58 (70.49) | 5.18 (5.11) | 13.95 (13.91) |
| **6** | *o*-$NO_2C_6H_4$ | $C_{16}H_{14}N_4O_4$ | 104 | 58.89 (58.94) | 4.32 (4.26) | 17.17 (17.20) |
| **7** | 2-furyl | $C_{12}H_{12}N_2O_2$ | 121 | 66.65 (66.31) | 5.59 (5.70) | 12.96 (12.91) |

## CONCLUSIONS

In this study, we reported a highly efficient MW assisted rapid and solvent-free synthesis of substituted 1H imidazoles in the presence of zeolite. MW chemistry is a green chemical method that improves reaction conditions and product yields, while reducing solvent amounts and reaction times. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches. It also simplifies the laborious procedures and offers considerable advantages, such as: elimination of solvents, use of substances without any modification or activation, high yields, short reaction times, employment of reusable solid catalysts, and environmentally friendly character over the existing methodologies.

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### REFERENCES AND NOTES

[1] Caddick, S. Tetrahedron 1995, 51, 10403.
[2] Galema, S. A. Chem Soc Rev 1997, 26, 233.
[3] Fini, A.; Breccia, A. Pure Appl Chem 1999, 71, 573.
[4] Varma, R. S. Green Chem 1999, 1, 43.
[5] Varma, R. S. J Heterocycl Chem 1999, 36, 1565.
[6] Balalaie, S.; Arabanian, A. Green Chem 2000, 2, 274.
[7] Hoelderich, W. F. Appl Catal A 2000, 487, 194.
[8] Sreekumar, R.; Padmakumar, R.; Rugmini, P. Tetrahedron Lett 1998, 39, 2695.
[9] Hoefnagel, A. J.; van Bekkum, H. Appl Catal A 1993, 87, 97.
[10] Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V. Tetrahedron: Asymmetry 1992, 3, 859.
[11] Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J. Organometallics 1994, 13, 2493.
[12] Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Rousell, J. Tetrahedron Lett 1986, 27, 279.
[13] Yulin, J.; Yuncheng, Y. Synth Commun 1994, 24, 1045.
[14] Jones, G. B.; Chapman, B. J. J Org Chem 1993, 58, 5558.
[15] Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. J Org Chem 1991, 56, 6968.
[16] Villemin, D.; Martin, B. J Chem Res Synop 1994, 146.
[17] Lantos, I.; Zhang, W. Y.; Shiu, X.; Eggleston, D. S. J Org Chem 1993, 58, 7092.
[18] Kamaraj, K.; Kim, E.; Galliker, B.; Zakharov, L. N.; Rheingold, A. R.; Zuberbuhler, A. D.; Karlin, K. D. J Am Chem Soc 2003, 15, 6028.
[19] Moore L. R.; Cooks S. M.; Anderson M. S.; Schanz H.-J.; Griffin S. T.; Rogers R. D.; Kirk M. C.; Shaughnessy K. H. Organometallics 2006, 25, 5151.
[20] Wiglenda T.; Gust R. J Med Chem 2007, 50, 1475.
[21] O'Malley D. P.; Li K.; Maue M.; Zografos A. L.; Baran P. S. J Am Chem Soc 2007, 129, 4762.
[22] Kan H.-C.; Tseng M.-C.; Chu Y.-H. Tetrahedron 2007, 63, 1644.
[23] Zhang, C.; Moran, E. J.; Woiwade, T. F.; Short, K. M.; Mjalli, A. M. Tetrahedron Lett 1996, 37, 751.
[24] Sarshar, S.; Siev, D.; Mjalli, A. M. M. Tetrahedron Lett 1996, 37, 835.
[25] Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. Tetrahedron Lett 1998, 39, 8939.
[26] Yu, H. M.; Chen, S. T.; Wang, K. T. J Org Chem 1992, 57, 4781.
[27] Lambardino, J. G.; Wiseman, E. H. J Med Chem 1974, 17, 1182.
[28] Nakamura, I.; Yamamoto, Y. Chem Rev 2004, 104, 2127.
[29] (a) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. Org Lett 2009, 11, 221. (b) Csekei, M.; Novak, Z.; Kotschy, A. Tetrahedron 2008, 64, 8992. (c) Lu, B. Z.; Zhao, W. Y.; Wei, H. X.; Dufour, M; Farina, V.; Senanayake, C. H. Org Lett 2006, 8, 3271. (d) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. Org Lett., 2008, 10, 4275. (e) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. Org Lett 2008, 10, 3535. (f) Rivero, M. R.; Buchwald, S. L. Org Lett 2007, 9, 973. (g) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. J Org Chem 2008, 73, 7841. (h) Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. Tetrahedron 2006, 62, 5109. (i) McLaughlin, M.; Palucki, M.; Davies, I. W. Org Lett 2006, 8, 3307. (j) Roesch, K.; Larock, R. C. J Org Chem 2002, 67, 86. (k) Zhu, J.; Xie, H.; Chen, Z.; Li, S.; Wu, Y. Chem Commun 2009, 2338. (l) Li, L.; Wang, M.; Zhang, X.; Jiang, Y.; Ma, D. Org Lett 2009, 11, 1309. (m) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Z.; Ma, D. Org Lett 2008, 10, 2761. (n) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. Org Lett 2008, 10, 625. (o) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. Angew Chem Int Ed Engl 2009, 48, 1138. (p) Viirre, R. D.; Evindar, G.; Batey, R. A. J Org Chem 2008, 73, 3452. (q) Bossharth, E.; Desbordes, P.; Monteiro, B. N.; Balme, G. Org Lett 2003, 5, 2441. (r) Martin, R.; Cuenca, A.; Buchwald, S. L. Org Lett 2007, 9, 5521. (s) Yuan, Q.; Ma, D. J Org Chem 2008, 73, 5159. (t) Vina, D.; del Olmo, E.; Lopez-Perez, J.; Feliciano, A. S. Org Lett 2007, 9, 525.

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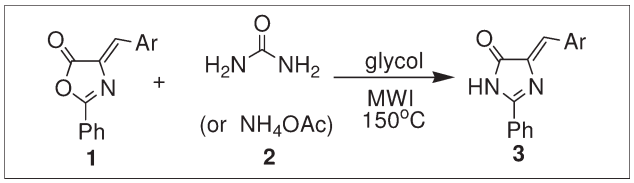


A facile microwave-assisted synthesis of imidazol-5(4*H*)-one derivatives is accomplished *via* reactions of 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones with urea (or ammonium acetate) in ethylene glycol. The cascade reaction is simple to perform and occurs under mild conditions with broad scope of applicability.

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## INTRODUCTION

Green fluorescent protein (GFP) including imidazolidinone skeleton (Fig. 1) [1], is an autofluorescent protein of 238 amino acid residues that is derived from the Pacific Northwest jellyfish, *Aequorea victoria* [2]. The GFP chromophore exhibits promising applications in molecular and cell biology due to its intrinsic visible fluorescence, which is easily detectable by fluorescence spectroscopy [3–5]. Therefore, much interest has been geared toward the engineering of novel color variants [6,7] of the GFP in light of its wide applicability in the life sciences.

In addition, the imidazolone core represents an attractive pharmacophore that displays extensively pharmacological and medicinal activities [8,9]. In particular, imidazol-5(4*H*)-one and its derivatives have possessed an unique role in drug discovery and crop protection [10,11], serving as combinatorial chemistry groups. In general routes, the imidazolone ring is formed by condensing glycine ester of acetimidic or phenylacetimidic acid in the solvents, such as benzene, dioxane, and acetone [12–14]. All these methods [12–17] have one or more limitations such as inaccessibility of precursors, narrow substrate scope, and operational complexity. Recently, a microwave-improved synthesis of imidazolones using graphite as support has been reported [15]. In the light of current studies, the development of a practically simple, economical, and high-yielding route to a wide variety of imidazol-5(4*H*)-one derivative (Fig. 2) is strongly desired. Herein, we like to report a cascade reaction of 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones **1** (Compounds **1** were conveniently prepared following a literature procedure: [18]) with urea **2** (or ammonium acetate) for synthesis of imidazol-5(4*H*)-ones under microwave irradiation (MWI) at 150°C in ethylene glycol (Scheme 1).

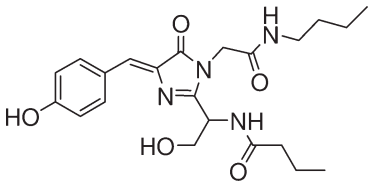


**Figure 1.** GFP chromophore.

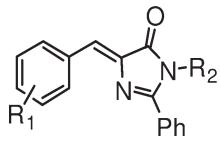
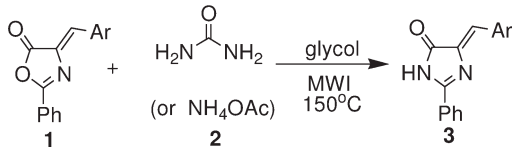



**Figure 2.** Compounds **3**.

## RESULTS AND DISCUSSION

To choose the most appropriate solvents, the MW-assisted reaction (Scheme 2) of 4-(4-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (**1c**, 1 mmol) and urea (**2**, 1.5 mmol) was examined using glacial acetic acid (HOAc), ethylene glycol, ethanol (EtOH), *N*,*N*-dimethyl

**Scheme 1**




formamide (DMF), water as the solvent (2.0 mL) at 150°C, respectively. All the reactions were carried out at the maximum power of 300 W. As shown in Table 1, we could see the reaction in glycol gave the best results (Table 1, entry 2).

To further optimize reaction conditions, the same reaction was performed in ethylene glycol and 300 W at the temperatures ranging from 110 to 180°C in increments of 10°C each time. The yield of product **3c** was improved from 23 to 93%, when the temperature was raised from 110 to 150°C (Table 2, entries 1–5). However, no significant increase in the yield of product **3c** was observed as the reaction temperature was raised from 150 to 180°C (Table 2, entries 5–8). Therefore, 150°C phenyloxazol-5(4*H*)-ones were performed, which leads to the corresponding 4-arylmethylene-2-phenyl-1*H*-imidazol-5(4*H*)-ones with good yields.

Under the optimal conditions [glycol, 150°C, 300 W (maximum power)], reactions of different 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones were performed, which leads to the corresponding 4-arylmethylene-2-phenyl-1*H*-imidazol-5(4*H*)-ones with good yields. The electronic effect of the aryl group in 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones was investigated. As shown in Table 3, both electron-withdrawing (such as nitro) and electron-donating (such as alkoxy) groups readily provided compounds 3 in good yields. Moreover, the heterocyclic phenyloxazol-5(4*H*)-ones such as 2-phenyl-4-((thiophen-2-yl)methylene) oxazol-5(4*H*)-one (Table 3, entry 9) still displayed a high reactivity under this standard condition.

We envisaged that ammonia, obtained by urea (or ammonium acetate), attacks on carbonyl group in 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones **1** as a nucleophile. Bond formation should lead directly to intermediate **7** *via* ring opening, which then poised to attack adjacent reactive carbonyl group. Finally, an intramolecular condensation occurred and 4-arylmethylene-2-phenyl-1*H*-imidazol-5(4*H*)-ones **3** were obtained (Scheme 3).

**Scheme 2**

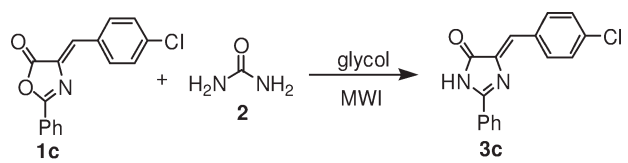



**Table 1**

Solvent optimization for the synthesis of **3c** under MWI.

| Entry | Solvent | Temp (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | HOAc | 150 | 5 | trace |
| 2 | Glycol | 150 | 5 | 93 |
| 3 | EtOH | 150 | 5 | 63 |
| 4 | DMF | 150 | 5 | 79 |
| 5 | Water | 150 | 5 | 32 |

In a further study, aromatic amine **4** was employed instead of urea **2** in this case. The reactions proceeded smoothly too. However, the desired products **3** were not detected. Instead, a series of open-chain products **5** were obtained in high yields (Scheme 4). The reason may be attributed to the nucleophilicity of amine. When R is a phenyl group, the resulting *N*-phenylformamide derivative decreases the nucleophilicity of amine, which is difficult to form closed-ring products **3**. The synthesis of these compounds has reported in our previous study (Compounds **5** were conveniently prepared following a literature procedure: [19]).

In summary, we demonstrated a simple method, using readily available starting materials and simple experimental procedures, for the efficient synthesis of imidazol-5(4*H*)-one derivative and related compounds. Particularly, valuable features of this cascade reaction included operational simplicity, high yields, increased safety for small-scale high-speed synthesis, and broader substrate scope.

## EXPERIMENTAL

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FTIR-tensor 27 spectrometer in KBr. $^1$H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-$d_6$ as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

**Table 2**

Temperature optimization for the synthesis of **3c** under MWI.

| Entry | Temp (°C) | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | 110 | 5 | 23 |
| 2 | 120 | 5 | 58 |
| 3 | 130 | 5 | 75 |
| 4 | 140 | 5 | 82 |
| 5 | 150 | 5 | 93 |
| 6 | 160 | 5 | 71 |
| 7 | 170 | 5 | 58 |
| 8 | 180 | 5 | 41 |

**Table 3**

Physical and analytical data of compounds **3**.

| Entry | Compd. | Ar | Time (min) | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|
| 1 | **3a** | $C_6H_5$ | 5 (3) [15] | 87 (85) [15] | >300 (272–273) [15] |
| 2 | **3b** | 4-$FC_6H_4$ | 5 | 84 | 286–287 |
| 3 | **3c** | 4-$ClC_6H_4$ | 5 (5) [15] | 93 (91) [15] | >300 (289–290) [15] |
| 4 | **3d** | 2,4-$Cl_2C_6H_3$ | 6 (4) [15] | 83 (97) [15] | 268–269 (273–274)[15] |
| 5 | **3e** | 3,4-$Cl_2C_6H_3$ | 6 | 85 | 277–278 |
| 6 | **3f** | 4-$CH_3C_6H_4$ | 5 (4) [15] | 95 (70) [15] | 278–279 (288–289) [15] |
| 7 | **3g** | 2-$CH_3OC_6H_4$ | 6 | 82 | 278–279 (254–255) [15] |
| 8 | **3h** | 4-$CH_3OC_6H_4$ | 5 (3) [15] | 87 (84) [15] | >300 (289–290) [15] |
| 9 | **3i** | Thien-2-yl | 5 (2) [15] | 86 (80) [15] | >300 (291–292) [15] |

**Sample experimental**

***4-Arylmethylene-2-phenyl-1H-imidazol-5(4H)-one (3).*** In a 10 mL Emrys™ reaction vial, 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones (1 mmol) with urea (1.5 mmol), ammonium acetate (1.5 mmol), in ethylene glycol (2.0 mL) were mixed and then capped. The mixture was irradiated by microwave at 300 W and 150°C for a given time. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water, filtered to give the crude products, which were further purified by recrystallization from 95% EtOH. The reaction time and the yields are listed in Table 3. The analytical data of new products are as following:

***4-Benzylidene-2-phenyl-1H-imidazol-5(4H)-one (3a).*** IR (KBr): 3124, 3067, 2989, 1698, 1639, 1539, 1496, 1452, 1419, 1322, 1266, 1187, 1031, 922, 775, 687 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO) (δ, ppm): 12.12 (s, 1H, NH), 8.32 (d, $J$ = 7.2 Hz, 2H, ArH), 8.18 (d, $J$ = 7.6 Hz, 2H, ArH), 7.67–7.69 (m, 3H, ArH), 7.52–7.44 (m, 3H, ArH), 7.04 (s, 1H, CH).

HRMS (ESI): $m/z$ $[M+H]^+$ calcd for $C_{16}H_{12}N_2O$: 249.1023; found: 249.1023.

Anal calcd. For $C_{16}H_{12}N_2O$, C, 77.40; H, 4.87; N, 11.28; found C, 77.50; H, 4.79; N, 11.32%.

***4-(4-Fluorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3b).*** IR (KBr): 3159, 3128, 3071, 2991, 1707, 1645, 1595, 1500, 1457, 1235, 1157, 921, 842, 784, 691 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO) (δ, ppm): 12.14 (s, 1H, NH), 8.41 (t, $J$ = 8.0 Hz, 2H, ArH), 8.18 (d, $J$ = 8.0 Hz, 2H, ArH), 7.68–7.59 (m, 3H, ArH), 7.35 (t, $J$ = 8.8 Hz, 2H, ArH), 7.06 (s, 1H, CH).

Anal calcd. For $C_{16}H_{11}FN_2O$, C, 72.17; H, 4.16; N, 10.52; found C, 72.24; H, 4.14; N, 10.59%.

***4-(4-Chlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3c).*** IR (KBr): 3153, 3124, 3066, 2987, 1703, 1641, 1541, 1456, 1261, 1180, 1092, 923, 788, 691 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO) (δ, ppm): 12.18 (s, 1H, NH), 8.36 (d, $J$ = 8.4 Hz, 2H, ArH), 8.19 (d, $J$ = 8.4 Hz, 2H, ArH), 7.67–7.56 (m, 5H, ArH), 7.05 (s, 1H, CH).

Anal calcd. For $C_{16}H_{11}ClN_2O$, C, 67.97; H, 3.92; N, 9.91; found C, 67.88; H, 3.89; N, 9.99%.

***4-(2,4-Dichlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3d).*** IR (KBr): 3159, 3129, 3062, 2986, 1708, 1638, 1536, 1455, 1413, 1361, 1249, 1181, 1098, 915, 694 $cm^{-1}$.

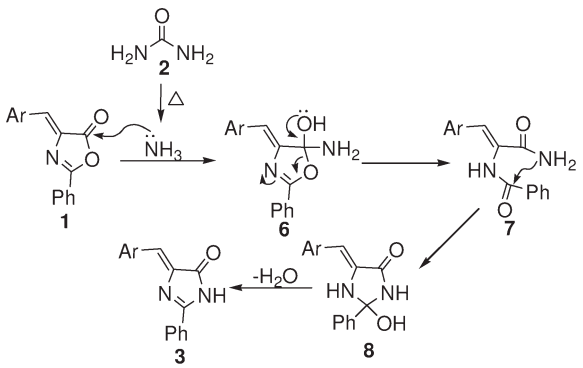
$^1$H NMR (400 MHz, DMSO) (δ, ppm): 12.36 (s, 1H, NH), 9.06 (s, 1H, ArH), 8.15 (d, $J$ = 7.2 Hz, 2H, ArH), 7.70–7.61(m, 4H, ArH), 7.51 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, 1H, ArH), 7.18 (s, 1H, CH).

Anal calcd. For $C_{16}H_{10}Cl_2N_2O$, C, 60.59; H, 3.18; N, 8.83; found C, 60.65; H, 3.14; N, 8.89%.

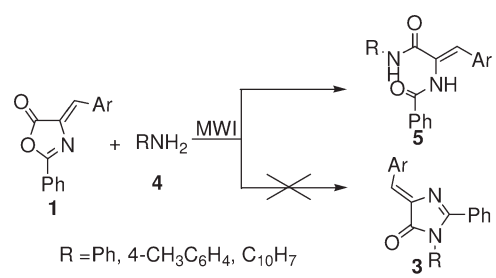
***4-(3,4-Dichlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3e).*** IR (KBr): 3127, 3068, 2986, 1711, 1646, 1547, 1455, 1416, 1355, 1249, 1125, 908, 784, 685 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO) (δ, ppm): 12.23 (s, 1H, NH), 8.60 (s, 1H, ArH), 8.33 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.2 Hz, 1H, ArH), 8.18 (d, $J$ = 7.2 Hz, 2H, ArH), 7.76 (d, $J$ = 8.4 Hz, 1H, ArH), 7.68–7.61 (m, 3H, ArH), 7.04 (s, 1H, CH).

**Scheme 3**




**Scheme 4**



Anal calcd. For $C_{16}H_{10}Cl_2N_2O$, C, 60.59; H, 3.18; N, 8.83; found C, 60.51; H, 3.25; N, 8.78%.

***4-(4-Methylbenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3f).*** IR (KBr): 3152, 3122, 3062, 2984, 1701, 1638, 1598, 1496, 1456, 1256, 1180, 1028, 922, 816, 789, 690 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO) (δ, ppm): 12.09 (s, 1H, NH), 8.22 (d, $J$ = 7.8 Hz, 2H, ArH), 8.17 (d, $J$ = 8.0 Hz, 2H, ArH), 7.67–7.59 (m, 3H, ArH), 7.32 (d, $J$ = 8.0 Hz, 2H, ArH), 7.01 (s, 1H, CH), 2.38 (s, 3H, $CH_3$).

Anal calcd. For $C_{17}H_{14}N_2O$, C, 77.84; H, 5.38; N, 10.68; found C, 77.89; H, 5.31; N, 10.79%.

***4-(2-Methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3g).*** IR (KBr): 3147, 3071, 2985, 2839, 1691, 1633, 1455, 1249, 1168, 1026, 923, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO) (δ, ppm): 12.11 (s, 1H, NH), 8.92 (d, $J$ = 8.0 Hz, 1H, ArH), 8.17 (d, $J$ = 8.0 Hz, 2H, ArH), 7.65–7.58 (m, 3H, ArH), 7.46–7.41 (m, 2H, ArH), 7.13–7.10 (d, $J$ = 7.6 Hz, 1H, ArH), 7.09 (s, 1H, CH), 3.92 (s, 3H, $OCH_3$).

Anal calcd. For $C_{17}H_{14}N_2O_2$, C, 73.37; H, 5.07; N, 10.07; found C, 73.42; H, 5.11; N, 10.00%.

***4-(4-Methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3h).*** IR (KBr): 3121, 3065, 2969, 1699, 1596, 1456, 1304, 1264, 1172, 1028, 922, 827, 690 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO) (δ, ppm): 12.03 (s, 1H, NH), 8.31 (d, $J$ = 8.4 Hz, 2H, ArH), 8.16 (d, $J$ = 7.8 Hz, 2H, ArH), 7.65–7.58 (m, 3H, ArH), 7.08 (d, $J$ = 8.0 Hz, 2H, ArH), 7.02 (s, 1H, CH), 3.84 (s, 3H, $OCH_3$).

Anal calcd. For $C_{17}H_{14}N_2O_2$, C, 73.37; H, 5.07; N, 10.07; found C, 73.30; H, 5.17; N, 9.98%.

***2-Phenyl-4-((thiophen-2-yl)methylene)-1H-imidazol-5(4H)-one (3i).*** IR (KBr): 3116, 3061, 2985, 1698, 1634, 1457, 1419, 1320, 1256, 1200, 1121, 922, 891, 788, 692 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO) (δ, ppm): 12.06 (s, 1H, NH), 8.16 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.2 Hz, 2H, ArH), 7.92 (d, $J$ = 5.2 Hz, 1H, ArH), 7.74 (d, $J$ = 2.7 Hz, 1H, ArH), 7.64–7.60 (m, 3H, ArH), 7.39 (s, 1H, CH), 7.21–7.18 (m, 1H, ArH).

HRMS (ESI): $m/z$ $[M+H]^+$ calcd for $C_{14}H_{10}N_2OS$: 255.0587; found: 255.0580.

Anal calcd. For $C_{14}H_{10}N_2OS$, C, 66.12; H, 3.96; N, 11.02; found C, 66.19; H, 3.90; N, 11.11%.

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## REFERENCES AND NOTES

[1] Bourotte, M.; Schmitt, M.; Follenius-Wund, A.; Pigault, C.; Haiech, J.; Bourguignon, J. J. Tetrahedron Lett 2004, 45, 6343.

[2] Nantasenamat, C.; Isarankura-Na-Ayudhya, C.; Tansila, N.; Naenna, T.; Prachayasittikul, V. J Comput Chem 2007, 28, 1275.

[3] Cubitt, A. B.; Heim, R.; Adams, S. R.; Boyd, A. E.; Gross, L. A.; Tsien, R. Y. Trends Biochem Sci 1995, 20, 448.

[4] Tsien, R. Y. Annu Rev Biochem 1998, 67, 509.

[5] Zimmer, M. Chem Rev 2002, 102, 759.

[6] Bae, J. H.; Pal, P. P.; Moroder, L.; Huber, R.; Budisa, N. Chembiochem 2004, 5, 720.

[7] Heim, R.; Prasher, D. C.; Tsien, R. Y. Proc Natl Acad Sci USA 1994, 91, 12501.

[8] Durant, G. J. Chem Soc Rev 1985, 14, 375.

[9] Cafieri, F.; Gattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. Tetrahedron Lett 1996, 37, 3587.

[10] Los, M. Pestic Sci Biotechnol, Proc Int Congr Pestic Chem 1987, pp. 35–42.

[11] D. L. Pestic Outlook 1991, 2, 21.

[12] Verschave, P.; Vekemans, J.; Hoornaert, G. Tetrahedron 1984, 40, 2395.

[13] Cornforth, J. W.; Huang, H. T. J Chem Soc 1948, 1960.

[14] Lehr, H.; Karlan, S.; Goldberg, M. W. J Am Chem Soc 1953, 3640.

[15] Fozooni, S.; Tikdari, A. M. Catal Lett 2008, 120, 303.

[16] Lange, U. E. W. Tetrahedron Lett 2002, 43, 6857.

[17] Cherouvrier, J. R.; Carreaux, F.; Bazureau, J. P. Tetrahedron Lett 2002, 43, 3581.

[18] Tu, S. J.; Jia, H.; Zhuang, Q. Y.; Miao, C. B.; Shi, D. Q.; Wang, X. S.; Gao, Y. Chin J Org Chem 2003, 23, 491.

[19] Tu, S. J.; Zhang, J. Y.; Jia, R. H.; Zhang, Y.; Jiang, B.; Shi, F. Synthesis 2007, 558.

# An Efficient Synthesis of 5,6-Dihydrobenzo[*h*]quinazoline Derivatives under Solvent-Free Conditions



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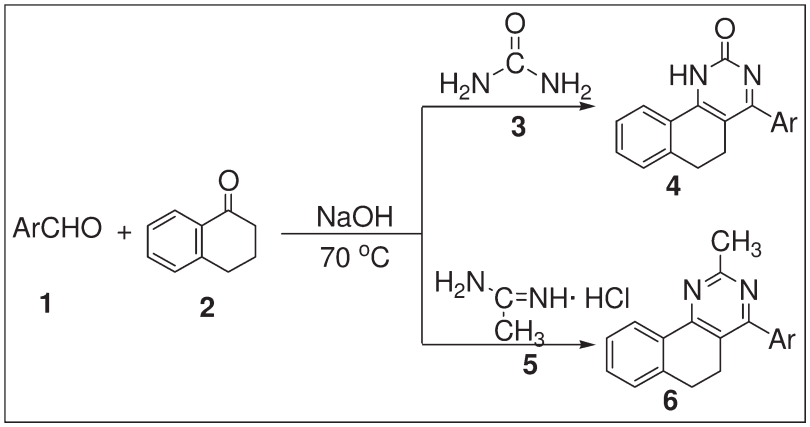


An efficient and convenient method for the preparation of 5,6-dihydrobenzo[*h*]quinazoline derivatives by the multicomponent reactions of aromatic aldehydes, 3,4-dihydronaphthalen-1(2*H*)-one and urea or acetamidine hydrochloride, in the presence of sodium hydroxide under solvent-free conditions was reported. This method has the advantages of excellent yields, mild reaction conditions, easy work-up, and environmentally friendly procedure.

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## INTRODUCTION

The quinazoline skeleton is a very important and useful scaffold in medicinal chemistry: it can be found as a pharmacophore in a wide variety of biologically active compounds, such as antitumors [1], antimicrobials [2], antivirals [3,4]. Benzoquinazoline, the important containing quinazoline skeleton system derivatives, is often found in different natural alkaloids, and these compounds also display specific biological activities, and often used as asdiuretic, anticancer, anticonvulsant, and antihypertensive agents [5–8].

Recently, there was an increasing emphasis on developing new environmentally safer chemical transformations by lessening/removing the toxic waste, where by-products from the chemical processes were avoided or minimized making them ecologically more acceptable. It is highly desirable to develop eco-friendly methods for producing organic fine chemicals. One of the major problems encountered in various chemical processes is the use of organic solvents. Hence, the organic transformations under solvent-free conditions are attracting increasing attentions [9–11]. Herein, we would like to report an efficient and facile method to synthesize 5,6-dihydrobenzo[*h*]quinazoline derivatives under solvent-free conditions.

## RESULTS AND DISCUSSION

The synthesis process could be depicted as follows: at first, we try to prepare 4-aryl-5,6-dihydrobenzo[*h*]quinazolin-2(1*H*)-one derivatives under solvent-free conditions (Scheme 1). The aromatic aldehydes **1** (1 mmol), 3,4-dihydronaphthalen-1(2*H*)-one **2** (1 mmol) and urea **3** (1.5 mmol) were chosen as starting materials, and the reactants were blent enough in a mortar in presence of NaOH (0.1 g) as catalyst, then the mixture was introduced into a round flask and reacted under 70°C. To our delight, the reaction could be finished about 30 min and the 4-aryl-5,6-dihydrobenzo[*h*]quinazolin-2(1*H*)-one

**Scheme 1**

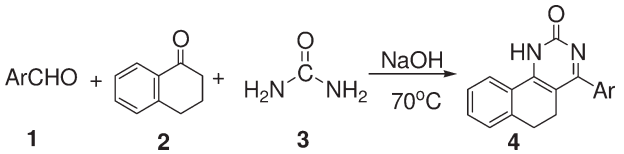


**Table 1**

The results of synthesis of 4-aryl-5,6-dihydrobenzo[*h*]quinazolin-2(1*H*)-one.

| Entry | Ar | Product | Yields (%) |
|---|---|---|---|
| 1 | $C_6H_5$ | **4a** | 80 |
| 2 | 4-$CH_3C_6H_4$ | **4b** | 85 |
| 3 | 3,4-$(CH_3)_2C_6H_3$ | **4c** | 83 |
| 4 | 3,4-$(CH_3O)_2C_6H_3$ | **4d** | 87 |
| 5 | 4-$FC_6H_4$ | **4e** | 90 |
| 6 | 4-$BrC_6H_4$ | **4f** | 88 |
| 7 | 2-$ClC_6H_4$ | **4g** | 80 |
| 8 | 4-$ClC_6H_4$ | **4h** | 91 |
| 9 | 2,4-$Cl_2C_6H_3$ | **4i** | 82 |
| 10 | 3,4-$Cl_2C_6H_3$ | **4j** | 80 |

**Table 2**

The results of synthesis of 4-aryl-5,6-dihydro-2-methylbenzo[*h*] quinazoline.

| Entry | $Ar^1$ | Product | Yields (%) |
|---|---|---|---|
| 1 | 4-$CH_3C_6H_4$ | **6a** | 78 |
| 2 | 4-$CH_3OC_6H_4$ | **6b** | 80 |
| 3 | 3,4-$(CH_3O)_2C_6H_3$ | **6c** | 76 |
| 4 | 4-$FC_6H_4$ | **6d** | 85 |
| 5 | 3-$ClC_6H_4$ | **6e** | 79 |
| 6 | 4-$ClC_6H_4$ | **6f** | 89 |
| 7 | 3,4-$Cl_2C_6H_3$ | **6g** | 88 |

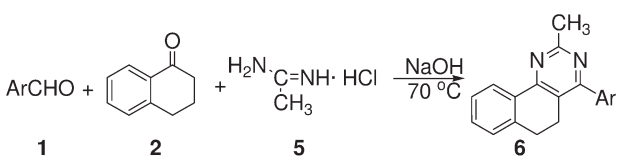
derivatives could be gained with excellent yields. The result of reaction is shown in Table 1. From Table 1 we could see the reaction was carried out smoothly and a series of 4-aryl-5,6-dihydrobenzo[*h*]quinazolin-2(1*H*)-one derivatives were obtained ignoring the properties of substitute groups on the aromatic aldehydes. So, we could say that substitute groups on the aromatic aldehydes do not affect this reaction. In addition, in this reaction the catalyst NaOH was necessary.

To extend this reaction to prepare more benzo[*h*]quinazoline derivatives, we replaced urea by acetamidine hydrochloride to react with aromatic aldehydes **1** and 3,4-dihydronaphthalen-1(2*H*)-one **2** under similar condition (Scheme 2), and we found that other benzo[*h*]quinazoline derivatives, 4-aryl-5,6-dihydro-2-methylbenzo[*h*]-quinazoline could be gained with good yields. The result of reaction was listed in Table 2. In this reaction, we thought that two functions were played by NaOH, one it was used as catalyst to promote the reaction, and the another it reacted with acetamidine hydrochloride to release acetamidine.

The structures of **4** and **6** were characterized by $^1$H NMR, IR, and HRMS spectra, and the structures of **6d** [12] was additionally confirmed by X-ray diffraction analysis. The crystal structure of is shown in Figure 1.

In conclusion, we have developed an efficient and facile process to synthesize a variety of 4-aryl-5,6-dihydrobenzo[*h*]quinazolin-2(1*H*)-one and 4-aryl-5,6-dihydro-2-methylbenzo[*h*] quinazoline derivatives *via* one-pot reaction of different aromatic aldehydes, 3,4-dihydronaphthalen-1(2*H*)-one, and urea or acetamidine hydrochloride under solvent-free conditions. The mild reaction conditions, short reaction times, good to high yields, low cost, easy preparation, easy handling, and reusability of catalyst are the advantages of this method.

**Scheme 2**




## EXPERIMENTAL

Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. $^1$H NMR spectra were obtained from solution in DMSO-$d_6$ with $Me_4Si$ as internal standard using a Bruker-400 spectrometer. X-ray diffractions were recorded on a Siemens P4 or Simart-1000 diffractometer. HRMS spectra were obtained with a Bruker micrOTOF-Q 134 instrument.

**General procedure for the synthesis of 5,6-dihydrobenzo[*h*]quinazoline derivatives.** The mixture of aromatic aldehydes **1** (1 mmol), 3,4-dihydronaphthalen-1(2*H*)-one **2** (1 mmol), urea **3** (1.5 mmol) or acetamidine hydrochloride **5** (1.5 mmol), and NaOH (0.1 g) was put in a reaction flask, and the reagents were reacted at 70°C about 30 min. When the reactions were completed, the reaction mixture was poured into water (0.5% HCl), and then washed with water thoroughly. The product was filtered, dried, and recrystallized from 95% ethanol.

***5,6-Dihydro-4-phenylbenzo[h]quinazolin-2(1H)-one (4a).*** m.p. 251–253°C; IR (KBr, n, $cm^{-1}$): 3327, 3232, 3089, 3019, 2943, 2890, 2830, 1689, 1550, 1488, 1454, 1431, 1366, 1342, 1319, 1298, 1279, 1262, 1228, 1191, 1180, 1162, 1122, 1072, 1046, 1026, 981, 943, 895, 826, 770, 723, 700, 656, 638, 608, 595 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.59 (2H, t, $J$ = 7.6 Hz, $J$ = 7.6 Hz, $CH_2$), 2.69 (2H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, $CH_2$), 7.15 (1H, d, $J$ = 6.4 Hz, ArH), 7.20 (2H, t, $J$ = 5.2 Hz, $J$ = 5.4 Hz, ArH), 7.32–7.38 (4H, m, ArH), 7.58 (1H, d, $J$ = 6.8 Hz, ArH), 8.57 (1H, br, ArH), 11.95 (1H, s, NH); HRMS $m/z$ calculated for $C_{18}H_{14}N_2O$ [M+H]: 275.1184, found: 275.1185.

***5,6-Dihydro-4-p-tolylbenzo[h]quinazolin-2(1H)-one (4b).*** m.p. 243–244°C; IR (KBr, n, $cm^{-1}$): 3462, 3275, 3062, 3000, 2909, 2859, 1667, 1595, 1509, 1465, 1427, 1375, 1323, 1231, 1150, 1091, 1064, 824, 759, 733 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.39 (3H, s, $CH_3$), 2.67 (2H, t, $J$ = 6.0 Hz, $J$ = 7.6 Hz, $CH_2$), 2.80 (2H, t, $J$ = 6.4 Hz, $J$ = 7.2 Hz, $CH_2$), 7.37

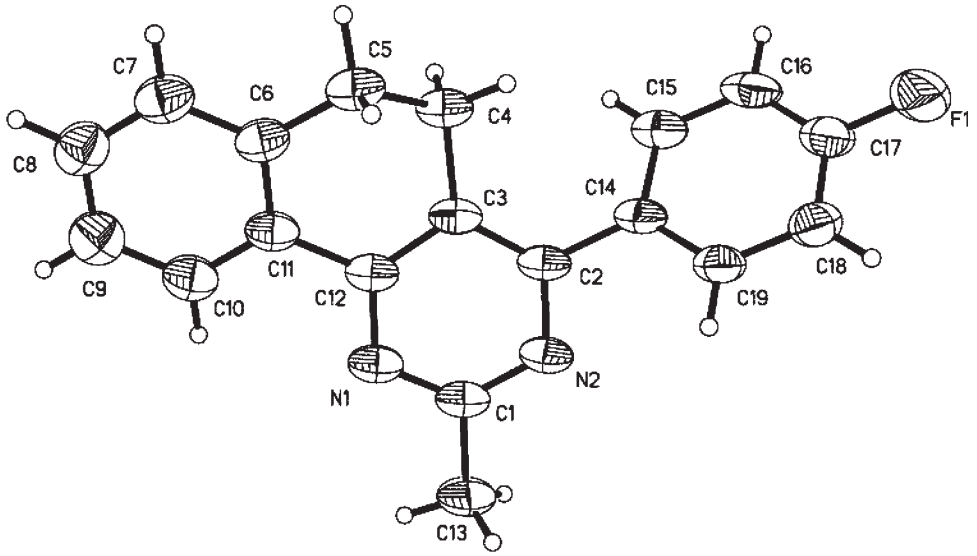



**Figure 1.** Structure of compound **6d**.

(3H, t, $J$ = 6.8 Hz, $J$ = 7.6 Hz, ArH), 7.41 (1H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, ArH), 7.49 (3H, t, $J$ = 5.6 Hz, $J$ = 7.6 Hz, ArH), 8.18 (1H, $J$ = 7.6 Hz, ArH), 11.84 (1H, s, NH); HRMS *m/z* calculated for $C_{19}H_{16}N_2O$ [M+H]: 289.1341, found: 289.1342.

***5,6-Dihydro-4-(3,4-dimethylphenyl)benzo[h]quinazolin-2(1H)-one (4c).*** m.p. 277–279°C; IR (KBr, ν, $cm^{-1}$): 3330, 3229, 3090, 3001, 2931, 2886, 2831, 1687, 1488, 1454, 1384, 1362, 1314, 1297, 1278, 1261, 1230, 1204, 1178, 1158, 1124, 1090, 1047, 1026, 998, 942, 891, 773, 735, 725, 639, 608 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.19 (3H, s, $CH_3$), 2.20 (3H, s, $CH_3$), 2.58 (2H, t, $J$ = 7.2 Hz, $J$ = 8.0 Hz, $CH_2$), 2.68 (2H, t, $J$ = 7.2 Hz, $J$ = 8.0 Hz, $CH_2$), 7.03 (1H, d, $J$ = 7.6 Hz, ArH), 7.09 (1H, d, $J$ = 8.6 Hz, ArH), 7.16–7.21 (3H, m, ArH), 7.57 (1H, d, $J$ = 6.8 Hz, ArH), 8.50 (1H, s, ArH), 11.82 (1H, s, NH); HRMS *m/z* calculated for $C_{20}H_{18}N_2O$ [M+H]: 303.1497, found: 303.1496.

***5,6-Dihydro-4-(3,4-dimethoxyphenyl)benzo[h]quinazolin-2(1H)-one (4d).*** m.p. 240–241°C; IR (KBr, ν, $cm^{-1}$): 3465, 3213, 2938, 2836, 1634, 1538, 1510, 1424, 1372, 1261, 1143, 1024, 853, 780, 765, 613 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.75 (2H, t, $J$ = 2.8 Hz, $J$ = 4.0 Hz, $CH_2$), 2.80 (2H, t, $J$ = 2.8 Hz, $J$ = 4.0 Hz, $CH_2$), 3.82 (3H, s, $OCH_3$), 3.83 (3H, s, $OCH_3$), 7.09 (1H, d, $J$ = 8.4 Hz, ArH), 7.14 (1H, d, $J$ = 8.4 Hz, ArH), 7.19 (1H, d, $J$ = 1.6 Hz, ArH), 7.33 (1H, d, $J$ = 7.2 Hz, ArH), 7.40 (1H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, ArH), 7.47 (1H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, ArH), 8.17 (1H, d, $J$ = 7.6 Hz, ArH), 11.81 (1H, s, NH); HRMS *m/z* calculated for $C_{20}H_{18}N_2O_3$ [M+H]: 335.1396, found: 335.1393.

***5,6-Dihydro-4-(4-fluorophenyl)benzo[h]quinazolin-2(1H)-one (4e).*** m.p. 270–273°C; IR (KBr, ν, $cm^{-1}$): 3334, 3068, 3009, 2944, 2901, 2835, 1628, 1587, 1506, 1467, 1426, 1376, 1228, 1146, 1062, 844, 762 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.69 (2H, t, $J$ = 6.4 Hz, $J$ = 6.4 Hz, $CH_2$), 2.80 (2H, t, $J$ = 6.4 Hz, $J$ = 6.4 Hz, $CH_2$), 7.33–7.43 (4H, m, ArH), 7.48 (1H, d, $J$ = 7.2 Hz, ArH), 7.66 (2H, t, $J$ = 5.6 Hz, $J$ = 7.2 Hz, ArH), 8.18 (1H, d, $J$ = 7.2 Hz, ArH), 11.89 (1H, s, NH); HRMS *m/z* calculated for $C_{18}H_{13}FN_2O$ [M+H]: 293.1090, found: 293.1089.

***4-(4-Bromophenyl)-5,6-dihydrobenzo[h]quinazolin-2(1H)-one (4f).*** m.p. 252–256°C; IR (KBr, ν, $cm^{-1}$): 3305, 3087, 2936, 2819, 1643, 1465, 1429, 1372, 1182, 1010,836,738 $cm^{-1}$; 2.68 (2H, t, $J$ = 6.4 Hz, $J$ = 6.4 Hz, $CH_2$), 2.81 (2H, t, $J$ = 6.4 Hz, $J$ = 6.4 Hz, $CH_2$), 7.34 (1H, d, $J$ = 7.8 Hz, ArH), 7.41 (1H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, ArH), 7.49 (1H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, ArH), 7.55 (2H, d, $J$ = 7.8 Hz, ArH), 7.74 (2H, d, $J$ = 8.0 Hz, ArH), 8.18 (1H, d, $J$ = 7.2 Hz, ArH), 1.91 (1H, s, NH); HRMS *m/z* calculated for $C_{18}H_{13}BrN_2O$ [M+H]: 353.0290, found: 353.0278.

***4-(2-Chlorophenyl)-5,6-dihydrobenzo[h]quinazolin-2(1H)-one (4g).*** m.p. > 290°C; IR (KBr, ν, $cm^{-1}$): 3322, 3238, 3103, 2945, 2893, 2833, 1683, 1596, 1483, 1328, 1276, 1162, 1046, 822, 756 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.57 (2H, t, $J$ = 6.4 Hz, $J$ = 6.4 Hz, $CH_2$), 2.69 (2H, t, $J$ = 6.4 Hz, $J$ = 6.4 Hz, $CH_2$), 7.15 (1H, s, ArH), 7.27 (2H, s, ArH), 7.36 (2H, d, $J$ = 3.2 Hz, ArH), 7.42 (1H, s, ArH), 7.99 (2H, d, $J$ = 6.4 Hz, ArH), 11.89 (1H, s, NH); HRMS *m/z* calculated for $C_{18}H_{13}ClN_2O$ [M+H]: 309.0795, found: 309.0778.

***4-(4-Chlorophenyl)-5,6-dihydrobenzo[h]quinazolin-2(1H)-one (4h).*** m.p. 287–289°C; IR (KBr, ν, $cm^{-1}$): 3312, 3071, 3021, 2967, 2848, 1638, 1464, 1403, 1372, 1231, 1146, 1089, 1059, 888, 737 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.70 (2H, t, $J$ = 6.0 Hz, $J$ = 6.4 Hz, $CH_2$), 2.82 (2H, t, $J$ = 6.4 Hz, $J$ = 7.6 Hz, $CH_2$), 7.34 (1H, d, $J$ = 7.2 Hz, ArH), 7.41 (1H, t, $J$ = 7.2 Hz, $J$ = 7.6 Hz, ArH), 7.49 (1H, t, $J$ = 7.2 Hz, $J$ = 7.2 Hz, ArH), 7.62 (4H, dd, $J$ = 8.8 Hz, $J$ = 8.8 Hz, ArH), 8.18 (1H, d, $J$ = 7.6 Hz, ArH), 11.90 (1H, s, NH); HRMS *m/z* calculated for $C_{18}H_{13}ClN_2O$ [M+H]: 309.0795, found: 309.0791.

***4-(2,4-Dichlorophenyl)-5,6-dihydrobenzo[h]quinazolin-2(1H)-one (4i).*** m.p. 286–288°C; IR (KBr, ν, $cm^{-1}$): 3411, 3043, 2935, 2836, 1635, 1466, 1429, 1376, 1316, 1150, 1100, 1046, 847, 762 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.40 (2H, t, $J$ = 6.8 Hz, $J$ = 6.8 Hz, $CH_2$), 2.83 (2H, t, $J$ = 6.8 Hz, $J$ = 6.8 Hz,

$CH_2$), 7.34 (1H, d, $J$ = 7.2 Hz, ArH), 7.42 (1H, t, $J$ = 7.2 Hz, $J$ = 7.6 Hz, ArH), 7.50 (1H, t, $J$ = 6.4 Hz, $J$ = 7.6 Hz, ArH), 7.58–7.64 (2H, m, ArH), 7.80 (1H, br, ArH), 8.20 (1H, d, $J$ = 7.6 Hz, ArH), 12.02 (1H, s, NH); HRMS *m*/*z* calculated for $C_{18}H_{12}Cl_2N_2O$ [M+H]: 343.0405, found: 343.0413.

***4-(3,4-Dichlorophenyl)-5,6-dihydrobenzo[h]quinazolin-2(1H)-one (4j).*** m.p. > 290°C; IR (KBr, ν, $cm^{-1}$): 3378, 3069, 2894, 2843, 2737, 1743, 1600, 1469, 1393, 1199, 1065, 873, 738 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.72 (2H, t, $J$ = 7.6 Hz, $J$ = 8.8 Hz, $CH_2$), 2.82 (2H, t, $J$ = 7.6 Hz, $J$ = 5.6 Hz, $CH_2$), 7.35 (1H, d, $J$ = 7.6 Hz, ArH), 7.42 (1H, t, $J$ = 7.2 Hz, $J$ = 7.6 Hz, ArH), 7.50 (1H, t, $J$ = 6.8 Hz, $J$ = 7.2 Hz, ArH), 7.61 (1H, d, $J$ = 7.2 Hz, ArH), 7.81 (1H, t, $J$ = 4.0 Hz, $J$ = 4.0 Hz, ArH), 7.79 (1H, s, ArH), 8.18 (1H, d, $J$ = 7.6 Hz, ArH), 11.93 (1H, s, NH); HRMS *m*/*z* calculated for $C_{18}H_{12}Cl_2N_2O$ [M+H]: 343.0405, found: 343.0406.

***5,6-Dihydro-2-methyl-4-p-tolylbenzo[h]quinazoline (6a).*** m.p. 104–105°C; IR (KBr, ν, $cm^{-1}$): 3029, 2941, 2896, 2834, 1605, 1585, 1539, 1429, 1410, 1376, 1318, 1227, 1185, 1157, 1115, 1017, 894, 837, 805, 756, 725, 651, 571 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.39 (3H, s, $CH_3$), 2.67(3H, s, $CH_3$), 2.81 (2H, t, $J$ = 6.4 Hz, $J$ = 7.6 Hz, $CH_2$), 2.94 (2H, t, $J$ = 8.0 Hz, $J$ = 6.4 Hz, $CH_2$), 7.32 (3H, d, $J$ = 8 Hz, ArH), 7.38–7.46 (2H, m, ArH), 7.52–7.54 (2H, d, $J$ = 8.0 Hz, ArH), 8.27 (1H, d, $J$ = 6.8 Hz, ArH); HRMS *m*/*z* calculated for $C_{20}H_{18}N_2$ [M+H]: 287.1548, found: 287.1549.

***5,6-Dihydro-4-(4-methoxyphenyl)-2-methylbenzo[h]quinazoline (6b).*** m.p. 98–99°C; IR (KBr, ν, $cm^{-1}$): 3040, 2980, 2934, 2843, 1606, 1579, 1540, 1508, 1441, 1419, 1375, 1302, 1248, 1174, 1112, 1027, 847, 772, 759, 750, 729, 587 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.67 (3H, s, $CH_3$), 2.82 (2H, t, $J$ = 6.4 Hz, $J$ = 8.0 Hz, $CH_2$), 2.98 (2H, t, $J$ = 7.6 Hz, $J$ =6.4 Hz, $CH_2$), 3.83 (3H, s, $OCH_3$), 7.07 (2H, d, $J$ = 8.8 Hz, ArH), 7.33 (1H, d, $J$ = 7.2 Hz, ArH), 7.38–7.47 (2H, m, ArH), 7.62 (2H, d, $J$ = 8.4 Hz, ArH), 8.26 (1H, d, $J$ = 7.2 Hz, ArH); HRMS *m*/*z* calculated for $C_{20}H_{18}N_3O$ [M+H]: 303.1497, found: 303.1494.

***5,6-Dihydro-4-(3,4-dimethoxyphenyl)-2-methylbenzo[h]quinazoline (6c).*** m.p. 161–163°C; IR (KBr, ν, $cm^{-1}$): 3074, 2959, 2936, 2837, 1603, 1541, 1513, 1464, 1442, 1407, 1386, 1318, 1257, 1173, 1138, 1102, 877, 806, 762, 729, 680, 609 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.68 (3H, s, $CH_3$), 2.83 (2H, t, $J$ = 6.4 Hz, $J$ = 7.6 Hz, $CH_2$), 2.99 (2H, t, $J$ = 7.6 Hz, $J$ = 6.4 Hz, $CH_2$), 3.81 (3H, s, $OCH_3$), 3.84 (3H, s, $OCH_3$), 7.08 (1H, d, $J$ = 8.0 Hz, ArH), 7.20 (1H, d, $J$ = 8.4 Hz, ArH), 7.24 (1H, s, ArH), 7.33 (1H, d, $J$ = 6.8 Hz, ArH), 7.39–7.47 (2H, m, ArH), 8.26 (1H, d, $J$ = 7.6 Hz, ArH); HRMS *m*/*z* calculated for $C_{21}H_{20}N_2O_2$ [M+H]: 333.1603, found: 333.1602.

***4-(4-Fluorophenyl)-5,6-dihydro-2-methylbenzo[h]quinazoline (6d).*** m.p. 127–128°C; IR (KBr, ν, $cm^{-1}$): 3058, 2962, 2935, 2840, 1604, 1542, 1413, 1377, 1322, 1295, 1179, 1222, 1156, 1099, 1012, 895, 847, 812, 759, 749, 728, 665, 576 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.68 (3H, s, $CH_3$), 2.84 (2H, t, $J$ = 6.4 Hz, $J$ =7.6 Hz, $CH_2$), 2.95 (2H, t, $J$ = 6.4 Hz, $J$ =7.6 Hz, $CH_2$), 7.32–7.38 (3H, m, ArH), 7.39–7.46 (2H, m, ArH), 7.69–7.73 (2H, dd, $J$ = 5.6 Hz, $J$ = 5.6 Hz, ArH), 8.28 (1H, d, $J$ = 7.2 Hz, ArH); HRMS *m*/*z* calculated for $C_{19}H_{15}FN_2$ [M+H]: 291.1298, found: 291.1296.

***4-(3-Chlorophenyl)-5,6-dihydro-2-methylbenzo[h]quinazoline (6e).*** m.p. 97–98°C; IR (KBr, ν, $cm^{-1}$): 3020, 2939, 2898, 2839, 1604, 1585, 1572, 1478, 1441, 1369, 1321, 1228, 1184, 1079, 930, 892, 786, 762, 738, 722, 697, 657, 626 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.69 (3H, s, $CH_3$), 2.84 (2H, t, $J$ = 6.4 Hz, $J$ = 7.2 Hz, $CH_2$), 2.94 (2H, t, $J$ = 8.0 Hz, $J$ = 6.4 Hz, $CH_2$), 7.33 (1H, d, $J$ = 7.2 Hz, ArH), 7.40–7.48 (2H, m, ArH), 7.53–7.61 (3H, m, ArH), 7.69 (1H, s, ArH), 8.28 (1H, d, $J$ = 7.2 Hz, ArH); HRMS *m*/*z* calculated for $C_{19}H_{15}ClN_2$ [M+H]: 307.1002, found: 307.1000.

***4-(4-Chlorophenyl)-5,6-dihydro-2-methylbenzo[h]quinazoline (6f).*** m.p.120–121°C; IR (KBr, ν, $cm^{-1}$): 3044, 2940, 2901, 2837, 1595, 1587, 1574, 1541, 1490, 1431, 1413, 1373, 1317, 1275, 1225, 1183, 1157, 1110, 1091, 1036, 1012, 956, 919, 893, 874, 849, 830, 761, 732, 710, 647 $cm^{-1}$; $^1H$ NMR (400 Hz, DMSO-$d_6$), (d, ppm): 2.51 (3H, s, $CH_3$), 2.84 ( 2H, t, $J$ = 6.4 Hz, $J$ = 7.2 Hz, $CH_2$), 2.99 (2H, t, $J$ = 6.4 Hz, $J$ = 7.2 Hz, $CH_2$), 7.34 ( 1H, d, $J$ = 7.2 Hz, ArH), 7.40–7.45 (2H, m, ArH), 7.60 (2H, d, $J$ = 8.4 Hz, ArH), 7.68 (2H, d, $J$ = 8.4 Hz, ArH), 8.28 (1H, d, $J$ = 7.6 Hz, ArH); HRMS *m*/*z* calculated for $C_{19}H_{15}ClN_2$ [M+H]: 307.1002, found: 307.1001.

***4-(3,4-Dichlorophenyl)-5,6-dihydro-2-methylbenzo[h]quinazoline (6g).*** m.p. 98–101°C; IR (KBr, ν, $cm^{-1}$): 3084, 2939, 2899, 2836, 1603, 1586, 1540, 1470, 1431, 1411, 1363, 1315, 1222, 1183, 1133, 1021, 933, 905, 839, 763, 742, 728, 677, 641 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 2.69 (3H, s, $CH_3$), 2.84 (2H, t, $J$ = 6.4 Hz, $J$ = 7.8 Hz, $CH_2$), 2.95 (2H, t, $J$ = 7.6 Hz, $J$ = 6.0 Hz, $CH_2$), 7.33 (1H, d, $J$ = 7.2 Hz, ArH), 7.39 ~ 7.48 (2H, m, ArH), 7.63 (1H, dd, $J$ = 2.0 Hz, $J$ = 1.6 Hz, ArH), 7.79 (1H, d, $J$ = 8.4 Hz, ArH), 7.89 (1H, d, $J$ = 2.0 Hz, ArH), 8.27 (1H, d, $J$ = 7.2 Hz, ArH); HRMS *m*/*z* calculated for $C_{19}H_{14}N_2Cl_2$ [M+H]: 341.0612, found: 341.0613.

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## REFERENCES

[1] (a) Klutchko, S. R.; Zhou, H.; Winters, R. T.; Tran, T. P.; Bridges, A. J.; Althaus, I. W.; Amato, D. M.; Elliott, W. L.; Ellis, P. A.; Meade, M. A.; Roberts, B. J.; Fry, D. W.; Gonzales, A. J.; Harvey, P. J.; Nelson, J. M.; Sherwood, V.; Han, H.-K.; Pace, G.; Smaill, J. B.; Denny, W. A.; Showalter, H. D. H. J Med Chem 2006, 49, 1475; (b) Mazitschek, R.; Giannis, A. Curr Opin Chem Biol 2004, 8, 432.

[2] (a) Ellsworth, E. L.; Tran, T. P.; Showalter, H. D.; Sanchez, J. P.; Watson, B. M.; Stier, M. A.; Domagala, J. M.; Gracheck, S. J.; Joannides, E. T.; Shapiro, M. A.; Dunham, S. A.; Hanna, D. L.; Huband, M. D.; Gage, J. W.; Bronstein, J. C.; Liu, J. Y.; Nguyen, D. Q.; Singh, R. J Med Chem 2006, 49, 6435; (b) Kunes, J.; Bazant, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. Farmaco 2000, 55, 725.

[3] (a) Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. Antimicrob Agents Chemother 2004, 48, 4154; (b) Yang, H.; Kim, S.; Kim, M.; Reche, P. A.; Morehead, T. J.; Damon, I. K.; Welsh, R.-M.; Reinherz, E. L. J Clin Invest 2005, 115, 379.

[4] Vogtle, M. M.; Marzinzik, A. L. QSAR Comb Sci 2004, 23, 440.

[5] Chan, J. H.; Hong, J. S.; Kuyper, L. F.; Jones, M. L.; Baccanari, D. P.; Tansik, R. L.; Boytos, C. M.; Rudolph, S. K.; Brown, A. D. J Heterocycl Chem 1997, 34, 145.

[6] Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Tetrahedron 2005, 61, 10153.

[7] Dempcy, R. O.; Skibo, E. B. Biochemistry 1991, 30, 8480.

[8] Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Tetrahedron 2005, 61, 10153.

[9] (a) Tanaka,T.; Toda, F. Chem Rev 2000, 100, 1025; (b) Cave, G. W. V.; Raston, C. L. Chem Commun 2000, 22, 2199.

[10] Babak Kaboudin, B.; Karimi, M. Bioorg Med Chem Lett 2006, 16, 5324.

[11] Liang, B.; Wang, X. T. Wang, J. X.; Du, Z. Y. Tetrahedron, 2007, 63, 1981.

[12] X-ray crystallography for **5:** Empirical formula $C_{19}H_{15}FN_2$, $F_w = 290.33$, $T = 298(2)$ K, monoclinic, space group *p 2(1)/c*, $a = 12.6454$ (13) Å, $b = 15.214$ (2) Å, $c = 7.7432$ (10) Å, $\alpha = 90^{\circ}$, $\beta = 90.952(2)^{\circ}$, $\gamma = 90^{\circ\circ}$, $V = 1489.5$ (3) Å$^3$, $Z = 4$, $D_c = 1.295$ Mg/m$^3$, $\lambda$ (MoK$\alpha$) = 0.71073 Å, $\mu = 0.086$ mm$^{-1}$, $F(000) = 608$. $1.61^{\circ} < \theta < 25.00^{\circ}$, $R = 0.0536$ $R_w = 0.1424$. $S = 1.118$, largest diff. peak and hole: 0.141 and -0.146 e. Å$^{-3}$.

# A Green Procedure for the Synthesis of 1,8-Dioxodecahydroacridine Derivatives under Microwave Irradiation in Aqueous Media without Catalyst

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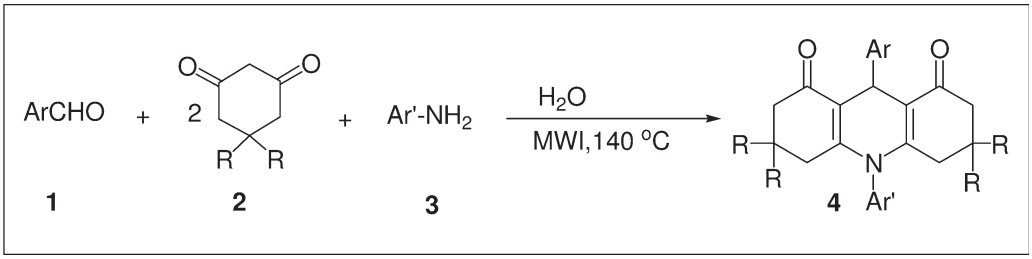


A green procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives is developed under microwave irradiation without catalyst in water. This method provides several advantages such as excellent yields (86–96%), simple workup procedure, and environment friendliness.

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## INTRODUCTION

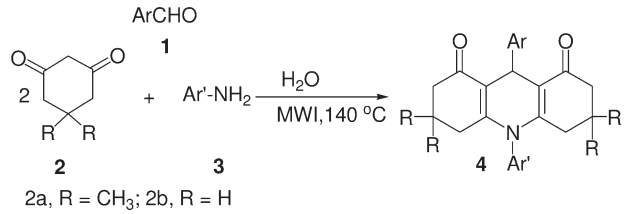
Water as a solvent has many advantages in organic synthesis, both from economic and from environmental points of view. Water has, therefore, become an attractive medium for many organic reactions. Many important types of heterocyclic compounds, such as triazines [1], acridines [2], quinolines [3], pyridines [4], indoles [5], pyrazines [6], furans [7], and pyrimidines [8] have been synthesized in aqueous media.

4-Aryl-1,4-dihydropyridines (1,4-DHPs) have proved to be valuable as drugs for the treatment of cardiovascular disorders [9] and constitute an important class of calcium channel blockers [10]. It is well established that slight structural modification on the DHP ring may result in remarkable change of pharmacological effect [11–14]. With a 1,4-DHP parent nucleus, acridine-1,8-diones have been shown to have very high lasing efficiencies [15] and used as photoinitiators [16]. Recently, many methods have become available for the synthesis of these important class of derivatives, We have synthesized these compounds from schiff's base and dimedone or 1,3-cyclohexanedione or three-component (aldehyde, dimedone, and arylamines) in glycol under microwave [17,18]. Jin et al. [19] reported that this reaction could be carried out catalyzed by *p*-dodecylben-zensulfonic acid (DBSA) in water. However, these reactions must be carried out by impetus of catalyst or in organic solvents. Wang et al. [20] reported the same reaction proceeded in an ionic medium, and Wang and Miao [21] achieved the reactions in aqueous solvent at traditional heating. The reaction time was 10 h, the yield was 72–75%. Arylamine used was only *p*-toluidine. Microwave-assisted organic reaction using water as solvent has peculiarity of ''safe solvents'' and ''energy efficiency.'' It was widely used in the organic synthesis [22]. In this article, we would like to report the green synthesis of 1,8-dioxo-9,10-diaryl-decahydracidines without catalyst *via* the combination of aqueous solvent and microwave heating, using a variety of arylamines including the anilines contained electron-withdrawing groups and electron-donating groups (Scheme 1).

## RESULTS AND DISCUSSION

When treating aldehyde **1** with dimedone or 1,3-cyclohexanedione **2** and primary arylamines **3** under microwave irradiation, the target compound **4** were obtained.

**Scheme 1**




To demonstrate the efficiency and the applicability of this method, we investigated the reaction of a variety of aromatic aldehydes **1**, dimedone, and a variety of primary arylamines **3** at 140°C in aqueous media. As shown in Table 1, a series of **1** and **3**, in which the aromatic ring contained electron-withdrawing groups (such as halo or nitro) or electron-donating groups (such as methyl or methyloxy), reacted with **2a** under the same reaction conditions to give the corresponding product **4** in good yields (entries 1–14), We thus concluded that there were no obvious electronic effect of the substituents on the aromatic rings. To further expand the scope of the present method, the replacement of dimedone **2a** with 1,3-cyclohexanedione **2b** was examined. To our delight, under the same conditions, the reactions proceeded steadily to afford a series of 1,8-dioxo-decahydroacridine derivatives in good yields (Table 1, entries 15–25).

The structures of all the synthesized compounds were established on the basis of their spectroscopic data (IR and $^1$H NMR). In addition, the X-ray diffraction analysis of product **4e** [23], **4k** [24], **4l** [25], **4n** [26], was carry out to confirm its structure. The crystal structure of **4k** is shown in Figure 1.

In conclusion, we have developed a green chemistry method for the synthesis of 1,8-dioxo-decahydroacridine derivatives. Excellent yields were obtained not only for anilines substituted with electron-donating groups but also for ones containing electron-withdrawing groups, The method avoided using organic solvents and had the main advantages of convenient procedure and environmental friendliness.

## EXPERIMENTAL

Microwave irradiation was carried out with microwave oven Emrys$^{TM}$ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a TENSOR 27 spectrometer in KBr and reported in cm$^{-1}$. $^1$H NMR spectra were measured on a Bruke DPX 400 MHz spectrometer in DMSO-$d_6$ with chemical shift (δ) given in ppm relative to TMS as internal standard, Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

**General procedure for the synthesis of compound 4 with microwave irradiation.** In a 10 mL Emrys$^{TM}$ reaction vial, an aldehyde **1**(1 mmol), dimedone or 1,3-cyclohexanedione **2**(2 mmol), primary arylamines **3**(1 mmol) and water (1.0 mL)

**Table 1**

Physical data of compounds **4**.

| Entry | Product | Ar | 2 | Ar′-NH$_2$ | Time (min) | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | 4-Chlorophenyl | **2a** | *p*-Toluidine | 7 | 283–285 | 96 |
| 2 | **4b** | 4-Bromophenyl | **2a** | *p*-Toluidine | 8 | 277–278 | 93 |
| 3 | **4c** | 4-Nitrophenyl | **2a** | *p*-Toluidine | 8 | >300 | 87 |
| 4 | **4d** | 4-Methoxyphenyl | **2a** | *p*-Toluidine | 10 | 241–243 | 90 |
| 5 | **4e** | Benzo[*d*][1,3]dioxol-5-yl | **2a** | *p*-Toluidine | 10 | 263–264 | 92 |
| 6 | **4f** | 4-Chlorophenyl | **2a** | 4-Aminophenol | 8 | >300 | 90 |
| 7 | **4g** | 4-Bromophenyl | **2a** | 4-Aminophenol | 8 | >300 | 88 |
| 8 | **4h** | 4-Chlorophenyl | **2a** | 4-Chlorobenzenamine | 8 | >300 | 89 |
| 9 | **4i** | 4-Bromophenyl | **2a** | 4-Chlorobenzenamine | 8 | >300 | 87 |
| 10 | **4j** | 4-Nitrophenyl | **2a** | 4-Chlorobenzenamine | 8 | >300 | 85 |
| 11 | **4k** | Benzo[*d*][1,3]dioxol-5-yl | **2a** | 4-Chlorobenzenamine | 10 | 287–288 | 88 |
| 12 | **4l** | 4-Methoxyphenyl | **2a** | 4-Chlorobenzenamine | 8 | 269–270 | 87 |
| 13 | **4m** | 4-Bromophenyl | **2a** | Aniline | 8 | 245–247 | 92 |
| 14 | **4n** | 4-Fluorophenyl | **2b** | *p*-Toluidine | 8 | 267–269 | 95 |
| 15 | **4o** | Benzo[*d*][1,3]dioxol-5-yl | **2b** | *p*-Toluidine | 8 | 236–238 | 89 |
| 16 | **4p** | 4-Fluorophenyl | **2b** | *p*-Toluidine | 8 | 263–264 | 93 |
| 17 | **4q** | 4-Bromophenyl | **2b** | *p*-Toluidine | 9 | >300 | 89 |
| 18 | **4r** | 4-Nitrophenyl | **2b** | *p*-Toluidine | 8 | >300 | 87 |
| 19 | **4s** | 4-Methoxyphenyl | **2b** | *p*-Toluidine | 8 | 261–262 | 88 |
| 20 | **4t** | 4-Chlorophenyl | **2b** | 4-Aminophenol | 8 | >300 | 92 |
| 21 | **4u** | 4-Methoxyphenyl | **2b** | 4-Chlorobenzenamine | 8 | 270–272 | 86 |
| 22 | **4v** | 4-Fluorophenyl | **2b** | 4-Chlorobenzenamine | 8 | 298–300 | 91 |
| 23 | **4w** | 4-Chlorophenyl | **2b** | 4-Chlorobenzenamine | 8 | 255–257 | 89 |
| 24 | **4x** | 4-Chlorophenyl | **2b** | Aniline | 8 | 288–290 | 92 |
| 25 | **4y** | 4-Methoxyphenyl | **2b** | Aniline | 8 | 290–291 | 87 |

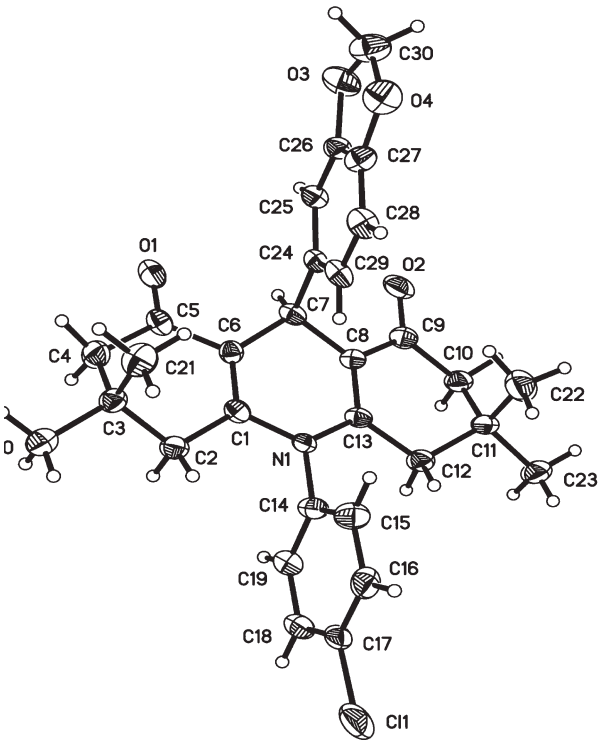



**Figure 1.** Molecular structure of **4k**.

was mixed and then capped. The mixture was irradiated for a given time at power of 200 W at 140°C. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was filtered to give the crude product, which was further purified by recrystallization from EtOH (95%).

***9-(4-Chlorophenyl)-10-(p-tolyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4a).*** mp 283–285°C. (lit. mp: 265–267°C) [19]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3058, 2958, 2888, 1639, 1575, 1511, 1486, 1450, 1361, 1278, 1221, 1144, 1089, 841. $^1$H NMR: 7.41 (d, 2H, ArH, $J$ = 8.4 Hz), 7.29–7.31 (m, 6H, ArH), 5.02 (s, 1H, CH), 2.50 (s, 3H, $CH_3$), 2.17–2.22 (m, 4H, $2CH_2$), 2.00 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.77 (d, 2H, $CH_2$, $J$ = 17.2 Hz), 0.88 (s, 6H, $CH_3$), 0.71 (s, 6H, $CH_3$). Anal calcd. for $C_{30}H_{32}ClNO_2$: C, 76.01; H, 6.80; N, 2.95. Found: C, 76.25; H, 6.71; N, 3.02.

***9-(4-Bromophenyl)-10-(p-tolyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4b).*** mp 277–278°C. (lit. mp: 265–267°C) [20]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3035, 2957, 2870, 1640, 1576, 1511, 1471, 1362, 1278, 1222, 1145, 1069, 842. $^1$H NMR: 7.40–7.45 (m, 4H, ArH), 7.25–7.32 (m, 4H, ArH), 5.00 (s, 1H, CH), 2.42 (s, 3H, $CH_3$), 2.17–2.22 (m, 4H, $2CH_2$), 1.99 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.77 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 0.88 (s, 6H, $CH_3$), 0.71(s, 6H, $CH_3$). Anal calcd. for $C_{30}H_{32}BrNO_2$: C, 69.50; H, 6.22; N, 2.70. Found: C, 69.39; H, 6.13; N, 2.82.

***9-(4-Nitrophenyl)-10-(4-tolyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]dione (4c).*** mp >300°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2959, 2930, 1639, 1573, 1512, 1343, 1222, 1146, 834. $^1$H NMR: 8.14–8.16 (m, 2H, ArH), 7.57–7.59 (m, 2H, ArH), 7.42 (d, 2H, ArH, $J$ = 6.8), 7.35 (d, 2H, ArH, $J$ = 7.6), 5.14 (s, 1H, CH), 2.43 (s, 3H, $CH_3$), 2.19–2.24 (m, 4H, $2CH_2$), 2.00 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.80 (d, 2H, $CH_2$, $J$ = 17.2 Hz), 0.88 (s, 6H, $CH_3$), 0.70 (s, 6H, $CH_3$). Anal calcd. for $C_{30}H_{32}N_2O_4$, C, 74.36; H, 6.66; N, 5.78. Found: C, 74.16; H, 6.79; N, 5.73.

***9-(4-Methoxyphenyl)-10-(4-tolyl)-3,3,6,6-tetrameth-yl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4d).*** mp: 281–283°C. (lit. mp: 285–287°C) [20]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3039, 2947, 2865, 1672, 1572, 1484, 1359, 1175, 1010, 837. $^1$H NMR: 7.41 (d, 3H, ArH, $J$ = 8.0 Hz), 7.20 (d, 3H, ArH, $J$ = 8.8 Hz), 7.80 (d, 2H, ArH, $J$ = 8.4 Hz), 4.98 (s, 1H, CH), 3.69 (s, 3H, $OCH_3$), 2.43 (s, 3H, $CH_3$), 2.16–2.22 (m, 4H, $2CH_2$), 1.99 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.76 (d, 2H, $CH_2$, $J$ = 17.2 Hz), 0.88 (s, 6H, $CH_3$), 0.72 (s, 6H, $CH_3$). Anal calcd. for $C_{31}H_{35}NO_3$. C, 79.28; H, 7.51; N, 2.98. Found: C, 79.47; H, 7.62; N, 2.79.

***9-(Benzo[d][1,3]dioxo-5-yl)-10-(p-tolyl)-3,3,6,6-tetra methyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4e).*** mp 263–264°C. (lit. mp: 272–274°C) [20]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2954, 2871, 1640, 1576, 1486, 1420, 1361, 1278, 1254, 1142, 1042, 813. $^1$H NMR: 7.16–7.21(m, 4H, ArH), 6.72–6.83 (m, 3H, ArH), 5.94 (s, 2H, $CH_2$) 4.96 (s, 1H, CH), 2.50 (s, 3H, $CH_3$), 2.16–2.20 (m, 4H, $2CH_2$), 2.02 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.78 (d, 2H, $CH_2$, $J$ = 17.2 Hz), 0.88 (s, 6H, $CH_3$), 0.74 (s, 6H, $CH_3$). Anal calcd. for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.88; N, 2.90. Found: C, 76.78; H, 6.98; N, 2.69.

***9-(4-Chlorophenyl)-10-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4f).*** mp >300°C. (lit. mp: >300°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3262, 2960, 2875, 1642, 1640, 1566, 1515, 1451, 1364, 1316, 1264, 1225, 1177, 1145, 1090, 1013, 886, 852, 782. $^1$H NMR: 10.0 (s, 1H, OH), 6.92–7.30 (m, 8H, ArH), 5.01 (s, 1H, CH), 2.17–2.22 (m, 4H, $2CH_2$), 1.83–2.00 (m, 4H, $2CH_2$), 0.90 (s, 6H, $CH_3$), 0.72 (s, 6H, $CH_3$). Anal calcd. for $C_{29}H_{30}ClNO_3$: C, 73.17; H, 6.35; N, 2.94. Found: C, 73.32; H, 6.21; N, 3.02.

***9-(4-Bromophenyl)-10-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4g).*** mp >300°C. (lit. mp: >300°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3162, 2958, 2875, 1638, 1564, 1513, 1463, 1365, 1316, 1264, 1178, 1146, 1070, 1009, 887, 850, 734, 779. $^1$H NMR: 10.0 (s, 1H, OH), 7.42 (d, 2H, ArH, $J$ = 8.0 Hz), 7.24 (d, 2H, ArH, $J$ = 8.0 Hz), 6.90–7.22 (m, 4H, ArH), 5.1 (s, 1H, CH), 2.16–2.23 (m, 4H, $2CH_2$), 1.83–2.00 (m, 4H, $2CH_2$), 0.90 (s, 6H, $CH_3$), 0.72 (s, 6H, $CH_3$). Anal calcd. for $C_{29}H_{30}BrNO_3$. C, 66.92; H, 5.81; N, 2.69. Found: C, 67.08; H, 5.65; N, 2.54.

***9-(4-Chlorophenyl)-10-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4h).*** mp >300°C. (lit. mp: 284–286°C) [20]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2958, 2870, 1639, 1578, 1490, 1361, 1361, 1263, 1221, 1145, 1090, 1014, 840, 739. $^1$H NMR: 7.68 (d, 2H, ArH, $J$ = 12.0 Hz), 7.47–7.49 (m, 2H, ArH), 7.28–7.33 (m, 4H, ArH), 5.01 (s, 1H, CH), 2.17–2.22 (m, 4H, $2CH_2$), 2.01

(d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.77 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 0.89 (s, 6H, $CH_3$), 0.72 (s, 6H, $CH_3$). Anal calcd. for $C_{29}H_{29}Cl_2NO_2$: C, 70.44; H, 5.91; N, 2.83. Found: C, 70.21; H, 6.02; N, 2.71.

***9-(4-Bromophenyl)-10-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4i).*** mp: 254–256°C. (lit. mp: 249–251°C) [20]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2958, 2869, 1639, 1578, 1577, 1491, 1361, 1221, 1145, 1089, 1009, 839. $^1$H NMR: 7.68 (d, 2H, ArH, $J$ = 8.0 Hz), 7.42–7.48 (m, 4H, ArH), 7.26 (d, 2H, ArH, $J$ = 8.0 Hz), 4.99 (s, 1H, CH), 2.17–2.23 (m, 4H, $2CH_2$), 2.01 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.76 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 0.89 (s, 6H, $CH_3$), 0.72 (s, 6H, $CH_3$). *Anal* calcd. for $C_{29}H_{29}BrClNO_2$: C, 64.63; H, 5.42; N, 2.60. Found: C, 64.81; H, 5.28; N, 2.68.

***9-(4-Nitrophenyl)-10-(4-chlorophenyl)-3,3,6,6-tetra methyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4j).*** mp >300°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2959, 2870, 1638, 1577, 1491, 1361, 1342, 1222, 1145, 1089, 1009, 831. $^1$H NMR: 7.67–7.70 (m, 2H, ArH), 7.48–7.50 (m, 2H, ArH), 7.28–7.33 (m, 4H, ArH), 5.01 (s, 1H, CH), 2.17–2.22 (m, 4H, $2CH_2$), 2.02 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.77 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 0.89 (s, 6H, $CH_3$), 0.72 (s, 6H, $CH_3$). Anal calcd. for $C_{29}H_{29}ClN_2O_4$: C, 68.97; H, 5.79; N, 5.55. Found: C, 69.14; H, 5.61; N, 5.42.

***9-(Benzo[d][1,3]dioxo-5-yl)-10-(4-chlorophenyl)-3,3, 6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4k).*** mp 287–288°C. (lit. mp: 287–288°C) [24]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2955, 2871, 1641, 1578, 1490, 1360, 1254, 1221, 1141, 1042, 921, 813. $^1$H NMR: 7.68 (d, 2H, ArH, $J$ = 8.8 Hz), 7.42–7.45 (m, 2H, ArH), 6.77–6.79 (m, 3H, ArH), 5.94 (s, 2H, $CH_2$), 4.96 (s, 1H, CH), 2.16–2.20 (m, 4H, $2CH_2$), 2.03 (d, 2H, $CH_2$, $J$ = 17.6 Hz), 1.78 (d, 2H, $CH_2$, $J$ = 17.2 Hz), 0.89 (s, 6H, $CH_3$), 0.75 (s, 6H, $CH_3$). Anal calcd. for $C_{30}H_{30}ClNO_4$: C, 71.49; H, 6.00; N, 2.78. Found: C, 71.23; H, 6.18; N, 2.69.

***9-(4-Methoxyphenyl)-10-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine1,8-[2H,5H]-dione (4l).*** mp 269–270°C. (lit. mp: 269–271°C) [27]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2952, 1641, 1578, 1491, 1361, 1259, 1173, 1140, 998, 834, 740. $^1$H NMR: 7.68 (d, 2H, ArH, $J$ = 8.0), 7.44–7.47 (m, 2H, ArH ), 7.21 (d, 2H, ArH, $J$ = 8.0 Hz), 6.80 (d, 2H, ArH, $J$ = 8.0 Hz), 4.97 (s, 1H, CH), 3.69 (s, 3H, $OCH_3$), 2.16–2.22 (m, 4H, $2CH_2$), 2.00 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.77 (d, 2H, $CH_2$, $J$ = 17.6 Hz), 0.89 (s, 6H, $CH_3$), 0.73 (s, 6H, $CH_3$). Anal calcd. for $C_{30}H_{32}ClNO_3$: C, 73.53; H, 6.58; N, 2.86. Found: C, 73.73; H, 6.62; N, 2.71.

***9-(4-Bromophenyl)-10-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4m).*** mp 285–287°C. (lit. mp: > 300°C) [20]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3060, 2956, 2869, 1639, 1577, 1491, 1452, 1361, 1261, 1176, 1008, 838. $^1$H NMR: 7.55–7.64 (m, 3H, ArH), 7.45 (d, 4H, ArH, $J$ = 8.0 Hz), 7.27 (d, 2H, ArH, $J$ = 8.0 Hz), 5.01 (s, 1H, CH), 2.18–2.23 (m, 4H, $2CH_2$), 2.01 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.75 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 0.87 (s, 6H, $CH_3$), 0.71 (s, 6H, $CH_3$). Anal calcd. for $C_{29}H_{30}BrNO_2$: C, 69.05; H, 5.99; N, 2.78. Found: 69.18; H, 5.76; N, 2.54.

***9-(4-Fluorophenyl)-10-(4-tolyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine1,8-[2H,5H]-dione (4n).*** mp 267–269°C. (lit. mp: 262–294°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3063, 2931, 2870, 1651, 1575, 1508, 1451, 1142, 1000, 843. $^1$H NMR: 7.41 (d, 2H, ArH, $J$ = 7.6 Hz), 7.30–7.34 (m, 4H, ArH), 7.04–7.08 (m, 2H, ArH), 5.03 (s, 1H, CH), 2.42 (s, 3H, $CH_3$), 2.20–2.22 (m, 4H, $2CH_2$), 2.00 (d, 2H, $CH_2$, $J$ = 16.0 Hz), 1.77 (d, 2H, $CH_2$, $J$ = 17.6 Hz), 0.88 (s, 6H, $CH_3$), 0.71 (s, 6H, $CH_3$). Anal calcd. for $C_{30}H_{32}FNO_2$: C, 78.75; H, 7.05; N, 3.06. Found: C, 78.94; H, 7.18; N, 3.02.

***9-(Benzo[d][1,3]dioxo-5-yl)-10-(4-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4o).*** mp 236–238°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3031, 2945, 2888, 1642, 1570, 1486, 1362, 1285, 1231, 1135, 1040, 857, 799. $^1$H NMR: 7.37 (d, 3H, ArH, $J$ = 8.0 Hz), 7.16–7.18 (m, 1H, ArH), 6.72–6.79 (m, 3H, ArH), 5.94 (s, 2H, $CH_2$), 5.06 (s, 1H, CH), 2.97 (s, 3H, $CH_3$), 2.18–2.24 (m, 6H, $3CH_2$), 1.91–1.96 (m, 2H, $CH_2$), 1.76–1.84 (m, 2H, $CH_2$), 1.59–1.65 (m, 2H, $CH_2$). Anal calcd. for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: 75.81; H, 6.01; N, 3.41.

***9-(4-Fluorophenyl)-10-(p-tolyl)-3,4,6,7,9,10-hexahy-droacridine-1,8-[2H,5H]-dione (4p).*** mp 263–264°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3059, 2929, 2870, 1633, 1571, 1507, 1360, 1284, 1231, 1134, 839. $^1$H NMR: 7.37–7.39 (m, 3H, ArH), 7.19–7.31 (m, 3H, ArH), 7.02–7.07 (m, 2H, ArH), 5.13 (s, 1H, CH), 2.40 (s, 3H, $CH_3$), 2.18–2.22 (m, 6H, $3CH_2$), 1.92–1.97 (m, 2H, $CH_2$), 1.79–1.84 (m, 2H, $CH_2$), 1.63–1.65 (m, 2H, $CH_2$). Anal calcd. for $C_{26}H_{24}FNO_2$: C, 77.78; H, 6.03; N, 3.49. Found: C, 77.94; H, 5.85; N, 3.31.

***9-(4-Bromophenyl)-10-(p-tolyl)-3,4,6,7,9,10-hexahy-droacridine-1,8-[2H,5H]-dione (4q).*** mp >300°C. (lit. mp: > 300°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3040, 2923, 2867, 1644, 1572, 1510, 1485, 1361, 1283, 1230, 1134, 1069, 831. $^1$H NMR: 7.37–7.43 (m, 5H, ArH), 7.24 (d, 2H, ArH, $J$ = 8.4 Hz), 7.14 (d, 1H, ArH, $J$ = 8.4 Hz), 5.10 (s, 1H, CH), 2.40 (s, 3H, $CH_3$), 2.18–2.21 (m, 8H, $4CH_2$), 1.92–1.97 (m, 2H, $CH_2$), 1.77–1.85 (m, 2H, $CH_2$). Anal calcd. for $C_{26}H_{24}BrNO_2$: C, 67.54; H, 5.23; N, 3.03. Found: C, 67.72; H, 5.06; N, 3.19.

***9-(4-Nitrophenyl)-10-(p-tolyl)-3,4,6,7,9,10-hexahy-droacridine-1,8-[2H,5H]-dione (4r).*** mp >300°C. (lit. mp: > 300°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2953, 2915, 1631, 1600, 1574, 1511, 1342, 1284, 1230, 1179, 1132. $^1$H NMR: 7.31–8.13 (m, 8H, ArH), 5.23 (s, 1H, CH), 2.40 (s, 3H, $CH_3$), 1.94–2.89 (m, 8H, $4CH_2$), 1.79–1.85 (m, 2H, $CH_2$), 1.62–1.65 (m, 2H, $CH_2$). Anal calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.72; H, 5.84; N, 6.70.

***9-(4-Methoxyphenyl)-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4s).*** mp 241.2–243.0°C. (lit. mp: 256–257°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2938, 1637, 1569, 1509, 1360, 1287, 1232, 1181, 1130, 954, 913, 825, 758. $^1$H NMR: 7.37–7.86 (m, 4H, ArH), 7.18 (d, 2H, ArH, $J$ = 8.8 Hz), 6.80 (d, 2H, ArH, $J$ = 8.4 Hz), 5.07 (s, 1H, CH), 3.70 (s, 3H, $OCH_3$), 2.40 (s, 3H, $CH_3$), 2.18–2.25 (m, 6H, $3CH_2$), 1.80–1.83 (m, 4H, $2CH_2$), 1.59–1.61 (m, 2H, $CH_2$). Anal calcd. for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.69; H, 6.72; N, 3.12.

***9-(4-Chlorophenyl)-10-(4-hydroxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4t).*** mp >300°C. (lit. mp: >300°C) [17]. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3161, 1636, 1561, 1489, 1453, 1385, 1362, 1269, 1234, 1140, 1088, 959. $^1$H NMR: 9.94 (s, 1H, OH), 6.89–7.28 (m, 8H, ArH), 5.11 (s, 1H, CH), 2.17–2.25 (m, 6H, $3CH_2$), 1.96–2.04(m, 2H, $CH_2$), 1.80–1.86 (m, 2H, $CH_2$), 1.59–1.67 (m, 2H, $CH_2$). Anal calcd. for $C_{25}H_{22}ClNO_3$: C, 71.51; H, 5.28; N, 3.34. Found: C, 71.38; H, 5.32; N, 3.40.

***9-(4-Methoxyphenyl)-10-(4-chlorophenyl)-3,4,6,7,9, 10-hexahydro acridine-1,8-[2H,5H]-dione (4u).*** mp 270–272°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2938, 1634, 1569, 1509, 1363, 1284, 1230, 1181, 1132, 955, 846, 756. $^1$H NMR: 7.68 (d, 2H, ArH, $J$ = 12.0), 7.45–7.47 (m, 2H, ArH), 7.21 (d, 2H, ArH, $J$ = 8.0 Hz), 6.80 (d, 2H, ArH, $J$ = 8.0 Hz), 4.97 (s, 1H, CH), 3.69 (s, 3H, $OCH_3$), 2.19–2.23 (m, 6H, $3CH_2$), 1.82–1.84 (m, 4H, $2CH_2$), 1.59–1.62 (m, 2H, $CH_2$). Anal calcd. for $C_{26}H_{24}ClNO_3$: C, 71.97; H, 5.57; N, 3.23. Found: C, 72.12; H, 5.38; N, 3.32.

***9-(4-fluorophenyl)-10-(4-chlorophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4v).*** mp 298–299°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2962, 1634, 1572, 1505, 1360, 1283, 1232, 1182, 1132, 956, 839, 759. $^1$H NMR: 7.65 (d, 2H, ArH, $J$ = 8.0), 7.29–7.33 (m, 3H, ArH), 7.02–7.06 (m, 3H, ArH), 5.12 (s, 1H, CH), 2.19–2.24 (m, 6H, $3CH_2$), 1.92–1.97 (m, 2H, $CH_2$), 1.80–1.84 (m, 2H, $CH_2$), 1.62–1.65 (m, 2H, $CH_2$). Anal calcd. for $C_{25}H_{21}ClFNO_2$: C, 71.17; H, 5.02; N, 3.32. Found: C, 71.02; H, 5.18; N, 3.21.

***9-(4-Chlorophenyl)-10-(4-chlorophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8[2H,5H]-dione (4w).*** mp 255–257°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 2946, 1633, 1571, 1489, 1362, 1284, 1183, 1134, 1089, 858, 821, 757. $^1$H NMR: 7.63–7.66 (m, 2H, ArH), 7.53–7.57 (m, 2H, ArH), 7.17–7.20 (m, 2H, ArH), 6.79 (d, 2H, ArH, $J$ = 8.0), 5.06 (s, 1H, CH), 2.18–2.26 (m, 6H, $3CH_2$), 1.91–1.97 (m, 2H, $CH_2$), 1.80–1.85 (m, 2H, $CH_2$), 1.59–1.65 (m, 2H, $CH_2$). Anal calcd. For $C_{25}H_{21}Cl_2NO_2$: C, 68.50; H, 4.83; N, 3.20. Found: C, 68.38; H, 4.99; N, 3.07.

***9-(4-Chlorophenyl)-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8-[2H,5H]-dione (4x).*** mp 288–290°C. This compound was obtained according to earlier general procedure. IR (potassium bromide): 3044, 2953, 1637, 1570, 1489, 1425, 1360, 1269, 1281, 1137, 1088, 956, 835. $^1$H NMR: δ7.53–7.60 (m, 3H, ArH), 7.19–7.33 (m, 6H, ArH), 5.13 (s, 1H, CH), 2.19–2.25 (m, 6H, $3CH_2$), 1.90–1.95 (m, 2H, $CH_2$), 1.79–1.81 (m, 2H, $CH_2$), 1.60–1.63 (m, 2H, $CH_2$). Anal calcd. for $C_{25}H_{22}ClNO_2$: C, 74.34; H, 5.49; N, 3.47. Found: C, 74.18; H, 5.62; N, 3.31.

***9-(4-Methoxyphenyl)-10-phenyl-3,4,6,7,9,10-hexa-hydroacridine-1,8-[2H,5H]-dione (4y).*** mp 290–291°C. (lit. mp: 270–272°C) [28]. IR (potassium bromide): 2943, 2887, 1635, 1569, 1509, 1359, 1284, 1229, 1181, 1132, 953, 857. $^1$H NMR: 7.55–7.57 (m, 4H, ArH), 7.30–7.35 (m, 1H, ArH), 7.18–7.21 (m, 2H, ArH), 6.79–7.82 (m, 2H, ArH), 5.09 (s, 1H, CH), 3.70 (s, 3H, $OCH_3$), 2.19–2.24 (m, 6H, $3CH_2$), 1.84–1.90 (m, 2H, $CH_2$), 1.79–1.81 (m, 2H, $CH_2$),1.60–1.64 (m, 2H, $CH_2$). Anal calcd. for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.01; H, 6.52; N, 3.58.

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## REFERENCES AND NOTES

[1] Dandia, A.; Arya, K.; Sati, M.; Sarawgi, P. J Fluorine Chem 2004, 125, 1273.

[2] Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. Tetrahedron Lett 2005, 46, 7169.

[3] Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. Tetrahedron 2000, 56, 7747.

[4] Khadilkar, B. M.; Gaikar, V. G.; Chitnavis, A. A. Tetrahedron Lett 1995, 36, 8083.

[5] Cho, C. S.; Kim, J. H.; Shim, S. C. Tetrahedron Lett 2000, 41, 1811.

[6] Totlani, V. M.; Peterson, D. G. J Agric Food Chem 2005, 53, 4130.

[7] Wnorowski, A.; Yaylayan, V. A. J Agric Food Chem 2000, 48, 3549.

[8] Bose, D. S.; Fatima, L.; Mereyala, H. B. J Org Chem 2003, 68, 587.

[9] Bossert, F.; Meyer, H.; Wehinger, E. Angew Chem Int Ed Engl 1981, 20, 762.

[10] Stou, D. M.; Meyers, A. I. Chem Rev 1982, 82, 223.

[11] Chorvat, R. J.; Rorig, K. J. J Org Chem 1988, 53, 5779.

[12] Goldmann, S.; Stoltefuss, J. Angew Chem Int Ed Engl 1991, 30, 1559.

[13] Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. J Med Chem 1974, 17, 956.

[14] Schramm, M.; Thomas, G.; Tower, R.; Franckowiak, G. Nature 1983, 303, 535.

[15] Shanmugasundaram, P.; Murugan, P.; Ramakrishnan, V. T.; Ramamurthy, P. Heteroat Chem 1996, 7, 17.

[16] Timpe, H. J.; Ulrich, S.; Decker, C.; Forassier, J. P. Macormolecules 1993, 26, 4560.

[17] Tu, S. J.; Li, T. J.; Zhang, Y.; Shi, F.; Xu J. N.; Wang, Q.; Zhang, J. P.; Zhu, X. T.; Jiang, B.; Jia, R. H.; Zhang, J. Y. J Heterocycl Chem 2007, 44, 83.

[18] Wang, X. S.; Shi, D. Q.; Wang, S. H.; Tu, S. J. Chin J Org Chem 2003, 23, 1291.

[19] Jin, T. S.; Zhang, J. S.; Guo, T. T.; Wang, A. Q.; Li, T. S. Synthesis 2004, 12, 2001.

[20] Wang, X. S.; Zhang, M. M.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. Synthesis 2006, 24, 4187.

[21] Wang, G. W.; Miao, C. B. Green Chem 2006, 8, 1080.

[22] The 12 principles are as follows: prevention, atom economy, less hazardous chemical synthesis, designing safer chemicals, safer solvents, design for energy efficiency, use of renewable feedstocks, reduce derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, inherently safer chemistry for accident prevention.

[23] Tang, Z. Q.; Cao, X. D.; Jiang, B.; Li, C. M.; Zhou, D. X. Acta Cryst 2007, E63, o3811.

[24] Liu, Q. D.; Tang, Z. Q.; Du, X. H. Acta Cryst 2007, E63, o3924.

[25] Chen, Y.; Hao, W. J.; Tang, Z. Q.; Jiang, B.; Li, C. M. Acta Cryst 2007, E63, o3934.

[26] Tang, Z. Q.; Liu, C. N.; Hao, W. J.; Wu, S. S. Acta Cryst 2008, E64, o1844.

[27] Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S. J Heterocycl Chem 2008, 45, 653.

[28] Chandrasekhar, S.; Rao, Y. S.; Sreelakshmi, L.; Mahipal, B.; Reddy, C. R. Synthesis 2008, 1737.

# Ternary Condensation of Biginelli Thiones, Chloroacetic Acid, and Aldehydes as an Effective Approach towards Thiazolo[3,2-a] pyrimidines and 5-Arylidenethiazolidine-2,4-diones

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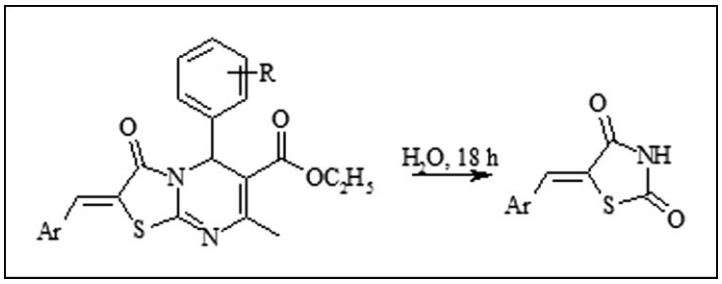


At the process of ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates condensation with aryl aldehydes and chloroacetic acid the unexpected formation of 5-arylidenethiazolidine-2,4-diones was determined in high yields as the reaction time was increased to 20 h. The latter represent the products of destructive hydrolyzes of ethyl 2-benzylidene-7-methyl-3-oxo-5-aryl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylates which have been proved by independent synthesis.

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## INTRODUCTION

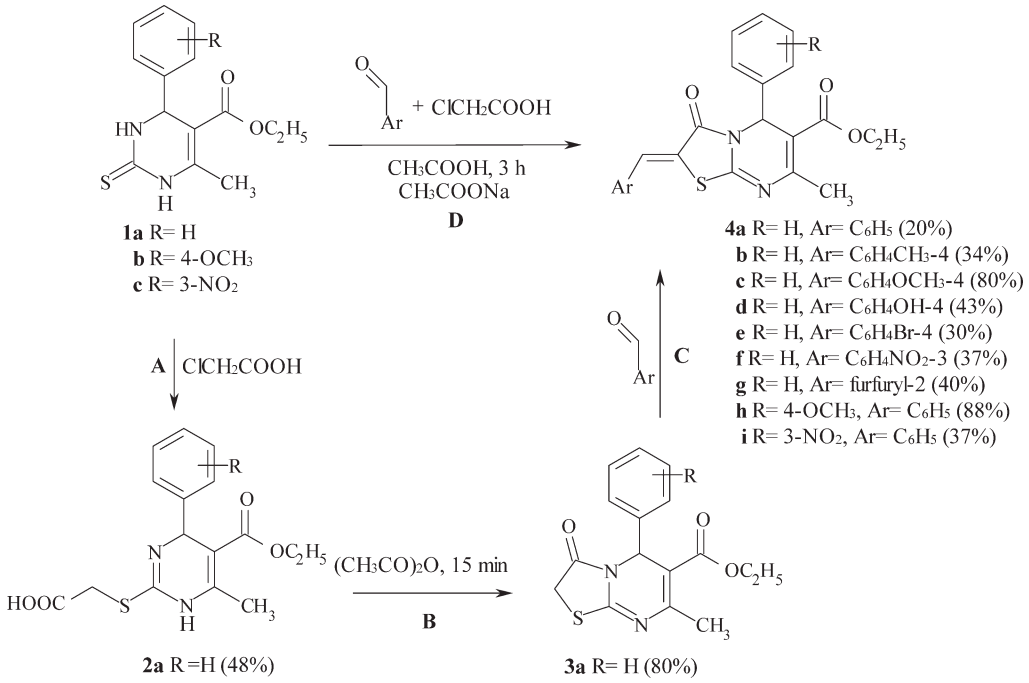
Multicomponent reactions (MCRs) have been widely used in organic and medicinal chemistry over the last years for producing a number of libraries for bioscreening [1]. A three-component condensation of aromatic aldehydes with ureas (thioureas) and β-ketoesters known as Biginelli reaction [2] takes an important place among MCRs. The reaction allows forming a dihydropyrimidine cycle where the nature of the subsistent in the basic structure can be widely modified. Dihydropyimidines (DHPMs) found their use as antimicrobial [3], antiviral [4], antiinflammatory [5], anticarcenogenic preparations [6], and calcium channel modulators [7]. The principle of Biginelli condensation is employed to construct complex heterocyclic scaffolds analogous to those isolated from Batzelladines A-B which have been found to be potent HIVgp-120-CD4 inhibitors [8]. To broaden the study on the range of biological activity of 2-thioxo-DHPM derivatives the library of substituted ethyl 5-aryl-3-oxo-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates (**4a–i**) have been synthesized [9].

A standard method of a multicomponent one-step condensation of substituted pyrimidine-2-thiones **1a** [9], **1b** [9], **1c** [2(b,f)], haloacetic acids, aryl(heteryl)aldehydes and surplus of anhydrous sodium acetate using glacial acetic acid as solvent has been employed. The formation of corresponding thiazolo[3,2-*a*]pyrimidine derivatives **4a–i** (**D**, Scheme 1) results in three consecutive stages which include alkylation leading to the compound **2a** (**A**, Scheme1) formation [2(c)], intramolecular heterocyclisation **3a** (**B**, Scheme 1) [9(c,h)], and condensation (**C**, Scheme 1) [9(a)] of primary DHPMs **1a–c**. Thus, a newly formed heterocyclic system **3a**, readily reacts with carbonyl compounds giving rise to substituted arylidene derivarives **4a–i**. The reaction time depends on the carbonyl reagent and lasts for 1–3 h. It is obvious that at the condensation of this type 7*H* isomer may be formed together with the 5*H* one (**4a–i**). Unambiguous formation of **4a–i** type ending products has been previously established with the extensive X-ray study [9(c)].

## RESULTS AND DISCUSSION

Quite unexpectedly, as the reaction time (**D**, Scheme 1) was increased to 18–20 h, the final products, extracted from the reaction mixture, were identified as 5-arylidene-2,4-thiazolidinediones (**5a–g**, Scheme 2) [10]. Thus, thiazolo[3,2-*a*]pyrimidines **4a–i** represent

**Scheme 1**



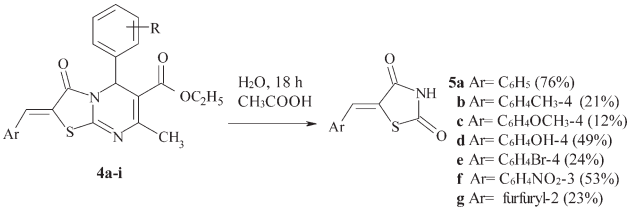

intermediate products for the synthesis of **5**-arylidene-2,4-thiazolidinediones (**5a–g**).

To determine the conditions when the destruction process takes place, a series of technical mixtures extracted from the mother liquor on different stages of the reaction time has been studied. A sample, taken in 30 min of reaction mixture reflux revealed the presence of the primary compound **1a** 27% and the intermediate product **4a** 72%. The destruction product **5a** was not determined on this reaction stage. Specimen, extracted in 3 h of reflux, revealed the presence of thiazolo[3,2-*a*]pyrimidine **4a** at the amount of 88% and 11% of 5-arylidene-thiazolidine-2,4-dione (**5a**). Sample, taken in 18 h of reaction mixture reflux contained both **5a** 76 and **4a** 20%, respectively. It should be noted that refluxing **4a** as a starting compound under the condensation conditions (glacial acetic acid, anhydrous sodium acetate, corresponding aromatic aldehyde), for 20 h did not reveal the presence of 5-arylidene thiazolidine-2,4-dione (**5a**). As water was added to the analogous reaction mixture to **4e**, the ratio of target products was **5e** 24, to **4e** 30%. 5-Arylidenethiazolidine-2,4-dione (**5a**) was formed in 55% yield when alkylated dihydropyrimidine-2-thione (**2a**) was used as a primary compound and cyclization took place under standard reaction duration and conditions. As analogous reaction conditions were followed excluding presence of water for **3a** as a primary compound the destruction process was not determined and reaction mixture contained 95% of thiazolo[3,2-*a*]pyrimidine **4a**. The exclusion of anhydrous sodium acetate from the reaction somewhat speeds up the destruction process and in 8 h of reaction time the ratio of **4a** to **5a** was 38 to 42%.

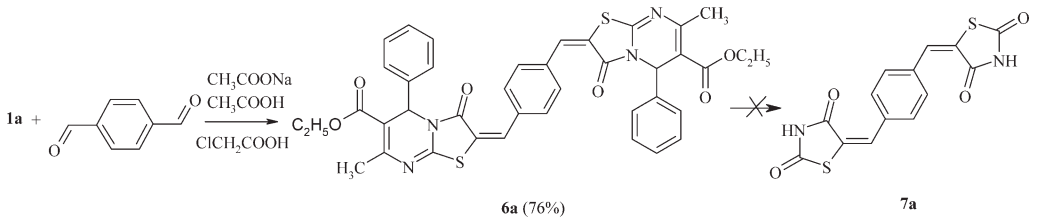
Thus, it may be concluded that the destruction process takes place due to slow hydrolyses of **4a–i** with water emitted during the condensation course. Therefore, the presence of anhydrous sodium acetate is obviously not enough to exclude the influence of water on the reaction course. As acetic anhydride surplus is added to the reaction mixture the process of destructive hydrolyses had not been determined either on the 3rd or on the 18th h of the reaction duration and the presence of formed thiazolo[3,2-*a*]pyrimidines (**4a**) was 97% and 98% respectively.

As terephthalic aldehyde was employed in ethyl thiazolo[3,2-*a*]pyrimidine-6-carboxylates synthesis, bis-thiazolo[3,2-*a*]pyrimidine of **6a** type (Scheme 3) has been obtained as a target product. It should be mentioned that possible destruction product (**7a**, Scheme 3) was not determined even under rigid reaction conditions such as

**Scheme 2**



**Scheme 3**




synthesis of **6a** in a sealed tube at 180°C for 12 h due to **6a** possessing low ability to dissolve in organic solvents.

The structure of compounds **5a–g** has been determined by NMR ($^1$H, $^{13}$C), IR, elemental, LC/MS analyses. $^1$H NMR spectra of compounds **5a–g** are characterized with the presence of the representative singlet at 6.0–6.1 ppm corresponding to the one of pyrimidine cycle at C4, and also with the singlet at 7.6–7.9 ppm relevant to the proton of methine group of the multiple bond C=CH-Ar. For **6a** corresponding signals are determined at 6.52 and 8.31 ppm at $CF_3COOD$.

$^{13}$C NMR spectroscopy was also applied to determine the structure of **5a** revealing eight signals. APT experiment determined the presence of four quaternary carbon atoms including two carbonyle and four protonated tertiary carbon atoms: δ = 167.65 (q), 167.09 (q), 132.85 (q), 131.61 (t), 130.20 (t), 129.83 (t), 129.10 (t), 123.36 (q) ppm. IR spectra of **5a–g** (KBr platelets) revealed broadened picks due to the intermolecular bonds of ÑH and C=O groups. The structure of **5a** has been unambiguously determined by the single crystal X-ray diffraction. The perspective view of the molecule **5a** and selected geometrical parameters are given in Figure 1. The molecule **5a** is almost planar (deviations of nonhydrogen atoms from the least-square plane do not exceed 0.069 Å). The N(1) atom has trigonal-planar bond configuration (sum of the bond angles 360.0°).

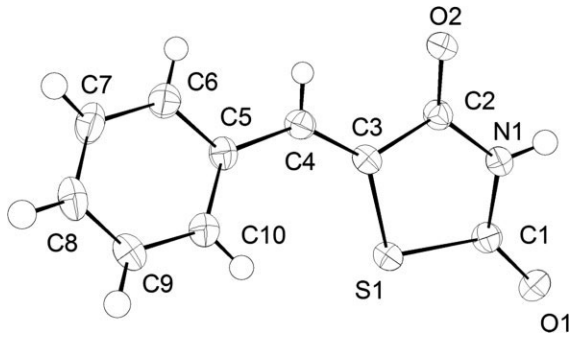



**Figure 1.** Perspective view and labeling scheme for the molecule **5a.** Selected bond lengths (Å) and angles (°): S(1)-C(1) 1.786(2), S(1)-C(3) 1.756(2), N(1)-C(1) 1.369(2), N(1)-C(2) 1.365(2), C(2)-C(3) 1.484(2), C(3)-C(4) 1.331(2); C(1)S(1)C(3) 91.68(8), C(1)N(1)C(2) 117.9(1).

Because of the $n_N$-$\pi_{C=O}$ conjugation both the N(1)-C(1) 1.369(2) Å and the N(1)-C(2) 1.365(2) Å bonds are significantly shortened in comparison with the standard value for the N($sp^2$)-C($sp^2$) single bonds of 1.43–1.45 Å [11,12]. In the solid state the molecules of **5a** are joined in the centrosymmetric dimers by the N(1)-H...O(2) (N...O 2.834(2), O...H 1.96(2) Å, NHO 169(23)° intermolecular hydrogen bonds.

## CONCLUSIONS

The formation of 5-arylidene-2,4-thiazolidinediones has been determined during the synthesis of substituted ethyl 5-aryl-3-oxo-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates library. Therefore, it is strongly suggested to reconsider the traditional reaction conditions and to take special care on the exclusion of water influence on the reaction process (*e.g.* acetic anhydride should be employed at the reaction rather than waterfree sodium acetate). Otherwise, as the reaction time expanded for the period of 18 h and more, allowing the emitted water to hydrolyze the desired thiazolo[3,2-*a*]pyrimidines the formation of 5-arylidene-2,4-thiazolidinediones reaches up to 76%.

## EXPERIMENTAL

All chemicals were obtained from commercial sources and used without further purification. Melting points (mp) were measured on an electrothermal capillary melting point apparatus and are uncorrected. IR spectra were recorded with a UR-20 spectrophotometer (KBr platelets). The NMR measurements were carried out on a Varian GEMINI 2000 spectrometer with $^1$H and $^{13}$C frequencies of 400.07 and 100.61 MHz, respectively at 293 K. $^1$H NMR spectra were recorded with spectral width 8000 Hz and numbers of points 32,000; $^{13}$C NMR spectra were recorded with spectral width 30,000 Hz and numbers of points 128,000. DMSO-$d_6$ and $CF_3COOD$ were used as solvents and TMS as internal standard. HPLC-MS was carried out on a system consisting of an Agilent 1100 Series high-pressure liquid chromatograph equipped with a diode matrix and Agilent LC/MSD SL mass-selective detector. HPLC-MS parameters: column: Zorbax SB-C18, 1.8 μm, 4.6 × 30 mm$^2$; solvents: Me-CN-$H_2O$ (95:5), 0.1% TFA; eluent flow: 3 mL s$^{-1}$; injected sample volume: 1 μL; UV detector: λ = 215, 254, 265 nm; ionization method: chemical ionization

under atmospheric pressure (APCI); ionization mode; simultaneous scanning of positive and negative ions in *m/z* range 100–650. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Crystallographic data of **5a** including atomic coordinates, bond lengths and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Camridge CB2 1EZ, UK, fax: +44 1223 336 033, or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 734605.

**General procedures.** ***4-Phenyl-5-carbethoxy-6-methylpyrimidine-2-mercaptoacetic acid (2a).*** A solution of **1a** 2.76 g (0.01 mole) and bromoacetic acid 1.5 g (0.011 mole) was refluxed in 15 mL acetic acid for 30 min. Then the mixture was taken to dryness *in vacuo*. The remained residue was neutralized with sodium carbonate solution to pH 5, filtered, washed with 100 mL of hot water. Recrystallized from EtOH. Compound **2a** was obtained as yellow solid in 68% yield. Mp and spectral data has appeared to be identical to those reported in literature [2(c)].

***Ethyl 5-phenyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a]pyrimidine-6-carboxylate (3a).*** Compound **2a** 1.82 g, (0.005 mole) was dissolved in 5 mL acetic anhydride and refluxed for 15 min, and then allowed to cool. The precipitate formed was filtered off and recrystallized from *i*-PrOH. Compound **3a** was obtained as yellow solid in 80% yield. Mp and spectral data has appeared to be identical to those reported in literature [2(c),10(a,b)].

**General procedure for the synthesis of ethyl 5-arylmethylene-3-oxo-7-methyl-2,3-dihydro-5H-thazolo[3,2-*a*]pyrimidine-6-carboxylates (4a–i).** A mixture of **1a–c** (0.01 mole), anhydrous sodium acetate 1.0 g, (0.015 mole), chloroacetic acid 1.0 g, (0.011 mole), and the appropriate aldehyde (0.01 mole) was refluxed for 3 h in 10 mL of glacial AcOH. After cooling, the mixture was poured onto crushed ice. The precipitate formed **4a–i** was filtered off and recryatllized from *i*-PrOH.

Compounds (Yield) **4a** [9(c)] (20%), **4b** [9(c)] (34%), **4c** [9(c,g)] (80%), **4e** [9(f)] (30%), **4h** [9(e)] (88%), **4i** [9(c)] (37%) have been described in the literature.

***Ethyl 5-phenyl-2-(4-hydroxyphenylmethylene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4d).*** Yellow solid, yield 43%, mp 192°C (*i*-PrOH); IR (KBr): ν 1545 (C=N), 1695 (C=O), 2990 (CH) 3430 (OH) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 10.22 [s, 1 H, OH], 7.66 [s, 1H, $HOC_6H_4CH$], 7.39 [d, $^3J$(H,H) = 8.8 Hz, 2 H, H2 H6 $C_6H_4OH$], 7.30 [m, 5 H, $C_6H_5$], 6.87 [d, $^3J$(H,H) = 8.8 Hz, 2 H, H3 H5 $C_6H_4OH$], 6.03 [s, 1 H, $C_6H_5CH$], 4.05 [m, 2 H, $CH_2CH_3$], 2.40 [s, 3 H, $NCCH_3$], 1.16 [t, $^3J$(H,H) = 8.0 Hz, 3 H, $CH_2CH_3$]; ms: *m/z* 419 ($M^-$). *Anal*. *C*alcd. for $C_{23}H_{20}N_2O_4S$: C, 65.70; H, 4.79; N, 6.66. Found: C, 64.39; H, 4.70; N, 6.73.

***Ethyl 5-phenyl-2-(3-nitrophenylmethylene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4f).*** Yellow solid in 37% yield, mp 173°C (*i*-PrOH); IR (KBr): ν 1330, 1540 ($NO_2$), 1610 (C=N), 1690, 1730 (C=O) 2980 (CH) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.39 [deg. s, 1 H, H2 $C_6H_4NO_2$], 8.25 [d, $^3J$(H,H) = 8.0 Hz, 1 H, H6 $C_6H_4NO_2$], 7.96 [d, $^3J$(H,H) = 7.6 Hz, 1 H, H4 $C_6H_4NO_2$], 7.90 [s, 1 H, $O_2NC_6H_4CH$], 7.78 [m. 1 H, H5 $C_6H_4NO_2$], 7.32 [m, 5 H, $C_6H_5$], 6.08 [s, 1 H, $C_6H_5CH$], 4.08 [m, 2 H, $CH_2CH_3$], 2.42 [s, 3 H, $CH_3$], 1.16 [t, $^3J$(H,H) = 6.8 Hz, 3 H, $CH_2CH_3$]; ms: *m/z* 450 ($M^+$). *Anal*. Calcd. for $C_{23}H_{19}N_3O_5S$: C: 61.46; H, 4.26; N, 9,35. Found: C, 60.24; H, 4.19; N, 9.42.

***Ethyl 5-phenyl-(2-furfuryl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4g).*** Grey solid in 40% yield, mp 149–150°C (*i*-PrOH); IR (KBr): ν 1600 (C=N), 1690 (C=O) 2960 (CH) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.06 [deg. s, 1 H, 5-H fur], 7.61 [s, 1 H, furCH], 7.33 [m, 5 H, $C_6H_5$], 7.09 [deg. s, 1 H, 3-H fur], 6.74 [deg. s, 1 H, 4-H fur], 6.05 [s, 1 H, $C_6H_5CH$], 4.06 [m, 2 H, $CH_2CH_3$], 2.39 [s, 3 H, $CH_3$], 1.13 [t, $^3J$(H,H) = 7.2 Hz, 3 H, $CH_2CH_3$]; *m/z* 395 ($M^+$). *Anal*. Calcd. for $C_{21}H_{18}N_2O_3S$: C, 63.95; H, 4.60; N, 7.10. Found: C, 62.69; H, 4.53; N, 7.18.

**General procedure for the synthesis of substituted 5-arylidene-2,4-thiazolidinedione (5 a–g).** A mixture of **1a–c** (0.01 mole), anhydrous sodium acetate 1.0 g (0.015 mole), chloroacetic acid 1.0 g (0.011 mole), and the appropriate aldehyde (0.01 mole) was refluxed for 18 h in 10 mL of glacial AcOH. Sodium acetate was separated by decantation. The reaction mixture was left for 24 h at ambient temperature, and the precipitate (**5a–g**) was filtered off and purified by recrystallization from 2-PrOH/DMF.

Compounds (Yield) **5a** [10(a,g,h,i)] (76%), **5b** [10(b,e)] (54%), **5c** [10(a,g)] (12%), **5d** [10(b,d,g)] (49%), **5e** [10(g)] (24%), **5f** [10(b,c)] (53%), **5g** [10(b,f)] (23%) have been described in the literature.

***4,4′-Bis(5-phenyl-6-carbethoxy-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidinyl-2-ylmethylene)benzene (6a).*** A mixture of **1a** 2.76 g (0.01 mole), anhydrous sodium acetate 1.0 g (0.015 mole), chloroacetic acid 1.0 g (0.011 mole), terephthalic aldehyde 0.67 g (0,005 mole) at 10 mL glacial AcOH was thoroughly sealed in a tube and allowed to stand at 180°C for 12 h. The precipitate formed was filtered off, washed with 100 mL of hot water, and purified with recrystallization from DMF.

Red solid, yield 76%, mp: <300°C (DMF); IR (KBr): ν 1560 (C=N), 1715 (C=O) 2990 (CH) $cm^{-1}$. $^1H$ NMR (400 MHz, $CF_3COOD$): δ = 8.31 [s, 2 H, $C_6H_4(CH)_2$], 7.81 [s, 4 H, $C_6H_4$], 7.47 [m, 10 H, 2 × $C_6H_5$], 6.52 [s, 2 H, 2 × $C_6H_5CH$], 4.34 [m, 4 H, 2 × $CH_2CH_3$], 2.75 [s, 6 H, 2 × $NCCH_3$], 1.32 [t, 6 H, 2 × $CH_2CH_3$]. *Anal*. Calcd. for $C_{40}H_{34}N_4O_6S_2$: C, 65.74; H, 4.69; N, 7.67. Found: C, 64.45; H, 4.61; N, 7.81.

**X-ray structure determination of 5a.** ***Crystal data.*** $C_{10}H_7NO_2S$, $M$ = 205.2, monoclinic, $a$ = 9.5115(6), $b$ 11.6786(7), $c$ = 8.2306(6) Å, β = 96.146(4)°, $V$ = 909.0(1) $Å^3$, $Z$ = 4, $d$ = 1.50 g $cm^{-1}$, space group $P2_1/c$ (N 14), μ = 3.24 $cm^{-1}$, $F(000)$ = 424, crystal size ca. 0.12 × 0.44 × 0.45 $mm^3$. All crystallographic measurements were performed at 293°C on a Bruker Apex II CCD diffractometer. The intensity data were collected within the range $2.8 < \theta < 26.3°$ ($-11 < h < 11$, $-14 < k < 14$, $-10 < l < 8$) using graphite monochromated Mo-$K_\alpha$ radiation (λ = 0.71073 Å). Intensities of 6416 reflections (1846 unique, $R_{int}$ = 0.003) were measured. Data were corrected for Lorentz and polarisation effects and an absorption correction using the Sadabs procedure was applied [13]. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic

approximation using the CRYSTALS program package [14]. In the refinement 1313 reflections with $I > 3\sigma(I)$ were used. All hydrogen atoms were located in the different Fourier maps and refined isotropically). Convergence was obtained at $R = 0.029$ and $R_w = 0.030$, GOF = 1.109 (155 refined parameters; obs./variabl. 8.5). Chebushev weighting scheme [15] with parameters 1.59, 1.50, 1.79, 0.55, and 0.47 was used.

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## REFERENCES AND NOTES

[1] Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, D.; Keating, T. A. Acc Chem Res 1996, 29, 123.

[2] (a) Biginelli, P. Gazz Chim Ital 1893, 23, 360; (b) Begum, N. Sh.; Vasundhara, D. E. Acta Crystallogr Sect E 2006, E62, o5796; (c) Kappe, C. O.; Roschger, P. J Heterocycl Chem 1989, 26, 55; (d) Valpuesta, M. F.; Lopez, F. J. H.; Lupion, T. C. Heterocycles 1986, 24, 679; (e) Atwal, K. S.; Rovnyak, G. S.; O'Reilly, B. C.; Schwartz, J. J Org Chem 1989, 54, 5898; (f) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. Heterocycles 1987, 26, 1189.

[3] McKinstry, D. W.; Reading, E. H. J Franklin Inst 1944, 237, 422.

[4] Jesus, A.; Yves, C. Fr. Pat.2,222,375 (1974); Chem Abstr 1975, 82, 171031.

[5] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[6] Luo, L.; Carson, J. D.; Dhanak, D.; Jackson, J. R.; Huang, P. S.; Lee, Y.; Sakowicz, R.; Copeland, R. A. Biochemistry 2004, 43, 15258.

[7] Jauk, B.; Pernat, T.; Kappe, C. O. Molecules 2000, 5, 227.

[8] Heys, L.; Moore, C. G.; Murphy, P. J Chem Soc Rev 2000, 29, 57.

[9] (a) Sherif, Sh. M.; Yossef, M. M.; Mobarak, K. M.; Abdel-Fattah, A.-S. M. Tetrahedron 1993, 49, 9561; (b) Akhtar, M. Sh.; Seth, M.; Bhaduri, A. P. Ind J Chem 1987, 26B, 556; (c) Tozkoparan, B.; Ertan, M.; Krebs, B.; Lage, M.; Kelicen, P.; Demirdamar, R. Arch Pharm 1998, 331, 201; (d) Ashok, M.; Holla, B. Sh.; Kumari, N. S. Eur J Med Chem 2007, 42, 380; (e) Tozkoparan, B.; Ertan, M.; Krebs, B.; Kelicen, P.; Demirdamar, R. Il Farmaco 1999, 54, 588; (f) Mobinikhaledi, A.; Foroughivar, N. Phosphorus Sulfur Silicon Relat Elem 2000, 56, 4531; (g) Ghorab, M. M.; Mohamed, Y. A.; Mohamed, S. A.; Ammar, Y. A. Phosphorus Sulfur Silicon Relat Elem 1996, 108, 249.

[10] (a) Okazaki, M.; Uchino, N.; Ishihara, M.; Fukunaga, H. Bull Chem Soc Jpn 1998, 71, 1713; (b) Yang, D.; Chen, Z.; Chen, S.; Zgeng, Q. J Chem Res Synop 2003, 6, 330; (c) Levshin, I. B.; Tsurkan, I. B.; V'yunov, K. A.; Ginak, A. I. Zh Prikl Khim 1983, 56, 1453; (d) Zubenko, V. G. Trudy L'vov Med Inst 1957, 12, 80; Chem Abstr 1960, 54, 21059; (e) Musial, L.; Staniec, J. Roczniki Chem 1965, 39, 839; Chem Abstr 1966, 64, 3516a; (f) Zubenko, V. G. Trudy L'vov Med Inst 1957, 12, 80; Zubenko, V. G. Chem Abstr 1958, 55, 17623d; (g) Giles, R. G.; Lewis, N. J.; Quick, J. K.; Sasse, M. J.; Urquhart, M. W. J.; Youseff, L. Tetrahedron 2000, 56, 4531; (h) Hulin, B.; Clark, D. A.; Goldstein, S. W.; Dermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, Ch. H; Lewis, D.; Rizzi, J. P. J Med Chem 1992, 35, 1853; (i) Rudorf, W.-F.; Schwarz, R. Heterocycles 1986, 24, 3459.

[11] Burke-Laing, M.; Laing, M. Acta Crystallogr Sect B 1976, 32, 3216.

[12] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. J Chem Soc Perkin Trans 2 1987, 12, 1.

[13] Sheldrick, G. M. SADABS: Program for Scaling and Correction of Area Detector Data; University of Gottingen: Germany, 1996.

[14] Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W. CRYSTALS Issue 10; Chemical Crystallography Laboratory, University of Oxford: Oxford, 1996.

[15] Carruthers, J. R.; Watkin, D. J. Acta Crystallogr Sect A 1979, 35, 698.

# Efficient Synthesis of Benzimidazo[1,2-*a*]pyrimidinone Derivatives *via* Catalyst-Free Reactions of Baylis–Hillman Acetates, Alcohols, and Amines with 2-Aminobenzimidazole



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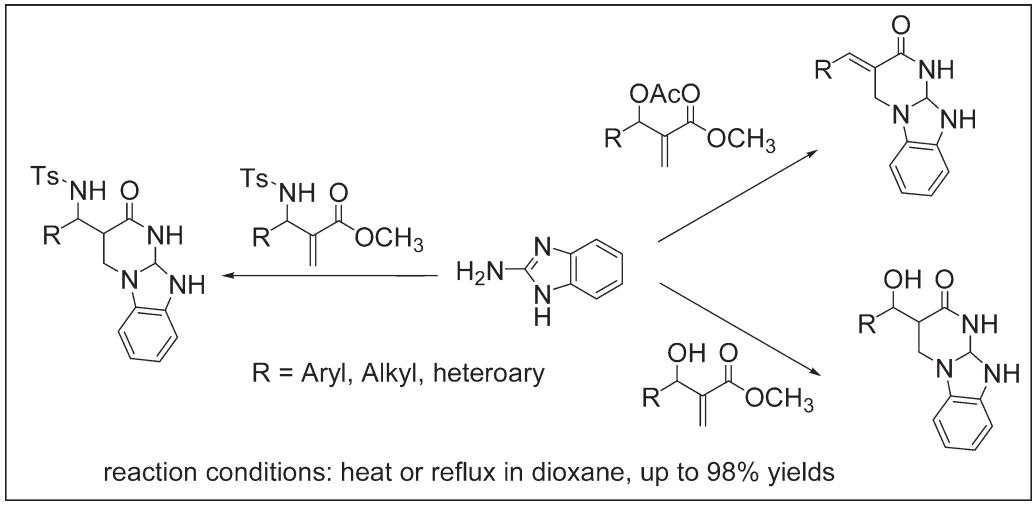


Benzimidazo[1,2-*a*]pyrimidinone and its derivatives were easily prepared in good to excellent yields *via* tandem reactions of 2-aminobenzimidazole with Baylis–Hillman acetates, alcohols, and amines without the use of catalyst and additive in one-pot process. The method provided an efficient and facile route to the title fused heterocyclic compounds with different functional groups.

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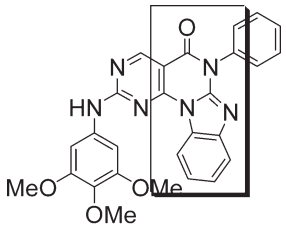
## INTRODUCTION

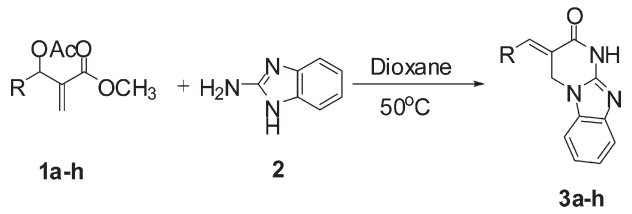
Imidazo[1,2-*a*]pyrimidines are very important intermediates and widely used in pharmaceutical chemistry [1]. Among them, benzimidazo[1,2-*a*]pyrimidinone and its derivatives have attracted considerable attention [2,3]. For example, the compound **A** is a kind of inhibitor of Lck kinase, which is a member of Src family of cytoplasmic tyrosine kinases. The inhibitor might be a useful immunosuppressive agent for the treatment of graft rejection and/or T-cell-mediated autoimmune diseases [4]. There were several approaches to develop the benzimidazo[1,2-*a*]pyrimidinones: the intramolecular substitution reaction of halide with amines [2], the reaction of 2-aminobenzimidazole with propiolic esters and α,β-unsaturated esters [3], and so on. To enhance the diversity of benzimidazo[1,2-*a*]pyrimidinone compounds, a new type of substrate is still required.




Compound **A**

Recently, it was noteworthy that the reactions of 2-aminobenzimidazole with several electrophiles, including nitrile, α,β-unsaturated carbonyl compounds, cyanoacetate, and acetylene-dicarboxylate, have been developed to construct heterocyclic structural unit [5]. The Baylis–Hillman adduct offers an excellent platform for several chemical transformations because of the presence of three functional groups including hydroxyl

**Scheme 1**




(or substituted amino), double bond, and electron-withdrawing group (alkoxycarbonyl or nitrile) in close proximity. The Baylis–Hillman adducts were illustrated as valuable precursor for the synthesis of heterocycles and many biologically active molecules [6]. It was envisaged that the reaction of 2-aminobenzimidazole with Baylis–Hillman adducts and their derivatives would provide an efficient route for the synthesis of annulated benzimidazole derivatives.

Herein, we wish to report the catalyst-free reactions of Baylis–Hillman acetates, alcohols, and amine for the synthesis of benzimidazo-[1,2-*a*]pyrimidinone and their derivatives bearing different functional groups with significant convenience [7].

## RESULTS AND DISCUSSION

**The reactions of Baylis–Hillman acetates (1) with 2-aminobenzoimidazole (2).** Initially, the reaction of Baylis–Hillman acetate **1a** (R = Ph) and 2-aminobenzimidazole **2** was carried out in dioxane at room temperature without any catalyst, but no reaction was observed even after long period of time. However, on raising the temperature to 50°C, light yellow precipitates formed only after 30 min, affording (*E*)-6-benzylidene-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]-pyrimidin-7-one **3a** in 93% yield (Scheme 1, Table 1, entry 1).

In $^1$H-NMR spectrum of **3a**, only one signal of N—H was observed, which showed the formation of cyclic product. The formation of lactam structure was further supported by the IR spectrum, in which an amide carbonyl vibration band appeared at 1657 cm$^{-1}$. The stereochemistry of the newly formed double bond in the products was established as (*E*)-configuration by X-ray diffraction analysis of the single crystal of the product **3d** (R = 2-$F_3CC_6H_4$) (Fig. 1). The structure of the single crystal was also an evidence for the formation of the three nitrogen-containing fused heterocycle.

As shown in Table 1, the substrate scope for the benzimidazo[1,2-*a*]pyrimidine forming process was quite broad, and the reaction demonstrated that various Baylis–Hillman acetates bearing aryl, heteroaryl, or alkyl groups can be used for this transformation. The reaction proceeded smoothly regardless of the electronic character of the substituents existed on the Baylis–Hillman acetates to afford the desired fused heterocycle, benzimidazo[1,2-*a*]pyrimidine derivatives in good to excellent yields (71–97%).

**Table 1**

Reaction of B-H acetates (**1**) with **2**.[a]

| Entry | B-H acetate | Time (h) | Product (R) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **1a**, $C_6H_5$ | 0.5 | **3a**, $C_6H_5$ | 85 |
| 2 | **1b**, 4-$ClC_6H_4$ | 0.5 | **3b**, 4-$ClC_6H_4$ | 93 |
| 3 | **1c**, 2-furyl | 1.5 | **3c**, 2-furyl | 76 |
| 4 | **1d**, 2-$F_3CC_6H_4$ | 0.5 | **3d**, 2-$F_3CC_6H_4$ | 90 |
| 5 | **1e**, 3-$BrC_6H_4$ | 1.0 | **3e**, 3-Br $C_6H_4$ | 97 |
| 6 | **1f**, 3-$MeOC_6H_4$ | 1.0 | **3f**, 3-$MeOC_6H_4$ | 90 |
| 7 | **1g**, $C_2H_5$ | 1.0 | **3g**, $C_2H_5$ | 71 |

[a] **1**:**2** = 1:1.2; in dioxane at 50°C.
[b] Isolated yield.

## THE REACTIONS OF BAYLIS–HILLMAN ALCOHOLS (4) WITH 2

In contrast, when the Baylis–Hillman alcohols were used, the hydroxyl group remained in the product. However, as indicated by Batra and coworkers [8], the hydroxyl group was very sensitive to the reaction condition and ease to be removed out during the intramolecular cyclization by debenzylation. To our delight, under the same reaction conditions for Baylis–Hillman acetate, the fused heterocyclic compounds bearing hydroxyl group could be obtained in one-pot process (Scheme 2). As shown in Table 2, various Baylis–Hillman alcohols (**4a–i**) derived from aryl aldehydes reacted smoothly with **2** to give 6-[aryl(hydroxyl)methyl]-benzoimidazo[1,2-*a*]pyrimidines (**5a–i**) in good to excellent yields. The presence of substitute in the *ortho* position of the phenyl ring (**4f–g**) resulted in slow reactivity of the Baylis–Hillman adduct leading to increase in

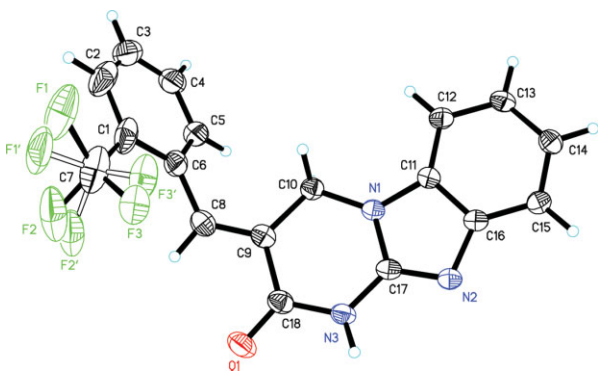
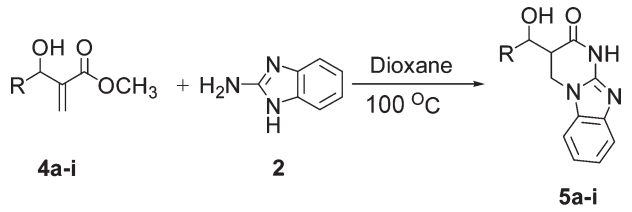



**Figure 1.** ORTEP drawing of **3d**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2**




reaction time (entries 6 and 7). Moreover, the substrate bearing aromatic heterocyclic (**4h**) and alkyl group (**4i**) also exhibited good ability for the reaction with **2**, affording the corresponding products (**5h** and **5i**) in 78 and 93% yields, respectively (entries 8 and 9).

**The reactions of Baylis–Hillman amines (6) with 2.** Recently, Lamaty and coworkers assimilated all applications of the aza-Baylis–Hillman adducts for the synthesis of nitrogen-containing compounds. It was demonstrated that when the aza-Baylis–Hillman adduct (Baylis–Hillman amine) was attacked by a nucleophile, the reaction could afford a Michael addition product or an allylic substitution product depending on the reaction conditions, which resulted in the amino group of aza-Baylis–Hillman adducts remaining either in the product or eliminating from the product [9]. When various Baylis–Hillman amines (**6a–g**) were used in the reaction with **2**, under the same condition for Baylis–Hillman acetate the reactions carried out smoothly to afford the Michael addition products **7** in high yields (Table 3). When the substituents in the phenyl ring were electron-withdrawing groups (**6b–f**), the reactions proceeded better than the substrate bearing electron-donating group in the phenyl ring (**6g**) (Entry 7) (Scheme 3).

In conclusion, we have developed an efficient method for the synthesis of benzimidazo[1,2-*a*]pyrimidine derivatives in good to excellent yields. The developed protocol was simple, and no additives or catalysts were required to promote the reaction. The reaction underwent the Michael addition or allylic substitution reaction, followed by intramolecular cyclization. The produced compounds possessed different functions, double bond, hydroxyl and amino groups, which provided an opportunity to do derivatization further for enhancing the diversity of benzimidazo[1,2-*a*]pyrimidine compounds.

**Table 2**

Reaction of B-H alcohols (**4**) with **2**.[a]

| Entry | B-H alcohol | Time (h) | Product (R) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **4a**, $C_6H_5$ | 2.0 | **5a**, $C_6H_5$ | 89 |
| 2 | **4b**, 4-$FC_6H_4$ | 2.0 | **5b**, 4-$FC_6H_4$ | 93 |
| 3 | **4c**, 4-$ClC_6H_4$ | 2.0 | **5c**, 4-$ClC_6H_4$ | 94 |
| 4 | **4d**, 4-$NO_2C_6H_4$ | 1.5 | **5d**, 4-$NO_2C_6H_4$ | 97 |
| 5 | **4e**, 3-$NO_2C_6H_4$ | 2.0 | **5e**, 3-$NO_2C_6H_4$ | 98 |
| 6 | **4f**, 2-$NO_2C_6H_4$ | 3.0 | **5f**, 2-$NO_2C_6H_4$ | 93 |
| 7 | **4g**, 2-$F_3CC_6H_4$ | 3.0 | **5g**, 2-$F_3CC_6H_4$ | 93 |
| 8 | **4h**, 2-furyl | 1.5 | **5h**, 2-furyl | 78 |
| 9 | **4i**, H | 3.0 | **5i**, H | 95 |

[a] **4**:**2** = 1:1.2; in dioxane at 100°C.
[b] Isolated yield.

**Table 3**

Reaction of B-H amines (**6**) with **2**.[a]

| Entry | B-H amine | Time (h) | Product (R) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **6a**, $C_6H_5$ | 2.5 | **7a**, $C_6H_5$ | 86 |
| 2 | **6b**, 4-$FC_6H_4$ | 5.0 | **7b**, 4-$FC_6H_4$ | 91 |
| 3 | **6c**, 4-$ClC_6H_4$ | 1.0 | **7c**, 4-$ClC_6H_4$ | 94 |
| 4 | **6d**, 4-$NO_2C_6H_4$ | 0.5 | **7d**, 4-$NO_2C_6H_4$ | 81 |
| 5 | **6e**, 3-$NO_2C_6H_4$ | 1.5 | **7e**, 3-$NO_2C_6H_4$ | 97 |
| 6 | **6f**, 2-$NO_2C_6H_4$ | 2.0 | **7f**, 2-$NO_2C_6H_4$ | 96 |
| 7 | **6g**, 4-$MeC_6H_4$ | 3.0 | **7g**, 4-$MeC_6H_4$ | 75 |

[a] **6**:**2** = 1:1.2; in dioxane at 100°C.
[b] Isolated yield.

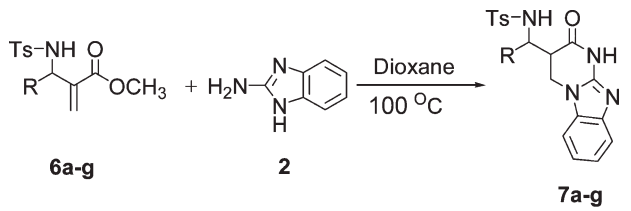
## EXPERIMENTAL

IR spectra were recorded with a Perkin–Elmer 782 IR spectrometer. $^1$H-NMR and $^{13}$C-NMR spectra were obtained with a Bruker DMX-300 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), and the center of the multiplet of the DMSO was also defined as 39.53 ppm for $^{13}$C-NMR spectra. HRMS (EI) spectra were measured on a JEOL JMS-DX303. Melting points were measured with a Beijing-Taike X-4 apparatus and are uncorrected. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification.

According to reference's method [10], starting from α,β-unsaturated ester, with aryl or alkyl aldehydes the B-H alcohols (**4a–i**), and with imines the B-H amines (**6a–g**) were synthesized, respectively. B-H acetates (**1a–h**) were derived from B-H alcohols by acetyl chloride.

**General procedure for the reaction of Baylis–Hillman acetates (1a–h) with 2-aminobenzimidazole (2).** To a solution of B-H acetate **1a–h** (1 mmol) in dioxane was added 2-aminobenimidazole **2** (1.2 mmol), and the resultant reaction mixture was heated at 50°C. Upon completion as judged by TLC or the reaction time given in Table 1, precipitates were formed, which were filtered and washed with ether. The crude product was recrystallized from dichloromethane/

**Scheme 3**



petroleum ether to give corresponding products, benzimidazo[1,2-*a*]pyrimidinone derivatives (**3a–g**).

**(*E*)-6-Benzylidene-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (3a).** A light brown solid, m.p. > 300°C (decom.); FTIR (KBr): 3271, 2923, 1668, 1589, 1338 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 5.33 (s, 2H, $CH_2$), 7.13 (s, 2H, ArH), 7.28–7.65 (m, 7H, ArH), 7.90 (s, 1H, CH), 11.80 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ = 42.3, 109.2, 117.1, 120.6, 121.6, 121.8, 128.9, 129.7, 130.6, 133.1, 133.8, 138.1, 141.5, 146.4, 161.8; HR MS(EI): *m/z* calcd. for $C_{17}H_{13}N_3O$ ($M^+$): 275.1059, found 275.1057.

**(*E*)-6-(4-Chlorobenzylidene)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidine-7-one (3b).** A light brown solid, m.p. > 300°C (decom.); FTIR (KBr): 3271, 2923, 1668, 1589, 1338 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 5.31 (s, 2H, $CH_2$), 6.88 (s, 2H, ArH), 7.42–7.67 (m, 7H, ArH), 7.88 (s, 1H, CH), 11.83 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 42.2, 109.2, 117.1, 120.6, 121.6, 122.7, 128.9, 132.4, 132.8, 133.1, 134.3, 136.7, 141.5, 146.4, 161.6; HR MS(EI): *m/z* calcd. for $C_{17}H_{13}N_3O$ ($M^+$): 309.0669, found 309.0672.

**(*E*)-6-(Furan-2-ylmethylene)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (3c).** A light yellow solid, m.p. > 300°C (decom.); FTIR (KBr): 3430, 3118, 1684, 1532, 1348 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 5.30 (s, 2H, $CH_2$), 6.80 (d, 1H, *J* = 1.4 Hz, ArH), 7.14–7.20 (m, 3H, ArH), 7.42–7.54 (m, 2H, ArH), 7.69 (s, 1H, ArH), 8.01 (s, 1H, CH), 11.8 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 42.6, 109.0, 113.2, 117.1, 117.9, 120.6, 121.6, 123.9, 133.1, 141.5, 146.6, 146.7, 150.4, 161.2; HRMS(EI): *m/z* calcd. for $C_{15}H_{11}N_3O_2$ ($M^+$): 265.0851, found 265.0849.

**(*E*)-6-(*o*-Trifluoromethylbenzylidene)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (3d).** A white solid, m.p. > 300°C (decom.); FTIR (KBr): 3157, 1692, 1531, 1457, 1351 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 5.14 (s, 2H, $CH_2$), 7.05–7.14 (m, 3H, ArH), 7.36–7.44 (dd, 2H, *J* = 7.2, 7.6 Hz, ArH), 7.70 (t, 1H, *J* = 6.7 Hz, ArH), 7.83–7.92 (dd, 2H, *J*= 7.9, 7.5 Hz, ArH), 8.01 (s, 1H, CH), 11.9 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 41.5, 109.2, 117.1, 120.8, 121.7, 125.6, 126.3, 126.3, 127.5, 129.6, 130.4, 132.1, 132.9, 133.0, 134.0, 141.4, 146.5, 161.4; HRMS(EI): *m/z* calcd. for $C_{18}H_{12}N_3OF_3$ ($M^+$): 343.0932, found 343.0929. The crystal used for the X-ray study had the dimensions 0.41 mm × 0.38 mm × 0.06 mm. Crystal data: $C_{18}H_{12}F_3N_3O$, *M* = 343.31, monoclinic, space group *P*2(1)/*c*, *a* = 6.5560(13), *b* = 33.361(7), *c* = 7.1651(14) Å, β = 99.55(3)°, *V* = 1545.4(5) Å$^3$, *Z* = 4, $D_{calcd}$ = 1.476 g/cm$^3$, $F_0$ = 704, reflections collected: 8887, λ = 0.71073 Å. CCDC: 738372.

**(*E*)-6-(3-Bromobenzylidene)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidine-7-one (3e).** A light yellow solid, m.p. > 300°C (decom.); FTIR (KBr): 3271, 2923, 1668, 1589, 1338 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 5.31 (s, 2H, $CH_2$), 7.12 (t, 2H, *J* = 2.1 Hz, ArH), 7.41 (m, 1H, CH), 7.50 (m, 2H, ArH), 7.67 (t, 2H, *J* = 8.0 Hz, ArH), 7.84–7.86 (m, 2H, ArH); 11.9 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 42.1, 109.2, 117.1, 120.7, 121.7, 122.1, 123.5, 129.0, 130.9, 132.2, 132.9, 133.0, 136.2, 136.5, 141.5, 146.5, 161.5; HRMS(EI): *m/z* calcd. for $C_{17}H_{13}N_3O$ ($M^+$): 355.0143, found 355.0148.

**(*E*)-6-(3-Methoxybenzylidene)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidine-7-one (3f).** A white solid; m.p. > 300°C (decom.); FTIR (KBr): 3271, 2923, 1668, 1589, 1338 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.85 (s, 3H, $CH_3$), 5.33 (s, 2H,$CH_2$), 7.06–7.44 (m, 5H, ArH), 7.44–7.47 (m, 3H, ArH), 7.89 (s, 1H, CH); 11.84 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 42.2, 55.2, 109.2, 115.6, 115.8, 117.1, 120.6, 121.6, 122.1, 122.6, 129.9, 133.1, 135.2, 138.2, 141.5, 146.4, 159.4, 161.8; HRMS(EI): *m/z* calcd. for $C_{17}H_{13}N_3O$ ($M^+$): 305.1164, found 305.1167.

**(*E*)-6-Propylidene-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (3g).** A white solid; m.p. = 267–268°C (decom.); FTIR (KBr): 3422, 2888, 1685, 1535, 1349 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 1.06 (t, 3H, *J* = 7.5 Hz, $CH_3CH_2$), 2.29 (p, 2H, *J* = 7.6, 7.4 Hz, $CH_3CH_2$), 4.99 (s, 2H, $CH_2$), 6.93 (t, 1H, *J* = 7.4 Hz, $CHCH_2$), 7.11 (dd, 2H, *J* = 7.3, 0.7 Hz, ArH), 7.38–7.44 (m, 2H, ArH), 11.5 (brs, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 13.1, 21.6, 41.1, 109.6, 117.7, 121.1, 121.9, 122.1, 133.7, 142.2, 144.9, 147.4, 161.9; HRMS(EI): *m/z* calcd. for $C_{13}H_{13}N_3O$ ($M^+$): 227.1059, found 227.1057.

According to the same procedure, starting from Baylis–Hillman alcohols (**4**) and amines (**6**) with 2-aminobenzimidazole (**2**), **5a–i** and **7a–g** were synthesized and the diastereoselectivities were around 1:1 determined by NMR.

**6-(Phenylhydroxymethyl)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (5a).** A white solid, m.p. = 233–235°C (decom.); FTIR (KBr): 3390, 3064, 1665, 1515, 1458, 1334 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.26 (m, 1H, CHCO), 3.97 (m, 1H, $CH_2$), 4.19 (m, 1H, $CH_2$), 5.08 (5.28) (m, 1H, OH), (the data in parentheses are for diastereomeric peaks, the same below), 5.80 (m, 1H, $CHOH$), 7.01–7.16 (m, 2H, ArH), 7.19–7.33 (m, 2H, ArH), 7.33–7.52 (m, 5H, ArH), 11.53 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 36.9, 46.6, 69.8, 108.6, 117.1, 120.6, 121.2, 125.9, 127.1, 128.1, 133.0, 141.7, 142.8, 147.6, 168.6; HRMS(EI): *m/z* calcd. for $C_{17}H_{16}N_3O_2$ ($M^+$+1): 294.1234, found 294.1237.

**6-[(4-Fluorophenyl)hydroxymethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (5b).** A white solid, m.p. = 225–227°C (decom.); FTIR (KBr): 3382, 3056, 1678, 1510, 1457, 1223 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.27 (m, 1H, CHCO), 3.96–4.25 (m, 2H, $CH_2$), 5.07 (5.25) (m, 1H, OH), 5.87–5.90 (m, 1H, $CHOH$), 6.91–6.97 (m, 1H, ArH), 7.06–7.12 (m, 2H, ArH), 7.15–7.24 (m, 1H, ArH), 7.24–7.34 (m, 2H, ArH), 7.38–7.45 (m, 2H, ArH), 11.50 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 37.0, 46.7, 69.2, 108.7, 114.7, 115.0, 117.1, 120.6, 121.2, 127.9, 128.0, 133.0, 141.7, 147.6, 168.5; HRMS(EI): *m/z* calcd. for $C_{17}H_{15}N_3O_2F$ ($M^+$ + 1): 312.1141, found 312.1143.

**6-[(4-Chlorophenyl)hydroxymethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (5c).** A white solid, m.p. = 206–208°C (decom.); FTIR (KBr): 3414, 3054, 1689, 1526, 1458, 1238 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.28 (m, 1H, CHCO), 3.97–4.27 (m, 2H, $CH_2$), 5.09 (2.27) (m, 1H, OH), 5.76–5.93 (m, 1H, $CHOH$), 6.85–7.50 (m, 8H, ArH), 11.53 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 36.9, 46.6, 69.8, 108.6, 117.1, 120.6, 121.2, 125.9, 127.1, 127.9, 128.1, 133.0, 142.8, 147.6, 168.6; HRMS (EI): *m/z* calcd. for $C_{17}H_{15}N_3O_2Cl$ ($M^+$ + 1): 328.0845, found 328.0847.

**6-[(4-Nitrophenyl)hydroxymethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]-pyrimidin-7-one (5d).** A white solid, m.p. = 231–233°C (decom.); FTIR (KBr): 3373, 3052, 1667, 1521, 1456, 1348 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.40 (m, 1H, CHCO), 3.98–4.34 (m, 2H, $CH_2$), 5.15 (5.05) (m,

1H, OH), 6.17–6.18 (m, 1H, C*H*OH), 7.06–7.09 (m, 2H, ArH), 7.28–7.38 (m, 2H, ArH), 7.52–7.72 (m, 2H, ArH), 7.97–8.26 (m, 2H, ArH), 11.60 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 36.9, 46.3, 69.0, 108.8, 117.1, 120.6, 121.3, 123.3, 127.4, 133.0, 141.6, 146.7, 147.5, 150.8, 168.1; HRMS(EI): *m/z* calcd. for $C_{17}H_{13}N_4O_4$ ($M^+$ + 1): 339.1086, found 339.1087.

**6-[(3-Nitrophenyl)hydroxymethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]-pyrimidin-7-one (5e).** A white solid, m.p. = 211–213°C (decom.); FTIR (KBr): 3378, 3051, 1671, 1523, 1456, 1351 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.42 (m, 1H, CHCO), 4.01–4.29 (m, 2H, $CH_2$), 5.25 (5.50) (m, 1H, OH), 5.75–6.19 (m, 1H, C*H*OH), 7.04–7.11 (m, 2H, ArH), 7.26–7.45 (m, 2H, ArH), 7.64–7.69 (m, 1H, ArH), 7.85–7.92 (m, 1H, ArH), 8.11–8.17 (m, 1H, ArH), 8.27 (m, 1H, ArH), 11.60 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 36.9, 46.3, 68.7, 108.9, 117.1, 120.6, 120.8, 121.3, 122.1, 129.6, 132.8, 133.0, 141.6, 145.3, 147.5, 147.8, 168.2; HRMS(EI): *m/z* calcd. for $C_{17}H_{13}N_4O_4$ ($M^+$ + 1): 339.1086, found 339.1087.

**6-(2-Nitrophenylhydroxymethzyl)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]-pyrimidin-7-one (5f).** A white solid, m.p. = 204–206°C (decom.); FTIR (KBr) 3360, 3055, 1671, 1523, 1456, 1340 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 3.34 (m, 1H, CHCO), 4.11 (m, 1H, $CH_2$), 4.28 (m, 1H, $CH_2$), 5.53 (5.86) (m, 1H, OH), 6.14 (m, 1H, C*H*OH), 7.10 (m, 2H, ArH), 7.30 (m, 1H, ArH), 7.41 (m, 1H, ArH), 7.59 (m 1H, ArH), 7.82 (m, 1H, ArH), 7.91 (m, 1H, ArH), 8.03 (m, 1H, ArH), 11.60 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$) δ 37.3, 45.4, 65.1, 108.8, 117.1, 120.6, 121.2, 124.3, 128.6, 129.3, 133.0, 133.5, 138.1, 141.7, 147.2, 147.6, 168.0; HRMS(EI): *m/z* calcd. for $C_{17}H_{13}N_4O_4$ ($M^+$ + 1): 339.1086, found 339.1087.

**6-[(2-Trifluoromethylphenyl)hydroxymethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (5g).** A white solid, m.p. = 175–177°C (decom.); FTIR (KBr): 3393, 3054, 1674, 1525, 1456, 1312 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 3.15 (m, 1H, CHCO), 4.16 (m, 1H, $CH_2$), 4.35 (m, 1H, $CH_2$), 5.20 (5.62) (m, 1H, OH), 5.93–6.11 (m, 1H, C*H*OH), 6.75–7.95 (m, 8H, ArH), 11.58 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 36.9, 46.2, 65.1, 108.8, 117.1, 120.6, 121.2, 125.4, 125.5, 127.9, 129.2, 132.4, 133.0, 141.6, 141.8, 147.5, 167.9; HRMS(EI): *m/z* calcd. for $C_{18}H_{13}N_3O_2F$ ($M^+$ + 1): 362.1106, found 362.1101.

**6-(Furan-2-ylmethyl)-5,6-dihydro-8*H*-benzo[4,5]-imidazo[1,2-*a*]pyrimidin-7-one (5h).** A yellow solid, m.p. = 206–208°C (decom.); FTIR (KBr) 3434, 3054, 1685, 1522, 1456, 1384 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 3.39 (m, 1H, CHCO), 4.04–4.34 (m, 2H, $CH_2$), 5.09 (5.25) (m, 1H, OH), 5.98–5.99 (m, 1H, C*H*OH), 6.23–7.64 (m, 7H, ArH), 11.55 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$) δ 37.4, 44.2, 64.6, 106.8, 108.8, 110.3, 117.1, 120.6, 121.3, 133.0, 141.7, 142.2, 147.5, 155.2, 169.1; HRMS(EI): *m/z* calcd. for $C_{15}H_{14}N_3O_2$ ($M^+$ + 1): 284.1026, found 284.1029.

**6-(Methylhydroxymethyl)-5.6-dihydro-8*H*-benzo-[4,5]imidazo[1,2-*a*]pyrimidin-7-one (5i).** A white solid, m.p. = 260–262°C (decom.); FTIR (KBr) cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 3.05 (m, 1H, CHCO), 3.76 (m, 2H, C$H_2$OH), 4.13 (m, 1H, C$H_2$CH), 4.42 (m, 1H, C$H_2$CH), 5.00 (5.02) (m, 1H, OH), 7.11 (m, 2H, ArH), 7.41 (m, 2H, ArH), 11.47 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$) δ 38.7, 42.0, 59.1, 108.8, 117.1, 120.6, 121.3, 133.0, 141.7, 147.7, 168.9; HRMS(EI): *m/z* calcd. for $C_{15}H_{14}N_3O_2$ ($M^+$+1): 218.0924, found 218.0924.

**6-[(Phenyl)tosylaminomethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (7a).** A white solid, m.p. = 239–241°C (decom.); FTIR (KBr): 3343, 3059, 1680, 1457, 1328, 1239 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.24 (s, 3H, $CH_3$), 3.17–3.32 (m, 1H, CHCO), 3.70–4.50 (m, 2H, C$H_2$CH), 4.60–4.80 (m, 1H, C*H*NH), 6.90–7.50 (m, 13H, ArH), 8.40 (8.70) (m, 1H, $NHSO_2$) (the data in parentheses are for diastereomeric peaks, the same below), 11.53 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 20.8, 46.2, 56.3, 66.0, 108.8, 120.8, 121.3, 126.3, 127.0, 127.3, 127.8, 129.0, 129.1, 132.6, 133.0, 137.1, 138.6, 142.2, 147.1, 167.6; HRMS(EI): *m/z* calcd. for $C_{24}H_{23}N_4O_3S$ ($M^+$ + 1): 447.1480, found 447.1485.

**6-[(4-Fluorophenyl)tosylaminomethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (7b).** A white solid, m.p. > 300°C (decom.); FTIR (KBr): 3415, 3050, 1680, 1510, 1456, 1160 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), 3.15–3.31 (m, 1H, CHCO), 3.70–4.50 (m, 2H, C$H_2$CH), 4.55–4.85 (m, 1H, C*H*NH), 6.81–7.43 (m, 12H, ArH), 8.38 (8.80) (m, 1H, $NHSO_2$), 11.56 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 20.8, 46.1, 55.5, 55.7, 108.9, 114.3, 114.6, 117.2, 120.8, 121.4, 126.4, 129.0, 129.1, 132.6, 133.0, 137.8, 137.9, 142.2, 147.1, 167.5; HRMS(EI): *m/z* calcd. for $C_{24}H_{22}N_4O_3SF$ ($M^+$ + 1): 465.1389, found 465.1391.

**6-[(4-Chlorophenyl)tosylmethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (7c).** A white solid, m.p. = 260–262°C (decom.); FTIR (KBr) 3263, 3053, 1689, 1456, 1331, 1159 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 2.27 (s, 3H, $CH_3$), 3.20–3.32 (m, 1H, CHCO), 3.57–4.32 (m, 2H, C$H_2$CH), 4.55–4.71 (m, 1H, C*H*NH), 7.00–7.42 (m, 12H, ArH), 8.40 (8.70) (m, 1H, $NHSO_2$), 11.54 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$) δ 20.8, 30.6, 46.0, 55.7, 108.9, 117.3, 120.9, 121.4, 126.4, 127.7, 129.0, 129.1, 131.8, 132.0, 136.1, 137.6, 137.8, 142.4, 147.1, 167.4; HRMS(EI): *m/z* calcd. for $C_{24}H_{22}N_4O_3SCl$ ($M^+$ + 1): 481.1092, found 481.1095.

**6-[(4-Nitrophenyl)tosylaminomethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-2-one (7d).** A white solid, m.p. = 268–270°C (decom.); FTIR (KBr): 3306, 3056, 1684, 1519, 1348, 1157 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.24 (s, 3H, $CH_3$), 3.34–3.45 (m, 1H, CHCO), 3.70–4.40 (m, 2H, C$H_2$CH), 4.70–4.95 (m, 1H, C*H*NH), 7.00–8.00 (m, 12H, ArH), 8.50 (8.83) (m, 1H, $NHSO_2$), 11.56 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 20.8, 38.7, 45.3, 51.0, 108.8, 117.1, 120.7, 121.3, 124.1, 126.2, 128.7, 129.1, 130.3, 132.8, 133.0, 133.1, 137.2, 141.3, 142.4, 147.2, 148.1, 167.0; HRMS(EI): *m/z* calcd. for $C_{24}H_{22}N_5O_5S$ ($M^+$ + 1): 492.1339, found 492.1336.

**6-[(3-Nitrophenyl)tosylaminomethyl]-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (7e).** A white solid, m.p. = 281–283°C (decom.); FTIR (KBr): 3300, 3065, 1692, 1530, 1329, 1157 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.21 (s, 3H, $CH_3$), 3.32–3.45 (m, 1H, CHCO), 3.80–4.40 (m, 2H, C$H_2$CH), 4.72–4.95 (m, 1H, C*H*NH), 6.80–8.00 (m, 12H, ArH), 8.50 (8.85) (m, 1H, $NHSO_2$), 11.56 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 20.7, 30.6, 45.6, 55.5, 108.9, 117.1, 120.8, 121.4, 121.9, 122.1, 126.4, 129.0, 129.3, 132.9, 134.1, 137.7, 140.8, 141.6, 142.3, 147.2, 147.3, 166.7;

HRMS(EI): *m*/*z* calcd. for $C_{24}H_{22}N_5O_5S$ ($M^+ + 1$): 492.1339, found 492.1336.

**6-[(2-Nitrophenyl)tosylaminomethyl)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (7f).** A white solid, m.p. = 178–180°C (decom.); FTIR (KBr): 3381, 3051, 1697, 1525, 1346, 1160 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.25 (s, 3H, $CH_3$), 3.35–3.50 (m, 1H, CHCO), 3.80–4.45 (m, 2H, C*H*$_2$CH), 5.30–5.48 (m, 1H, C*H*NH), 7.05–7.85 (m, 12H, ArH), 8.65 (8.75) (m, 1H, $NHSO_2$), 11.58 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 20.8, 38.7, 45.3, 51.0, 108.8, 117.1, 120.7, 121.3, 124.1, 126.2, 128.7, 129.1, 130.3, 132.8, 133.0, 133.1, 137.2, 141.3, 142.4, 147.2, 148.1, 167.0; HRMS(EI): *m*/*z* calcd. for $C_{24}H_{22}N_5O_5S$ ($M^+ + 1$): 492.1339, found 492.1336.

**6-[(4-Methylphenyl)tosylaminomethyl)-5,6-dihydro-8*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-7-one (7g).** A white solid, m.p. = 251–253°C (decom.); FTIR (KBr): 3274, 3052, 1692, 1456, 1323, 1159 $cm^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), 3.14–3.24 (m, 1H, CHCO), 3.57–4.40 (m, 2H, C*H*$_2$CH), 4.57–4.64 (m, 1H, C*H*NH), 6.79–7.39 (m, 12H, ArH), 8.30 (8.85) (m, 1H, $NHSO_2$), 11.49 (s, 1H, NHCO); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 20.5, 20.8, 46.2, 56.1, 108.8, 117.2, 119.1, 120.8, 121.3, 127.0, 128.4, 129.0, 132.6, 134.0, 135.6, 136.5, 138.0, 141.1, 147.4, 167.6; HRMS(EI): *m*/*z* calcd. for $C_{25}H_{25}N_4O_3S$ ($M^+ + 1$): 461.1637, found 481.1642.

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## REFERENCES AND NOTES

[1] (a) Almirante, L.; Polo, L.; Mugnani, A.; Provincialli, E.; Rugarli, P.; Gambá, A.; Olivi, A.; Murmann, W. J Med Chem 1965, 9, 29; (b) Rival, Y.; Grassy, G.; Michel, G. Chem Pharm Bull 1992, 40, 1170; (c) Gueiffieri, A.; Blache, Y.; Chapat, J. P.; Elhakmaoui, E. M. E.; Andrei, G.; Snoeck, R.; De Clercq, E.; Chavignon, O.; Teulade, J. C.; Fauvelle, F. Nucleosides Nucleotides 1995, 14, 551; (d) Trapani, G.; Franco, M.; Latrofa, A.; Genchi, G.; Iacobazzi, V.; Ghiani, C. A.; Maciocco, E.; Liso, G. Eur J Med Chem 1997, 32, 83.

[2] (a) Descours, D.; Festal, D. Synthesis 1983, 1033; (b) LaMattina, J. L.; Mularski, C. J.; Muse, D. E. Tetrahedron 1988, 44, 3073.

[3] (a) Nawrocka, W. Pol J Chem 1995, 69, 1158; (b) Zanatta, N.; Amaral, S. S.; Esteves-Souza, A.; Echevarria, A.; Brondani, P. B.; Flores, D. C.; Bonacorso, H. G.; Flores, A. F. C.; Martins, M. P. Synthesis 2006, 2305, and references cited therein.

[4] Martin, M. W.; Newcomb, J.; Nunes, J. J.; Boucher, C.; Chai, L.; Epstein, L. F.; Faust, T.; Flores, S.; Gallant, P.; Gore, A.; Gu, Y.; Hsieh, F.; Huang, X.; Kim, J. L.; Middleton, S.; Morgenstem, K.; Oliveire-dos-Santos, A.; Patel, V. F.; Powers, D.; Rose, P.; Tudor, Y.; Turci, S. M.; Welcher, A. A.; Zack, D.; Zhao, H.; Zhu, L.; Zhu, X.; Ghiron, C.; Ermann, M.; Johnston, D.; Saluste, C.-G. J Med Chem 2008, 51, 1637.

[5] (a) Asobo, P. F.; Wahe, H.; Mbafor, J. T.; Nkengfack, A. E.; Fomum, Z. T.; Sopbue, E. F.; Döpp, D. J Chem Soc Perkin Trans 1 2001, 457; (b) Da Settimo, A.; Primofiore, G.; Da Settimo, F.; Marini, A. M.; Taliani, S.; Salermo, S.; Via, L. D. J Heterocycl Chem 2003, 40, 1091; (c) Shaabani, A.; Rahmati, A.; Naderi, S. Bioorg Med Chem Lett 2005, 15, 5553; (d) Karci, F.; Demircali, A.; Sener, I.; Tilki, T. Dyes Pigments 2006, 71, 90; (e) Troxler, F.; Weber, H. P. Helv Chim Acta 1974, 57, 255.

[6] Selected reviews, see: (a) Basavaiah, D.; Rao, K. V.; Reddy, R. J Chem Soc Rev 2007, 36, 1581; (b) Singh, V.; Batra, S. Tetrahedron 2008, 64, 4511; (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. Bull Korean Chem Soc 2005, 26, 1481; (d) Shi, Y.-L.; Shi, M. Org Biomol Chem 2007, 5, 1499; (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Chem Rev 2003, 103, 811; (d) Ciganek, E. In Organic Reactions; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 51, pp 201–350.

[7] Very recently, the reaction of 2-aminothiazole with Baylis–Hillman acetates was reported: Zhong, W.; Guo, B.; Lin, F.; Liu, Y.; Su, W. Synthesis 2009, 10, 1615.

[8] Nag, S.; Pathak, R.; Kumar, M.; Shukla, P. K.; Batra, S. Bioorg Med Chem Lett 2006, 16, 3824.

[9] Declerck, V.; Martinez, J.; Lamaty, F. Chem Rev 2009, 109, 1.

[10] (a) Cai, J. X.; Zhou, Z. L.; Zhao, G. F.; Tang, C. C. Org Lett 2002, 4, 4723; (b) Yu, C. Z.; Liu, B.; Hu, L. Q. J Org Chem 2001, 66, 5413; (c) Xu, Y. M.; Shi, M. J Org Chem 2004, 69, 417.

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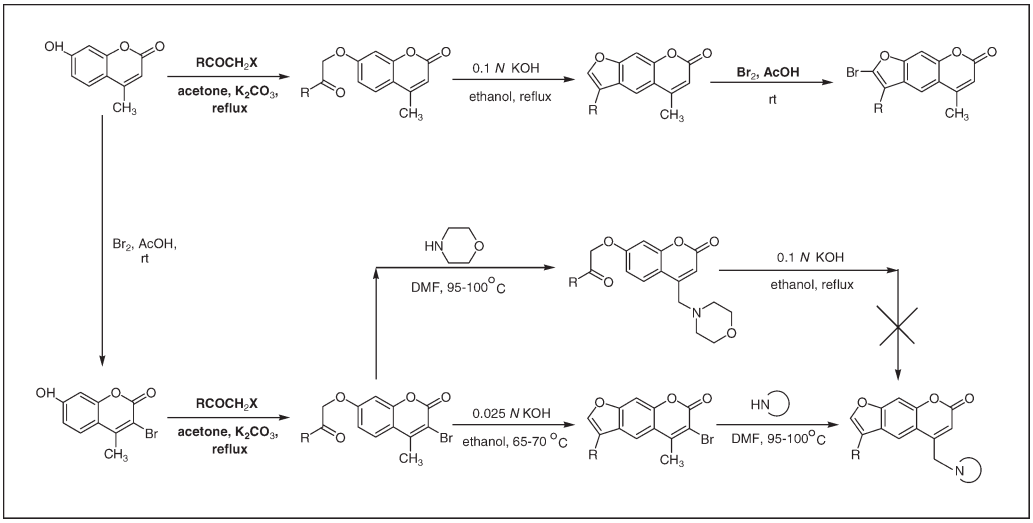


New amino psoralen derivatives have been synthesized *via* bromination. Bromination of 3,5-substituted psoralens has been studied. The second position of the furan ring is more susceptible to bromination than the α-position of the chromen-2-one ring in psoralens. Hence, the target psoralenamines were synthesized starting with 3-bromo-7-hydroxy-4-methyl-chromen-2-one, which was condensed with different α-halo ketones and cyclized in ethanolic potassium hydroxide to get the desired 6-bromo psoralens, which were finally converted into psoralenamines.

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## INTRODUCTION

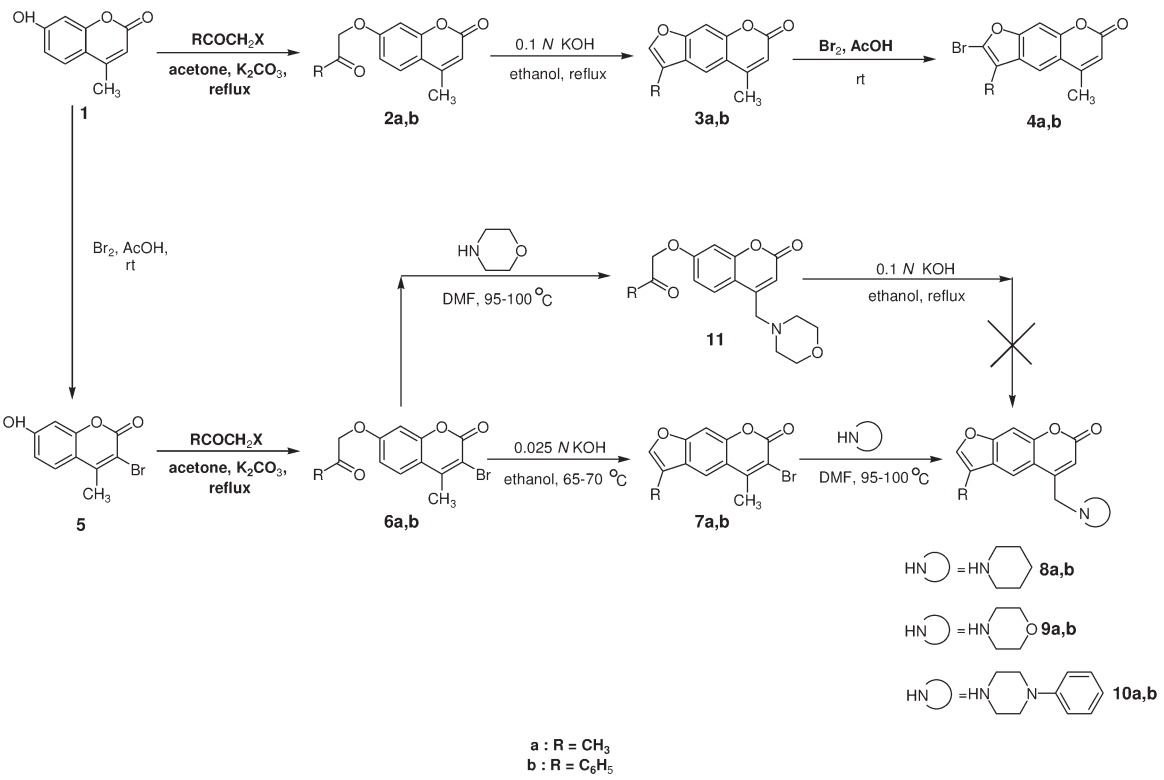
Furocoumarins such as Psoralens (5-methoxy psoralen or bergapton, 8-methoxy psoralen or xanthotoxin, 4,5′,8-trimethyl psoralen) are well known photosensitizing drugs used in Psoralen Ultra Violet-A therapy for the treatment of dermatological disorders, such as psoriasis, vitiligo, mycosis, and atropic eczema [1]; as well as fungal, viral, and bacterial infections [2]. Recently, Psoralen derivatives have also been used in the treatment of cutaneous T-cell lymphoma [3], human immunodeficiency diseases [4], and prevention of rejection of organ transplants [5]. Introduction of aminomethyl group in furocoumarins enhances antibacterial activity [6]. Aminopsoralens are used for nucleic acid probe preparations, preparation of conjugates, inhibition of cell proliferation, inactivation of virus for vaccine preparation, and in particular, for the inactivation of pathogens in blood products [7].

Because of the wide spread and increasing interest in aminopsoralens for their pharmacological action, this study was undertaken to synthesize some new amino psoralen derivatives *via* bromination. Moreover, it was of considerable interest to study the reactivity and orientation of 3,5-substituted psoralens toward bromination. Although it is evident that the third position of furan ring in psoralens is the most reactive towards electrophilic substitution, the behaviour of psoralens in which the third position is blocked has not been reported for bromination. The synthetic pathway followed by MacLeod *et al*. [8] has been employed to prepare the title compounds as outlined in Scheme 1.

## RESULTS AND DISCUSSION

β-Methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) **1**, [9] was condensed with different α-haloketones, *e.g*., mono chloroacetone and phenacylbromide to give the aryloxyketones **2** which when subjected to cyclization in 0.1*N* ethanolic potassium hydroxide gave the corresponding furocoumarin (psoralen) **3** as shown

**Scheme 1**

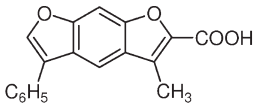



in Scheme 1. Furocoumarin **3** was brominated with bromine in acetic acid to get the desired 6-bromo psoralen, but from the $^1$H nuclear magnetic resonance (NMR) it was revealed that the product formed was 2-bromo psoralen **4**. This shows that the second position of the furan ring is more reactive towards halogenation compared to the α-position of the chromen-2-one ring in psoralens. In the $^1$H-NMR of compound 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4a**, signal at δ 6.27–6.28 ppm corresponding to one proton for C6—H (or α-H of chromen-2-one) and the absence of signal at δ 7.5 ppm for C2—H proton alongwith C3—$CH_3$ signal at δ 2.24 ppm confirmed the structure. The UV spectrum in dichloromethane showed absorption at 284, 302, 324, 333, 340, and 347 nm. Consequently, the target amino psoralens could not be prepared.

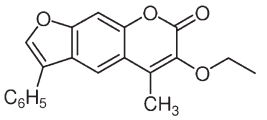
In a slightly modified methodology, β-methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) **1** was first brominated using bromine in acetic acid to give 3-bromo-7-hydroxy-4-methyl-chromen-2-one **5** [10] in an addition-elimination reaction, which was then condensed with different α-halo ketones and cyclized to 6-bromo psoralens **7** in a similar fashion as shown in Scheme 1. In the $^1$H NMR of compound 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7a**, the absence of signal at δ 6.28 ppm for C6—H proton and singlet for C5—$CH_3$ signal at δ 2.74 ppm confirmed the substitution of bromine at C—6 position. Further doublets at δ 7.50 ppm (1H, $J$ = 1.6 Hz) for C2—H and δ 2.31–2.32 ppm (3H, $J$ = 1.6 Hz) for C3—$CH_3$ corroborated the structure **7a**. The mass spectrum (LCMS) was obtained as *m/z* (relative intensity, 100%): 317 (8.88) M+23 (from $Na^+$), 295.1 (100) M+1, 292.9 (100) $M^+$ using mobile phase Acetonitrile: Ammonium acetate 1 m*M* (90:10% v/v). The UV spectrum in dichloromethane showed absorption at 282, 302, 323, 331, 342, 355, and 362 nm. Cyclization of 3-bromo aryloxyketones **6** to 6-bromo psoralens **7** was the bottleneck of the process. Cyclization in 0.1*N* ethanolic potassium hydroxide at reflux temperature lowered the over all yield of the reaction drastically due to the formation of mixture of products. One of the product was identified as furocoumarilic acid formed due to alkaline ring contraction [11], which has been confirmed from the $^1$H NMR and infrared (IR) spectra of 3-methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*′]difuran-2-carboxylic acid **12** obtained during cyclization of 3-bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one **6b**. The furocoumarilic acid was obtained as white amorphous powder; mp 250°C dec. and whose sodium and potassium salts are hydrophobic. The other product was identified as 6-ethoxy-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one **13** formed by nucleophilic attack of ethanol, which also has been confirmed from $^1$H NMR. The yield of 6-bromo psoralen was lowered due to these

side reactions. Weaker bases like tri ethylamine and potassium carbonate failed to give the expected results. Cyclization in polyphosphoric acid and phosphorus (III) oxychloride failed. Even the idea of first condensing 3-bromo aryloxyketones **6** with amines, followed by cyclization to yield amino psoralens failed, since the cyclization reaction gave several decomposition products. Condensation of 3-bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one **6a** with morpholine gave 4-morpholin-4-ylmethyl-7-(2-oxo-propoxy)-chromen-2-one **11** as confirmed from $^1$H NMR, but could not be cyclized as shown in Scheme 1. Consequently the concentration of ethanolic potassium hydroxide was reduced from 0.1 to 0.025*N* and the cyclization of 3-bromo aryloxyketones **6** to 6-bromo psoralens **7** was carried out at 65–70°C, which gave the desired results. Finally, 6-bromo psoralens were condensed with different amines to give the corresponding amino methyl psoralens **(8, 9, 10)**. $^1$H NMR of compound 3-methyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one **8a** showed singlets at δ 6.51 ppm corresponding to one proton for C6—H proton and δ 3.66 ppm corresponding to two protons for C5—$CH_2$—, which confirmed the formation of 5-amino methyl psoralens. In the $^{13}$C NMR, δ values 99.59 ppm for C6 and 59.91 ppm for C5—*C*$H_2$— further confirmed the structure. The UV spectrum in dichloromethane showed absorption at 281, 301, 305, 329, 337 nm. The mass spectrum (LCMS) for 3-methyl-5-morpholin-4-ylmethyl-furo[3,2-*g*]chromen-7-one **9a**. was obtained as *m/z* (relative intensity, 100%): 338.1 (7.27) M+39 (from $K^+$), 322.2 (38.18) M+23 (from $Na^+$), 301.2 (70.90) M+2, 299.9 (100) M+1 using mobile phase acetonitrile:ammonium acetate 1 m*M* (90:10% v/v).

The structures of all compounds have been established on the basis of their elemental analyses and spectral (IR, NMR) data.




**3-Methyl-5-phenyl-benzo[1,2-*b*;5,4-*b*']difuran-2-carboxylic acid 12**




**6-Ethoxy-5-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one 13**

## EXPERIMENTAL

Melting points (uncorrected) were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by thin layer chromatography on Acme's silica gel G plates using UV/Iodine vapour as visualizing agent and Acme's silica gel (60–120 mesh) was used for column chromatographic purification. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400). IR spectra were recorded on Perkin-Elmer FTIR spectrometer (spectrum RX1) using potassium bromide optics. UV spectra were recorded on Perkin Elmer Lambda 35 UV/Vis spectrophotometer. The mass spectrum was obtained on Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS Mass Spectrometer (Model-016932) using Ion Spray source. NMR spectra were recorded on Brucker 400 MHz. Spectrophotometer. Chemical shifts are relative to tetramethylsilane on δ-scale. Coupling constants are given in Hz and relative peak areas were in agreement with all assignments.

**General procedure for the preparation of 2a, 2b, 6a and 6b.** To a stirred solution of 7-hydroxy-4-methyl-chromen-2-one **1** (5 g, 0.028 moles), anhydrous potassium carbonate (4.90 g, 0.035 moles) and catalytic amount(0.05–0.1g) of potassium iodide in (40 mL) of dry acetone was added dropwise a solution of mono chloroacetone (2.62 g, 0.028 moles) in (20 mL) dry acetone at reflux temperature. It was refluxed for 12 h. The reaction mixture was concentrated to dryness and then poured into ice water and the solid collected by filtration. The crude product was crystallized from ethanol to give white crystals (3 g, 46%) of 4-methyl-7-(2-oxo-propoxy)-chromen-2-one **2a**, mp 154–156°C lit. [12] 157°C; IR (KBr): $\nu_{max}$, cm$^{-1}$: 3061, 1705, 1609, 1591, 1454, 1384, 1360, 1288, 1220, 1166, 958; $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.32 (d, 3H, $J$ = 0.8 Hz, C4—$CH_3$), 2.42 (s, 3H, —$COCH_3$), 4.66 (s, 2H, —$OCH_2CO$—), 6.18 (d, 1H, $J$ = 0.8 Hz, C3—H), 6.77–6.78 (d, 1H, $J$ = 2.8 Hz, C8—H), 6.89–6.92 (dd, 1H, $J$ = 2.8 Hz and $J$ = 8.8 Hz, C6—H), 7.54–7.56 (d, 1H, $J$ = 8.8 Hz, C5—H). Anal. calcd. for $C_{13}H_{12}O_4$ (232.23): C, 67.23; H, 5.20. Found: C, 67.02; H, 5.11. Potassium iodide is not required for the preparation of compounds **6a** and **6b**.

***4-Methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one (2b).*** This compound was obtained by column chromatographic purification using petroleum ether (60–80°C): ethyl acetate eluent, as white crystals, 43% yield, mp 169–171°C lit. [13] 173°C; IR (KBr): $\nu_{max}$, cm$^{-1}$: 3071, 1698, 1612, 1596, 1451, 1391, 1366, 1283, 1230, 1160, 968; $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.34 (d, 3H, $J$ = 0.9 Hz, C4—$CH_3$), 4.58 (s, 2H, —$OCH_2CO$—), 6.19 (d, 1H, $J$ = 0.9 Hz, C3—H), 6.79–6.80 (d, 1H, $J$ = 2.8 Hz, C8—H), 6.89–6.93 (dd, 1H, $J$ = 2.8 Hz and $J$ = 8.8 Hz, C6—H), 7.52–7.68 (m, 6H, C5—H and C2′-H to C6′-H phenyl protons). Anal. calcd. for $C_{18}H_{14}O_4$ (294.30): C, 73.46; H, 4.79. Found: C, 72.99; H, 4.34.

***3-Bromo-4-methyl-7-(2-oxy-propoxy)-chromen-2-one (6a).*** This compound was obtained as white crystals (DMF/ethanol), 68% yield, mp 204–206°C; IR (KBr): $\nu_{max}$, cm$^{-1}$: 3062, 2910, 1719, 1698, 1628, 1593, 1392, 1218; $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.32 (s, 3H, C4—$CH_3$), 2.62 (s, 3H, —$COCH_3$), 4.67 (s, 2H, —$OCH_2CO$—), 6.78–6.79 (d, 1H, $J$ = 2.4 Hz, C8—H), 6.92–6.95 (dd, 1H, $J$ = 2.4 Hz and $J$ = 9.2 Hz, C6—H), 7.60–7.62 (d, 1H, $J$ = 9.2 Hz, C5—H). Anal. calcd. for $C_{13}H_{11}O_4Br$ (311.12): C, 50.18; H, 3.56. Found: C, 50.06; H, 3.23.

***3-Bromo-4-methyl-7-(2-oxo-2-phenyl-ethoxy)-chromen-2-one (6b).*** This compound was obtained as white crystals (toluene), 63% yield, mp 181–182°C; IR (KBr): $\nu_{max}$, cm$^{-1}$: 3060, 2907, 1717, 1698, 1623, 1598, 1384, 1210; $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H, C4—$CH_3$), 4.61 (s, 2H, —$OCH_2CO$—), 6.79–6.80 (d, 1H, $J$ = 2.4 Hz, C8—H), 6.93–

6.95 (dd, 1H, $J$ = 2.4 Hz and $J$ = 9.2 Hz, C6—H), 7.50–7.66 (m, 6H, C5—H and C2′-H to C6′-H phenyl protons). Anal. calcd. for $C_{18}H_{13}O_4Br$ (373.20): C, 57.93; H, 3.51. Found: C, 57.61; H, 3.31.

**General procedure for the preparation of 3a, 3b, 7a and 7b.** Compound 4-methyl-7-(2-oxo-propoxy)-chromen-2-one **2a** (1 g, 0.0043 moles) was dissolved in 0.1*N* ethanolic potassium hydroxide (100 mL) and refluxed for 12 h. The excess ethanol was removed by distillation *in vacuo* and the reaction mixture was poured into ice-hydrochloric acid and the solid collected by filtration. The crude product was crystallized from ethanol to give white crystals (0.38 g, 41%) of 3,5-dimethyl-furo[3,2-*g*]chromen-7-one **3a**, mp 224–226°C lit. [12] 220°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3090, 1728, 1639, 1610, 1580, 1388, 1144, 1082; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.21–2.22 (d, 3H, $J$ = 1.5 Hz, C3—$CH_3$), 2.51–2.52 (d, 3H, $J$ = 1.08 Hz, C5—$CH_3$), 6.27–6.28 (d, 1H, $J$ = 1.08 Hz, C6—H), 7.36 (s, 1H, C9—H), 7.52 (d, 1H, $J$ = 1.5 Hz, C2—H), 7.58 (s, 1H, C4—H). Anal. calcd. for $C_{13}H_{10}O_3$ (214.21): C, 72.88; H, 4.70. Found: C, 72.62; H, 4.51.

In the preparation of compounds **7a** and **7b** the concentration of ethanolic potassium hydroxide was reduced from 0.1 to 0.025*N* and the reaction was maintained at 65–70°C for 12 h.

***5-Methyl-3-phenyl-furo[3,2-g]chromen-7-one (3b).*** This compound was obtained as white crystals (ethanol), 41% yield, mp 181–182°C lit. [13] 185°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3090, 1720, 1632, 1612, 1575, 1385, 1142, 1075; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.48–2.49 (d, 3H, $J$ = 1.1 Hz, C5—$CH_3$), 6.29–6.30 (d, 1H, $J$ = 1.1 Hz, C6—H), 7.48–7.49 (m, 1H, C4′-H), 7.54–7.59 (m, 2H, C3′-H and C5′-H), 7.54 (s, 1H, C2—H), 7.65–7.67 (m, 2H, C2′-H and C6′-H), 7.86 (s, 1H, C9—H), 7.90 (s, 1H, C4—H). Anal. calcd. for $C_{18}H_{12}O_3$ (276.28): C, 78.25; H, 4.37. Found: C, 77.85; H, 4.30.

***6-Bromo-3,5-dimethyl-furo[3.2-g]chromen-7-one (7a).*** This compound was obtained as yellow crystals (toluene), 30% yield, mp 224–226°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3088, 2925, 1733, 1693, 1639, 1602, 1556, 1350, 1151, 1074; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.31–2.32 (d, 3H, $J$ = 1.6 Hz, C3—$CH_3$), 2.74 (s, 3H, C5—$CH_3$), 7.42 (s, 1H, C9—H), 7.50 (d, 1H, $J$ = 1.6 Hz, C2—H), 7.74 (s, 1H, C4—H); LCMS: *m/z* (relative intensity, 100%): 317 (8.88) M+23 (from $Na^+$), 295.1 (100) M+1, 292.9 (100) $M^+$. Anal. calcd. for $C_{13}H_9O_3Br$ (293.11): C, 53.27; H, 3.09. Found: C, 52.98; H, 3.11.

***6-Bromo-5-methyl-3-phenyl-furo[3,2-g]chromen-7-one (7b).*** This compound was obtained as yellow crystals (ethanol), 24% yield, mp 208–210°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3085, 2925, 1734, 1687, 1631, 1605, 1559, 1345, 1154, 1070; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.69 (s, 3H, C5—$CH_3$), 7.47–7.49 (m, 1H, C4′-H), 7.54–7.58 (m, 2H, C3′-H and C5′-H), 7.56 (s, 1H, C2—H), 7.64–7.66 (m, 2H, C2′-H and C6′-H), 7.87 (s, 1H, C9—H), 8.02 (s, 1H, C4—H). Anal. calcd. for $C_{18}H_{11}O_3Br$ (355.18): C, 60.86; H, 3.12. Found: C, 60.50; H, 3.07.

**General procedure for the preparation of 4a and 4b.** Compound 3,5-dimethyl-furo[3,2-*g*]chromen-7-one **3a** (1 g, 0.0046 moles) was dissolved in acetic acid (40 mL) by warming and to this stirred solution, a solution of bromine (0.24 mL, 0.0046 moles) in acetic acid (10 mL) was added gradually. It was stirred for 3 h at room temperature and then poured into ice water and the solid collected by filtration. The crude product was crystallized from ethanol to give yellow crystals (0.9 g, 66%) of 2-bromo-3,5-dimethyl-furo[3,2-*g*]chromen-7-one **4a**, mp 230–232°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3085, 1758, 1689, 1640, 1577, 1341, 1121; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, C3—$CH_3$), 2.52 (d, 3H, $J$ = 1.08 Hz, C5—$CH_3$), 6.27–6.28 (d, 1H, $J$ = 1.08 Hz, C6—H), 7.36 (s, 1H, C9—H), 7.58 (s, 1H, C4—H). Anal. calcd. for $C_{13}H_9O_3Br$ (293.11): C, 53.27; H, 3.09. Found: C, 52.98; H, 3.11.

***2-Bromo-5-methyl-3-phenyl-furo[3,2-g]chromen-7-one (4b).*** This compound was obtained as yellow crystals (ethanol), 61% yield, mp 238–239°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3084, 1750, 1686, 1636, 1578, 1347, 1110; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.46 (d, 3H, $J$ = 1.05 Hz, C5—$CH_3$), 6.28 (d, 1H, $J$ = 1.05 Hz, C6—H), 7.47–7.64 (m, 6H, C3—phenyl protons and C9—H), 7.75 (s, 1H, C4—H). Anal. calcd. for $C_{18}H_{11}O_3Br$ (355.18): C, 60.86; H, 3.12. Found: C, 60.82; H, 2.94.

**General procedure for the preparation of 8a, 8b, 9a, 9b, 10a and 10b.** A solution of 6-bromo-3,5-dimethyl-furo[3.2-*g*]chromen-7-one **7a** (0.5 g, 0.0017 moles) and piperidine (0.35 mL, 0.0035 moles) in dry DMF (10 mL) was heated at 95–100°C for 1 hour. The reaction mixture was poured into ice water and the solid collected by filtration. The crude product was crystallized from ethanol to give light brown crystals (0.28 g, 55%) of 3-methyl-5-piperidin-1-ylmethyl-furo[3,2-*g*]chromen-7-one **8a**, mp 185°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3059, 2971, 1718, 1639, 1616, 1579, 1454, 1337, 1158, 1120, 1096; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.47–1.48 (t, 2H, C4′—$CH_2$-), 1.59–1.65 (m, 4H, C3′—$CH_2$- and C5′—$CH_2$—), 2.27–2.28 (d, 3H, $J$ = 1.2 Hz, C3—$CH_3$), 2.51 (t, 4H, C2′—$CH_2$- and C6′—$CH_2$—), 3.66 (s, 2H, C5—$CH_2$—), 6.51 (s, 1H, C6—H), 7.35 (s, 1H, C9—H), 7.43–7.44 (d, 1H, $J$ = 1.2 Hz, C2—H), 7.92 (s, 1H, C4—H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 7.84 (C2—*C*$H_3$), 24.10 (C3′ and C5′), 26.07 (C4′), 55.05 (C2′ and C6′), 59.91 (C5—*C*$H_2$—), 99.59 (C6), 112.51 (C9), 114.92–115.73 (C4, C4a and C3), 126.23 (C3a), 143 (C2), 151.86 (C8a), 153.04 (C9a), 156.42 (C5), 161.57 (C7). Anal. calcd. for $C_{18}H_{19}O_3N$ (297.35): C, 72.70; H, 6.44; N, 4.71. Found: C, 72.56; H, 6.18; N, 4.44.

***3-Phenyl-5-piperidin-1-ylmethyl-furo[3,2-g]chromen-7-one (8b).*** This compound was obtained by column chromatographic purification using petroleum ether (60–80°C): ethyl acetate eluent, as light brown crystals, 52% yield, mp 158–160°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3051, 2971, 1710, 1633, 1611, 1571, 1450, 1333, 1158, 1122, 1091; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.51 (t, 2H, C4′—$CH_2$—), 1.64–1.66 (t, 4H, C3′—$CH_2$— and C5′—$CH_2$-), 2.52 (t, 4H, C2′—$CH_2$- and C6′—$CH_2$—), 3.67 (s, 2H, C5—$CH_2$—), 6.52 (s, 1H, C6—H), 7.43–7.70 (m, 5H, C3—phenyl protons), 7.55 (s, 1H, C2—H), 7.86 (s, 1H, C9—H), 8.50 (s, 1H, C4—H).

Anal. calcd. for $C_{23}H_{21}O_3N$ (359.42): C, 76.86; H, 5.88; N, 3.89. Found: C, 76.52; H, 5.61; N, 3.67.

***3-Methyl-5-morpholin-4-ylmethyl-furo[3,2-g]chromen-7-one (9a).*** This compound was obtained as light brown crystals (DMF/ethanol), 60% yield, mp 236–238°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3060, 2969, 1719, 1632, 1611, 1577, 1455, 1337, 1153, 1115, 1094; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.30 (d, 3H, $J$ = 1.2 Hz, C3—$CH_3$), 2.62–2.63 (t, 4H, C3′—$CH_2$— and C5′—$CH_2$—), 3.75–3.79 (m, 6H, C2′—$CH_2$— C6′—$CH_2$— & C5—$CH_2$-), 6.56 (s, 1H, C6—H), 7.41 (s, 1H, C9—H), 7.48 (d, 1H, $J$ = 1.2 Hz, C2—H), 7.92 (s, 1H, C4—H); lcms: *m/z* (relative intensity, 100%): 338.1 (7.27) M+39 (from $K^+$), 322.2 (38.18) M+23 (from $Na^+$), 301.2 (70.90) M+2, 299.9 (100) M+1.

Anal. calcd. for $C_{17}H_{17}O_4N$ (299.32): C, 68.21; H, 5.72; N, 4.67. Found: C, 67.91; H, 5.56; N, 4.33.

***5-Morpholin-4-ylmethyl-3-phenyl-furo[3,2-g]chromen-7-one (9b).*** This compound was obtained by column chromatographic purification using petroleum ether (60–80°C): ethyl acetate eluent, as light brown crystals, 57%, mp 185–187°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3057, 2966, 1712, 1632, 1606, 1573, 1454, 1330, 1152, 1115, 1091; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.64–2.66 (t, 4H, C3′—$CH_2$— and C5′—$CH_2$—), 3.76–3.79 (m, 6H, C2′—$CH_2$— C6′—$CH_2$- and C5—$CH_2$—), 6.59 (s, 1H, C6—H), 7.45–7.76 (m, 6H, C2—H and C3—phenyl protons), 7.80 (s, 1H, C9—H), 8.13 (s, 1H, C4—H).

Anal. calcd. for $C_{22}H_{19}O_4N$ (361.39): C, 73.11; H, 5.29; N, 3.87. Found: C, 72.88; H, 5.10; N, 3.77.

***3-Methyl-5-(4-phenyl-piperazin-1-ylmethyl)-furo[3,2-g]chromen-7-one (10a).*** This compound was obtained as light brown crystals (ethanol), 64% yield, mp 214–216°C; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3064, 2963, 1720, 1637, 1619, 1579, 1460, 1340, 1158, 1119, 1084; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.31 (d, 3H, $J$ = 1.2 Hz, C3—$CH_3$), 2.80 (t, 4H, C3′—$CH_2$- and C5′—$CH_2$−), 3.27–3.30 (t, 4H, C2′—$CH_2$- and C6′—$CH_2$—), 3.83 (s, 2H, C5—$CH_2$—), 6.60 (s, 1H, C6—H), 6.89–7.32 (m, 5H, N4′-phenyl protons), 7.45 (s, 1H, C9—H), 7.49 (d, 1H, $J$ = 1.2 Hz, C2—H), 7.98 (s, 1H, C4—H).

Anal. calcd. for $C_{23}H_{22}O_3N_2$ (374.43): C, 73.77; H, 5.92; N, 7.48. Found: C, 73.51; H, 5.77; N, 7.09.

***3-Phenyl-5-(4-phenyl-piperazin-1-ylmethyl)-furo[3,2-g]chromen-7-one (10b).*** This compound was obtained as light brown crystals (ethanol/toluene), 62% yield, mp 180°C dec.; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3061, 2963, 1713, 1631, 1611, 1578, 1450, 1337, 1157, 1108, 1088; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.79 (t, 4H, C3′—$CH_2$— and C5′—$CH_2$—), 3.3 (t, 4H, C2′—$CH_2$— and C6′—$CH_2$—), 3.80 (s, 2H, C5—$CH_2$—), 6.57 (s, 1H, C6—H), 6.92–7.68 (m, 10H, C3—phenyl protons and N4′-phenyl protons), 7.55 (s, 1H, C2—H), 7.86 (s, 1H, C9—H), 8.45 (s, 1H, C4—H).

Anal. calcd. for $C_{28}H_{24}O_3N_2$ (436.50): C, 77.04; H, 5.54; N, 6.41. Found: C, 76.72; H, 5.41; N, 6.22.

***4-Morpholin-4-ylmethyl-7-(2-oxo-propoxy)-chromen-2-one (11).*** This product was obtained by column chromatographic purification using petroleum ether (60–80°C): ethyl acetate eluent, as white crystals, 50% yield, mp 138–140°C; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H, —$COCH_3$), 2.53–2.55 (t, 4H, C3′—$CH_2$— and C5′—$CH_2$—), 3.59 (s, 2H, C4—$CH_2$—), 3.72–3.74 (t, 4H, C2′—$CH_2$— and C6′—$CH_2$—), 4.64 (s, 2H, C7—$OCH_2CO$—), 6.40 (s, 1H, C3—H), 6.75–6.76 (d, 1H, $J$ = 2.56 Hz, C8—H), 6.86–6.89 (dd, 1H, $J$ = 2.6 Hz and $J$ = 8.88 Hz, C6—H), 7.78–7.80 (d, 1H, $J$ = 8.88 Hz, C5—H).

Anal. calcd. for $C_{17}H_{11}O_5N$ (309.27): C, 66.02; H, 3.58; N, 4.52. Found: C, 66.01; H, 3.33; N, 4.41.

***3-Methyl-5-phenyl-benzo[1,2-b;5,4-b′]difuran-2-carboxylic acid (12).*** This compound was obtained as white amorphous powder (ethanol), 52% yield, mp 250°C dec.; IR (KBr): $\nu_{max}$, $cm^{-1}$: 3433, 3107, 3030, 2922, 1682, 1627, 1598, 1440, 1366, 1332, 1318, 1165, 1119; $^1H$ NMR ($(CD_3)_2SO$, 400 MHz): δ 2.58 (s, 3H, C3—$CH_3$), 7.32–7.36 (m, 1H, C4′-H), 7.44–7.47 (m, 2H, C2′-H and C6′-H), 7.63–7.66 (m, 3H, C6—H, C3′-H and C5′-H), 7.93 (s, 1H, C4—H), 7.96 (s, 1H, C8—H).

Anal. calcd. for $C_{18}H_{12}O_4$ (292.28): C, 73. 96; H, 4.13. Found: C, 73.84; H, 4.03.

***6-Ethoxy-5-methyl-3-phenyl-furo[3,2-g]chromen-7-one (13).*** This compound was obtained by column chromatographic purification using petroleum ether (60–80°C): ethyl acetate eluent, as white crystals, 55% yield, mp 169–171°C; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.46–1.50 (t, 3H, C6—$OCH_2CH_3$), 2.66 (s, 3H, C5—$CH_3$), 4.46–4.51 (q, 2H, C6—$OCH_2CH_3$), 7.42–7.46 (m, 1H, C4′-H), 7.52–7.56 (m, 2H, C2′-H and C6′-H), 7.68–7.70 (m, 3H, C2—H, C3′-H and C5′-H), 7.81 (s, 1H, C4—H), 7.94 (s, 1H, C9—H).

Anal. calcd. for $C_{20}H_{16}O_4$ (320.34): C, 74.98; H, 5.03. Found: C, 74.73; H, 4.98.

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## REFERENCES AND NOTES

[1] Grundmann, K. M.; Ludwig, R.; Zollner, T. M.; Ochsendorf, F.; Thaci, D.; Boehncke, W. H.; Krutmann, J.; Kaufmann, R.; Podda, M. J Am Acad Dermatol 2004, 50, 734; Park, J. H.; Lee, M. H. Int J Dermatol 2004, 43, 138; Petering, H.; Breuer, C.; Herbst, R.; Kapp, A.; Werfel, T. J Am Acad Dermatol 2004, 50, 68.

[2] Diederen, P. V. M. M.; Weelden, H.; Sanders, C. J. G.; Toonstra, J.; Vloten, W. A. J Am Acad Dermatol 2003, 48, 215; Miolo, G.; Tomanin, R.; Rossi, A. D.; Dall'Acqua, F.; Zacchello, F.; Scarpa, M. J Photochem Photobiol B. 1994, 26, 241; Lage, C.; Padula, M.; Alencar, T. A. M.; Goncalves, S. R. F.; Vidal, L. S.; Cabral-Neto, J.; Leitao, A. C. Mutat Res Rev Mutat 2003, 544, 143.

[3] Edelson, R. L.; Russell-Jones, R.; Whittaker, S.; Fraser-Andrews, E. Arch Dermatol 1999, 135, 600.

[4] Goupil, J. J. Fr. Add 2,698,270, 1994; Goaster, J. L. Fr. Add 2,691,629, 1993.

[5] Legitimo, A.; Consolini, R.; DiStefano, R.; Bencivelli, W.; Mosca, F. Blood Cells Mol Dis 2002, 29, 24.

[6] Nagesam, M.; Mohan Raju K.; Subramanyam Raju M. J. Indian Chem Soc 1988, 65, 380.

[7] Wollowitz, S.; Isaacs, S. T.; Rapoport, H.; Spielmann, H. P.; Nerio, A. US Pat. 5,593,823 (1994); Wollowitz, S. I.; Nerio A. US Pat. 6,455,286 B1 (2000).

[8] MacLeod, J. K.; Worth, B. R. Tetrahedron Lett 1972, 237.

[9] Pechmann, H. V.; Duisberg, C. Ber. 1883, 16, 2122.

[10] Nofal, Z. M.; El-Masry, A. H.; Fahmy, H. H.; Sarhan, A. I. Egypt J Pharm Sci 1997, 38, 1.

[11] Bray, W.; Mayer, R. Z. Chem 1963, 3, 150.

[12] Ray, J. N.; Silooja, S. S.; Vaid, V. R. J Chem Soc 1935, 813.

[13] Caporale, G.; Antenello, C. Farmaco (Pavia), Ed. Sci 1958, 13, 363; Chem Abstr 1959, 53, 21917.

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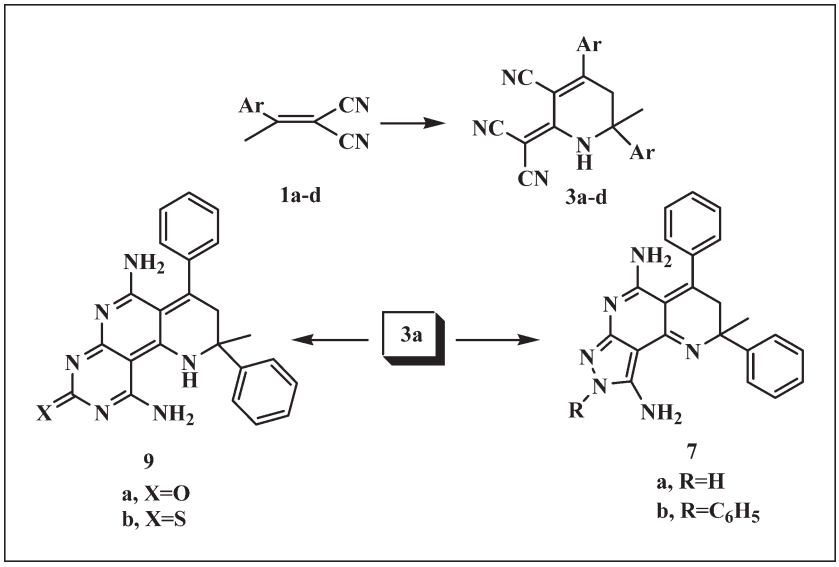


2-(1-Aryl-ethylidene)-malononitriles **1a-d** undergo self dimerization in ethanol catalyzed by sodium ethoxide to afford 2-[4,6-diaryl-3-cyano-6-methyl-5,6-dihydropyridin-2(1*H*)-ylidene]-malononitrile derivatives **3a-d,** respectively. The structure of the dimer was elucidated by X-ray crystallography and a plausible mechanism for its formation is depicted. Compound **3a** couples with arene diazonium salts **4a-d** to afford the hydrazo derivatives **5a-d**; and reacts with hydrazine hydrate and phenylhydrazine **6a,b** to afford the pyrazolo[3,4-h][1,6]naphthyridine derivatives**7a,b**; and with urea and thiourea **8a,b** to afford the pyrimido[4,5-h][1,6]naphthyridine derivatives **9a,b**, respectively.

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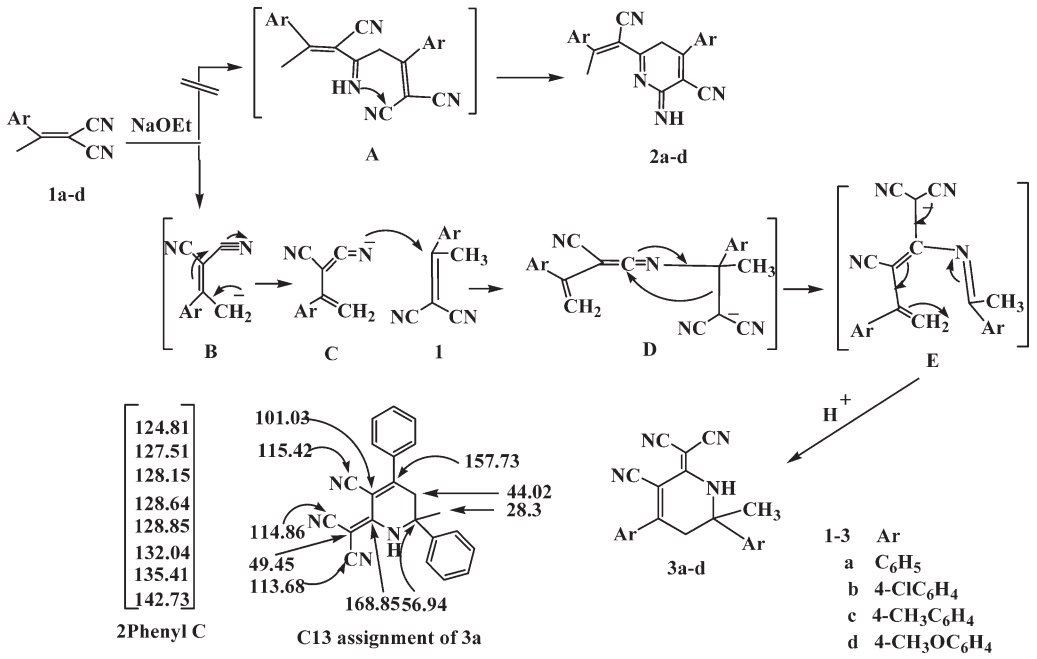
## INTRODUCTION

Pyridines and pyrido-fused derivatives are important heterocyclic compounds that find many pharmaceutical and agrochemical applications [2–6]. In the last two decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest [7–18]. In the context of this program, some newly substituted pyridines and pyrido-fused heterocyclic derivatives were required for biological evaluation. 2-(1-Arylethylidene)-malononitrile derivatives **1a-d** seemed good candidates to fulfill this objective *via* their dimerization through the intermediate **A** to afford the pyridine-imine derivatives **2a-d** and then coupling of these expected pyridine derivatives (Scheme 1) with arene diazonium salts followed by cyclization of the products to afford pyrido[3,2-c]pyridazine derivatives.

## RESULTS AND DISCUSSION

Thus 2-(1-phenyl-ethylidene)-malononitrile derivative **1a** (obtained from the condensation of acetophenone with malononitrile according to the literature method) [19] was refluxed in ethanol catalyzed by sodium ethoxide and we could isolate an analytically pure product with mp 202°C and in quantitative yield. The mass spectrum of this obtained product showed a molecular ion peak at $m/z = 336$; which points out to a dimer of **1a**. Theoretically different possible structures can be assumed for this dimmer, however, based on the spectral data it was thought that we have obtained the pyridine-imine derivative **2a** (Scheme 1). The $^1$H NMR spectrum of this product revealed signals at δ 1.74 (s, 3H,) assignable to one methyl group, 3.33 (d, 1H; $J = 18.6$ Hz), 3.75 (d, 1H; $J = 18.6$ Hz) assignable to two chemically nonequivalent protons of a methylene group and

**Scheme 1.** Preparation of compounds **3a-d**.




aromatic multiplet (10H) at 7.29–7.56 beside an exchangeable singlet (1H) at δ 8.55 ppm assignable to NH. These $^{1}$H NMR data seemed applicable to a structure like **2a**. However the $^{13}$C NMR spectrum of this reaction product revealed 18 signals at $\delta_C$ = 28.3 (q); 44.02 (t); 49.45 (s), 56.94 (s); 101.03 (s); 113.68 (s); 114.86 (s); 115.42 (s); [124.81 (d), 127.51 (d), 128.15 (d), 128.64 (d), 128.85 (d), 132.04 (d), 135.41 (s), 142.73 (s) phenyl carbons], 157.73 (s), 168.85 (s). (*cf.* Scheme 1 and Experimental section). These $^{13}$C NMR values are not completely applicable to structure **2a**.

Furthermore, when this product was allowed to couple with the diazotized aromatic amines **4a-d** (aniline, *p*-chloroaniline, *p*-toluidine and *p*-anisidine) it afforded highly colored hydrazo derivatives analyzed correctly as derivatives of **2a**; however, trials to cyclize these hydrazo derivatives into the expected pyrido[3,2-c]pyridazine derivatives failed under the different conditions reported to effect such cyclizations[14,20]. This behavior led us to the fact that the hydrazo group is not in the vicinity of the cyano group and the structure is not **2a**. Thus it was mandatory to have an X-ray crystallographic picture of this compound. Fortunately, we could obtain this X-ray [21,22] (Fig. 1). It shows clearly that the cyano groups are located far away from the hydrazo groups attached to the active methylene and that the methyl and one phenyl group are attached to the same carbon (C-2). The X-ray picture shows also that the structure appears with one molecule of ethyl acetate; the crystallization solvent. Thus structure **3a** was unambiguously established for this product (Scheme 1). All spectral and analytical data are now completely applicable to this structure and also those of the hydrazo derivatives **5a-d** (*cf.* Schemes 1 and 2 and the Experimental section).

It is assumed that the ethoxide anion abstracts one proton from **1** to afford the anion **B**, which is electronically rearranged to the keteneimine **C**. This latter attacks another molecule of **1** at the C=C to afford **D**, which undergoes rearrangement with migration of the malonyl anion to the C=N to afford **E**. Such rearrangement in the keteneimine series are known in the literature [23]. The intermediate **E** undergoes cyclization and regains its lost proton to afford the final isolable product **3a**. The cyclization of alkylidenemalononitriles under Michael reaction conditions is reported also to afford pyridine derivatives [24].

The ethylidenemalononitrile derivatives **1b-d** (obtained from the condensation of the corresponding aryl methyl ketone with malononitrile according to literature method) [19] followed the same pathway under the same reaction conditions, and we could obtain the pyridine derivatives **3b-d**, respectively (Scheme 1). All analytical and spectral data are in complete agreement with their proposed structures (*cf.* Experimental).

It is worth to mention that this dimerization of **1** to give **3** could be catalyzed by aqueous NaOH in ethanol, aqueous $Na_2CO_3$ in ethanol, or NaOEt in ethanol. All these led to the same product in each case however the maximum yields and the cleanest products were achieved with NaOEt.

Although the obtained products are not the same which we expected, however these products were found

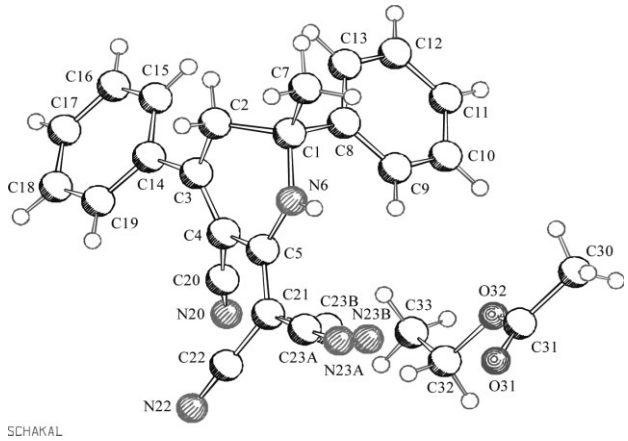



**Figure 1.** X-ray crystallographic structure of compound **3a** [21,22].

suitable also to fulfill our objective. Recently pyrazoles were found to be potentially biologically active compounds [25–27]. Also naphthyridine derivatives represent an important class of heterocyclic compounds due to their marked wide range of biological activities, such as anticonvulsant, antibacterial, anticancer, insecticidal, and fungicidal effects [28–31]. Thus, in continuation with our interest in naphthyridine synthesis [32], we describe here the synthesis of some novel fused naphthyridine derivatives.

Thus compound **3a** reacts with hydrazine hydrate and phenyl hydrazine **6a,b** to afford the pyrazolo-naphthyridine derivatives **7a,b**, respectively.

Compound **3a** reacts also with the urea derivatives **8a,b** to afford the pyrimido-naphthyridine derivatives **9a,b**, respectively. It is apparent that the hydrazines and ureas undergo cycloaddition to the two gem cyano groups with the aid of the labile hydrogen of the pyridine NH followed by further addition of the resulting $NH_2$ to the 5-cyano group.

The IR spectra of compounds **7a,b** and **9a,b** are all void of any cyano absorption bands at the region of $\upsilon_{max}$= 1980–2240 $cm^{-1}$. All spectral and analytical data are in complete agreement with these structures (*cf.* Experimental).

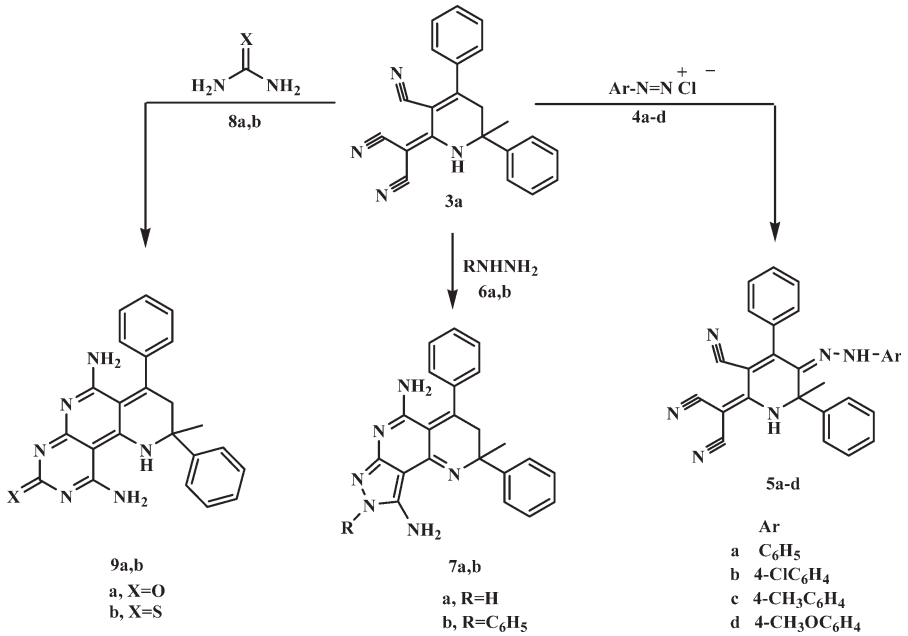
## CONCLUSION

We could prepare some novel heterocyclic derivatives of biological interest. All the reactions were carried out using simple and clean eco-friendly synthetic methods. No heavy metals or hazardous solvents are involved: just ethanol, DMF, or water as solvents, sodium salts are used as a catalyst.

## EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The $^1$H NMR and $^{13}$C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-$d_6$ using TMS as internal standard and chemical shifts are expressed in δ (ppm) values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out by the Microanalytical Center at Cairo University. The X-ray crystallography was carried out in the Institute of Organic Chemistry, Technical University of Dresden, Germany.

**Scheme 2.** Preparation of compounds **5**, **7**, and **9**.



**The dimerization of 2-(1-aryl-ethylidene)-malononitrile derivatives 1a-d: [Preparation of 3a-d].** To a solution of each of **1a-d** (10 mmol) in 15 mL of absolute ethanol was added 2 mL of saturated sodium ethoxide solution (obtained by dissolving 0.1 g of sodium metal in the least amount of absolute ethanol). The reaction mixture was refluxed on a water bath for 1 h, then left to cool to room temperature and poured on ice cold water and acidified with drops of conc. HCl till just neutral. The precipitated solids were collected by filtration, washed with water, dried, and recrystallized to afford **3a-d,** respectively.

***2-(3-Cyano-6-methyl-4,6-diphenyl-5,6-dihydropyridin-2(1H)-ylidene)-malononitrile 3a.*** Yellow crystals; yield (3.26 g; 96%), mp: 201–203°C (EtOH/DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3445 & 3260 (NH), 2213, 2214, 2217 (3CN). MS, $m/z$ = 336 [$M^+$]; $\delta_H$: 1.74 (s, 3H, $CH_3$), 3.33 (d, 1H; $J$ = 18.6 Hz), 3.75 (d, 1H; $J$ = 18.6 Hz), 7.29–7.56 (m, 10H, 2Ph), 8.55 (s, 1H $D_2O$ exchangeable, NH). $\delta_C$ = 28.3 (q); 44.02 (t); 49.45 (s), 56.94 (s); 101.03 (s); 113.68 (s); 114.86 (s); 115.42 (s); [124.81 (d), 127.51 (d), 128.15 (d), 128.64 (d), 128.85 (d), 132.04 (d), 135.41 (s), 142.73 (s) phenyl carbons], 157.73 (s), 168.85 (s).

X-ray crystallographic data [21,22]: Yellow crystals, $C_{22}H_{16}N_4{*}C_4H_8O_2$ ($M_r$ = 424.49 g $mol^{-1}$), monoclinic, space group $P2_1/n$ (No. 14), a [Å] = 10.637(2), b [Å] = 19.286(4), c[Å] = 12.072(2), α[°] = 90.00, β[°] = 113.27(3), γ[°] = 90.00; $V$[Å$^3$] = 2282.8(9), $Z$ = 4, $D_{calc}$ = 1.235 g $cm^{-3}$, $F(000)$ = 896 e, $\mu(M_o\ K_\alpha)$ = 0.080 $cm^{-1}$; the final difference Fourier ρ = 0.45 (−0.39) e Å$^{-3}$.crystal size = 0.35 mm × 0.13 mm × 0.07 mm. Max. resolution [sin θ/$\lambda_{max}$] = 0.61 Å$^{-1}$/ 99.8%. Data were collected using a Bruker Nonius area detector at $T$[°C]=−75(2), with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) using the CCD data collection and SADABS absorption correction method; min. 85.1%; max 99.4%. Total No. of reflections are 57431, No. of independent reflections 4201 were counted with observed reflections 2726. No. of refined parameters 312/10 restrains. $R_{av}$= 0.099. The final $R$= 0.067 and $R_W{}^2$ = 0.177 with error of fit 1.048.

Anal. Calcd. for $C_{22}H_{16}N_4$ (336.39): C 78.55, H 4.79, N 16.66. Found: C 78.50, H 4.90, N 16.80.

***2-[3-Cyano-4,6-bis-(4-chlorophenyl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 3b.*** Deep green powder; yield (3.93 g; 97%), mp: 158–160°C (EtOH). IR: $\upsilon_{max}$ ($cm^{-1}$) 3442 & 3230 (NH), 2211–2117 (3CN). $\delta_H$: 1.72 (s, 3H, $CH_3$), 3.38 (d, 1H; $J$ = 18.5 Hz), 3.74 (d, 1H; $J$ = 18.5 Hz), 7.33–7.63 (m, 8H, Ar. H), 9.71 (s, 1H $D_2O$ exchangeable, NH).

Anal. Calcd. for $C_{22}H_{14}\ Cl_2N_4$ (405.28): C 65.20, H 3.48, Cl 17.50, N 13.82. Found: C 65.35, H 3.55, Cl 17.80, N 13.90.

***2-[3-Cyano-4,6-bis-(4-methylphenyl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene]- malononitrile 3c.*** Brown powder; yield (3.20 g; 88%), mp: 169–172°C (EtOH). IR: $\upsilon_{max}$ ($cm^{-1}$) 3442 & 3230 (NH), 2218–2224 (3CN). MS, $m/z$= 364 [$M^+$]; $\delta_H$: 1.74 (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 3.26 (d, 1H, $J$ = 18.6 Hz), 3.36 (d, 1H; $J$ = 18 Hz), 7.05–7.42 (m, 8H, Ar. H), 9.65 (s, 1H $D_2O$ exchangeable, NH).

Anal. Calcd. for $C_{24}H_{20}N_4$ (364.44): C 79.10, H 5.53, N 15.37. Found C 79.25, H 5.55, N 15.60.

***2-[3-Cyano-4,6-bis-(4-methoxyphenyl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 3d.*** Coffee brown powder; yield (3.72 g; 94%), mp: 181–183°C (EtOH). IR: $\upsilon_{max}$ ($cm^{-1}$) 3443 & 3232 (NH), 2215–2226 (3CN). MS, $m/z$= 397 [$M^+$+1]; $\delta_H$: 1.70 (s, 3H, $CH_3$), 3.29 (d, 1H, $J$ = 18.6 Hz), 3.37 (s, 1H, $J$ = 18.6 Hz), 3.65 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 7.24–7.44 (m, 8H, Ar. H), 9.66 (s, 1H $D_2O$ exchangeable, NH).

Anal. Calcd. for $C_{24}H_{20}N_4O_2$ (396.44): C 72.71, H 5.08, N 14.13. Found: C 72.75, H 5.15, N 14.20.

**Azo coupling of 3a with arene diazonium chloride derivatives 4a-d.** Arene diazonium salts **4a-d** (0.01 mol) were freshly prepared by adding a solution of 0.01 mol of sodium nitrite in 5 mL $H_2O$ to a cold solution of the hydrochloride (0.01 mol) of the respective aryl amine: (aniline, *p*-chloroaniline, *p*-toluidine, or *p*-anisidine, respectively, in 5 mL conc. HCl) with stirring. The resulting solutions of the aryl diazonium salts were added to a cold solution of **3a** (0.01 mol), in ethanol (35 mL) containing sodium acetate (2 g). The reaction mixture was stirred at room temperature for 1 h in each case and the solid products, so formed, were collected by filtration and recrystallized from ethanol/DMF.

***2-(3-Cyano-6-methyl-4,6-diphenyl-5-(2-phenylhydrazono)-5,6-dihydropyridin-2(1H)-ylidene)-malononitrile 5a.*** Reddish brown powder; yield (3.78 g; 85 %), mp: 195–197°C (EtOH/DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3372, 3307 and 3229 (NH), 2207–2215 (CN). MS, $m/z$ = 441 [$M^+$+1]; $\delta_H$: 1.94 (s, 3H, $CH_3$), 6.89–7.54 (m, 15H, Ar. H), 9.51 (s, 1H $D_2O$ exchangeable, NH), 10.02 (s, 1H, $D_2O$ exchangeable, hydrazone NH).

Anal. Calcd. for $C_{28}H_{20}N_6$ (440.50): C 76.35, H 4.58, N 19.08. Found: C 76.40, H 4.55, N 19.05.

***2-(5-(2-(4-Chlorophenyl)-hydrazono)-3-cyano-6-methyl-4,6-diphenyl-5,6-dihydropyridin-2(1H)-ylidene)-malononitrile 5b.*** Dark red crystals; yield (4 g; 86%), mp: 234–235°C (EtOH/ DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3338, 3290, and 3231 (NH), 2208–2217 (CN). $\delta_H$: 1.98 (s, 3H, $CH_3$), 6.49–7.72 (m, 14H, Ar. H), 9.63 (s, 1H $D_2O$ exchangeable, NH), 10.07 (s, 1H, $D_2O$ exchangeable, hydrazone NH).

Anal. Calcd. for $C_{28}H_{19}ClN_6$ (474.94): C 70.81, H 4.03, Cl 7.46, N 17.69. Found: C 70.85, H 4.13, Cl 7.56, N 17.60.

***2-[3-Cyano-6-methyl-4,6-diphenyl-5-(2-(4-tolyl-hydrazono))-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 5c.*** Brown crystals; yield (3.77 g; 83%), mp: 225–227°C (EtOH/DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3336, 3291, and 3233 (NH), 2205–2216 (CN). $\delta_H$: 1.93 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 6.86–7.73 (m, 14H, Ar. H), 9.65 (s, 1H $D_2O$ exchangeable, NH), 10.05 (s, 1H, $D_2O$ exchangeable, hydrazone NH).

Anal. Calcd. for $C_{29}H_{22}N_6$ (454.53): C 76.63, H 4.88, N 18.49. Found: C 76.65, H 4.90, N 18.55.

***2-[3-Cyano-6-methyl-4,6-diphenyl-5-(2-(4-methoxyphenyl)-hydrazono)-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 5d.*** Light brown crystals; yield (3.99 g; 85%), mp: 237–239°C (EtOH/DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3335, 3292, and 3232 (NH), 2208 & 2219 (CN). $\delta_H$: 1.89 (s, 3H, $CH_3$), 3.69 (s, 3H, $CH_3$), 6.95–7.50 (m, 14H, Ar. H), 9.66 (s, 1H $D_2O$ exchangeable, NH), 10.02 (s, 1H, $D_2O$ exchangeable, hydrazone NH).

Anal. Calcd. for $C_{29}H_{22}N_6O$ (470.52): C 74.03, H 4.71, N 17.86. Found: C 74.10, H 4.76, N 17.92.

**The reaction of 3a with hydrazine hydrate and phenyl hydrazine 6a,b.** To a solution of **3a** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of either hydrazine hydrate **6a** or phenyl hydrazine **6b**. The reaction mixture was refluxed for 2h in each case, left overnight. The reaction mixture was then poured on ice cold water and acidified with dil. HCl till just neutral. The precipitated solids were filtered off and recrystallized from ethanol.

***2-Methyl-2,4-diphenyl-3,8-dihydro-2H-pyrazolo[3,4-h][1,6] naphthyridine-5,9-diamine 7a.*** Yellow crystals; yield (2.9 g; 80%), mp: 120–122°C (EtOH). IR: $\upsilon_{max}$ ($cm^{-1}$) 3330, 3286–3231 (NH & $NH_2$). MS, $m/z$ = 368 [$M^+$]; $\delta_H$: 1.89 (s, 3H, $CH_3$), 3.32 (d, 1H; $J$ = 18.65 Hz), 3.45 (d, 1H; $J$ = 18.65 Hz), 6.60 (br. s, 4H, $2NH_2$), 7.15–7.56 (m, 10H, 2Ph), 11.65 (s, 1H $D_2O$ exchangeable, NH).

Anal. Calcd. for $C_{22}H_{20}N_6$ (368.43): C 71.72, H 5.47, N 22.81. Found: C 71.75, H 5.52, N 22.87.

***2-Methyl-2,4,8-triphenyl-3,8-dihydro-2H-pyrazolo[3,4-h][1,6] naphthyridine-5,9-diamine 7b.*** Yellow crystals; yield (3.46 g; 78%), mp: 128–129°C (EtOH). IR: $\upsilon_{max}$ ($cm^{-1}$) 3333, 3285 ($NH_2$). MS, $m/z$ = 444 [$M^+$]; $\delta_H$: 1.76 (s, 3H, $CH_3$), 3.22 (d, 1H; $J$ = 18.65 Hz), 3.46 (d, 1H; $J$ = 18.65 Hz), 6.56 (br. s, 4H, $2NH_2$), 6.75–7.55 (m, 15H, 3Ph).

Anal. Calcd. for $C_{28}H_{24}N_6$ (444.53): C 75.65, H 5.44, N 18.91. Found: C 75.68, H 5.50, N 19.03.

**The reaction of 3a with urea and thiourea 8a,b.** To a solution of **3a** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of either urea **8a** or thiourea **8b** followed by few drops of triethylamine. The reaction mixture was refluxed for 2 h in each case and then left to cool overnight. The precipitated solids were collected by filtration and recrystallized from ethanol/DMF.

***5,10-Diamino-2-methyl-2,4-diphenyl-2,3-dihydropyrimido[4,5-h][1,6]naphthyridin-8(1H)-one 9a.*** Yellow crystals; yield (3 g; 78%), mp: 147–149°C (EtOH/DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3332, 3289, and 3230 (NH & $NH_2$), 1667 (CO). MS, $m/z$ = 395 [$M^+$-1]. $\delta_H$: 1.74 (s, 3H, $CH_3$), 3.32 (d, 1H; $J$ = 18.3 Hz), 3.75 (d, 1H; $J$ = 18.3 Hz), 7.29–7.57 (m, 14H, 2Ph+$2NH_2$), 9.71 (s, 1H $D_2O$ exchangeable, NH).

Anal. Calcd. for $C_{23}H_{20}N_6O$ (396.44): C 69.68, H 5.08, N 21.20. Found: C 69.65, H 5.10, N 21.28.

***5,10-Diamino-2-methyl-2,4-diphenyl-2,3-dihydropyrimido[4,5-h][1,6]naphthyridine-8(1H)-thione 9b.*** Dark yellow crystals; yield (3.2 g; 78%), mp: 160–162°C (EtOH/DMF). IR: $\upsilon_{max}$ ($cm^{-1}$) 3335, 3291, and 3232 (NH & $NH_2$). MS, $m/z$ = 412 [$M^+$]. $\delta_H$: 1.75 (s, 3H, $CH_3$), 3.31 (d, 1H; $J$ = 18.32 Hz), 3.64 (d, 1H; J = 18.32 Hz), 7.28–7.58 (m, 14H, 2Ph+$2NH_2$), 9.66 (s, 1H $D_2O$ exchangeable, NH).

Anal. Calcd. for $C_{23}H_{20}N_6S$ (412.51): C 66.97, H 4.89, N 20.37, S 7.77. Found: C 67.05, H 4.95, N 20.42, S 7.92.

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## REFERENCES AND NOTES

[1] This work is abstracted in part from the PhD thesis of Mrs. Nehal A. Sobhy.

[2] Miszke, A.; Foks, H.; Kedzia, A.; Kwapisz, E.; Zwolska, Z. Heterocycles 2008, 75, 2251.

[3] Worbel, J.; Li, Z.; Dietrich, A.; McCaleb, M.; Mihan, B.; Serdy, J.; Sullivan, D. J Med Chem 1998, 41, 1084.

[4] Robertson, R. M.; Robertson, D. In The Pharmacological Basis of Therapeutics, Goodman and Gilman's, 9th ed.; Gillman, A. G., Eds.; Mc Graw-Hill Health Professions Divisions: New York, 1996; p 759.

[5] Mizuta, E.; Nishikawa, K.; Omura, K.; Oka, Y. Chem Pharm Bull 1976, 24, 2078.

[6] Kuczynski, L.; Leonard, M.; Aleksander, A.; Banaszkiewicz, W.; Responds, S. Pol J Pharmacol Pharm 1983, 34, 223.

[7] Abdelrazek, F. M.; Salah El-Din, A. M.; Mekky, A. E. Tetrahedron 2001, 57, 1813.

[8] Abdelrazek, F. M.; Salah El-Din, A. M.; Mekky, A. E. Tetrahedron 2001, 57, 6787.

[9] Abdelrazek, F. M.; Metwally, N. H. Afinidad 2003, 60, 554.

[10] Abdelrazek, F. M.; Metz, P.; Farrag, E. K. Arch Pharm Pharm Med Chem (weinheim) 2004, 337, 482.

[11] Abdelrazek, F. M. Synth Commun 2005, 35, 2251.

[12] Abdelrazek, F. M.; Michael, F. A. J Heterocycl Chem 2006, 43, 7.

[13] Abdelrazek, F. M.; Metwally, N. H.; Synth Commun 2006, 36, 83.

[14] Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. Arch Pharm Chem life Sci (Weinheim) 2006, 339, 456.

[15] Abdelrazek, F. M.; Michael, F. A.; Mohamed, A. E. Arch Pharm Chem life Sci (Weinheim) 2006, 339, 305.

[16] Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Arch Pharm Chem Life Sci (Weinheim) 2007, 340, 543.

[17] Abdelrazek, F. M.; Ghozlan, S. A.; Michael, F. A. J Heterocycl Chem 2007, 44, 63.

[18] Abdelrazek, F. M.; Mohamed, A. M. Afinidad 2008, 65, 56.

[19] Wang, G.-W; Cheng, B. O. Arkivoc 2004, 9, 4.

[20] Abdelrazek, F. M.; Salah, A. M. Bull Chem Soc Jpn 1993, 66, 1722.

[21] Crystallographic data (excluding structure factors) for the structure **2a** reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-744590. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 441223/336–033; e-mail: deposit@ccdc.cam.ac.uk.

[22] Keller, E. SCHAKAL 99, A Computer Program for the Graphic Representation of Molecular and Crystallographic Models; Universität Freiburg, Germany, 1999.

[23] Barker, M. W.; McHenry, W. E.; In The Chemistry of Ketenes, Allenes and Related Compounds; Patai, S. Ed.; John Wiley: New York, 1980; p 702.

[24] Igarashi, M.; Nakano, Y.; Takezawa, K.; Watanabe, T.; Sato, S. Synth Commun 1987, 68.

[25] Wang, A. X.; Qinghua, X.; Lane, B.; Mollison, K. W.; Hsieh, G. C.; Marsh, K.; Sheets, M. P.; Luly, J. R.; Coghlan, M. J. Bioorg Med Chem Lett 1998, 8, 2787.

[26] Kim, H. H.; Park, T. G.; Moon, T. C.; Chang, H. W.; Jahng, Y. Arch Pharm Res 1999, 2, 372.

[27] Park, H.-J.; Lee, K.; Park, S-J.; Ahn, B.; Lee, J.-C.; Yeong, H.; Lee, C. K.-I. Bioorg Med Chem Lett 2005, 15, 3307.

[28] Bellacova, A.; Seman, M.; Milata, V.; Llavsky, D.; Ebringer, L. Folia Microbiol (Praha) 1997, 42, 193.

[29] Bachowska, B.; Zujewska, T. Aust J Chem 2001, 54, 105.

[30] Bachowska, B.; Zujewska, T. Arkivoc 2001, 6, 77.

[31] Matsuda, T.; Yamagata, K.; Tomioka, Y.; Yamazaki, M. Chem pharm Bull 1985, 33, 937.

[32] Abdelrazek, F. M.; Michael, F. A. Afinidad 2006, 63, 229.

# Tandem Michael Addition/Imino-Nitrile Cyclization Synthesis of 2-Amino-6-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4yl)-4-phenylpyridine-3-carbonitrile



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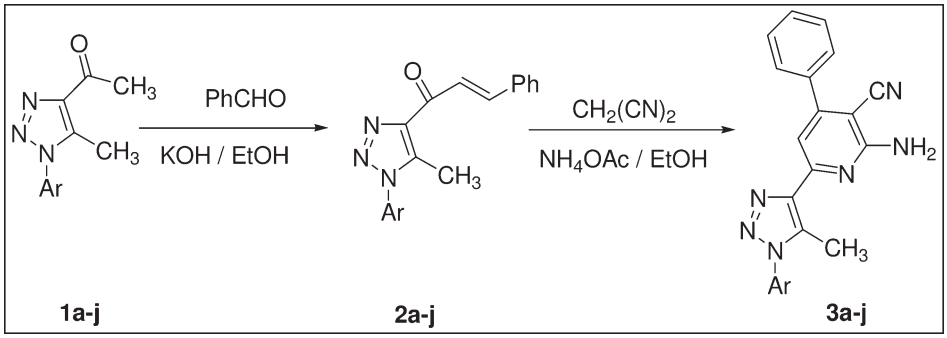


Several 2–amino-6-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-phenylpyridine-3-carbonitrile have been synthesized by Tandem Michael addition/imino-nitrile cyclization and the structures of these compounds were established by MS, IR, CHN, and $^1$H NMR spectral data. The crystal structure of 2-amino-6-[1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-4-phenylpyridine-3-carbonitrile was established by X-ray diffraction.

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## INTRODUCTION

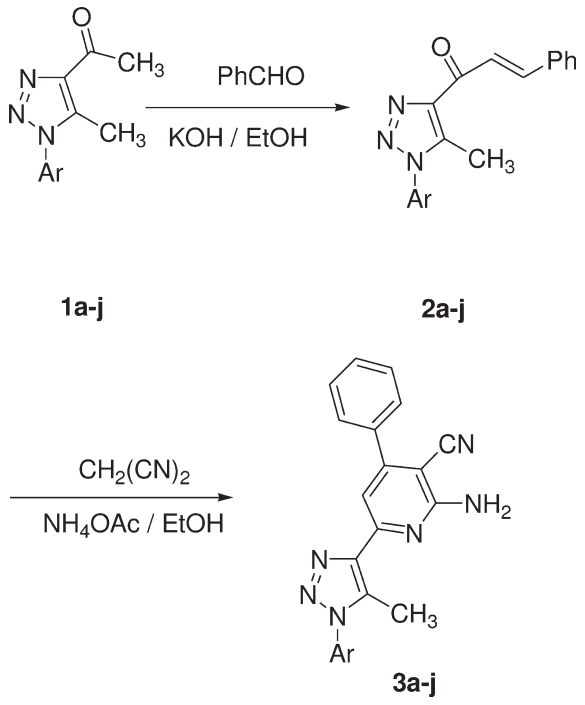
The pyridine ring is one of the most well-known systems among the naturally occurring heterocycles [1]. Pyridine and fused pyridine moieties was shown in numerous natural products such as quinoline and isoquinoline alkaloids [2], and nicotine and its analogs [3], 2-aminopyridines are promising substituted pyridines which have been shown to be biologically active molecules [4]. Additionally, because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry [5]. If substituted with optically active groups, they could potentially serve for chiral auxiliaries or chiral ligands in asymmetric reactions. For this reaction, 2-aminopyridine derivatives are valuable synthetic target compounds. The synthesis of 2-aminopyridine derivatives has been extensively reviewed [4–10]. In addition there have been some reports concerning biological interest for 1,2,3-triazole nucleus have been reported as antibacterial [11], antifungal [12], antiviral [13], anti-inflammatory and analgesic [14] and 1,2,3-triazole derivatives have been synthesized to inhibit tumor proliferation, invasion, and metastasis [15]. However, there is a little data describing compounds containing the two heterocyclic moieties, thiazoline and 1,2,3-triazole. Interest in this class of compounds prompted the synthesis, several new 2-amino-6-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-phenylpyridine-3-carbonitrile have been synthesized by Tandem Michael addition/amino-nitrile cyclization.

## RESULTS AND DISCUSSION

The some new 2-amino-6-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4yl)-4-phenylpyridine-3-carbonitrile (**3a–j**) have been synthesized by Tandem Michael addition/imino-nitrile cyclization [16] with (*E*)-1-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one from 1-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-ethanone derivatives (Scheme 1).

Our own interest in the development of new 2–amino-6-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-4-phenylpyridine-3-carbonitrile derivatives and in extending this type of tandem reaction prompted us to examine potential applications and generalizations to the synthesis of substituted pyridine. The reactivity of (*E*)-1-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one would be regarded particularly closely during the cyclization step to shed further light on the course of this short transformation and, also, to gain further insight into the mechanistic aspects of this tandem reaction.

**Scheme 1**




**1a-j** **2a-j** **3a-j**

**2a, 3a** Ar=4-$CH_3C_6H_4$-; **2b, 3b** Ar=Ph; **2c, 3c** Ar=4-$ClC_6H_4$-; **2d, 3d** Ar=2,5-di$ClC_6H_3$-; **2e, 3e** Ar=3-$ClC_6H_4$-; **2f, 3f** Ar=2-$ClC_6H_4$-; **2g, 3g** Ar=4-$BrC_6H_4$-; **2h, 3h** Ar=β-$C_{10}H_7$-; **2i, 3i** Ar=3-$BrC_6H_4$-; **2j, 3j** Ar=4-$MeOC_6H_4$-

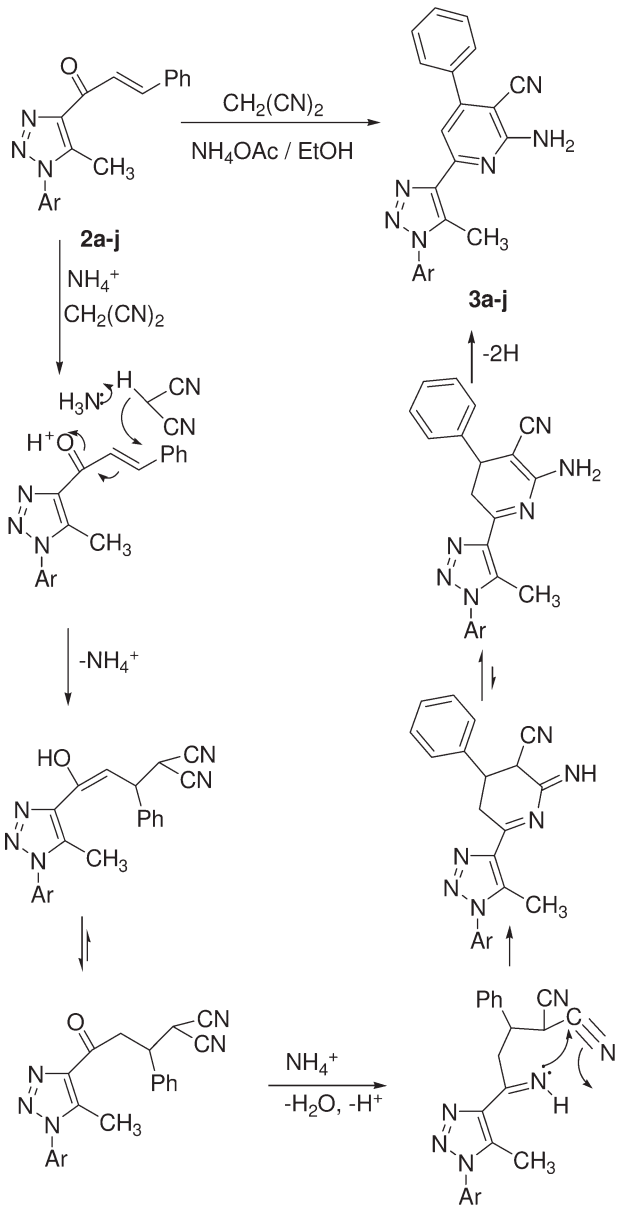
Identified as a cyano compound showing IR absorption at 2207–2213 $cm^{-1}$ and amino at 3436–3494, 3353–3374 $cm^{-1}$ of **3a–j**, as a carbonyl compound showing strong IR absorption at 1679–1683 $cm^{-1}$ of **1a–j** and 1659–1666 $cm^{-1}$ of **2a–j**. $^1$H NMR —CO—$CH_3$ peak at 2.694–2.778 ppm of **1a–j** and showing  $^1$H NMR dual peak 8.057–8.173 ppm, 7.809–8.076 ppm, $J$ = 15.6–15.9 Hz of **2a–j** but it is disappearance in compounds **3a–j** (Scheme 2).

**Compound 2-amino-6-[1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-4-phenylpyridine-3-carbonitrile.** This consists of a substituted triazolyl ring and a phenyl ring is not planar (torsion angles is shown for dihedral angle of $C_{triazolyl}$—$N_{triazolyl}$—$C_{phenyl}$—$C_{phenyl}$ is 48.6(4)° by the hindering of triazole ring C9—$CH_3$ and benzene ring C2—H or C6—H, and so dihedral angle of $C_{pyridyl}$—$C_{pyridyl}$—$C_{phenyl}$—$C_{phenyl}$ is 38.3(4)° in stable conformation of the crystal). The substituted triazolyl ring and substituted pyridyl ring is an approximation planar (torsion angles is shown for dihedral angle of $N_{triazolyl}$—$C_{triazolyl}$—$C_{pyridyl}$—$N_{pyridyl}$ is 176.5(3)°) by the π–π conjugation of triazole ring π bond and pyridine ring π bond, C10—C11 bond 1.475 Å is shorter than nonconjugation $Csp^2$-$Csp^2$ bond C13—C17 1.484 Å (Fig. 1; Table 1).

On pyridine ring, the p-π conjugation was indicated between amino N5 and ring C15, N5—C15 length is 1.343(4) Å, C15—N5—H, H—N5—H angle is 120°, dihedral angle of C11—N4—C15—N5 is 179.4°, dihedral angle of N5—C15—C14—C13 is 178.2°, N5 is came under the action of $sp^2$ hybridized.

On pyridine ring, 2-amino has two N—H bond and two intermolecular hydrogen bonds as the superamolecular structure in the crystal. The intermolecular O′1···H5A-N5 hydrogen-bond between the O1 atoms of the $CH_3O$ group and N5—H, intermolecular N′6···H5A—N5 hydrogen bond between the N atoms of the CN group and N5—H was given (Fig. 2; Table 2). The orderly range of the structure forms stratification polymer in the crystal. The intermolecular hydrogen bond connects the translated molecules into an infinite chain on a layer.

**Scheme 2**



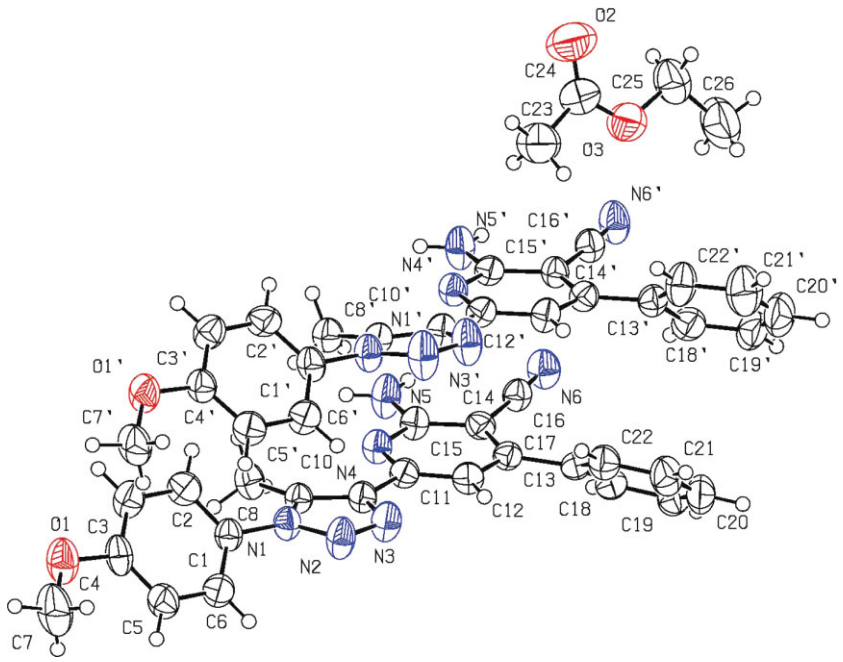



**Figure 1.** A *PLATON* (Spek, 2001) view of the molecular structure of (*I*), the asymmetric unit showing 50% probability displacement ellipsoids. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

## EXPERIMENTAL

All melting points were determined on an XT4-100× microscopic melting point apparatus and are uncorrected. Mass spectrum was performed on a ESQ6K esquire6000 spectrometer (**3a–j**) and HP-5988A (**2a–j**) spectrometer (EI at 70 eV). IR spectra were obtained in KBr discus using a Nicolet NEXUS 670 FTIR spectrometer. $^1$H NMR spectroscopy ($CDCl_3$) was recorded on Avance Mercury plus-300 with TMS as an internal standard. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer.

**General procedure for the preparation of 1-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-ethanone derivatives (1a–j).** 1-(1-Aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-ethanone **1a–j** was prepared following condensation methods of 1-azido-4-methylbenzene [17] with pentane-2,4-dione. A cold solution of sodium methanolate (0.23 mol, in 120 mL absolute methanol) was added to the mixture of pentane-2,4-dione (17 mL, 0.165 mol) and 1-azido-4-methylbenzene (about 0.15 mol) and stirred for 1 h at 0–5°C. Then the mixture was heated under reflux on an oil-bath for 10 h. Finally the mixture was neutralized with concentrated hydrochloric acid. 1-(1-Aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone **1a–j** was separated and crystallized from methanol.

***1-(5-Methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl) ethanone (1a).*** Yield: 52.6%; buff crystals; mp: 105–107°C (Lit 106–107°C); $^1$H NMR: 7.360–7.384(d, 2H, $J$ = 7.2 Hz, Ar-2,6), 7.306–7.333(d, 2H, $J$ = 8.1 Hz, Ar-3,5), 2.757(s, 3H, $CH_3CO$), 2.573(s, 3H, TRZ-$CH_3$), 2.468(s, 3H, Ar—$CH_3$); MS: 215($M^+$,19); CA 194478-14-3 [17].

***1-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethanone (1b).*** Yield: 58.5%; buff crystals; mp: 99–100°C (Lit 108°C); $^1$H NMR: 7.552–7.578(m, 3H, $J$ = 7.8 Hz, Ar-3,4,5), 7.408–7.432(m, 2H, $J$ = 7.2 Hz, Ar-2,6), 2.729(s, 3H, $CH_3CO$), 2,571(s, 3H, TRZ-$CH_3$); MS: 201($M^+$, 13) CA 51118-32-2 [18].

***1-[1-(4-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]ethanone (1c).*** Yield: 53.2%; white crystals; mp: 108–110°C (Lit 119°C); $^1$H NMR: 7.546–7.564(d, 2H, $J$ = 5.4 Hz, Ar-2, 6), 7.399–7.429(d, 2H, $J$ = 9.0 Hz, Ar-3,5), 2.757(s, 3H, $CH_3CO$), 2.599(s, 3H, TRZ-$CH_3$); MS: 235($M^+$, 4). Found: C, 56.47; H, 4.42; N, 17.57 CA 33821-38-4 [18].

**Table 1**

Selected geometric parameters (Å, °).

| Atom-atom | Bond (Å, °) | Atom-atom | Bond (Å, °) |
|---|---|---|---|
| C10—C11 | 1.475 (4) | C15—N5 | 1.343 (4) |
| C13—C17 | 1.484 (4) | | |
| C15—N5—H5A | 120.0 | H5A—N5—H5B | 120.0 |
| C15—N5—H5B | 120.0 | | |
| N3—C10—C11—N4 | −176.5 (3) | C2—C1—N1—C9 | −48.6 (4) |
| C13—C14—C15—N5 | −178.2 (3) | N5—C15—N4—C11 | −179.4 (3) |
| C12—C13—C17—C22 | −38.3 (4) | | |

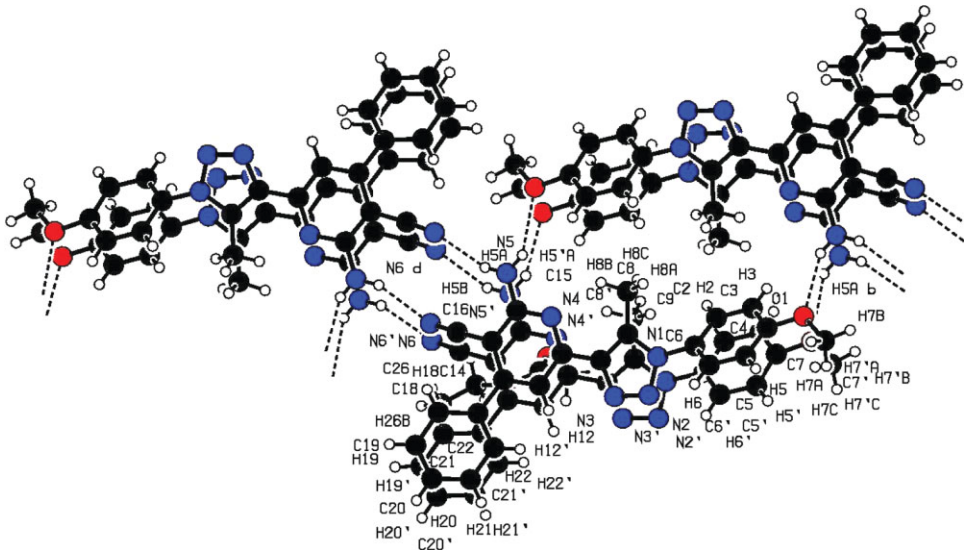



**Figure 2.** A *PLATON* (Spek, 2001) view of the hydrogen-bonded motif of the superamolecular structure. Hydrogen bonds are shown as dashed lines (Symmetry codes: (i) −x + 1, −y + 1, −z; (ii) −x, −y, −z). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

***1-[1-(2,5-Dichlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl] ethanone (1d).*** Yield: 54.9%; white crystals; mp: 100–102°C; IR: 3458, 3356, 3098(—$CH_3$), 1895, 1682(C=O), 1557, 1487(Ar), 1395, 1360, 1280, 1231, 1092, 955(N—N=N), 877, 810(Ar—H), 680; $^1$H NMR: 7.534–7.545(d, 2H, $J$ = 3.3 Hz, Ar-3,4), 7.448(s, 1H, Ar-6), 2.735(s, 3H, $CH_3CO$), 2.451(s, 3H, TRZ-$CH_3$); MS: 269(M+, 3), 241(1), 226(4), 199(11), 186(3), 172(3), 145(9), 109(14), 74(10), 43(100); Anal. Calcd. for $C_{11}H_9Cl_2N_3O$: C, 48.91; H, 3.36; N, 15.56; Found: C, 48.67; H, 3.21; N, 15.86 CA 668471-36-1.

***1-[1-(3-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]ethanone (1e).*** Yield: 57.5%; white crystals; mp: 78–80°C; IR: 3422, 3334, 3061(—$CH_3$), 1896, 1679(C=O), 1554, 1489(Ar), 1436, 1413, 1370, 1290, 1240, 1084, 955(N—N=N), 869, 792(Ar-H), 683; $^1$H NMR: 7.503–7.528(m, 3H, $J$ = 7.5 Hz, Ar-4,5,6), 7.325–7.354(s, 1H, $J$ = 8.7 Hz, Ar-2), 2.733(s, 3H, $CH_3CO$), 2.598(s, 3H, TRZ-$CH_3$); MS: 235(M+,3), 207(1), 192(4), 178(1), 164(16), 130(3), 111(20), 75(33), 65(1), 43(100); Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83; Found: C, 56.53; H, 4.33; N, 17.67 CA 1017399-61-9.

***1-[1-(2-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]ethanone (1f).*** Yield: 58.5%; buff crystals; mp: 92–94°C; IR: 3441, 3344, 3069(—$CH_3$), 1936, 1681(C=O), 1552, 1489(Ar), 1420, 1365, 1282, 1216, 1080, 951(N—N=N), 764(Ar-H), 654; $^1$H NMR: 7.374–7.606(m, 4H, Ar-3,4,5,6), 2.753(s, 3H, $CH_3CO$), 2.428(s, 3H, TRZ-$CH_3$); MS: 235(M+,9), 207(2), 192(15), 178(2), 164(35), 130(5), 111(32), 75(49), 65(1), 43(100); Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83; Found: C, 56.47; H, 4.39; N, 17.57 CA 1017471-30-5.

***1-[1-(4-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]ethanone (1g).*** Yield: 64.2%; yellow crystals; mp: 108–110°C (Lit 120°C); $^1$H NMR: 7,720–7.751(d, 2H, $J$ = 9.3 Hz, Ar-2,6), 7.364–7.396(d, 2H, $J$ = 9.6 Hz, Ar-3,5), 2.739(s, 3H, $CH_3CO$), 2.601(s, 3H, TRZ-$CH_3$); MS: 279(M+,3). Found: C, 47.46; H, 3.24; N, 15.31 CA 33722-11-1 [18].

***1-[5-Menthyl-1-(naphthalene-2-yl)-1H-1,2,3-triazol-4-yl] ethanone (1h).*** Yield: 73.8%; buff crystals; mp: 146–148°C; IR: 3429, 3346, 3057(—$CH_3$), 1927, 1681(C=O), 1598, 1557(Ar), 1420, 1363, 1272, 1215, 1079, 951(N—N=N), 865, 826(Ar-H), 755; $^1$H NMR: 7.896–8.038(m, 4H, Ar-1,4,5,8), 7.501–7.624(m, 3H, Ar-3,6,7), 2.778(s, 3H, $CH_3CO$), 2.642(s, 3H, TRZ-$CH_3$); MS: 251($M^+$, 17), 222(3), 208(9), 194(3), 180(61), 153(14), 127(63), 101(12), 77(22), 63(10), 51(13), 43(100); Anal. Calcd. for $C_{15}H_{13}N_2O$: C, 71.70; H, 5.21; N, 16.72; Found: C, 71.57; H, 5.45; N, 16.56.

***1-[1-(3-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]ethanone (1i).*** Yield:59.8%; white crystals; mp: 102–104°C; IR: 3444, 3348, 3073(—$CH_3$), 1683(C=O), 1554, 1494(Ar), 1420, 1365, 1282, 1219, 1066, 1029, 952(N—N=N), 765(Ar-H), 671; $^1$H NMR: 7.790(s, 1H, Ar-2), 7.505–7.528(m, 3H,Ar-4,5,6), 2.728(s, 3H, $CH_3CO$), 2.452(s, 3H, TRZ-$CH_3$); MS: 279(M+, 5), 251(1), 236(7), 211(13), 196(4), 182(3), 157(18), 144(7), 102(8), 75(25), 63(9), 50(22), 43(100); Anal. Calcd. for $C_{11}H_{10}BrN_3O$: C, 47.16; H, 3.60; N, 15.00; Found: C, 47.36; H, 3.19; N, 15.13.

***1-[1-(4-Menthoxyphenyl)-5-methyl-1H-1,2,3-triazol-4-yl] ethanone (1j).*** Yield: 58.4%; buff crystals; mp: 117–119°C (Lit 120°C); $^1$H NMR: 7.299–7.329(d, 2H, $J$ = 9.0 Hz, Ar-2,6), 7.012–7.032(d, 2H, $J$ = 6.0 Hz, Ar-3,5), 3.837(s, 3H,

**Table 2**

Hydrogen-bond geometry (Å, °).

| D—H···A | D—H | H···A | D···A | D—H···A |
|---|---|---|---|---|
| N5′—H5′A···O1[a] | 0.86 | 2.25 | 3.023 (5) | 150 |
| N5′—H5′B···N6[b] | 0.86 | 2.30 | 3.119 (5) | 159 |
| N5—H5A···O1′[a] | 0.86 | 2.42 | 3.200 (4) | 151 |
| N5—H5B···N6′[b] | 0.86 | 2.22 | 3.039 (5) | 160 |

Symmetry codes:
[a] −x + 1, −y + 1, −z.
[b] −x, −y, −z.

$CH_3O$), 2.694(s, 3H, $CH_3CO$), 2.501(s, 3H, TRZ-$CH_3$); MS: 231(M+, 13) CA 1017399-41-5 [18].

**General procedure for the preparation of (*E*)-1-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one derivatives (2a–j) [19].** A mixture of the aromatic aldehyde (12 mmol) and compound **1a–j** (10mmol) dissolved in ethanol (70 mL) was added slowly to an aqueous solution of potassium hydroxide (12.8 mmol) in water (10 mL). The reaction mixture was stirred in crushed-ice bath for 2 h, stirred at 20–25°C for 4 h. The mixture was filtrated and the solid was washed with cold water and cold alcohol. The product was crystallized from ethanol to give **2a–j.** All products were new compounds.

***(E)-1-(5-Methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one (2a).*** Yield: 92.5%; white crystals; mp: 178–180°C; IR:1664(C=O), 1611(C=C), 1034, 1074, 1110, 997, 979(N—N=N), 899, 855, 838(Ar-H), 815, 789, 684(Ar-H); $^1$H NMR: 8.080–8.132 (d, 1H, $J$ = 15.6 Hz, CH=C—CO), 7.809–7.862(d, 1H, $J$ = 15.6 Hz, C=CH—CO), 7.721–7.434(m, 2H, Ph-3,5), 7.417–7.434(m, 3H, Ph-2,4,6), 7.376–7.405(d, 2H, $J$ = 8.7 Hz, Ar-2,6), 7.339–7.368(d, 2H, $J$ = 8.7 Hz, Ar-3,5), 2.666(s, 3H, TRZ-$CH_3$), 2.479(s, 3H, $CH_3$); MS: 303($M^+$, 5), 274(3), 260(3), 247(31), 194(36), 144(13), 132(98), 115(34), 103(65), 91(100), 77(63.3), 65(78.6), 51(35.3), 39(31.5); Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85; Found: C, 75.53; H, 5.43; N, 13.76.

***(E)-1-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one (2b).*** Yield: 95.2%; white crystals; mp: 123–125°C; IR: 1664(C=O), 1602(C=C), 1554, 1499, 1420, 1276, 1113, 1035, 980 (N—N=N), 765(Ar-H), 687; $^1$H NMR: 8.101–8.154(d, 1H, $J$ = 15.9 Hz, CH=C—CO), 7.907–7.960(d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.726–7.757(m, 2H, Ph-2,6), 7.575–7.610(m, 3H, Ar-3,4,5), 7.476–7.509(m, 2H, Ar-2,6), 7.421–7.438(m, 3H, Ph-3,4,5), 2.691(s, 3H, TRZ-$CH_3$); MS: 289($M^+$, 12), 260(4), 233(24), 180(24), 131(31), 118(59), 103(36), 77(100), 65(5), 51(44), 39(9); Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52; Found: C, 74.89; H, 5.34; N, 14.15.

***(E)-1-[1-(4-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2c).*** Yield: 91.1%; white crystals; mp: 171–173°C; IR: 1665(C=O), 1601(C=C), 1552, 1498, 1427, 1276, 1092, 1032, 990(N—N=N), 844, 776(Ar-H), 733, 690; $^1$H NMR: 8.074–8.126 (d, 1H, $J$ = 15.6 Hz, CH=C—CO), 7.904–7.956 (d, 1H, $J$ = 15.6 Hz, C=CH—CO), 7.718–7.749 (m, 2H, Ph-2,6), 7.565–7.595 (d, 2H, $J$ = 9.0 Hz, Ar-2,6), 7.456–7.474 (m, 2H, Ar-3,5), 7.419–7.442 (m, 3H, Ph-3,4,5), 2.687(s, 3H, TRZ-$CH_3$); MS: 323($M^+$, 21), 294(3), 267(70), 214(47), 152(66), 131(100), 111(62), 103(59), 77(58), 51(28), 39(9); Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98; Found: C, 66.34; H, 4.65; N, 12.79.

***(E)-1-[1-(2,5-Dichlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2d).*** Yield: 92.9%; white crystals; mp: 163–165°C; IR: 1659(C=O), 1600(C=C), 1552, 1486, 1448, 1396, 1357, 1282, 1201, 1096, 1032, 984(N—N=N), 815(Ar-H), 682; $^1$H NMR: 8.075–8.128 (d, 1H, $J$ = 15.9 Hz, CH=C—CO), 7.921–7.974 (d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.718–7.749 (m, 2H, Ph-2,6), 7.595(s, 1H, Ar-6), 7.554–7.567 (m, 2H, Ph-3,5), 7.493–7.497 (m, 1H, Ph-4), 7.417–7.446 (m, 2H, Ar-3,4), 2.562(s, 3H, TRZ-$CH_3$); MS: 357($M^+$, 6), 328(2), 301(11), 248(28), 186(100), 145(45), 131(58), 115(40), 103(82), 77(79), 51(36), 39(20); Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O$: C, 60.35; H, 3.66; N, 11.73; Found: C, 60.54; H, 3.54; N, 11.63.

***(E)-1-[1-(3-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2e).*** Yield: 91.1%; white crystals; mp: 128–130°C; IR: 1663(C=O), 1612(C=C), 1555, 1489, 1447, 1404, 1306, 1281, 1079, 987(N—N=N), 839(Ar-H), 680; $^1$H NMR: 8.078–8.131 (d, 1H, $J$ = 15.9 Hz, CH=C—CO), 7.910–7.963 (d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.725–7.757 (m, 2H, Ph-2,6), 7.538–7.566 (m, 3H, Ar-4,5,6), 7.414–7.446 (m, 4H, Ar-2 and Ph-3,4,5), 2.716(s, 3H, TRZ-$CH_3$); MS: 323($M^+$, 9), 294(3), 267(18), 214(34), 152(100), 131(57), 111(83), 103(67), 77(55), 51(29), 39(14); Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98; Found: C, 66.29; H, 4.39; N, 12.76.

***(E)-1-[1-(2-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2f).*** Yield: 91.2%; white crystals; mp: 116–118°C; IR: 1669(C=O), 1608(C=C), 1553, 1493, 1447, 1393, 1360, 1278, 1200, 1070, 1033, 988(N—N=N), 770; $^1$H NMR: 8.103–8.156(d, 1H, $J$ = 15.9 Hz, CH=C-CO), 7.925–7.978 (d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.735–7.751 (m, 2H, Ph-2,6), 7.429–7.640 (m, 7H, Ar-3,4,5,6 and Ph-3,4,5), 2.554(s, 3H, TRZ-$CH_3$); MS: 323($M^+$,1), 294(3), 267(20), 214(33), 152(100), 131(34), 111(73), 103(65), 77(71), 51(49), 39(24); Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98; Found: C, 66.47; H, 4.56; N, 12.81.

***(E)-1-[1-(4-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2g).*** Yield: 185–187%; white crystals; mp: 185–187°C; IR: 1662(C=O), 1599(C=C), 1551, 1494, 1443, 1402, 1361, 1275, 1196, 1066, 1031, 987(N—N=N), 838(Ar-H), 687; $^1$H NMR: 8.057–8.110(d, 1H, $J$ = 15.9 Hz, CH=C—CO) 7.890–7.943 (d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.708–7.735 (m, 4H, Ar-2,3,5,6), 7.388–7.415 (m, 5H, Ph-2,3,4,5,6), 2.667(s, 3H, TRZ-$CH_3$); MS: 367($M^+$,3), 311(16), 260(24), 217(8), 196(68), 155(56), 131(94), 115(43), 103(100), 77(89), 51(50), 39(25); Anal. Calcd. for $C_{18}H_{14}BrN_3O$: C, 58.71; H, 3.83; N, 11.41; Found: C, 58.47; H, 3.77; N, 11.71.

***(E)-1-[5-Methyl-1-(naphthalene-2-yl)-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2h).*** Yield: 97.7%; white crystals; mp: 178–180°C; IR: 1664(C=O), 1600(C=C), 1556, 1488, 1446, 1421, 1302, 1269, 1206, 1074, 1033, 989(N—N=N), 826(Ar-H), 689; $^1$H NMR: 8.120–8.173 (d, 1H, $J$ = 15.9 Hz, CH=C—CO), 8.023–8.076 d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.919–7.972 (m, 4H, Ar-1,4,5,8), 7.718–7.747 (m, 2H, Ph-2,6), 7.544–7.632 (m, 3H, Ar-3,6,7), 7.409–7.438 (m, 3H, Ph-3,4,5), 2.732(s, 3H, TRZ-$CH_3$); MS: 339($M^+$,1), 310(3), 283(23), 268(3), 251(7), 230(22), 180(27), 168(42), 127(100), 115(20), 103(51), 77(61), 51(24), 39(11); Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38; Found: C, 77.65; H, 5.27; N, 12.46.

***(E)-1-[1-(3-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2i).*** Yield: 89.8%; white crystals; mp: 168–170°C; IR: 1662(C=O), 1599(C=C), 1551, 1494, 1443, 1402, 1361, 1275, 1196, 1066, 1031, 987(N—N=N), 838(Ar-H), 687; $^1$H NMR: 8.078–8.131 (d, 1H, $J$ = 15.9 Hz, CH=C—CO), 7.910–7.963 (d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.725–7.757 (m, 2H, Ph-2,6), 7.538–7.566 (m, 3H, Ar-4,5,6), 7.414–7.446 (m, 4H, Ar-2 and Ph-3,4,5), 2.667(s, 3H, TRZ-$CH_3$); MS: 367($M^+$,2), 311(16), 260(24), 217(8), 196(68), 155(56), 131(94), 115(43), 103(100), 77(89), 51(50), 39(25); Anal. Calcd. for $C_{18}H_{14}BrN_3O$: C, 58.71; H, 3.83; N, 11.41; Found: C, 58.57; H, 3.67; N, 11.86.

***(E)-1-[1-(4-Methoxyphenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-3-phenylprop-2-en-1-one (2j).*** Yield: 92.2%; white crystals; mp: 153–155°C; IR: 1666(C=O), 1604(C=C), 1549, 1511, 1445,

1412, 1363, 1283, 1256, 1036, 987(N—N=N), 837(Ar-H), 627; $^1$H NMR: 8.087–8.140 (d, 1H, $J$ = 15.9 Hz, CH=C—CO), 7.890–7.947 (d, 1H, $J$ = 15.9 Hz, C=CH—CO), 7.696–7.741 (m, 2H, Ph-2,6), 7.370–7.425 (m, 5H, Ar-2,6 and Ph-3,4,5), 7.050–7.091 (m, 2H, Ar-3,5), 2.638(s, 3H, TRZ-$CH_3$); MS: 319($M^+$,1), 290(2), 263(25), 210(19), 188(8), 161(20), 148(58), 131(77), 115(21), 103(69), 77(100), 51(30), 39(18); Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16; Found: C, 71.76; H, 5.54; N, 13.02.

**General procedure for the preparation of 2-amino-6-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4yl)-4-phenylpyridine-3-carbonitrile derivatives (3a–j) [20].** Chalcone **2a–j** (10 mmol), malononitrile (10 mmol, 0.66 g, 1 equiv.), and ammonium acetate (80 mmol, 0.62 g, 8 equiv.) were dissolved in EtOH (10 mL) and refluxed for 15 h, whereupon no starting material was evident by TLC. The reaction mixture was allowed to cool to RT and the solvent was evaporated to leave a yellow solide, dried, and purified by column chromatography using a mixture of EtOAc /petroleum ether 60–90°C 1:4 as eluent to give the corresponding **3a–j.**

***2-Amino-6-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4yl)-4-phenylpyridine-3-carbonitrile (3a).*** Yield: 63.5%; yellow crystals; mp: 168–170°C; IR: 3487, 3368($NH_2$), 2922(—$CH_3$), 2212(-CN), 1731, 1619, 1581, 1562, 1516, 1420, 1258(C—N), 1111, 977(N—N=N), 839(Ar-H), 702; $^1$H NMR: 7.795(s, 1H, Py-), 7.682–7.698 (m, 2H, Ph-2,6), 7.513–7.528 (m, 3H, Ph-3,4,5), 7.392–7.404 (m, 4H, Ar-2,3,5,6), 5.415 (s, 2H, —$NH_2$), 2.712(s, 3H, TRZ-$CH_3$), 2.443(s, 3H, Ar-$CH_3$); MS: 367($M^+$+1). Anal. Calcd. for $C_{22}H_{18}N_6$: C, 72.11; H, 4.95; N, 22.94; Found: C, 72.43; H, 4.83; N, 22.74.

***2-Amino-6-(5-methyl-1-phenyl-1H-1,2,3-triazol-4yl)-4-phenylpyridine-3-carbonitrile (3b).*** Yield: 60.0%; yellow crystals; mp: 80–82°C; IR: 3471, 3355($NH_2$), 2924(—$CH_3$), 2210(-CN), 1709, 1614, 1589, 1558, 1501, 1419, 1264(C—N), 1114, 977(N—N=N), 765(Ar-H), 696; $^1$H NMR: 7.827(s, 1H, Py-), 7.480–7.569(m, 10H, Ar-2,3,4,5,6 and Ph-2,3,4,5,6), 5.299(s, 2H, —$NH_2$), 2.786(s, 3H, TRZ-$CH_3$); MS: 353($M^+$+1). Anal. Calcd. for $C_{21}H_{16}N_6$: C, 71.58; H, 4.58; N, 23.85; Found: C, 71.79; H, 4.69; N, 23.53.

***2-Amino-6-[1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3c).*** Yield: 59.7%; yellow crystals; mp: 192–194°C; IR: 3495, 3369($NH_2$), 2923(—$CH_3$), 2212(-CN), 1730, 1617, 1581, 1560, 1498, 1420, 1259(C-N), 1090, 977(N—N=N), 839(Ar-H), 700; $^1$H NMR: 7.689(s, 1H, Py-), 7.442–7.591 (m, 9H, Ar-2,3,5,6 and Ph-2,3,4,5,6), 5.420(s, 2H, —$NH_2$), 2.726(s, 3H, TRZ-$CH_3$); MS: 387 ($M^+$+1). Anal. Calcd. for $C_{21}H_{15}ClN_6$: C, 65.20; H, 3.91; N, 21.72; Found: C, 65.65; H, 3.75; N, 21.65.

***2-Amino-6-[1-(2,5-dichlorophenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3d).*** Yield: 52.3%; yellow crystals; mp: 94–96°C; IR: 3464, 3353($NH_2$), 2926(—$CH_3$), 2213(—CN), 1710, 1681, 1588, 1562, 1490, 1426, 1264(C—N), 1097, 979(N—N=N), 770(Ar-H), 700; $^1$H NMR: 7.663(s, 1H, Py-), 7.528–7.575 (m, 8H, Ar-3,4 and Ph-2,3,4,5,6), 5.422(s, 2H, —$NH_2$), 2.599(s, 3H, TRZ-$CH_3$); MS: 421($M^+$+1). Anal. Calcd. for $C_{21}H_{14}Cl_2N_6$: C, 59.87; H, 3.35; N, 19.35; Found: C, 59.54; H, 3.54; N, 19.19.

***2-Amino-6-[1-(3-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3e).*** Yield: 58.7%; yellow crystals; mp: 164–166°C; IR: 3436, 3354($NH_2$), 2923(—$CH_3$), 2207(-CN), 1733, 1685, 1586, 1544, 1489, 1427, 1261(C—N), 1082, 982(N—N=N), 782(Ar-H), 699; $^1$H NMR: 7.669(s, 1H, Py-), 7.509–7.591 (m, 9H, Ar-2,4,5,6 and Ph-2,3,4,5,6), 5.434(s, 2H, —$NH_2$), 2.716(s, 3H, TRZ-$CH_3$); MS: 387($M^+$+1). Anal. Calcd. for $C_{21}H_{15}ClN_6$: C, 65.20; H, 3.91; N, 21.72; Found: C, 65.55; H, 3.65; N, 21.59.

***2-Amino-6-[1-(2-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3f).*** Yield: 65.0%; yellow crystals; mp: 98–100°C; IR: 3469, 3354($NH_2$), 2926(—$CH_3$), 2211(—CN), 1710, 1681, 1589, 1544, 1497, 1420, 1262(C-N), 1078, 979(N—N=N), 766(Ar-H), 701; $^1$H NMR: 7.630(s, 1H, Py-), 7.489–7.560(m, 9H, Ar-3,4,5,6 and Ph-2,3,4,5,6), 5.420(s, 2H, —$NH_2$), 2.595(s, 3H, TRZ-$CH_3$); MS: 387($M^+$+1). Anal. Calcd. for $C_{21}H_{15}ClN_6$: C, 65.20; H, 3.91; N, 21.72; Found: C, 65.61; H, 3.55; N, 21.55.

***2-Amino-6-[1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3g).*** Yield: 54.7%; yellow crystals; mp: 215–217°C; IR: 3494, 3370($NH_2$), 2923(—$CH_3$), 2211(-CN), 1730, 1616, 1580, 1542, 1494, 1418, 1258(C—N), 1070, 977(N—N=N), 837(Ar-H), 699; $^1$H NMR: 7.794(s, 1H, Py-), 7.673–7.751 (m, 4H, Ar-3,5 and Ph-2,6), 7.507–7.524 (m, 3H, Ph-3,4,5), 7.378–7.407 (m, 2H, Ar-2,6), 5.426(s, 2H, —$NH_2$), 2.685(s, 3H, TRZ-$CH_3$); MS: 431($M^+$+1). Anal. Calcd. for $C_{21}H_{15}BrN_6$: C, 58.48; H, 3.51; N, 19.49; Found: C, 58.84; H, 3.32; N, 19.28.

***2-Amino-6-[5-methyl-1-(naphthalene-2-yl)-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3h).*** Yield: 56.6%; yellow crystals; mp: 104–106°C; IR: 3464, 3374($NH_2$), 2923(—$CH_3$), 2208(—CN), 1732, 1610, 1587, 1542, 1481, 1418, 1263(C—N), 1113, 976(N—N=N), 859(Ar-H), 701; $^1$H NMR: 7.945–8.040 (m, 6H, Ar-1,4,5,8 and Ph-2,6), 7.685(s, 1H, Py-), 7.517–7.616 (m, 6H, Ar-3,6,7 and Ph-3,4,5), 5.423(s, 2H, —$NH_2$), 2.712(s, 3H, TRZ-$CH_3$). MS: 415($M^+$+1). Anal. Calcd. for $C_{25}H_{18}N_6$: C, 74.61; H, 4.51; N, 20.88; Found: C, 74.86; H, 4.26; N, 20.88.

***2-Amino-6-[1-(3-bromophenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3i).*** Yield: 61.3%; yellow crystals; mp: 105–107°C; IR: 3466, 3354($NH_2$), 2925(—$CH_3$), 2212(-CN), 1710, 1618, 1590, 1561, 1494, 1422, 1264(C—N), 1119, 976(N—N=N), 767(Ar-H), 701; $^1$H NMR: 7.825(s, 1H, Py-), 7.487–7.528 (m, 9H, Ar-2,4,5,6 and Ph-2,3,4,5,6), 5.430(s, 2H, —$NH_2$), 2.642(s, 3H, TRZ-$CH_3$); MS: 431($M^+$+1). Anal. Calcd. for $C_{21}H_{15}BrN_6$: C, 58.48; H, 3.51; N, 19.49; Found: C, 58.74; H, 3.52; N, 19.38.

***2-Amino-6-[1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazol-4yl]-4-phenylpyridine-3-carbonitrile (3j).*** Yield: 57.2%; yellow crystals; mp: 181–183°C; IR: 3449, 3354($NH_2$), 2928(—$CH_3$), 2210(-CN), 1731, 1633, 1584, 1559, 1516, 1423, 1250(C—N), 1112, 979(N—N=N), 839(Ar-H), 697; $^1$H NMR: 7.755(s, 1H, Py-), 7.669–7.700 (m, 2H, Ph-2,6), 7.493–7.513 (m, 3H, Ar-2,6 and Ph-4), 7.370–7.384 (m, 2H, Ph-3,5), 7.057–7.085 (d, 2H, $J$ = 8.4 Hz, Ar-3,5), 5.412(s, 2H, —$NH_2$), 2.565(s, 3H, TRZ-$CH_3$). MS: 383($M^+$+1). Anal. Calcd. for $C_{22}H_{18}N_6O$: C, 69.10; H, 4.74; N, 21.98; Found: C, 69.45; H, 4.56; N, 21.87.

X-ray structure determination of **3j**. Colourless Block, $C_{22}H_{18}N_6O$, Mr = 852.95, Triclinic, space group P-1, a = 10.398 (7), b = 14.925 (10), c = 15.475 (10) Å, $\alpha$ = 115.975 (10), $\beta$ = 94.707 (12), $\gamma$ = 91.049 (11)°, V = 2148 (3) Å$^3$, Z = 2, $D_x$ = 1.319 Mg m$^{-3}$, $F_{000}$ = 896, $\mu$ = 0.09 mm$^{-1}$. Intensity data were collected using a Siemens SMART diffractometer at 293(2) K, graphite monochromator MoK$\alpha$ radiation ($\lambda$ = 0.071073 nm), using the $\omega$-2$\theta$ scan technique to a maximum 1.5–26.5°. A total of 11,896 reflections were collected with 8563 unique ones ($R$ = 0.0732), of which 4049 reflections were observed with $I > 2\sigma(I)$. The final int $R$ and $wR$ values were 0.0732 and 0.1717, $s$ = 0.988,

$(\Delta/\sigma)$ max = 0.000. The maximum peak and minimum peak in the final difference map is 0.20 and -0.32 e $Å^{-3}$.

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## REFERENCES AND NOTES

[1] Yates, F.; Courts, R. T.; Casy, A. F. In Pyridine and Its Derivatives; Suppl IV, ed.; Abramovith, 5R. A., Ed.; Wiley: New York, 1975; p 455.

[2] Yates, F. S. In Comprehensive Heterocyclic Chemistry; Katritzki, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 2, p 511.

[3] (a) Forlano, E. A.; Deferrari, J. O.; Dukat, M. Med Chem Res 1996, 465; (b) McDonlad, I. A.; Cosford, N.; Vemier, J. M. Annu Rep Med Chem 1995, 30, 41.

[4] (a) Schwid, S. R.; Petrie, M. D.; McDermontt, M. P.; Tierney, D. S.; Mason, D. H.; Goodman, A. D. Neurology 1997, 48, 817; (b) Sellin, L. C. Med Biol 1981, 59, 11; (c) Davidson, M.; Zemishlany, J. H.; Brunnemann, R. C.; Bunten, D. C. Am J Ther 2002, 9, 29; (d) Manna, F.; Chimenti, F.; Bolasco, A.; Bizzarri, B.; Filippelli, W.; Gagliardi, L. Eur J Med Chem 1999, 34, 245.

[5] (a) Kempte, R.; Brenner, S.; Arndt, P. Orgamometallics 1996, 15, 1071; (b) Fuhrmann, H.; Brenner, S.; Arndt, P.; Kempe, R. Inorg Chem 1996, 35, 6742.

[6] (a) Henke, B. R.; Drewry, D. H.; Jones, S. A.; Weaver, S. L.; Wiethe, R. W. Bioorg Med Chem Lett 2001, 11, 1939; (b) Hashimoto, S.; Otani, S.; Okamoto, T.; Matsumoto, K. Heterocycles 1988, 27, 319; (c) Kotsuki, H.; Sakai, H.; Shinohara, T. Synlett 2000, 116.

[7] Perron-Sierra, F.; Dizier, S. D.; Bertrand, M.; Genton, A.; Tucker, G. C.; Casasra, P. Bioorg Med Chem Lett 2002, 12, 3291.

[8] (a) Wagaw, S.; Buchwald, S. L. J Org Chem 1996, 61, 7240; (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Verkade, J. G. Org Lett 2000, 2, 1423; (c) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. Org Lett 2003, 5, 815; (d) Viciu, M. S.; Kelly, R. A.; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. Org Lett 2003, 5, 1479; (e) Basu, B.; Mridha, N. K.; Bhuiyan, Md. M. H. Tetrahedron Lett 2002, 43, 7967; (f) Brenner, E.; Schneider, R.; Fort, Y. Tetrahedron 1999, 55, 12829.

[9] Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. Org Lett 2003, 5, 3867.

[10] (a) Leer, M. T. In Organic Reactions; Adams, R. Ed.; Wiley: New York, 1942; Vol. 1, p 91; (b) Tomcufcik, A. S.; Starker, L. N. In the Chemistry of Heterocyclic Compouds, Pyridine and Its Derivatives, Part III; Klingsberg, E., Ed.; Interscience: NY, 1962; p 1; (c) Scriven, E. F. V. In Comprehensive Heterocyclic Chemistry, Part IIA; Boulton, A. J., Mckilop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2, p 165.

[11] Zhang, Z. Y.; Liu, Y.; Yang, S. Y. Pharm Sim 1991, 26, 809 (Chem Abstr 1992, 116, 128807).

[12] Abdou, N. A.; Soliman, I. N.; Sier Abou, A. H. Bull Facpharm (Cair Univ) 1990, 28, 29 (Chem Abstr 1992, 117, 69793).

[13] Srivatava, A. J.; Swarup, S.; Saxena, V. K. J Indian Chem Soc 1991, 68, 103.

[14] Cooper, K.; Steele, J. EP 329,357 (Chem Abstr 1990, 112, 76957).

[15] Raymond, E.; Raymond, S.; Alan, G. S. GB 2,175,301 (Chem Abstr 1987, 107, 134310).

[16] Marchalin, Š.; Baumlová, B.; Baran, P.; Oulyadi, H.; Daich, A. J Org Chem 2006, 71, 9114.

[17] Dong, H.-S.; Cao, Z.-P. Indian J Heterocycl Chem 2008, 17, 295.

[18] Kamalraj, V. R.; Senthil, S.; Kannan, P. J Mol Struct 2008, 892, 210.

[19] Dong, H.-S.; Wang, D.-D.; Jin, C.-Q. J Chin Chem Soc (Taipei) 2005, 52, 1011.

[20] Chang, L. C. W.; von Frijtag Drabbe Kunzel, J. K.; Mulder-Krieger, T.; Westerhout, J.; Brussee, J.; IJzerman, A. P. J Med Chem 2007, 50, 828.

# Nitrone Cycloaddition to Quinones: A Novel Strategy for the Synthesis of Benzisoxazolidenes

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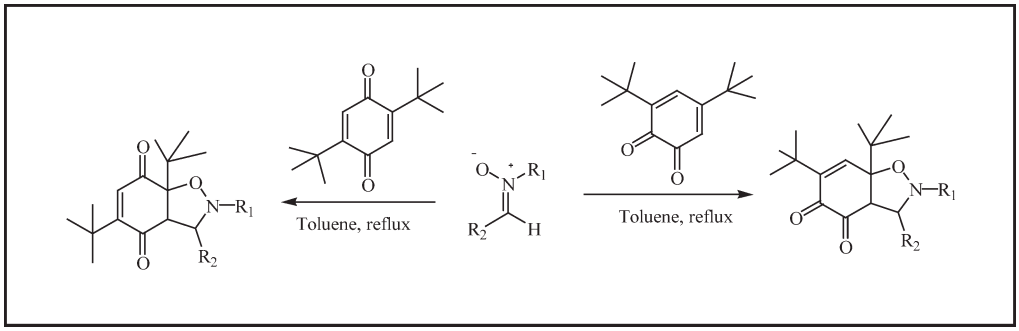


1,3-Dipolar cycloaddition reaction involving nitrones and benzoquinones resulting in the formation of benzisoxazolidene is described. As the nitrone is selectively added to carbon–carbon double bond of the benzoquinone, the quinone-nitrone reaction is considered as a special case among quinone-1,3-dipole cycloaddition reactions. Molecular orbital calculation was performed to examine the electronic effects involved in the regioselectivity of the reaction.

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## INTRODUCTION

The 1,3-dipolar cycloaddition reactions of nitrones with alkenes leading to the formation of isoxazolidenes is a fundamental reaction in organic chemistry [1]. In 1982 Deshong *et al*. reported the first 1,3-dipolar cycloaddition reaction of electron rich alkenes, such as vinyl acetate and vinyl ethers, with nitrones [2]. This work was extended to other functionalized alkenes synthesizing a variety of isoxazolidenes that served as key synthetic intermediates in the synthesis of γ-amino acids, β-lactams, amino sugars, and alkaloids [3]. A variety of isoxazolidines have been prepared using 1,3-dipolar nitrone cycloaddition to functionalized alkenes. In most cases, the nitrone cycloadditions to alkenes proceeded with high regioselectivity to yield isoxazolidenes with three new contiguous stereogenic centers. The stereoselectivity seems to be influenced by both electronic and steric factors. Recently, several asymmetric syntheses of isoxazolidines giving special emphasis on their effective use as chiral auxilaries in the synthesis of biologically active molecules have been reported [3e,4]. Shortly, decades ago itself nitrone cycloaddition chemistry was enriched with versatility of substrates, catalysts, and solvents used in the reaction. Still, organic chemistry demands for new reactions for the synthesis of appropriately substituted isoxazolidenes.

The quinones and their derivatives have attracted the continuous attention in view of their antitumor activitites [5]. The biological processes involved with the antitumor activities of quinones are DNA intercalation, bioreductive alkylation of biomolecules, and generation of oxyradicals through redox cycling. The chemistry of *o*-quinones has invoked considerable interest, and the cycloaddition reactions of these versatile compounds have been the subject of a number of investigations [1,6]. A wide variety of dipolar species, including diazomethane [3], nitrile oxides [7–10], and mesoionic compounds [11–15], have been used in these reactions. Most of the dipolar cycloadditions to quinones, however, involved addition across carbon–oxygen double bonds. In contrast, nitrone cycloaddition occur across carbon–carbon double bond of the *o*-quinones to afford substituted benzisoxazolidenes, and it is the subject matter of present investigations.

## RESULTS AND DISCUSSION

Present studies were initiated by the reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone with 1,2-diphenylnitrone. Preliminary investigations showed that the nitrone cycloaddition to 1,2-benzoquinone occured at carbon–carbon

**Scheme 1**

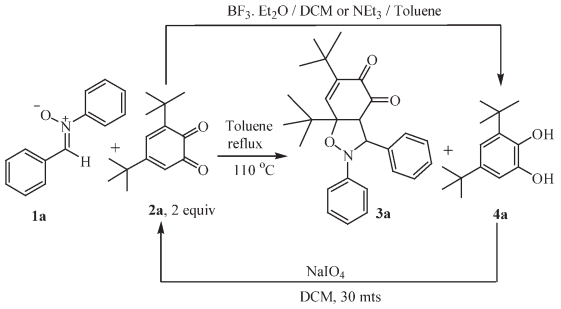


**Table 1**

The reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone **2** with 1,2-diphenylnitrone **1**.

| | | Yield (%) | |
|---|---|---|---|
| Entry | Reaction conditions | **3a** | **4a** |
| 1 | DCM, rt, 48 h | 0 | 0 |
| 2 | DCM, $BF_3.Et_2O$, rt, 1 h | 0 | 12 |
| 3 | DCM, Net3, rt, 1 h | 0 | 48 |
| 4 | Acetonitrile, 70 °C, 18 h | 0 | 7 |
| 5 | Benzene, 70 °C, 18 h | 0 | 0 |
| 6 | Toluene, 110 °C, 18 h, Ar | 15 | 61 |
| 7 | Toluene (excess), 110 °C, 18 h | 32 | 19 |
| [a]8 | Toluene (excess), 110 °C, 18 h | 57 | 23 |
| 9 | Toluene, 110 °C, 48 h | Complex reaction mixture | |
| 10 | Xylene, 140 °C, 2 h | Complex reaction mixture | |

[a] Quinone nitrone = 2:1.

double bond to afford benisoxazolidene **3a**, which is a rare case among the 1,3-dipole-quinone cycloaddition reactions. Then, suitable reaction condition for the proposed cycloaddition was identified by treating 3,5-di-*tert*-butyl-1,2-benzoquinone with 1,2-diphenylnitrone under different conditions (Scheme 1, Table 1). Under most of the reaction conditions, the quinone was easily reduced to corresponding catechol. To our surprise, even under perfectly dry conditions using aprotic solvents like benzene and toluene, the catechol formation dominated over the product formation. Close investigations on the reaction made us to conclude that any proton source including the cycloaddition product facilitate the catechol formation, and so, the yield of the reaction is decreased. At higher temperature, quinone underwent cycloaddition with another molecule of quinone, and the nitrones were fragmented to corresponding amines and aldehydes. However, the expected cycloaddition product was obtained in moderate yield, when a dilute solution of 3,5-di-*tert*-butyl-1,2-benzoquinone and 1,2-diphenyl

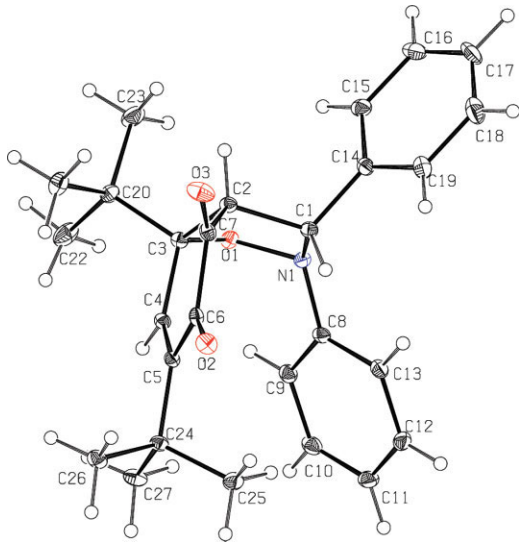


**Figure 1.** Energy level diagram for HOMOnitrone-LUMOquinone interaction. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

nitrone in toluene was refluxed at 110°C for 18 h. The yield was further optimized by screening the number of equivalents of the substrates. Thus, when 3,5-di-*tert*-butyl-1,2-benzoquinone (2 mmol) was treated with 1,2-diphenyl nitrone (1 mmol) in toluene (20 mL) for 18 h at 110°C, bezisoxazolidene **3a** was obtained in 57% yield. The product **3a** was characterized on the basis of common spectroscopic analysis and ultimately by single crystal X-ray analysis (Fig. 1).

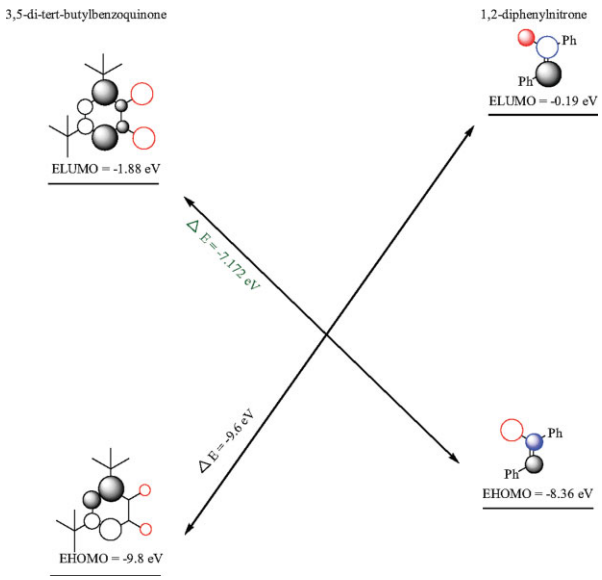


**Figure 2.** ORTEP diagram (40% probability factor for the thermal ellipsoids) of compound 6,7a-di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione **3a.** [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2**

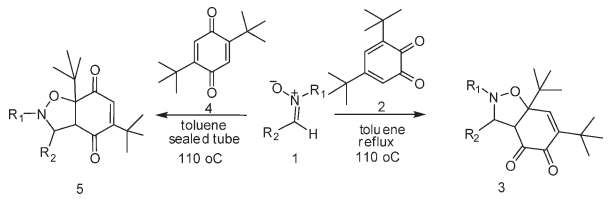


**Table 2**

Synthesis of tetrahydrobenzisoxazolediones **3** and **5**.

| Entry | 3, 5 | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|---|
| 1 | **3a** | $C_6H_5$ | $C_6H_5$ | 57 |
| 2 | **3b** | 4-$CH_3C_6H_5$ | $C_6H_5$ | 72 |
| 3 | **3c** | 4-$ClC_6H_5$ | $C_6H_5$ | 98 |
| 4 | **3d** | 4-$CH_3C_6H_5$ | 4-$CH_3C_6H_5$ | 33 |
| 5 | **3e** | 2-Naphthyl | $C_6H_5$ | 45 |
| 6 | **3f** | 9-Anthracenyl | $C_6H_5$ | 0 |
| 7 | **5a** | $C_6H_5$ | $C_6H_5$ | 22 |
| 8 | **5b** | 4-$CH_3OC_6H_5$ | $C_6H_5$ | 9 |

To explain the mechanism of cycloaddition of nitrone to quinone, we have carried out some MNDO and AM1 calculations on 3,5-di-*tert*-butyl-1,2-benzoquinone and 1,2-diphenyl nitrone using MOPAC (version 5.01) program. The HOMO and LUMO energies were derived from this program. Most of the 1,3-dipolar cycloaddition reactions of *o*-quinones undergo inverse electron demand Diels-Alder reaction (Type II mechanism) [4–13] at carbon–oxygen double bond. The molecular orbital coefficients calculated from the eigen vectors for the orbital interactions of 3,5-di-tert-butyl-1,2-benzoquinone and 1,2-diphenyl nitrone (Fig. 2) favoured the addition of nitrone oxygen to a highly substituted carbon atom to form 6,7a-di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione **3a**, which follows a normal diels-Alder mode of cyclization involving $HOMO_{nitrone}$-$LUMO_{quinone}$ interaction (Type I mechanism).

On extending the strategy to other benzoquinones and diaryl nitrones, tetrahydrobenzisoxazolediones **3a-f** and **5a-b** were synthesized (Scheme 2, Table 2). However, the presence of bulky substituents like anthraceneyl groups on nitrone and diphenylmethane group on quinone adversely affected the product formation.

## CONCLUSION

The reaction of nitrones with benzoquinones resulted in the formation of benzisoxazolidenes. As the nitrone is selectively added to carbon–carbon double bond of the benzoquinone, the quinone–nitrone reaction is considered as a special case among quinone-1,3-dipole cycloaddition reactions.

## EXPERIMENTAL

**General remarks.** Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 MHz ($^1H$) and 75 MHz ($^{13}C$), respectively on a Brüker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported (δ) relative to TMS ($^1H$) and $CDCl_3$ ($^{13}C$) as the internal standards. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. IR spectra were recorded on Nicolet Impact 400D FTIR spectrophotometer. Commercial grade solvents were distilled before use.

**General procedure for the synthesis of 6,7a-di(*tert*-butyl)-2,3-diaryl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-diones (3a-e) and 5,7a-Di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,7-dione (5a-b).** A solution of 3,5-di-*tert*-butyl-1,2-benzoquinone (220 mg, 1 mmol) and 1,2-diaryl nitrone (0.5 mmol) in toluene (10 mL) was refluxed at 110°C for 18 h. The solvent was removed under vacuum, and the crude reaction mixture was purified by silica gel (100-200 mesh) column chromatography using hexane-ethyl acetate (98:2) as the eluent to get the title compounds in good to moderate yields.

**6,7a-Di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3a).** This compound was obtained as yellow crystalline solid; mp: 144–146°C; yield: 119 mg (57%); $^1H$ NMR: δ = 0.82 (s, 9H, $CH_3$), 1.05 (s, 9H, $CH_3$), 3.88 (d, 1H, *J* = 9 Hz, CH), 4.77 (d, 1H, *J* = 9 Hz, CH), 6.78–6.85 (m, 4H, ArH), 7.12–7.19 (m, 3H, ArH), 7.23–7.31 (m, 4H, ArH) ppm; $^{13}C$ NMR: δ = 25.9, 28.1, 35.0, 37.3, 66.5, 71.6, 93.7, 112.6, 121.2, 126.1, 128.3, 128.9, 129.2, 140.0, 147.5, 150.2, 152.3, 181.5, 191.0 ppm; hrms (EI): m/z calcd for $C_{27}H_{31}NO_3$: 417.2304; found: 417.1793; ir (KBr): 3030, 2914, 1663, 1643, 1566 $cm^{-1}$.

**6,7a-Di(*tert*-butyl)-3-(4-methylphenyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3b).** This compound was obtained as yellow crystalline solid, mp: 132–134°C; yield: 155 mg (72%); $^1H$ NMR: δ = 0.89 (s, 9H, $CH_3$), 1.11 (s, 9H, $CH_3$), 2.34 (s, 3H, $CH_3$), 3.93 (d, 1H, *J* = 7.8 Hz, CH), 4.80 (d, 1H, *J* = 7.8 Hz, CH), 6.85 (d, 2H, *J* = 8 Hz, ArH), 6.89 (s, 1H, vinylic), 7.15-7.33 (m, 7H, ArH) ppm; $^{13}C$ NMR: δ = 21.2, 25.8, 28.2, 35.0, 37.3, 67.1, 93.7, 112.8, 125.8, 126.1, 128.1, 129.6, 129.8, 130.8, 136.9, 138.0, 150.1, 152.4, 181.5, 190.9 ppm; hrms (EI): m/z calcd for $C_{28}H_{33}NO_3$: 431.2460; found: 431.2700; ir (KBr): 3029, 2916, 1659, 1645, 1563 $cm^{-1}$.

**3-(4-Chlorophenyl)-6,7a-di(*tert*-butyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3c).** This compound was obtained as yellow crystalline solid, mp: 126–128°C; yield: 221 mg (98%); $^1H$ NMR: δ = 0.88 (s, 9H, $CH_3$), 1.11 (s, 9H, $CH_3$), 3.90 (d, 1H, *J* = 9 Hz, CH), 4.82 (d, 1H, *J* = 9 Hz, CH), 6.81-6.93 (m, 4H, ArH), 7.19–7.26 (m, 2H, ArH), 7.30–7.36 (m, 4H, ArH) ppm; $^{13}C$ NMR: δ = 25.9, 28.2, 35.1, 37.3, 66.2, 93.7, 112.6, 121.4, 127.4, 128.3, 129.0, 129.4, 129.8, 134.3, 138.5, 147.3, 150.3, 152.0, 181.2, 190.7 ppm;

hrms (EI): m/z calcd for $C_{27}H_{30}ClNO_3$: 451.1914; found: 451.0599; ir (KBr): 3026, 2915, 1659, 1643, 1560 $cm^{-1}$.

**6,7a-Di(*tert*-butyl)-2,3-di(4-methylphenyl)-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3d).** This compound was obtained as yellow crystalline solid, mp: 102–104°C; yield: 73 mg (33%); $^1$H NMR: δ = 0.91 (s, 9H, $CH_3$), 0.96 (s, 9H, $CH_3$), 2.26 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 3.92 (d, 1H, $J$ = 9 Hz, CH), 4.77 (d, 1H, $J$ = 9 Hz, CH), 6.75 (d, 2H, $J$ = 9Hz, ArH), 6.86 (s, 1H, vinylic), 7.00 (d, 2H, $J$ = 9Hz, ArH), 7.15 (d, 2H, $J$ = 9Hz, ArH), 7.24 (d, 2H, $J$ = 9Hz, ArH) ppm; $^{13}$C NMR: δ = 21.2, 25.9, 28.2, 30.1, 35.0, 37.4, 71.6, 93.3, 113.0, 119.1, 122.3, 126.1, 126.6, 129.3, 129.9, 130.6, 137.0, 137.9, 147.8, 149.8, 181.5, 191.0 ppm; hrms (EI): m/z calcd for $C_{29}H_{35}NO_3$: 445.5931; found: 445.5021; IR (KBr): 3029, 2914, 1659, 1642, 1561 $cm^{-1}$.

**6,7a-Di(*tert*-butyl)-3-(2-naphthyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3e).** This compound was obtained as yellow crystalline solid, mp: 114–116°C; yield: 105 mg (45%); $^1$H NMR: δ = 0.91 (s, 9H, $CH_3$), 1.14 (s, 9H, $CH_3$), 4.03 (d, 1H, $J$ = 9 Hz, CH), 5.01 (d, 1H, $J$ = 9 Hz, CH), 6.87 (s, 1H, vinylic), 6.90 (d, 2H, $J$ = 9Hz, ArH), 7.21 (t, 3H, $J$ = 9Hz, ArH), 7.46–7.52 (m, 3H, ArH), 7.79–7.90 (m, 4H, ArH) ppm; $^{13}$C NMR: δ = 25.4, 28.3, 35.1, 37.4, 67.0, 93.8, 112.4, 123.1, 124.3, 125.1, 125.9, 127.0, 127.2, 127.8, 128.1, 129.2, 133.4, 137.2, 150.3, 152.3, 181.5, 190.9 ppm; hrms (EI): m/z calcd for $C_{31}H_{33}NO_3$: 467.5987; found: 467.6065; IR (KBr): 3030, 2914, 1660, 1643, 1562 $cm^{-1}$.

**5,7a-Di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,7-dione (5g).** This compound was obtained as yellow crystalline solid, mp: 108–110°C; yield: 46 mg (22%); $^1$H NMR: δ = 1.09 (s, 9H, $CH_3$), 1.27 (s, 9H, $CH_3$), 3.89 (d, 1H, $J$ = 9 Hz, CH), 4.52 (d, 1H, $J$ = 9 Hz, CH), 6.60 (s, 1H, vinylic), 6.88 (d, 2H, $J$ = 9Hz, ArH), 7.12 (t, 3H, $J$ = 9Hz, ArH), 7.25–7.38 (m, 5H, ArH) ppm; $^{13}$C NMR: δ = 26.0, 30.0, 35.5, 36.5, 68.4, 73.8, 92.5, 115.3, 122.0, 127.0, 128.5, 128.5, 129.1, 136.1, 138.9, 149.9, 158.8, 194.7, 199.0 ppm; hrms (FAB): m/z calcd. for $C_{27}H_{31}NO_3$: 417.2304; found: 417.1175; IR (KBr): 3026, 2966, 1651, 1483, 1474, 1438, 796, 686 $cm^{-1}$.

**5,7a-Di(*tert*-butyl)-3-(4-methoxyphenyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,7-dione (5b).** This compound was obtained as yellow crystalline solid, mp: 144–146°C; yield: 20 mg (9%); $^1$H NMR: δ = 1.09 (s, 9H, $CH_3$), 1.26 (s, 9H, $CH_3$), 3.86 (d, 1H, $J$ = 9 Hz, CH), 3.89 (s, 3H, $OCH_3$), 4.52 (d, 1H, $J$ = 9 Hz, CH), 6.59 (s, 1H, vinylic), 6.85–6.90 (m, 3H, ArH), 6.99 (d, 2H, $J$ = 9Hz, ArH), 7.09–7.20 (m, 5H, ArH) ppm; $^{13}$C NMR: δ = 26.3, 33.0, 35.8, 37.5, 55.7, 68.2, 73.6, 92.7, 115.8, 121.0, 127.0, 128.5, 128.5, 129.4, 133.1, 133.9, 149.9, 158.8, 159.3, 194.7, 199.0 ppm; hrms (FAB): m/z calcd for $C_{28}H_{33}NO_4$: 447.2410; found: 447.2292; IR (KBr): 3029, 1844, 1444, 687 $cm^{-1}$.

**3a: X-ray crystallographic data.** Single crystals were grown from $CDCl_3$. Crystal system: triclinic; space group: P-1; $T$ = 100 (2) K; $a$ = 9.8727 (8) A°, $b$ = 10.6520 (8) A°, $c$ = 22.0592 (17) A°, α = 94.8130 (10)°, β = 92.3670 (10)°, γ = 90.1150 (10)°, z = 4, $D_{calcd}$ = 1.201 mg/m$^3$; crystal size 0.66 × 0.45 × 0.12 mm; θ range for data collection 1.85° to 28.27°. Limiting indices −13$h$12, −14$k$13, −29$l$29; reflections collected 20146, independent reflections: 10519. Refinement method: full-matrix least squares on $F^2$; goodness of fit on $F^2$: 1.053; final $R$ indices [I > 2σ (I)] $R_1$ = 0.0623, $wR_2$ = 0.1329; largest difference peak and hole o.422 and −0.224 eA°$^{-3}$. Selected bond lengths (A°) and angles (°): O(1)-C(3): 1.454(2), C(1)-C(2): 1.557(2), O(1)-N(1): 1.4296(18), N(1)-C(1): 1.478(2), C(3)-C(7): 1.506(2), C(3)-C(20): 1.5496(2), C(5)-C(24): 1.532(2), C(1)-C(14): 1.514(2), N(1)-C(8): 1.417(2), O(1)-C(3)-C(4): 106.51(13), O(1)-C(3)-C(2): 102.19(13), C(2)-C(7)-C(6): 116.44(14), C(1)-C(2)-C(7): 111.06(14), N(1)-C(1)-C(2): 104.95(13), O(1)-N(1)-C(1): 107.33(12), C(4)-C(5)-C(24): 123.40(16), C(4)-C(3)-C(20): 113.92(14), O(1)-C(3)-C(20): 106.48(13).

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## REFERENCES AND NOTES

[1] (a) Padwa, A., Ed. 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, 1984; (b) Torssell, K. B. G., Ed. Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis; VCH: Weinheim, 1988.

[2] Deshong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. J Org Chem 1982, 47, 4397.

[3] (a) Asrof Ali, S. K. B.; Khan, J. H.; Wazeer, M. I. M. Tetrahedron 1988, 44, 5911; (b) Hall, A.; Meldrum, K. P.; Therand, P. R.; Wightman, R. H. Synlett 1997, 123; (c) Kametani, T.; Chu, S.-D.; Honda, T. J Chem Soc Perkin Trans I 1988, 1593; (d) Annuziata, R.; Chinquini, M.; Cozzi, F.; Raimondi, L. Tetrahedron 1988, 44, 5911; (e) Gothelf, K. V.; Jorgenson, K. A. Chem Rev 1998, 98, 863; (f) Kobayashi, S.; Jorgensen, K. A., Eds. Cycladdition Reactions in Organic Synthesis; Wiley-VCH: Weinheim, 2001.

[4] (a) Kumar, R. S.; Perumal, S.; Kagan, H. B.; Guillot, R. Tetrahedron Asymmetry 2007, 18, 170; (b) Chow, S. s.; Nevalainen, M.; Evans, C. A.; Johannes, C. W. Tetrahedron Lett 2007, 48, 277; (c) Zagozda, M.; Plenkiewicz J. Tetrahedron Asymmetry 2007, 18, 1457.

[5] Valderrama, J. A.; González, M. F.; Mahana, D. P.; Tapia, R. A.; Fillion, H.; Pautet, F.; Rodriguez, J. A.; Theoduloz, C.; Hirschmann, G. S. Biorg Med Chem 2006, 14, 5003.

[6] Kommissarova, N. L.; Belostotskaya, I. S.; Vol'eva, V. B.; Dzhurayan, E. V.; Novikova, I. A.; Ershov, V. V. Izv Akad Nauk SSSR Ser Khim (Eng Transl) 1981, 22, 2360.

[7] Awad, W. I.; Omran, S. M. A. R.; Sobhy, M. J Org Chem 1966, 31, 331.

[8] Awad, W. I.; Sobhy, M. Can J Chem 1969, 47, 1471.

[9] Nair, V.; Radhakrishnan, K. V.; Nair, A. G.; Bhadbhade, M. M. Tetrahedron Lett 1996, 37, 5623.

[10] Nair, V.; Radhakrishnan, K. V.; Sheela, K. C.; Rath, N. P. Tetrahedron 1999, 55, 14199.

[11] Friedrichsen, W.; Schmidt, R.; van Hummel, G. J.; van den Ham, D. H. W. Justus Liebigs Ann Chem 1981, 3, 521.

[12] Friedrichsen, W.; Kappe, T.; Bottcher, A. Hetrocycles 1982, 19, 1083.

[13] Nair, V.; Nair, J. S.; Vinod, A. U.; Rath, N. P. J Chem Soc Perkin Trans 1 1997, 3129.

[14] Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P. Tetrahedron Lett 2002, 44, 729.

[15] Nair, V.; Sheela, K. C.; Sethumadhavan, D.; Dhanya, R.; Rath, N. P. Tetrahedron 2002, 58, 10341.

# [4+2] Cycloaddition of α,β-Unsaturated Acid Anhydrides to 2-Furylpiperidin-4-ones: The Short Route to Annulated 8,10a-Epoxypyrido[2,1-*a*]isoindoles

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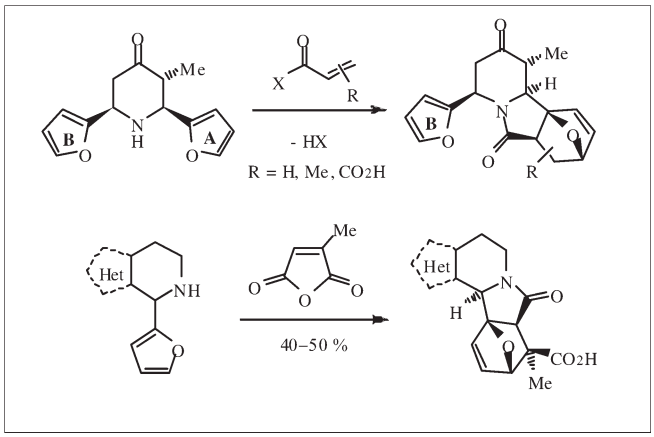


A one-step preparation procedure of 8,10a-epoxypyrido[2,1-*a*]isoindoles and their 7-carboxylic derivatives is reported. The key synthetic step includes the intramolecular *exo*-Diels–Alder reaction (IMDAF) of *N*-furfurylacrylamide, produced *in situ* from 2-furylpiperidin-4-ones and α,β-unsaturated acid anhydrides. The synthesis of the title compounds can be performed under mild conditions with a high level of regio- and stereoselectivity. The same strategy has been successfully used for the synthesis of 9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole-8-carboxylic acid from maleic anhydride and the spinacine derivatives – 4-(2-furyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines.

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## INTRODUCTION

Substituted and hydrogenated pyrido[2,1-*a*]isoindoles possess a wide range of pharmacological activity. For example, they are known to have a protective effect against nitrogen-induced hypoxia [1] and are potential inhibitors of tumor cell proliferation [2]. It is known as well that compounds containing heterocyclic fragments of spinacine and β-carboline are of great biological importance. Thus, the aminoacid spinacine (separated first from shark liver [3], found also in ginseng roots [4] and cheese [5]) shows the properties of an inhibitor of γ-aminobutyric acid uptake in neurons [6]. The heterocyclic structure of β-carboline serves as a framework for well-known alkaloids: *Elaeagnine*, *Harman*, and *Harmine* [7] (Fig. 1).

Therefore, one of the aims of this work was the development of a convenient method of synthesis for potentially biologically active heterocycles—benzo[1,2]indolizino[8,7-*b*]indole and imidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole, combining the above fragments into one structure.

To achieve the aforementioned goal, we used an intramolecular variant of the Diels-Alder reaction in the piperidone series (IMDAF), containing the unsaturated moiety [8–10]. We have used the same strategy before for various preparations of heterocyclics – particularly for isoindolo[2,1-*a*]quinolines [11], isoindolo[2,1-*b*][2]benzazepines [12], and isoindolo[1,2-*a*]isoquinolines [13], with the structure close to natural alkaloids.

## RESULTS AND DISCUSSION

Starting materials for pyrido[2,1-*a*]isoindoles preparation, the furfuryl amines **1**, were synthesized from readily accessible ketones and from furfural (5-methylfurfural), according to the known method [14] with small variations

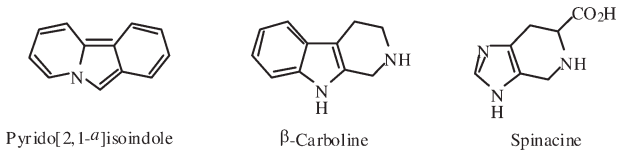



**Figure 1.** Some of the targeted alkaloid-like structures.

(see Experimental section). The piperidones **1a–d** were separated after the recrystallization in moderate yield (Scheme 1) as individual *all-e*-diastereoisomers.

It should be noted that the yields of symmetrically substituted amino ketones **1b**,**d** turned out ~20% higher than for unsymmetric **1a**,**c**.

Interaction of α,β-unsaturated acid derivatives (methacrylic and cinnamic acid chlorides) with symmetric furfuryl amines **1b**,**d** proceeds smoothly in boiling toluene (Scheme 2). It was established during experiment that after initial acylation on the nitrogen atom, a spontaneous intramolecular [4+2] cycloaddition of an unsaturated fragment to the furan ring occurs in intermediate *N*-acryloyl amides. The final products of the reaction are hydrogenated 2*H*-8,10a-epoxypyrido[2,1-*a*]isoindole-2,6(6a*H*)-diones **2**, **3**. The substituent's size in olefin moiety exerts a considerable influence on the yield of adducts **2**, **3**—the yield of 6a-methylsubstituted derivatives **2** is 15–30% higher compared to their more sterically hindered 7-phenyl analogues **3**.

In both cases the Diels-Alder reaction occurs stereoselectively as *exo*-[4+2]-cycloaddition with *endo*-position of methyl (phenyl) group in oxabicyclo[2.2.1]heptene fragment of adducts **2** and **3**. Axial-axial constant of piperidine ring protons $^3J_{1,10b} = 11.8-12.2$ Hz and vicinal constant of bicyclic fragment's low-field protons $^3J_{9,10} = 5.5-6.2$ Hz are most evident in their $^1$H NMR spectra.

Acylation of piperidones **1b**,**d** by citraconic anhydride proceeds in both carbonyl groups, leading to the formation of stereoisomers **4bA**,**4dA/4bB**,**4dB** mixtures with different methyl group positions (see Scheme 2 for the total yield of stereoisomeric mixture). 7-Methylsubstituted isomers **4bA**, **4dA** dominate in crude reaction mixtures; the A/B ratio fluctuates in different experiments and is usually within the 4:1–3:1 interval. Major isomers **4bA**, **4dA** were separated as individual compounds by fractional recrystallization from *i*-PrOH–DMF mixture (their yields are summarized in Experimental section).

Cycloaddition of methacryloyl chloride, crotonyl chloride, and cinnamoyl chloride to unsymmetric difurylpiperidines **1a**,**c** proceeds stereoselectively as well as regioselectively, giving *exo*-products of Diels-Alder **2a**,**c**, **3a**,**c**,**e** with moderate yield (Scheme 3). Citraconic anhydride, being added to piperidones **1a**,**c**, forms diastereomeric mixtures, from which we could separate only major adducts **4aA**, **4cA** after the recrystallization.

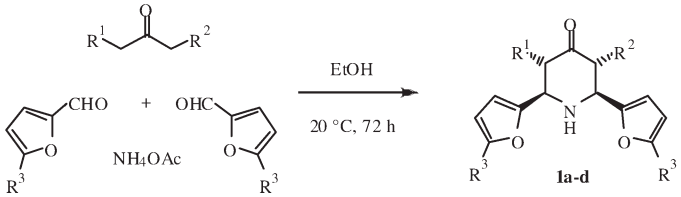
It should be noted if the three-fold excess of dienophile is used in reaction with furfuryl amines **1**, the cycloaddition of a second alkene molecule to the free furan nucleus of isoindoles **2–4** does not occur.

Interestingly enough, from two furan fragments (**X** and **Y**) present in unsymmetrical piperidones **1a**,**c**, [4+2]-cycloaddition passes regiospecifically to 2-furyl ring **Y**. In our opinion, such selectivity is related to the fact that the furan cycle **Y** in intermediate lactam **4*** (Scheme 4) is fixed strictly favorably to the Diels-Alder reaction (due to steric interaction with 3-alkyl substituent). Alternative 6-furyl substituent (**X**) can rotate freely, and is consequently less predisposed to cycloaddition.

Cycloaddition adducts of 2,6-dioxo-8,10a-epoxypyrido[2,1-*a*]isoindole-7-carboxylic acids (**4**) are white powders with low solubility in most organic solvents, so for the unequivocal determination of their spatial structure we have synthesized methyl ester **5** from the acid **4aA** (Scheme 5). Slow recrystallization of this ester from a hexane-ethyl acetate mixture gave us a monocrystal suitable for X-ray analysis.

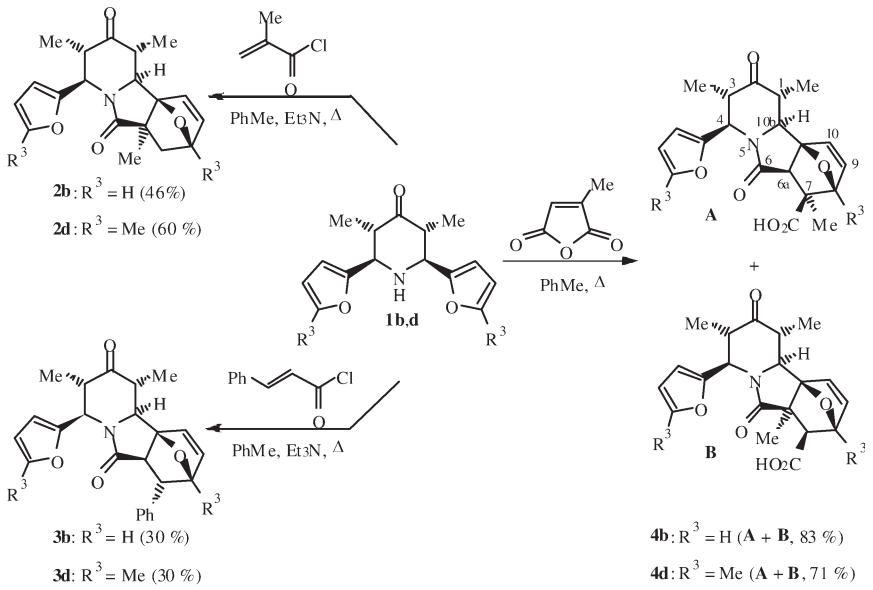
Adduct **5** comprises a fused tetracyclic system containing three five-membered (pyrrolidinone, dihydro- and tetrahydrofurans) rings and one six-membered ring (piperidinone) (Fig. 2). The five-membered rings have the usual *envelope* conformation. The six-membered ring adopts a *twist-boat* conformation (the C3 and C10B carbon atoms are out of the mean plane as defined by the other atoms of the ring by 0.577 and 0.559 Å, respectively). The N5 nitrogen atom has a trigonal-planar geometry (the sum of the bond angles about N5 is 359.5°). The dihedral angle between the planes of the pyrrolidinone and piperidinone rings is 19.1°. The methyl substituent at the C1 carbon atom is in equatorial position, whereas the furyl substituent at the C4 carbon

**Scheme 1.** Synthesis of the initial piperidones **1a-d**.




| Comp. | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| **1a** | H | Me | H | 34 |
| **1b** | Me | Me | H | 63 |
| **1c** | H | Et | H | 33 |
| **1d** | Me | Me | Me | 41 |

**Scheme 2.** Cycloaddition with symmetrical substituted piperidones **1b**,**d**.

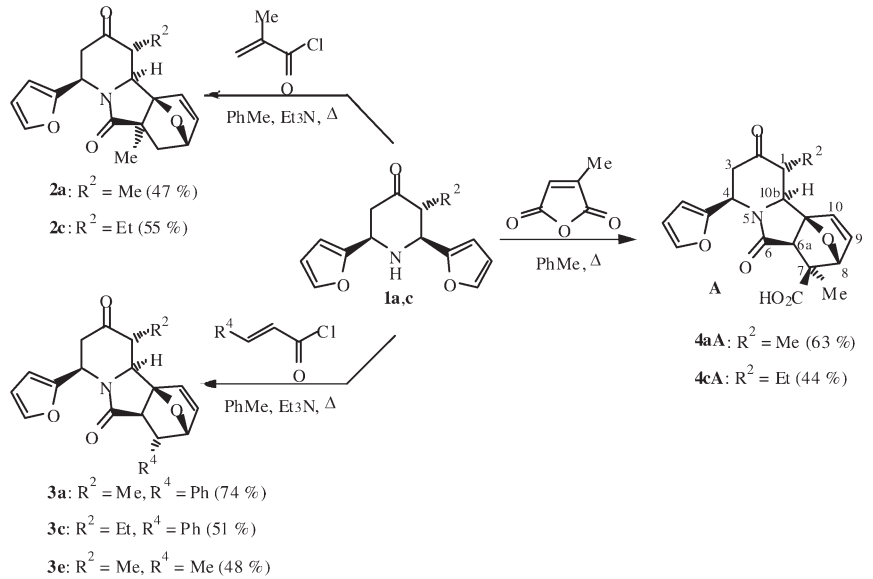



atom is in axial position. The sterically unfavorable axial arrangement of the furyl substituent is apparently explained by both the structure of the initial compound **1a** and the structure of the [4+2] cycloaddition reaction intermediate.

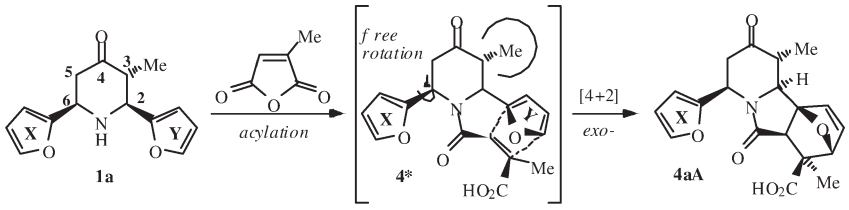
The synthesis of 2,6-unsymmetrically substituted piperidine-4-ones by condensation of α,β-unsaturated ketone, an aldehyde and ammonia was described earlier for the dendrobatid frog alkaloid 241D [15]. In this case the yield of target piperidine-4-ones did not exceed 10−12%. We used this method for the synthesis of 6-aryl-2-furylpiperidine-4-ones **6** (Scheme 6). The reaction conditions were standard [14c,15], and furfural and 5-methylfurfural were used as aldehydes. The usual work-up gives a mixture of products, from which the target piperidones **6** can be separated easily (although with low yield) as hydrochlorides (see Experimental section). 2-Furylpiperidones **6a-c** react smoothly with acryloyl chloride and maleic anhydride in boiling toluene, giving *exo*-products of cycloaddition—2*H*-8,10a-epoxypirido[2,1-*a*]isoindoles (**8**) and their 7-carboxylic acids (**7**)—with moderate yields.

The most low-field chemical shifts of C-2 (δ 208−211 ppm) and C-6 (δ 170−176 ppm) carbon atoms, together with well-identified C-10a and C-8 (δ

**Scheme 3.** Cycloaddition with unsymmetrical substituted piperidones **1a**,**c**.



**Scheme 4.** Mechanistic explanation for the high regioselectivity of Diels-Alder reaction.




79−91 ppm) carbon atom signals are the most characteristic in $^{13}$C NMR spectra of cycloaddition products **2**−**5**, **7**, **8**.

A large number of methods for pentacyclic indolizinoindole core synthesis are known [16], and the similarity of this heterocyclic system to some alkaloids encourages further research. Several short studies [17] dedicated to the synthesis of benzo[1,2]indolizino[8,7-*b*]indol-4-carboxylic acids of type **10** from maleic anhydride and *N*-furfurylidene(indol-3-yl)ethanamines have been published recently. An elegant reaction sequence (acylation/ Pictet-Spengler/ IMDAF) proceeds in mild conditions (Scheme 7). To build some alkaloid-like polycyclic structures by Suzuki coupling, we needed to synthesize 3-halosubstituted adducts **10**.

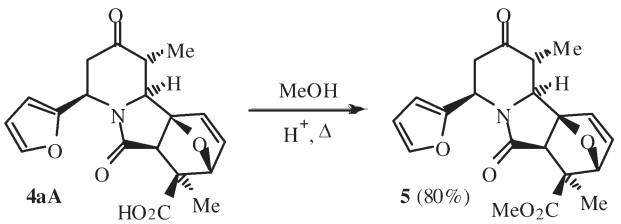
As was shown earlier [17], the condensation of *N*-furfurylidenetriptamines **9a**,**b** with maleic anhydride proceeds stereoselectively, yielding the single *exo*-diastereoisomer **10a**,**b**. Analogous interaction of azomethine **9c** with citraconic anhydride leads with good yield to the mixture of polycycles **12A** and **12B** (in approximatively equal amounts), isomeric by methyl group position, that we could not separate by recrystallization.

Haloderivatives **10a**,**b** are white powders, low soluble even in DMSO, so to determinate their structure by $^{1}$H and $^{13}$C NMR we have synthesized esters **11**. The spatial structure of these latter was established by NOE spectra, in which we can observe a significant change of H-13b proton integral intensity, while irradiating H-4a (and *vice versa*). This fact indicated the spatial closeness (*cis*-orientation) of the above protons.

In the last part of our work we have applied an analogous method for the synthesis of spinacines annelated with epoxyisoindole moiety. The condensation of histamine with aromatic aldehydes in an alkaline medium leading to spinacines (Fig. 1) was already described [18]. However, no examples of 4-furyl substituted imidazo[4,5-*c*]pyridines have been published until now. Furylspinacines **13** were synthesized with moderate yield according to modified method [18b] (Scheme 8).

Acylation of spinacines **13** with maleic anhydride at room temperature occurs exclusively on the *N*-5 nitrogen atom of the tetrahydropyridine ring – products of anhydride addition to imidazole cycle were not found in the reaction mixture. Acylation (same as in previous cases) is accompanied by simultaneous [4+2] cycloaddition giving *exo*-adducts **14**. We suppose the *cis*-position of H-7a and H-11b protons by analogy with adducts **2**-**4**, **7**, **8**, and **10**. Cycloaddition products are extremely hard-soluble and hard-crystallizing tawny powders. The low-field singlet signal of H-2 proton at δ ∼7.5 ppm and broaded one of H-11b at δ ∼5.3 ppm, as well as associated *exo*-protons H-7a, H-8 with $^{3}J_{7a,8}$ = 8.9−9.1 Hz (at δ 2.5−3.0 ppm), can be considered as characteristic. In the carbon spectrum, C-2 and C-11a peaks at δ 135−136 and 90−91 ppm, respectively, are remarkable.

**Scheme 5.** Esterification of the carboxylic acid **4aA**.



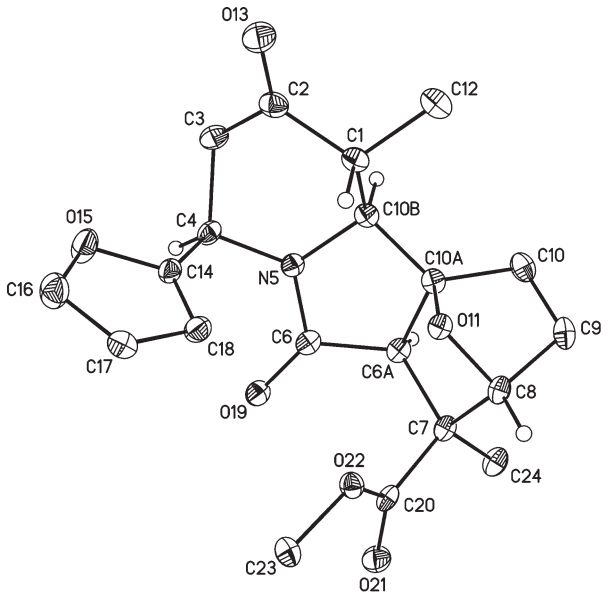
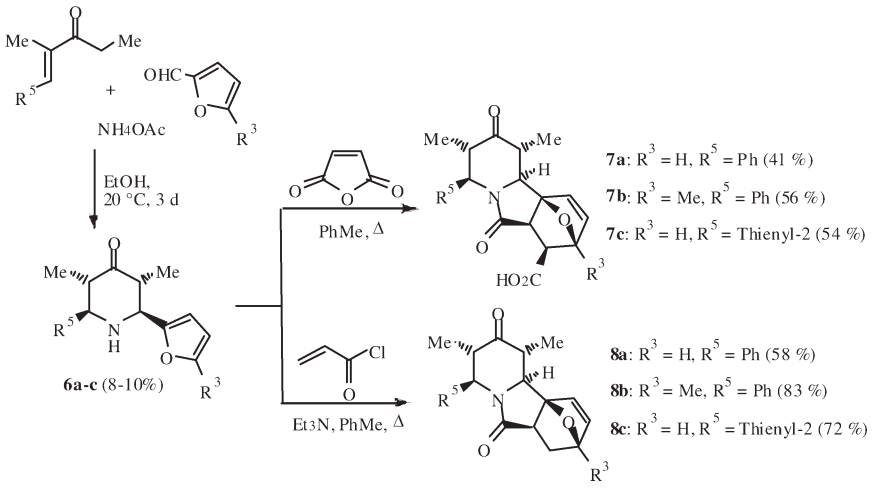




**Figure 2.** Molecular structure of ester **5**, depicting anisotropic displacement ellipsoids at the 50% probability level. Only hydrogen atoms at the asymmetric centers are shown.

**Scheme 6.** Synthesis and [4+2] cycloaddition of 2-aryl-6-furylpiperidine-4-ons **6**.

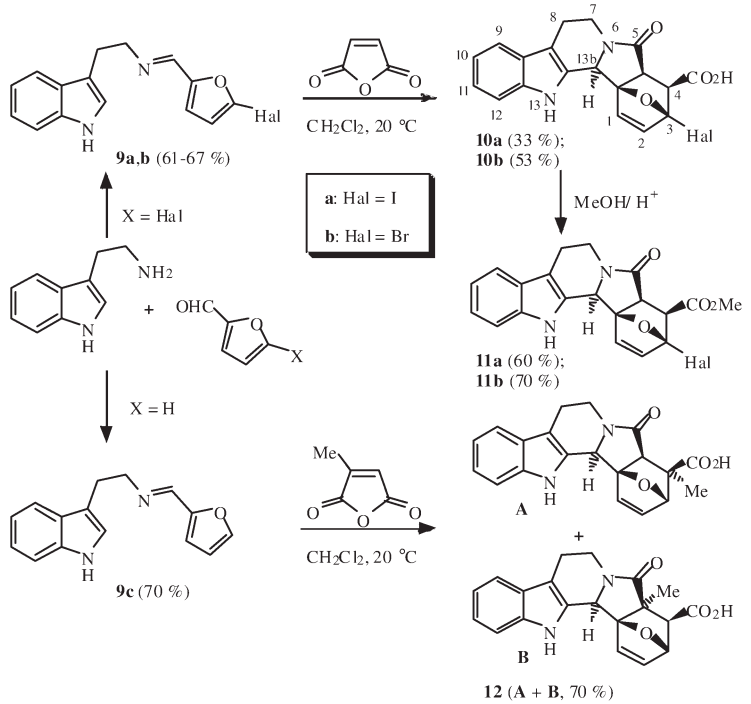



Therefore, in the current study we have demonstrated the possibility of synthesis of various heterocyclic systems condensed with an epoxyisoindole fragment: 8,10a-epoxypyrido[2,1-*a*]isoindoles, 3,13c-epoxybenzo[1,2]indolizino[8,7-*b*]indoles and 9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindoles, based on IMDAF-reaction of annelated furfuryl amines with α,β-unsaturated acid anhydrides. It was shown that in the majority of cases the Diels-Alder reaction proceeds with a high degree of regio- and stereoselectivity as *exo*-[4+2] cycloaddition.

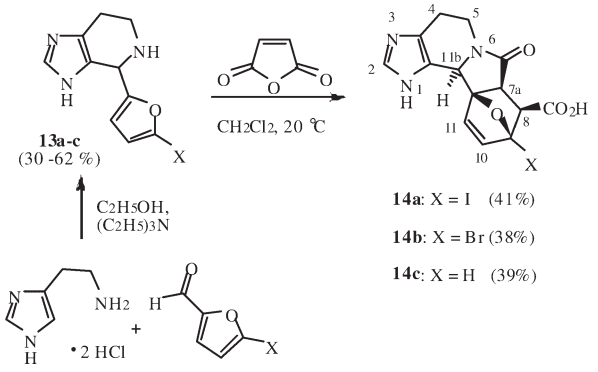
## EXPERIMENTAL

All reagents were purchased from Acros Chemical Co. All solvents were used without further purification. Melting points were determined using SMP10 and are uncorrected. IR spectra were obtained in KBr pellets using an IR-fourier spectrometer Infralum FT-801. $^{1}$H and $^{13}$C NMR spectra were recorded on Jeol JNM-ECA 600 (600 MHz for $^{1}$H and 150.9 MHz for $^{13}$C) or Bruker Uniti + (400 MHz for $^{1}$H and 100.6 MHz for $^{13}$C) spectrometers in $CDCl_3$ or DMSO-$d_6$ at 27°C, and residual signals of chloroform ($^{1}$H NMR δ 7.26 ppm and $^{13}$C NMR 76.9 ppm) or DMSO-$d_5$H ($^{1}$H NMR δ 2.49 ppm and $^{13}$C NMR 39.4 ppm) were used as the internal standard. Mass spectra

**Scheme 7.** Synthesis of 3,13c-epoxybenzo[1,2]indolizino[8,7-*b*]indol-4-carboxylic acids **10-12**.



**Scheme 8.** Synthesis of 9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole-8-carboxylic acids **14a-c**.




were measured either on Thermo Focus DSQ II (electron ionization, 70 eV, ion source temperature 200°C, gas chromatographic inlet with Varian FactorFour VF-5ms column) or on Thermo Trace DSQ (electron ionization, 70 eV, ion source temperature was 200°C, direct inlet probe) spectrometers. Positive-ion electrospray ionization (ESI+) mass spectra were acquired using an API4000 instrument (Applied Biosystems) in the ESI+ mode (sample MeOH-$H_2O$ solution). Nitrogen was used as nebulizer and argon as collision gas, needle voltage was set at 3000 V with ion source at 100°C. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC Sorbfile plates. The separation of the final products was carried out by column chromatography on $Al_2O_3$ (activated, neutral, 50–200 mm) or by fractional crystallization. Microanalyses were performed for C, H, N on a Vario Macro Cube C,H,N,O,S-analyser and were within ±0.4% of theoretical values.

The crystal of ester **5** ($C_{20}H_{21}NO_6$, $M$ = 371.38) is monoclinic, space group $P2_1/c$, at $T$ = 100 K: $a$ = 18.8819(12), $b$ = 8.6778(5), $c$ = 10.7027(7) Å, β = 102.2460(10)°, $V$ = 1713.77(18) Å$^3$, $Z$ = 4, $d_{calc}$ = 1.439 g/cm$^3$, $F(000)$ = 784, μ = 0.107 mm$^{-1}$. 19,911 total reflections (4560 unique reflections, $R_{int}$ = 0.053) were measured on a Bruker SMART APEX II CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, ω and ϕ scan mode, $2\theta_{max}$ = 58°). The structure was determined by direct methods and refined by full-matrix least squares technique on $F^2$ with anisotropic displacement parameters for nonhydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters ($U_{iso}$(H) = 1.5 $U_{eq}$(C) for the $CH_3$-groups and $U_{iso}$(H) = 1.2 $U_{eq}$(C) for the other groups). The final divergence factors were $R_1$ = 0.043 for 3182 independent reflections with $I > 2\sigma$ ($I$) and $wR_2$ = 0.083 for all independent reflections, $S$ = 1.007. All calculations were carried out using the *SHELXTL* program [19]. CCDC No. 741777 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

**General procedure for preparation of piperidones 1a-d.** A solution of corresponding furaldehyde (~25 mL, 0.3 mol) and ammonium acetate (23 g, 0.3 mol) in ethanol (150 mL) was added to a solution of ketone **1a–d** (0.15 mol) in ethanol (50 mL). The resulting clear mixture was allowed to remain at room temperature for 3 d. Then the obtained brown mixture was diluted with diethyl ether (400 mL) and washed with water (3 × 200 mL). The organic layer was separated, dried ($MgSO_4$), filtered, evaporated, and purified by column chromatography on alumina (eluant: hexane) to give corresponding piperidones **2a-d** as white prisms in good to moderate yields.

***(2S*,3R*,6R*)-2,6-Di(2-furyl)-3-methylpiperidin-4-one (1a).*** Yield 34%; mp 63−64°C (hexane-ethyl acetate) lit. [14b]: 40°C; ir: NH 3317, C=O 1706 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $J_{3,Me}$ = 6.5 Hz, 3 H, $CH_3$-3), 2.35 (brs, 1 H, *N*H), 2.71 (dd, $J_{5B,6}$ = 3.0, $^2J_{5,5}$ = 13.6 Hz, 1 H, H-5B), 2.84 (dq, $J_{3,2}$ = 10.7, $J_{3,Me}$ = 6.5 Hz, 1 H, H-3), 2.85 (dd, $J_{5A,6}$ = 12.1, $^2J_{5,5}$ = 13.6 Hz, 1 H, H-5A), 3.80 (d, $J_{2,3}$ = 10.7 Hz, 1 H, H-2), 4.17 (dd, $J_{6,5A}$ = 12.1, $J_{6,5B}$ = 3.0 Hz, 1 H, H-6), 6.21 (brd, $J_{\beta',\beta}$ = 3.2 Hz, 1 H, H-β*)†, 6.29 (dd, $J_{\alpha,\beta}$ = 1.8, $J_{\beta',\beta}$ = 3.2 Hz, 1 H, H-β), 6.32 (m, 2 H, H-β′ and H-β′*), 7.36 (dd, $J_{\beta',\alpha}$ = 0.8, $J_{\alpha,\beta}$ = 1.8 Hz, 1 H, H-α), 7.39 (dd, $J_{\beta',\alpha}$ = 0.6, $J_{\alpha,\beta}$ = 1.8 Hz, 1 H, H-α*); ms (EI, 70 eV): *m/z* 245 (28) [M]$^+$, 175 (3), 174 (10), 150 (2), 146 (2), 136 (5), 123 (14), 122 (31), 108 (10), 95 (30), 94 (100), 93 (97), 79 (31), 66 (40), 65 (35), 56 (23), 40 (12). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.48; H, 6.20; N, 5.93.

***(2R*,3S*,5R*,6S*)-2,6-Di(2-furyl)-3,5-dimethylpiperidin-4-one (1b).*** Yield 63%; mp 73.5–74.5°C (hexane-ethyl acetate) lit. [14b]: 57°C; ir: NH 3315, C=O 1705 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, $J_{Me,3(Me,5)}$ = 6.6 Hz, 6 H, $CH_3$-3 and $CH_3$-5), 2.27 (brs, 1 H, *N*H), 2.95 (dq, $J_{2,3(5,6)}$ = 10.8, $J_{Me,3(Me,5)}$ = 6.6 Hz, 2 H, H-3 and H-5), 3.76 (d, $J_{2,3(5,6)}$ = 10.8 Hz, 2 H, H-2 and H-6), 6.27 (dd, $J_{\alpha,\beta'}$ = 0.8, $J_{\beta',\beta}$ = 3.2 Hz, 2 H, H-β′), 6.31 (dd, $J_{\alpha,\beta}$ = 1.8, $J_{\beta',\beta}$ = 3.2 Hz, 2 H, H-β), 7.38 (dd, $J_{\beta',\alpha}$ = 0.8, $J_{\alpha,\beta}$ = 1.8 Hz, 2 H, H-α); ms (EI, 70 eV): *m/z* (%) 259 (13) [M]$^+$, 174 (14), 146 (3), 136 (29), 123 (23), 108 (100), 96 (16), 80 (16), 79 (54), 77 (27), 55 (14), 53 (15), 39 (42). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.30; H, 6.51; N, 5.61.

***(2S*,3R*,6R*)-3-Ethyl-2,6-di(2-furyl)piperidin-4-one (1c).*** Yield 33%; mp 45–47°C (hexane-ethylacetate) lit. [14b]: 47°C; ir: NH 3316, CO 1707 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, $J_{CH2,Me}$ = 7.0 Hz, 3 H, $CH_3$), 1.28 (m, 1 H, $CH_2$ACH$_3$), 1.60 (m, 1 H, $CH_2$BCH$_3$), 2.31 (brs, 1 H, *NH*), 2.70 (dd, $J_{5B,6}$ = 2.5, $^2J_{5,5}$ = 13.0 Hz, 1 H, H-5B), 2.73 (m, 1 H, H-3), 2.84 (dd, $^2J_{5,5}$ = $J_{5A,6}$ = 13.0 Hz, 1 H, H-5A), 3.91 (d, $J_{2,3}$ = 10.9 Hz, 1 H, H-2), 4.15 (dd, $J_{6,5B}$ = 2.5, $J_{6,5A}$ = 13.0 Hz, 1 H, H-6), 6.21 (brd, $J_{\beta',\beta}$ = 3.1 Hz, 1 H, H-β′), 6.31 (m, 3 H, H-β, H-β*, H-β′*), 7.35 (brd, $J_{\alpha,\beta}$ = 1.6 Hz, 1 H, H-α), 7.39 (brd, $J_{\alpha,\beta}$ = 1.6 Hz, 1 H, H-α*); ms (EI, 70 eV): *m/z* (%) 259 (15) [M]$^+$, 174 (10), 149 (3), 137 (9), 122 (21), 107 (6), 96 (14), 94 (100), 77 (8), 65 (10), 55 (14), 39 (27). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.39; H, 6.55; N, 5.45.

***(2R*,3S*,5R*,6S*)-3,5-Dimethyl-2,6-bis(5-methyl-2-furyl)-piperidin-4-one (1d).*** Yield 41%; mp 85–86°C (hexane-ethyl acetate); ir: NH 3282, C=O 1704 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $J_{Me,3(Me,5)}$ = 6.5 Hz, 6 H, $CH_3$-3 and $CH_3$-5), 2.27 (d, $J_{Me,\beta'}$ = 0.6 Hz, 6 H, $CH_3$-Fur and $CH_3$-Fur*), 2.75 (brs, 1 H, *N*H), 2.90 (dq, $J_{3,2\ (5,6)}$ = 10.8 Hz, $J_{Me,3(Me,5)}$ = 6.5 Hz, 2 H, H-3 and H-5), 3.66 (d, $J_{3,2(5,6)}$ = 10.8 Hz, 2 H, H-2 and H-6), 5.88 (dq, $J_{Me,\beta'}$ = 0.6, $J_{\beta',\beta}$ = 3.0 Hz, 2 H, H-β′ and H-β′*), 6.12 (brd, $J_{\beta',\beta}$ = 3.0 Hz, 2 H, H-β and H-β*); ms (EI, 70 eV): *m/z* (%) 287 (35) [M]$^+$, 244 (5),

† α*, β* and β′*—the protons of the second furan ring.

202 (20), 150 (40), 137 (13), 122 (100), 110 (20), 101 (8), 79 (7), 77 (6), 43 (7). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.98; H, 7.50; N, 4.75.

**General procedure for preparation of 6a-methylepoxypyrido[2,1-*a*]isoindolones 2a-d.** A mixture of corresponding piperidone **1a-d** (4.0 mmol), methacryloyl chloride (0.6 mL, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in toluene (25 mL) was refluxed for 4 h. The reaction progress was monitored by TLC (until disappearance of the starting compound's spot). At the end of the reaction the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ~6 and organic substances extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude products. Further crystallization from hexane-ethyl acetate gave corresponding compounds **2a-d** as white needles.

***(1R*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1,6a-dimethyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2a).*** Yield 47%; mp 136–138°C (hexane-ethyl acetate); ir: NH 3282, C=O 1724, N–C=O 1695 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): δ = 1.09 (brs, 3 H, $CH_3$-6a), 1.11 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, $CH_3$-1), 1.12 (d, $J_{7endo,7exo}$ = 11.8 Hz, 1 H, H-7*endo*), 2.45 (dd, $J_{7exo,8}$ = 4.8, $J_{7exo,7endo}$ = 11.8 Hz, 1 H, H-7*exo*), 2.91 (dq, $J_{1,10b}$ = 11.9, $J_{1,Me\text{-}1}$ = 6.8 Hz, 1 H, H-1), 2.91 (dd, $J_{3B,4}$ = 6.2, $^2J_{3,3}$ = 17.2 Hz, 1 H, H-3B), 2.99 (dd, $J_{3A,4}$ = 2.1, $^2J_{3,3}$ = 17.2 Hz, 1 H, H-3A), 4.20 (d, $J_{10b,1}$ = 11.9 Hz, 1 H, H-10b), 5.00 (dd, $J_{8,9}$ = 1.7, $J_{8,7exo}$ = 4.8 Hz, 1 H, H-8), 5.32 (brdd, $J_{4,3B}$ = 2.1, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.20 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.25 (dd, $J_{3',5'}$ = 0.7, $J_{3',4'}$ = 3.2 Hz, 1 H, H-3′), 6.33 (d, $J_{10,9}$ = 5.8 Hz, 1 H, H-10), 6.43 (dd, $J_{9,8}$ = 1.7 Hz, $J_{9,10}$ = 5.8 Hz, 1 H, H-9), 7.23 (dd, $J_{5',3'}$ = 0.7, $J_{5',4'}$ = 1.8 Hz, 1 H, H-5′); $^{13}C$ nmr (100.6 MHz, $CDCl_3$): δ = 208.1 ($C_2$), 177.1 ($C_6$), 152.6 ($C_{2'}$), 142.1 ($C_{5'}$), 137.0 and 131.6 ($C_9$ and $C_{10}$), 110.4 and 107.7 ($C_{3'}$ and $C_{4'}$), 92.7 ($C_{10a}$), 78.6 ($C_8$), 57.9 ($C_4$), 52.7 ($C_{6a}$), 46.2 and 44.3 ($C_1$ and $C_{10b}$), 41.8 ($C_3$), 36.6 ($C_7$), 20.0 ($CH_3$-6a), 10.3 ($CH_3$-1); ms (EI, 70 eV): *m*/*z* (%) 313 [$M^+$] (22), 228 (20), 176 (9), 162 (12), 149 (19), 121 (10), 108 (38), 94 (52), 69 (48), 66 (26), 41 (100). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.21; N, 4.51.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1,3,6a-trimethyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2b).*** Yield 46%; mp 134–136°C (hexane-ethyl acetate); ir: C=O 1717, N–C=O 1678 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3 H, $CH_3$-6a), 1.14 (d, *J* = 6.6 Hz, 3 H, $CH_3$-1), 1.18 (d, $J_{7exo,7endo}$ = 11.7 Hz, 1 H, H-7*exo*), 1.39 (d, $J_{3,Me\text{-}3}$ = 7.6 Hz, 3 H, $CH_3$-3), 2.51 (dd, $J_{7exo,8}$ = 4.8, $J_{7exo,7endo}$ = 11.7 Hz, 1 H, H-7*exo*), 3.00 (dq, $J_{1,Me\text{-}1}$ = 6.6, $J_{1,10b}$ = 12.0 Hz, 1 H, H-1), 3.10 (dq, $J_{3,Me\text{-}3}$ = 7.6, $J_{3,4}$ = 2.0 Hz, 1 H, H-3), 4.21 (d, $J_{10b,1}$ = 12.0 Hz, 1 H, H-10b), 5.03 (dd, $J_{4,3'}$ = 0.6, $J_{4,3}$ = 2.0 Hz, 1 H, H-4), 5.07 (dd, $J_{8,9}$ = 1.7, $J_{8,7exo}$ = 4.8 Hz, 1 H, H-8), 6.25 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.32 (dt, $J_{3',5'}$ = $^4J_{4,3'}$ = 0.6, $J_{3',4'}$ = 3.2 Hz, 1 H, H-3′), 6.40 (d, $J_{10,9}$ = 5.9 Hz, 1 H, H-10), 6.49 (dd, $J_{9,8}$ = 1.8, $J_{9,10}$ = 5.9 Hz, 1 H, H-9), 7.28 (dd, $J_{5',3'}$ = 0.6, $J_{5',4'}$ = 1.8 Hz, 1 H, H-5′); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 210.6 ($C_2$), 178.0 ($C_6$), 152.5 ($C_{2'}$), 142.0 ($C_{5'}$), 136.9 and 131.5 ($C_9$ and $C_{10}$), 110.3 and 107.6 ($C_{3'}$ and $C_{4'}$), 93.0 ($C_{10a}$), 78.7 ($C_8$), 57.6 ($C_4$), 52.8 ($C_{6a}$), 52.6 ($C_{10b}$), 46.4 and 43.8 ($C_1$ and $C_3$), 36.6 ($C_7$), 20.0 ($CH_3$-6a), 17.5 ($CH_3$-3), 10.3 ($CH_3$-1); ms (EI, 70 eV): *m*/*z* (%) 327 [$M^+$] (86), 312 (13), 242 (85), 176 (100), 163 (90), 148 (38), 108 (74), 79 (43), 69 (46). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 4.28; N, 6.47. Found: C, 69.42; H, 4.32; N, 6.73.

***(1R*,4R*,6aR*,8S*,10aS*,10bS*)-1-Ethyl-4-(2-furyl)-1,3,4,7,8,10b-hexahydro-6a-methyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2c).*** Yield 55%; mp 140°C (hexane-ethyl acetate); ir: C=O 1720, N–C=O 1698 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): δ = 0.93 (t, $J_{CH2,Me}$ = 7.3 Hz, 1 H, $CH_2CH_3$), 1.12 (s, 3 H, $CH_3$-6a), 1.14 (d, $J_{7endo,7exo}$ = 12.1 Hz, 1 H, H-7*endo*), 1.58 (m, 1 H, $CH_{2(B)}CH_3$), 1.93 (m, 1 H, $CH_{2(A)}CH_3$), 2.47 (dd, $J_{7exo,8}$ = 5.0, $^2J_{7exo,7endo}$ = 12.1 Hz, 1 H, H-7*exo*), 2.89 (dd, $J_{3B,4}$ = 6.2, $^2J_{3,3}$ = 17.0 Hz, 1 H, H-3B), 2.89 (m, 1 H, H-1), 3.00 (brd, $^2J_{3,3}$ = 17.0 Hz, 1 H, H-3A), 4.46 (d, $J_{10b,1}$ = 12.1 Hz, 1 H, H-10b), 5.02 (brd, $J_{8,7exo}$ = 5.0 Hz, 1 H, H-8), 5.30 (brd, $J_{3B,4}$ = 6.2 Hz, 1 H, H-4), 6.23–6.25 (m, 2 H, H-3′ and H-4′), 6.41 (d, $J_{10,9}$ = 6.0 Hz, 1 H, H-10), 6.45 (brd, $J_{9,10}$ = 6.0 Hz, 1 H, H-9), 7,25 (brd, $J_{4',5'}$ =1.6 Hz, 1 H, H-5′); $^{13}C$ nmr (100.6 MHz, $CDCl_3$): δ = 207.9 ($C_2$), 177.1 ($C_6$), 152.6 ($C_{2'}$), 142.2 ($C_{5'}$), 137.2 ($C_{10}$), 131.3 ($C_9$), 110.4 and 107.6 ($C_{3'}$ and $C_{4'}$), 92.6 ($C_{10a}$), 78.7 ($C_8$), 55.0, 49.6, 46.29 ($C_1$, $C_{10b}$, and $C_4$), 52.8 ($C_{6a}$), 42.9 ($C_3$), 36.6 ($C_7$), 20.1 ($CH_3$-6a), 18.4 ($CH_2CH_3$), 10.4 ($CH_2CH_3$); ms (EI, 70 eV): *m*/*z* (%) 327 [$M^+$] (100), 300 (12), 256 (15), 242 (25), 162 (31), 148 (63), 122 (40), 94 (56), 67 (42), 41 (49). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; N, 6.47; H, 4.28. Found: C, 69.51; N, 6.59; H, 4.62.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-4-(5-Methyl-2-furyl)-1,3,4,7,8,10b-hexahydro-1,3,6a,8-tetramethyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2d).*** Yield 60%; mp 182°C (hexane-ethyl acetate); ir: C=O 1713, N–C=O 1688 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, $CH_3$-6a), 1.05 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, $CH_3$-1), 1.19 (d, $^2J_{7exo,7endo}$ = 12.1 Hz, 1 H, H-7*exo*), 1.31 (d, $J_{3,Me\text{-}3}$ = 7.7 Hz, 3 H, $CH_3$-3), 1.56 (s, 3 H, $CH_3$-8), 2.13 (s, 3 H, $CH_3$-5′), 2.17 (d, $^2J_{7endo,7exo}$ = 12.1 Hz, 1 H, H-7*endo*), 2.90 (dq, $J_{1,Me\text{-}1}$ = 6.8, $J_{1,10b}$ = 12.2 Hz, 1 H, H-1), 3.03 (dq, $J_{3,Me\text{-}3}$ = 7.7, $J_{3,4}$ = 1.0 Hz, 1 H, H-3), 4.06 (d, $J_{10b,1}$ = 12.2 Hz, 1 H, H-10b), 4.93 (brs, 1 H, H-4), 5.74 (brd, $J_{4',3'}$ = 2.9 Hz, 1 H, H-4′), 6.10 (brd, $J_{3',4'}$ = 2.9 Hz, 1 H, H-3′), 6.22 (d, $J_{9,10}$ = 6.1 Hz, 1 H, H-10), 6.30 (d, $J_{9,10}$ = 6.1 Hz, 1 H, H-9); $^{13}C$ NMR (150.9 MHz, $CDCl_3$): δ = 211.2 ($C_2$), 178.3 ($C_6$), 151.6 and 150.7 ($C_{2'}$ and $C_{5'}$), 140.1 ($C_9$), 132.1 ($C_{10}$), 107.9 ($C_{3'}$), 106.3 ($C_{4'}$), 86.8 (2C, $C_{10a}$ and $C_8$), 57.6, 56.0 and 52.5 ($C_{6a}$, $C_{10b}$, and $C_4$), 46.7, 43.8 and 42.9 ($C_1$, $C_3$, and $C_7$), 19.8, 19.1 and 17.7 ($CH_3$-5′, $CH_3$-6a and $CH_3$-8), 13.5 ($CH_3$-3), 10.3 ($CH_3$-1); ms (EI, 70 eV): *m*/*z* (%) 355 [$M^+$] (67), 270 (86), 242 (9), 190 (100), 162 (29), 149 (36), 122 (95), 107 (30), 93 (14), 79 (39), 69 (22), 41 (66). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 3.94; N, 7.09. Found: C, 70.88; H, 3.89; N, 7.13.

**General procedure for preparation of 7-phenylepoxypyrido[2,1-*a*]isoindolones 3a-d.** A mixture of corresponding piperidone **1a-d** (4.0 mmol), cinnamoyl chloride (1.0 g, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in toluene (25 mL) was refluxed for 5–6 h. The reaction progress was monitored by TLC (until disappearance of the starting compound's spot). At the end of the reaction the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ~6 and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude products. Further crystallization from hexane-ethyl

acetate gave corresponding compounds **3a–d** as colourless needles.

***(1R*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1-methyl-7-phenyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3a).*** Yield 74%; mp 137−138°C (hexane-ethyl acetate); ir: C=O 1724, N─C=O 1692 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, $CH_3$-1), 2.83 (d, $J_{6a,7}$ = 4.4 Hz, 1 H, H-6a), 2.97 (dd, $J_{3A,4}$ = 5.6, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3A), 2.99 (dq, $J_{1,Me\text{-}1}$ = 6.9, $J_{1,10b}$ = 11.8 Hz, 1 H, H-1), 3.02 (dd, $J_{3B,4}$ = 2.5, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3B), 3.84 (t, $J_{7exo,8} = J_{6a,7}$ = 4.4 Hz, 1 H, H-7*exo*), 4.37 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.25 (dd, $J_{8,9}$ = 1.9, $J_{8,7exo}$ = 4.4 Hz, 1H, H-8), 5.39 (dd, $J_{4,3B}$ = 2.5, $J_{4,3A}$ = 5.6 Hz, 1 H, H-4), 6.29 (dd, $J_{4',5'}$ = 1.9, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.34 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.30 (dd, $J_{9,8}$ = 1.9, $J_{9,10}$ = 6.2 Hz, 1 H, H-9), 6.57 (d, $J_{10,9}$ = 6.2 Hz, 1 H, H-10), 7.29–7.15 (m, 6H, H-Ph, and H-5′); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 207.8 ($C_2$), 172.9 ($C_6$), 152.5 ($C_{2'}$), 142.1 ($C_{5'}$), 138.8 ($C_{1''}$), 135.4 and 134.0 ($C_9$ and $C_{10}$), 128.3 and 127.8 (each by 2C, $C_{2''}$, and $C_{6''}$, $C_{3''}$ and $C_{5''}$), 126.8 ($C_{4''}$), 110.3 and 107.5 ($C_{3'}$ and $C_{4'}$), 91.9 ($C_{10a}$), 82.3 ($C_8$), 59.2 and 55.6 ($C_{10b}$ and $C_4$), 47.4, 46.2 and 44.3 ($C_1$, $C_{6a}$, and $C_7$), 41.8 ($C_3$), 10.2 ($CH_3$-1); ms (EI, 70 eV): *m*/*z* (%) 375 [$M^+$] (9), 307 (2), 245 (5), 238 (13), 228 (50), 224 (11), 210 (5), 169 (5), 162 (12), 148 (17), 131 (81), 108 (59), 103 (86), 94 (100), 77 (79), 66 (41), 65 (26), 55 (14), 39 (23). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.73; H, 5.37; N, 4.04.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1,3-dimethyl-7-phenyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3b).*** Yield 30%; mp 153−155°C (hexane-ethyl acetate); ir: C=O 1724, N─C=O 1683 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, $J_{3,Me\text{-}3}$ = 6.9 Hz, 3 H, $CH_3$-3), 1.35 (d, $J_{1,Me\text{-}1}$ = 7.5 Hz, 3 H, $CH_3$-1), 2.83 (d, $J_{6a,7}$ = 4.4 Hz, 1 H, H-6a), 3.11−2.96 (m, 2 H, H-1 and H-3), 3.85 (t, $J_{7,6a} = J_{7,8}$ = 4.4 Hz, H-7), 4.30 (d, $J_{1,10b}$ = 12.5 Hz, H-10b), 5.00 (d, $J_{3,4}$ = 2.5 Hz, 1 H, H-4), 5.26 (dd, $J_{8,9}$ = 1.3, $J_{8,7}$ = 4.4 Hz, 1 H, H-8), 6.28 (dd, $J_{9,8}$ = 1.3, $J_{9,10}$ = 6.2 Hz, 1 H, H-9), 6.27 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.56 (d, $J_{10,9}$ = 6.2 Hz, 1 H, H-10), 7.30–7.13 (m, 5 H, H-Ph), 7.30 (brd, $J_{4',5'}$ = 1.8 Hz, H-5′); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 210.3 ($C_2$), 173.8 ($C_6$), 152.3 ($C_{2'}$), 142.1 ($C_{5'}$), 138.8 ($C_{1''}$), 135.5 and 134.0 ($C_9$ and $C_{10}$), 128.4 and 127.9 (each by 2C, $C_{2''}$ and $C_{6''}$, $C_{3''}$, and $C_{5''}$), 126.8 ($C_{4''}$), 110.3 and 107.7 ($C_{3'}$ and $C_{4'}$), 92.1 ($C_{10a}$), 82.4 ($C_8$), 59.4, 55.6, 53.0, 47.6, 46.5 and 43.9 ($C_{10b}$, $C_4$, $C_1$, $C_{6a}$, $C_7$, and $C_3$), 17.0 ($CH_3$-3), 10.2 ($CH_3$-1); ms (EI, 70 eV): *m*/*z* (%) 389 [$M^+$] (21), 281 (8), 256 (19), 242 (75), 238 (11), 207 (9), 191 (6), 174 (12), 162 (45), 146 (18), 131 (85), 108 (100), 103 (97), 94 (18), 77 (84), 75 (84), 65 (16). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.76; H, 5.88; N, 3.37.

***(1R*,4R*,6aR*,7S*,8S*,10aS*,10bS*)-1-Ethyl-4-(2-furyl)-7-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3c).*** Yield 51%; mp 140°C (hexane-ethyl acetate); ir: C=O 1715, N─C=O 1689 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, $J_{CH2,Me}$ = 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 1.62 (m, 1 H, $CH\underline{H_B}CH_3$), 1.97 (m, 1 H, $C\underline{H_A}HCH_3$), 2.81 (d, $J_{6a,7}$ = 4.4 Hz, 1 H, H-6a), 2.90 (dd, $J_{3A,4}$ = 1.8, $^2J_{3A,3B}$ = 16.2 Hz, 1 H, H-3A), 2.91 (m, 1 H, H-1), 2.91 (dd, $J_{3B,4}$ = 6.2, $^2J_{3B,3A}$ = 16.2 Hz, 1 H, H-3B), 3.82 (t, $J_{7,6a} = J_{7,8}$ = 4.4 Hz, 1 H, H-7), 4.61 (d, $J_{1,10b}$ = 11.8 Hz, 1 H, H-10b), 5.24 (dd, $J_{8,9}$ = 1.8, $J_{7,8}$ = 4.4 Hz, 1 H, H-8), 5.35 (dd, $J_{4,3A}$ = 1.8, $J_{4,3B}$ = 6.2 Hz, 1 H, H-4), 6.26 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.29 (dd, $J_{9,8}$ = 1.8, $J_{9,10}$ = 6.2 Hz, 1 H, H-9), 6.30 (dd, $J_{3',5'}$ = 0.7, $J_{3',4'}$ = 3.2 Hz, 1 H, H-3′), 6.59 (d, $J_{10,9}$ = 6.2 Hz, 1 H, H-10), 7.26–7.14 (m, 5 H, H″-Ph), 7.28 (brd, $J_{3',5'}$ = 1.8 Hz, 1 H, H-5′); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 207.7 ($C_2$), 173.1 ($C_6$), 152.6 ($C_{2'}$), 142.4 ($C_{5'}$), 138.9 ($C_{1''}$), 135.9 and 133.8 ($C_9$ and $C_{10}$), 128.5 (2C, $C_{3''}$ and $C_{5''}$), 128.0 (2C, $C_{2''}$, and $C_{6''}$), 127.0 ($C_{4''}$), 110.5 ($C_{3'}$), 107.7 ($C_{4'}$), 91.9 ($C_{10a}$), 82.5 ($C_8$), 56.7, 55.9, 49.8, 47.6 and 46.5 ($C_1$, $C_4$, $C_{6a}$, $C_7$, and $C_{10b}$), 43.1 ($C_3$), 18.5 ($\underline{CH_2}CH_3$), 10.5 ($CH_2\underline{CH_3}$); ms (EI, 70 eV): *m*/*z* (%) 389 [$M^+$] (11), 360 (2), 321 (3), 266 (7), 258 (11), 242 (98), 238 (81), 210 (8), 176 (10), 148 (58), 131 (100), 122 (35), 103 (54), 94 (31), 77 (37), 65 (10). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.31; H, 5.68; N, 3.91.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3,8-Trimethyl-4-(5-methyl-2-furyl)-7-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3d).*** Yield 30%; mp 160°C (hexane-ethyl acetate); ir: C=O 1722, N─C=O 1683 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): δ = 1.15 (d, $J_{Me\text{-}1,1}$ = 6.6 Hz, 3 H, $CH_3$-1), 1.35 (d, $J_{Me\text{-}3,3}$ = 7.7 Hz, 3 H, $CH_3$-3), 1.57 (s, 3 H, $CH_3$-8), 2.19 (brs, 3 H, $CH_3$-5″), 2.95 (d, $J_{6a,7exo}$ = 3.9 Hz, 1 H, H-6a), 2.98 (dq, $J_{1,Me\text{-}1}$ = 6.6, $J_{1,10b}$ = 12.1 Hz, 1 H, H-1), 3.05 (dq, $J_{3,4}$ = 2.5, $J_{3,Me\text{-}3}$ = 7.7 Hz, 1 H, H-3), 3.99 (d, $J_{7exo,6a}$ = 3.9 Hz, 1 H, H-7*exo*), 4.24 (d, $J_{10b,1}$ = 12.1 Hz, H-10b), 4.97 (brd, $J_{4,3}$ = 2.5 Hz, 1 H, H-4), 5.82 (dq, $J_{4',Me\text{-}5'}$ = 1.1, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.05 (d, $J_{10,9}$ = 5.5 Hz, 1 H, H-10), 6.19 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.60 (d, $J_{9,10}$ = 5.5 Hz, 1 H, H-9), 7.11 (m, 2 H, H-2″ and H-6″), 7.25–7.18 (m, 3 H, H-3″−H-5″); $^{13}C$ NMR (150.9 MHz, $CDCl_3$): δ = 210.9 ($C_2$), 173.9 ($C_6$), 151.8 and 150.7 ($C_{2'}$ and $C_{5'}$), 138.8 and 134.2 ($C_9$ and $C_{10}$), 128.2 (5C, $C_{2''}$−$C_{6''}$), 127.1 ($C_{1''}$), 108.0 ($C_{3'}$), 106.3 ($C_{4'}$), 91.4 and 90.5 ($C_8$ and $C_{10a}$), 59.44, 59.40, 53.3 and 53.0 ($C_{10b}$, $C_{6a}$, $C_7$, and $C_4$), 46.8 ($C_3$), 44.0 ($C_1$), 17.7 ($CH_3$-5′), 17.5 ($CH_3$-8), 13.6 ($CH_3$-3), 10.4 ($CH_3$-1); ms (EI, 70 eV): *m*/*z* (%) 417 [$M^+$] (3), 270 (100), 252 (45), 224 (10), 176 (22), 150 (16), 149 (10), 131 (49), 122 (24), 107 (7), 103 (23), 79 (8), 77 (17). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.66; H, 6.49; N, 3.21.

***(1R*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,7-dimethyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3e).*** A mixture of piperidone **1a** (0.98 g, 4.0 mmol), crotonyl chloride (0.6 mL, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in toluene (25 mL) was refluxed for 6 h. The reaction progress was monitored by TLC. At the end of the reaction the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ∼6 and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude product. Further crystallization from hexane-ethyl acetate gave compound **3e** as white needles. Yield 48%, mp 160 °C (hexane-ethyl acetate); ir: C=O 1722, N─C=O 1687 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): δ = 0.97 (d, $J_{7,Me\text{-}7}$ = 7.1 Hz, 3 H, $CH_3$-7), 1.11 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, $CH_3$-1), 2.04 (d, $J_{6a,7}$ = 3.8 Hz, 1 H, H-6a), 2.58 (dq, $J_{1,Me\text{-}1}$ = 6.9, $J_{1,10b}$ = 11.9 Hz, 1 H, H-1), 2.89 (ddq, $J_{7,6a}$ = 3.8, $J_{7,8}$ = 4.5, $JMe_{\text{-}7,7}$ = 7.1 Hz, 1 H, H-7), 2.90 (dd, $J_{3B,4}$ = 6.2, $^2J_{3B,3A}$ = 17.1 Hz, 1 H, H-3B), 2.97 (dd, $J_{3A,4}$ = 2.0, $^2J_{3A,3B}$ = 17.1 Hz, 1 H, H-3A), 4.23 (d, $J_{10b,1}$ = 11.9 Hz, 1 H, H-10b), 4.90 (dd, $J_{8,9}$ = 1.6, $J_{8,7exo}$ = 4.5 Hz, 1H, H-8), 5.31 (dd, $J_{3A,4}$ = 2.0,

$J_{4,3B}$ = 6.2 Hz, 1 H, H-4), 6.20 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.23 (brdd, $J_{3',4'}$ = 3.2, $J_{3',5'}$ = 0.5 Hz, 1 H, H-3′), 6.35 (dd, $J_{9,8}$ = 1.6, $J_{9,10}$ = 5.8 Hz, 1 H, H-9), 6.45 (d, $J_{10,9}$ = 5.8 Hz, 1 H, H-10), 7.24 (dd, $J_{3',5'}$ = 0.5, $J_{4',5'}$ = 1.8 Hz, 1 H, H-5′); $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 208.0 ($C_2$), 173.4 ($C_6$), 152.5 ($C_{2'}$), 142.1 ($C_{5'}$), 134.8 and 134.1 ($C_9$ and $C_{10}$), 110.3 and 107.4 ($C_{3'}$ and $C_{4'}$), 91.3 ($C_{10a}$), 82.1 ($C_8$), 59.3 and 55.5 ($C_{10b}$ and $C_4$), 46.1, 44.3 and 37.0 ($C_{6a}$, $C_7$, and $C_1$), 41.7 ($C_3$), 17.0 ($CH_3$-7), 10.1 ($CH_3$-1); ms (EI, 70 eV): *m/z* (%) 313 [$M^+$] (25), 228 (22), 176 (10), 162 (13), 149 (20), 148 (14), 108 (33), 94 (55), 79 (41), 69 (44), 66 (25), 65 (20), 41 (100). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.07; N, 4.52.

**General procedure for preparation of carboxylic acids 4a-d.** A solution of piperidone **1a-d** (4.0 mmol) and citraconic anhydride (0.54 mL, 6.0 mmol) in toluene (30 mL) was refluxed for 4−6 h. At the end of the reaction the resulting mixture was cooled, and formation of white, yellow, or brown solids was observed. The crystals were filtered off, washed first with toluene (2 × 30 mL), then with acetone (2 × 20 mL) and air-dried to give corresponding acids **4a-d** as regioisomer mixtures (total yields of isomers **4b**,**dA** and **4b**,**dB** given on the Scheme 2). After recrystallization from isopropanol-DMF mixture the major isomers **4a-dA** were isolated as white powders.

***(1R*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-4-(2-Furyl)-1,7-dimethyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4aA).*** Yield 63%; mp 168−170°C; ir: C=O 1722, $CO_2H$ 1698 and N−C=O 1674 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.00 (d, $J_{1,Me-1}$ = 7.5 Hz, 3 H, $CH_3$-1), 1.11 (s, 3 H, $CH_3$-7), 2.49 (s, 1 H, H-6a), 2.50 (dq, $J_{1,10b}$ = 11.8, $J_{1,Me-1}$ = 7.5 Hz, 1 H, H-1), 2.73 (dd, $J_{3B,4}$ = 1.9, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3B), 3.27 (dd, $J_{3A,4}$ = 6.2, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3A), 4.58 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.02 (d, $J_{8,9}$ = 1.2 Hz, 1 H, H-8), 5.18 (dd, $J_{4,3B}$ = 1.9, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.27 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.37 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.52 (dd, $J_{8,9}$ = 1.2, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.65 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.49 (brd, $J_{5',4'}$ = 1.8 Hz, 1 H, H-5′); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): δ = 208.6 ($C_2$), 174.8 ($CO_2H$), 170.0 ($C_6$), 153.2 ($C_{2'}$), 142.3 ($C_{5'}$), 136.2 and 135.4 ($C_9$ and $C_{10}$), 110.4 and 107.0 ($C_{3'}$ and $C_{4'}$), 84.0 ($C_8$), 79.2 ($C_{10a}$), 58.9 ($C_{6a}$), 57.1, 46.0 and 44.0 ($C_1$, $C_4$, and $C_{10b}$), 50.4 ($C_7$), 42.1 ($C_3$), 22.1 (Me-7), 10.0 (Me-1); ms (EI, 70 eV): m/z (%) 357 [$M^+$] (3), 245 (39), 228 (14), 176 (9), 174 (13), 122 (21), 108 (16), 96 (10), 94 (100), 79 (11), 77 (9), 68 (22), 66 (12), 65 (13), 39 (14). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.91; H, 5.51; N, 4.26.

***(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-4-(2-Furyl)-1,3,7-trimethyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4bA).*** Yield 63%; mp 206−208°C; ir: C=O and $CO_2H$ brd 1704, N−C=O 1638 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.08 (d, 3H, $J_{Me-1,1}$ = 6.7 Hz, $CH_3$-1), 1.11 (s, 3H, $CH_3$-7), 1.32 (d, 3H, $J_{Me-3,3}$ = 7.8 Hz, $CH_3$-3), 2.52 (s, 1H, H-6a), 2.63 (dq, 1H, $J_{1,10b}$ = 11.8, $J_{1,Me-1}$ = 6.7 Hz, H-1), 2.93 (dq, 1H, $J_{3,4}$ = 2.5, $J_{3,Me-3}$ = 7.8 Hz, H-3), 4.54 (d, 1H, $J_{1,10b}$ = 11.8 Hz, H-10b), 4.92 (brd, 1H, $J_{3,4}$ = 2.5 Hz, H-4), 5.06 (d, 1 H, $J_{8,9}$ = 1.9 Hz, H-8), 6.28 (dd, 1 H, $J_{3',4'}$ = 3.1, $J_{4',5'}$ = 1.9 Hz, H-4′), 6.48 (dt, 1 H, $J_{3',4'}$ = 3.1, $^4J_{3',4}$ = $J_{3',5'}$ = 0.9 Hz, H-3′), 6.53 (dd, 1 H, $J_{9,10}$ = 5.6, $J_{8,9}$ = 1.9 Hz, H-9), 6.66 (d, 1 H, $J_{9,10}$ = 5.6 Hz, H-10), 7.51 (dd, 1 H, $J_{5',4'}$ = 1.9, $J_{3',5'}$ = 0.9 Hz, H-5′), 12.31 (brs, 1H, $CO_2H$); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): δ = 210.1 ($C_2$), 176.3 ($CO_2H$), 172.1 ($C_6$), 151.6 ($C_{2'}$), 142.2 ($C_{5'}$), 136.1 and 135.0 ($C_9$ and $C_{10}$), 110.6 and 108.1 ($C_{3'}$ and $C_{4'}$), 91.3 ($C_{10a}$), 84.9 ($C_8$), 59.2, 58.7, 53.1, 46.4 and 43.9 ($C_1$, $C_{6a}$, $C_4$, $C_3$, $C_{10b}$ and $C_{6a}$), 52.4 ($C_7$), 22.5 (Me-7), 17.4 (Me-3), 10.2 (Me-1); ms (EI, 70 eV): m/z (%) 371 [$M^+$] (16), 327 (3), 290 (15), 258 (31), 242 (92), 235 (7), 217 (22), 190 (51), 176 (38), 162 (20), 136 (54), 123 (74), 108 (100), 95 (23), 78 (83), 68 (25), 58 (34), 43 (66), 39 (76), 33 (96). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: 64.51; H, 5.31; N, 3.98.

***(1R*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1-Ethyl-4-(2-furyl)-7-methyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4cA).*** Yield 44%; mp 160 °C; ir: C=O 1719, $CO_2H$ 1678 and N−C=O 1675 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 0.86 (t, $J_{CH2,Me}$ = 7.5 Hz, 3 H, $CH_2CH_3$), 1.11 (s, 3 H, $CH_3$-7), 1.48 (m, 1 H, $CH_2ACH_3$), 1.70 (m, 1 H, $CH_2BCH_3$), 2.47 (m, 1 H, H-1), 2.46 (s, 1 H, H-6a), 2.73 (dd, $J_{3B,4}$ = 1.9, $^2J_{3,3}$ = 16.2 Hz, 1 H, H-3B), 3.25 (dd, $J_{3A,4}$ = 6.2, $^2J_{3,3}$ = 16.2 Hz, 1 H, H-3A), 4.77 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.02 (d, $J_{8,9}$ = 1.9 Hz, 1 H, H-8), 5.16 (dd, $J_{4,3B}$ = 1.9, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.26 (dd, $J_{4',5'}$ = 1.9, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.35 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.53 (dd, $J_{8,9}$ = 1.9, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.69 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.48 (brd, $J_{5',4'}$ = 1.9 Hz, 1 H, H-5′); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): δ = 208.6 ($C_2$), 174.8 ($CO_2H$), 170.0 ($C_6$), 153.2 ($C_{2'}$), 142.4 ($C_{5'}$), 136.3 and 135.3 ($C_9$ and $C_{10}$), 110.4 ($C_{3'}$), 107.0 ($C_{4'}$), 84.0 ($C_8$), 79.2 ($C_{10a}$), 59.0 ($C_{6a}$), 54.8, 49.5 and 46.1 ($C_1$, $C_4$ and $C_{10b}$), 50.4 ($C_7$), 43.1 ($C_3$), 22.2 (Me-7), 18.3 ($CH_2CH_3$), 10.5 ($CH_2CH_3$); ms (EI, 70 eV): m/z (%) 371 [$M^+$] (24), 259 (17), 258 (28), 242 (87), 204 (26), 176 (80), 175 (35), 148 (16), 138 (15), 136 (30), 135 (18), 122 (69), 107 (16), 94 (100), 79 (18), 77 (18), 66 (19), 65 (19). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.71; H, 5.37; N, 3.81.

***(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3,7,8-Tetramethyl-4-(5-methyl-2-furyl)-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4dA).*** Yield 55%; mp 136−140°C; ir: C=O 1721, $CO_2H$ 1698, N−C=O 1672; $^1$H NMR (600 MHz, DMSO-$d_6$): δ = 0.99 (d, $J_{1,Me-1}$ = 6.8 Hz, 3 H, $CH_3$-1), 1.05 (s, 3 H, $CH_3$-7), 1.27 (d, $J_{3,Me-3}$ = 7.7 Hz, 3 H, $CH_3$-3), 1.50 (s, 3 H, $CH_3$-8), 2.18 (brs, 3 H, $CH_3$-5′), 2.56 (s, 1 H, H-6a), 2.61 (brdq, $J_{1,Me-1}$ = 6.8, $J_{1,10b}$ = 12.2 Hz, 1 H, H-1), 2.87 (dq, $J_{3,Me-3}$ = 7.7, $J_{3,4}$ = 2.2 Hz, 1 H, H-3), 4.45 (d, $J_{10b,1}$ = 12.2 Hz, 1 H, H-10b), 4.80 (d, $J_{4,3}$ = 2.2 Hz, 1 H, H-4), 5.86 (dq, $J_{4',3'}$ = 3.0, $J_{4',Me-5'}$ = 1.0 Hz, 1 H, H-4′), 6.32 (d, $J_{9,10}$ = 5.5 Hz, 1 H, H-10), 6.41 (brd, $J_{3',4'}$ = 3.0 Hz, 1 H, H-3′), 6.62 (d, $J_{9,10}$ = 5.5 Hz, 1 H, H-9); $^{13}$C nmr (DMSO-$d_6$, 100.6 MHz): δ = 210.7 ($C_2$), 173.8 ($CO_2H$), 170.9 ($C_6$), 151.2 and 150.6 ($C_{2'}$ and $C_{5'}$), 139.2 ($C_9$), 136.2 ($C_{10}$), 108.1 and 106.4 ($C_{3'}$ and $C_{4'}$), 91.4 and 89.4 ($C_8$ and $C_{10a}$), 61.9 and 57.2 ($C_4$ and $C_{10b}$), 53.2 ($C_7$), 52.2, 47.1 and 43.7 ($C_1$, $C_3$, and $C_{6a}$), 22.1 (Me-7), 16.6, 14.6, 13.3 (Me-3, Me-8, and Me-5″), 10.1 (Me-1); ms (EI, 70 eV): m/z (%) 399 [$M^+$] (5), 304 (3), 287 (44), 270 (51), 244 (14), 204 (65), 202 (53), 190 (21), 162 (15), 150 (60), 136 (50), 122 (100), 110 (59), 95 (60), 77 (62), 68 (49), 55 (65), 44 (44). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.18; H, 6.45; N, 3.78.

***Methyl (1R*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-4-(2-furyl)-1,7-dimethyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylate (5).*** A mixture of acid **4a** (5.0 g, 13.0 mmol) and sulphuric acid (0.5 mL) in methanol (80 mL) was refluxed for 12 h. At the end, the mixture was cooled, poured into water (400 mL), and extracted with $CH_2Cl_2$ (5 × 80 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give crude product. Further crystallization from hexane-ethyl acetate gave ester **5** as colourless prisms. Yield 80%; mp 168 °C; ir: $CO_2Me$ 1739, C=O 1720, N─C=O 1670 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, $CH_3$-1), 1.27 (s, 3 H, $CH_3$-7), 2.42 (s, 1 H, H-6a), 2.91 (dd, $J_{3A,4}$ = 6.2, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3A), 2.96 (dq, $J_{1,10b}$ = 11.8, $J_{1,Me\text{-}1}$ = 6.9 Hz, 1 H, H-1), 3.02 (dd, $J_{3B,4}$ = 1.9, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3B), 3.58 (s, 3 H, $CO_2CH_3$), 4.25 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.09 (d, $J_{8,9}$ = 1.7 Hz, 1 H, H-8), 5.32 (dd, $J_{4,3B}$ = 1.9, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.26 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.40 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.50 (dd, $J_{8,9}$ = 1.7, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.52 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.27 (dd, $J_{5',4'}$ = 1.8, $J_{5',3'}$ = 0.7 Hz, 1 H, H-5′); $^{13}C$ NMR (150.9 MHz, $CDCl_3$): δ = 207.8 ($C_2$), 173.9 ($\underline{C}O_2Me$), 170.3 ($C_6$), 152.2 ($C_{2'}$), 142.4 ($C_{5'}$), 136.7 and 134.9 ($\overline{C}_9$ and $C_{10}$), 110.4 ($C_{4'}$), 107.8 ($C_{3'}$), 90.9 ($C_8$), 84.4 ($C_{10a}$), 59.4 and 58.7 ($C_{6a}$ and $C_7$), 52.4 ($CO_2\ \underline{C}H_3$), 46.3, 44.6 and 41.8 ($C_1$, $C_3$ and $C_4$), 22.1 ($CH_3$-7), 10.1 ($\overline{C}H_3$-1); ms (EI, 70 eV): m/z (%) 371 (40) $[M]^+$, 343 (9), 295 (12), 244 (46), 228 (90), 190 (62), 176 (100), 127 (54), 122 (65), 99 (25), 79 (16), 53 (19). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.91; H, 5.42; N, 3.87.

***(2S*,3R*,5S*,6R*)-2-(2-Furyl)-3,5-dimethyl-6-phenylpiperidin-4-one (6a).*** A homogeneous solution of furfural (7.5 mL, 9.0 mmol), 2-methyl-1-phenylpent-1-en-3-on (15.7 g, 9 mmol), ammonium acetate (13.0 g, 1.8 mmol) and $NH_3$ (5 mL of 25% aqueous solution) in ethanol (100 mL) was stirred for a week at room temperature. The resulting mixture was put into water (400 mL), extracted with ethyl acetate (3 × 100 mL), and the organic layer separated, dried ($MgSO_4$), filtered, and evaporated. The residue (viscous brown oil) was transferred into oxalate by the following method: to the residue, dissolved in 200 mL of absolute ether, a saturated ether solution of the anhydrous oxalic acid (∼100 mL) was added until the end of the pale-brown precipitate formation. Obtained residue was filtered off, washed with acetone (2 × 70 mL), and then boiled in 100 mL of acetone. Remaining solids were filtered off and air-dried to give oxalate of piperidone **6a** as white powder. For further transformations, the obtained oxalate was dissolved in water (80 mL), a 10% solution of $NH_4OH$ was added until pH 9−10, and free base was extracted with ether (3 × 70 mL). The organic layers were separated, dried ($MgSO_4$), filtered, and evaporated to give a pale-yellow viscous oil, which crystallized when left to stand into **c**olourless needles; yield 8%; mp 68−69°C (hexane-ethyl acetate); ir: NH 3312, C=O 1704 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$): δ = 0.80 and 0.99 (two d, $J_{3(5),Me\text{-}3(Me\text{-}5)}$ = 6.7 Hz, each to 3 H, $CH_3$-3 and $CH_3$-5), 2.12 (brs, 1 H, *N*H), 2.76 (ddq, $^4J_{3,5}$ = 1.2, $J_{3,2}$ = 10.6, $J_{3,Me\text{-}3}$ = 6.7 Hz, 1 H, H-3), 2.95 (ddq, $^4J_{3,5}$ = 1.2, $J_{5,6}$ = 10.7, $J_{5,Me\text{-}5}$ = 6.7 Hz, 1 H, H-5), 3.55 (d, $J_{3,2}$ = 10.6 Hz, 1 H, H-2), 3.78 (d, $J_{5,6}$ = 10.7 Hz, 1 H, H-6), 6.25 (dd, $J_{3',4'}$ = 3.2, $J_{5',3'}$ = 0.6 Hz, 1 H, H-3′), 6.30 (dd, $J_{3',4'}$ = 3.2, $J_{4',5'}$ = 1.8 Hz, 1 H, H-4′), 7.37 (dd, $J_{5',3'}$ = 0.6, $J_{5',4'}$ = 1.8, 1 H, H-5′), 7.26−7.44 (m, 5H, H-Ph); $^{13}C$ NMR (150.9 MHz, $CDCl_3$): δ = 210.6 ($C_4$), 154.5 ($C_{2'}$), 142.2 ($C_{5'}$), 141.6 ($C_{1''}$), 128.7 (2C, $C_{2''}$ and $C_{6''}$), 128.2 ($C_{4''}$), 127.8 (2C, $C_{3''}$ and $C_{5''}$), 110.2 ($C_{4'}$), 107.5 ($C_{3'}$), 68.6 ($C_6$), 61.9 ($C_2$), 51.9 and 49.9 ($C_3$ and $C_5$), 10.65 and 10.62 ($CH_3$-1 and $CH_3$-3); ms (EI, 70 eV): m/z (%) 269 (21) $[M]^+$, 184 (20), 146 (17), 123 (21), 117 (30), 108 (44), 79 (42), 77 (36), 56 (100). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.43; H, 7.30; N, 5.05.

***(2S*,3R*,5S*,6R*)-3,5-Dimethyl-2-(5-methyl-2-furyl)-6-phenylpiperidin-4-one (6b).*** A homogeneous solution of 5-methyl furfural (9.80 mL, 9.7 mmol), 2-methyl-1-phenylpent-1-en-3-one (17.05 g, 9.7 mmol), ammonium acetate (15.09 g, 19.6 mmol) and $NH_3$ (5 mL of 25% aqueous solution) in ethanol (80 mL) was stirred for a week at room temperature. The resulting mixture was treated as stated earlier for compound **6a**. Piperidone **6b** was obtained as colourless needles; yield 8%; mp 105−106°C (hexane-ethyl acetate); ir: NH 3317, C=O 1703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 0.81 and 0.95 (two d, $J_{3(5),Me\text{-}3(Me\text{-}5)}$ = 6.9 Hz, each to 3 H, $CH_3$-3 and $CH_3$-5), 2.11 (brs, *N*H), 2.27 (d, $^4J_{4',Me\text{-}5'}$ = 1.2 Hz, 3 H, $CH_3$-5′), 2.75 (dq, $J_{3,2}$ = 11.2, $J_{3,Me\text{-}3}$ = 6.9 Hz, 1 H, H-3), 2.94 (dq, $J_{5,6}$ = 10.6, $J_{5,Me\text{-}5}$ = 6.9 Hz, 1 H, H-5), 3.55 (d, $J_{5,6}$ = 10.6 Hz, 1 H, H-6), 3.71 (d, $J_{3,2}$ = 11.2 Hz, 1 H, H-2), 5.88 (dq, $J_{3',4'}$ = 3.1, $^4J_{4',Me\text{-}5'}$ = 1.2 Hz, 1 H, H-4′), 6.12 (d, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 7.25−7.54 (m, 5H, H-Ph); $^{13}C$ NMR (150.9 MHz, $CDCl_3$): δ = 210.8 ($C_4$), 152.7 and 151.8 ($C_{2'}$ and $C_{5'}$), 141.6 ($C_{1''}$), 128.6 (2C, $C_{2''}$ and $C_{6''}$), 128.7 (2C, $C_{3''}$ and $C_{5''}$), 128.0 ($C_{4''}$), 108.2 ($C_{3'}$), 106.1 ($C_{4'}$), 68.5 ($C_6$), 62.0 ($C_2$), 51.8 ($C_1$), 49.7 ($C_1$), 13.7 ($CH_3$-5′), 10.7 and 10.6 ($CH_3$-3 and $CH_3$-5); ms (EI, 70 eV): m/z (%) 283 (54) $[M]^+$, 240 (3), 226 (3), 198 (20), 149 (9), 137 (47), 122 (100), 117 (30), 104 (16), 91 (35), 79 (34), 57 (16), 56 (93), 43 (83). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.43; H, 7.26; N, 5.01.

***(2S*,3R*,5S*,6R*)-2-(2-Furyl)-3,5-dimethyl-6-(2-thienyl)piperidin-4-one (6c).*** A homogeneous solution of furfural (4.2 mL, 51.4 mmol), 2-methyl-1-(α-thienyl)pent-1-en-3-one (9.22 g, 51.4 mmol), ammonium acetate (7.9 g, 100 mmol) and $NH_3$ (2.2 mL of 25% aqueous solution) in ethanol (40 mL) was stirred for 72 h at room temperature. The resulting mixture was treated as stated earlier for piperidone **6a**. Piperidone **6c** was obtained as colourless needles; yield 10%; mp 86−88°C (hexane-ethyl acetate); ir: NH 3307, C=O 1704 $cm^{-1}$; $^1$HNMR (600 MHz, $CDCl_3$): δ 0.93 and 0.95 (two d, $J_{3(5),Me\text{-}3(Me\text{-}5)}$ = 6.7 Hz, each to 3 H, $CH_3$-3 and $CH_3$-5), 2.35 (brs, 1 H, *N*H), 2.73 (ddq, $J_{3,2}$ = 10.7, $J_{3,Me\text{-}3}$ = 6.7, $^4J_{3,5}$ = 1.2 Hz, 1 H, H-3), 2.98 (ddq, $J_{5,6}$ = 10.6, $J_{5,Me\text{-}5}$ = 6.7, $^4J_{3,5}$ = 1.2 Hz, 1 H, H-5), 3.81 (d, $J_{2,3}$ = 10.6 Hz, 1 H, H-2), 3.95 (d, $J_{5,6}$ = 10.6 Hz, 1 H, H-6), 6.31 (dd, $J_{5',3'}$ = 0.7, $J_{4',5'}$ = 3.2 Hz, 1 H, H-3′furyl), 6.35 (dd, $J_{5',4'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′furyl), 6.96 (dd, $J_{5',4'}$ = 5.1, $J_{3',4'}$ = 3.5 Hz, 1 H, H-4′thienyl), 7.02 (dd, $J_{5',3'}$ = 1.1, $J_{4',3'}$ = 3.5 Hz, 1 H, H-3′thienyl), 7.28 (dd, $J_{5',3'}$ = 5.1, $J_{5',4'}$ = 1.1 Hz, 1 H, H-5′thienyl),7.41 (dd, $J_{5',4'}$ = 1.8, $J_{5',3'}$ = 0.7 Hz, 1 H, H-5′furyl); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 209.3 ($C_4$), 154.2 ($C_{2'furyl}$), 145.3 ($C_{2'thienyl}$), 142.1 ($C_{5'furyl}$), 126.3, 125.2, and 125.0 ($C_{3'thienyl}$, $C_{4'thienyl}$, and $C_{5'thienyl}$), 110.2 and 107.4 ($C_{3'furyl}$ and $C_{4'furyl}$), 63.7 ($C_2$), 61.4 ($C_6$), 53.1 ($C_5$), 49.7 ($C_3$), 10.6 and 10.5 ($CH_3$-3 and $CH_3$-5); ms (EI, 70 eV): m/z (%)275 (4) $[M]^+$, 228 (2), 190 (19), 163 (5), 152 (25), 124

(97), 108 (100), 96 (42), 79 (70), 77 (43), 55 (28), 45 (35), 41 (40), 39 (72). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.23; H, 6.31; N, 5.42.

**General procedure for preparation of carboxylic acids 7a-c.** A solution of piperidone **6a-c** (21.0 mmol) and maleic anhydride (2.06 g, 21.0 mmol) in toluene (30 mL) was refluxed for 6–8 h. At the end of the reaction, the resulting mixture was cooled, and formation of yellow-brown solids was observed. The crystals were filtered off, washed first with toluene (2 × 30 mL), then with acetone (2 × 20 mL) and air-dried to give corresponding acids **7a–c**. Subsequent recrystallization from isopropanol-DMF mixture gave target products as colourless powders.

***(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3-Dimethyl-2,6-dioxo-4-phenyl-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (7a).*** Yield 41%; mp 224−225°C; ir: OH br 3245, $CO_2H$ 1736, C=O 1718, N─C=O 1681 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.03 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, $CH_3$-1), 1.42 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, $CH_3$-3), 2.60 (d, $J_{6a,7}$ = 9.4 Hz, 1H, H-6a), 2.62 (dq, $J_{1,Me\text{-}1}$ = 6.9, $J_{1,10b}$ = 12.5 Hz, 1 H, H-1), 2.83 (dq, $J_{3,Me\text{-}3}$ = 7.5, $J_{3,4}$ = 1.8 Hz, 1 H, H-3), 3.01 (d, $J_{6a,7}$ = 9.4 Hz, 1 H, H-7), 4.69 (d, $J_{1,10b}$ = 12.5 Hz, 1 H, H-10b), 4.96 (brd, $J_{8,9}$ = 1.1 Hz, 1 H, H-8), 5.22 (d, $J_{3,4}$ = 1.8 Hz, 1 H, H-4), 6.49 (dd, $J_{8,9}$ = 1.1, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.65 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.15 (brt, $J_{meta,para}$ = 7.5 Hz, 1 H, H-*para*), 7.21 (brt, $J_{meta,ortho}$ = $J_{meta,para}$ = 7.5 Hz, 2 H, H-*meta*), 7.40 (brd, $J_{ortho,meta}$ = 7.5 Hz, 2 H, H-*ortho*), 8.27 (s, 1 H, $CO_2H$); $^{13}C$ NMR (150.9 MHz, DMSO-$d_6$): δ = 211.6 ($C_2$), 173.5 ($CO_2H$), 171.3 ($C_6$), 142.0 ($C_{1'}$), 136.7 and 136.1 ($C_9$ and $C_{10}$), 128.6 (2C, $C_{2''}$, and $C_{6'}$), 127.0 ($C_{4'}$), 126.7 (2C, $C_3$, and $C_{5'}$), 90.9 ($C_{10a}$), 81.7 ($C_8$), 57.6 and 57.3 ($C_4$ and $C_{10b}$), 51.4, 51.3, 45.4 and 44.7 ($C_1$, $C_3$, $C_7$, $C_{6a}$), 18.6 (Me-3), 11.0 (Me-1); ms (EI, 70 eV): m/z (%) 367 (15) [$M^+$], 323 (13), 269 (19), 268 (77), 252 (56), 213 (19), 203 (19), 186 (53), 176 (74), 149 (22), 135 (22), 122 (32), 118 (69), 108 (100), 105 (32), 94 (22), 79 (26), 59 (35), 43 (47). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.61; H, 5.81; N, 3.95.

***(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3,8-Trimethyl-2,6-dioxo-4-phenyl-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (7b).*** Yield 56%; mp 223−224 °C; ir OH br 3227, $CO_2H$ 1740, C=O 1719, N─C=O 1679 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.03 (brd, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, $CH_3$-1), 1.35 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, $CH_3$-3), 1.66 (s, 3 H, $CH_3$-8), 2.60 (d, $J_{6a,7}$ = 9.3 Hz, 1 H, H-6a), 2.64 (m, 1 H, H-3), 2.79 (m, 1 H, H-1), 3.01 (d, $J_{6a,7}$ = 9.3 Hz, 1 H, H-7), 4.60 (d, $J_{1,10b}$ = 11.8 Hz, 1 H, H-10b), 4.88 (brs, 1 H, H-4), 6.31 (d, $J_{10,9}$ = 5.3 Hz, 1 H, H-10), 6.68 (d, $J_{9,10}$ = 5.3 Hz, 1 H, H-9), 7.15 (brt, $J_{meta,para}$ = 7.5 Hz, 1 H, H-*para*), 7.22 (brt, $J_{meta,ortho}$ = $J_{meta,para}$ = 7.5 Hz, 2 H, H-*meta*), 7.44 (brd, $J_{ortho,meta}$ = 7.5 Hz, 2 H, H-*ortho*), 8.27 (s, 1 H, $CO_2H$); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz): δ = 211.0 ($C_2$), 171.7 and 171.0 ($CO_2H$ and $C_6$), 141.6 ($C_{1'}$), 139.3 and 136.7 ($C_9$ and $C_{10}$), 127.9 (2C, $C_{2'}$ and $C_{6'}$), 126.5 ($C_{4'}$), 126.4 (2C, $C_{3'}$ and $C_{5'}$), 89.6 and 88.6 ($C_8$ and $C_{10a}$), 79.2 ($C_4$), 57.7, 54.1, 51.0, 48.2 and 44.2 ($C_1$, $C_3$, $C_{6a}$, $C_7$, and $C_{10b}$), 17.5 and 16.0 (Me-8 and Me-3), 10.5 (Me-1); ms (EI, 70 eV): m/z (%) 381 (44) [$M^+$], 337 (10), 290 (30), 283 (56), 266 (67), 235 (23), 217 (29), 202 (21), 198 (53), 190 (97), 175 (78), 164 (22), 148 (70), 131 (62), 121 (98), 117 (100), 107 (68), 91 (82), 84 (23), 79 (96), 65 (39), 59 (46), 55 (77), 45 (12), 43 (47). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.12; H, 6.11; N, 3.71.

***(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3-Dimethyl-2,6-dioxo-4-(2-thienyl)-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (7c).*** Yield 54%; mp 200−202°C; ir: OH 3221, $CO_2H$ 1734, C=O 1718, N─C=O 1677 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$): δ = 1.00 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, $CH_3$-1), 1.40 (d, $J_{3,Me\text{-}3}$ =7.5 Hz, 3 H, $CH_3$-3), 2.61 (d, $J_{6a,7}$ = 9.1 Hz, 1 H, H-6a), 2.62 (dq (septet), $J_{1,Me\text{-}1}$ = 6.8, $J_{1,10b}$ = 12.4 Hz, 1 H, H-1), 2.89 (dq, $J_{3,Me\text{-}3}$ = 7.5, $J_{3,4}$ = 1.6 Hz, 1 H, H-3), 3.04 (d, $J_{6a,7}$ = 9.1 Hz, 1 H, H-7), 4.67 (d, $J_{1,10b}$ = 12.4 Hz, 1 H, H-10b), 5.17 (d, $J_{8,9}$ = 1.5 Hz, 1 H, H-8), 5.21 (d, $J_{3,4}$ = 1.6 Hz, 1 H, H-4), 6.48 (dd, $J_{8,9}$ = 1.5, $J_{9,10}$ = 5.7 Hz, 1 H, H-9), 6.61 (d, $J_{9,10}$ = 5.7 Hz, 1 H, H-10), 6.82 (dd, $J_{5',4'}$ = 4.8, $J_{3',4'}$ = 3.5 Hz, 1 H, H-4′), 7.17 (brd, $J_{3',4'}$ = 3.5 Hz, 1 H, H-3′), 7.36 (brd, $J_{4',5'}$ = 4.8 Hz, 1 H, H-α); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 211.2 ($C_2$), 173.6 ($CO_2H$), 171.4 ($C_6$), 145.1 ($C_{2'}$), 136.9 and 135.8 ($C_9$ and $C_{10}$), 127.0, 126.3 and 125.6 ($C_{3'}$, $C_{4'}$ and $C_{5'}$), 90.9 ($C_{10a}$), 81.7 ($C_8$), 57.1 ($C_{10b}$), 53.9 ($C_4$), 51.9, 51.3, 45.5 and 44.1 ($C_1$, $C_3$, $C_7$, $C_{6a}$), 17.9 (Me-3), 10.6 (Me-1); ms (EI, 70 eV): m/z (%) 373 (22) [$M^+$], 276 (20), 274 (40), 258 (70), 219 (71), 203 (32), 192 (85), 178 (52), 176 (100), 162 (50), 151 (68), 139 (64), 138 (83), 124 (84), 108 (74), 97 (50), 79 (40), 78 (81), 59 (32), 55 (83), 45 (54), 43 (75). Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75; S, 8.59. Found: C, 60.97; H, 5.09; N, 3.65.

**General procedure for preparation of isoindolones 8a-c.** A mixture of corresponding piperidone **6a-c** (10 mmol), acryloyl chloride (1.3 mL, 15 mmol) and triethylamine (2.5 mL, 20 mmol) in benzene (25 mL) was refluxed for 6 h. The reaction progress was monitored by TLC. At the end of the reaction, the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ~6 and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude products. Further crystallization from hexane-ethyl acetate gave corresponding compounds **8a–c** as colourless prisms.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3-Dimethyl-4-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypirido[2,1-a]isoindole-2,6(6aH)-dione (8a).*** Yield 58%; mp 161−162°C; ir: C=O br 1719, N─C=O 1680 and 1694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 1.16 (d, $J_{1,Me\text{-}1}$ = 6.2 Hz, 3 H, $CH_3$-1), 1.45 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, $CH_3$-3), 1.66 (dd, $^2J_{7endo,7exo}$ = 11.8, $J_{7endo,6a}$ = 8.7 Hz, 1 H, H-7*endo*), 2.27 (ddd, $^2J_{7endo,7exo}$ = 11.8, $J_{6a,7exo}$ = 3.7, $J_{7exo,8}$ = 4.4 Hz, 1 H, H-7*exo*), 2.59 (dd, $J_{7endo,6a}$ = 8.7, $J_{6a,7exo}$ = 3.7 Hz, 1 H, H-6a), 2.85−2.94 (m, 2 H, H-1 and H-3), 4.41 (d, $J_{1,10b}$ = 12.5 Hz, 1 H, H-10b), 5.06 (d, $J_{3,4}$ = 1.9 Hz, 1 H, H-4), 5.22 (d, $J_{7exo,8}$ = 4.4 Hz, 1 H, H-8), 6.44 (s, 2 H, H-10 and H-9), 7.16−7.28 (m, 5H, H-Ph); $^{13}C$ NMR (150.9 MHz, $CDCl_3$): δ = 210.8 ($C_2$), 174.5 ($C_6$), 140.8 ($C_{1'}$), 136.8 and 133.1 ($C_9$ and $C_{10}$), 128.7 (2C, $C_{2'}$ and $C_{6'}$), 127.3 ($C_{4'}$), 125.7 (2C, $C_{3'}$ and $C_{5'}$), 91.2 ($C_{10a}$), 79.1 ($C_8$), 59.4 and 58.3 ($C_4$ and $C_{10b}$), 51.0, 48.1 and 44.7 ($C_1$, $C_3$, $C_{6a}$), 28.6 ($C_7$), 18.9 ($CH_3$-3), 10.7 ($CH_3$-1); ms (EI, 70 eV): m/z (%) 323 (100) [$M^+$], 295 (5), 252 (17), 187 (7), 172 (9), 162 (23), 149 (12), 117 (25), 108 (12), 79 (17), 55 (70), 39 (5). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.58; N, 4.29.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3,8-Trimethyl-4-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypirido[2,1-a]isoindole-2,6(6aH)-dione (8b).*** Yield 83%; mp 185−186°C; ir: C=O and N─C=O br 1694 $cm^{-1}$; $^1H$ NMR (400 MHz,

$CDCl_3$): δ = 1.15 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, $CH_3$-3), 1.44 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, $CH_3$-3), 1.72 (s, 3 H, $CH_3$-8), 1.74 (dd, $^2J_{7endo,7exo}$ = 12.0, $J_{7endo,6a}$ = 8.7 Hz, 1 H, H-7*endo*), 2.00 (dd, $J_{7endo,6a}$ = 8.7, $J_{6a,7exo}$ = 3.7 Hz, 1 H, H-6a), 2.68 (dd, $^2J_{7endo,7exo}$ = 12.0, $J_{6a,7exo}$ = 3.7 Hz, 1 H, H-7*exo*), 2.84−2.92 (m, 2 H, H-1 and H-3), 4.32 (d, $J_{1,10b}$ = 12.5 Hz, 1 H, H-10b), 5.05 (d, $J_{3,4}$ = 1.9 Hz, 1 H, H-4), 6.25 (d, $J_{9,10}$ = 5.6 Hz 1 H, H-10), 6.42 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 7.17 (m, 1 H, H-Ph*para*), 7.23−7.21 (m, 4 H, H-Ph); $^{13}$C NMR (150.9 MHz, $CDCl_3$): δ = 208.5 ($C_2$), 172.3 ($C_6$), 138.5 ($C_{1'}$), 137.6 ($C_9$). 131.2 ($C_{10}$), 126.2 (2C, $C_{2'}$ and $C_{6'}$), 124.8 ($C_{4'}$), 123.4 (2C, $C_{3'}$ and $C_{5'}$), 88.6 ($C_{10a}$), 85.0 ($C_8$), 57.3 and 55.9 ($C_4$ and $C_{10b}$), 48.9, 48.6 and 42.3 ($C_1$, $C_3$, $C_{6a}$), 32.4 ($C_7$), 16.5 (2C, Me-3 and Me-8), 8.3 (Me-1); ms (EI, 70 eV): m/z (%) 337 (85) $[M]^+$, 309 (5), 266 (17), 246 (18), 191 (23), 176 (30), 122 (41), 117 (34), 55 (100), 25 (18). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.79; H, 6.91; N, 4.08.

***(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3-Dimethyl-4-(2-thienyl)-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypirido[2,1-a]isoindole-2,6(6aH)-dione (8c).*** Yield 72%; mp 150−151°C; ir: C=O br 1716, N−C=O 1691 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, $J_{1,Me\text{-}1}$ = 6.7 Hz, 3 H, $CH_3$-1), 1.42 (d, $J_{3,Me\text{-}3}$ = 7.7 Hz, 3 H, $CH_3$-3), 1.65 (dd, $J_{7,6a}$ = 8.8, $^2J_{7endo,7exo}$ = 11.9 Hz,1 H, H-7*endo*), 2.25 (dd, $J_{7exo,6a}$ = 3.5, $J_{8,7exo}$ = 4.5 Hz, 1 H, H-7*exo*), 2.57 (dd, $J_{7endo,6a}$ = 8.8, $J_{6a,7exo}$ = 3.5 Hz, 1 H, H-6a), 2.91 (dq, $J_{1,Me\text{-}1}$ = 6.7, $J_{1,10b}$ = 12.3 Hz, 1 H, H-1), 3.03 (dq, $J_{3,Me\text{-}3}$ = 7.7, $J_{3,4}$ = 1.5 Hz, 1 H, H-3), 4.34 (d, $J_{1,10b}$ = 12.3 Hz, 1 H, H-10b), 5.15 (dd, $J_{8,9}$ = 1.3, $J_{8,7exo}$ = 4.5 Hz 1 H, H-8), 5.30 (brd, $J_{3,4}$ = 1.5 Hz, 1 H, H-4), 6.38 (d, $J_{9,10}$ = 5.8 Hz, 1 H, H-10), 6.39 (dd, $J_{8,9}$ = 1.3, $J_{9,10}$ = 5.8 Hz, 1 H, H-9), 6.82 (dd, $J_{3',4'}$ = 3.5, $J_{5',4'}$ = 5.0 Hz, 1 H, H-4′), 6.93 (brdd, $J_{3',5'}$ = 1.0, $J_{3',4'}$ = 3.5 Hz, 1 H, H-3′), 7.12 (dd, $J_{5',4'}$ = 5.0, $J_{3',5'}$ = 1.0 Hz, 1 H, H-5′); $^{13}$C NMR (150.9 MHz, $CDCl_3$): δ = 210.6 ($C_2$), 174.7 ($C_6$), 144.7 ($C_{2'}$), 136.9 ($C_9$), 132.9 ($C_{10}$), 126.7, 124.88, and 124.91 ($C_{4'}$, $C_{3'}$ and $C_{5'}$), 91.1 ($C_{10a}$), 79.0 ($C_8$), 59.1 ($C_{10b}$), 54.1, 50.7, 48.1 and 44.1 ($C_1$, $C_3$, $C_4$, $C_{6a}$), 28.7 ($C_7$), 18.4 (Me-3), 10.5 (Me-1); ms (EI, 70 eV): *m/z* (%) 329 (7) $[M]^+$, 300 (1), 258 (8), 192 (4), 178 (19), 123 (20), 108 (36), 97 (19), 79 (34), 66 (22), 55 (100), 20 (43). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.51; H, 5.57; N, 4.09.

**General procedure for preparation of imines 9a-c.** Powder of $MgSO_4$ (10 g, 83 mmol) was added to the solution of tryptamine (10.0 g, 62.5 mmol) and corresponding furfural (62.5 mmol) in dichloromethane (200 mL) at vigorous stirring. After 1 h, the reaction mixture was allowed to stay at room temperature for 24 h. Then $MgSO_4$ was filtered off, washed with dichloromethane (2 × 75 mL), the organic layers combined and evaporated. Further crystallization of solid residue from hexane-ethyl acetate gave the corresponding imines **9a-c**.

***N-(5-Iodo-2-furyl)methylene-2-(1H-indol-3-yl)ethanamine (9a).*** Bright yellow needles, yield 67%; mp 138−140°C; ir: C=N 1643 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.20 (t, $J_{1,2}$ = 7.2 Hz, 2 H, H-2), 3.94 (dt, $J_{N=CH,1}$ = 0.8, $J_{1,2}$ = 7.2 Hz, 2 H, H-1), 6.58 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-4′furyl), 6.63 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-3′furyl), 7.01 (dd, $J_{2'',NH}$ = 2.1, $J_{2,2'}$ = 0.8 Hz, 1 H, H-2″), 7.15 (ddd, $^4J_{5'',7''}$ = 0.7, $J_{5'',4''}$ = 8.0, $J_{5'',6''}$ = 7.5 Hz, 1 H, H-5″), 7.22 (ddd, $^2J_{6'',4''}$ = 0.7, $J_{6'',5''}$ = 7.5, $J_{6'',7''}$ = 8.0 Hz, 1 H, H-6″), 7.37 (dd, $J_{7'',6''}$ = 8.0, $^4J_{5'',7''}$ = 0.7 Hz, 1 H, H-7″), 7.67 (brd, $J_{4'',5''}$ = 8.0 Hz, 1 H, H-4″), 7.84 (t, $J_{N=CH,1}$ = 0.8 Hz, 1 H, HC=N), 8.15 (brs, 1 H, *N*H). Anal. Calcd for $C_{15}H_{13}N_2OI$: C, 49.48; H, 3.61; I, 34.86; N, 7.70. Found: C, 49.73; H, 3.45; N, 7.65.

***N-(5-Bromo-2-furyl)methylene-2-(1H-indol-3-yl)ethanamine (9b).*** Yellow needles, yield 61%; mp 138−140°C; ir: C=N 1645 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.19 (t, $J_{1,2}$ = 7.3 Hz, 2 H, H-2), 3.92 (dt, $J_{N=CH,1}$ = 0.8, $J_{1,2}$ = 7.3 Hz, 2 H, H-1), 6.40 (d, $J_{3',4'}$ = 3.5 Hz, 1 H, H-4′furyl), 6.63 (d, $J_{3',4'}$ = 3.5 Hz, 1 H, H-3′furyl), 7.01 (brd, $J_{2'',NH}$ = 2.2 Hz, 1 H, H-2″), 7.14 (ddd, $^4J_{5'',7''}$ = 1.0, $J_{5'',4''}$ = 8.1, $J_{5'',6''}$ = 7.7 Hz, 1 H, H-5″), 7.21 (dt, $^2J_{6'',4''}$ = 1.0, $J_{6'',5''}$ = $J_{6'',7''}$ = 7.7 Hz, 1 H, H-6″), 7.37 (brd, $J_{7'',6''}$ = 7.7 Hz, 1 H, H-7″), 7.67 (brd, $J_{4'',5''}$ = 7.7 Hz, 1 H, H-4″), 7.84 (d, $J_{N=CH,1}$ = 0.8 Hz, 1 H, HC=N), 8.18 (brs, 1 H, *N*H). Anal. Calcd for $C_{15}H_{13}N_2OBr$: C, 56.80; H, 4.13; Br, 25.19; N, 8.83. Found: C, 56.65; H, 4.29; N, 8.91.

***N-(2-Furylmethylene)-2-(1H-indol-3-yl)ethanamine (9c).*** Bright yellow needles, yield 70%; mp 135−138°C; ir: C=N 1647 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.19 (dt, $J_{1,2}$ = 7.4, $J_{2'',2}$ = 0.7 Hz, 2 H, H-2), 3.91 (dt, $J_{N=CH,1}$ = 1.2, $J_{1,2}$ = 7.4 Hz, 2 H, H-1), 6.47 (dd, $J_{3',4'}$ = 3.4, $J_{5',4'}$ = 1.8 Hz, 1 H, H-4′furyl), 6.68 (dd, $J_{3',4'}$ = 3.4, $J_{3',5'}$ = 0.6 Hz, 1 H, H-3′furyl), 7.02 (brd, $J_{2'',NH}$ = 2.3 Hz, 1 H, H-2″), 7.12 (ddd, $^4J_{5'',7''}$ = 1.0, $J_{5'',4''}$ = 8.0, $J_{5'',6''}$ = 7.0 Hz, 1 H, H-5″), 7.19 (ddd, $^2J_{6'',4''}$ = 1.2, $J_{6'',5''}$ = 7.0, $J_{6'',7''}$ = 8.2 Hz, 1 H, H-6″), 7.36 (dd, $J_{7'',6''}$ = 8.2, $J_{7'',5''}$ = 1.0 Hz, 1 H, H-7″), 7.51 (dd, $J_{5',4'}$ = 1.8, $J_{3',5'}$ = 0.6 Hz, 1 H, H-5′furyl), 7.65 (dd, $J_{4'',5''}$ = 8.0, $J_{6'',4''}$ = 1.2 Hz, 1 H, H-4″), 7.96 (brt, $J_{N=CH,1}$ = 1.2 Hz, 1 H, HC=N), 8.04 (brs, 1 H, *N*H); ms (EI, 70 eV): m/z (%) 238 $[M^+]$ (10), 143 (5), 131 (16), 130 (100), 115 (7), 108 (16), 107 (16), 81 (26), 77 (31), 63 (7), 53 (25), 39 (21). Anal. Calcd for $C_{15}H_{14}NO_2$: C, 75.60; H, 5.93; N, 11.77. Found: C, 75.46; H, 5.72; N, 12.01.

**General procedure for preparation of benzo[1,2]indolizino[8,7-*b*]indol-4-carboxylic acids 10a,b.** A solution of azomethine **9a**,**b** (42.0 mmol) and maleic anhydride (4.5 g, 46 mmol) in $CH_2Cl_2$ (100 mL) was stirred at room temperature for 24 h. Formation of yellow solids was observed. The crystals were filtered off, washed first with $CH_2Cl_2$ (2 × 30 mL), then with acetone (2 × 20 mL) and air-dried. The corresponding acids **10a**,**b** were obtained as white powder.

***(3R*,4S*,4aS*,13bR*,13cR*)-3-Iodo-5-oxo-3,4,4a,5,7,8,13,13b-octahydro-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (10a).*** Yield 33%; mp >210°C (decomp.) (*i*-PrOH-DMF); ir: $CO_2H$ 1687, N−C=O 16 and 1610 $cm^{-1}$; $^1$H NMR (600 MHz, DMSO-$d_6$): δ = 2.56 (m, 1 H, H-8B), 2.80 (m, 1 H, H-8A), 2.92 (d, $J_{4,4a}$ = 8.8 Hz, 1 H, H-4), 3.00 (m, 1 H, H-7B), 3.15 (d, $J_{4a,4}$ = 8.8 Hz, 1 H, H-4a), 4.28 (dd, *J* = 5.7, $^2J_{7,7}$ = 12.8 Hz, 1 H, H-7A), 5.63 (brs, 1 H, H-13b), 6.63 (d, $J_{2,1}$ = 5.4 Hz, 1 H, H-2), 6.80 (d, $J_{1,2}$ = 5.4 Hz, 1 H, H-1), 7.00 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.09 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.37 (brd, $J_{12,11}$ = 7.7 Hz, 1 H, H-12), 7.43 (brd, $J_{9,10}$ =7.7 Hz, 1 H, H-9), 10.95 (s, 1 H, *N*H), 12.44 (brs, 1 H, $CO_2H$); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): δ = 170.4 and 168.0 ($CO_2H$ and $C_5$), 142.9 ($C_2$), 137.2 ($C_1$), 136.5 ($C_{12a}$), 128.2 and 126.3 ($C_{13a}$ and $C_{8b}$), 121.2, 118.6, 117.8 ($C_9$−$C_{11}$), 111.2 ($C_{12}$), 108.3 ($C_{8a}$), 89.7 ($C_{13c}$), 65.6 ($C_3$), 53.8, 53.2 and 52.9 ($C_4$, $C_{4a}$ and $C_{13b}$), 37.1 ($C_7$), 20.9 ($C_8$); ms (EI, 70 eV): m/z (%) 364 $[M^+$-98] (26), 363 (40), 335 (32), 290 (29), 262 (8), 254 (52), 237 (47), 222 (26),

209 (65), 207 (57), 181 (47), 180 (97), 169 (46), 152 (32), 143 (46), 131 (70), 130 (100), 127 (90), 104 (24), 98 (77), 83 (96), 77 (77), 54 (98). Anal. Calcd for $C_{19}H_{15}IN_2O_4$: C, 49.37; H, 3.27; I, 27.45; N, 6.06. Found: C, 49.51; H, 3.32; N, 6.12.

***(3R*,4S*,4aS*,13bR*,13cR*)-3-Bromo-5-oxo-3,4,4a,5,7,8,13,13b-octahydro-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (10b).*** Yield 53%; mp >230°C (decomp.) (*i*-PrOH-DMF); ir: $CO_2H$ 1745, N─C=O 1663 and 1644 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.58 (m, 1 H, H-8B), 2.80 (m, 1 H, H-8A), 3.02 (d, $J_{4,4a}$ = 8.9 Hz, 1 H, H-4), 3.02 (m, 1 H, H-7B), 3.23 (dd, $J_{4a,4}$ = 8.8, $J_{4a,13b}$ = 0.8 Hz, 1 H, H-4a), 4.29 (dd, $J$ = 5.4, $^2J_{7,7}$ = 12.9 Hz, 1 H, H-7A), 5.63 (brs, 1 H, H-13b), 6.58 (d, $J_{2,1}$ = 5.6 Hz, 1 H, H-2), 6.98 (d, $J_{1,2}$ = 5.6 Hz, 1 H, H-1), 7.01 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.10 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.36 (brd, $J_{12,11}$ = 7.7 Hz, 1 H, H-12), 7.44 (brd, $J_{9,10}$ =7.7 Hz, 1 H, H-9), 10.98 (s, 1 H, *N*H), 12.46 (brs, 1 H, $CO_2H$); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 170.1 and 168.4 ($C_5$ and $CO_2H$), 140.1 and 138.4 ($C_2$ and $C_1$), 136.9 ($C_{12a}$), 128.6 ($C_{13a}$), 126.8 ($C_{8b}$), 121.8 ($C_{10}$), 119.1 and 118.3 ($C_9$ and $C_{11}$), 111.7 ($C_{12}$), 108.8 ($C_{8a}$), 91.2 and 89.7 ($C_{13c}$ and $C_3$), 54.62 and 54.57 ($C_4$ and $C_{13b}$), 51.7 ($C_{4a}$), 37.6 ($C_7$), 21.4 ($C_8$); ms (EI, 70 eV): m/z (%): 318 [$M^+$−98] (46), 316 (44), 290 (64), 288 (63), 261 (16), 237 (51), 229 (23), 223 (13), 220 (15), 208 (40), 191 (9), 180 (100), 169 (26), 154 (27), 152 (34), 144 (32), 130 (27), 128 (25), 115 (20), 102 (16), 98 (14), 89 (18), 81 (35), 79 (70), 59 (26), 54 (48), 43 (55). Anal. Calcd for $C_{19}H_{15}BrN_2O_4$: C, 54.96; H, 3.64; Br, 19.24; N, 6.75. Found: C, 54.89; H, 3.41; N, 6.93.

**General procedure for preparation of esters 11a,b.** Corresponding acid **10a**,**b** (10.5 mmol) was dissolved in methanol (130 mL) and sulphuric acid (0.5 mL) was added. The resulting solution was refluxed for 12 h. The reaction progress was monitored by TLC. At the end of the reaction the mixture was cooled, poured into water (400 mL) and extracted with $CH_2Cl_2$ (5 × 80 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. Further crystallization of solid residue from ethanol gave the corresponding esters **11a**,**b** as pale-brown powders.

***Methyl (3R*,4S*,4aS*,13bR*,13cR*)-3,4,4a,5,7,8,13,13b-octahydro-3-iodo-5-oxo-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylate (11a).*** Pink powder, yield 60%; mp >215°C (decomp.); ir: $CO_2Me$ 1752, N─C=O 1683 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.58 (m, 1 H, H-8B), 2.80 (brdd, $J$ = 3.7, $^2J_{8,8}$ = 15.0 Hz, 1 H, H-8A), 2.99 (m, 1 H, H-7B), 3.10 (d, $J_{4,4a}$ = 9.3 Hz, 1 H, H-4), 3.20 (brd, $J_{4a,4}$ = 9.3 Hz, 1 H, H-4a), 3.58 (s, 3 H, $CO_2CH_3$), 4.29 (dd, $J$ = 5.6, $J_{7,7}$ = 13.1 Hz, H-7A), 5.64 (s, 1 H, H-13b), 6.63 (d, $J_{1,2}$ = 5.3 Hz, 1 H, H-1), 6.82 (d, $J_{2,1}$ = 5.3 Hz, 1 H, H-2), 7.00 and 7.09 (two brt, $J \sim$ 7.5 Hz, each to1 H, H-10 and H-11), 7.36 (d, $J_{11,12}$ = 8.1 Hz, 1 H, H-12), 7.44 (brd, $J_{9,10}$ = 7.5 Hz, 1 H, H-9), 10.94 (brs, 1 H, *N*H); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 169.8 and 168.1 ($C_5$ and $\underline{C}O_2CH_3$), 142.9 ($C_2$), 137.3 ($C_1$), 136.5, 128.1 and 126.3 ($C_{12a}$, $C_{13a}$, $C_{8b}$), 121.3 ($C_{11}$), 118.7 and 117.9 ($C_9$ and $C_{10}$), 111.3 ($C_{12}$), 108.4 ($C_{8a}$), 90.0 ($C_{13c}$), 64.9 ($C_3$), 53.9, 53.6, 53.0, and 51.4 ($C_4$, $C_{4a}$, $CO_2\underline{C}H_3$, and $C_{13b}$), 37.2 ($C_7$), 20.9 ($C_8$); ms (ESI+): m/z 499 [28, ($\overline{M}$+Na)$^+$], 477 [100, (M+H)$^+$]. Anal. Calcd for $C_{20}H_{17}IN_2O_4$: C, 50.44; H, 3.60; I, 26.65; N, 5.88. Found: C, 50.18; H, 3.51; N, 5.94.

***Methyl (3R*,4S*,4aS*,13bR*,13cR*)-3-bromo-3,4,4a,5,7,8,13,13b-octahydro-5-oxo-3,13c-epoxybenzo[1,2]indolizino[8,7-b ]indole-4-carboxylate acid (11b).*** Straw-coloured powder, yield 70%; mp >225°C (decomp.); ir: $CO_2Me$ 1734, C=O 1662 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.60 (m, 1 H, H-8B), 2.80 (m, 1 H, H-8A), 3.00 (m, 1 H, H-7B) 3.19 (d, $J_{4,4a}$ = 9.0 Hz, 1 H, H-4), 3.29 (brd, $J_{4a,4}$ = 9.0 Hz, 1 H, H-4a), 3.58 (s, 3 H, $CO_2CH_3$), 4.29 (dd, $J$ = 5.6, $J_{7,7}$ = 13.1 Hz, 1 H, H-7A), 5.65 (brs, 1 H, H-13b), 6.57 (d, $J_{1,2}$ = 5.6 Hz, 1 H, H-1), 7.00 (d, $J_{1,2}$ = 5.6 Hz, 1 H, H-2), 7.00 (brdd, $J_{10,11}$ = 7.5, $J_{11,12}$ = 8.1 Hz, 1 H, H-11), 7.09 (dt, $^4J_{10,12}$ = 1.2, $J_{10,11}$ = $J_{9,10}$ = 7.5 Hz, 1 H, H-10), 7.36 (brd, $J_{11,12}$ = 8.1 Hz, 1 H, H-12), 7.43 (brd, $J_{9,10}$ = 7.5 Hz, 1 H, H-9), 10.96 (s, 1 H, *N*H); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 168.9 and 168.0 ($C_5$ and $\underline{C}O_2CH_3$), 139.6 and 138.0 ($C_2$ and $C_1$), 136.5, 127.9 and 126.3 ($C_{12a}$, $C_{13a}$, and $C_{8b}$), 121.4 ($C_{10}$), 118.7 and 117.9 ($C_9$ and $C_{10}$), 111.3 ($C_{12}$), 108.5 ($C_{8a}$), 90.3 and 89.5 ($C_{13c}$ and $C_3$), 54.40, 54.26, 51.5, and 51.2 ($C_4$, $C_{13b}$, $C_{4a}$, $CO_2\underline{C}H_3$), 37.3 ($C_7$), 20.9 ($C_8$); ms (ESI+): m/z 452 [33, ($M+\overline{Na}$)$^+$, $^{81}$Br], 450 [35, (M+Na)$^+$, $^{79}$Br], 430 [98, (M+H)$^+$, $^{81}$Br], 428 [100, (M+H)$^+$, $^{79}$Br]. Anal. Calcd for $C_{20}H_{17}BrN_2O_4$: C, 55.96; H, 3.99; Br, 18.61; N, 6.53. Found: C, 55.94; H, 3.82; N, 6.82.

***(3S*,4R*,4aS*,13bR*,13cR*)-3,4,4a,5,7,8,13,13b-Octahydro-4a-methyl-5-oxo-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (12A) and (3S*,4R*,4aS*, 13bR*,13cR*)-4-methyl-5-oxo-3,4,4a,5,7,8,13,13b-octahydro-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (12B).*** A solution of citraconic anhydride (7.6 mL, 84 mmol) in dichloromethane (10 mL) was added to a solution of imine **9c** (10 g, 42 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 24 h. Obtained crystals were filtered off, washed with dichloromethane (3 × 20 mL) and air-dried to give corresponding acid as a mixture of the regioisomers **12A**:**12B**, in the ratio 1.3:1. Following data is cited for isomer mixture. White powder, yield 70%; mp >220°C (decomp.) (*i*-PrOH-DMF); ir: $CO_2H$ 1725, C=O br 1667 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): **12A** maj: δ = 1.20 (s, 3 H, $CH_3$-4), 2.09 (s, 1 H, H-4a), 2.52 (m, 1 H, H-8B), 2.77 (m, 1 H, H-8A), 3.00 (m, 1 H, H-7B), 4.25 (m, 1 H, H-7A), 4.75 (d, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 5.53 (brs, 1 H, H-13b), 6.58 (dd, $J_{1,2}$ = 5.7, $J_{3,2}$ = 1.6 Hz, 1 H, H-2), 6.81 (d, $J_{2,1}$ = 5.7 Hz, 1 H, H-1), 6.98 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.07 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.34 (brd, $J_{12,11}$ = 8.0 Hz, 1 H, H-12), 7.41 (brd, $J_{9,10}$ = 7.7 Hz, 1 H, H-9), 10.86 (s, 1 H, *N*H), 12.10 (brs, 1 H, $CO_2H$); **12B** min: δ = 1.09 (s, 3 H, $CH_3$-4a), 2.54 (s, 1 H, H-4), 2.52 (m, 1 H, H-8B), 2.77 (m, 1 H, H-8A), 2.98 (m, 1 H, H-7B), 4.29 (m, 1 H, H-7A), 4.78 (d, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 5.54 (brs, 1 H, H-13b), 6.53 (dd, $J_{1,2}$ = 5.7, $J_{3,2}$ = 1.6 Hz, 1 H, H-2), 6.87 (d, $J_{2,1}$ = 5.7 Hz, 1 H, H-1), 6.98 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.07 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.34 (brd, $J_{12,11}$ = 8.0 Hz, 1 H, H-12), 7.41 (brd, $J_{9,10}$ = 7.7 Hz, 1 H, H-9), 10.86 (s, 1 H, *N*H), 12.10 (brs, 1 H, $CO_2H$); $^{13}C$ NMR **12A**+**12B** (100.6 MHz, DMSO-$d_6$): δ = 174.7, 172.8, 172.7, 169.4, 137.6, 136.5, 136.3, 135.7, 133.2, 129.00, 128.92, 126.4, 121.1 (2C), 118.6 (2C), 117.7 (2C), 111.2 (2C), 108.2 (2C), 92.6, 91.3, 84.0, 80.3, 79.2 (2C), 59.4, 57.0, 54.3, 53.1, 52.6, 50.2, 37.0, 36.8, 22.3, 21.4, 20.94, 20.86; ms (EI, 70 eV): *m*/*z* (%) 261 [$M^+$−89] (25), 259 (40), 257 (13), 203 (27), 201 (67), 199 (26), 180 (23), 178 (31), 121 (54), 119 (50), 101 (74), 98 (45), 82 (36), 72 (80), 59 (100), 57 (56), 55 (44), 43 (79). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.53; H, 5.41; N, 8.12.

**General procedure for preparation of 3*H*-imidazo[4,5-*c*]pyridines 13a-c.** A solution of corresponding furfural (10.0 mmol) in ethanol (30 mL) was added to a mixture of histamine dihydrochloride (1.84 g, 10.0 mmol) and triethylamine (2.8 mL, 25.0 mmol) in ethanol (50 mL) while stirring. The resulting mixture was refluxed for 3 h. At the end of the reaction the solvent was evaporated, and obtained brown oil was triturated with acetone to give corresponding spinacine in moderate yield. Spinacine **13c** was used in the next step without further purification and spectral identification.

***4,5,6,7-Tetrahydro-4-(5-iodo-2-furyl)- 3H-imidazo[4,5-c]pyridine (13a).*** Red powder, yield 30%, mp >150°C (decomp.) (*i*-PrOH-DMF); ir: NH 3414 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.51 (brt, $J_{6,7}$ = 5.7 Hz, 2 H, H-7), 2.90 (brt, $J_{6,7}$ = 5.7 Hz, 2 H, H-6), 4.94 (s, 1 H, H-4), 5.97 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-3′), 6.57 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-4′), 7.44 (s, 1 H, H-2); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 160.2 ($C_{2'}$), 134.9 ($C_2$), 129.4 and 126.6 ($C_{3a}$ and $C_{7a}$), 120.5 ($C_{4'}$), 111.1 ($C_{3'}$), 90.2 ($C_{5'}$), 50.0 ($C_4$), 40.0 ($C_6$), 22.5 ($C_7$); ms (EI, 70 eV): m/z (%) 315 [$M^+$] (22), 314 (39), 286 (22), 251 (23), 188 (100), 159 (26), 132 (33), 131 (37), 104 (14), 95 (13), 79 (15), 77 (19), 51 (12), 45 (12). Anal. Calcd for $C_{10}H_{10}IN_3O$: C, 38.12; H, 3.20; I, 40.27; N, 13.34. Found: C, 38.39; H, 3.04; N, 13.58.

***4-(5-Bromo-2-furyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (13b).*** Yellow powder, yield 62%, mp > 150°C (decomp.) (*i*-PrOH-DMF); ir: NH 3426 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.78 (m, 2 H, H-7), 3.20 (m, 2 H, H-6), 5.44 (brs, 1 H, H-4), 6.39 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-3′), 6.57 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-4′), 7.60 (s, 1 H, H-2); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 158.5 ($C_{2'}$), 133.5 ($C_2$), 130.1 and 126.7 ($C_{3a}$ and $C_{7a}$), 119.6 ($C_{5'}$), 111.9 and 110.1 ($C_{3'}$ and $C_{4'}$), 50.1 ($C_4$), 39.9 ($C_6$), 23.1 ($C_7$); ms (ESI+): m/z 291 [17, $(M+Na)^+$, $^{81}Br$], 389 [20, $(M+Na)^+$, $^{79}Br$], 369 [95, $(M+H)^+$, $^{81}Br$], 367 [100, $(M+H)^+$, $^{79}Br$]. Anal. Calcd for $C_{10}H_{10}BrN_3O$: C, 44.80; H, 3.76; N, 15.67; Br, 29.80. Found: C, 44.66; H, 3.81; N, 15.71.

**General procedure for preparation of imidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole-8-carboxylic acids 14a-c.** A solution of maleic anhydride (0.57 g, 5.8 mmol) in ethanol (10 mL) was added to a solution of corresponding spinacine **13a–c** (5.3 mmol) in ethanol (20 mL). The reaction mixture was stirred at room temperature for 24 h. Formation of off-white precipitates was observed. At the end of the reaction the obtained solids were filtered off and washed with ethanol (3 × 20 mL) giving amino acids **14a-c** as poorly dissolved pale-yellow powders in most organic solvents.

***(7aS*,8S*,9R*,11aR*,11bR*)-9-Iodo-1,4,5,7,7a,8,9,11b-octahydro-7-oxo-9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-a]isoindole-8-carboxylic acid (14a).*** Yield 41%, mp > 220°C (decomp.) (*i*-PrOH-DMF); ir: $CO_2H$ 1756, C=O 1687 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.59 (m, 1 H, H-4B), 2.90−2.98 (m, 2 H, H-4A and H-5B), 2.88 (d, $J_{8,7a}$ = 8.1 Hz, 1 H, H-8), 3.06 (brd, $J_{7a,8}$ = 8.1 Hz, 1 H, H-7a), 4.20 (dd, $^2J_{5,5}$ = 13.1, $J_{5A,4B}$ = 5.6 Hz, 1 H, H-5A), 5.32 (brs, 1 H, H-11b), 6.54 (d, $J_{10,11}$ = 5.8 Hz, 1 H, H-11), 6.72 (d, $J_{11,10}$ = 5.8 Hz, 1 H, H-10), 7.51 (s, 1 H, H-2); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 170.8 and 168.7 ($CO_2H$ and $C_7$), 143.4 ($C_{10}$), 137.8 ($C_{11}$) 135.1 ($C_2$), ∼114.4 (br 2C, $C_{11c}$, and $C_{3a}$), 90.2 ($C_{11a}$), 66.3 ($C_9$), 55.2 ($C_{11b}$), 53.6 and 53.5 ($C_{7a}$ and $C_8$), 37.1 ($C_5$), 22.4 ($C_4$); ms (EI, 70 eV): m/z (%) 315 [$M^+$−98] (5), 314 (15), 286 (75), 182 (53), 127 (100), 98 (35); ms (ESI+): m/z 436 [23, $(M+Na)^+$], 414 [100, $(M+H)^+$]. Anal. Calcd for $C_{14}H_{12}IN_3O_4$: C, 40.70; H, 2.93; I, 30.72; N, 10.17. Found: C, 40.67; H, 2.86; N, 10.23.

***(7aS*,8S*,9R*,11aR*,11bR*)-9-Bromo-1,4,5,7,7a,8,9,11b-octahydro-7-oxo-9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-a]isoindole-8-carboxylic acid (14b).*** Yield 38%, mp > 230°C (decomp.) (*i*-PrOH-DMF); ir: $CO_2H$ 1761, C=O 1685 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 2.61 (m, 1 H, H-4B), 2.90−2.95 (m, 2 H, H-4A, and H-5B), 2.97 (d, $J_{8,7a}$ = 9.0 Hz, 1 H, H-8), 3.13 (brd, $J_{7a,8}$ = 9.0 Hz, 1 H, H-7a), 4.21 (dd, $^2J_{5,5}$ = 13.1, $J_{5A,4B}$ = 5.6 Hz, 1 H, H-5A), 5.32 (brs, 1 H, H-11b), 6.48 (d, $J_{10,11}$ = 5.3 Hz, 1 H, H-11), 6.91 (d, $J_{11,10}$ = 5.8 Hz, 1 H, H-10), 7.51 (s, 1 H, H-2); $^{13}C$ NMR (150.9 MHz, DMSO-$d_6$): δ = 170.0 and 168.6 ($CO_2H$ and $C_7$), 140.1 ($C_{10}$), 138.4 ($C_{11}$), 135.1 ($C_2$), 113.6 (br 2C, $C_{11c}$, and $C_{3a}$), 90.2 ($C_{11a}$), 89.7 ($C_9$), 55.5 ($C_{11b}$), 54.5 and 51.8 ($C_{7a}$ and $C_8$), 37.2 ($C_5$), 22.4 ($C_4$); ms (ESI+): m/z 389 [30, $(M+Na)^+$, $^{81}Br$], 387 [29, $(M+Na)^+$, $^{79}Br$], 367 [98, $(M+H)^+$, $^{81}Br$], 365 [100, $(M+H)^+$, $^{79}Br$]. Anal. Calcd for $C_{14}H_{12}BrN_3O_4$: C, 45.92; H, 3.30; Br, 21.82; N, 11.48. Found: C, 45.98; H, 3.55; N, 11.54.

***(7aS*,8R*,9S*,11aR*,11bR*)-1,4,5,7,7a,8,9,11b-Octahydro-7-oxo-9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-a]isoindole-8-carboxylic acid (14c).*** Yield 39%, mp > 220°C (decomp.) (*i*-PrOH-DMF); ir: $CO_2H$ and C=O br 1687 $cm^{-1}$; $^1H$ NMR (400 MHz, $D_2O$/$(CD_3)_2CO$ (5:1)/$K_2CO_3$ (5 mol %), traces of $(CD_3)COCD_2H$ at δ 2.06 ppm were used as the internal standard): δ = 2.34 (m, $^2J_{4,4}$ = 15.6, $J_{4B,5A}$ = 6.2, $J_{4B,5B}$ = 11.6, $^5J_{11b,Hb\text{-}4}$ = 2.2 Hz, 1 H, H-4B), 2.48 (m, $^2J_{4,4}$ = 15.6, $J_{4A,5B}$ = 4.8, $J$ = 1.3 Hz, 1 H, H-4A), 2.50 (d, $J_{8,7a}$ = 9.3 Hz, 1 H, H-8), 2.90 (dddd, $^2J_{5,5}$ = 13.4, $J_{5B,4B}$ = 11.6, $J_{5B,4B}$ = 4.8, $J$ = 1.4 Hz, 1 H, H-5B), 2.95 (dd, $J_{7a,8}$ = 9.3, $^4J_{11b,7a}$ = 1.3 Hz, 1 H, H-7a), 4.14 (dd, $^2J_{5,5}$ = 13.4, $J_{5A,4B}$ = 6.2 Hz, 1 H, H-5A), 4.84 (d, $J_{9,10}$ = 1.8 Hz, 1 H, H-9), 5.27 (brdd, $^5J_{11b,4B}$ = 2.2, $^4J_{11b,7a}$ = 1.3 Hz, 1 H, H-11b), 6.44 (dd, $J_{10,11}$ = 5.8, $J_{10,9}$ = 1.8 Hz, 1 H, H-10), 6.65 (d, $J_{11,10}$ = 5.8 Hz, 1 H, H-11), 7.50 (s, 1 H, H-2); $^{13}C$ NMR (100.6 MHz, $D_2O$/$(CD_3)_2CO$ (5:1)/$K_2CO_3$ (5 mol %), the signal of $(CD_3)_2CO$ at δ 29.2 ppm was used as the internal standard): δ = 178.9 ($CO_2H$), 172.6 ($C_7$), 137.5 ($C_{10}$), 135.6 ($C_2$), 133.5 ($C_{11}$), 127.7 ($C_{11c}$), 125.2 ($C_{3a}$), 90.40 ($C_{11a}$), 81.8 ($C_9$), 55.8 ($C_{11b}$), 50.8 ($C_{7a}$), 47.0 ($C_8$), 36.6 ($C_5$), 20.5 ($C_4$); ms (EI, 70 eV): m/z (%) 287 [$M^+$] (3), 241 (5), 225 (4), 189 (32), 188 (55), 161 (16), 160 (88), 159 (19), 133 (13), 132 (22), 131 (100), 120 (11), 104 (11), 95 (13), 77 (6), 54 (35), 44 (6), 28 (5), 26 (13). Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.54; H, 4.57; N, 14.64. Found: C, 58.58; H, 4.65; N, 14.81.

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## REFERENCES AND NOTES

[1] Ishihara, Y.; Kiyota, Y.; Goto, G. Chem Pharm Bull 1990, 38, 3024.

[2] Shaozhong, W.; Liya, C.; Haijian, S.; Yanmei, D.; Jianwei, S.; Yuefei, H. Chem Pharm Bull 2005, 53, 67.

[3] Ackermann, D.; Mohr, M. Z Biol 1936, 98, 37.

[4] Han, Y. N.; Ryu, S. Y.; Han B. H.; Woo, L. K. Arch Pharm Res 1987, 10, 258.

[5] Restani, P.; Campagner, P.; Fiecchi, A.; Resmini, P.; Galli, C. L. Food Chem Toxicol 1988, 26, 441.

[6] (a) Boreisha, I. K.; Dolzhenko, A. T.; Komissarov, S. I.; Yutilov, Y. M.; Eilazyan, O. G.; Khabarova, T. V. Pharm Chem J (Engl Transl) 1988, 22, 15; (b) Smolyar, N. N.; Yutilov, Y. M.; Abramyants, M. G. Pharm Chem J (Engl Transl) 2006, 40, 63.

[7] Ihara, M.; Fukumoto, K. Nat Prod Rep 1996, 13, 241.

[8] Last review on IMDAF: Zubkov, F. I.; Nikitina, E. V.; Varlamov, A. V. Russ Chem Rev 2005, 74, 639.

[9] Selected recent articles on IMDAF: (a) Murali, R.; Rao, H. S. P.; Scheeren, H. W. Tetrahedron 2001, 57, 3165; (b) Paulvannan, K.; Jacobs, J. W. Tetrahedron 1999, 55, 7433; (c) Paulvannan, K.; Chen, T.; Jacobs, J. W. Synlett 1999, 1609; (d) Murali, R.; Prakash Rao, H. S.; Scheeren, H. W. Tetrahedron 2001, 57, 3165; (e) Varlamov, A. V.; Boltukhina, E. V.; Zubkov, F. I.; Sidorenko, N. V.; Chernyshev, A. I.; Grudinin, D. G. Chem Heterocycl Compd (Engl Transl) 2004, 40, 22; (f) Milkiewicz, K. L.; Neagu, I. B.; Parks, D. J.; Lu, T. Tetrahedron Lett 2003, 44, 7341.

[10] For early articles on IMDAF: (a) Prajapati, D.; Borthakur, D. R.; Sandhu, J. S. J Chem Soc Perkin Trans 1 1993, 1197; (b) Gschwend, H. W.; Hillman, M. J.; Kisis, B. J Org Chem 1979, 41, 104; (c) Bilović, D. Croat Chem Acta 1966, 38, 293; (d) Bilović, D. Chem Abstr 1967, 66, 55416.

[11] (a) Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Borisov, R. S.; Varlamov, A. V. Tetrahedron 2005, 61, 4099; (b) Boltukhina, E. V.; Zubkov, F. I.; Nikitina, E. V.; Varlamov, A. V. Synthesis 2005, 1859.

[12] Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Varlamov, A. V. Tetrahedron, 2004, 60, 8455.

[13] Zubkov, F. I.; Ershova, J. D.; Orlova, A. A.; Zaytsev, V. P.; Nikitina, E. V.; Peregudov, A. S.; Gurbanov, A. V.; Borisov, R. S.; Khrustalev, V. N.; Maharramov, A. M.; Varlamov, A. V. Tetrahedron 2009, 65, 3789.

[14] (a) Bhargava, P. N.; Singh, R. P. J Indian Chem Soc 1957, 34, 105; (b) Jayabharathi, J.; Sivakumar, R.; Praveena, A. Med Chem Res 2005, 14, 1985; (c) Jayabharathi, J.; Manimekalai, A.; Selvaraj, S. Eur J Med Chem 2007, 42, 593; (d) Vatsadze, S. Z.; Krainova, Y. V.; Kovalkina, M. A.; Zyk, N. V. Chem Heterocycl Compds (Engl Transl) 2000, 36, 1185.

[15] Edwards, M. W.; Garraffo, M. H. Synthesis 1994, 1167.

[16] (a) Kim, H. S.; Chung, Y. M.; Park, Y. J.; Kim, J. N. Bull Korean Chem Soc 2000, 21, 371; (b) El Gihani, M. T.; Heaney, H.; Shuhaibar, K. F. Synlett 1996, 871; (c) Laguerre, M.; Boyer, C.; Atfani, M.; Tetrahedron Lett 1988, 44, 7109; (d) Atta-ur-Rahman; Ghazala, M.; Sultana, N.; Bashir, M. Tetrahedron Lett 1980, 21, 1773.

[17] (a) Fokas, D.; Patterson, J. E.; Slobodkin, G.; Baldino, C. M. Tetrahedron Lett 2003, 44, 5137; (b) Paulvannan, K.; Hale, R.; Mesis, R.; Chen, T. Tetrahedron Lett 2002, 43, 203; (c) Fokas, D.; Yu, L.; Baldino, C. M. Mol Diversity 2005, 9, 81.

[18] (a) Klutchko, S.; Hodges, J. C.; Blankley, C. J.; Colbry, N. L. J Heterocycl Chem 1991, 28, 97; (b) Vitali, T.; Mossini, F.; Bertaccini, G.; Il Farmaco Ed Sci 1967, 22, 821; (c) Stocker, F. B.; Fordice, M. W.; Larson, J. K.; Thorstenson, J. H. J Org Chem 1966, 31, 2380.

[19] Sheldrick, G. M. Acta Crystallogr 2008, A64, 112.

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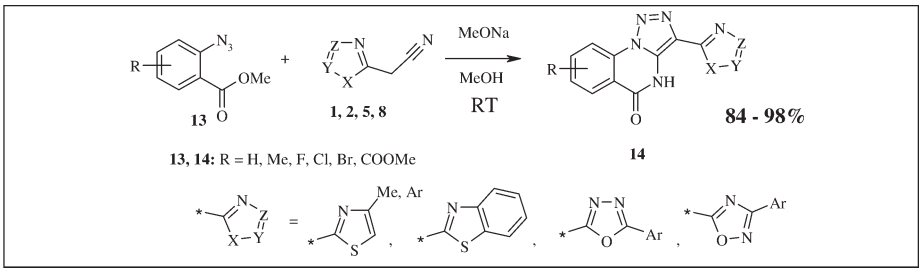


Synthesis of novel 3-substituted-1,2,3-triazolo[1,5-a]quinazolinones in high yields was performed *via* anionic hetero-domino reaction of appropriate substituted 2-azidobenzoates prepared from isatines and acetonitriles activated by 1,3-thiazole, 1,3-benzothiazole, 1,3,4-oxadiazole, and 1,2,4-oxadiazole rings. It was shown that acetonitriles exhibited high reactivity and were convenient methylenic compounds for such reactions providing rapid structural variation.

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## INTRODUCTION

1,2,3-Triazolo[1,5-a]quinazolines are an important class of heterocycles, which have been the subject of great interest because of their biological activities. For instance, in the works of Jones and coworkers [1] the synthesis and evaluation of the biological affinity of a large number of C-5 substituted 1,2,3-triazolo[1,5-a]quinazolines are reported. It was shown that compounds of the current class were new ligands for $GABA_A$ receptors and potentially pharmaceutically acceptable for treatment of Alzheimer's disease. Moreover, Biagi et al [2]. found the activity of some 3-ethoxycarbonyl- or 3-phenyl-substituted 1,2,3-triazolo[1,5-a]quinazolines towards benzodiazepine, $A_1$ and $A_{2A}$ adenosine receptors. The promising biological activity and the unique structure of these families make them attractive synthetic targets. Furthermore, in the article [1b,c] it was underlined that 1,2,3-triazolo[1,5-a]quinazolines were first synthesized in 1966 [3], however, this class of compounds has subsequently received little attention [1,4]. Their syntheses, using readily available raw materials with short and facile routes, continue to be challenging endeavors.

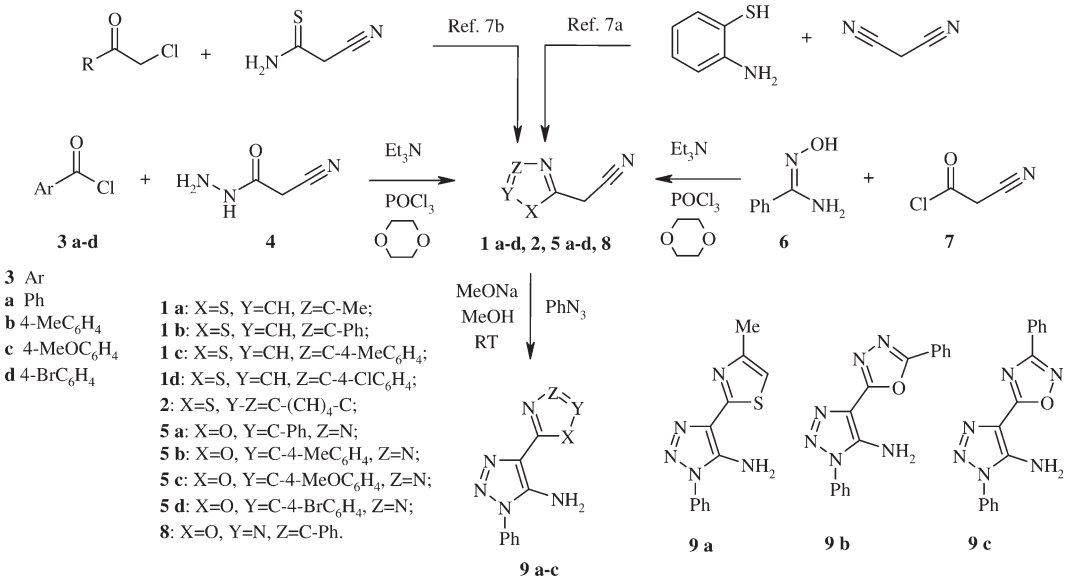
It is noteworthy that more attention was drawn to synthetic strategies, which have been developed to allow easy variation of the C-5 position of triazoloquinazolinone [1]. On the contrary, diversification of other positions has been discussed insufficiently. 2-Azidobenzoic acid and cyanoacetic acid derivatives were mostly used for construction of triazoloquinazolinone framework [4]. At the same time, the reaction of azides with acetonitriles activated by (het)aryl substituents is a perspective synthetic approach. The exclusive examples of the reaction of arylazides with (5-methylisoxazol-3-yl)acetonitrile [1] and phenylacetonitrile [5] have been described. In addition, introduction of new heterocyclic fragments to the C-3 position may extend the spectrum of biological activity of such compounds.

Recently, we have reported [6] the synthesis of 1*H*-1,2,3-triazole derivatives by cyclization of arylazides with (1,3-benzothiazol-2-yl)/(4-aryl-1,3-thiazol-2-yl)acetonitriles. It was shown that (1,3-benzothiazol-2-yl)acetonitrile undergoes an anionic domino reaction with methyl 2-azidobenzoate or 2-azidobenzonitrile to give [1,2,3]triazolo[1,5-a]quinazoline derivatives [6a]. Furthermore, it was found that acetonitrile possesses high reactivity, as an active methylenic compound for such reactions, for construction of [1,2,3]triazolo[1,5-a]pyrimidines system [6b] with heterocyclic substituents.

## RESULTS AND DISCUSSION

In the current work we present the results of a study of hetarylacetonitriles in the reaction with substituted methyl 2-azidobenzoates. Starting hetarylacetonitriles were obtained by several synthetic procedures. First the required precursors **1a–d**, **2** were synthesized in moderate to good yields according to the literature procedure [7]. Then we developed a synthetic protocol for preparation of acetonitriles activated by 1,3,4-oxadiazole and 1,2,4-oxadiazole. Compounds containing the oxadiazole

**Scheme 1**




ring have been widely studied recently since they exhibit biological activity [8] and possess some attractive photophysical properties [9]. Initial (5-aryl-1,3,4-oxadiazol-2-yl)acetonitriles **5a–d** were synthesized by one-pot cyclization of diacylhydrazines prepared *in situ* by acylation of cyanoacetic acid hydrazide **4** with the corresponding substituted benzoyl chlorides **3a**–**d**, *via* modification of known procedures [10]. (5-Phenyl-1,2,4-oxadiazol-2-yl)acetonitrile **8** was prepared by heating phenylamide oxime **6** with cyanoacetyl chloride **7** in anhydrous DMF in the presence of pyridine (Scheme 1).

The obtained hetarylacetonitriles **1a, 5a, 8** were examined in the reaction with phenylazide in sodium methoxide solution at room temperature. These conditions allowed to avoid possible Dimroth rearrangement [11] occurring when 5-aminotriazoles were heated in a strong base medium. As a result, new triazole derivatives **9a–c** were isolated in high yields and no by-products were formed. The corresponding 1,2,3-triazoles **9a–c** precipitated in good yields from the reaction medium.

In an effort to diversify the azido component, the method of 2-azidobenzoate synthesis from isatines, prepared from the corresponding anilines **10** by the Sandmeyer method [12], was used. By the reaction of anilines **10a,b** with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate, isonitrosoacetanilides were formed. The obtained isonitrosoacetanilides were treated with concentrated sulfuric acid and yielded isatines **11b,c** [12]. Compounds **11d,e** were prepared from isatine **11a** by the reaction with brome [13] or chlorine generated *in situ* from HCl and hydrogen peroxide [14] correspondingly. Isatines **11a–e** were oxidated with alkaline hydrogen peroxide to form substituted 2-aminobenzoic acids [15], which were converted into esters **12a–e** by the following reaction with methanol in the presence of sulphuric acid [16]. It is of note that compound **12d** can be prepared from commercially available methyl anthranilate **12a** *via* chlorization by the use of calcium hypochlorite [17]. Finally, compound **12f** was prepared by subsequent nitration and reduction of dimethyl benzene-1,4-dicarboxylate. Anthranilates **12a–f** were readily converted into 2-azidobenzoic acid esters **13a–f** by diazotisation and displacement with sodium azide (Scheme 2).

To obtain [1,2,3]triazolo[1,5-*a*]quinazolines, substituted methyl 2-azidobenzoates were allowed to react with acetonitriles **1, 2, 5, 8**. The reaction was carried out using 1 equiv. of sodium methoxylate at room temperature. It was found that the reaction exhibited an appreciable exothermal effect and was completed within 1–2 min. In general, the reaction product was formed immediately after mixing the reagents and precipitated from the reaction medium. The polycyclic compounds **14a–o** were isolated in excellent yields (84–98%) (Table 1). It is noteworthy that esters **13** used in such a reaction are more convenient instead of 2-azidobenzoic acids. In the reaction of 2-azidobenzoic acids, yields were lower and the reaction required more time. Moreover, in some cases the reaction mixture must be heated. For instance, in the work [1a] triazoloquinazolinone framework was prepared by treatment of an equimolar mixture of 2-azidobenzoic acid with isoxazole acetonitrile in the presence of sodium ethoxide at 80°C for 5 h. Bertelli et al. [2b] reported that 2-carboxy-4/5-chloro-phenylazide reacted with ethyl cyanoacetate in absolute ethanol in the presence of two equivalents of sodium ethoxide at

**Scheme 2**

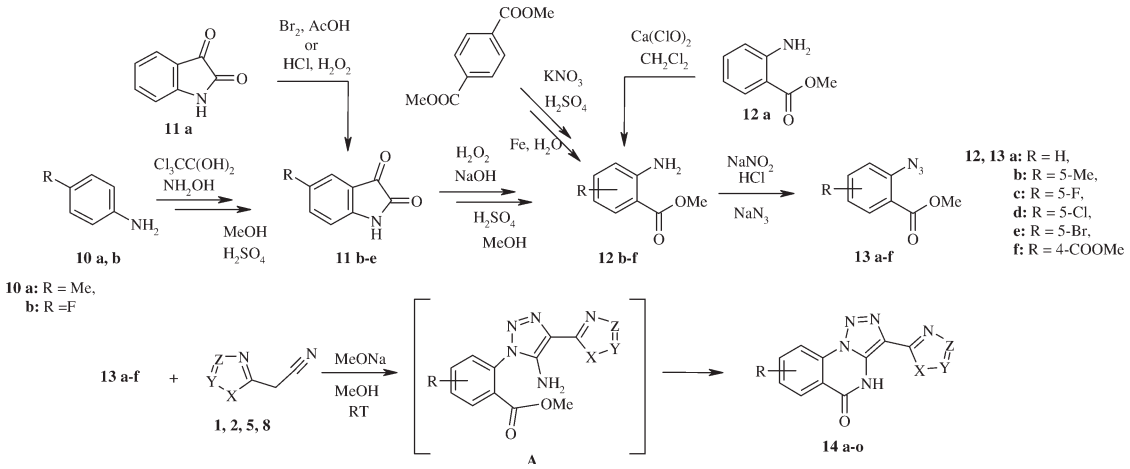



**Table 1**

Physical and analytical data of compounds **14a–o**.

| Compound | *R* | C-3 substituent | Mp (°C) | Yield, %[a] | IR, $\nu_{max}$ ($cm^{-1}$)[b] | MS (CI): $[M+H^+]$ | Molecular formula | Analysis % Calcd./Found | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H | N |
| **14a** | H | 4-methyl-1,3-thiazol-2-yl | >300 | 90 | 1679 | 284 | $C_{13}H_9N_5OS$ | 55.11 | 3.20 | 24.72 |
| | | | | | | | | 55.28 | 3.02 | 24.93 |
| **14b** | 7-Br | – | >300 | 92 | 1683 | 362, 364 | $C_{13}H_8BrN_5OS$ | 43.11 | 2.23 | 19.34 |
| | | | | | | | | 43.28 | 2.01 | 19.17 |
| **14c** | H | 4-phenyl-1,3-thiazol-2-yl | >300 | 96 | 1677 | 346 | $C_{18}H_{11}N_5OS$ | 62.60 | 3.21 | 20.28 |
| | | | | | | | | 62.44 | 3.34 | 20.06 |
| **14d** | – | 4-(4-methylphenyl)-1,3-thiazol-2-yl | >300 | 95 | 1680 | 360 | $C_{19}H_{13}N_5OS$ | 63.49 | 3.65 | 19.49 |
| | | | | | | | | 63.36 | 3.37 | 19.66 |
| **14e** | – | 4-(4-chlorophenyl)-1,3-thiazol-2-yl | >300 | 98 | 1671 | 380 | $C_{18}H_{10}ClN_5OS$ | 56.92 | 2.65 | 18.44 |
| | | | | | | | | 57.08 | 2.41 | 18.38 |
| **14f** | 7-Me | 1,3-benzothiazol-2-yl | >300 | 98 | 1674 | 334 | $C_{17}H_{11}N_5OS$ | 61.25 | 3.33 | 21.01 |
| | | | | | | | | 61.15 | 3.19 | 21.77 |
| **14g** | 7-F | – | >300 | 94 | 1690 | 338 | $C_{16}H_8FN_5OS$ | 56.97 | 2.39 | 20.76 |
| | | | | | | | | 56.84 | 2.30 | 20.52 |
| **14h** | 7-Cl | – | >300 | 97 | 1678 | 354 | $C_{16}H_8ClN_5OS$ | 54.32 | 2.28 | 19.80 |
| | | | | | | | | 54.26 | 2.46 | 19.99 |
| **14i** | 8-$CO_2$Me | – | >300 | 94 | 1724, 1680, 1276 | 378 | $C_{18}H_{11}N_5O_3S$ | 57.29 | 2.94 | 18.56 |
| | | | | | | | | 57.19 | 2.78 | 18.44 |
| **14j** | H | 5-phenyl-1,3,4-oxadiazol-2-yl | >300 | 87 | 1688 | 330 | $C_{17}H_{10}N_6O_2$ | 61.82 | 3.05 | 25.44 |
| | | | | | | | | 61.73 | 2.92 | 25.35 |
| **14k** | – | 5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl | >300 | 84 | 1672 | 345 | $C_{18}H_{12}N_6O_2$ | 62.79 | 3.51 | 24.41 |
| | | | | | | | | 62.87 | 3.39 | 24.28 |
| **14l** | – | 5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl | >300 | 93 | 1684 | 361 | $C_{18}H_{12}N_6O_3$ | 60.00 | 3.36 | 23.32 |
| | | | | | | | | 60.15 | 3.15 | 23.41 |
| **14m** | – | 5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl | >300 | 93 | 1677 | 409, 411 | $C_{17}H_9BrN_6O_2$ | 49.90 | 2.22 | 20.54 |
| | | | | | | | | 49.77 | 2.13 | 20.31 |
| **14n** | | 3-phenyl-1,2,4-oxadiazol-5-yl | >300 | 90 | 1680 | 331 | $C_{17}H_{10}N_6O_2$ | 61.82 | 3.05 | 25.44 |
| | | | | | | | | 61.97 | 2.93 | 25.36 |
| **14o** | 7-Cl | – | >300 | 97 | 1686 | 365 | $C_{17}H_9ClN_6O_2$ | 55.98 | 2.49 | 23.04 |
| | | | | | | | | 55.87 | 2.40 | 23.19 |

[a] Isolated yields.
[b] All compounds 14 showed a similar stretching peaks of associated NH (OH) groups with $\nu_{max}$ approximately 3400 $cm^{-1}$.

**Table 2**

$^1$H NMR spectra of products **14a–o** (J, Hz) 500 MHz.

| | | [1,2,3]triazolo[1,5-*a*]quinazoline protons | | | | |
|---|---|---|---|---|---|---|
| Compound | Me | H-6 | H-9 | H-7 | H-8 | (Het)Aryl fragment |
| **14a** | 2.42 | 8.18 (t, J 9.2) | | 7.78 (t, J 7.1) | 7.52 (t, J 7.1) | 7.08 (s, 1H) |
| **14b** | 2.41 | 8.24 (s) | 8.15 (d, J 7.0) | – | 7.94 (d, J 7.0) | 7.09 (s, 1H) |
| **14c**[a] | | 8.22 (t, J 7.6) | | 7.75 (t, J 7.6) | 7.49 (t, J 7.6) | 7.29 (t, J 7.4, 1H), 7.42 (t, J 7.6, 2H), 7.70 (s, 1H), 8.04 (d, J 7.2, 2H) |
| **14d** | 2.39 | 8.20–8.25 (m) | | 7.74 (t, J 7.4) | 7.51 (t, J 7.6) | 7.22 (d, J 8.0, 2H, H-3,5), 7.70 (s, 1H, $H_{Tz}$), 7.86 (d, J 8.0, 2H, H-2,6) |
| **14e** | | 8.24 (t, J 8.0) | | 7.77 (t, J 7.6) | 7.50 (t, J 7.6) | 7.43 (d, J 8.8, 2H, H-3,5), 7.86 (s, 1H, $H_{Tz}$), 8.02 (d, J 8.8, 2H, H-2,6) |
| **14f** | 2.42 | 7.89 (d, J 2.0) | 7.87 (d, J 8.4) | – | 7.62 (dd, J 8.4, 2.0), | 7.32 (t, J 7.0, 1H, H-6), 7.44 (t, J 7.4, 1H, H-5), 7.99 (d, J 7.8, 1H, H-7), 8.05 (d, J 7.4, 1H, H-8) |
| **14g** | | 8.29 (dd, J 8.4, 3.9) | 7.85 (dd, J 8.9, 1.7), | – | 7.70 (dt, J 8.6, 2.5) | 7.34 (t, J 7.0, 1H, H-6), 7.47 (t, J 7.4, 1H, H-5), 7.98 (d, J 8.0, 1H, H-7), 8.06 (d, J 7.4, 1H, H-8) |
| **14h** | | 8.12 (s) | 8.25 (d, J 8.4) | – | 7.85 (d, J 8.7) | 7.31-7.38 (m, 1H, H-6), 7.47 (t, J 7.1, 1H, H-5), 7.97 (d, J 7.2, 1H, H-7), 8.07 (d, J 7.0, 1H, H-8) |
| **14i** | 3.97 | 8.30 (d, J 7.6) | 8.73 (s) | 8.08 (d, J 7.6) | – | 7.35 (t, J 7.1, 1H, H-6), 7.48 (t, J 6.7, 1H, H-5), 7.98 (d, J 7.4, 1H, H-7), 8.08 (d, J 7.3, 1H, H-8) |
| **14ja** | | 8.35 (d, J 8.0) | 8.26 (d, J 7.9) | 7.94 (t, J 7.1) | 7.65 (t, J 7.6) | 7.57-7.62 (m, 3H), 8.19 (m, 2H) |
| **14k** | 2.47 | 8.34 (d, J 8.00) | 8.28 (d, J 7.7) | 7.94 (t, J 7.9) | 7.67 (t, J 7.7) | 7.40 (d, J 7.9, 2H), 8.04 (d, J 7.9, 2H) |
| **14l** | 3.88 | 8.37 (d, J 8.0) | 8.25 (d, J 8.0) | 7.97 (t, J 7.9) | 7.70 (t, J 7.9) | 7.12 (d, J 8.2, 2H), 8.09 (d, J 8.2, 2H) |
| **14m** | | 8.22 (d, J 8.1) | 8.09 (d, J 8.0) | 7.80 (t, J 7.6) | 7.56 (t, J 7.6) | 7.86 (d, J 7.9, 2H), 8.03 (d, J 8.1, 2H) |
| **14n** | | 8.34 (d, J 8.0) | 8.27 (d, J 7.9) | 7.97 (t, J 7.9) | 7.64 (t, J 8.0) | 7.53-7.59 (m, 3H), 8.17 (m, 2H) |
| **14o** | | 8.14 (s) | 8.27 (d, J 8.7) | – | 7.83 (d, J 8.7) | 7.55-7.62 (m, 3H), 8.19 (m, 2H) |

[a] Recorded at 400 MHz.

room temperature, affording 1-(4- or 5-chloro-2-carboxy-phenyl)-4-ethoxycarbonyl-5-amino-1H-1,2,3-triazole intermediates, and the corresponding triazoloquinazolinones were formed after acidification of the alkaline solution. The reaction of such azides with phenylacetonitrile required refluxing of the reaction mixture but it proceeded in the same manner [2b]. Obviously, replacement of the carboxylic group into the carboxylate one increased the rate of the reaction of the amino group in the intermediate triazole **A**, which was formed at the first stage of the reaction. The carboxylate function provided the formation of the pyrimidine ring without any additional procedures.

The structures of all new compounds were confirmed by analytical and spectroscopic data (Tables 1 and 2, Fig. 1). In the $^1$H NMR spectra of compounds **14a–o** there were characteristic shift values for the H6, H7, H8, and H9 protons typical for the 1,2,3-triazolo[1,5-a]quinazoline system (Table 2). Furthermore, aryloxadiazolyl fragments were easily identified *via* low-field shifted aromatic protons *ortho* to the oxadiazole rings, usually found at 8.03–8.19 ppm.

In conclusion, in the current work we described efficient and economic routes to 1,2,3-triazolo[1,5-a]quinazolines from cheap abundant starting materials and with a possibility of substituent variation in triazoloquinazoline framework. Moreover, new active methylenic compounds were used for anionic domino reactions leading to formation of triazoloquinazolines.

## EXPERIMENTAL

All melting points were determined in capillary tubes in a Thiele apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for $^1$H) and Bruker 500 (500 MHz for $^1$H, 125 MHz for $^{13}$C) with

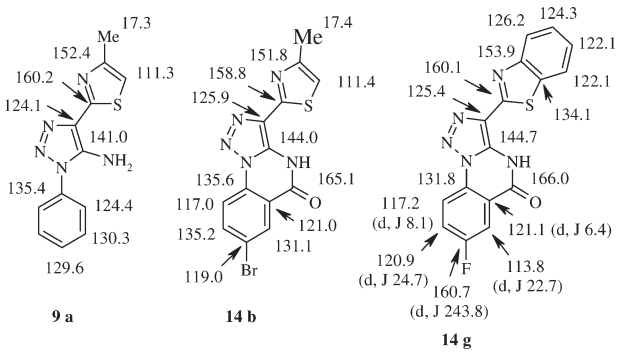



**Figure 1.** $^{13}$C NMR chemical shifts of compounds **9a**, **14b**, **14g**.

TMS or deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. IR spectra were recorded on a Specord 80M spectrophotometer in KBr pellets. The evolution of the reactions and purity of the synthesized compounds were monitored chromatographically on Silufol UV-254 plates. $^{13}C$ NMR spectra of product **9b**,**c** and **14a**, **c–f**, **h–o** are not reported due to their very low solubility.

**(5-Aryl-1,3,4-oxadiazol-2-yl)acetonitriles 5a–d (general procedure).** The solution of 21 mmol of substituted benzoyl chloride **3** in 10 mL of anhydrous dioxane was added under continuous stirring to the solution of 2.1 g (21 mmol) of 2-cyanoacetohydrazide and 2.9 mL (21 mmol) of triethylamine in 30 mL of anhydrous dioxane. The mixture was stirred for 0.5 h at room temperature and 10 mL of $POCl_3$ was added. The mixture was heated for 3 h at 80°C, cooled to room temperature and poured onto ice. The precipitate was filtered off and dried in air. The crude product was purified by flash chromatography followed by recrystallization from ethanol.

**(3-Phenyl-1,2,4-oxadiazol-5-yl)acetonitrile 8.** Cyanoacetyl chloride **6** (0.52 g, 5 mmol) was added to the solution of 5 mmol of *N*'-hydroxybenzenecarboximidamide **7** in 2 mL of pyridine. The mixture was kept for 0.5 h and 5 mL of DMF was added. The mixture was heated for 3 h at 80°C, cooled to room temperature and mixed with 30 mL of water. The precipitate was filtered off, washed with water on a filter, recrystallized from alcohol and dried in air.

**Azides 13a–f preparation.** The solution of sodium nitrite (7.1 g, 0.1 mol) in water (30 mL) was added dropwise to a stirred solution of substituted anthranilic esters (0.1 mol) in 40 mL of concentrated HCl and 20 mL of water keeping the temperature below 5°C. After that the mixture was stirred for 10 min and rapidly filtered. To the obtained solution $NaN_3$ (6.5 g, 0.1 mol) in water (125 mL) was added dropwise. The mixture was stirred for 15 min at 0°C and then for 30 min at room temperature. Azides **13a,b** were extracted by diethyl ether (3 × 10 mL). Ether was evaporated *in vacuo*. Azides **13c–f** were filtered and washed with water twice. Azides were used without subsequent cleaning: **methyl 2-azidobenzoate 13a**, yield 11.5 g, 65%; dark red oil; MS: (CI) *m*/*z* (%) = 178 (100%) [M+H$^+$]; **methyl 2-azido-5-methylbenzoate 13b**, yield 13.7 g, 72%; dark red oil; MS: (CI) *m*/*z* (%)= 192 (100%) [M+H$^+$]; **methyl 2-azido-5-fluorobenzoate 13c**, yield 13.8 g, 71%; pink solid, mp: 28–29°C; MS: (CI) *m*/*z* (%)= 196 (100%) [M+H$^+$]; **methyl 2-azido-5-chlorobenzoate 13d**, yield 16.7 g, 79%; white pink solid, mp: 50–52°C; MS: (CI) *m*/*z* (%) = 212(100%) [M+H$^+$]; **methyl 2-azido-5-bromobenzoate 13e**, yield 20.8 g, 81%; white solid, mp: 71–72°C; MS: (CI) *m*/*z* (%) = 256 (100%) [M+H$^+$], 258 (100%) [M+H$^+$]; **dimethyl 2-azidobenzene-1,4-dicarboxylate 13f**, yield 17.7 g, 75%; white solid, mp: 83–85°C; MS: (CI) *m*/*z* (%) = 236 (100%) [M+H$^+$]. (Caution! All azides are potentially explosive and should not be heated).

**General procedure for the synthesis of 1*H*-1,2,3-triazol-5-amines 9a–c and [1,2,3]triazolo[1,5-*a*]quinazolin-5(4*H*)-one 14a–o.** To the solution of sodium methoxide (540 mg, 10.0 mmol) in dry methanol (20 mL) an appropriate substituted acetonitrile **1, 2, 5** or **8** (10.0 mmol) was added. To this solution substituted methyl 2-azidobenzoate **2** (10.0 mmol) in dry methanol (2 mL) was added dropwise and the solid started to precipitate. The mixture was stirred for 1 h. The resulting suspension was filtered and the solid product was washed with water and methanol to give the corresponding 1*H*-1,2,3-triazol-5-amines **9a–c** and [1,2,3]triazolo[1,5-*a*]quinazolin-5(4*H*)-ones **14a–o**.

**4-(4-Methyl-1,3-thiazol-2-yl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (9a).** Yield: 2.2 g (87%); as white crystals; mp 168–169°C (DMF–EtOH); $^1H$ NMR (DMSO-$d_6$ 400MHz): δ 2.45 (s, 3H, Me), 6.47 (s, 2H, $NH_2$), 6.95 (s, 1H, thiazole), 7.52 (t, $^3J$ = 7.1 Hz, 1H, $H_{Ph}$-4), 7.61 (t, $^3J$ = 7.2 Hz, 2H, $H_{Ph}$-3,5), 7.66 (d, $^3J$ = 7.2 Hz, 2H, $H_{Ph}$-2,6); MS: (CI) *m*/*z* (%) = 258 (100%) [M+H$^+$]. Anal. Calcd. for $C_{12}H_{11}N_5S$ (257.31): C 56.01; H 4.31; N 27.22. Found: C 56.19; H 4.24; N 27.07.

**1-Phenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-1*H*-1,2,3-triazol-5-amine (9b).** Yield: 2.8 g (93%); as white crystals; mp 214–215°C (DMF–EtOH); $^1H$ NMR (DMSO-$d_6$ 400MHz): δ 6.58 (s, 2H, $NH_2$), 7.50–7.72(m, 8H, arom.), 8.11–8.16 (m, 2H, $H_{Ph}$-2,6); MS: (CI) *m*/*z* (%) = 305 (100%) [M+H$^+$]. Anal. Calcd. for $C_{16}H_{12}N_6O$ (304.31): C 63.15; H 3.97; N 27.62. Found: C 63.01; H 3.74; N 27.48.

**1-Phenyl-4-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-1,2,3-triazol-5-amine (9c).** Yield: 2.7 g (90%); as white crystals; mp 230–231°C (DMF–EtOH); $^1H$ NMR (DMSO-$d_6$ 400MHz): δ 6.80 (s, 2H, $NH_2$), 7.52–7.59 (m, 5H, arom.), 7.63–7.66 (m, 3H, arom.), 8.16–8.18 (m, 2H, $H_{Ph}$-2,6); MS: (CI) *m*/*z* (%) = 305 (100%) [M+H$^+$]. Anal. Calcd. for $C_{16}H_{12}N_6O$ (304.31): C 63.15; H 3.97; N 27.62. Found: C 63.06; H 3.88; N 27.64.

## REFERENCES AND NOTES


[1] (a) Bryant, H. J.; Chambers, M. S.; Jones, P.; MacLeod, A. M.; Maxey, R. J. WO Patent 0,144,250, 2001; (b) Jones, P.; Chambers, M. Tetrahedron, 2002, 58, 9973; (c) Bryant, H. J.; Chambers, M. S.; Jones, P.; MacLeod, A. M.; Maxey, R. J. US Patent 7,144,887 B2, 2006.

[2] (a) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Velo, S.; Lucacchini, A.; Senatore, G.; De Santis, B.; Martinelli, A. Farmaco 1996, 51, 131; (b) Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Lucacchini, A.; Giannaccini, G.; Barili, P. L. Eur J Med Chem 2000, 35, 333.

[3] Tennant, G. J Chem Soc (C) 1966, 2290.

[4] (a) Shaban, M. A. E.; Taha, M. A. M.; Sharshira, E. M. Adv Heterocycl Chem 1991, 52, 1; (b) Krivopalov, V. P.; Shkurko, O. P. Russ Chem Rev 2005, 74, 339.

[5] Da Settimo, A.; Livi, O.; Biagi, G.; Primofiore, G.; Masoni, G. Farmaco, 1982, 37, 728.

[6] (a) Pokhodylo, N. T.; Matiychuk, V. S.; Obushak.M. D. Chem Heterocycl Compds 2009, 45, 483; (b) Pokhodylo, N. T.; Matiychuk, V. S.,Obushak, M. D. Tetrahedron 2009, 65, 2678.

[7] (a) Saito, K.; Kambe, S.; Nakano, Y. Synthesis 1983, 210; (b) Volovenko, Y. M.; Resnyanska, E. V.; Tverdokhlebov, A. V. Collect Czech Chem Commun 2002, 67, 365.

[8] Obushak, N. D.; Pokhodylo, N. T.; Pidlypnyi, N. I.; Matiichuk, V. S. Russ J Org Chem 2008, 44, 1522.

[9] (a) Xu, Z.; Li, Y.; Ma, X.; Gao, X.; Tian, H. Tetrahedron 2008, 64, 1860; (b) Paul, P. K.; Hussain, S. A.; Bhattacharjee, D. J Luminescence 2008, 128, 41; (c) Feng, L.; Wang, X.; Chen, Z. Spectrochimica Acta Part A: Mol Biomol Spectrosc 2008, 71, 312; (d) Ono, K.; Ito, H.; Nakashima, A.; Uemoto, M.; Tomura, M.; Saito, K. Tetrahedron Lett 2008, 49, 5816; (e) Xiao, F.; Liu, Y.; Hu, Z.; Gan, Q.; Wang, L.; Wen, Z.; Zhu, M.; Zhu, W. Synth Met 2009, 159, 1308; (f) Hegde, P. K.; Adhikari, A. V.; Manjunatha, M. G.; Suchand Sandeep, C. S.; Philip, R. Synth Met 2009, 159, 1099.

[10] (a) Ignatenko, O. A.; Kuznetsov, M. A.; Selivanov, S. I. Russ J Org Chem 2007, 43, 1042; (b) Ol'khovik, V. K.; Pap, A. A.; Vasilevskii, V. A.; Galinovskii, N. A.; Tereshko, S. N. Russ J Org Chem 2008, 44, 1172.

[11] (a) Dimroth, O.; Michaelis, W. Lieb Ann Chem 1927, 459, 39; (b) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. Adv Heterocycl Chem 1999, 75, 79.

[12] (a) Sandmeyer, T. Helv Chim Acta 1919, 2, 230; (b) Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[13] Bayer, O.; Eckert, W. In Methoden der organischen Chemie (Houben-Weyl), Bd. 7/4, S.5, Thieme Verlag: Stuttgart, 1968.

[14] Leulier, P. Bull Soc Chim France 1924, 35, 1328.

[15] (a) Cassebaum, H. J Prakt Chem 1964, 23, 301; (b) Kambli, E. Helv Chim Acta 1964, 47, 2155; (c) Prinz, W.; Kayle, A.; Levy, P. R. J Chem Res (S) 1978, 116.

[16] Falcao da Fonseca, L. Rev Portug Farmac 1965, 15, 317.

[17] Okabe, M.; Sun, R.-C. Tetrahedron 1995, 51, 1861.

# One-Pot, Three-Component Synthesis of Spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indolines in Water



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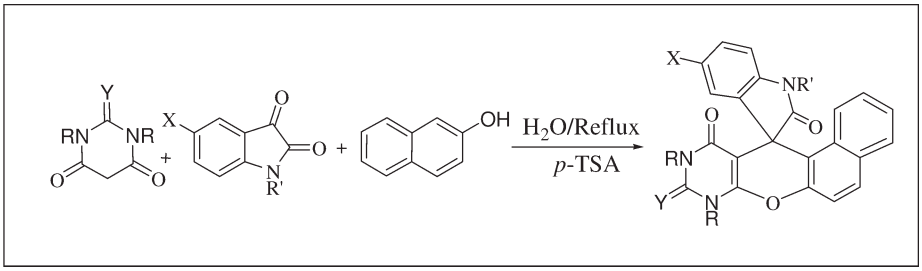


A clean, one-pot and three-component synthesis of new spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives by cyclo-condensation reaction of isatins, 2-naphthol, and barbituric acids in aqueous media is reported.

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## INTRODUCTION

Multicomponent reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [1,2]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [3,4]. As such processes avoid time-consuming and costly purification processes, and protection-deprotection steps, they are inherently more environmentally benign and atom economic [5]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds and small and drug-like heterocycles [6]. Designing of MCRs in water is another attractive area in green chemistry [7], because water is a cheap, safe, and environmentally benign solvent. There is need for developing MCRs in water with a suitable catalyst and without the use of any harmful organic solvents.

Indole moiety is probably the most well-known heterocycle and a common and important feature of a variety of natural products and medicinal agents [8]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity [9,10]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [11–13]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [14–17].

Substituted amino-pyrans take a significant place among the 6-membered oxygen-containing heterocycles. Some of them possess anticancer and antimicrobial activity [18,19]. Serotonin receptor modulators (pteropodine and its stereoisomers) and natural alkaloids, containing both spiro-indole and pyran cycles, were isolated from stem bark of *Uncaria tomentosa* (Fig. 1) [11]. Several spiroheterocycles containing both indole and pyran heterocycles possess anticonvulsant and analgetic [20], herbicidal and antibacterial activities [21].

Pyrimidine and its derivatives have been studied for over a century because of a variety of chemical and biological significance. They have been reported as antibacterial, antiviral, and antitumor agents [22]. A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities [23–26]. Similarly, naphthopyran derivatives are an important class of compounds with excellent photochromic properties [27–29], some of which are also structural motifs present in many biologically active compounds [30–32]. For example, some naphthopyran derivatives could have potential applications in biochemical research as photoswitch tag compounds [33].

As part of our continuing efforts on the synthesis of biologically active heterocyclic compounds [34–41], we recently described an efficient synthesis of spiropyrimidoquinoline-pyrrolopyrimidines and spiroindoline-pyridodipyrimidines via a condensation reaction between amino-uraciles and isatines [42,43]. We have also

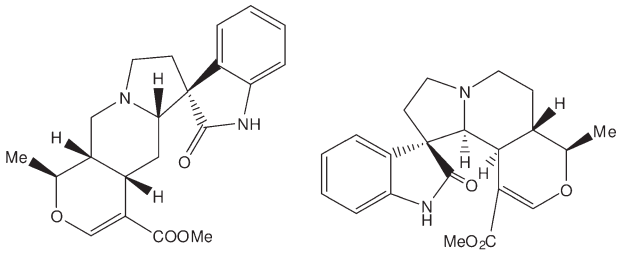



**Figure 1.** Spirooxindole natural alkaloids.

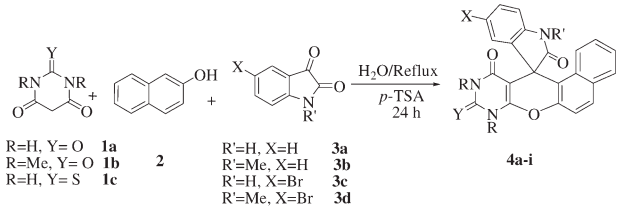
developed an efficient synthesis of spiro[dibenzo[*b*,*i*]-xanthene-13,3′-indoline]-pentaones via a reaction of isatins and 2-hydroxy-naphthoquinone in water [44].

Considering the important biological properties of spirooxindole-fused heterocycles, we report herein a one-pot, three-component and clean synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indolines 4 through a one-pot, three-component condensation reaction of barbituric acids **1a–c**, 2-naphthol **2**, and isatins **3a–d** in water (Scheme 1).

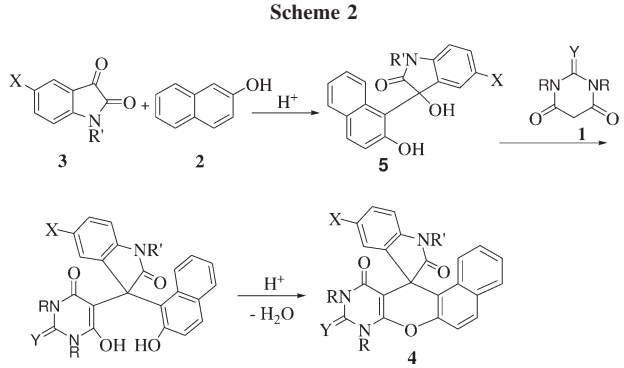
## RESULTS AND DISCUSSION

In a pilot experiment, a mixture of barbituric acid **1a**, 2-naphthol **2**, and isatin **3a** at refluxing water was stirred in the presence of catalytic *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst to afford the spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione **4a** in 85% for 24 h. Then, to delineate this approach, particularly in regard to library construction, this methodology was evaluated using three commercially available barbituric acids **1a–c**, 2-naphthol **2**, and four substituted isatins **2a–d**, and the corresponding spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives **4a–i** were synthesized by the one-pot, three-component condensation reaction for good yields under similar conditions (Table 1). $^{1}$H- and $^{13}$C-NMR spectra of the crude products clearly indicated the formation of spirooxindol-fused naphthopyranopyrimidine **4**. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4a–i** are stable solids whose structures were established by IR, $^{1}$H- and $^{13}$C-NMR spectroscopy and elemental analysis.

**Scheme 1**




**Scheme 2**




The results were good in terms of yields and product purity in the presence of *p*-TSA, whereas without *p*-TSA the yields of products were trace even after 48 h.

To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives. This method, based on three-component *p*-TSA-catalyzed reaction in water, is the most simple and convenient and would be applicable for the synthesis of different types of spironaphthopyranopyrimidine-indolines.

We have not established an exact mechanism for the formation of spironaphthopyranopyrimidine-indolines **4**; however, the formation of products **4** can be rationalized via initial formation of intermediate **5** by condensation of 2-naphthol **2** and isatin **3** [45]. Subsequent addition of barbituric acids **1** to the intermediate **5**, followed by cyclization afforded the **4** and water (Scheme 2).

In conclusion, we have demonstrated an efficient, a clean, and a simple method for the preparation spironaphthopyranopyrimidine-indolines using readily available starting materials. Prominent among the advantages of this new method are novelty, operational simplicity, good yields, and easy work-up procedures used. Moreover, it is worth noting that two C—C and one C—O bonds were formed with concomitant creation of a spirooxindol-fused naphthopyranopyrimidine in this one-pot, three-component process.

## EXPERIMENTAL

Melting points were measured on an Elecrtothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. $^{1}$H- and $^{13}$C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using a Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

**Table 1**

Synthesis of spironaphthopyranopyrimidine-indolines **4**.

| Product **4** | R | R′ | X | Y | Yield (%) |
|---|---|---|---|---|---|
| **a** | H | H | H | O | 85 |
| **b** | H | Me | H | O | 83 |
| **c** | H | H | Br | O | 80 |
| **d** | H | Me | Br | O | 82 |
| **e** | Me | H | H | O | 79 |
| **f** | Me | Me | H | O | 77 |
| **g** | H | H | H | S | 81 |
| **h** | H | H | Br | S | 82 |
| **i** | H | Me | Br | S | 80 |

**Typical procedure for the preparation of spiro[naphtho [1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4a).** A mixture of barbituric acid **1a** (0.13 g, 1 mmol), 2-naphthol **2** (0.14 g, 1 mmol), isatin **3a** (0.15 g, 1 mmol), and *p*-TSA (0.1 g) in refluxing water (5 mL) was stirred for 24 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with water (10 mL) and recrystallized by EtOH to afford the pure product **4a** as with powder (85%); m.p > 300°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3265, 3013, 1723, 1645, 1627. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.62–8.01 (m, 10H, ArH), 9.67 (s, 1H, NH), 10.79 (s, 1H, NH), 10.87 (s, 1H, NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 50.36, 83.2, 111.9, 117.5, 120.4, 121.4, 124.5, 124.9, 127.1, 127.5, 128.2, 129.6, 130.1, 130.6, 131.4, 135.1, 146.5, 149.7, 150.3, 162.4, 178.7. MS(EI, 70 eV) *m*/*z*: 383 ($M^+$). Anal. Calcd for $C_{22}H_{13}N_3O_4$: C, 68.93; H, 3.42; N, 10.96. Found: C, 68.79; H, 3.39; N, 10.90.

**1′-Methyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*, 3*H*)-trione (4b).** Gray powder (83%); m.p > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3324, 2921, 1720, 1680, 1600. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.34 (3H, s, $CH_3$), 6.85–8.03 (10H, m, H-Ar), 10.98 (1H, s, NH), 12.25 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 397 ($M^+$). Anal. Calcd for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10.57. Found: C, 69.57; H, 3.76; N, 10.50.

Because of very low solubility of the product **4b**, we cannot report the $^{13}$C-NMR data for this product.

**5′-Bromo-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*, 3*H*)-trione (4c).** Light brown powder (80%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3316, 3065, 1781, 1712, 1651. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.68–8.03 (9H, m, H-Ar), 9.88 (1H, s, NH), 10.85 (1H, s, NH), 11.05 (1H, s, NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 50.3, 83.2, 112.1, 115.5, 120.5, 121.3, 122.6, 125.1, 126.5, 128.1, 128.5, 129.4, 130.3, 131.1, 131.5, 132.6, 135, 146.4, 149.7, 162.4, 178.3. MS(EI, 70 eV) *m*/*z*: 463 ($M^+$), 461 ($M^+$). Anal. Calcd for $C_{22}H_{12}BrN_3O_4$: C, 57.16; H, 2.62; N, 9.09. Found: C, 57.20; H, 2.67; N, 9.14.

**5′-Bromo-1′-methyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*] pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4d).** Gray powder (82%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3178, 3055, 1719, 1663, 1601. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.31(3H, s, $CH_3$), 6.79–8.05 (9H, m, H-Ar), 11.03 (1H, s, NH), 12.29 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 477 ($M^+$), 475 ($M^+$). Anal. Calcd for $C_{23}H_{14}BrN_3O_4$: C, 58.00; H, 2.96; N, 8.82. Found: C, 57.94; H, 2.91; N, 8.90.

Because of very low solubility of the products **4d–i**, we cannot report the $^{13}$C-NMR data for these products.

**1,3-Dimethyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4e).** Gray powder (79%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3296, 1710, 1607, 1528. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 2.97 (3H, s, $CH_3$), 3.62 (3H, s, $CH_3$), 6.61–7.98 (10H, m, H-Ar), 9.83 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 411 ($M^+$). Anal. Calcd for $C_{24}H_{17}N_3O_4$: C, 70.07; H, 4.16; N, 10.21. Found: C, 70.02; H, 4.20; N, 10.26.

**1′,1,3-Trimethyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4f).** Gray powder (77%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3034, 17129, 1667, 1632. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.02 (3H, s, $CH_3$), 3.34 (3H, s, $CH_3$), 3.53 (3H, s, $CH_3$), 6.85–8.05 (10H, m, H-Ar). MS(EI, 70 eV) *m*/*z*: 425 ($M^+$). Anal. Calcd for $C_{25}H_{19}N_3O_4$: C, 70.58; H, 4.50; N, 9.88. Found: C, 70.52; H, 4.45; N, 9.81.

**2-Thioxo-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2′,4(1*H*,3*H*)-dione (4g).** Gray powder (81%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3334, 2921, 1771, 1613, 1570. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.63-8.01 (11H, m, NH and H-Ar), 9.41 (1H, s, NH), 12.26 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 399 ($M^+$). Anal. Calcd for $C_{22}H_{13}N_3O_3S$: C, 66.15; H, 3.28; N, 10.52. Found: C, 66.21; H, 3.32; N, 10.61.

**5′-Bromo-2-Thioxo-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*] pyrimidine-5,3′-indoline]2′,4(1*H*,3*H*)-dione (4h).** Gray powder (82%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3311, 2921, 1771, 1647, 1559. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.70–8.04 (10H, m, NH and H-Ar), 9.56 (1H, s, NH), 12.29 (1H, s, NH). MS (EI, 70 eV) *m*/*z* (%): 479 ($M^+$), 477 ($M^+$). Anal. Calcd for $C_{22}H_{12}BrN_3O_3S$: C, 55.24; H, 2.53; N, 8.78. Found: C, 55.20; H, 2.50; N, 8.73.

**5′-Bromo-1′-methyl-2-hioxo-spiro[naphtho[1′,2′:5,6]pyrano [2,3-*d*]pyrimidine-5,3′-indoline]2′,4(1*H*,3*H*)-dione (4i).** Gray powder (80%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3311, 2921, 1767, 1647, 1559. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.22 (3H, s, $CH_3$), 715–8.37 (9H, m, H-Ar), 9.60 (1H, s, NH), 12.43 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 493 ($M^+$), 491 ($M^+$). Anal. Calcd for $C_{23}H_{14}BrN_3O_3S$: C, 55.11; H, 2.87; N, 8.53. Found: C, 55.17; H, 2.93; N, 8.45.

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## REFERENCES AND NOTES

[1] Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[2] Dömling, A. Chem Rev 2006, 106, 17.

[3] El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. Org Lett 2006, 8, 4019.

[4] Zhu, J.; Bienaymé, H. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2005.

[5] Trost, B. M. Angew Chem Int Ed Engl 1995, 34, 259.

[6] Weber, L. Curr Med Chem 2002, 9, 2085.

[7] Herrerias, C. I.; Yao, X.; Li, Z.; Li, C. Chem Rev 2007, 107, 2546.

[8] Sundberg, R. J. The Chemistry of Indoles; Academic Press: New York, NY, 1996.

[9] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[10] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. Bioorg Med Chem 2006, 12, 2483.

[11] Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39.

[12] Ma, J.; Hecht, S. M. Chem Commun 2004, 1190.

[13] Usui, T.; Kondoh, M.; Cui, C.-B.; Mayumi, T.; Osada, H. Biochem J 1998, 333, 543.

[14] Zhu, S.-L.; Ji, S.-J.; Zhang, Y. Tetrahedron 2007, 63, 9365.

[15] Kumar, R. S.; Perumal, S. Terahedron Lett 2007, 48, 7164.

[16] Redkin, R. Gr.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. Tetrahedron 2007, 63, 11444.

[17] Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. Tetrahedron 2007, 63, 2057.

[18] Al-Haiza, M. A.; Mostafa, M. S.; El-Kady, M. Y. Molecules 2003, 8, 275.

[19] Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zho, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. J Med Chem 2004, 47, 6299.

[20] Joshi, K. C.; Jain, R.; Sharma, K. J Indian Chem Soc 1988, 65, 202.

[21] Higashiyama, K.; Otomasu, H. Chem Pharm Bull 1980, 28, 648.

[22] Fellahi, Y.; Dubois, P.; Agafonov, V.; Moussa, F.; Ombetta-Goka, J. E.; Guenzet, J.; Frangin, Y. Bull Soc Chim Fr 1996, 133, 869.

[23] Sharma, P.; Rane, N.; Gurram, V. K. Bioorg Med Chem Lett 2004, 14, 4185.

[24] Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. F. Adv Heterocycl Chem 1987, 41, 319.

[25] Suzuki, N. Chem Pharm Bull 1980, 28, 761.

[26] Parakash, L.; Shaihla, M.; Mital, R. L. Pharmazie 1989, 44, 490.

[27] Hepworth, J. D.; Heron, B. M. In Progress in Heterocyclic Chemistry; Gribble, G., Joule, J., Eds.; Elsevier: Amsterdam, 2005; Vol. 17, pp 33–62.

[28] Nakatsuji, S. Chem Soc Rev 2004, 33, 348.

[29] Shilova, E. A.; Pepe, G.; Samat, A.; Moustrou, C. Tetrahedron 2008, 64, 9977.

[30] Dell, C. P. Curr Med Chem 1998, 5, 179.

[31] Karnik, A. V.; Kulkarni, A. M.; Malviya, N. J.; Mourya, B. R.; Jadhav, B. L. Eur J Med Chem. 2008, 43, 2615.

[32] Hussein, A. A.; Barberena, I.; Capson, T. L.; Kursar, T. A.; Coley, P. D.; Solis, P. N.; Gupta, M. P. J Nat Prod 2004, 67, 451.

[33] Kumar, S.; Hernandez, D.; Hoa, B.; Lee, Y.; Yang, J. S.; McCurdy, A. Org Lett 2008, 10, 3761.

[34] Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. Tetrahedron Lett 2007, 48, 8790.

[35] Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 2375.

[36] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. J Heterocycl Chem 2007, 44, 1009.

[37] Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. Heterocycles 2008, 75, 87.

[38] Dabiri, M.; Delbari, A. S.; Bazgir, A. Synlett 2007, 821.

[39] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2007, 63, 1770.

[40] Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543.

[41] Ghahremanzadeh, R.; Shakibaei, G. I.; Bazgir, A. Synlett 2008, 1129.

[42] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. Tetrahedron 2009, 65, 2005.

[43] Dabiri, M.; Azimi, S. C.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 7307.

[44] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. Terahedron Lett 2008, 49, 5165.

[45] (a) Kumar, V. P.; Reddy, V. P.; Sridhar, R.; Srinivas, B.; Narender, M.; Rao, K. R. J Org Chem 2008, 73, 1646; (b) Ramachary, D. B.; Reddy, G. B.; Mondal, R. Tetrahedron Lett 2007, 48, 7618.

# Imidazoline-4-thiones from Cyanothioformamides and Aldehyde Imines: Formation, Aromatization, and Acetylation



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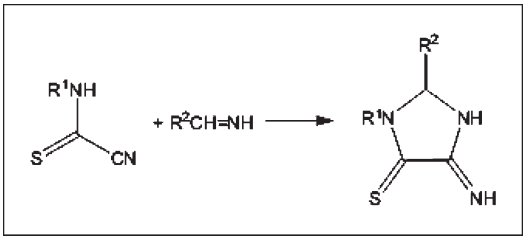


The reaction of *N*-methyl- (**3a**) or *N*-phenylcyanothioformamide (**3b**) with acetaldimine (**5a**, as 1-amino-1-ethanol) gives 5-(amino)imidazolidine-4-thiones **6B**. Product **6a** reacts with a second equivalent of **3a** to give **8** which in turn is oxidized to disulfide **9**. Using araldimines **5b**,**c**, only 1:2 intermediates **10** derived from **3a**, **b** and two moles of the imine **5** are formed, but proved to be easily oxidized to disulfides **11**. Acetylation of **6** occurs chemoselectively on the exocyclic nitrogen and finally also on the thione sulfur to give **14** *via* **13**.

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## INTRODUCTION

There is continuing interest in the design and evolution of novel antioxidants as a means to alleviate oxidative stress in biochemical processes [1–3]. For the heterocyclic chemist, an attractive lead structure appears to be the unusual amino acid family of ovothiols **1a–c** [4–7]. So, imidazole-4-thiols **2** have become attractive targets for synthesis (Scheme 1).

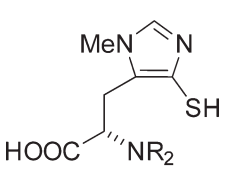
*N*-Acylaminoacid thioamides are possible precursors of ovothiols **1** [4], but their cyclization is not always reproducible [5]. Similarly, the *Asinger* group has reported the formation of imidazolethiols **2** from α-oxothioamides and aldimines [8]. Recently, we have reported the synthesis of oxazolidines **4** from cyanothioformamides **3** and aldehydes or ketones [9] as part of our study on heterocyclic ring-closure reactions [10–16] and now envisaged that cyanothioformamides **3** and *N*-unsubstituted aldimines should give products of type **2**, though with a 5-amino group as additional feature which may assist in free-radical trapping. However, the position of the tautomeric equilibrium in the probable cyclization products **6** between iminothiones **6A**, aminothiones **6B**, and aminothiols **6C** is a priori open (Scheme 2). On the other hand, heterocycles **6** are also of special interest as precursors of the elusive bicyclic heteroaromatic products of type **12** (Scheme 5).

## RESULTS AND DISCUSSION

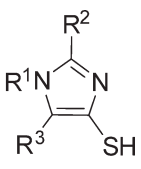
We selected *N*-methyl- (**3a**) and *N*-phenylcyanothioformamide (**3b**) as nucleophiles, and acetaldimine **5a** (as 1-amino-1-ethanol [17]) or benzaldimines **5b**,**c** as electrophiles. Triethylamine was used as a catalyst.

Thioamide **3a** and acetaldimine **5a** give a smooth reaction to furnish 1:1 product **6a** as the only defined

**Scheme 1.** Imidazole-4-thiols.

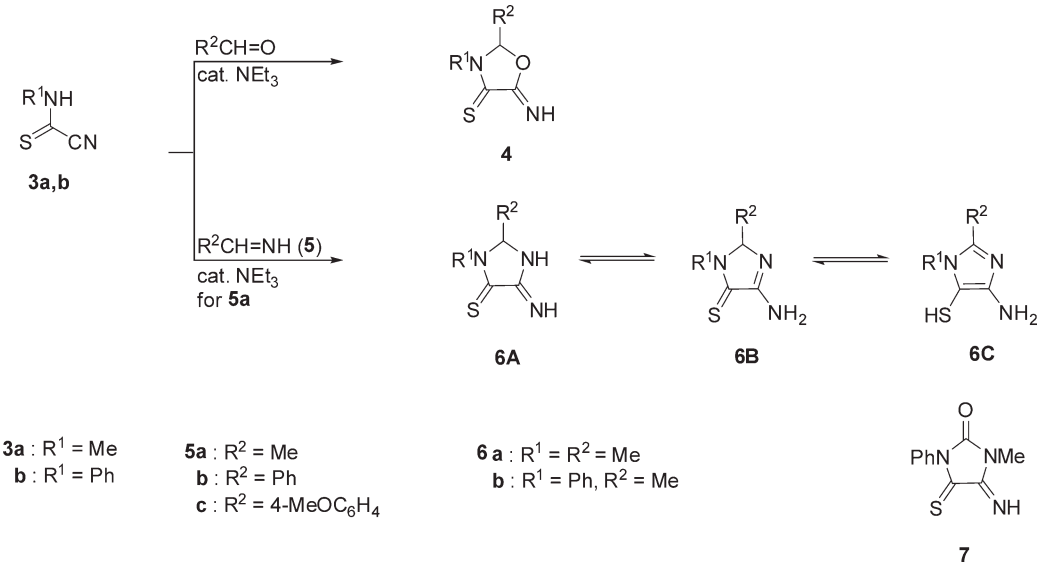



**1a**: R = H
**1b**: $NR_2$ = NHMe
**1c**: R = Me




**2**

**Scheme 2.** Reactions of cyanothioformamides with aldehydes or acetaldimine.




product. An analogous product **6b** is formed from thioamide **3b** und **5a** (Scheme 2). As to the position of the tautomeric equilibrium, appearance of the 2-methyl signal of **6a** as a doublet in the $^1$H NMR spectrum and a low-field $^{13}$C NMR signal (ca. 182 ppm) pointing toward the presence of a thiocarbonyl carbon as in **6A** and **6B** allow to rule out tautomer **6C**. Another low-field $^{13}$C NMR peak at δ about 159 ppm occurs at definitely lower field than for the exocyclic imino group in model compound **7** (δ 154.2 ppm) [10,11,18], and in the $^1$H NMR spectrum, the two NH protons are magnetically equivalent as expected for **6B**. Moreover, the IR spectra lack a strong vibration in the 1650–1670 cm$^{-1}$ range which is observed for **7** (1659 cm$^{-1}$) and in other authentic 5-imino-imidazolidine-4-thiones [13,18]. So obviously, tautomer **6B** is preferred indicating that the greatest degree of stabilization is achieved by conjugation within the transoid S═C─C═N unit of tautomer **6B** when compared with the corresponding cisoid system in **6A** or the aromaticity of **6C**.

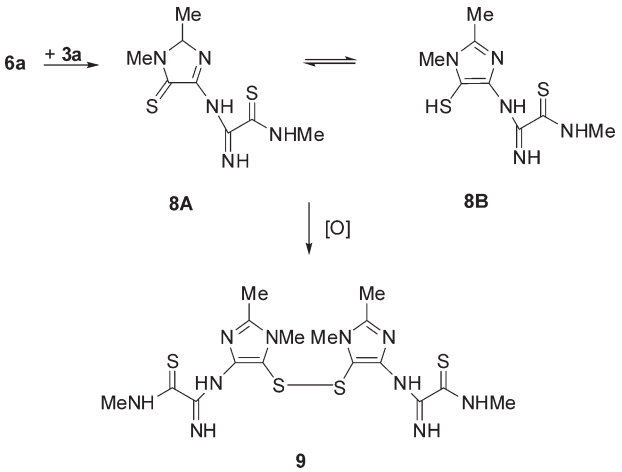
Prolonged reaction times in the addition of **3a** to **5a** showed that the thioamide **3a** adds faster to cyclization product **6a** than to **5a** giving rise to a 2:1 adduct **8** as well as aromatic disulfide **9** as oxidation product (Scheme 3).

An X-ray crystallographic study revealed the structure of **9** and so implicitly also of precursor **8**. As the spectroscopic data for **8** are similar to those of **6**, we assume that the imidazole unit in **8** has structure **B** as in the preferred tautomer **B** of **6**. In the formation of **8**, the second mole of **3a** has been incorporated *via* its nitrile function by addition to the exocyclic imino group of **6a** and this is obviously followed by aromatization and oxidation to the disulfide **9** (Fig. 1).

Reactions of thioamides **3** with aromatic aldimines **5b**,**c** take a different course (Scheme 4). Here, invariably dehydrogenated 2:1 products **11a–c** are formed obviously *via* intermediate **6**, followed by Schiff base formation with a second equivalent of the imine **5** to give azomethines **10** with loss of ammonia, and finally oxidative aromatization. Even when the reactions were run under nitrogen, conventional work-up led to oxidation to give the aromatic disulfides **11**. So, there is a striking difference in the sensitivity to oxidation between the 2-methyl ($R^2$ = Me) products **6a**,**b** and their 2-aryl congeners **10**.

Attempts to cyclize **6a**,**b** using acetic anhydride gave no indication for the formation of the bicyclic hetarene **12**, but simple monoacetylation is observed (Scheme 5). The spectroscopic data allow no unambiguous

**Scheme 3.** Oxidation of imidazolinethione **6a**.



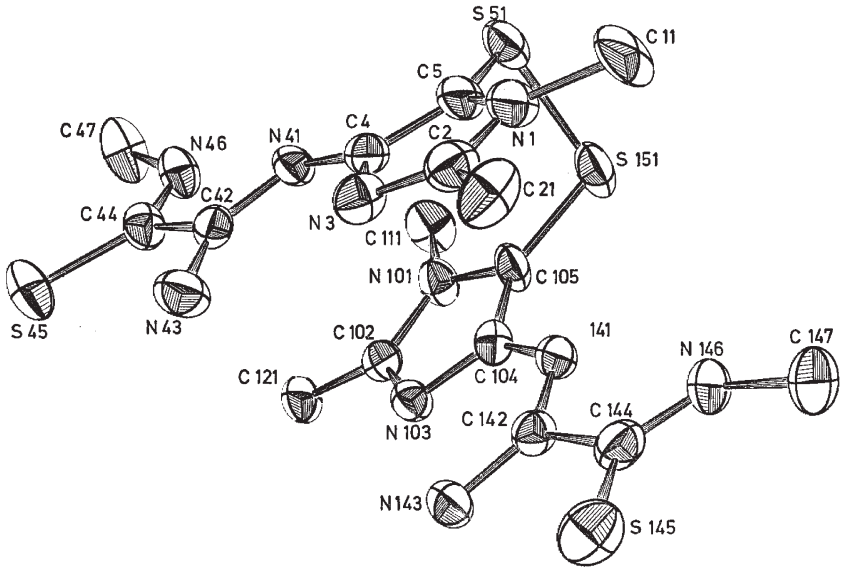


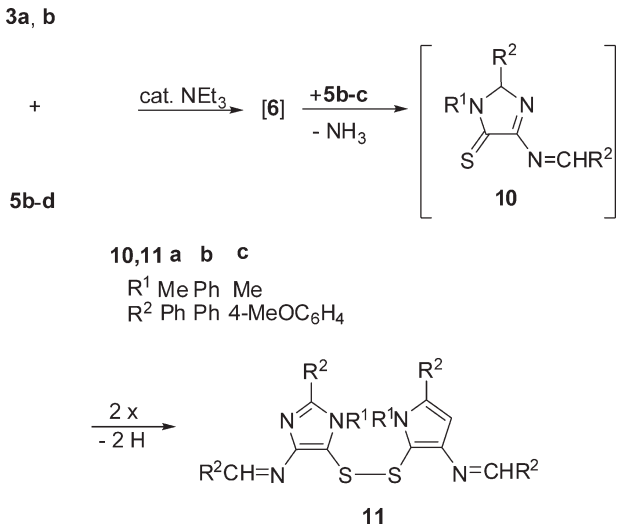

**Figure 1.** ORTEP drawing of disulfide **9** with salient bond lengths [Å]: S51-C5 1.840(9), S51-S151 2.176(4), N1-C2 1.367(11), N3-C2 1.323(10), N3-C4 1.402(10), C4-C5 1.395(10), N41-C42 1.298(9), N43-C42 1.385(10), S45-C-44 1.676(8), N46-C44 1.295(9), S151-C105 1.712(7), N101-C105 1.405(9), N101-C102 1.356(9), N103-C102 1.320(9), N103-C104 1.365(8), C104-C105 1.401(10), N141-C142 1.270(8), N143-C142 1.331(9), S145-C144 1.751(8), N146-C144 1.303(10).

distinction between acetylation of the endocyclic or the exocyclic nitrogen, but further acetylation of the product derived from **6b** yields a triacetylated product for which structure **14** is suggested based on the magnetic equivalence of two acetyl residues. Mutatis mutandis this leads to structure **13** for the *N*-monoacetylated products. Similarly, monoacetylation in the exocyclic position is observed when the hydrolysis product **15** of imine **6a** is acetylated to give apparently an ester derivative **16**. This is evident particularly from the high-wavenumber carbonyl absorptions (1762, 1731 $cm^{-1}$) of the product.

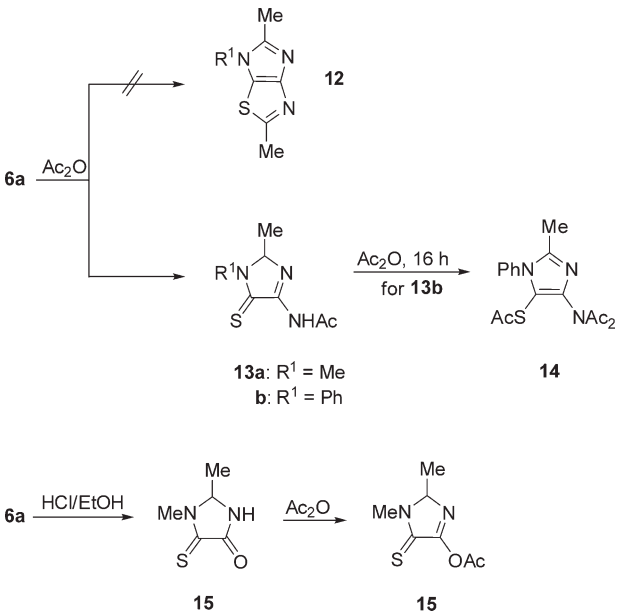
## CONCLUSIONS

The reaction of cyanothioformamides **3** with aldimines **5** takes the expected initial course when the

**Scheme 4.** Cyanothioformamides and araldimines.




**Scheme 5.** Acylation of imidazolinethiones **6**.



nitrogen in the thioamide moiety in **3** attacks the electrophilic imine carbon of **5**, whereas the nitrile function provides the opportunity for subsequent cyclization to give imidazolidines **6**. However, among the possible tautomers **6B** is apparently preferred and can be isolated for $R^2$ = methyl whereas compounds with $R^2$ = aryl tend to add a second equivalent of imine **5** and easily undergo oxidative dimerization. The ready oxidation of imidazole-4-thiols had been seen before in similar examples [5,8]. Unfortunately, the disulfide form of L-ovothiol A (**1a**) is biologically inactive [6] and this may also be anticipated for the disulfides of this work.

## EXPERIMENTAL

**General.** NMR: Bruker WP 80–FT, AMX 400, or Varian FT–80A; $CDCl_3$ as solvent unless stated otherwise, with TMS as internal standard; coupling constants *J* are given in Hz. IR: Perkin–Elmer FTIR 1720 X or Pye-Unicam SP3-200 spectrometers. Elemental analyses: Institut für Pharmazeutische Chemie, TU Braunschweig.

*N*-Methylcyanothioformamide (**3a**) [9] and cyanothioformanilide (**3b**) [19] were prepared as previously described, though in the preparation of **3b** we found use of THF as solvent advantageous. For the synthesis of imine **5a** see ref. [17], for benzaldimine (**5b**) see ref. [20]; imine **5c** [21] was prepared analogously.

***5-Amino-2,3-dimethyl-5-imidazoline-4-thione (6a).*** An ethereal (20 mL) solution of **3a** (2.38 g, 20 mmol), **5a** (3.66 g, 20 mmol), and triethylamine (three drops) was stirred for 30 min at 20°C to give **6a** as reddish–brown crystals (745 mg, 26%); m.p. 137°C (dec.). IR (KBr): $\tilde{\nu}$ = 3370, 3180, 2950, 1470, 1140 $cm^{-1}$. $^1H$ NMR: δ = 1.44 (d, *J* = 6.4, 3 H, $CCH_3$), 3.36 (s, 3 H, $CH_3N$), 5.13 (q, *J* = 6.4, 1 H, CH), 5.58 (broad, 2 H, NH). $^{13}C$ NMR: δ = 181.96 (C═S), 159.37 (N═C), 84.64 (C─Me), 32.28 (N─Me), 18.80 (Me). MS: m/z (%) = 143 (100) [M], 128 (23) [M─$CH_3$], 74 (28), 69 (31). HRMS for ($C_5H_9N_3S$ + H): calcd 144.0595, found 144.0601.

***5-Amino-2-methyl-3-phenyl-5-imidazoline-4-thione (6b).*** An ethereal (25 mL) solution of **3b** (1.62 g, 10 mmol), **5a** (1.83 g, 10 mmol), and triethylamine (three drops) was stirred for 15 min and then diluted with hexane. The gummy residue was extracted several times with hexane. These extracts were combined with the ether-hexane solution. Removal of the solvents under reduced pressure gave **6b** as reddish brown crystals (308 mg, 15%); m.p. 125–127°C. IR (KBr): $\tilde{\nu}$ = 3350, 3270, 2950, 1470, 1130 $cm^{-1}$. $^1H$ NMR: δ = 1.33 (d, *J* = 6.4 Hz, 3 H, $CH_3$), 5.78–5.60 (q, *J* = 6.4, 1 H, CH and broad, 2 H, $NH_2$, exchangeable with $D_2O$), 7.48 (m, 5 H, ArH). $^{13}C$ NMR: δ = 181.80 (C═S), 159.03 (N═C), 129.49, 128.44, 125.01 (Ph), 85.47 (*C*─Me), 19.63 (Me). MS: *m/z* (%) = 205 (68) [M], 204 (8), 190 (7), 135 (12), 70 (100). $C_{10}H_{11}N_3S$ (205.3); calcd C 58.51, H 5.40, N 20.47, S. 15.62; found C 58.31, H 5.52, N 20.10, S 15.23.

***5-Imino-1-methyl-3-phenyl-4-thioxoimidazolidin-2-one (7).*** The compound had been prepared before [10,16]. IR (KBr): 1766 (C═O), 1659 (C═N) $cm^{-1}$. $^{13}C$ NMR ($CH_3$): δ =181.9 (C═S), 154.8 (C═O), 154.2. (C═NH), 132.5 (Ar), 129.4, 129.3, 126.9 (ArH), 26.8 ($NCH_3$).

***2-(1,2-Dimethyl-5-mercaptoimidazol-4-yl)amino-2-imino-N-methyl-thioacetamide (8B) and bis[4-(imino-(N-methylthiocarbamoyl)methyl)amino-1,2-dimethylimidazol-5-yl] disulfide (9).*** An ethereal (20 mL) solution of **3a** (3.24 g, 20 mmol), **6a** (3.66 g, 20 mmol), and triethylamine (three drops) was stirred at 20°C for 30 min and then allowed to stand for 16 h. The solid product was extracted several times with cold ethanol. The remaining solid was recrystallized from boiling ethanol to give **8** as yellow crystals (9.73 g, 20%); m.p. 173–175°C. IR (KBr): $\tilde{\nu}$ = 3150–3300, 2930–2970, 1450, 1130 $cm^{-1}$. $^1H$ NMR: δ = 2.50 (s, 3 H, $CCH_3$), 2.90 (d, *J* = 6 Hz, 3 H, NHC*H*$_3$, collapses to s with $D_2O$), 3.56 (s, 3 H, $CH_3N$), 7.63, 9.33, 10.40 (each s, 3H, broad NH, exchanges with $D_2O$). Concentration of the ethanolic extract from earlier gave **9** as reddish crystals (145 mg, 30%); m.p. 195–197°C. IR (KBr): $\tilde{\nu}$ = 3350–3230 (broad, NH), 2910–2980, 1470, 1150 $cm^{-1}$. $^1H$ NMR: δ = 2.29 (s, 6 H, $CH_3C$), 3.21 (s, 6 H, C*H*$_3$NH), 3.3 (s, 6 H, $CH_3N$), 7.47, 8.99, 9.88 (each broad, NH; exchanges with $D_2O$). $C_{16}H_{24}N_{10}S_4$. (484.7): calcd. C 39.65, H 4.99, N 28.90, S 26.46; found C 39.60, H 5.00, N 29.00, S 26.50.

***Bis(4-benzylidenamino-1-methyl-2-phenyl-imidazole)-5,5′-diyl disulfide (11a).*** An ethereal solution (20 mL) of **3a** (1.0 g, 10 mmol), **5b** (1.05 g, 10 mmol), and triethylamine was stirred at 20°C for 0.5–2 h to provide yellow crystals (750 mg, 51%), m.p. 187–190°C. IR (KBr): $\tilde{\nu}$ = 1605, 1573. $^1H$ NMR: δ = 3.85 (s, 3 H, $CH_3$), 7.2–7.78 (m, 10 H, Ph, CH), 8.99 (s, 1 H, PhCH═N). $^{13}C$ NMR: δ = 158.6 (N═CH), 155.7 (C-2), 149.8 (C-4), 136.3, 130.9, 128.9, 128.7, 128.6, 128.4, 128.2 (Ar), 116.4 (C-5), 32.5 ($NCH_3$). MS: m/z (%) = 585 (48) [M + H], 481 (58), 437 (59), 393 (92), 349 (100). $C_{34}H_{28}N_6S_2$ (584.8): calcd. for C 69.83, H 4.83, N 14.37, S 10.97; found C 69.13, H 4.96, N 14.51, S. 10.65.

***Bis(4-benzylidenamino-1,2-diphenyl-imidazole)-5,5′-diyl disulfide (11b).*** An ethereal solution (20 mL) of **3a** (1.62 g, 10 mmol), benzaldimine **5b** (2.10 g, 20 mmol), and triethylamine (three drops) was stirred for 30 min and allowed to stand overnight. The yellow crystals were collected and recrystallized from dichloromethane/methanol; yield 1.60 g (45%). m.p. 195°C (dec.). Repeated crystallization afforded a product with m.p. 207°C (dec.). IR (KBr): $\tilde{\nu}$ = 1605, 1573, 1503, 1316 $cm^{-1}$. $^1H$ NMR: δ = 6.96–7.48 (m, 13H), 9.11 (s, 1 H, PhCH═N). $^{13}C$ NMR: δ = 159.3 (N═CH), 155.7 (C-4), 148.6 (C-2), 136.62, 136.41, 129.52 (Ar), 130.94, 129.07, 128.90, 128.58, 128.48, 128.43, 127.88 (ArH), 119.0 (C-5). MS: *m/z* (%) = 709 (100) [M + H], 337 (18), 289 (9), 161 (19), 105 (8). $C_{44}H_{32}N_6S_2$ (708.9): calcd C 74.55, H 4.55, N 11.86; S 9.05 found C 74.19; H 4.69; N 11.82; S 8.82.

***Bis[4-(4-methoxybenzylidenamino)-1-methyl-2-(4-methoxyphenyl)-imidazole]-5,5′-diyl disulfide (11c).*** Prepared by the procedure described for **11** using **5c** in place of **5b**. Yield 55%, m.p. 155°C. IR (KBr): $\tilde{\nu}$ = 1600, 1470, 1210 $cm^{-1}$. MS: *m/z* (%) = 352 (25) [M/2], 351 (100), 176 (14), 151 (48). $C_{38}H_{36}N_6O_4S_2$ (704.86) calcd. C 64.75 H 5.15 N 11.92, S 9.10; found C 64.70, H 5.50, N 12.00, S 9.10.

**N-*(1,2-Dimethyl-5-thioxo-3-imidazolin-4-yl)acetamide (13a).*** A solution of **6a** (100 mg, 0.7 mmol) in acetic anhydride (1.4 mL, 14.8 mmol) was allowed to stand for 16 h. Removal of acetic anhydride under reduced pressure gave a gummy product which was triturated with water to afford dark pink crystals of **13a** (36 mg, 28%); m.p. 107–109°C. IR: $\tilde{\nu}$ = 3191, 1686, 1666, 1537 $cm^{-1}$. $^1H$ NMR: δ = 1.63 (d, *J* = 5.6, 3 H, $CH_3CN_2$), 2.67 (s, 3 H, $CH_3CO$), 3.39 (s, 3 H, $CH_3N$), 5.51

(q, $J$ = 5.6, 1 H, CH). $^{13}$C NMR: δ = 181.02 (C═S), 170.07 (C═O), 155.77 (C═N), 74.28 (C-2), 84.64 (C─Me), 31.2 (N─Me), 25.72 (Ac-$CH_3$), 18.68 (2-Me). MS: $m/z$ (%) = 185 (89) [M], 143 (100), 128 (14). HRMS for ($C_7H_{11}N_3OS$ + H): calcd 186.0701, found 186.0696.

**N-*(2-Methyl-1-phenyl-5-thioxo-3-imidazolin-4-yl)acetamide (13b).*** A solution of **6b** (4.10 g, 20 mmol) in acetic anhydride (10 mL) was allowed to stand at 20°C for 30 min. Removal of the reagent under reduced pressure gave **13b** as yellow crystals (990 mg, 20%); m.p. 115–117°C. IR (KBr): $\tilde{\nu}$ = 3210, 1720, 1450, 1120 cm$^{-1}$. $^1$H NMR: δ = 1.5 (d, $J$ = 6.0, 3 H, 2-$CH_3$), 2.7 (s, 3 H, $CH_3CO$), 5.5 (q, $J$ = 6.0, 1 H, 2-H), 7.5 (m, 5 H, ArH,), 9.4 (broad s, 1 H, NH, exchanges with $D_2O$). $C_{12}H_{13}N_3OS$ (247.3): calcd C 58.28, H 5.30, N 16.99, S 12.97; found C 58.19, H 5.16, N 17.11, S 12.89.

**N-*(5-Acetylthio-2-methyl-1-phenyl-imidazol-4-yl)diacetamide (14).*** The earlier reaction was repeated, but allowed to run for 16 h to give **14** as yellow crystals (1.66 g, 25%); m.p. 110–111°C. IR (KBr): $\tilde{\nu}$ = 2970, 2910, 1690 cm$^{-1}$. $^1$H NMR: δ = 2.1, 2.3 (each, s, 3 H, $CH_3$), 2.4 (s, 6 H, $Ac_2N$), 7.0–7.6 (m, 5 H, ArH). MS: $m/z$ (%) = 331 (3) [M], 289 (20), 247 (93), 205 (100). $C_{16}H_{17}N_3O_3S$ (331.4): calcd. C 57.99, H 5.17, N 12.68, S 9.68; found C 57.80, H 5.26, N 12.66, S 9.55.

***1,2-Dimethyl-5-thioxoimidazolidin-4-one (15) and (1,2-dimethyl-5-thioxo-3-imidazolin-4-yl) acetate (16).*** A suspension of thione **6a** (50 mg, 0.35 mmol) in EtOH (2.1 mL), and 2*M* HCl (0.35 mL) was refluxed for 30 min. After cooling, water (3.5 mL) was added. Sticky yellow crystals could be removed by filtration and were used as such in the subsequent step. Yield 20 mg (40%). IR (KBr): 3455, 3368, 3211, 1731 cm$^{-1}$. $^1$H NMR (MeOD): 1.64 (d, $J$ = 6.2 Hz, 2-$CH_3$), 3.42 (d, $J$ = 1.2 Hz, 1-$CH_3$), 5.52 (q + q), $J$ = 1.2; 6.2 Hz, 2-H). $^{13}$C NMR (MeOD): δ =177.7 (C═S), 157.5 (C═O), 77.9 (C-2), 32.9 (1-$CH_3$), 18.2 (2-$CH_3$). Lactam **15** (17 mg, 0.12 mmol) was added to $Ac_2O$ (0.24 mL, 2.54 mmol) and the mixture allowed to stand at room temperature for 16 h. After concentration *in vacuo*, water was added and the precipitate isolated by filtration. Yield 10 mg (46%), m. p. 125°C. IR: $\tilde{\nu}$ = 1762, 1731, 1533 cm$^{-1}$. $^1$H NMR: δ = 1.68 (d, $J$ = 5.8 Hz, 3 H, 2-$CH_3$), 2.65 (s, 3 H, Ac─$CH_3$), 3.42 (s, 3 H, $CH_3N$), 5.44 (q, $J$ = 5.8 Hz, 1 H, 2-H). $^{13}$C NMR: δ = 180.6 (C═S), 169.8 (C═O), 156.1 (C═N), 72.3 (C-2), 33.3 (1-$CH_3$), 25.2 (Ac─$CH_3$), 18.7 (1-$CH_3$). MS: m/z (%) = 186 (74) [M], 144 (75), 129 (18), 74 (100).

***Crystal structure determinations of disulfide 9.*** Intensity data were collected with a CAD 4-SDP single-crystal diffractometer (Enraf-Nonius) using graphite-monochromated Cu Kα radiation in the rage θ < 60°. The final refinements were based on 1657 symmetry-independent reflections with $I > 3\sigma$ for I. The structure was solved by the direct-methods program MULTAN. The $E$ map revealed the position of all the heavy atoms. Because of the thinness of the crystal, the positions of the hydrogen atoms were geometrically calculated, but difficult to refine. Convergence was achieved at $R$ = 0.060 ($R_w$ = 0.071). $C_{16}H_{24}N_{10}S_4$, $M_r$ = 484.7, monoclinic, $a$ = 755.2(1), $b$ = 22726(1), $c$ = 1992.8(1) pm, β = 100.32(1)°, $V$ = 2.352 × 10$^9$ pm$^3$, $T$ = room temp., space group Cc, $Z$ = 4, $d_{cal.}$ 1.38 g cm$^{-1}$, $\mu_{Cu\ K\alpha}$ = 38.7 cm$^{-1}$ [22].

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## REFERENCES AND NOTES

[1] (a) Sies, H. Angew Chem 1986, 98, 1061; (b) Sies, H. Angew Chem Int Ed 1986, 25, 1058.

[2] Schafer, F. Q.; Buettner, G. R. Free Radic Biol Med 2001, 30, 1191.

[3] Bhabak, K. P.; Mugesh, G. Chem Eur J 2008, 14, 8640.

[4] Spaltenberg, A.; Holler, T. P.; Hopkins, P. B. J Org Chem 1987, 52, 2977.

[5] Zoete, V.; Bailly, F.; Catteau, J.-P.; Bernier, J.-L. J Chem Soc Perkin Trans 1 1997, 2983.

[6] Röhl, I.; Schneider, B.; Schmidt, B.; Zeeck, E. Z Naturforsch 1999, 54c, 1145.

[7] Bailly, F.; Zoete, V.; Vamecq, J.; Catteau, J.-P.; Bernier, J.-L. FEBS Lett 2000, 486, 19.

[8] Asinger, F.; Saus, A.; Offermanns, H.; Krings, P.; Andree, H. Liebigs Ann Chem 1971, 744, 51.

[9] Ketcham, R.; Schaumann, E.; Niemer, T. Synthesis 1980, 869.

[10] Ketcham, R.; Schaumann, E. J Org Chem 1980, 45, 3748.

[11] Khattak, I.; Ketcham, R.; Schaumann, E.; Adiwidjaja, G. J Org Chem 1985, 50, 3431.

[12] Ketcham, R.; Schaumann, E.; Adiwidjaja, G. Eur J Org Chem 2001, 1695.

[13] El-Sharief, A. M. Sh.; El-Gaby, M. S. A.; Atalla, A. A.; El-Adasy, A.-B. A. A. M. Heteroatom Chem 2005, 16, 218.

[14] El-Sharief, A. M. Sh.; Ammar, Y. A.; El-Gaby, M. S. A. Afinidad 2004, 61, 240.

[15] El-Sharief, A. M. Sh.; Al-Amri, A. M.; Al-Raqa, S. Y. J Sulfur Chem 2006, 27, 245.

[16] Al-Raqa, S. Y.; El-Sharief, A. M. Sh.; Khalil, S. M. E.; Al-Amri, A. M. Heteroatom Chem 2006, 17, 634.

[17] Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. J Org Chem 1973, 38, 3288.

[18] Papadopoulos, E. P. J Org Chem 1979, 44, 3858.

[19] Reissert, A.; Brüggemann, K. Ber Dtsch Chem Ges 1924, 57, 981.

[20] Gazzola, C.; Kenyon, G. L. J Labelled Comp Radiopharm 1978, 15, 181.

[21] Busch, M.; Wolff, J. J Prakt Chem 1899, 60, 197.

[22] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 733961 The data can be obtained free of charge from the CCDC, via www.ccdc.cam.ac.uk/data_request/cif.

# Microwave Assisted One-Pot Synthesis of Pyrrolo[2,1-*b*]thiazol-6-ones from α-Aroyl Ketene-*N*,*S*-acetals

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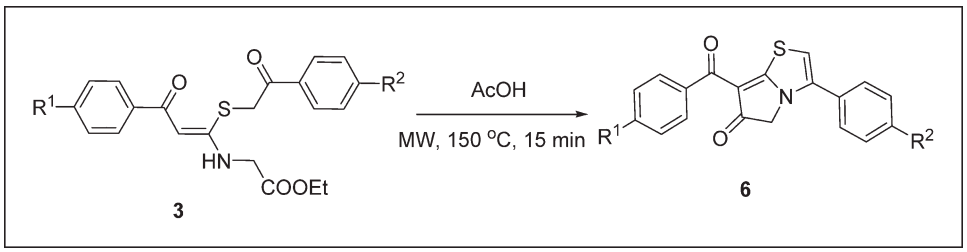
*This article is dedicated to our research guide Dr. C. V. Asokan who died on February 3, 2007.*




α-Aroyl ketene-*N*,*S*-acetals **3** prepared by the reaction of β-oxothioamides **1** with phenacyl bromides **2**, underwent sequential cyclizations under microwave irradiation to afford pyrrolo[2,1-*b*]thiazol-6-ones **6** in good yields. A double cyclization takes place regioselectively in one pot and variety of functionalized pyrrolo[2,1-b]thiazol-6-ones were prepared by this protocol. The mode of cyclization under microwave condition is different from conventional heating.

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## INTRODUCTION

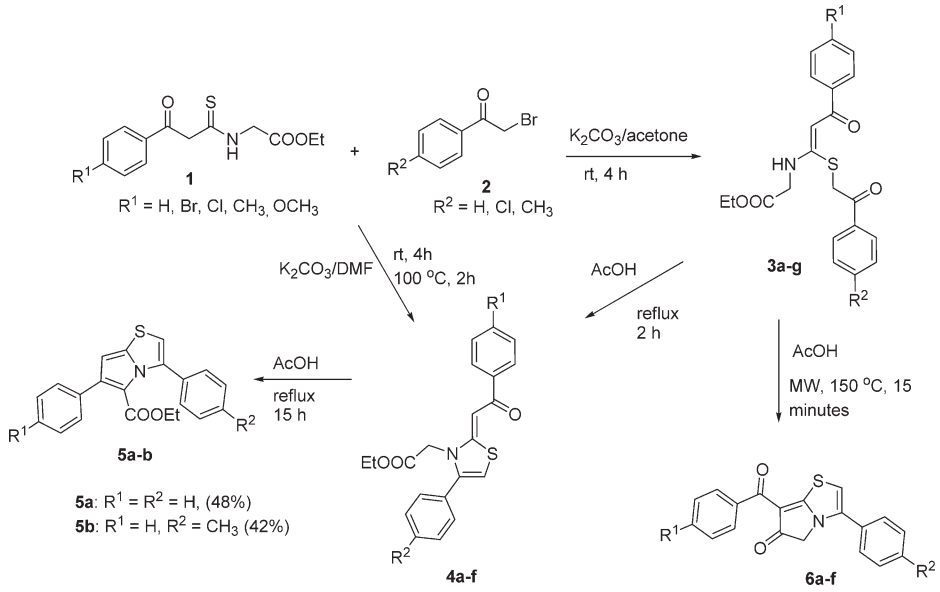
The structural diversity and biological importance exhibited by pyrrolothiazoles have made them attractive targets for synthesis [1]. Pyrrolo[2,1-*b*]thiazoles are known to display a wide range of biological activities such as antileukemic [2], platelet-activating factor antagonistic [3] and for prevention and treatment of various liver diseases [4]. The common strategy for their syntheses involves ring annelation of appropriately functionalized pyrroles [5,6] or thiazoles [7,8]. Other approaches are based on the cycloaddition reactions of thiazolium ylides [9], imidazo[2,1-*b*]thiazoles [10] or mesoionic thiazolo[3,2-*c*]oxazoles [2] with dimethyl acetylenedicarboxylate and related unsaturated acid derivatives. Recently, thiazadiene, an unsymmetrical polyhetropolyene, on sequential reaction with α-carbonyl bromide was converted into pyrrolo[2,1-*b*]thiazoles [11]. Ring contraction strategy is also used for constructing this heterobicyclic system [12]. All these reported methods needed multistep reaction sequences. Recently, microwave-assisted organic synthesis has attracted considerable attention due to enhanced reaction rates, high yields, improved selectivity, and cleaner products [13]. Herein, we report an efficient, microwave assisted, and environmentally benign one pot method for the preparation of pyrrolo[2,1-*b*]thiazol-6-ones **6** from easily accessible α-aroyl ketene-*N*,*S*-acetals **3**. To the best of our knowledge, this is the first report on the direct transformation of an open chain system into pyrrolo[2,1-*b*]thiazole derivative using a one pot strategy.

Direct alkylation of thioamides using alkyl halide affords ketene-*N*,*S*-acetals which is widely used as a synthon in heterocyclic synthesis [14]. Recently we have explored the synthetic potential of α-aroyl ketene-*N*,*S*-acetals prepared by the alkylation of β-oxothioamides **1** for the synthesis of functionalised pyrroles [15]. α-Aroyl ketene-*N*,*S*-acetals were previously prepared in our laboratory as an intermediate for the synthesis of functionalized thiophenes *via* alkylation of thioamides using 1,2-bielectrophiles in presence of base [16].

## RESULTS AND DISCUSSION

Initially, alkylation of thioamide **1** with one equiv. of a 1,2-bielectrophile—phenacyl bromide in the presence of $K_2CO_3$ (2 equiv.) as the base in acetone at room temperature was carried out expecting monoalkylation at sulphur followed by *in situ* cyclization to form thiazole **4**, which could be further transformed into the pyrrolothiazoles. However, we isolated only the monoalkylated α-aroyl ketene-*N*,*S*-acetals **3** in nearly quantitative yields (Scheme 1, Table 1). The unexpected complex pattern of peaks observed in the $^1$H NMR (360 MHz) spectrum of **3** is apparently due to the diastereotopic nature of the methylene protons. For example, in **3a**, ethyl moiety showed a triplet at δ 1.27 and two sets of doublets each at δ 3.40 and 3.50 ($J$ = 12). Another doublet of doublet appeared at 3.79 (1H, $J$ = 12 Hz) and 4.08 (1H, $J$ = 12 Hz) due to S$CH_2$ moiety. The N$CH_2$ moiety showed a

**Scheme 1**




multiplet at δ 4.18–4.26 ppm. By recording the $^1$H NMR spectrum at higher frequency (500 MHz), we further confirmed these sets of peaks as doublet of doublet rather than peaks arising from the possible geometrical isomeric forms.

Next, taking **3a** as a model substrate, its cyclization to thiazole **4a** was attempted. Initial experiments using $K_2CO_3$ as the base in acetone under reflux conditions failed to afford thiazole. Use of a strong base like KOH in ethanol or NaH in DMF afforded only intractable mixture of products. Further studies using acid catalysts showed that the ketene-*N*,*S*-acetals **3** can be easily transformed into thiazoles **4**. Thus, a solution of the ketene-*N*,*S*-acetal **3a** in acetic acid was heated at 70°C for 4 h; the thiazole **4a** was formed quantitatively. Using a similar protocol the thiazole **4b** was prepared (Table 2). Alternatively, when the alkylation of the thioamide **1a** was attempted in the presence of excess of $K_2CO_3$ (8 equiv.) in DMF, thiazole **4a** was formed in good yields. The same strategy was used for the preparation of thiazoles **4b–f** (Table 2).

Since the thiazole **4** containing structural units that can be easily transformed into pyrrolo[2,1-*b*]thiazoles, we attempted their pyrrole ring annulation studies. Similar cyclization has been previously reported by our group for the synthesis of pyrroles from ketene-*N*,*S*-acetals using Vilsmeier Haack reagent ($POCl_3$/DMF) [15]. Tverdokhlebov *et al*. used the same reagent for the synthesis of pyrrolo[2,1-*b*]thiazoles from thiazoles [17]. Attempts using base catalysts or Vilsmeier Haack reagent failed to afford pyrrolothiazoles. However, the thiazole **4a** or **4b** after heating under reflux in acetic acid for a period of 15 h, we observed the formation of pyrrolo[2,1-*b*]thiazoles **5a** and **5b** in 48% and 42% yields respectively (Scheme 1). To our surprise, other thiazoles (**4c–4f**) even after refluxing in acetic acid for 24 h, it was possible to isolate only the unreacted starting material. Failure of the above cyclization was apparently due to the unfavorable orientation of the aroyl moiety in the thiazole **4**.

The observation that the *N*,*S*-acetal **3a** underwent facile cyclization in presence of acetic acid prompted us to irradiate a solution of **3a** in acetic acid under

**Table 1**

Ketene-*N*,*S*-acetals **3** prepared from thioamide **1**.

| Product | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **3a** | $CH_3$ | H | 92 |
| **3b** | $OCH_3$ | Cl | 88 |
| **3c** | H | Cl | 92 |
| **3d** | Br | Cl | 94 |
| **3e** | $OCH_3$ | H | 85 |
| **3f** | Br | H | 94 |
| **3g** | H | H | 96 |

**Table 2**

Thiazoles **4** prepared from thioamide **1** or from ketene-*N*,*S*-acetal **3**.

| Product | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **4a** | H | H | 88 |
| **4b** | Br | H | 87 |
| **4c** | Cl | $CH_3$ | 85 |
| **4d** | Cl | H | 86 |
| **4e** | $OCH_3$ | $CH_3$ | 80 |
| **4f** | H | $CH_3$ | 82 |

**Table 3**

Pyrrolo[2,1-*b*]thiazol-6-ones **6** prepared from ketene-*N*,*S*-acetal **3**.

| Product | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **6a** | $CH_3$ | H | 81 |
| **6b** | $OCH_3$ | Cl | 85 |
| **6c** | H | Cl | 82 |
| **6d** | $OCH_3$ | H | 80 |
| **6d** | Br | H | 76 |
| **6f** | H | H | 84 |

microwave. Thus, by dissolving **3a** in acetic acid followed by microwave irradiation for 15 min at 150°C in a microwave synthesizer, transformation to the corresponding pyrrolo[2,1-*b*]thiazole **6a** was observed in 81% yield. Using a similar protocol we have prepared other pyrrolothiazoles (**6b–f**) in good yields (Table 3). Electron withdrawing or donating substituents have little effect on the mode of cyclization or on the overall yield of the pyrrolothiazoles **6** formed. When we reduced only the reaction time to 10 min, the reaction was incomplete and could be possible to isolate a mixture of the intermediate thiazole **4a** and the pyrrolothiazole **6a** in a ratio 1 : 3. In an independent experiment, transformation of **4a** to **6f** was observed under microwave heating. It is interesting to note that the mode of cyclization during pyrrole ring annelation step in conventional heating is different from that in microwave conditions. Thus, under microwave conditions pyrrolothiazoles **6** were formed which is structurally different form the pyrrolothiazoles **5**, formed during conventional heating. This is apparently due to the fact that under microwave conditions, the geometry of the exocyclic double bond present in the initially formed thiazole **4** was affected to a lesser extend and the ethyl carboxylate functionality underwent rapid conformational changes favoring the regioselective formation of pyrrolothiazoles **6**. While in conventional heating the reverse is true leading to the formation of pyrrolothiazole **5**.

In summary, we have developed a convenient and efficient one-pot procedure for the synthesis of a variety of pyrrolo[2,1-*b*]thiazoles from less expensive as well as easily accessible ketene-*N*,*S*-acetals under microwave conditions in a regioselective and efficient manner. The reaction is very fast and the product can be easily separated from the reaction medium by dilution using water followed by filtration.

## EXPERIMENTAL

Thioamide **1** was prepared as reported [15(b)]. Microwave-assisted reactions were done in a multimode microwave reactor (Biotage Initiator™). Melting points were obtained on a Buchi-530 melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX-300 MHz or AM-360 MHz spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million. Coupling constants *J* are given in Hertz. Mass spectra-EIMS, FAB, were obtained on a Finngen-Mat 312, Jeol SX 102/Da-600 instruments respectively. Elemental analyses were recorded on an elementar vario EL III analyzer.

**General procedure for the synthesis of α-aroyl ketene-*N*,*S*-acetals (3).** A suspension of the thioamide **1** (10 mmol) and anhyd $K_2CO_3$ (20 mmol) in dry acetone (30 mL) was refluxed with stirring for 30 min. The mixture was cooled and phenacyl bromide **2** (10 mmol) was added followed by stirring at room temperature for 4 h. When the reaction was completed (TLC), the mixture was poured into ice-cold water and extracted using $CH_2Cl_2$ (2 × 50 mL). The organic layer was washed with water (2 × 100 mL), dried using anhyd $Na_2SO_4$ and evaporated. The crude product thus obtained was purified by column chromatography over silica gel using hexane: ethyl acetate (7 : 3) as eluent afforded the α-aroyl ketene-*N*,*S*-acetals **3a–g** (Table 1).

***Ethyl[3-(4-methylphenyl)-3-oxo-1-(2-oxo-2-phenyl-ethylsulfanyl)-propenylamino]acetate (3a).*** White solid; mp 143–145°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 2.39 (s, 3H, $ArCH_3$), 3.40 (1H, *J* = 12 Hz, $CH_2CH_3$), 3.50 (1H, *J* = 12 Hz, $CH_2CH_3$), 3.79 (1H, *J* = 12 Hz, $SCH_2$), 4.08 (1H, *J* = 12 Hz, $SCH_2$), 4.18–4.26 (m, 2H, $NCH_2$), 6.09 (s, 1H, vinylic), 7.21 (d, 2H, *J* = 8 Hz, 2H, ArH), 7. 39 (m, 3H, ArH), 7.59 (m, 2H, ArH), 7.77 (d, 2H, *J* = 8 Hz, ArH) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$): δ 14.5, 22.2, 48.1, 52.5, 62.3, 97.4, 126.4, 129.3, 129.7, 130.0, 133.7, 135.0, 141.9, 145.8, 156.5, 168.8, 195.9, 196.1. EIMS: *m*/*z* (%) 397.16 ($M^+$, 12), 379.16 (100), 306.15 (38), 246.14 (45), and 119.1 (70). Anal. Calcd. for $C_{22}H_{23}NO_4S$ (397.13): C, 66.48; H, 5.83; N, 3.52. Found: C, 66.35; H, 5.87; N, 3.58.

***Ethyl{1-[2-(4-chlorophenyl-2-oxo-ethylsulfanyl]-3-(4-methoxyphenyl)-3-oxo-propenylamino}acetate (3b).*** White solid; mp 95–97°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 3.36 (d, 1H, *J* = 12 Hz, $CH_2CH_3$), 3.43 (1H, *J* = 12 Hz, $CH_2CH_3$), 3.85 (d, 1H, *J* = 18 Hz, $SCH_2$), 3.84 (s, 3H, $ArOCH_3$), 4.05 (d, 1H, *J* = 18 Hz, $SCH_2$), 4.16–4.30 (m, 2H, $NCH_2$), 5.04 (bs, 1H, NH), 6.06 (s, 1H, vinylic), 6.91 (d, 2H, *J* = 8 Hz, 2H, ArH), 7. 38 (d, 3H, *J* = 8Hz, ArH), 7.55 (d, 2H, *J* = 8 Hz, ArH), 7.86 (d, 2H, *J* = 8 Hz, ArH) ppm. MS (FAB): *m*/*z* 448 ($M^+$ + H). Anal. Calcd. for $C_{22}H_{22}ClNO_5S$ (447.09): C, 58.99; H, 4.95; N, 3.13. Found: C, 58.76; H, 4.90; N, 3.17.

***Ethyl{1-[2-(4-chloro-phenyl-2-oxo-ethylsulfanyl]-3-oxo-3-phenyl propenylamino}acetate (3c).*** White solid. mp 98–100°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.2 Hz, $CH_2CH_3$), 3.39 (d, 1H, *J* = 10 Hz, $CH_2CH_3$), 3.47 (d, 1H, *J* = 10 Hz, $CH_2CH_3$), 3.77 (d, 1H, *J* = 18 Hz, $SCH_2$), 4.07 (d, 1H, *J* = 18 Hz, $SCH_2$), 4.15–4.32 (m, 2 H, $NCH_2$), 4.99 (bs, 1H, NH), 6.10 (s, 1H, vinylic), 7.39–7.45 (m, 3H, ArH), 7. 56 (d, *J* = 8Hz, 2H, ArH), 7.89 (d, 2H, *J* = 7 Hz, ArH) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$): δ 14.5, 44.8, 48.0, 63.1, 90.6, 96.2, 127.7, 128.5, 128.7, 129.1, 129.4, 131.8, 135.5, 139.3, 139.7, 166.1, 170.7, 187.7 ppm. MS (FAB): *m*/*z* 418 ($M^+$ + H). Anal. Calcd. for $C_{21}H_{20}ClNO_4S$ (417.08): C, 60.35; H, 4.82; N, 3.35. Found: C, 60.49; H, 4.91; N, 3.28.

***Ethyl{3-(4-bromophenyl)-1-[2-(4-chloro-phenyl)-2-oxo-ethylsulfanyl]-3-oxo propenylamino}acetate (3d).*** White solid. mp 147–149°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* =

10 Hz, $CH_2CH_3$), 3.43 (q, 2H, $J$ = 10 Hz, $CH_2CH_3$), 3.78 (d, 1H, $J$ = 18 Hz, $SCH_2$), 4.08 (d, 1H, $J$ = 18 Hz, $SCH_2$), 4.16–4.32 (m, 2 H, $NCH_2$), 4.99 (bs, 1H, N*H*), 6.10 (s, 1H, vinylic), 7.40 (d, $J$ = 10 Hz, 2H, ArH), 7.55–7.57 (m, 4 H, ArH), 7.88 (d, 2H, $J$ = 10 Hz, ArH) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$): δ 14.2, 49.0, 62.4, 95.9, 106.9, 125.1, 128.5, 129.4, 130.7, 131.5, 136.2, 138.3, 139.8, 164.3, 166.9, 181.8, 185.7 ppm. EIMS: *m/z* (%) 497.1 ($M^+$ + 2, 14), 479.1 (82), 406.1 (48), 324.2 (22), 240.2 (25), 183.1 (82) and 139.1 (100). Anal. Calcd. for $C_{21}H_{19}BrClNO_4S$ (494.99): C, 50.77; H, 3.85; N, 2.82. Found: C, 50.65; H, 3.89; N, 2.76.

***Ethyl[3-(4-methoxyphenyl)-3-oxo-1-(2-oxo-2-phenyl-ethyl-sulfanyl)-propenylamino]acetate (3e).*** Pale yellow glass. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.26 (t, 3H, $J$ = 7.2 Hz, $CH_2CH_3$), 3.38 (d, 1H, $J$ = 14 Hz, $CH_2CH_3$), 3.49 (1H, $J$ = 14 Hz, $CH_2CH_3$), 3.79 (d,1H, $J$ = 18 Hz, $SCH_2$), 3.84 (s, 3H, $ArOCH_3$ + 1H, $SCH_2$), 4.06 (d, 1H, $J$ = 18 Hz, $SCH_2$), 4.15–4.28 (m, 2H, $NCH_2$), 4.50 (bs, 1H, N*H*), 6.07 (s, 1H, vinylic), 6.92 (d, 2H, $J$ = 9 Hz, 2H, ArH), 7. 41 (m, 3H, ArH), 7.61 (d, 2H, $J$ = 7 Hz, ArH), 7.87 (d, 2H, $J$ = 9 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 14.1, 44.3, 47.6, 55.3, 62.4, 89.6, 96.1, 113.4, 126.5, 128.7, 129.2, 132.1, 140.3, 162.1, 165.2, 170.3, 186.1, 187.1 ppm. EIMS ($CHCl_3/CH_3CN+H^+$): *m/z* (%) 414.1, ($M^+$ + H 12), 396.2 (100), 366.2 (18), 248.1 (35). Anal. Calcd. for $C_{22}H_{23}NO_5S$ (413.13): C, 63.90; H, 5.61; N, 3.39. Found: C, 63.82; H, 5.67; N, 3.43.

***Ethyl[3-(4-bromophenyl)-3-oxo-1-(2-oxo-2-phenyl-ethylsul-fanyl) propenylamino]acetate (3f).*** White solid. mp 98–99°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.27 (t, 3H, $J$ = 7.2 Hz, $CH_2CH_3$), 3.43 (d, 1H, $J$ = 10 Hz, $CH_2CH_3$), 3.53 (d, 1H, $J$ = 10 Hz, $CH_2CH_3$), 3.81 (d, 1H, $J$ = 18 Hz, $SCH_2$), 4.08 (d, 1H, $J$ = 18 Hz, $SCH_2$), 4.20–4.30 (m, 2 H, $NCH_2$), 4.51 (s, 1H, N*H*), 6.03 (s, 1H, vinylic), 7.31 (d, 2H, $J$ = 7 Hz, 2H, ArH), 7. 43 (m, 3H, ArH), 7.60 (m, 2H, ArH), 7.82 (d, 2H, $J$ = 7 Hz, ArH) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$): δ 14.5, 44.8, 53.8, 62.7, 96.8, 126.9, 129.0, 129.3, 130.5, 131.9, 132.5, 138.6, 140.5, 166.9, 170.6, 182.6, 186.2 ppm. MS (FAB): *m/z* 462 ($M^+$ + H). Anal. Calcd. for $C_{21}H_{20}BrNO_4S$ (461.03): C, 54.55; H, 4.36; N, 3.03. Found: C, 54.62; H, 4.29; N, 3.06.

***Ethyl[3-oxo-1-(2-oxo-2-phenyl-ethylsulfanyl)-3-phenyl-propenylamino]acetate (3g).*** White solid. mp 118–120°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 1.29 (t, 3H, $J$ = 7.2 Hz, $CH_2CH_3$), 3.42 (1H, $J$ = 10 Hz, $CH_2CH_3$), 3.53 (1H, $J$ = 10 Hz, $CH_2CH_3$), 3.81 (1H, $J$ = 18 Hz, $SCH_2$), 4.11 (1H, $J$ = 18 Hz, $SCH_2$), 4.18–4.32 (m, 2 H, $NCH_2$), 4.82 (s, 1H, N*H*), 6.11 (s, 1H, vinylic), 7.40–7.48 (m, 6H, ArH), 7.61 (d, 2H, ArH), 7.90 (d, 2H, $J$ = 8 Hz, ArH) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$): δ 14.5, 44.8, 48.1, 62.9, 90.4, 97.6, 126.9, 127.7, 128.7, 129.3, 129.4, 131.7, 139.8, 140.6, 166.4, 170.8, 187.6 ppm. MS (FAB): *m/z* 385 ($M^+$ + H). Anal. Calcd. for $C_{21}H_{21}NO_4S$ (383.12): C, 65.78; H, 5.52; N, 3.65. Found: C, 65.86; H, 5.59; N, 3.60.

**General procedure for the synthesis of thiazoles (4).** Method (a): From ketene-*N*,*S*-acetal **3**: To a suspension of the ketene-*N*,*S*-acetal **3a** or **3b** (10 mmol) in glacial acetic acid (10 mL) was heated at 70°C with stirring for 4 h. The reaction mixture was cooled, diluted with water (50 mL), and the precipitated product was filtered, recrystallized from ethanol to afford the thiazole **4a** or **4b** in moderate yields.

Method (b): From thioamide **1**: To a suspension of the thioamide **1** (10 mmol) in anhyd DMF (30 mL) was added $K_2CO_3$ (80 mmol) followed by phenacyl bromide **2** (10 mmol). The mixture was stirred at room temperature for 4 h then at 100°C for 2 h. It was then cooled, poured into ice-cold water and extracted using ethyl acetate (2 × 50 mL). The organic layer was washed with water (2 × 100 mL), dried using anhyd $Na_2SO_4$ and evaporated. The crude product thus obtained was purified by column chromatography over silica gel using hexane: ethyl acetate (7 : 3) as eluent to give **4a–f** (Table 2).

***Ethyl 2-{2-[(Z)-oxo(phenyl)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (4a).*** Pale yellow needles; mp. 130–131°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 4.26 (q, 2H, $J$ = 7 Hz, $CH_2CH_3$), 4.50 (s, 1H, $NCH_2$), 6.32 (s, 1H, vinylic), 6.40 (s, 1H, tzol C*H*), δ 7.42 (m, 6H, ArH), δ 7.94 (m, 4H, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 14.1 ($CH_2CH_3$), 48.9 ($NCH_2$), 62.2 ($CH_2CH_3$), 86.4 (tzol *C*H), 106.0 (vinylic), 126.8 (*C*4, tzol CH), 164.0 (*C*2, tzol), 128.1, 128.9, 129.3, 129.7, 129.9, 130.4, 139.6, 140.9 (ArC), δ 167.1 and 183.1 (carbonyl). EIMS: *m/z* (%) 365 ($M^+$, 82), 336 (41), 292 (51), 275 (15), 214 (33), 186 (36), 147 (54), 134 (58), and 105 (100). Anal. Calcd. for $C_{21}H_{19}NO_3S$ (365.45): C, 69.02; H, 5.24; N, 3.83. Found: C, 68.72; H, 5.36; N, 3.57.

***Ethyl 2-{2-[(Z)-(4-bromophenyl)(oxo)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (4b).*** Pale yellow crystalline solid; mp 118–120°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 4.20 (q, 2H, $J$ = 7 Hz, $CH_2CH_3$), 4.53 (s, 1H, $NCH_2$), 6.46 (s, 1H, vinylic), 7.19 (s, 1H, tzol C*H*), 7.30–7.47 (m, 7H, ArH), 7.75 (d, 2H, $J$ = 8 Hz, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 14.2 ($CH_2CH_3$), 49.1 ($NCH_2$), 62.3 ($CH_2CH_3$), 86.2 (tzol *C*H), 106.4 (vinylic), 125.0 (*C*4, tzol), 164.5 (*C*2, tzol), 128.6, 128.3, 129.1, 129.5, 129.9, 131.4, 138.7, and 141.2 (ArC), 167.09 and δ 181.82 (carbonyl) ppm. EIMS: *m/z* (%) 443 ($M^+$, 50), 445 ($M^+$ + 2, 51), 411 (32), 260 (21), 216 (22), 185 (100), 157 (74), 134 (74), and 105 (51). Anal. Calcd. for $C_{21}H_{18}BrNO_3S$ (444.34): C, 56.76; H, 4.08; N, 3.15. Found: C, 56.52; H, 4.16; N, 3.02.

***Ethyl 2-{2-[(Z)-(4-chlorophenyl)(oxo)ethylidene]-4-(4-methylphenyl)-1,3-thiazol-3-yl}acetate (4c).*** White crystalline solid; mp 148–149°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 2.41 (s, 3H, $CH_3$), 4.28 (q, 2H, $J$ = 7.2 Hz, $CH_2CH_3$), 4.51 (s, 1H, NH $CH_2$), 6.25 (s, 1H, vinylic), 6.40 (s, 1H, tzol CH), 7.27 (m, 4H, ArH), 7.37 (d, 2H, $J$ = 8 Hz, ArH), 7.86 (d, 2H, $J$ = 8 Hz, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$) 14.2 ($CH_2CH_3$), 49.1 ($NCH_2$), 62.2 ($CH_2CH_3$), 86.3 (tzol *C*H), 106.0 (vinylic), 126.4 (*C*4, tzol), 164.5 (*C*2 tzol), 127.0, 128.4, 129.4, 129.8, 136.4, 138.3, 140.2, 141.3 (ArC), 167.2, and δ 181.6 (carbonyl) ppm. EIMS: *m/z* (%) 415 ($M^+$ + 2, 23), 413 ($M^+$, 72), 396 (41), 340 (38), 263 (15), 200 (26), 188 (34) and 139 (100). Anal. Calcd. for $C_{22}H_{20}ClNO_3S$ (413.92): C, 63.84; H, 4.87; N, 3.38. Found: C, 64.08; H, 4.56; N, 3.24.

***Ethyl 2-{2-[(Z)-(4-chlorophenyl)(oxo)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (4d).*** White crystalline solid; mp 110–111°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 4.27 (q, 2H, $J$ = 7 Hz, $CH_2CH_3$), 4.51 (s, 1H, $NCH_2$), 6.26 (s, 1H, vinylic), 6.44 (s, 1H, tzol CH), 7.37–7.48 (m, 7H, ArH), 7.87 (d, 2H, $J$ = 8 Hz, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$), 14.2 ($CH_2CH_3$), 48.1 ($NCH_2$), 62.3 ($CH_2CH_3$), 86.4 (tzol *C*H), 106.0 (vinylic), 126.8 (*C*4 tzol) 164.0 (*C*2 tzol), 127.7, 128.4, 129.2, 129.9, 136.4, 138.3, 141.2 (ArC ), 167.1, and δ 181.6 (carbonyl) ppm. EIMS: *m/z* (%) 401, ($M^+$ +2, 28), 399 ($M^+$, 85), 382 (27), 326 (34), 298 (24), 249 (21), 183 (53), 141 (54), 139 (100), and 111 (100). Anal. Calcd. for

$C_{21}H_{18}ClNO_3S$ (399.89): C, 63.07; H, 4.54; N, 3.50. Found: C, 62.74; H, 4.78; N, 3.45.

***Ethyl 2-{2-[(Z)-(4-methoxyphenyl)(oxo)ethylidene]-4-(4-methylphenyl)-1,3-thiazol-3-yl}acetate (4e).*** Pale yellow glass. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 2.17 (s, 3H, $CH_3$), 4.27 (q, 2H, $J$ = 7 Hz, $CH_2CH_3$), 4.69 (s, 1H, $NCH_2$), 6.46 ppm (s, 1H, vinylic), 6.48 ppm (s, 1H, tzol C*H*), 6.77 (d, 2H, $J$ = 8 Hz, ArH), 6.90 (d, 2H, $J$ = 8 Hz, ArH), 7.04 (d, 2H, $J$ = 8 Hz, ArH), 7.28 (d, 2H, $J$ = 8 Hz, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$) 14.2 ($CH_2CH_3$), 21.3 ($CH_3$), 49.1 ($NCH_2$), 55.3 ($OCH_3$), 62.2 ($CH_2CH_3$), 86.1 (tzol *C*H), 105.5 (vinylic) 127.3 (*C*4 tzol), 161.6 (*C*2 tzol ), 113.5, 128.8, 129.4, 129.7, 132.7, 139.9, 140.9, and 163.8 (ArC), 167.4 and 182.5 (carbonyl) ppm. EIMS: *m/z* (%) 409 ($M^+$, 78), 336 (32), 306 (15), 228 (25), 200 (16), 172 (11), 135 (100), and 121 (92). Anal. Calcd. for $C_{23}H_{23}NO_4S$ (409.50): C, 67.46; H, 5.66; N, 3.42. Found: C, 67.32; H, 5.73; N, 3.48.

***Ethyl 2-{4-(4-methylphenyl)-2-[(Z)-oxo(phenyl)ethylidene]-1,3-thiazol-3-yl}acetate (4f).*** Pale yellow crystalline solid; mp 128–129°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 2.41 (s, 3H, $CH_3$), 4.27 (q, 2H, $J$ = 7 Hz, $CH_2CH_3$), 4.51 (s, 1H, $NCH_2$), 6.26–7.95 (m, 10H, ArH + tzol H). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 14.1 ($CH_2CH_3$), 21.3 ($CH_3$), 48.9 ($NCH_2$), 62.4 ($CH_2CH_3$), 90.0 (tzol *C*H), 105.8 (vinylic), 126.5 (*C*4 tzol), 165.9 (*C*2 tzol), 127.3, 128.3, 129.3, 129.7, 130.4, 131.2, 137.4, and 138.9 (ArC), 170.3 and 187.1 (carbonyl). EIMS: *m/z* (%) 379 ($M^+$, 84), 362 (31), 306 (51), 278 (18), 232 (13), 188 (16), 147 (34), 119 (58) and 105 (100). Anal. Calcd for $C_{22}H_{21}NO_3S$ (379.47): C, 69.63; H, 5.58; N, 3.69. Found: C, 69.32; H, 5.67; N, 3.76.

**General procedure for the synthesis of pyrrolothiazoles (5).** A suspension of the thiazole **3** (10 mmol) in glacial acetic acid (10 mL) was refluxed with stirring for 15 h. The mixture was cooled and poured into ice cold water and extracted using $CHCl_3$ (2 × 50 mL). The organic layer was washed with water (2 × 50 mL) and dried using anhyd $Na_2SO_4$. The solvent was evaporated and the crude product thus obtained was purified by column chromatography over silica gel using hexane: ethyl acetate as eluent (4 : 1) to afford **5a** or **5b**.

***Ethyl 3,6-diphenylpyrrolo[2,1-b]-[1,3]thiazole-5-carboxylate (5a).*** Pale yellow glass. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.65 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), 3.45 (q, 2H, $J$ =7 Hz, $CH_2CH_3$), 6.34 (s, 1H pyrrole CH), 6.52 (s, 1H, tzol CH(7.07–8.07 (m, 10H, ArH) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 59.0, 99.6 (tzol CH), 109.7, 112.3, 125.3, 126.2, 127.4, 127.5, 127.6, 128.8, 129.1, 131.7, 132.7, 135.6, 137.7 (ArH), 159.48. EIMS: *m/z* (%) 347 ($M^+$, 48), 302 (24), 275(100), 241 (18), 215 (15), 202 (12), 172 (15), 145 (20), and 102 (27). Anal. Calcd. for $C_{21}H_{17}NO_2S$ (347.43): C, 72.60; H, 4.93; N, 4.03. Found: C, 72.43; H, 4.86; N, 4.14.

***Ethyl 3-(4-methylphenyl)-6-phenylpyrrolo[2,1-b][1,3]thiazole-5-carboxylate (5b).*** Pale yellow glass.$^1$H NMR (300 MHz, CDCl3) δ 0.68 (t, 3H, $J$ = 7 Hz, $CH_2CH_3$), δ 3.50 (q, 2H, $J$ = 7 Hz, $CH_2CH_3$), δ 2.30 (s, 3H, $CH_3$), δ 6.33 (s, 1H, pyrrole CH), δ 6.49 (s, 1H, tzol CH), δ 7.13–7.53 (m, 9H, ArH) ppm. $^{13}$C NMR (75.5 MHz, CDCl3) δ 14.0, 21.7, δ 60.4, 101.0 (tzol CH). 110.6, 126.7, 127.6, 128.0, 128.9, 129.6, 130.2, 130.5, 134.0, 135.8, 137.8, 137.2, 139.0, 160.9. EIMS: *m/z* (%) 361 ($M^+$, 47), 316 (22), 289 (100), 273 (14), 210 (8), 145 (15), and 115 (31). Anal. Calcd. for $C_{22}H_{19}NO_2S$ (361.46): C, 73.10; H, 5.30; N, 3.88. Found: C, 73.28; H, 5.43; N, 3.74.

**General procedure for the synthesis of pyrrole[2,1-*b*]thiazol-6-ones (6).** To a 10 mL glass vial equipped with a small magnetic stirring bar, α-aroyl ketene-*N*,*S*-acetal **2** (1.0 mmol) was added followed by glacial acetic acid (3 mL). The mixture was then irradiated in a microwave synthesizer for 15 min at 150°C. After completion of the reaction, the vial was cooled to 50°C by air jet cooling before it was opened. It was then diluted with water (20 mL), and the precipitated product was collected by filtration, washed with cold water and recrystallized from ethyl acetate to afford **6a–f** (Table 3).

***7-(4-Methyl-benzoyl)-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6a).*** White solid; mp 206–207°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 2.40 (s, 3H $ArCH_3$), 4.62 (s, 2H, $NCH_2$), 6.80 (s, 1H tzol), 7.53 (s, 7H, ArH), 8.05 (d, 2H, $J$ = 7 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 22.1, 59.3, 109.2, 127.7, 128.4, 128.9, 129.6, 129.9, 130.8, 135.5, 141.5, 142.7, 179.8, 185.4, 185.9. HRMS: calcd. for $C_{20}H_{15}NO_2S$ 333.0823, found 333.0809.

***3-(4-Chloro-phenyl)-7-(4-methoxy-benzoyl)pyrrolo[2,1-b]thiazol-6-one (6b).*** White solid; mp 211–213°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 3.84 (s, 3H, $OCH_3$), 4.93 (s, 2H, $NCH_2$), 6.99–7.01 (d, 2H, $J$ = 7.2 Hz, ArH), 7.47 (s, 1H tzol), 7.61–7.63 (d, 2H, $J$ = 7.2 Hz, ArH), 7.79–7.81 (d, 2H, $J$ = 7.2 Hz, Ar*H*), 8.12–8.14 (d, 2H, $J$ = 7.2 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 54.8, 59.9, 108.5, 127.6, 129.8, 131.0, 131.5, 135.1, 139.9, 162.4, 178.5, 183.0, 186.2. EIMS (THF/HCOOH): *m/z* (%) 384.1, $M^+$ + H 100), 316.4 (56), 288.4 (78), 244.3 (12), 166.2 (18). Anal. Calcd. for $C_{20}H_{14}ClNO_3S$ (383.04): C, 62.58; H, 3.68; N, 3.65. Found: C, 62.69; H, 3.74; N, 3.58.

***7-Benzoyl-3-(4-chloro-phenyl)-pyrrolo[2,1-b]thiazol-6-one (6c).*** White solid. mp 200–202°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 4.93 (s, 2H, $NCH_2$), 7.46–7.48 (m, 7H, ArH), 6.50 (s, 1H tzol), 7.61–7.63 (d, 2H, $J$ = 7.2 Hz, ArH), 7.79–7.81 (d, 2H, $J$ = 7.2 Hz, ArH), 7.97–7.99 (d, 2H, $J$ = 7.2 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 59.7, 108.2, 127.4, 127.8, 128.2, 129.1, 129.4, 129.7, 130.1, 135.0, 138.5, 139.8, 178.0, 184.1, 186.3. MS (FAB): *m/z* 354 ($M^+$ + H). Anal. Calcd. for $C_{19}H_{12}ClNO_2S$ (353.03): C, 64.50; H, 3.42; N, 3.96. Found: C, 64.41; H, 3.38; N, 3.99.

***7-(4-Methoxy-benzoyl)-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6d).*** White solid. mp 216–218 °C. $^1$H NMR (360 MHz, $CDCl_3$): δ 3.78 (s, 3H, $OCH_3$), 4.88 (s, 2H, $NCH_2$), 6.93–6.95 (d, 2H, $J$ = 7.2 Hz, ArH), 7.36 (s, 1H tzol), 7.47 (s, 3H, ArH), 7.70 (s, 2H, ArH), 8.07–8.09 (d, 2H, $J$ = 7.2 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 55.7, 59.7, 108.3, 127.9, 128.9, 129.3, 129.6, 130.9, 131.2, 131.4, 140.9, 162.2, 178.3, 182.8, 186.1. MS (FAB): *m/z* 350 ($M^+$ + H). Anal. Calcd. for $C_{20}H_{15}NO_3S$ (349.08): C, 68.75; H, 4.33; N, 4.01. Found: C, 68.62; H, 4.38; N, 4.07.

***7-(4-Bromo-benzoyl)-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6e).*** White solid; mp 222–224°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 4.63 (s, 2H, $NCH_2$), 6.84 (s, 1H tzol), 7.54–7.60 (m, 7H, ArH), 8.04 (d, 2H, $J$ = 7.2 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 59.3, 109.2, 109.4, 126.9, 127.8, 128.3, 129.9, 129.9, 130.9, 131.4, 136.9, 141.6, 179.9, 184.6, 185.4. MS (FAB): *m/z* 398 ($M^+$ + H), 400 ($M^+$ + H + 2). Anal. Calcd. for $C_{19}H_{12}BrNO_2S$ (396.98): C, 57.30; H, 3.04; N, 3.52. Found: C, 57.18; H, 3.10; N, 3.55.

***7-Benzoyl-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6f).*** White solid; mp 216–217°C. $^1$H NMR (360 MHz, $CDCl_3$): δ 4.62 (s, 2H, $NCH_2$), 6.80 (s, 1H tzol), 7.45–7.53 (m, 8H, ArH), 8.12 (d, 2H, $J$ = 7.2 Hz, ArH). $^{13}$C NMR (90 MHz, $CDCl_3$): δ

59.3, 109.2, 109.3, 127.7, 128.2, 128.4, 129.5, 129.9, 130.8, 132.2, 138.2, 141.6, 179.8, 185.4, 186.0. MS (FAB): *m*/*z* 320 ($M^+ + H$). Anal. Calcd. for $C_{19}H_{13}NO_2S$ (319.07): C, 71.45; H, 4.10; N, 4.39. Found: C, 71.58; H, 4.16; N, 4.32.

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## REFERENCES AND NOTES

[1] Tverdokhlebov, A. V. Heterocycles 2007, 71, 761.

[2] Lalezari, I.; Schwartz, E. L. J Med Chem 1988, 31, 1427.

[3] Davidsen, S. K.; Summers, J. B.; Sweeny, D. J.; Holms, J. H.; Albert, D. H.; Carrera, G. M.; Tapang, P.; Magoc, T. J.; Conway, R. G.; Rhein, D. A. Bioorg Med Chem Lett 1995, 5, 2913.

[4] Hasegawa, M.; Nakayama, A.; Yokohama, S.; Hosokami, T.; Kurebayashi, Y.; Ikeda, T.; Shimoto, Y.; Ide, S.; Honda, Y.; Suzuki, N. Chem Pharm Bull 1995, 43, 1125.

[5] Hamid, A.; Oulyadi, H.; Daïch, A. Tetrahedron 2006, 62, 6398.

[6] Shevchenko, N. E.; Nenajdenko, V. G.; Balenkova, E. S. Synthesis 2003, 1191.

[7] Song, Y. K.; Lee, K.-J. Synthesis 2007, 3037.

[8] (a) Tverdokhlebov, A. V.; Andrushko, A. P.; Tolmachev, A. A. Synthesis 2006, 1433; (b) Tverdokhlebov, A. V.; Andrushko, A. P.; Resnyanska, E. V.; Tolmachev, A. A. Synthesis 2004, 2317.

[9] Berry, C. R.; Zificsak, C. A.; Gibbs, A. C.; Hlasta, D. J. Org Lett 2007, 9, 4099.

[10] Abe, N.; Nishiwaki, T.; Komoto, N. Bull Chem Soc Jpn 1980, 53, 3308.

[11] Landreau, C.; Janvier, P.; Julienne, K.; Meslin, J. C.; Deniaud, D. Tetrahedron 2006, 62, 9226.

[12] Geyer, A.; Agoston, K. Tetrahedron Lett 2004, 45, 1895.

[13] (a) Kappe, C. O. Angew Chem Int Ed Engl 2004, 43, 6250; (b) Kappe, C. O. Chem Soc Rev 2008, 37, 1127; (c) Kappe, C. O.; Dallinger, D.; Murphee, S. Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments and Protocols; Wiley-VCH: Weinheim, Germany, 2009.

[14] (a) Chakrabarti, S.; Panda, K.; Ila, H.; Junjappa, H. Synlett 2005, 309; (b) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. J Org Chem 2007, 72, 1246; (c) Venkatesh, C.; Singh, B.; Mahata, P. K.; Ila, H.; Junjappa, H. Org Lett 2005, 7, 2169.

[15] (a) Mathew, P.; Asokan, C. V. Tetrahedron Lett 2005, 46, 475; (b) Mathew, P.; Asokan, C. V. Tetrahedron 2006, 62, 1708.

[16] (a) Suma, S.; Ushakumari, N. K.; Asokan, C. V. Phosphorus Sulfur Silicon Relat Elem 1997, 131, 161; (b) Samuel, R.; Chandran, P.; Retnamma, S.; Sasikala, K. A.; Sreedevi, N. K.; Anabha, E. R.; Asokan, C. V. Tetrahedron 2008, 64, 5944.

[17] Tverdokhlebov, A. V.; Resnyanska, E. V.; Tolmachev, A. A.; Andrushko, A. P. Synthesis 2003, 2632.

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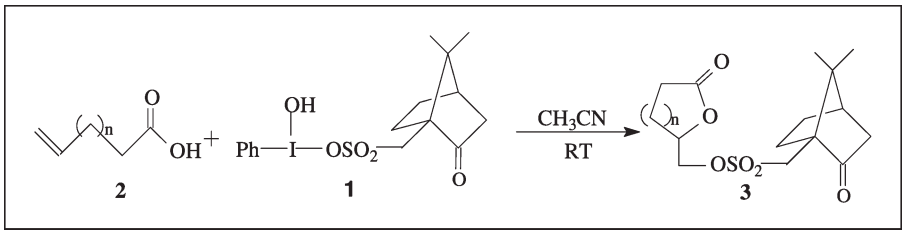


The novel reaction of [hydroxyl (((+)-10-camphorsulfonyl)oxy)iodo]benzene (1) with alkenoic acids was reported. When **1** reacted with various 4-pentenoic acids in $CH_3CN$, camphorsulfonylactons were obtained in excellent yields in short times, some had two diastereoisomers, whereas **1** reacted with 5-hexenoic acid, giving middle yield of camphorsulfonylacton; however, 3-butenoic and *trans*-3-hexenoic acids reacted with **1** slowly in $CH_2Cl_2$, only unsaturated lactones were provided.

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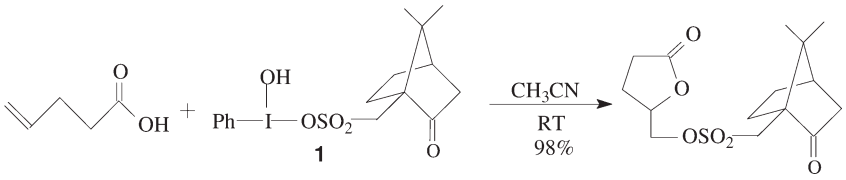
## INTRODUCTION

Lactonizations have been studied extensively, and this type of transformation serves as an important key reaction in a variety of syntheses [1]. Among them, halolactonization and phenylselenolactonization are general used methods [2]. Recently, organic hypervalent iodine reagents have found broad application in organic chemistry and frequently used in synthesis due to their chemical properties and reactivity are similar to those of Hg (II), Tl (III), and Pb (IV), but without the toxic and environmental problems of these heavy metal congeners [3]. Koser and coworkers first reported the tosyloxylactonization of alkenoic acids with the hypervalent iodine reagent, [hydroxyl(tosyloxy)iodo]benzene (HTIB, Koser's reagent), which mechanism was different with halolactonization and phenylselenolactonization and received much attention [4]. The ability of HTIB to introduce the tosylate ligand into alkenoic acids prompted us to investigate the camphorsulfonyloxylactonization of alkenoic acids with the analogous reagent, [hydroxyl (((+)-10-camphorsulfonyl)oxy)iodo]benzene (1) [5], a stable and incorporating a chiral ligand hypervalent iodine reagent. Here, we would like to report a novel and convenient camphorsulfonyloxylactonization of alkenoic acids, a series of new 5-camphorsulfonyloxy-4-pentanolactones and 6-camphorsulfonyloxy-5-hexanolactone were synthesized.

Initially, we prepared [hydroxyl (((+)-10-camphorsulfonyl)oxy)iodo]benzene (1) according to the literature procedure [5]. Then, we investigated the reaction of 4-pentenoic acid with **1**, we found that when the equal equivalent of both them were mixed and stirred in $CH_3CN$ at room temperature, the reaction was carried out fluently and finished in 0.5 h, the novel compound of 5-camphorsulfonyloxy-4-pentanolactone was obtained in nearly quantitative (Scheme 1). Prompted by the good result, a series of experiments were performed on the reaction of 4-pentenoic acid with **1** in order to determine the suitable reaction conditions, and $CH_3CN$ and $CH_2Cl_2$ were found to be the most preferred solvents. Finally, the reaction of a series of alkenoic acids (2) with **1** in $CH_3CN$ or $CH_2Cl_2$ at room temperature were investigated, several new camphorsulfonylactons (3) were provided (Scheme 2), the good results are summarized in Table 1.

It is shown from Table 1 that 4-pentenoic acid (2a), 2-methyl-4-pentenoic acid (2b), 3-methyl-4-pentenoic acid (2c) and 2, 2-dimethyl-4-pentenoic acid (2d) all reacted with **1** fast, and gave the corresponding 5-camphorsulfonyloxy-4-pentanolactones, respectively, in excellent yields (entries **1–4**); Similar treatment of 5-hexenoic acid needed longer time compared with 4-pentenoic acid and provided 6-camphorsulfonyloxy-5-hexanolactone (3e) in middle yield (entry **5**), which meant that five-membered lactone ring was formed easier than six-membered lactone ring in the camphorsulfonyloxylactonization of alkenoic acids. We also checked the reaction of 6-heptenoic acid with **1**, found that after 48 h it had not been completed and the desired seven-membered lactone ring was obtained in poor yield. When 3-butenoic and *trans*-3-hexenoic acids were treated with **1**

**Scheme 1**




in same reaction conditions, the reaction was somewhat difficult to carry out in $CH_3CN$ and slowly; then using $CH_2Cl_2$ in place of $CH_3CN$, we found that after 24 h the reaction was finished. However, the products were not the desired camphorsulfonylactons, two unsaturated lactones were found (entries **6** and **7**). It was revealed by $^1$H-NMR technique that the desired 3-sulfonyloxy-4-butanolactones were first formed, but then transformed into the unsaturated lactones during workup procedure by elimination. 2-Cyclopenteneacetic acid reacted with **1** also fluently, but gave another unsaturated lactone (entry **8**), which agreed with Koser and coworkers report [4].

Koser et al. in 1988 reported another lactonizaton using the similar hypervalent iodine reagent, [hydroxyl ((bis(phenyloxy)phosphoryl)oxy)iodo]benzene, and they found that when 2-methyl-4-pentenoic acid was treated with the hypervalent iodine reagent, the products were a mixture of diastereomers, with a ratio varied from 1.2 to 1.4:1 [6]. Because of [hydroxyl (((+)-10-camphorsulfonyl)oxy)-iodo]benzene is a chiral hypervalent iodine reagent, the lactonizaton of it may be stereoselectivity, and some evidence was obtained by examination of the $^1$H-NMR spectrum of camphorsulfonylactons: when 2-methyl-4-pentenoic acid (2b) and 3-methyl-4-pentenoic acid (2c) were treated with **1** at room temperature, the provided products were mixtures of diastereomers, the ratios of them were 3.1:1 and 2.3:1, respectively. Then, we checked the effect of temperature on the stereoselectivity of **2b** and found that the camphorsulfonylactonization got diastereomers with higher ratio at lower of temperature; The reaction was investigated at room temperature, $-20^\circ$C and $-50^\circ$C, respectively, the ratios of diastereomers varied from 3.1, 4.0 to 4.8:1. However, except **2b** and **2c**, other alkenoic acids were not observed having the stereoselectivity in the camphorsulfonylactonization at room temperature. Solvents also had small effect on the stereoselectivity, we found that $CH_3CN$ was better than $CH_2Cl_2$ to get high diastereomers ratio for **2b** in the reaction.

[Hydroxyl (((+)-10-camphorsulfonyl)oxy)iodo]benzene was made from (diacetoxyiodo)benzene and (+)-10-camphorsulfonic acid in $CH_3CN$. To extend the scope of camphorsulfonylactonization, find simpler and more convenient camphorsulfonylactonization, the ''one-pot'' reaction was investigated; when equal equivalent of (diacetoxyiodo)benzene, (+)-10-camphorsulfonic acid and 4-pentenoic acid were mixed in $CH_3CN$ at room temperature and stirred the mixture, we found that the reaction was completed in 0.5 h, giving the desired **3a** in 95% of yield. When [bis(trifluoroacetoxy)iodo]benzene was used in place of (diacetoxyiodo)benzene, the same result was obtained in 94% of yield. Therefore, the simpler and more convenient ''one-pot'' camphorsulfonylactonization was found (Scheme 3). Further investigation of the reaction will be reported later.

The plausible mechanism is similar to the literature procedure [4], which included the electrophilic addition of hypervalent iodine reagent **1** on the alkene, then an intramolecular nucleophilic displacement was happened, followed by another nucleophilic displacement to give the camphorsulfonylactone (Scheme 4).

In conclusion, we have successfully developed a novel and convenient reaction of [hydroxyl-(((+)-10-camphorsulfonyl)oxy)iodo]benzene with alkenoic acids, several new 5-camphorsulfonyloxy-4-pentanolactones in excellent yields and 6-camphorsulfonyloxy-5-hexanolactone in middle yield were prepared. The camphorsulfonylactonization has some advantages, such as, mild reaction conditions, simple procedure, and good yields. Furthermore, the scope of hypervalent iodine reagents in organic synthesis could be extended.

**Scheme 2**

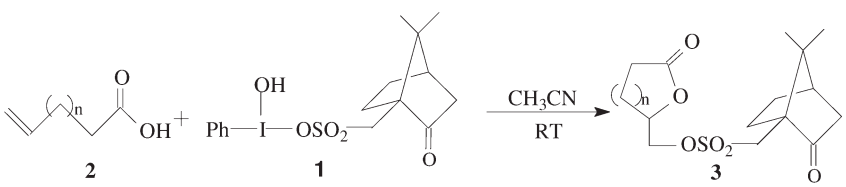
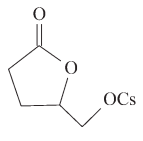
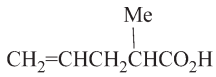
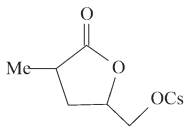
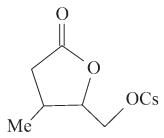
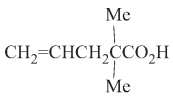
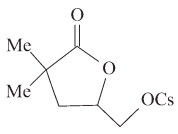
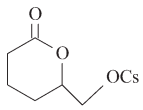
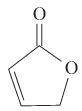
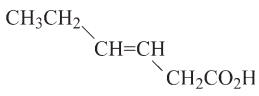
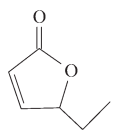
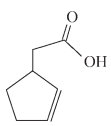
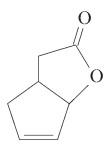


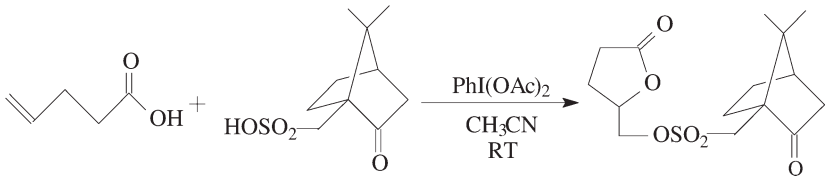
**Table 1**

The result of the camphorsulfonylactonization of alkenoic acids.

| Entry | Alkenoic acids (2) | Camphorsulfonyloxylactones (3)[a] | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $CH_2=CH(CH_2)_2CO_2H$ **2a** |  **3a** | 0.5 | 98 |
| 2 |  **2b** |  **3b** | 0.5 | 95 |
| 3 |  **2c** |  **3c** | 0.5 | 93 |
| 4 |  **2d** |  **3d** | 1.0 | 95 |
| 5 | $CH_2=CH(CH_2)_3CO_2H$ **2e** |  **3e** | 2.5 | 63 |
| 6 | $CH_2=CHCH_2CO_2H$ **2f** |  **3f** | 24 | 52[c] |
| 7 |  **2g** |  **3g** | 24 | 41[c] |
| 8 |  **2h** |  **3h** | 1.0 | 81 |

[a] Cs, (+)-10-camphorylsulfonyl.
[b] Isolated yield.
[c] $CH_2Cl_2$ was used as solvent.

**Scheme 3**




## EXPERIMENTAL

**General procedure for the iodination of terminal alkynes.** To $CH_3CN$ or $CH_2Cl_2$ (2 mL), alkenoic acid **2** (0.3 mmol), [hydroxyl (((+)-10-camphorsulfonyl)oxy)iodo]benzene **1** (0.3 mmol) were added. The mixture was stirred at room temperature for 0.5–24 h (shown in Table 1) and then separated on a silica gel plate using (3:1, hexane–ethyl acetate) as eluant to give camphorsulfonyloxylacton **3** in good to excellent yields.

**3a**: Oil. $^1$H-NMR (500 MHz, $CDCl_3$): 4.82–4.79 (m, 1H), 4.51 (ddd, $J$ = 22.0, 11.5, 3.0 Hz, 1H), 4.37 (ddd, $J$ = 21.5, 11.0, 4.5 Hz, 1H), 3.62 (dd, $J$ = 15.5, 6.0 Hz, 1H), 3.08 (dd, $J$ = 15.0, 4.0 Hz, 1H), 2.69–2.52 (m, 2H), 2.43–2.37 (m, 3H), 2.20–2.02 (m, 3H), 1.97 (d, $J$ = 17.5 Hz, 1H), 1.75–1.65 (m, 1H), 1.51–1.45 (m, 1H), 1.10 (s, 3H), 0.88 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 214.2, 176.1, 76.7 (d, $J$ = 7.5 Hz), 70.1, 69.9, 57.8 (d, $J$ = 2.5 Hz), 48.1, 47.2, 42.6 (d, $J$ = 2.5 Hz), 42.4 (d, $J$ = 1.3 Hz), 27.9, 26.8, 24.8 (d, $J$ = 7.5 Hz), 23.3 (d, $J$ = 8.8 Hz), 19.5 (t, $J$ = 2.5 Hz). IR (film): ν = 2963, 1781, 1746, 1456, 1418, 1360, 1282, 1167, 1070, 962 cm$^{-1}$. MS (EI, *m*/*z*, %): 330 ($M^+$, 100). HRMS: $C_{15}H_{22}O_6S$ calcd.: 330.1137, found: 330.1125.

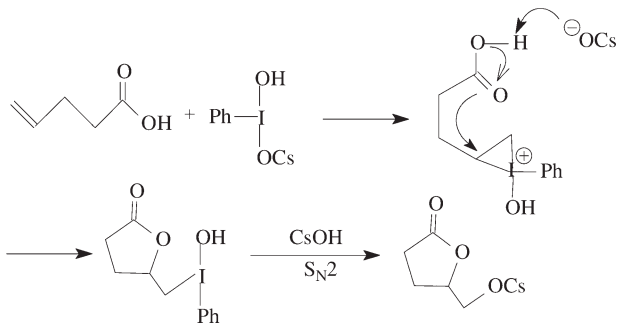
**3b**: Oil. $^1$H-NMR (500 MHz, $CDCl_3$): 4.79–4.72 (**3b$_1$**) and 4.68–4.62 (**3b$_2$**) (m, 1H), 4.51 (ddd, $J$ = 19.0, 11.5, 3.0 Hz, 1H), 4.37–4.31 (m, 1H), 3.66–3.59 (m, 1H), 3.09–3.03 (m, 1H), 2.83–2.78 (**3b$_1$**) and 2.77–2.70 (**3b$_2$**) (m, 1H), 2.56–2.49 (m, 1H), 2.46–2.37 (m, 2H), 2.16–2.13 (m, 1H), 2.10–2.03 (m, 1H), 1.97 (d, $J$ = 18.0 Hz, 1H), 1.79–1.68 (m, 2H), 1.50–1.44 (m, 1H), 1.31 (d, $J$ = 5.5 Hz, **3b$_1$**) and 1.30 (d, $J$ = 6.0 Hz, **3b$_2$**) (d, 3H), 1.10 (**3b$_1$**) and 1.09 (**3b$_2$**) (s, 3H), 0.89 (**3b$_1$**) and 0.88 (**3b$_2$**) (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 214.4, 214.3, 179.2, 178.3, 74.9, 74.5 (d, $J$ = 7.5 Hz), 70.5, 70.4, 69.7, 69.4, 57.9 (d, $J$ = 3.8 Hz), 48.2 (d, $J$ = 3.8 Hz), 47.4, 47.3 (d, $J$ = 6.3 Hz), 42.7, 42.5 (d, $J$ = 2.5 Hz), 35.2, 33.7, 32.2 (d, $J$ = 8.8 Hz), 31.6 (d, $J$ = 6.3 Hz), 26.9, 24.9 (t, $J$ = 3.8 Hz), 19.6 (d, $J$ = 5.0 Hz), 16.1, 15.1 (d, $J$ = 3.8 Hz). IR (film): ν = 2966, 1775, 1747, 1456, 1360, 1286, 1168, 1069, 972, 931 cm$^{-1}$. MS (EI, *m*/*z*, %): 344 ($M^+$, 100). HRMS: $C_{16}H_{24}O_6S$ calcd.: 344.1294, found: 344.1289.

**3c**: Oil. $^1$H-NMR (500 MHz, $CDCl_3$): 4.75–4.30 (m, 3H), 3.63 (dd, $J$ = 15.0, 4.5 Hz, 1H), 3.07 (dd, $J$ = 15.5, 4.0 Hz, 1H), 2.85–2.78 (m, 1H), 2.72–2.66 (**3c$_1$**) and 2.56–2.49 (**3c$_2$**) (m, 1H), 2.45–2.22 (m, 3H), 2.15–2.13 (m, 1H), 2.11–2.02 (m, 1H), 1.97 (d, $J$ = 18.5 Hz, 1H), 1.75–1.65 (m, 1H), 1.51–1.44 (m, 1H), 1.23 (dd, $J$ = 6.5, 3.0 Hz, **3c$_1$**) and 1.17 (d, $J$ = 7.5 Hz, **3c$_2$**) (3H), 1.10 (s, 3H), 0.88 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 214.3, 175.7(d, $J$ = 2.5 Hz), 175.4, 83.3 (d, $J$ = 2.5 Hz), 79.2 (d, $J$ = 5.0 Hz), 68.8, 68.6, 68.2, 68.0, 57.9 (d, $J$ = 3.8 Hz), 48.2, 47.4 (d, $J$ = 3.8 Hz), 47.2 (d, $J$ = 2.5 Hz), 42.7 (d, $J$ = 3.8 Hz), 42.5 (d, $J$ = 2.5 Hz), 36.4 (d, $J$ = 3.8 Hz), 36.2, 31.9, 31.8, 31.7, 26.9, 24.9 (d, $J$ = 2.5 Hz), 24.8, 19.6 (d, $J$ = 3.8 Hz), 18.0, 13.5. IR (film): ν = 2965, 1785, 1747, 1456, 1418, 1361, 1283, 1214, 1166, 1054, 975, 933 cm$^{-1}$. MS (EI, *m*/*z*, %): 344 ($M^+$, 100). HRMS: $C_{16}H_{24}O_6S$ calcd.: 344.1294, found: 344.1277.

**3d**: Oil. $^1$H-NMR (500 MHz, $CDCl_3$): 4.73–4.69 (m, 1H), 4.51 (ddd, $J$ = 20.0, 11.5, 3.5 Hz, 1H), 4.33 (ddd, $J$ = 19.5, 11.5, 5.5 Hz, 1H), 3.63 (dd, $J$ = 15.5, 8.0 Hz, 1H), 3.08 (d, $J$ = 15.0 Hz, 1H), 2.45–2.37 (m, 2H), 2.20–2.13 (m, 2H), 2.10–2.01 (m, 1H), 1.99–1.95 (m, 2H), 1.75–1.67 (m, 1H), 1.51–1.45 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 214.3 (d, $J$ = 8.8 Hz), 180.8, 73.6 (d, $J$ = 3.8 Hz), 69.9, 69.6, 57.9, 48.2, 47.4 (d, $J$ = 10.0 Hz), 42.7, 42.5 (d, $J$ = 2.5 Hz), 40.0 (d, $J$ = 2.5 Hz), 38.4 (d, $J$ = 7.5 Hz), 26.9, 24.9 (d, $J$ = 3.8 Hz), 24.8 (d, $J$ = 3.8 Hz), 24.7 (d, $J$ = 2.5 Hz), 19.6. IR (film): ν = 2967, 1775, 1747, 1457, 1361, 1280, 1207, 1169, 1130, 1067, 983, 926 cm$^{-1}$. MS (EI, *m*/*z*, %): 358 ($M^+$, 100). HRMS: $C_{17}H_{26}O_6S$ calcd.: 358.1451, found: 358.1441.

**3e**: Oil. $^1$H-NMR (500 MHz, $CDCl_3$): 4.65–4.55 (m, 1H), 4.45–4.34 (m, 2H), 3.64 (dd, $J$ = 15.0, 8.5 Hz, 1H), 3.09 (d, $J$ = 15.0 Hz, 1H), 2.65–2.60 (m, 1H), 2.52–2.35 (m, 3H), 2.15–1.85 (m, 6H), 1.80–1.70 (m, 2H), 1.51–1.42 (m, 1H), 1.10 (s, 3H), 0.89 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 214.4, 170.1, 70.4, 70.2, 57.9, 48.2 (d, $J$ = 2.5 Hz), 47.4 (d, $J$ = 2.5 Hz), 42.7 (d, $J$ = 3.8 Hz), 42.5, 29.5, 26.9, 24.9 (d, $J$ = 11.3 Hz), 23.9 (d, $J$ = 6.3 Hz), 19.6, 18.2. IR (KBr): ν = 2961, 1744, 1456, 1360, 1240, 1169, 1081, 1054, 963 cm$^{-1}$. MS (EI, *m*/*z*, %): 344 ($M^+$, 100). HRMS: $C_{16}H_{24}O_6S$ calcd: 344.1294, found: 344.1288.

**Scheme 4**

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## REFERENCES AND NOTES

[1] (a) Dowle, M. D.; Davies, D. I. Chem Soc Rev 1979, 8, 171; (b) Harding, K. E.; Tiner, T. H. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 363; (c) Rousseau, G.; Robin, S. Tetrahedron 1998, 54, 13681.

[2] (a) Bartlett, P. A.; Meyerson, J. J Am Chem Soc 1978, 100, 3950; (b) Haas, J.; Piguel, S.; Wirth, T. Org Lett 2002, 4, 297; (c) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. J Am Chem Soc 1979, 101, 3884.

[3] (a) Varvoglis, A. Tetrahedron 1997, 53, 1179; (b) Stang, P. J.; Zhdankin, V. V. Chem Rev 1996, 96, 1123; (c) Zhdankin, V. V.; Stang, P. J. Chem Rev 2002, 102, 2523; (d) Wirth, T.; Hirt, U. H. Synthesis 1999, 1271; (e) Kirschning, A. Eur J Org Chem 1998, 11, 2267; (f) Ochiai, M. J Organomet Chem 2000, 611, 494; (g) Okuyama, T. Acc Chem Res 2002, 35, 12; (h) Zhdankin, V. V.; Stang, P. J. Tetrahedron 1998, 54, 10927; (i) Grushin, V. V. Chem Soc Rev 2000, 29, 315.

[4] Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L. Tetrahedron Lett 1986, 27, 4557.

[5] Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M. J Org Chem 1990, 55, 315.

[6] Koser, G. F.; Lodaya, J. S.; Ray, D. G., III; Kokil, P. B. J Am Chem Soc 1988, 110, 2987.

# Synthesis and Antibacterial Screening of New 4-((5-(Difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)-tetrazolo[1,5-a]quinoline Derivatives



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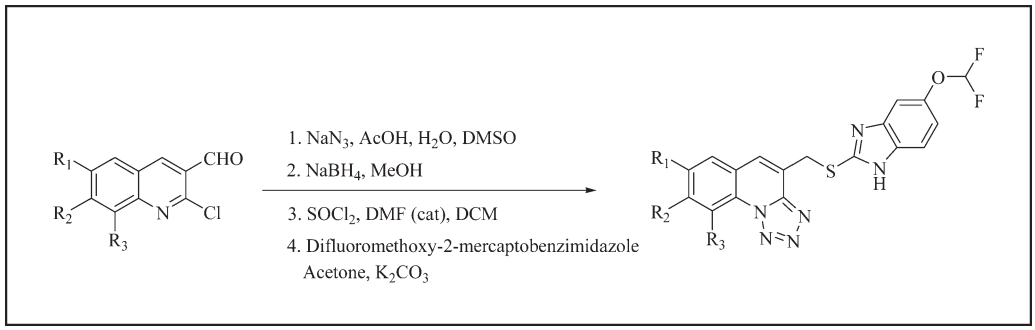


A method for the synthesis of previously unknown heterocyclic systems 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolines derivatives **6** has been developed based on various substitutes 2-chloroquinoline-3-carbaldehydes **1** *via* the consecutive steps of conversion into tetrazolo[1,5-a]quinoline-4-carbaldehyde **2** on treatment with sodium azide which upon reduction to the corresponding alcohol derivatives **3**, conversion to chlorides **4** with thionyl chloride followed by the coupling with 5-(difluoromethoxy)-1*H*-benzo[d]imidazole-2-thiol **5**. The synthesized titled compounds (**6a**–**e**) were screened for the antibacterial activity against gram positive and gram negative bacteria.

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## INTRODUCTION

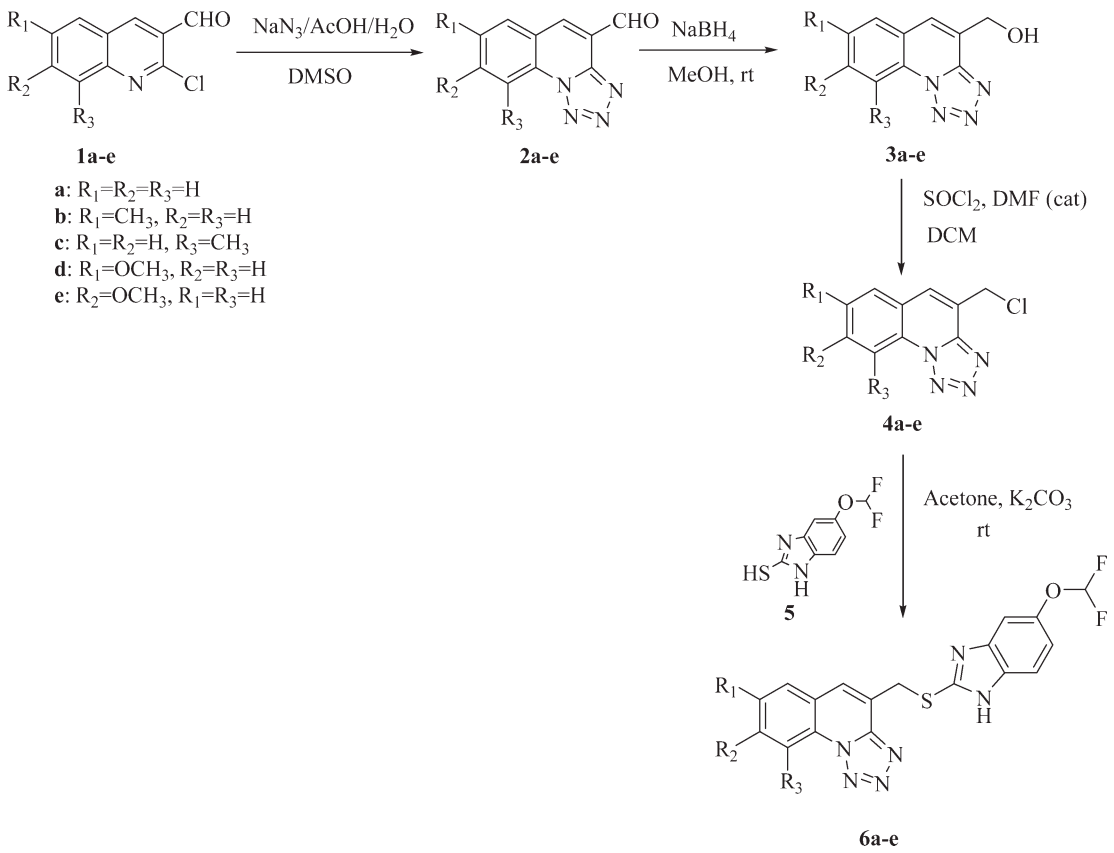
Quinoline ring systems represent a major class of heterocycles in which benzene ring is fused with pyridine ring. The derivatives of quinoline exhibit diverse biological and physiological activities such as antimalarial [1a], anti-inflammatory [1b], antitumor [1c], DNA binding capacity [1d], and antibacterial properties [1e]. Recently, quinoline has been employed in the study of bio-organic and bio-organometallic processes [1f]. The quinoline skeleton is often used as a key intermediate for the design of many pharmacologically important synthetic compounds [2].

The tetrazole group has considered analogous to carboxylic group [3] as a pharmacophore. Several substituted tetrazoles show pronounced activities such as antifertility [4a], CNS depressant [4b], antimicrobial [4c], anti-inflammatory [4d], and antiaids [4e]. The most prominent pharmaceutical application of tetrazoles is as angiotensin II receptor antagonists for the treatment of high-blood pressure [5]. The fusion of quinoline to the tetrazole ring is known to increase the biological activity [6]. In particular, tetrazolo[1,5-a]quinoline-4-carbaldehyde serves as a key synthetic intermediate for the synthesis of novel medicinally valuable compounds [7].

Benzimidazole scaffold has received extensive attention since the fact that it is a component of vitamin $B_{12}$ [8]. The derivatives of benzimidazole are possessed broad spectrum of biological activities including antibacterial, antiviral [9a], antitumor [9b], antimutagens [9c], cardiovascular [9d], anticalmodulin [9e], and many other activities are well documented [10]. In particular, mercapto benzimidazole is used for the synthesis of the most known prazole drugs pantoprazole [11a], omeprazole [11b], rabeprazole [11c], and lansoprazole [11d] which are antiulcerous agents useful in the treatment of stomach and duodenal ulcers. By all means, benzimidazole acts as ''privileged substructure'' for drug design [12]. Among these, pantoprazole is the proton pump inhibitor drug used in gastroesophageal reflux disease and as antihelicobacter agent [13] for the treatment of gastrointestinal disorders. Pyridine and 5-difluoromethoxy-2-mercapto-1*H*-benzimidazole are the two key constituents of this drug.

After the extensive literature search, it was observed that quinoline, tetrazole, 2-mercapto-1*H*-benzimidazole

**Scheme 1**




are the important pharmacophore, but till date enough efforts have not been made to combine these three moieties as a single molecular scaffold. So, our object was to synthesize and biological screening of a series of new compounds incorporating these moieties.

## RESULTS AND DISCUSSION

In continuation of our work [14] herein, we report a simple method for the synthesis of novel 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)tetrazolo [1,5-a]quinolines in excellent yields (Scheme 1).

The derivatives of tetrazolo[1,5-a]quinoline-4-carbaldehyde **2a–e** were prepared from substituted 2-chloroquinoline-3-carbaldehyde **1a–e** on treatment with sodium azide in the presence of acetic acid. The reactions were carried out using DMSO as a solvent at 40°C. The products formed in 81–85% yields (Table 1, entries 1–5).

The synthesized tetrazolo[1,5-a]quinoline-4-carbaldehydes **2a–e** on reduction with sodium borohydride at room temperature stirring in methanol formed the derivatives of (tetrazolo[1,5-a]quinolin-4-yl)methanol **3a–e** in excellent 94–97% yields within only 10 min (Table 1, entries 6–10).

These (tetrazolo[1,5-a]quinolin-4-yl)methanol **3a–e** derivatives when reacted with thionyl chloride in the presence of catalytic amount of DMF formed substituted 4-(chloromethyl)tetrazolo[1,5-a]quinolines **4a–e**. The reactions were carried out in DCM at reflux temperature to give the products in excellent yields (97–98%) (Table 1, entries 11–15).

The reaction of 4-(chloromethyl)tetrazolo[1,5-a]quinoline **4a–e** with 5-(difluoromethoxy)-1*H*-benzo[d]imidazole-2-thiol **5** afforded the titled compounds 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl) tetrazolo[1,5-a]quinolines **6a–e**. The mixture was stirred at room temperature in acetone. The progress of the reaction was monitored by thin layer chromatography (8:2—hexane: ethyl acetate solvent system). The reaction proceeded smoothly under basic condition ($K_2CO_3$ was used as a base), and completed in 1 h to afford the corresponding titled compounds in very high yields (93–98%) (Table 1, entries 16–20). The chemical structures of all the new compounds were confirmed by IR, $^1$H NMR, $^{13}$C NMR, mass spectroscopic data, and elemental analysis.

The titled compounds (**6a–e**) were screened for antibacterial activities against Gram positive *Bacillus subtilis*, *Staphylococcus aureus*, and Gram negative *Escherichia coli*, *Salmonella aboney* bacteria. The compounds

**Table 1**

Physical data of the synthesized compounds.

| Entry | Compound | $R_1$ | $R_2$ | $R_3$ | Yield (%) | M.P. (°C) |
|---|---|---|---|---|---|---|
| 1 | **2a** | H | H | H | 81 | 240–241 |
| 2 | **2b** | $CH_3$ | H | H | 83 | 230–231 |
| 3 | **2c** | H | H | $CH_3$ | 85 | 223–224 |
| 4 | **2d** | $OCH_3$ | H | H | 81 | 226–227 |
| 5 | **2e** | H | $OCH_3$ | H | 82 | 238–239 |
| 6 | **3a** | H | H | H | 96 | 189–190 |
| 7 | **3b** | $CH_3$ | H | H | 95 | 195–196 |
| 8 | **3c** | H | H | $CH_3$ | 94 | 199–200 |
| 9 | **3d** | $OCH_3$ | H | H | 96 | 219–220 |
| 10 | **3e** | H | $OCH_3$ | H | 97 | 231–232 |
| 11 | **4a** | H | H | H | 96 | 202–203 |
| 12 | **4b** | $CH_3$ | H | H | 97 | 188–189 |
| 13 | **4c** | H | H | $CH_3$ | 98 | 177–178 |
| 14 | **4d** | $OCH_3$ | H | H | 98 | 185–186 |
| 15 | **4e** | H | $OCH_3$ | H | 97 | 166–167 |
| 16 | **6a** | H | H | H | 93 | 225–226 |
| 17 | **6b** | $CH_3$ | H | H | 95 | 222–223 |
| 18 | **6c** | H | H | $CH_3$ | 97 | 227–228 |
| 19 | **6d** | $OCH_3$ | H | H | 94 | 205–206 |
| 20 | **6e** | H | $OCH_3$ | H | 98 | 195–196 |

tested are compared against the standard (Streptomycin) by measuring the diameter of zone of inhibition. Almost all the compounds tested exhibited moderate activity against Gram positive bacteria and a few compounds were found to be active against Gram negative bacteria used in this study (Table 2).

## EXPERIMENTAL

All the melting points were determined in open capillaries in a paraffin bath and are uncorrected. $^1$H NMR spectra were recorded on Mercury Plus Varian in DMSO-$d_6$ at 400 MHz and Bruker DRX-300 in $CDCl_3$ at 300 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR model as KBr discs. $^{13}$C NMR spectrum was recorded on Bruker DRX-300 at 75 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using Electrospray Ionization technique. The elemental analysis was carried out on Flash EA 1112, 50/60 Hz, 1400 VA CHN analyzer. The progress of the reactions was monitored by TLC.

**General procedure.** ***Tetrazolo[1,5-a]quinoline-4-carbaldehydes (2a–e).*** A mixture of 2-chloroquinoline-3-carbaldehyde (10 mmol), sodium azide (1.0 g) in water (5 mL), acetic acid (2 mL), and dimethyl sulphoxide (100 mL) was stirred at 40°C for 3 h. The reaction mixture was allowed to remain at room temperature overnight. A white crystalline solid formed was filtered off, washed with water, dried, and recrystallized from acetone.

***(Tetrazolo[1,5-a]quinolin-4-yl)methanol (3a–e).*** To the stirred solution of tetrazolo[1,5-a]quinoline-4-carbaldehydes (10 mmol) in 15 mL methanol was slowly added sodium borohydride (0.25 g) at room temperature. The progress of reaction was monitored on TLC (8:2—petroleum ether:ethyl acetate). After the completion of the reaction (10 min), the reaction mixture was concentrated under reduced pressure to obtain residue. To this residue, ice cold water was added and the solid obtained was filtered off to get product **3**. ES-MS: m/z 201 (m + 1).

***4-(Chloromethyl)tetrazolo[1,5-a]quinolines (4a–e).*** To the stirred solution of (tetrazolo[1,5-a]quinolin-4-yl)methanol (10 mmol) in DCM (10 mL) was added dropwise a solution of $SOCl_2$ (2 mL) in 5 mL DCM. After the complete addition, four to five drops of DMF was added to this mixture and stirred it for 1 h at reflux temperature. The reaction progress was monitored by the TLC (9:1—petroleum ether:ethyl acetate), after complete conversion, distilled out the solvent in a rota-evaporator under reduced pressure to get the product.

***4-((5-(Difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)methyl) tetrazolo[1,5-a]quinolines (6a–e).*** To the stirred solution of 5-(difluoromethoxy)-1*H*-benzo[d]imidazole-2-thiol **5** (10 mmol) in 20 mL of acetone was added $K_2CO_3$ (15 mmol) stirred the contents for 10 min. To this solution, 4-(chloromethyl)tetrazolo[1,5-a]quinoline (10 mmol) was added and continued the stirring for 50 min at room temperature. The reaction progress was monitored by the TLC (8:2—petroleum ether:ethyl acetate), after complete conversion, the solvent was removed in a rota-evaporator under reduced pressure. The obtained product was purified by silica gel (60–120 mesh) column chromatographic technique using petroleum ether:ethyl acetate (8:2) as an eluent.

**Antibacterial activity.** All the compounds (**6a–e**) were screened for antibacterial activities against Gram positive *Bacillus subtilis*, *Staphylococcus aureus* (ATCC 6538), and Gram negative *Escherichia coli* (ATCC 8739), *Salmonella aboney* (NCTC 6017) bacteria using Streptomycin (Strept.) as a standard. Petri dishes and necessary glassware were sterilized in hot air oven (190°C, 45 min). The nutrient agar and saline (0.82% NaCl) were sterilized in autoclave (121°C, 15 psi, 20 min). Inoculum was prepared in sterile saline (0.82% NaCl) and the optical density of all pathogens was adjusted to 0.10 at 625 nm on a Chemito Spectrascan UV 2600 Spectrophotometer that is equivalent to 0.5McFarland Standards [15]. The nutrient

**Table 2**

Antibacterial activity of 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolines (**6a–e**).

| | Antimicrobial zone of inhibition (mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gram positive | | | | Gram negative | | | |
| | *Bacillus subtilis* | | *S. aureus* | | *E. coli* | | *Salmonella aboney* | |
| | Conc. (mg/mL) | | Conc. (mg/mL) | | Conc. (mg/mL) | | Conc. (mg/mL) | |
| Entry | 10 | 20 | 10 | 20 | 10 | 20 | 10 | 20 |
| 6a | 12 | 15 | 9 | 11 | 10 | 12 | 11 | 14 |
| 6b | 11 | 13 | 10 | 14 | 14 | 15 | 13 | 16 |
| 6c | 13 | 16 | 9 | 13 | 15 | 17 | 11 | 13 |
| 6d | 10 | 13 | 7 | 10 | 13 | 15 | 10 | 13 |
| 6e | 12 | 16 | 10 | 15 | 17 | 19 | 14 | 17 |
| Strept. | 18 | – | 19 | – | 22 | – | 20 | – |

agar plates were prepared by the pour plate method. The activity of the compounds was tested by disc diffusion method (paper disc method). All the bacterial cells were cultured in nutrient agar plates and the compounds to be tested were dissolved in *N,N*-dimethylformamide and were soaked on paper disc. The discs were placed into the plates and incubated at 37°C for 24 h. The diameter (mm) of the zone of inhibition around each disc was measured and results were recorded (Table 2).

**Spectroscopic data.** (**3a**) IR (KBr, $cm^{-1}$): 3352 (OH), 1604 (C=C). $^1H$ NMR ($CDCl_3$+DMSO-$d_6$, 300 MHz, δ ppm): 5.20 (s, 2H, $CH_2$—OH), 7.71 (t, 1H, $J$ = 7.5 Hz, Ar-H), 7.84 (t, 1H, $J$ = 7.5, 7.8 Hz, Ar-H), 8.0 (d, 1H, $J$ = 7.8 Hz, Ar-H), 8.09 (s, 1H, Ar-H), 8.65 (d, 1H, $J$ = 8.1 Hz, Ar-H). ES-MS (m/z): 201 (M + 1).

(**4a**) IR (KBr, $cm^{-1}$): 1610 (C=C). $^1H$ NMR ($CDCl_3$, 300 MHz, δ ppm): 5.12 (s, 2H, $CH_2$—Cl), 7.74 (t, 1H, $J$ = 7.5 Hz, Ar-H), 7.90 (t, 1H, $J$ = 7.5, 7.8 Hz, Ar-H), 8.0 (d, 1H, $J$ = 7.8 Hz, Ar-H), 8.06 (s, 1H, Ar-H), 8.69 (d, 1H, $J$ = 8.4 Hz, Ar-H). ES-MS (m/z): 219 (M + 1), 221 (M + 3).

(**6a**) IR (KBr, $cm^{-1}$): 3241 (NH), 1606 (C=C). $^1H$ NMR (DMSO-$d_6$, 400 MHz, δ ppm): 4.98 (s, 2H, S—$CH_2$), 6.94–7.13 (m, 2H, O—CH—F and Ar-CH), 7.25 (s, 1H, Ar-CH), 7.44 (s, 1H, Ar-CH), 7.75 (t, 1H, $J$ = 7.2 Hz, Ar-CH), 7.92 (t, 1H, $J$ = 7.2 Hz, Ar-CH), 8.14 (d, 1H, $J$ = 8.0 Hz, Ar-CH), 8.28 (s, 1H, Ar-CH), 12.8 (s, 1H, NH). ES-MS: m/z 399.1 (M + 1). Elemental analysis: Calc.: C: 54.27%, H: 3.04%, N: 21.09%. Found: C: 53.92%, H: 2.83%, N: 20.79%.

(**6b**) IR (KBr, $cm^{-1}$): 3245 (NH), 1611 (C=C). $^1H$ NMR ($CDCl_3$+DMSO-$d_6$, 300 MHz, δ ppm): 2.54 (s, 3H, $CH_3$), 4.99 (s, 2H, S—$CH_2$), 6.28–6.81 (td, 1H, $J$ = 8.7, 66.6 Hz, O—CH—F), 6.96 (t, 1H, $J$ = 6.6 Hz, Ar-CH), 7.10 (s, 1H, Ar-CH), 7.27 (d, 1H, $J$ = 8.4 Hz, Ar-CH), 7.60–7.66 (m, 2H, Ar-CH), 8.06 (d, 1H, $J$ = 5.1 Hz, Ar-CH), 8.49 (d, 1H, $J$ = 8.4 Hz, Ar-CH), 12.25 (s, 1H, NH). $^{13}C$ NMR ($CDCl_3$+DMSO-$d_6$, 75 MHz, δ ppm): 20.79 (Ar-$CH_3$), 30.91 (S—$CH_2$), 108.55 (Ar-C), 110.39 (Ar-C), 113.76 (Ar-C), 114.34 (Ar-C), 115.69 (Ar-C), 116.03 (Ar-C), 117.86, (Ar-C), 122.12 (Ar-C), 123.45 (Ar-C), 127.56 (Ar-C), 128.07 (Ar-C), 131.51 (Ar-C), 131.82 (Ar-C), 137.86 (Ar-C), 146.01 (Ar-C), 146.52 (Ar-C), 158.08 (O—CH—$F_2$). ES-MS: m/z 413.4 (M + 1). Elemental analysis: Calc.: C: 55.33%, H: 3.42%, N: 20.38%. Found: C: 55.02%, H: 3.09%, N: 20.01%.

(**6d**) IR (KBr, $cm^{-1}$): 3250 (NH), 1606 (C=C). $^1H$ NMR ($CDCl_3$+DMSO-$d_6$, 300 MHz, δ ppm): 3.93 (s, 3H, O—$CH_3$), 4.98 (s, 2H, S—$CH_2$), 6.25–6.77 (td, 1H, $J$ = 8.7, 66.0 Hz, O—CH—F), 6.98 (td, 1H, $J$ = 2.1, 2.7 Hz, Ar-CH), 7.13 (d, 1H, $J$ = 2.1 Hz, Ar-CH), 7.22 (dd, 1H, $J$ = 2.1, 2.7 Hz, Ar-CH), 7.39–7.46 (m, 1H, Ar-CH), 7.63 (d, 1H, $J$ = 8.7 Hz, Ar-CH), 8.02 (d, 1H, $J$ = 7.2 Hz, Ar-CH), 8.52 (d, 1H, $J$ = 9.0 Hz, Ar-CH), 12.16 (s, 1H, NH). ES-MS: m/z 429.1 (M + 1). Elemental analysis: Calc.: C: 53.27%, H: 3.29%, N: 19.62%. Found: C: 52.96%, H: 3.03%, N: 19.28%.

## REFERENCES AND NOTES


[1] (a) Craig, J. C.; Person, P. E. J Med Chem 1971, 14, 1221; (b) Dillard, R. D.; Pavey, D. E.; Benslay, D. N. J Med Chem 1973, 16, 251; (c) Sukhova, N. M.; Lidak, M.; Zidermane, A.; Pelevina, I. S.; Voronia, S. S. Khim Farm Zh 1989, 23, 1226; (d) Atwell, G. J.; Bangaley, B. C.; Denny, W. A. J Med Chem 1989, 32, 396; (e) Patel, H. V.; Vyas, K. V.; Fernandes, P. S. Indian J Chem 1990, 29B, 836; (f) Saito, I.; Sando, S.; Nakatani, K. Bio Org Med Chem 2001, 9, 2381.

[2] (a) MethCohn, O.; Narine, B.; Tarnowski, B.; Hayes, R.; Keyzad, A.; Rhouti, S.; Robinson, A. J Chem Soc Perkin Trans 1 1981, 2509; (b) Bhaduri, A. P. Synlett 1990, 557.

[3] Herbst.R. M. Essay in Biochemistry; Groff, S., Ed.; Wiley: New York, 1956; pp 141.

[4] (a) Singh, H.; Bhutani, K. K.; Malhotra, R. K.; Paul, D. Experientia 1978, 34, 557; (b) Shukla, J. S.; Saxena, S. Indian Drugs 1980, 18, 15; (c) Ko, H.; Kang, H. R.; Yoo, J. C.; Kim, G. S.; Hong, S. S. Yakhak Hoechi 1992, 36, 150; (d) Kumar, P.; Knaus, E. E.; Drug Des Discov 1994, 11, 15; (e) Dereu, N.; Evers, M.; Poujade, C.; Soler, F.; PCT Int. Appl. WO 9,426,725 (1994); Chem Abstr 1995, 122, 214297.

[5] (a) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. J Med Chem 1996, 39, 625; (b) Naka, T.; Kubo, K. Curr Pharm Des 1999, 5, 453.

[6] Mukharjee, A.; Akhater, M. S.; Sharma, V. L.; Seth, M.; Bhaduri, A. P.; Agnihotri, A.; Mehrotra, P. K.; Kamboj, V. P. J Med Chem 1989, 32, 2297.

[7] (a) Gupta, R.; Gupta, A. K.; Paul, S. Indian J Chem 2000, 44B, 847. (b) Bekhit, A. A.; El-Sayed, O. A.; Aboulmagd, E.; Park, J. Y. Eur J Med Chem 2004, 39, 249; (c) Bekhit, A. A.; El-Sayed, O. A.; Al-Allaf, T. A. K.; Aboul-Enein, H. Y.; Kunhi, M.; Pulicat, S. A.; Al-Hussain, K.; Al-Khodairy, F.; Arif, J. Eur J Med Chem 2004, 39, 499; (d) Thota, S.; Argade, A.; Singh, R.; Lu, H. H.; Huang, P. US Pat. 7,358,259 B2 (2008).

[8] Hodgkin, D. C.; Pickworth, J.; Robertson, J. H.; Trueblood, K. N.; Prosen, R. J.; White, J. G. Nature 1955, 176, 325.

[9] (a) Buckheit, R. W.; Hollingshead, M. G.; Decker, J. G. Antiviral Res 1993, 21, 247; (b) Brana, M. F.; Castellano, J. M.; Keilhauer, G.; Machuca, A.; Martin, Y.; Redondo, C.; Schlick, E.; Walker, N. Anticancer Drug Des 1994, 9, 527; (c) Daugel-Dauge, N. O.; Dumev, A. D.; Kulakova, A. V. Vestn Ross Akad Med Nauk 1995, 1, 29; (d) Vander Heide, R. S.; Schwartz, L. M.; Reimer, K. A. Cardiovasc Res 1994, 28, 1526; (e) Sibiryakova, T. B.; Bakumov, P. A.; Larionov, N. P.; Spasov, A. A. Abstracts of Papers. All-Russia Science Conjugation "Creation of Drugs" Moscow, 26–30 October, 1996 [in Russian], Moscow, 1996; pp 171.

[10] Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. Pharm Chem J 1999, 33, 232; and references cited therein.

[11] (a) Mossner, J.; Holscher, A. H.; Herz, R.; Schneider, A. Aliment Pharmacol Ther 1995, 9, 321; (b) McTavish, D.; Buckley, M. M. T.; Heel, R. C. Drugs 1991, 42, 138; (c) Morii, M.; Takata,

H.; Fujisaki, H.; Takeguchi, N. Biochem Pharmacol 1990, 39, 661; (d) Sachs, G.; Shin, J. M.; Briving, C. Ann Rev. Pharmacol Toxicol 1995, 35, 277.

[12] Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hume, C.; Labaudiniere, R. F. J Med Chem 1999, 42, 3251.

[13] Kline, S. Eur. Pat. WO 92 03,135.

[14] (a) Diwakar, S. D.; Bhagwat, S. S.; Shingare, M. S.; Gill, C. H. Bioorg Med Chem Lett 2008, 18, 4678; (b) Sapkal, S. B.; Shelke, K. F.; Shingate, B. B.; Shingare, M. S. Tetrahedron Lett 2009, 50, 1754; (c) Jogdand, N. R.; Shingate, B. B.; Shingare, M. S. Tetrahedron Lett 2009, 50, 4019; (d) Sonar, S. S.; Kategaonkar, A. H.; Gill, C. H.; Shingate, B. B.; Shingare, M. S. Arkivoc 2009, ii, 138; (e) Gupta, S. V.; Baheti, K.; Bora, R.; Dekhane, D.; Chhabria, M.; Shingare, M. S.; Thore, S. N. Eur J Med Chem 2009, 44, 4721.

[15] Kilic, A.; Baysallar, M.; Besirbellioglu, B.; Salih, B.; Sorkun, K.; Tanyuksel, M. Ann Microbiol 2005, 55, 113.

# A Simple Synthesis of Pyrroles Catalyzed by Acidic Resin under Solvent-Free Condition



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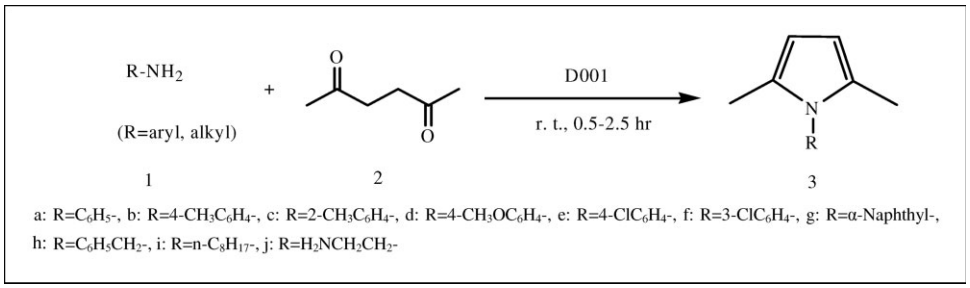


A simple and effective Paal-Knorr condensation of 2, 5-hexanedione with most amines has been carried out at room temperature under solvent-free condition. The pyrroles were obtained in high yields and in short reaction times.

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## INTRODUCTION

Pyrroles and their derivatives are very important heterocyclic compounds. They constitute the core unit of many natural products and serve as building blocks for porphyrin synthesis [1–3]. A few substituted pyrroles have been shown to possess extensively pharmacological activities and various interesting biological activities including anticancer, antimycobacterial, and antiviral properties [4–6].

The Paal-Knorr reaction is an important method for the synthesis of substituted pyrroles. Recently, clay-catalyzed [7,8], iodine [9], aluminum oxide [10], proton acid [11,12], Lewis acid [13,14], ionic liquids [15], microwave-assisted reactions [16,17], and solvent-free reaction [18,19] have been utilized for the preparation of pyrroles under Paal-Knorr condition. However, they are not very satisfactory with regard to reaction conditions, such as the use of the toxic solvent, prolonged reaction time, violence of reaction, difficulty of separation and purification. Therefore, it is necessary to develop a simple, efficient, and more general method for the synthesis of this useful heterocyclic nucleus.

## RESULTS AND DISCUSSION

Herein, we wish to report our study on the synthesis of pyrroles by using heterogeneous catalysts. It has been observed that macroporous strongly acidic styrene resin (D001), which equals to Amberlite 200 (USA) and Lewatit SP-210 (Germany), is an efficient catalyst for construction for substituted pyrroles from amines and 2,5-diketone (Scheme 1). Our initial study was started by reacting aniline with 2,5-diketone under various catalysts. The results are summarized in Table 1.

It was found that pyrrole **3a** products (**3**, Scheme 1) were obtained in low yields by using D152 as catalyst (entries **1**, Table 1). Although reaction yields were very high when the NKC-9 and NR-50 were first performed

**Scheme 1**

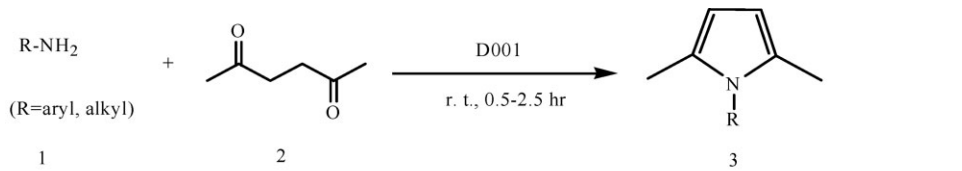


**Table 1**

Effect of various resin catalysts on the Paal-Knorr reaction between aniline (2.4 mmol) with 2,5-diketone (2.0 mmol).

| Entry | Catalyst | Functional group | Resin type | Raw catalyst yield (3a)/%[a,b,c] | Recycling catalyst yield (3a)/% [a,b,c] |
|---|---|---|---|---|---|
| 1 | D152 (0.05g) | —COOH | Acrylic acid | 47 | 31 |
| 2 | D072 (0.05g) | $-SO_3H$ | Styrene | 81 | 76 |
| 3 | NKC-9 (0.05g) | $-SO_3H$ | Styrene | 95 | 83 |
| 4 | NR-50 (0.05g) | $-SO_3H$ | Nafion-vinyl | 91 | 85 |
| 5 | D001 (0.05g) | $-SO_3H$ | Styrene | 90 | 88 |
| 6 | D001 (0.1g) | $-SO_3H$ | Styrene | 93 | 91 |
| 7 | D001 (0.15g) | $-SO_3H$ | Styrene | 91 | 90 |

[a] Products were identified by IR, $^1$H-NMR, $^{13}$C-NMR, and HRMS.
[b] Reaction time was 1.0 h.
[c] The reaction medium is solvent-free.

in this reaction as catalysts, the reaction yields were sharply decreased when recycling these catalysts (entries **3**, **4**, Table 1). Inspiringly, the reaction yield little reduced when recycling D001 as catalyst (entries **5**, **6**, **7**, Table 1). However, increasing amount of catalyst in excess had hardly raised yields of pyrrole **3a** (entries **7**, Table 1). After a comprehensive survey of the reaction conditions, acidic styrene resin (D001) was considered as appropriate catalysis for Paal-Knorr reaction. Subsequently, a variety of amines were examined using this method (Scheme 1). The results are listed in Table 2.

Aniline and its derivatives bearing whether electron withdraw group or electron donating group could implement Paal-Knorr reaction with 2,5-hexanedione in good yields at room temperature (entries **2**, **3**, **4**, **5**, **6**, Table 2). The position of substitution group seldom had effect on reaction yields. However, it was necessary that reaction time was prolonged when *meta*-substituted substrate was used for this reaction (entries **3**, **6**, Table 2). Moreover, naphthylamine and aliphatic amines also could afford the corresponding pyrroles under the same condition smoothly (entries **7**, **8**, **9**, **10**, Table 2). Inspiringly, when ethylene diamine was used in the present reaction, the product **3j** [1, 2-di (2, 5-dimethyl-1-pyrrole)-ethane] was formed with two units of pyrrole ring (entries **10**, Table 2).

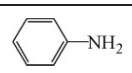
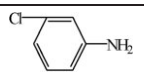
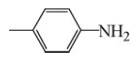
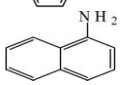
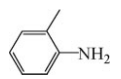
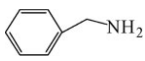
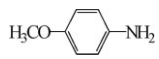
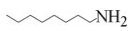
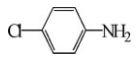
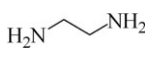
## EXPERIMENTAL

IR (Perkin-Elmer, 2000 FTIR), $^1$H-NMR ($CDCl_3$, 500 MHz), $^{13}$C-NMR ($CDCl_3$, 125.7 MHz), and MS-GC (HP5890 (II)/HP 5972, EI) spectra were obtained at the Center of Analytical Configuration of University of Science and Technology of China. Flash chromatographic sheet employed was purchased from Anhui Liangchen Silicon Material Co., and all material from Aldrich and used directly as received.

**General procedure for the synthesis of pyrroles.** To a mixture of an amine (3 mmol) and hexane-2,5-dione (3 mmol) resin (D001, 100 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with $CH_2Cl_2$, and filtered, the organic phase washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated

**Table 2**

Resin (D001) catalyzed Paal-Knorr condensation between amines and 2,5-dione.

| Entry | $RNH_2$ | Time (h) | Product[a,b] (Yield)/% | Ref | Entry | $RNH_2$ | Time (h) | Product[a,b] (Yield)/% | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | 1.0 | 3a (93) | 9 | 6 |  | 2.5 | 3f (83) | 19 |
| 2 |  | 1.0 | 3b (89)[c] | 19 | 7 |  | 1.0 | 3g (85)[c] | 9 |
| 3 |  | 1.5 | 3c (85) | 19 | 8 |  | 2.0 | 3h (91) | 16 |
| 4 |  | 0.5 | 3d (91)[c] | 9 | 9 |  | 1.5 | 3i (82) | 3i |
| 5 |  | 0.5 | 3e (87)[c] | 19 | 10 |  | 2.0 | 3j (76) | 9 |

[a] Products were identified by IR, $^1$H-NMR, $^{13}$C-NMR, and HRMS.
[b] Isolated yields.
[c] Reaction temp was at 60°C.

*in vacuo*. The pure products were obtained by flash chromatography on silica gel eluting with petroleum ether/EtOAc (1:4, *V*:*V*), and identified by IR, $^{1}$H-, $^{13}$C-NMR, and HRMS.

***1-Octyl-2,5-dimethylpyrrole (3i).*** IR: 3035.2, 2983.5, 1593.6, 1466.5, 1340.2, 976.3, 810.3 $cm^{-1}$; $^{1}$H-NMR ($CDCl_3$, 300 MHz) δ: 5.76 (s, 2H, 2×*CH*), 3.73 (t, $J$ = 7.8, 2H, $CH_2N$), 2.19 (s, 6H, 2×$CH_3$), 1.68–1.74 (m, 2H, $CH_2$), 1.33–1.45 (m, 12H, 6×$CH_2$), 0.97 (t, $J$ = 7.6, 3H, $CH_3$); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ: 12.71, 14.21, 24.62, 30.50, 31.10, 31.59, 32.30, 35.73, 47.82, 107.66, 129.84; HRMS: calcd for $C_{14}H_{27}N$: 209.3707, found: 209.3695.

In conclusion, it was very appropriate that macroporous strongly acidic styrol resin (D001) was employed as catalyst for the Paal-Knorr reaction. Various amines underwent the earlier reaction with 2,5-hexanedione to produce different substituted pyrroles in high yields. The majority of reactions were carried out at room temperature and a shorter period of time (0.5–2.5 h). The reaction conditions are very mild, and no solvent was used to carry out the reaction.

## REFERENCES AND NOTES

[1] Nonn, A. Angew Chem Int Ed 1995, 34, 1795.

[2] Weidner, M. F.; Sigurdsson, S. T. Biochemistry 1990, 29, 9225.

[3] Woo, J.; Sigurdsson, S. T. J Am Chem Soc 1993, 115, 3407.

[4] Cooney, J. V.; McEwen, W. E. J Org Chem 1981, 46, 2570.

[5] Lee, D.; Swager, T. M. J Am Chem Soc 2003, 125, 6870.

[6] Peschko, C.; Winklhofer, C.; Terpin, A.; Steglich, W. Synthesis 2006, 3048.

[7] Sanmadjar, S.; Besker, F. F.; Banik, B. K. Heterocycles 2001, 55, 1019.

[8] Song, G.; Wang, B.; Wang, G.; Kang, Y.; Yang, T.; Yang, L. Synth Commun 2005, 35, 1051.

[9] Banik, B. K.; Samajdar, S.; Bnik, I. J Org Chem 2004, 69, 213.

[10] Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. Synlett 2000, 391.

[11] Balme, G. Angew Chem Int Ed 2004, 43, 6238.

[12] Bianchi, I.; Forlani, R.; Minetto, G.; Peretto, I.; Regalia, N.; Taddei, M.; Raveglia, L. F. J Comb Chem 2006, 8, 491.

[13] Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. Tetrahedron Lett 2005, 46, 2643.

[14] Chen, J.; Wu, H.; Zheng, Z.; Jin, C.; Zhang, X.; Su, W. Tetrahedron Lett 2006, 47, 5383.

[15] Wang, B.; Gu, Y.; Luo, C.; Yang, T.; Yang, L.; Suo, J. Tetrahedron Lett 2004, 45, 3417.

[16] Danks, T. N. Tetrahedron Lett 1999, 40, 3957.

[17] Werner, S.; Iyer, P. S. Synlett 2005, 9, 1405.

[18] Das, B.; Reddy, K. R.; Teddy, M. R.; Thirupathi, P.; Rao, Y. K. Indian J Heterocycl Chem 2004, 45, 3417.

[19] Zhu, X. H.; Chen, G.; Xu, Z. L.; Wan, Y. Q. Chin J Org Chem 2008, 28, 115.

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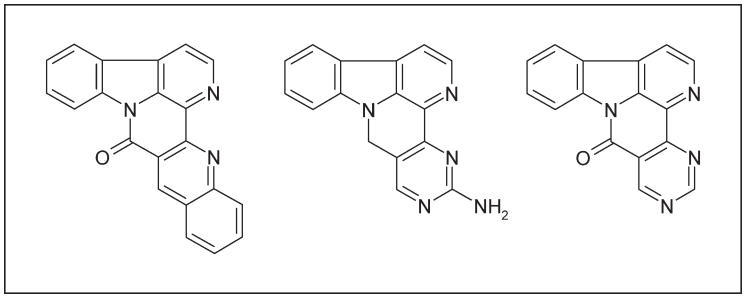

Starting from 5,6-dihydrocanthin-4-one, new penta- and hexacyclic ring systems (1,7b,14-triazadibenzo[e,k]acephenanthrylenes, 1,7b,10,12-tetraazabenzo[e]acephenanthrylenes) were built up using ring annelation reactions. The new compounds represent hybrids between the canthinones and several bioactive aromatic alkaloids

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## INTRODUCTION

Polycyclic aromatic compounds, especially alkaloids from terrestric and marine sources [1], have been shown to exhibit significant biological activities. Some prominent examples are the marine pyridoacridone type alkaloids [2], e.g., the cytotoxic metabolites ascididemine (**1a**) [3] and 2-bromoleptoclinidinone (**1b**) [4] from tunicates, the antifungal alkaloid sampangine (**2**) [5] from Annonaceae, the cytotoxic alkaloid camptothecin (**3**) [6], and the antileishmanial β-carboline annomontine (**4**) [7] (Scheme 1).

Very recently, we reported on the first efficient entry to the canthin-4-one ring system starting from 1-acyl-β-carbolines, including total syntheses of the alkaloids tuboflavine and norisotuboflavine [8]. In continuation of our concept on the synthesis of hybrids between biologically active natural products and established drugs [9], we intended to attach additional heterocyclic rings to the canthin-4-one ring system, to combine the said tetracyclic ring system with structural elements of the alkaloids **1**–**4**. Of special interest were polycyclic aromatic compounds containing quinoneimine partial structures, as can be found in the alkaloids **1a/b** and **2**. This structural element seems to be of importance for the biological activities of the alkaloids, even though hetero analogues missing the carbonyl group have been described to exhibit significant antimicrobial activities as well [10]. The new polycyclic compounds might act as DNA intercalators in cancer and microbial cells.

The target compounds were envisaged to contain either an anellated quinoline ring, to gain similarity to ascididemine (**1a**), related pyridoacridones, and camptothecin (**3**), or a pyrimidine ring, to obtain rigid analogues of the aminopyrimidyl-β-carboline alkaloid annomontine (**4**).

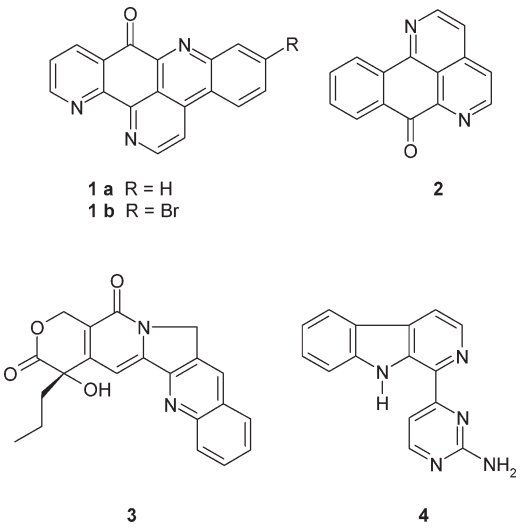
We intended to prepare the target compounds starting from 5,6-dihydrocanthin-4-one (**7**) [11] using established methods for the synthesis of fused heterocyclic ring systems.

## RESULTS AND DISCUSSION

So the first objective of this project was to work out an efficient synthesis of the central building block **7**. For this purpose different strategies were tackled.

In the first approach, canthin-4-one (**5**), which is conveniently accessible from 1-acetyl-β-carboline and Bredereck's reagent (*tert*-butoxy-bis(dimethylamino)-methane) [8] in a 1-pot reaction, was submitted to catalytic hydrogenation. Using Pd on charcoal as catalyst we observed only very poor (<5%) conversion, with the secondary alcohol **6** being produced in traces, accompanied by products of over-reduction. Hydrogenation with $PtO_2$ (Adams catalyst), however gave the alcohol **6** in 70% yield. Subsequent oxidation with manganese dioxide gave the desired 5,6-dihydrocanthin-4-one (**7**) in good yield (71%) (Scheme 2).

**Scheme 1**




We investigated an alternative approach to the ketone **7** via a Parham cyclization [12]. This reaction represents a convenient, but poorly applied method for the preparation of cyclic aryl ketones starting from an aryl bromide containing a neighboring alkoxycarbonylalkyl chain *via* intermediate bromo-lithium exchange, followed by intramolecular nucleophilic attack of the organolithium species at the ester group. A suitable precursor **9** for our purpose was obtained by Michael-type nucleophilic addition of 1-bromo-β-carboline (**8**) [13] to methyl acrylate. Bromo-lithium exchange of **9** was performed with *n*-butyllithium in THF at –100°C; upon warming to room temperature cyclization took place to give 5,6-dihydrocanthin-4-one (**7**) in 29% yield.

In conclusion, the first approach starting from canthin-4-one (**5**) remains the more effective one for the preparation of ketone **7**.

Friedländer-type condensation [14] of the ketone **7** with 2-aminobenzaldehyde, freshly prepared from 2-nitrobenzaldehyde [15], and ethanolic KOH gave the quinoline derivative **10** in 87% yield. This hexacyclic 1,7b,14-triazadibenzo[e,k]acephenanthrylene ring system has not yet been described in literature. To achieve a quinoneimine-like partial structure (compare the alkaloids **1a/b**, **2**) the methylene group in **10** had to be oxidized. This reaction proceeded with ease using manganese dioxide in chloroform [16], and the carbonyl compound **11** was obtained in 54% yield (Scheme 3).

The anellation of an aminopyrimidine ring to give a rigid analogue of annomontine (**4**) was performed in close analogy to our total synthesis of annomontine [14b]. Thus, 5,6-dihydrocanthin-4-one (**7**) was heated with Bredereck's reagent in DMF to give the enaminoketone **12**, which was further heated with guanidinium carbonate to give the aminopyrimidine **13** in 78% overall yield. Again, the resulting 1,7b,10,12-tetraazabenzo[e]acephenanthrylene ring system has not been described in literature before.

By treating the intermediate enaminoketone **12** with ammonium formate and formamide in formic acid [17] the pyrimidine **14** was obtained in 40% yield. Once again oxidation with manganese dioxide gave the corresponding carbonyl compound **15** containing a quinoneimine partial structure in high yield.

In conclusion, an effective approach towards 5,6-dihydrocanthin-4-one (**7**) has been developed. This ketone served as a versatile building block for the synthesis of hitherto unknown penta- and hexacyclic ring systems.

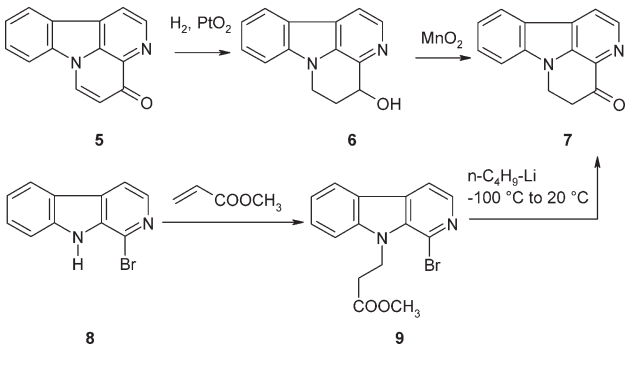
Presently, the new compounds undergo screenings for cytotoxic and antimicrobial activities, the results will be presented elsewhere in due time.

## EXPERIMENTAL

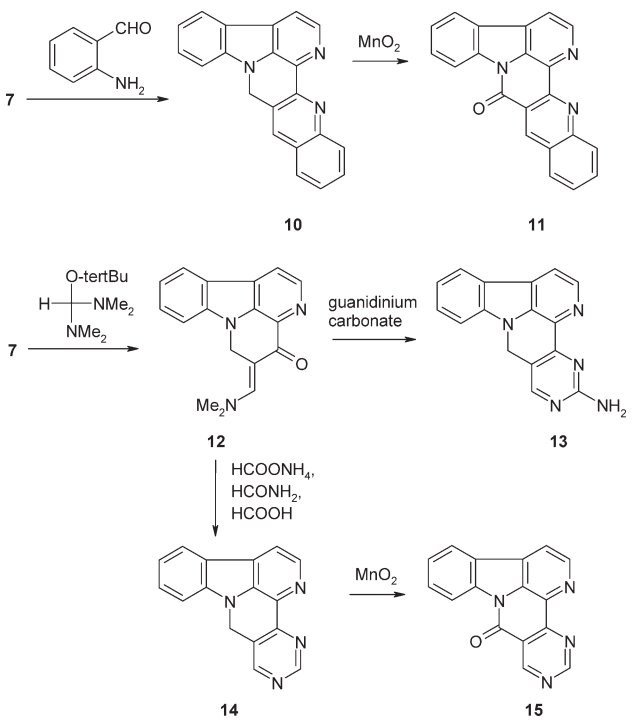
**General.** Elementar analysis: Heraeus CHN Rapid; MS: Hewlett Packard MS-Engine, electron ionization (EI) 70 eV, chemical ionization (CI) with $CH_4$ (300 eV); NMR: Jeol GSX 400 ($^1$H: 400 MHz, $^{13}$C: 100 MHz); Melting points were determined on a Büchi Melting Point B-540 apparatus and are uncorrected, flash column chromatography (FCC): silica gel 60 (230–400 mesh, E. Merck, Darmstadt).

**(±)-5,6-Dihydro-4*H*-indolo[3,2,1-de][1,5]naphthyridin-4-ol (6).** A suspension of canthin-4-one (**5**) [8] (100 mg, 0.454 mmol) and $PtO_2$ (25 mg) in 35 mL ethanol was stirred under a hydrogen atmosphere at atmospheric pressure for 30 min. After filtration and evaporating the solvent, the residual solid was purified by FCC (dichloromethane:ethanol, 14:1, v/v) to give 71 mg (70%) **6** as a light yellow solid. mp 171°C; $^1$H nmr (deuterochloroform): δ 8.26 (d, $J$ = 5.5 Hz, 1H, 2-H), 8.12 (ddd, $J$ = 8.0 Hz, $J$ = 1.7 Hz, $J$ = 0.7 Hz, 1H, 11-H), 7.82 (d, $J$ = 5.5 Hz, 1H, 1-H), 7.61 (ddd, $J$ = 8.3 Hz, $J$ = 7.2 Hz, $J$ = 1.2 Hz, 1H, 9-H), 7.48 (d, $J$ = 8.3 Hz, 1H, 8-H), 7.29 (ddd, $J$ = 8.0 Hz, $J$ = 7.2 Hz, $J$ = 1.0 Hz, 1H, 10-H), 5.35 (m, 1H, 4-H), 4.38 (m, 3H, 6-H, OH), 2.57 (m, 2H, 5-H); $^{13}$C nmr (deuterochloroform): 143.6 (C-3a), 141.0 (C-7a), 137.5 (C-2), 132.9 (C-11c), 128.5 (C-9), 126.8 (C-11b), 122.7 (C-11), 121.4

**Scheme 2**



**Scheme 3**




(C-11a), 119.8 (C-10), 114.7 (C-1), 109.6 (C-8), 64.9 (C-4), 37.8 (C-6), 30.8 (C-5); ms: *m/z* 224 (61, $M^+$), 205 (22), 168 (100), 140 (12); *Anal*. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12,49. Found: C, 74,42; H, 5,30; N, 12,33.

**5,6-Dihydroindolo[3,2,1-de][1,5]naphthyridin-4-one (7).** (a) $MnO_2$ (856 mg, 9.85 mmol) was added to a solution of **6** (170 mg, 0.758 mmol) in 7 mL chloroform, and the mixture was stirred for 5 h at room temperature. After filtration the solution was evaporated in vacuo, and the residue was purifieed by FCC (dichloromethane:ethanol, 14:1, v/v) to give 119 mg (71%) **7** as a yellow solid.

(b) A solution of **9** (259 mg, 0.777 mmol) in 7 mL anhydrous THF under nitrogen atmosphere was cooled to –100°C, then a solution of *n*-butyllithium (1.6*M* in hexane; 0.49 mL, 0.77 mmol) was added slowly. The mixture was stirred at –100°C for 1 h, and then at ambient temperature for 15 h. After addition of 40 mL water the mixture was extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried over $Na_2SO_4$ and evaporated in vacuo. The residue was purified by FCC (ethyl acetate) to give 50 mg (29%) of **7**.

mp 189°C; $^1$H nmr (deuterochloroform): δ 8.63 (d, $J$ = 5.0 Hz, 1H, 2-H), 8.17 (ddd, $J$ = 7.9 Hz, $J$ = 1.8 Hz, $J$ = 0.8 Hz, 1H, 11-H), 8.02 (d, $J$ = 5.0 Hz, 1H, 1-H), 7.68 (ddd, $J$ = 8.3 Hz, $J$ = 7.3 Hz, $J$ = 1.2 Hz, 1H, 9-H), 7.50 (d, $J$ = 8.3 Hz, 1H, 8-H), 7.38 (ddd, $J$ = 7.9 Hz, $J$ = 7.3 Hz, $J$ = 0.9 Hz, 1H, 10-H), 4.56 (t, $J$ = 6.9 Hz, 2H, 6-H), 3.31 (t, $J$ = 6.9 Hz, 2H, 5-H); $^{13}$C nmr (deuterochloroform): δ 191.5 (C=O), 141.5 (C-7a), 141.4 (C-11c), 140.9 (C-2), 133.9 (C-3a), 129.9 (C-11b), 129.6 (C-9), 123.0 (C-11), 121.7 (C-11a), 120.9 (C-10), 119.2 (C-1), 110.0 (C-8), 41.0 (C-6), 38.3 (C-5); ms: *m/z* 222 (49, $M^+$), 193 (14), 166 (24), 149 (35), 111 (40); *Anal*. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.78; H, 4.78; N, 12.50.

**Methyl 3-(1-bromopyrido[3,4-b]indol-9-yl)-propanoate (9).** To a solution of 1-bromo-β-carboline (**8**) [13] (200 mg, 0.809 mmol) in 5 mL anhydrous DMF under a nitrogen atmosphere, anhydrous potassium carbonate (250 mg, 1.81 mmol) and methyl acrylate (2.0 mL, 2.2 mmol) were added, and the mixture was stirred at 50°C for 24 h. After adding 80 mL water, the mixture was extracted with dichloromethane (2 × 60 mL), and the combined organic layers were dried over $Na_2SO_4$ and evaporated. The residue was purified by FCC (dichlormethane:ethanol, 14:1, v/v) to yield 71 mg (63%) **9** as a colorless solid. mp 86°C; $^1$H nmr (deuterochloroform): δ 8.20 (d, $J$ = 5.0 Hz, 1H, 3-H), 8.10 (ddd, $J$ = 7.9 Hz, $J$ = 1.0 Hz, $J$ = 0.8 Hz, 1H, 5-H), 7.92 (d, $J$ = 5.0 Hz, 1H, 4-H), 7.64 (ddd, $J$ = 8.4 Hz, $J$ = 7.1 Hz, $J$ = 1.1 Hz, 1H, 7-H), 7.57 (d, $J$ = 8.4 Hz, 1H, 8-H), 7.33 (ddd, $J$ = 7.9 Hz, $J$ = 7.1 Hz, $J$ = 0.9 Hz, 1H, 6-H), 5.11 (m, 2H, 3′-H), 3.67 (s, 3H, $CH_3$), 2.93 (m, 2H, 2′-H), $^{13}$C nmr (deuterochloroform): δ 171.5 (C=O), 141.6 (C-8a), 138.9 (C-3), 133.7 (C-9a), 132.1 (C-4a), 129.3 (C-7), 122.6 (C-1), 121.7 (C-5), 120.9 (C-6), 120.8 (C-4b), 114.5 (C-4), 110.1 (C-8), 52.0 ($CH_3$), 39.7 (C-3′), 35.3 (C-2′); ms: *m/z* 334 (27, $M^+$), 332 (29, $M^+$), 261 (100), 259 (92), 179 (38); *Anal*. Calcd. for $C_{15}H_{13}BrN_2O_2$ C, 54.07; H, 3.93; N, 8.41. Found: C, 54.99; H, 4.28; N, 8.15.

**8*H*-1,7b,14-Triazadibenzo[e,k]acephenanthrylene (10).** A solution of dihydrocanthin-4-one (**7**) (116 mg, 0.52 mmol) and 2-aminobenzaldehyde (63 mg, 0.520 mmol) in 7 mL ethanol (96%) was treated with a solution of potassium hydroxide (29 mg, 0.52 mmol) in 0.5 mL ethanol (96%), and then the mixture was refluxed for 18 h. The solvent was evaporated in vacuo and the residue purified by FCC (dichloromethane:ethanol, 19:1, v/v) to yield 139 mg (87%) **10** as a yellow solid. mp 189°C; $^1$H nmr ([D$_6$]DMSO): δ 8.48 (d, $J$ = 5.0 Hz, 1H, 2-H), 8.32 (s, 1H, 9-H), 8.27 (d, $J$ = 7.9 Hz, 1H, 4-H), 8.11 (d, $J$ = 8.5 Hz, 1H, 13-H), 8.04 (d, $J$ = 5.0 Hz, 1H, 3-H), 7.93 (d, $J$ = 8.0 Hz, 1H, 10-H), 7.75 (ddd, $J$ = 8.5 Hz, $J$ = 8.0 Hz, $J$ = 1.1 Hz, 1H, 12-H), 7.67 (m, 2H, 7-H, 6-H), 7.59 (dd, $J$ = 8.0 Hz, $J$ = 8.0 Hz, $J$ = 1.0 Hz, 1H, 11-H), 7.36 (ddd, $J$ = 7.9 Hz, $J$ = 6.8 Hz, $J$ = 1.5 Hz, 1H, 5-H), 5.87 (s, 2H, 8-H); $^{13}$C nmr ([D$_6$]DMSO): δ 148.2 (C-14a), 147.3 (C-13a), 140.4 (C-7a), 139.8 (C-2), 136.8 (C-14b), 136.1 (C-14c), 134.4 (C-9), 129.8 (C-12), 129.2 (C-13), 128.4 (C-6), 127.5 (C-10), 127.4 (C-9a), 127.2 (C-11), 126.5 (C-8a), 126.4 (C-3a), 122.5 (C-4), 121.1 (C-3b), 120.2 (C-5), 116.2 (C-3), 110.4 (C-7), 45.1 (C-8); ms: *m/z* 307 (69, $M^+$), 306 (100), 153 (27), 139 (8); HRMS Calcd. for $C_{21}H_{13}N_3$: 321.0904. Found: 321.0902.

**1,7b,14-Triazadibenzo[e,k]acephenanthrylen-8-one (11).** To a solution of **10** (222 mg, 0.723 mmol) in 25 mL chloroform was added $MnO_2$ (1.10 g, 12.7 mmol), and the mixture was stirred at room temperature for 12 h. The inorganic precipitates were filtered off and the filtrate was evaporated in vacuo. The residue was purified by FCC (dichloromethane: ethanol, 14:1, v/v), and the main fraction was crystallized from dichloromethane/heptane to give 126 mg (54%) **11** as a colorless solid. mp 313°C; $^1$H nmr ($CF_3COOD$): δ 9.28 (s, 1H, 9-H), 8.98 (d, $J$ = 6.2 Hz, 1H, 2-H), 8.77 (d, $J$ = 8.0 Hz, 1H, 7-H), 8.70 (d, $J$ = 6.2 Hz, 1H, 3-H), 8.46 (d, $J$ = 7.9 Hz, 1H, 4-H), 8.42 (d, $J$ = 8.2 Hz, 1H, 13-H), 8.38 (d, $J$ = 8.0 Hz, 1H, 10-H), 8.12 (dd, $J$ = 8.2 Hz, $J$ = 7.5 Hz, 1H, 12-H), 8.00 (dd, $J$ = 8.0 Hz, $J$ = 7.7 Hz, 1H, 6-H), 7.90 (dd, $J$ = 8.0 Hz, $J$ = 7.5 Hz, 1H, 11-H), 7.75 (dd, $J$ = 7.9 Hz, $J$ = 7.7 Hz, 1H, 5-H);

$^{13}$C nmr ($CF_3COOD$): δ 156.4 (C=O), 147.1 (C-13a), 140.3 (C-14a), 139.8 (C-7a), 139.6 (C-9), 135.9 (C-3a), 135.5 (C-2), 133.1 (C-12), 132.8 (C-6), 131.6 (C-14c), 128.4 (C-11), 128.3 (C-10), 127.2 (C-14b), 126.9 (C-13), 126.6 (C-9a), 125.2 (C-5), 122.9 (C-4), 121.6 (C-8a), 121.2 (C-3b), 116.6 (C-3), 115.2 (C-7); ms: *m/z* 321 (100, $M^+$), 293 (18), 265 (10), 149 (62), 133 (19); HRMS Calcd. for $C_{21}H_{11}N_3O$: 321.0899. Found: 321.0902.

**5-(Dimethylaminomethylene)-5,6-dihydroindolo[3, 2,1-de]-[1,5]naphthyridin-4-one (12).** To a solution of dihydrochanthin-4-one (**7**) (176 mg, 0.792 mmol) in 10 mL anhydrous THF, *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent; 0.18 mL, 0.84 mmol) was added dropwise. The mixture was stirred under a nitrogen atmosphere for 3 h at 50°C. The volatile components were evaporated in vacuo, and the residue was purified by FCC (dichloromethane: ethanol:triethylamine, 13:1:1, v/v) to give 166 mg (80%) **12** as a yellow solid. Due to partial hydrolysis of the enamine in the course of silica gel chromatography this compound could not be obtained in absolutely pure form. mp 223–225°C; $^1$H nmr ([$D_6$]DMSO): δ 8.42 (d, $J$ = 5.1 Hz, 1H, 1-H), 8.31 (d, $J$ = 7.9 Hz, 1H, 11-H), 8.14 (d, $J$ = 5.1 Hz, 1H, 2-H), 7.80 (d, $J$ = 8.2 Hz, 1H, 8-H), 7.77 (s, 1H, 1′-H), 7.67 (dd, $J$ = 8.2 Hz, $J$ = 7.1 Hz, 1H, 9-H), 7.36 (dd, $J$ = 7.9 Hz, $J$ = 7.1 Hz, 1H, 10-H), 5.67 (s, 2H, 6-H), 2.51 (s, 6H, $N(CH_3)_2$); $^{13}$C nmr ([$D_6$]DMSO): δ 178.4 (C=O), 151.7 (C-1′), 140.4 (C-7a), 139.2 (C-2), 138.9 (C-11c), 135.6 (C-3a), 128.5 (C-9), 126.6 (C-11b), 122.7 (C-11), 120.6 (C-11a), 120.1 (C-10), 117.6 (C-1), 110.8 (C-8), 98.6 (C-5), 43.7 ($CH_3$), 42.7 (C-6); ms: *m/z* 277 (22, $M^+$), 234 (20), 205 (12), 169 (8), 94 (100); HRMS Calcd. for $C_{17}H_{15}N_3O$: 277.1215. Found: 277.1218.

**11-Amino-8*H*-1,7b,10,12-tetraazabenzo[e]acephenanthrylene (13).** A solution of dihydrocanthin-4-one (**7**) (120 mg, 0.540 mmol) and *tert*-butoxy-bis(dimethylamino)methane (0.15 mL, 0.70 mmol) in 12 mL anhydrous DMF was refluxed under a nitrogen atmosphere for 1 h. Then guanidinium carbonate (283 mg, 2.02 mmol) was added and the mixture was refluxed for further 5 h. After cooling to ambient temperature 20 mL saturated sodium carbonate solution were added and the mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $Na_2SO_4$ and evaporated in vacuo, the residue was purified by FCC (dichlormethane:ethanol, 9:1, v/v) to give 115 mg (78%) **13** as a yellow solid. mp >300°C (dec.); $^1$H nmr ([$D_6$]DMSO): δ 8.40 (d, $J$ = 5.3 Hz, 1H, 2-H), 8.39 (s, 1H, 9-H), 8.30 (d, $J$ = 7.9 Hz, 1H, 4-H), 8.09 (d, $J$ = 5.3 Hz, 1H, 3-H), 7.66 (m, 2H, 7-H, 6-H), 7.36 (ddd, $J$ = 7.9 Hz, $J$ = 6.7 Hz, $J$ = 1.5 Hz, 1H, 5-H), 6.88 (s, 2H, $NH_2$), 5.57 (s, 2H, 8-H); $^{13}$C nmr ([$D_6$]DMSO): δ 163.5 (C-11), 157.6 (C-9), 155.1 (C-12a), 140.2 (C-7a), 139.3 (C-2), 136.3 (C-12c), 135.9 (C-12b), 128.5 (C-6), 125.8 (C-3a), 122.7 (C-4), 120.8 (C-3b), 120.2 (C-5), 117.0 (C-3), 113.6 (C-8a), 110.4 (C-7), 42.8 (C-8); ms: *m/z* 273 (16, $M^+$), 272 (32, $M^+$-H), 169 (100), 147 (44), 119 (60); HRMS Calcd. for $C_{16}H_{11}N_5$: 272.0935 [$M^+$-H]. Found: 272.0918.

**8*H*-1,7b,10,12-Tetraazabenzo[e]acephenanthrylene (14).** A solution of **12** (184 mg, 0.663 mmol), ammonium formate (416 mg, 6.60 mmol), formamide (159 mg, 3.54 mmol) and formic acid (159 mg, 3.46 mmol) was stirred at 160°C (temperature of the oil bath) in an open flask for 1 h. After cooling to ambient temperature 50 mL water were added, the mixture was neutralized with solid sodium carbonate and extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over $Na_2SO_4$ and evaporated, the residue was purified by FCC (dichloromethane:ethanol, 14:1, v/v) to give 68 mg (40%) **14** as a yellow solid. mp >237°C (dec.); $^1$H nmr ([$D_6$]DMSO): δ 9.23 (s, 1H, 11-H), 8.89 (s, 1H, 9-H), 8.46 (d, $J$ = 5.2 Hz, 1H, 2-H), 8.33 (dd, $J$ = 7.9 Hz, $J$ = 0.9 Hz, 1H, 4-H), 8.15 (d, $J$ = 5.2 Hz, 1H, 3-H), 7.70 (m, 2H, 7-H, 6-H), 7.40 (ddd, $J$ = 7.9 Hz, $J$ = 6.5 Hz, $J$ = 1.5 Hz, 1H, 5-H), 5.84 (s, 2H, 8-H); $^{13}$C nmr ([$D_6$]DMSO): δ 158.0 (C-11); 156.4 (C-9), 154.8 (C-12a), 140.2 (C-7a), 139.8 (C-2), 136.3 (C-12c), 134.9 (C-3a), 128.7 (C-6), 126.1 (C-12b and C-8a), 122.8 (C-5), 120.7 (C-3b), 120.4 (C-4), 117.7 (C-3), 110.4 (C-7), 43.1 (C-8); ms: *m/z* 258 (75, $M^+$), 257 (100), 203 (18), 115 (21); *Anal*. Calcd. for $C_{16}H_{10}N_4$: C, 74.41; H, 3.90; N, 21.69. Found: C, 73.43; H, 3.84; N, 21.13.

**1,7b,10,12-Tetraazabenzo[e]acephenanthrylen-8-one (15).** To a solution of **14** (68 mg, 0.26 mmol) in 10 mL chloroform was added $MnO_2$ (400 mg, 4.60 mmol), and the mixture was stirred at room temperature for 12 h. The inorganic precipitates were filtered off and the filtrate was evaporated in vacuo. The residue was purified by FCC (dichlormethane:ethanol, 14:1, v/v), and the main fraction was crystallized from dichloromethane/heptane to give 89 mg (64%) **15** as a colorless solid. mp 256°C; $^1$H nmr ([$D_6$]DMSO): δ 99.82 (s, 1H, 9-H), 9.65 (s, 1H, 11-H), 8.98 (d, $J$ = 4.9 Hz, 1H, 2-H), 8.63 (d, $J$ = 8.3 Hz, 1H, 7-H), 8.33 (d, $J$ = 4.9 Hz, 1H, 3-H), 8.30 (d, $J$ = 8.1 Hz, 4-H), 7.78 (ddd, $J$ = 8.3 Hz, $J$ = 7.5 Hz, $J$ = 1.1 Hz,1H, 6-H), 7.60 (ddd, $J$ = 8.1 Hz, $J$ = 7.5 Hz, $J$ = 1.0 Hz, 1H, 5-H); $^{13}$C nmr ([$D_6$]DMSO): δ 161.1 (C-11), 158.8 (C-9), 156.9 (C-12b), 156.2 (C-12a), 146.0 (C-2), 138.0 (C-7a), 133.6 (C-12c), 133.1 (C-3a), 130.8 (C-6), 125.6 (C-5), 124.0 (C-3b), 122.9 (C-4), 122.1 (C-8a), 118.4 (C-3), 116.4 (C-7); ms: *m/z* 272 (84, $M^+$), 244 (57), 217 (45), 193 (34), 105 (100); *Anal*. Calcd. for $C_{16}H_8N_4O$: C, 70.58; H, 2.96; N, 20.58. Found: C, 70.16; H, 3.09; N, 19.79.

## REFERENCES AND NOTES

[1] (a) Cave, A.; Leboeuf, M.; Waterman, P. G. In Alkaloids, Chemical and Biological Perspectives; Wiley Interscience Publ.: New York, 1987, Vol. 5, pp 133; (b) Bhakuni, D. S.; Rawar, D. S. Bioactive Marine Natural Products; Springer: The Netherlands, 2006.

[2] Molinski, T. F., Chem Rev 1993, 93, 1825.

[3] (a) Debnath, B.; Gayen, S.; Bhattacharya, S.; Jha, T. Bioorg Med Chem 2003, 11, 5493; (b) Matsumotu, S. S.; Biggs, J.; Copp, B. R.; Holden, J. A.; Barrows, L. R. Chem Res Toxicol 2003, 16, 113.

[4] (a) de Guzman, F. S.; Schmitz, F. J. Tetrahedron Lett 1989, 30, 1069; (b) Bracher, F. Pharmazie 1997, 52, 57.

[5] (a) Rao, J. U. M; Giri, G. S.; Hanumaiah, T.; Rao, K. V. J. J Nat Prod 1986, 49, 346; (b) Peterson, J. R.; Zjawioni, J. K.; Liu, S.; Hufford, C. D.; Clark, A. M.; Rogers, R. D. J Med Chem 1992, 35, 4069.

[6] Sriram, D.; Yogeeshwari, P.; Thirrumurugam, R.; Bal, T. R. Nat Prod Rep 2005, 19, 393.

[7] (a) Leboeuf, M.; Cave, A.; Forgacs, A.; Provost, J. J Chem Soc Perkin Trans 1, 1982, 1205. (b) Costa, E. V.; Pinheiro, M. L. B.; Xavier, C. M.; Silva, J. R. A.; Amaral, A. C. F.; Souza, A: D. L.; Barison, A.; Campos, F. R.; Ferreira, A. G.; Machado, G. M. C.; Leon, L. L. P. J Nat Prod 2006, 69, 292.

[8] Puzik, A.; Bracher, F. J Heterocyclic Chem 2009, 46, 770.

[9] (a) Dombeck, F.; Bracher, F. Pharmazie 2005, 60, 5; (b) Huber, K.; Bracher, F. Z. Naturforsch 2007, 62b, 1313.

[10] Mink, K.; Bracher, F. Arch Pharm Chem Life Sci 2007, 340, 429.

[11] Compound **7** has been mentioned in a patent: Ohashi, M.; Nishida, H.; Shudo, T. Jpn Pat 97-344164 (1997).

[12] Parham, W. E.; Bradsher, C. K. Acc Chem Res 1982, 15, 300. For an application in alkaloid total synthesis, see: Bracher, F. Arch Pharm (Weinheim) 1994, 327, 371.

[13] Bracher, F.; Hildebrand, D. Tetrahedron 1994, 50, 12329.

[14] (a) Review article: Cheng, C.-C.; Yan, S.-J. Org React 1982, 28, 37; (b) For a Friedländer reaction with 1-acetyl-β-carboline, see: Bracher, F.; Hildebrand, D. Liebigs Ann Chem 1993, 837.

[15] Smith, L. I.; Opie, J. W. Org Synth 1955, 3, 56.

[16] SanMartin, R.; Martinez de Marigorta, E.; Moreno, I.; Dominguez, E. Heterocycles 1997, 45, 757.

[17] Dominguez, E.; Martinez de Marigorta, E.; Olivera, R.; SanMartin, R. Synlett 1995, 955.

# Efficient Microwave-Assisted Synthesis of Ellipticine through *N*-(1,4-Dimethyl-9*H*-carbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde Diethyl Acetal



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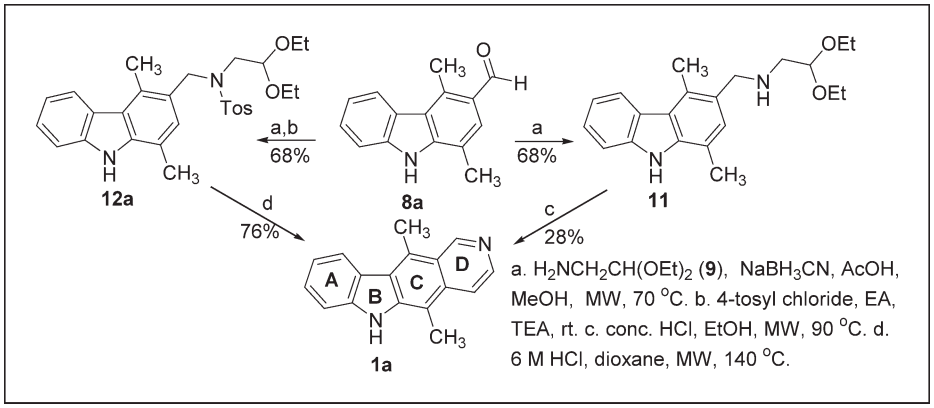


The long-lasting problematic low yield in the D-ring cyclization of ellipticine (**1a**) was dramatically improved through *N*-(1,4-dimethylcarbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde diethyl acetal with microwave irradiation. The overall yield of **1a** starting from indole was significantly increased by 25-fold. This new approach is superior to reported methods in yields and, reaction time, and it provides efficient access to a broad spectrum of ellipticine derivatives.

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## INTRODUCTION

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, **1a**), a tetracyclic natural alkaloid, was isolated from *Ochrosia elliptica* Labill. in 1959 [1] and found to be a potent anticancer agent [2]. Analogs bearing substituents on N-1 and C-9 of ellipticine such as 9-hydroxyellipticine (**2**) [3] and 9-hydroxy-2-methylellipticium (**3**) [4] possess potent antitumor activities as well. The structures of ellipticine and its analogs are shown in Figure 1.

In view of the interesting biological activity, it has attracted great attention to functionalize ellipticine. As shown in Scheme 1, a five-step synthetic pathway of ellipticine was first reported by Cranwell and Saxton [5]: starting from indole (**6a**) to give 1,4-dimethylcarbazole (C-ring formation), then through Vilsmeier-Haack formylation and Schiff base formation followed by reduction and isoquinoline cyclization (D-ring formation) to afford ellipticine. However, the final step of isoquinoline cyclization suffered a 9% low yield, and the total yield of **1a** starting from indole was as low as 0.8%.

The low yield of the D-ring closure leading to ellipticine has been improved to 30% *via* treating azomethine with orthophosphoric acid by Dalton et al. [6]. A perusal of literature revealed the general synthetic strategy to build up the tatracycline skeleton involving a connection of substituted indoles and various pyridines through Diels-Alder annulation, Friedel-Crafts acylation, and radical reactions. These methods could be simplified as [2 + 1] concept. For examples, Diels-Alder annulation from 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*] indole and 3,4-pyridyne gave a mixture of **1a** and isoellipticine (**4**) in Gribble's investigation [7]. In addition, synthesis of ellipticine quinone (**5**), which could be converted into ellipticine [8], demonstrated an alternative pathway of [2 + 1] annulation. Intramolecular reaction between 2-indolylacyl radicals derived from phenyl selenoester with pyridines [9] furnished polycyclic indolylpyridyl ketones including ellipticine quinone.

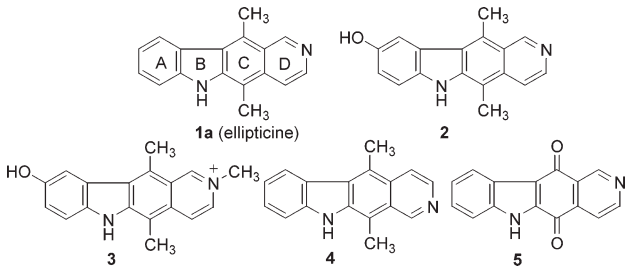
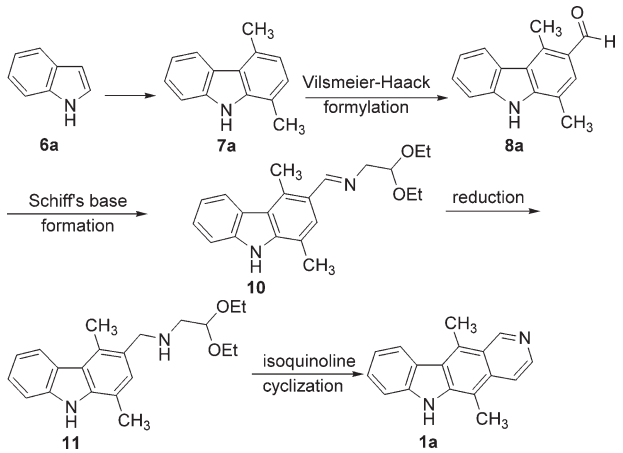



**Figure 1.** Ellipticine and its derivatives.

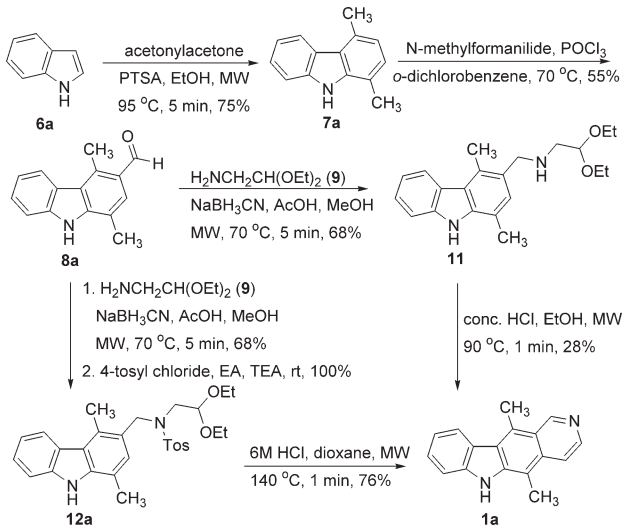
Friedel-Crafts acylation of *N*-protected indole with 3-chlorocarbonylisonicotinic acid methyl ester [8a] was followed by regioselective C-2 lithiation to yield ellipticine quinine (**5**). Recently, a radical cascade protocol has been used for the synthesis of ellipticine in higher yield [10]. Although these approaches provided better reaction yields and could be comprehensively applied in the development of ellipticine analogs, it underwent an intensively synthetic works to prepare intermediates for the last annulation steps in comparison to the Saxton's approach. Nevertheless, the reported methods were still unsatisfactory in preparing a number of derivatives for the development of ellipticine derivatives as potential anticancer drugs. Microwave (MW) irradiation has been illustrated to give superior results and to shorten reaction times in various aspects [11]. Further, MW irradiation has been widely applied to the organic synthesis including the total synthesis of natural products such as quinazolinobenzodiazepine alkaloids by a one-pot reaction [12] and biphenomycin B by the intramolecular Suzuki-Miyaura reaction [13] Herein, we report an efficient approach for the preparation of ellipticine by a modified Saxton's method with the assistance of MW irradiation.

A treatment of indole (**6a**) with acetonylacetone in the presence of *p*-toluenesulfonic acid (PTSA) in ethanol

**Scheme 1.** Saxton approach for the synthesis of ellipticine (**1a**).




**Scheme 2.** Synthesis of ellipticine (**1a**).




at 100°C for 5 min under MW irradiation afforded 1,4-dimethylcarbazole (**7a**) in 75% yield (Scheme 2). MW irradiation shortened the reaction time and improved the yield as compared with those in the conventional heating method (45 min, 36%) [5]. Subsequently, Vilsmeier-Haack formylation of **7a** by *N*-methylformanilide and $POCl_3$ in *o*-dichlorobenzene afforded aldehyde **8a** in 55% yield. The reaction was proceeded by Bobbitt-modified Pomeranz-Fritsch reaction [14] in which a Schiff base would be reduced to an amino-acetal and followed by a cyclization to isoquinoline. First, a one-pot reaction of **8a**, aminoacetaldehyde diethyl acetal (**9**), and $NaBH_3CN$ in the presence of catalytic amount of acetic acid at 70°C for 3 h furnished the desired hydrogenated *N*-(1,4-dimethylcarbazol-3-ylmethyl)-aminoacetaldehyde diethyl acetal (**11**) in 31% yield. Then, the use of MW irradiation in this one-pot reaction resulted in a twofold increase in the yield (68%). This modified MW-assisted one-pot reaction dramatically shortened the reaction time and increased the yield for the synthesis of secondary amine **11** in comparison to the Saxtons's method (2 h, 61%) [5]. Accordingly, **11** was subjected to cyclization reaction with concentrated HCl in ethanol at reflux by conventional heating. Unsurprisingly, ellipticine (**1a**) was obtained in a low yield of 9.0% as reported [5]. Then again, MW irradiation was used for the cyclization under the same condition to furnish **1a** in 28% yield. MW irradiation improved the long-lasting problematic low yield in the D-ring cyclization.

Nevertheless, a yield of 28% for the D-ring cyclization is still unsatisfactory in preparing a number of ellipticine derivatives. Birch et al. [15] illustrated that *N*-tosylated *N*-benzylaminoacetaldehyde dimethyl acetals were cyclized under mild acidic conditions and in good

**Table 1**

Comparison of reaction time and yields by microwave irradiation and conventional heating.

| | MW irradiation | | Heating[a] | |
|---|---|---|---|---|
| Reaction | Time (min) | Yield (%) | Time (min) | Yield (%) |
| **6a** → **7a** | 5 | 75 | 45 | 36 |
| **8a** → **11** | 5 | 68 | 120[b] | 61[b] |
| **8a** → **12a** | 5 | 68 | | |
| **11** → **1a** | 1 | 28 | 60 | 9 |
| **12a** → **1a** | 1 | 76 | | |

Overall yield from **6a** to **1a**

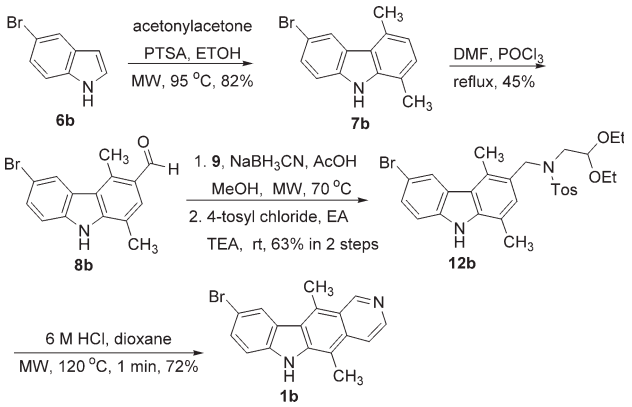
| Path | Method | Yield (%)[a] |
|---|---|---|
| **6a** → **7a** → **8a** → **10** → **11** → **1a** | Heating | 0.8 |
| **6a** → **7a** → **8a** → **11** → **1a** | MW | 7.8 |
| **6a** → **7a** → **8a** → **12a** → **1a** | MW | 21.3 |

[a] Data taken from ref. 5.
[b] Total yield in 2 steps of **8a** → **10** → **11**.

yields to isoquinolines in a one-pot reaction when the benzyl groups were substituted with sufficiently activating groups. The carbazole moiety is a well known strong electron donor [16]. We expected that the 1,4-dimethylcarbazol-3-ylmethyl group could act as an activated group, and an *N*-tosylated derivative of **11** might lead to ellipticine in an improved yield. Thus, *N*-(1,4-dimethylcarbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde diethyl acetal (**12a**) was obtained by a treatment of **11** with tosyl chloride in quantitative yield. Subsequently, *N*-tosylated diethyl acetal **12a** was subjected to cyclization to afford **1a** in 76% yield in a reaction time of 1 min under the same condition as for the cyclization of **11** to **1a**. As a result, a 51% yield of ellipticine from aldehyde **8a** was obtained through an *N*-tosylated acetal **12a** together with the assistance of MW irradiation. This approach improves the yield by nine folds in comparison to the Saxton's method (5.5%). Importantly, the overall yield of ellipticine starting from indole (**6a**) was significantly increased by 25-fold (21%) as compared to that (0.8%) reported by Saxton (Table 1).

To explore the general application of this approach, condensation of 5-bromoindole (**6b**) with acetonylacetone was proceeded, and the resulting carbazole **7b** was formylated to the aldehyde **8b** by *N*,*N*-dimethylformamide (DMF) and $POCl_3$ (Scheme 3). Compound **8b** then reacted with aminoacetaldehyde diethyl acetal (**9**) under MW irradiation, and the resulting Schiff base was reduced *in situ*. Removal of solvent followed by tosylation afforded *N*-tosylated derivative **12b**, which was cyclized under acidic condition with MW irradiation to 9-bromoellipticine (**1b**) in 72%. As a result, the bromo substituent has little effect to the reactions in this

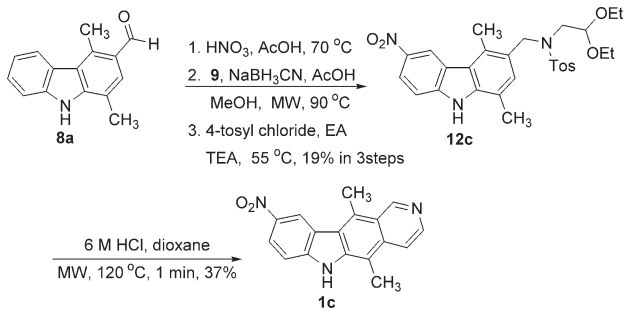
**Scheme 3.** Synthesis of 9-bromoellipticine (**1b**).




approach with MW irradiation. The slightly decrease in overall yield of **1b** with regard to ellipticine (**1a**) was due to the lower yield in the formylation reaction of 6-bromo-1,4-dimethylcarbazole (**7b**).

Birch et al. [15] reported that sufficiently activating substituents on the benzyl group were required for the cyclization of the *N*-benzyl-*N*-tosylaminoacetaldehyde dimethyl acetals to isoquinolines. Otherwise, cyclization failed and the *N*-benzyl-*N*-tosyl acetals would be first hydrolyzed to *N*-benzyl-*N*-tosylaminoacetaldehyde and then *N*-tosylbenzylamine. To investigate this substituent effect in the synthesis of ellipticine derivatives, a direct nitration of **8a** led to 1,4-dimethyl-6-nitrocarbazole-3-carbaldehyde (**8c**) which was condensed with aminoacetaldehyde diethyl acetal (**9**) to the Schiff base and reduced *in situ* under MW irradiation (Scheme 4). Without further isolation and purification, a subsequent treatment with tosyl chloride at 55°C yielded the *N*-tosylated compound **12c** in 19% (three steps). Then, compound **12c** was cyclized to 9-nitroellipticine (**1c**) in 37% yield under the same conditions as described above. The cyclization to isoquinoline was proposed as electrophilic substitution on the benzene ring [15], and lacking of sufficiently activated substituents on the aromatic ring failed in cyclization. Although a lower yield of 37% was obtained, the cyclization to 9-nitroellipticine was

**Scheme 4.** Synthesis of 9-nitroellipticine (**1c**).



still succeeded in this case. Apparently, the 1,4-dimethylcarbazole moiety could serve as an electron-efficient aromatic moiety even with a strong deactivated nitro group substituted at position 6.

In summary, we have developed a fast, efficient, and high-yield approach for the synthesis of ellipticine and its derivatives through *N*-(1,4-dimethylcarbazol-3-ylmethyl)-*N*-tosylaminoacetaldehyde diethyl acetals by the use of MW irradiation. In this modified process, MW irradiation increased the overall yield by 10-fold as compared with the reported yield (0.8%) in considerably shortened reaction time. In an effort to synthesize the derivatives of ellipticine efficiently, the key step of D-ring construction is modified by converting the secondary amine to *N*-tosylated derivative based on Birch's investigation [15]. The long-lasting problematic low yield in the D-ring cyclization was dramatically improved in this study. Even a strong electron-withdrawing substituent on the 1,4-dimethylcarbazole moiety was endured in this method. This new approach is superior to previously reported methods in yields, reaction time, and versatility, and it will allow a broad evaluation of this highly promising class of potential antitumor drugs.

## EXPERIMENTAL

The reactions assisted by microwave were achieved on Biotage Emrys™ Optimizer and Biotage Initiator™. Reaction temperatures were observed using built-in IR-sensor. Melting points were taken on Laboratory Devices, INC. (Box 6402) melting point apparatus and are uncorrected. $^1$H and $^{13}$C nuclear magnetic resonance spectra were obtained on Bruker AMX-400 and DPX-200 spectrometers. Mass spectra were obtained on Finnigan TSQ 7000 mass spectrometer. Elemental analysis for C, H, S, and N was carried out on Heraeus VarioEL III-CHNS apparatus. Thin layer chromatography (TLC) was carried out on precoated plates (silical gel, Kieselgel 60$F_{254}$, Merck). Column chromatography was performed with Kieselgel Si 60 (40–63 μm, Merck). All starting materials were obtained from commercial suppliers (Acros, Lancaster and Riedel-de Haën) and used without purification.

**General procedure for the synthesis of *N*-(2,2-Diethoxyethyl)-*N*-(1,4-dimethyl-9*H*-carbazol-3-ylmethyl)-4-methylbenzenesulfonamide (12).** A mixture of 3-formyl-1,4-dimethylcarbazole (8a, 1.0 g, 4.48 mmol), sodium cyanoborohydride (0.35 g, 5.57 mmol), 9 (0.7 mL, 5.25 mmol) and acetic acid (0.1 mL) in methanol (4 mL) was placed in a sealed tube. Reaction was heated by microwave (75 W) at 70°C for 5 min. Methanol was removed *in vacuo*, and then ethyl acetate (EA, 100 mL) was added. The solution was purified through column chromatography to afford viscous residue. To the residue, 4-tolueneulfonyl chloride (0.9 g, 4.72 mmol), triethylamine (0.5 mL, 4.94 mmol), and EA (30 mL) were added and stirred at room temperature for 2 h. The mixture was subsequently purified with column chromatography.

***N*-(2,2-Diethoxyethyl)-*N*-(1,4-dimethyl-9H-carbazol-3-ylmethyl)-4-methylbenzenesulfonamide (12a).** White solid, mp 183–184°C (lit. [17] 184°C); MS (ESI):*m*/*z* = 493.3 (M-H$^+$); $^1$H NMR (400 Hz, DMSO-$d_6$): δ = 0.88 (t, *J* = 7.0 Hz, 6H), 2.38 (s, 3H), 2.41 (s, 3H), 2.73 (s, 3H), 3.01 (d, J = 5.36 Hz, 2H, C$H_2$), 3.08 (m, 2H), 3.30 (m, 2H), 4.04 (t, *J* = 5.24 Hz, 1H), 6.94 (s, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.77 Hz, 1H), 7.41 (d, *J* = 7.97 Hz, 2H), 7.50 (d, *J* = 8.06 Hz, 1H), 7.75 (d, *J* = 8.05 Hz, 2H), 8.14 (d, *J* = 7.97 Hz, 1H),11.17 (s, 1H); $^{13}$C NMR (100 Hz, DMSO-$d_6$): δ = 15.5, 16.0, 17.1, 21.5, 49.8, 51.2, 62.6, 101.1, 111.5, 117.5, 119.2, 121.6, 122.8, 123.9, 123.7, 125.3, 127.6, 129.0, 130.1, 130.3, 136.9, 139.2, 140.7, 143.7.

***N*-(6-Bromo-1,4-dimethyl-9H-carbazol-3-ylmethyl)-*N*-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide (12b).** White solid, mp 196–197°C; MS (ESI): *m*/*z* = 571.2 (M-H$^+$); $^1$H NMR (200 Hz, DMSO-$d_6$): δ = 0.88 (t, *J* = 7.0 Hz, 6H), 2.39 (s, 3H), 2.41 (s, 3H), 2.70 (s, 3H), 3.0–3.2 (m, 4H), 3.3–4.1 (m, 2H), 4.49 (s, 2H), 7.00 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 11.40 (s, 1H); $^{13}$C NMR (50 Hz, DMSO-$d_6$): δ = 15.0, 15.5, 16.6, 21.0, 49.3, 50.5, 62.0, 100.6, 110.7, 112.9, 117.3, 120.2, 123.7, 124.4, 125.1, 127.1, 127.2, 129.2, 129.8, 129.9, 136.4, 138.9, 139.2, 143.2. Anal. Calcd for $C_{28}H_{33}BrN_2O_4S$): C, 58.64; H, 5.80; N, 4.88; S, 5.59. Found, C, 58.27; H, 6.08; N, 4.76; S, 5.38.

***N*-(2,2-Diethoxyethyl)-*N*-(1,4-dimethyl-6-nitro-9H-carbazol-3-ylmethyl)-4-methylbenzenesulfonamide (12c).** Yellow solid. mp 190–192°C; MS (ESI): *m*/*z* = 538.3 (M-H$^+$); $^1$H NMR (400 Hz, acetonitrile-$d_3$): δ = 0.92 (t, *J* = 7.0 Hz, 6H), 2.35 (s, 3H), 2.37 (s, 3H), 2.62 (s, 3H), 3.06 (d, *J* = 5.33 Hz, 2H), 3.13 (m, 2H), 3.35 (m, 2H), 4.14 (t, *J* = 5.31 Hz, 1H), 4.41 (s, 2H), 6.99 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 8.49 Hz, 1H), 7.71 (d, *J* = 8.07 Hz, 2H), 8.17 (d, *J* = 8.70 Hz, 1H), 8.80 (s, 1H), 9.99 (s, 1H); $^{13}$C NMR (50 Hz, DMSO-$d_6$): δ = 15.0, 15.4, 16.6, 21.0, 62.8, 100.7, 118.2, 120.8, 121.1, 122.7, 125.5, 127.2, 129.8, 130.0, 130.2, 136.4, 139.7, 140.0, 142.4, 143.3, 143.8. Anal. Calcd for $C_{28}H_{33}N_3O_6S{\cdot}0.33H_20$: C, 61.63; H, 6.22; N, 7.70. Found, C, 61.77; H, 6.00; N, 8.08.

**General procedure for the synthesis of Ellipticine (1).** A mixture of **12a** (1.0 g, 2.02 mmol), dioxane (3 mL), and 6*M* HCl (1.0 mL) was placed in a sealed microwave tube. The mixture was irradiated by microwave (180 W) at 140°C for 1 min and then purified with column chromatography to afford **1a**.

***Ellipticine (1a).*** Mp 309–310°C (dec.; lit. [5] 309–313°C, dec.); MS (ESI): m/z = 245.0 (M-H$^+$) $^1$H NMR (400 Hz, DMSO-$d_6$): δ = 2.78 (s, 3H), 3.24 (s, 3H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.95 Hz, 1H), 7.91 (d, *J* = 6.03 Hz, 1H), 8.36 (d, *J* = 7.90 Hz, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 9.68 (s, 1H), 11.59 (s, 1H); $^{13}$C NMR (100 Hz, DMSO-$d_6$): δ = 12.0, 14.4, 108.1, 110.8, 116.0, 119.2, 121.9, 123.1, 123.5, 123.8, 127.1, 128.1, 132.5, 140.2, 140.7, 142.7, 149.5.

***9-Bromoellipticine (1b).*** Mp 330–332°C (lit. [6] 318–319°C); MS (ESI): 323.0 (M-H$^+$); $^1$H NMR (200 Hz, DMSO-$d_6$): δ = 2.74 (s, 3H), 3.19 (s, 3H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 6.0 Hz, 1H), 8.41 (s, 2H), 9.68 (s, 1H), 11.53 (s, 1H); $^{13}$C NMR (50 Hz, DMSO-$d_6$): δ = 12.0, 14.3, 108.6, 111.0, 112.5, 116.0, 122.0, 122.9, 125.0, 125.9, 128.9, 129.6, 132.7, 140.6, 140.8, 141.4, 149.9.

***9-Nitroellipticine (1c).*** Mp (dec.) 352°C (dec., lit. [6] 350°C, dec.); MS (ESI): 290.1 (M-H$^+$); $^1$H NMR (400 Hz, DMSO-$d_6$): δ = 2.75 (s, 3H), 3.08 (s, 3H), 7.61 (d, *J* = 8.6

Hz, 1H), 7.91 (d, $J = 6.1$ Hz, 1H), 8.38 (d, $J = 9.0$ Hz, 1H), 9.47 (d, $J = 5.9$ Hz, 1H), 9.02 (s, 1H), 9.71 (s, 1H), 12.13 (s, 1H); $^{13}$C NMR (100 Hz, DMSO-$d_6$): $\delta = 11.9$, 14.3, 108.5, 110.9, 112.4, 115.9, 121.9, 122.3, 125.0, 125.8, 128.9, 129.5, 132.7, 140.6, 140.7, 141.4, 149.8.

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## REFERENCES AND NOTES

[1] Sindney, G.; Horning, E. E.; Smith, A. F. J Am Chem Soc 1959, 81, 1903.

[2] (a) Asche, C.; Demeunynck, M. Curr Med Chem Anticancer Agents 2007, 7, 247; (b) Garbett, N. C.; Graves, D. E. Curr Med Chem Anticancer Agents 2004, 4, 149; (c) Le Pecq, J. B.; Datxuong, N.; Gosse, C.; Paoletti, C. Proc Natl Acad Sci USA 1974, 71, 5078.

[3] Le Pecq, J. B.; Gosse, C.; Datxuong, N.; Paoletti, C. C R Hebd Seances Acad Sci Ser D 1973, 277, 2289.

[4] Paoletti, C.; Le Pecq, J. B.; Datxuong, N.; Juret, P.; Garnier, H.; Amiel, J.-L.; Rouesse, J. Recent Results Cancer Res 1980, 74, 107.

[5] Cranwell, P. A.; Saxton, J. E. J Chem Soc 1962, 3482.

[6] Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. Aust J Chem 1967, 20, 2715.

[7] (a) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. J Org Chem 1984, 49, 4518; (b) Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. J Org Chem 1992, 57, 5878.

[8] (a) Ketcha, D. M.; Gribble, G. W. J Org Chem 1985, 50, 5451; (b) Taylor, D. A.; Baradarani, M. M.; Martinez, S. J.; Joule, J. A. J Chem Res Synop 1979, 387; (c) Taylor, D. A.; Joule, J. A. J Chem Soc Chem Commun 1979, 642; (d) Watanabe, M.; Snieckus, V. J Am Chem Soc 1980, 102, 1457; (e) Robaut, C.; Rivalle, C.; Rautureau, M.; Lhoste, J.-M.; Bisagni, E. Tetrahedron 1985, 41, 1945; (f) Saulnier, M. G.; Gribble, G. W. J Org Chem 1983, 48, 2690.

[9] Bennasar, M.; Roca, T.; Ferrando, F. J Org Chem 2005, 70, 9077.

[10] Pedersen, J. M.; Rowman, W. R.; Elsegood, M. R. J.; Fletcher, A.; Lovell, P. J. J Org Chem 2005, 70, 10615.

[11] (a) Högermeier, J.; Reiβig, H.-U. Chem Eur J 2007, 13, 2410; (b) Cravotto, G.; Cintas, P. Chem Eur J 2007, 13, 1902.

[12] Liu, J.-F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C. M. J Org Chem 2005, 70, 10488.

[13] Lépine, R.; Zhu, J. Org Lett 2005, 7, 2981.

[14] Bobbitt, J. M.; Kiely, J. M.; Khanna, K. L.; Ebermann, R. J Org Chem 1965, 30, 2247.

[15] Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. J Chem Soc Perkin Trans 1 1974, 2185.

[16] (a) Velasco, D.; Castellanos, S.; López, M.; López-Calahorra, F.; Brillas, E.; Julia, L. J Org Chem 2007, 72, 7523; (b) Wang, Z.-S.; Koumura, N.; Cui, Y.; Takahashi, M.; Sekiguchi, H.; Mori, A.; Kubo, T.; Furube, A.; Hara, K. Chem Mater 2008, 20, 3993; (c) Han, F.; Chi, L.; Liang, X.; Ji, S.; Liu, S.; Zhou, F.; Wu, Y.; Han, K.; Zhao, J.; James, T. D. J Org Chem 2009, 74, 1333.

[17] Mustafin, A. G.; Khalilov, I. N.; Tal'vinskii, E. V.; Abdrakhmanov, I. B.; Spirikhin, L. V.; Tolstikov, G. A. Chem Nat Compd Engl 1992, 5, 549.

# Rearrangement of 2-Bromo-*N*-quinoline-8-yl-acetamide Leading to New Heterocycle



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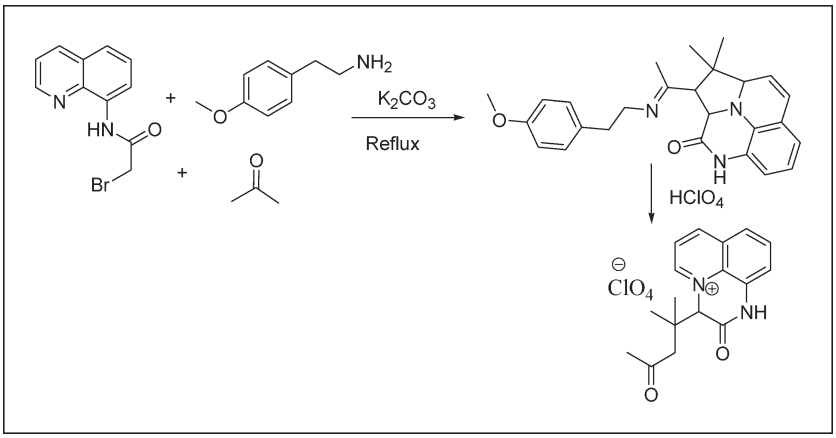


A four fused rings containing heterocyclic compound is formed in the reaction between 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(4-methoxyphenyl)ethylamine, and acetone in the presence of potassium carbonate; the heterocycle undergoes further reaction with perchloric acid to form a perchlorate salt of a quinoxaline derivative.

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## INTRODUCTION

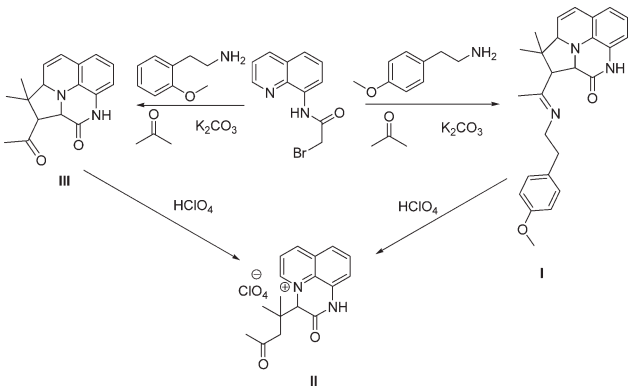
Intramolecular cyclization processes are very useful in heterocycle synthesis [1–6] and they are used for synthesis of variety of natural products and drugs. Among them, *N*-acylinium ion cyclization reactions are very attractive [7–10]. Such intramolecular reactions are carried out under catalytic conditions [11–18]. Several of these reactions require multiple steps [1]. Multicomponent reactions to prepare heterocycles help to reduce the inconvenience caused by the extra work involved in product purification [19–24] in each step and also to reduce the reaction time. We have serendipitously observed formation of a heterocycle from a reaction of 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(4-methoxyphenyl)ethylamine and acetone. The characterization of the fused four-member heterocyle along with its subsequent rearrangement to a quinoxaline derivative is described here. Some quinoxaline derivatives [1] have medicinal value, so new method of synthesis for such compounds are desirable.

## RESULTS AND DISCUSSION

A multicomponent reaction between 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(4-methoxyphenyl)ethylamine, and acetone in the presence of potassium carbonate gives a fused ring heterocyclic compound **I** as illustrated in Scheme 1. However, analogous multicomponent reaction between 2-bromo-*N*-quinoline-8-yl-acetamide, 2-(2-methoxyphenyl)ethylamine, and acetone in the presence of potassium carbonate gives a fused ring heterocyclic carbonyl compound **III**, not the imine that was obtained while 2-(4-methoxyphenyl)ethylamine was used. This compound transforms to perchlorate salt **II** of another heterocycle on reaction with perchloric acid. The compound **III** also undergoes rearrangement reaction with perchloric acid to form perchlorate salt **II**. The use of excess acetone in these reactions serves dual purposes of reactant as well as solvent.

All these compounds were characterized from their spectroscopic properties. The compound **I** has IR absorptions at 1676 $cm^{-1}$ and at 1635 $cm^{-1}$ due to carbonyl and C=N stretching, respectively. The high resolution mass spectrum of the compound shows the mass for the $M^+$ peak at 415.2688, that supports the composition. The $^1H$ NMR and $^{13}C$ NMR of the compounds have the desirable numbers of peaks to support the structure (for assignments of peaks please refer to supporting figures). The compound **I** is further characterized by X-ray crystallography and the structure of the compound is shown in Figure 1(a).

**Scheme 1.** Reaction leading to product **I** and **III**, which react with perchloric acid to form salt **II**.




As mentioned the compound **I** undergoes hydrolysis followed by ring opening reactions to give a quinoxaline derivative in the form of a perchlorate salt **II**. The salt **II** is characterized by conventional spectroscopic techniques as well as by X-ray crystallography [Fig. 1(b)]. The IR spectra of the salt **II** have characteristic sharp perchlorate absorption at 1100 $cm^{-1}$ and its carbonyl absorption appears at 1705 $cm^{-1}$.

Plausible reaction paths (Scheme 2) for the formation of the compound **I** may be through an initial condensation reaction of two molecules of acetone to form aldol type intermediate. The carbonyl group of the aldol gets condensed with 2-(4-methoxyphenyl)ethylamine to form an imine derivative as an intermediate species. This imine containing molecule has a hydroxy group, which is attached to a tertiary carbon and it would like to form C—C bond with the quinoiline ring through elimination of a water molecule. Presumably, this intermediate compound forms a bromide salt through cyclization reaction. The cyclized product thus formed, undergo a hydride shift to form a derivative that is suitable for further nucleophilic attack of an anion generated next to the C=N group. It forms the desired product **I**. Thus, by these reaction steps, two additional rings over the quinoline rings are constructed. The added advantage of this reaction is that it does not stop at the stage of formation of one ring, but continues to form multiple rings; that generally does not happen in intramolecular cyclization reactions [2–6].

The formation of the salt **II** can be explained by a three steps mechanistic path as illustrated in Scheme 2. The first step could be the generation of ketone from a hydrolytic reaction of perchloric acid by the conversion of imine to keto group. The keto group containing compound thus formed gets protonated under acidic condition to form enolised form of a cationic species with perchlorate as a counter anion. This process leads to opening of the five-member ring of the parent compound. The enolic cation thus formed, on aromatization leads to concomitant cleavage of a C—C bond along with the formation of a new C—C bond at a tertiary

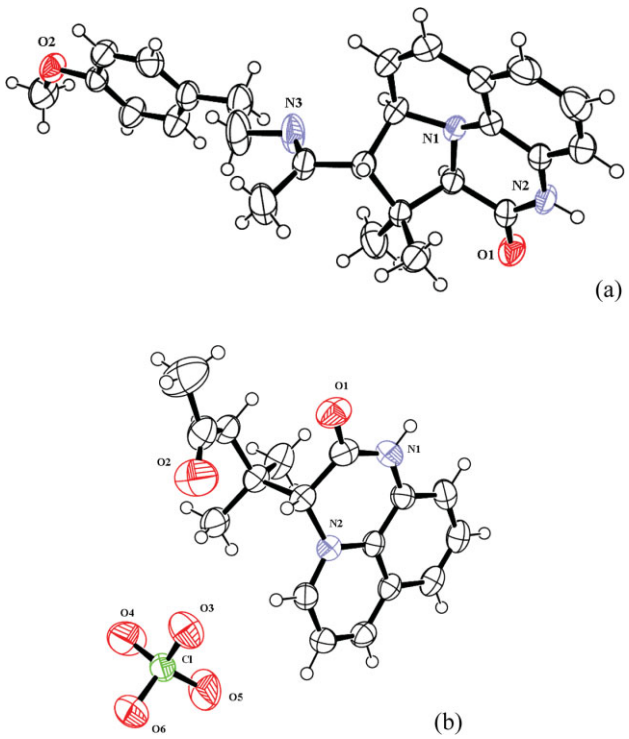
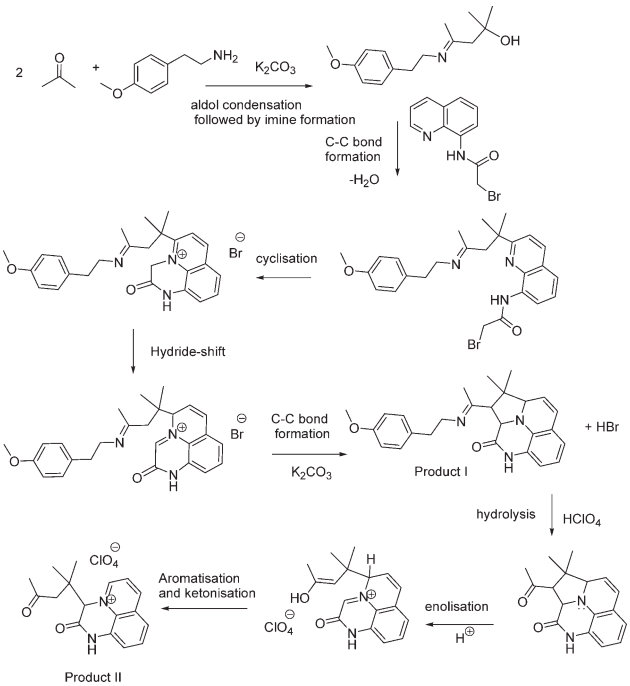
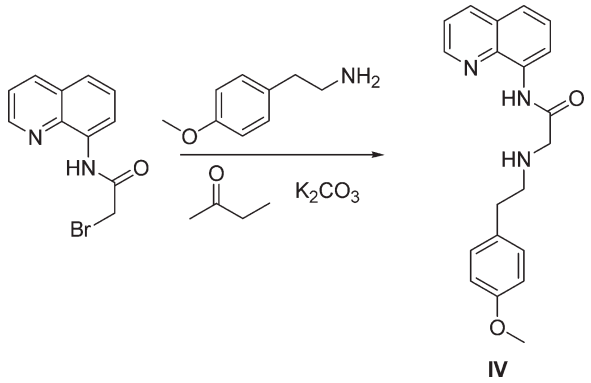



**Figure 1.** Crystal structure of (a) **I** and (b) **II** (ORTEP drawn with 50% thermal ellipsoid). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2.** Plausible paths for formation of **I** and **II**.



**Scheme 3.** Formation of product **IV** in ethyl methylketone.




**IV**

carbon. This new C—C bond formation along with enol to keto transformation as illustrated in Scheme 2 gives the final product **II**.

Furthermore, we did not observe any aldol condensation and cyclization reactions from the reaction between 2-bromo-*N*-quinoline-8-yl-acetamide and acetone in the presence of potassium carbonate without using an amine. When 2-(4-methoxyphenyl)ethylamine was reacted with acetone in the presence of potassium carbonate, it led to the corresponding imine. However, this imine did not react with 2-bromo-*N*-quinoline-8-yl-acetamide to give product **I**. This suggests that the aldol condensation and the formation of imine took place concomitantly in the presence of 2-bromo-*N*-quinoline-8-yl-acetamide. When the same reaction was carried out with 2-(2-methoxyphenyl)ethylamine, we obtained the product **III**. The formation of product, product **II** on treatment of **III** with perchloric acid, shows that formation of **II** does not depend on the amine used. The formation of a ketone instead of imine as the final product while using 2-(2-methoxyphenyl)ethylamine may be due to the hydrolysis of the corresponding imine. We also carried out similar reactions of 2-bromo-*N*-quinoline-8-yl-acetamide with other amines such as benzylamine, picolylamine, and no reaction was observed under analogous reaction conditions. However, aromatic amines such as 8-aminoquinoline replaced the bromide of 2-bromo-*N*-quinoline-8-yl-acetamide to form C—N bonded derivative. Use of ethylmethyl ketone as solvent did not lead to the aldol condensation reaction; instead, 2-(4-methoxyphynelamino)-*N*-(quinoline-8-yl)acetamide (**IV**) was formed by substitution of bromine by 2-(4-methoxyphenyl)ethylamine (Scheme 3).

In conclusion, these results demonstrate a new reaction leading to a novel heterocylic quinoxaline derivative **II**. The formation of compound **I** in one pot is advantageous, as synthesis of this compound by alternative routes would require multiple steps and less common reagents.

## EXPERIMENTAL

### Synthesis and characterization of compounds

***Compound I.*** 2-Bromo-*N*-quinoline-8-yl-acetamide (1.4 g, 5 mmol), 2-(4-methoxyphenyl)ethylamine (0.735 mL, 5 mmol) and anhydrous potassium carbonate (1.03 g, 7.5 mmol) were added to dry acetone (20 mL), and the reaction mixture was stirred at 70°C for 12 h (progress of the reaction was monitored at regular intervals by using TLC). The reaction mixture was filtered to remove the residue and the solvent was removed under reduced pressure. The product obtained was purified by preparative thin layer chromatography using silica gel with 30% ethylacetate in petroleum ether as eluant. Yield: 41%. IR (KBr, $cm^{-1}$): 3125 (w), 3059 (m), 3008 (m), 2960 (m), 2923 (m), 1676 (s), 1658 (w), 1635 (m), 1613 (m), 1584 (m), 1511 (s), 1482 (s), 1387 (s), 1369 (w), 1270 (m), 1246 (s), 1172 (m), 1028 (m), 798 (m), 724 (m). $^1$H NMR ($CDCl_3$): 8.4 (s, 1H), 7.1(d, $J$ = 8.4 Hz, 2H), 6.8 (d, $J$ = 6.4 Hz, 2H), 6.5 (m, 3H), 6.3 (d, $J$ = 10 Hz, 1H), 5.7 (dd, $J$ = 5.2, 10 Hz, 1H), 4.5 (dd, $J$ = 5.2, 10 Hz, 1H), 3.7 (s, 3H), 3.53 (s,1H), 3.50 (t, $J$ = 7.2 Hz, 2H), 2.8 (t, $J$ = 7.2 Hz, 2H), 2.5 (d, $J$ = 10.4 Hz,1H), 1.7 (s, 3H), 1.1 (s, 3H), 1.0 (s, 3H). $^{13}$C NMR ($CDCl_3$): 20.3, 24.7, 27.1, 36.6, 44.6, 53.2, 55.5, 59.5, 66.4, 71.5, 109.9, 113.9, 114.6, 118.7, 120.3, 121.8, 123.5, 124.8, 125.2, 129.0, 130.0, 132.9, 158.1, 166.5. LC-MS [$M^+$] calcd for $C_{26}H_{29}N_3O_2$, 415.2260; found 415.2688.

***Compound II.*** Compound **I** (0.41 g, 1 mmol) was dissolved in dilute perchloric acid (3*M*) and heated for 10 min. The solution was kept undisturbed, yellow colored crystal of compound **II** appeared after 6 days. Yield: 46%. IR (KBr, $cm^{-1}$): 3258 (m), 3110 (w), 3083 (m), 2962 (m), 1705 (s), 1608 (w), 1587 (m), 1541 (s), 1471 (m), 1427 (s), 1384 (m), 1361(m), 1239 (w), 1177 (m), 1100 (s), 927 (m), 839 (s), 764 (m), 623 (s). $^1$H NMR ($CDCl_3$/DMSO-$d_6$): 12.0 (s,1H), 9.4 (d, $J$ = 6 Hz, 1H), 9.2 (d, $J$ = 8.4 Hz, 1H), 8.2 (m, 1H), 8.0 (d, $J$ = 8.4 Hz, 1H), 7.9 (t, $J$ = 8.0 Hz, 1H), 7.6 (d, $J$ = 7.6 Hz, 1H), 6.0 (s, 1H), 2.9 (d, $J$ = 18.4 Hz, 1H), 2.6 (d, $J$ = 19.2 Hz, 1H), 2.1 (s, 3H), 1.0 (s, 3H), 0.7 (s, 3H). $^{13}$C NMR (DMSO-$d_6$): 24.0, 24.7, 31.5, 51.2, 72.9, 118.9, 122.9, 123.2, 127.3, 129.8, 131.0, 131.5, 148.3, 149.8, 162.1, 206.9. LC-MS [$M^+$] calcd for $C_{17}H_{19}N_2O_2ClO_4$, 283.1441; found 283.1651.

***Compound III.*** 2-Bromo-*N*-quinoline-8-yl-acetamide (1.4 g, 5 mmol), 2-(2-methoxyphenyl)ethylamine (0.735 mL, 5 mmol) and anhydrous potassiumcarbonate (1.03 g, 7.5 mmol) were added to dry acetone (20 mL) and the reaction mixture was stirred at 70°C for 12 h (progress of the reaction was monitored at regular intervals using TLC). The reaction mixture was filtered to remove the residue and the solvent was removed under reduced pressure. The product obtained was purified by preparative thin layer chromatography using silica gel with 30% ethylacetate in petroleum ether as eluant. Yield: 25%. IR (KBr, $cm^{-1}$): 3432 (b), 2924 (s), 2853 (m), 1681 (s), 1596 (m), 1527 (s), 1491 (m), 1458 (m), 1384 (m), 1325 (m), 1244 (s), 1174 (w), 1024 (m), 827 (m), 792 (m), 753 (s). $^1$H NMR ($CDCl_3$): 8.2 (s, 1H), 6.4 (m, 2H), 6.3 (d, $J$ = 7.2 Hz, 1H), 6.1 (d, $J$ = 10 Hz, 1H), 5.5 (m, 1H), 4.1 (m, 1H), 3.3 (s, 1H), 2.6 (d, $J$ = 10 Hz, 1H), 1.9 (s, 3H), 0.9 (s, 6H). $^{13}$C NMR (CDCl3): 24.7, 26.9, 33.1, 45.3, 59.8, 68.6, 71.3, 114.8, 116.7, 119.1, 120.7, 122.1, 123.3, 136.3, 148.7, 165.5. LC-MS [$M^+$] calcd for $C_{17}H_{18}N_2O_2$, 282.1368; found 283.1448 [$M^+$+1].

***Compound IV.*** 2-Bromo-*N*-quinoline-8-yl-acetamide (1.4 g, 5 mmol), 2-(4-methoxyphenyl)ethylamine (0.735 mL, 5

mmol), and anhydrous potassiumcarbonate (1.03 g, 7.5 mmol) were added to ethyl methylketone (20 mL), and the reaction mixture was stirred at 70°C for 12 h (progress of the reaction was monitored at regular intervals using TLC). The reaction mixture was filtered to remove the residue and the solvent was removed under reduced pressure. The product obtained was purified by preparative thin layer chromatography using silica gel with 30% ethylacetate in petroleum ether as eluant. Yield: 45%. IR (KBr, $cm^{-1}$): 3315 (m), 2925 (m), 2851 (w), 1655 (s), 1612 (w), 1579 (w), 1530 (s), 1488 (m), 1463 (m), 1424 (w), 1326 (s), 1245 (s), 1175 (m), 1033 (m), 786 (s), 750 (m). $^1$H NMR ($CDCl_3$): 10.5 (s, 1H), 8.7 (m, 2H), 8.1 (d, $J$ = 6.8 Hz, 1H), 7.5 (m,3H), 7.4 (q, $J$ = 4 Hz, 1H), 7.1 (d, $J$ = 8.4, 1H), 6.8 (d, $J$ = 8.8, 1H), 4.3 (s, 3H), 3.7 (s,2H), 3.5 (s, 1H), 2.9 (t, $J$ = 6.8 Hz, 2H), 2.8 (t, $J$ = 6.0 Hz, 2H). $^{13}$C NMR (DMSO-$d_6$/$CDCl_3$): 28.8, 34.9, 62.0, 85.4, 115.5, 121.1, 121.2, 126.4, 127.3, 129.0, 133.3, 135.6, 137.6, 147.8, 170.6. LC-MS [$M^+$] calcd for [$M^+$] $C_{20}H_{21}N_3O_2$, 335.1634; found 336.1679 [$M^+$+1].

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## REFERENCES AND NOTES

[1] Katritzky, A.; Pozhaskii, A. F. Handbook of Heterocyclic Chemistry, 2nd ed.; Pergamon: Amsterdam, 2000.

[2] Denmark, S. E.; Thorarensen, A. Chem Rev 1996, 96, 137.

[3] Winkler, J. D. Chem Rev 1996, 96, 167.

[4] Padwa, A., Ed. 1,3-Dipolar Cycloaddition Chemistry; Wiley-Interscience: New York, 1984; Vols. I and II.

[5] Hiemstra, H.; Speckamp, W. N. In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047–1082.

[6] Kapat, A.; Kumar, P. S.; Baskaran, S. Beilstein J Org Chem 2007, 3, 49.

[7] Padwa, A.; Weingarten, M. D. Chem Rev 1996, 96, 223.

[8] Padwa, A., Jr.; Marino, J. P.; Osterhout, M. H. J Org Chem 1995, 60, 2704.

[9] Hutchings, R. H.; Meyers, A. I. J Org Chem 1996, 61, 1004.

[10] Tsuda, Y.; Hosoi, S.; Nakai, A.; Sakai, Y.; Abe, T.; Ishi, Y.; Kiuchi, F.; Sano, T. Chem Pharm Bull 1991, 39, 1365.

[11] Joucla, L.; Putey, A.; Joseph, B. Tetrahedron Lett 2005, 46, 8177.

[12] Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. J Org Chem 1990, 55, 4518.

[13] Padwa, A.; Xu, S. L. J Am Chem Soc 1992, 114, 5881.

[14] Hoye, T. R.; Dinsmore, C. J. J Am Chem Soc 1991, 113, 4343.

[15] Mueller, P. H.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D.; Padwa, A. Tetrahedron Lett 1993, 34, 4285.

[16] Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. J Org Chem 1989, 54, 930.

[17] Davies, H. M. L.; Oldenburg, C. E. M.; McAfee, M. J.; Nordahl, J. G.; Henretta, J. P.; Romines, K. R. Tetrahedron Lett 1988, 29, 975.

[18] Deem, M. L. Synthesis 1982, 701.

[19] Ugi, I. Pure Appl Chem 2001, 73, 187.

[20] Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[21] Isambert, N.; Lavilla, R. Chem Eur J 2008, 14, 8444.

[22] Mihovilovic, M. D.; Stanetty, P. Angew Chem Int Ed Engl 2007, 46, 3612.

[23] Bremner, W. S.; Organ, M.G. J Comb Chem 2007, 9, 14.

[24] Kappe, O. Acc Chem Res 2000, 33, 879.

# Synthesis of New 2-Aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes *via* Vilsmeier-Haack Reaction



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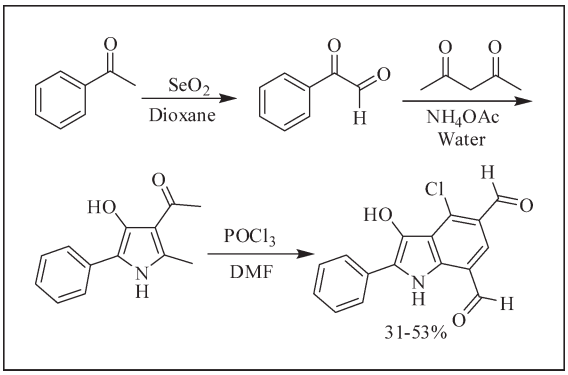


New 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes were synthesized in three steps from acetophenone derivatives. By oxidation of acetophenones to aryl glyoxals using selenium dioxide and condensation with acetylacetone in the presence of ammonium acetate in water 3-acetyl-5-aryl-4-hydroxy-2-methyl-1*H*-pyrrols were obtained. 2-Aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes were synthesized *via* Vilsmeier-Haack reaction of pyrrole derivatives in moderate yields.

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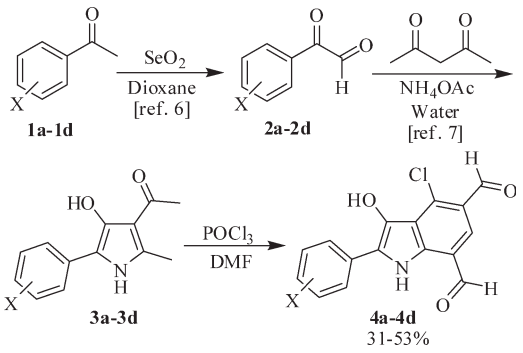
## INTRODUCTION

The synthesis of indoles has occupied organic chemists for well over a century [1]. And the invention of new synthetic routes to substituted indoles continues to command wide interest due to the numerous natural products [2], physiologically active natural products and important pharmaceuticals [3] whose structures incorporate this heterocyclic system. Indole derivatives are used as neuroprotective agents affecting oxidative stress [3f], potent opioid receptor agonists [3g], highly functionalized pharmacophores [3h], potent PPAR-γ binding agents with potential application for the treatment of osteoporosis [3i], drugs for the treatment of peripheral neuropathy and neurodegenerative diseases [3j,k], glucokinase activators [3l,m], the cytotoxic antibiotic CC-1065 and prodrugs [3n], PPAR-delta activators for the treatment of cardiovascular diseases [3o] and dyestuffs [4]. The combination of traditional and modern methods has provided accessibility to a wide variety of structural variations of this important class of heterocycles [3e,5]. A number of useful strategies are now available for the synthesis of indoles substituted on the five-membered ring, the majority of which involve the elaboration of the heterocyclic system from aniline, *o*-halo aniline, or other 2-substituted aniline derivatives. In contrast, few existing methods provide efficient and regiocontrolled access to indoles that are highly substituted on the benzenoid ring. Herein we disclose a method, based on Vilsmeier-Haack reaction of 3-acetyl-4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrols **3**, to provide new highly substituted indoles **4** with substituted on both five-membered and benzenoid ring of indole (Scheme 1).

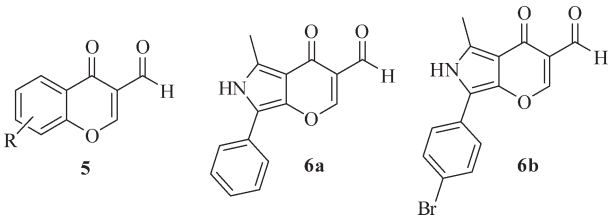
The Vilsmeier–Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds [8]. The reactions of aliphatic substrates [9], particularly carbonyl compounds [10] with chloromethylene iminium salts are highly versatile. They lead to multiple iminoalkylations in the presence of excess reagent and the resulting intermediates undergo cyclization to afford aromatic or heterocyclic compounds [11]. Multifunctional intermediates derived from these reactions (*e.g.*, β-chloroenaldehydes) are subsequently exploited for the synthesis of functionalized heterocycles or other valuable target molecules [12].

**Scheme 1.** Three steps synthesis of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes.




## RESULTS AND DISCUSSION

The reaction of 2-hydroxyacetophenones with Vilsmeier-Haack reagent also involves an iminoalkylation-cyclization sequence, leading to the formation of 3-formyl chromones **5** [13]. Similarly we expected to synthesis the 5-methyl-4-oxo-7-phenyl-4,6-dihydro-pyrano[2,3-c]pyrrole-3-carbaldehyde **6a** from the reaction of 3-acetyl-4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrol **3** with Vilsmeier-Haack reagent, but we did not obtained the expected compound **6a** instead the reaction gave compound **4**. In the case of 4-bromoacetophenone **1c**, not only **4c** was formed but also **6b** was obtained in low yield.




Four examples of the conversion of acetophenones **1a–1d** to various 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4a–4d** are listed in Table 1.

As shown in Scheme 2, the proposed mechanism involves the addition of enol **7** to the 2 equiv. chloromethyleneiminium salt **8**, then bis-iminium salt **9** undergoes iminoalkylation to result enamine **10**, that undergo cyclization and elimination of dimethylamine to afford the bis-iminium salt **12** which on hydrolysis leads to the formation of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4** [14].

4-Chloro-2-phenyl-5,7-bis-phenyliminomethyl-1*H*-indol-3-ol **14** and 4-chloro-5,7-bis[(2,4-dinitrophenyl)-hydrazonomethyl]-2-phenyl-1*H*-indol-3-ol **16** were synthesized from the reaction of **4a** with aniline **13** and 2,4-dinitrophenylhydrazine **15** in the presence of catalytic amount of $H_2SO_4$ respectively (Scheme 3).

In conclusion, we have reported the synthesis of new 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes *via* Vilsmeier-Haack reaction starting from acetophenone derivatives.

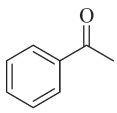
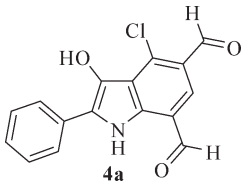
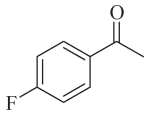
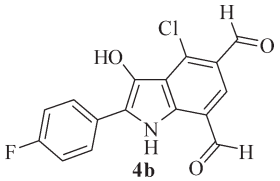
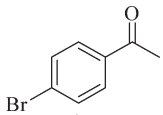
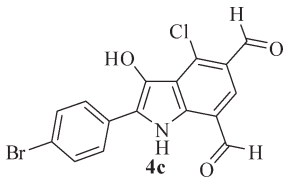
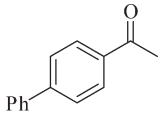
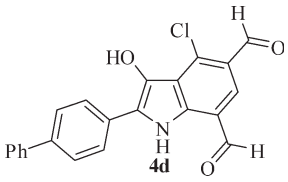
## EXPERIMENTAL

**General methods.** Chemical shifts of the $^1$H NMR spectra are reported in δ (ppm) from tetramethylsilane with the solvent as the internal standard (deuteriodimethyl sulfoxide, δ = 2.5 ppm), and coupling constants *J* were measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad). $^{13}$C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriodimethyl sulfoxide, δ = 39.0 ppm). Elemental analyses were carried out by using a CHN analyzer. IR analyses were performed with an FT-IR spectrophotometer. IR spectra of compounds are expressed by wavenumber ($cm^{-1}$).

***General procedure for synthesis of 2-aryl-4-chloro-3-hydroxy-1H-indole-5,7-dicarbaldehydes 4.*** $POCl_3$ (3 mmol) was added dropwise to dimethylformamide (DMF) (1.5 mL)

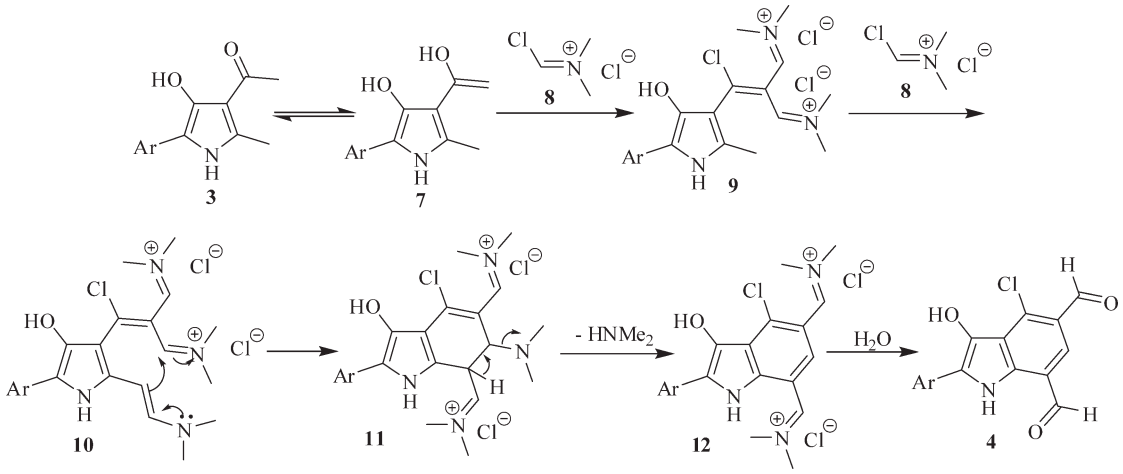
**Table 1**

Synthesis of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4** *via* Vilsmeier-Haack reaction.

| Acetophenone **1** | Indole **4** | Yield (%)[a] |
|---|---|---|
|  **1a** |  **4a** | 31 |
|  **1b** |  **4b** | 42 |
|  **1c** |  **4c** | 53 |
|  **1d** |  **4d** | 35 |

[a] Yield of indole from pyrrole (**3**).

**Scheme 2.** Proposed mechanism for conversion of pyrroles **3** to indoles **4**.



with stirring at 30–35°C, after the addition, the mixture was stirred at 50°C for 1 h. Then the solution of 3-acetyl-5-aryl-4-hydroxy-2-methyl-1*H*-pyrrol **3** (0.5 mmol) at least amount of DMF was added dropwise with stirring to the above mixture. After that the mixture was stirred at 45–55°C for 2 h, kept over the night at room temperature and poured over mixture of ice and water (10 g). Product was stirred for 0.5 h, then filtered off and recrystallized from ethanol.

***4-Chloro-3-hydroxy-2-phenyl-1H-indole-5,7-dicarbaldehyde (4a).*** A yellow solid, mp: decomposed at 258.2–261.2°C; IR (KBr) 3553, 3343, 3053, 2853, 1671, 1580, 1425, 1025, 902, 812, 683 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 11.55 (s, 1H, NH, Exchanged with $D_2O$), 10.49 (s, 1H, CHO), 10.39 (s, 1H, CHO), 8.75 (s, 1H, OH, Exchanged with $D_2O$), 8.17 (s, 1H, CH), 8.01 (d, $J$ = 7.5 Hz, 2H, CH), 7.51 (t, $J$ = 7.45 Hz, 2H, CH), 7.37 (t, $J$ = 7.3 Hz, 1H, CH) ppm; $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 192.6, 189.5, 136.6, 134.6, 134.4, 130.9, 130.7, 129.3, 128.4, 127.7, 127.3, 124.8, 122.1, 119.8 ppm; Anal. Calcd. for $C_{16}H_{10}ClNO_3$: C, 64.12; H, 3.36; N, 4.67. Found: C, 63.98; H, 3.50; N, 4.72.

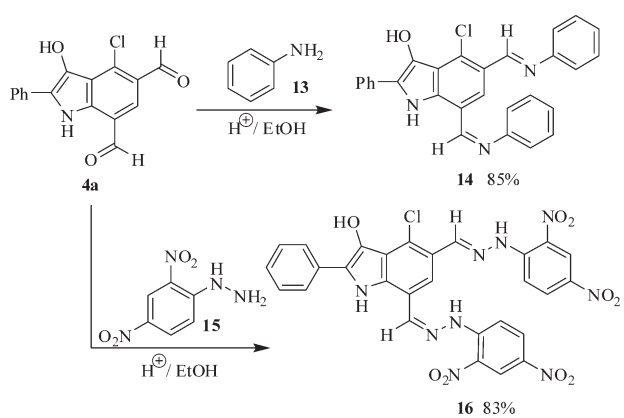
***4-Chloro-2-(4-fluorophenyl)-3-hydroxy-1H-indole-5,7-dicarbaldehyde (4b).*** A yellow solid, mp: decomposed at 286.2–289.3°C; IR (KBr) 3553, 3360, 3058, 2843, 1670, 1584, 1471, 1030, 901, 834, 634 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 11.60 (s, 1H, NH, Exchanged with $D_2O$), 10.48 (s, 1H, CHO), 10.37 (s, 1H, CHO), 8.74 (s, 1H, OH, Exchanged with $D_2O$), 8.16 (s, 1H, CH), 8.04 (dd, $J_{H,F}$ = 8.07 Hz, $J_{H,H}$ = 5.75 Hz, 2H, CH), 7.35 (t, $J$ = 8.75 Hz, 2H, CH) ppm; $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 192.5, 189.6, 161.3, 136.6, 134.5, 134.4, 129.9, 127.5, 127.1, 124.8, 122.0, 119.9, 116.4, 116.2 ppm; Anal. Calcd. for $C_{16}H_9ClFNO_3$: C, 60.49; H, 2.86; N, 4.41. Found: C, 60.60; H, 2.73; N, 4.16.

***2-(4-Bromophenyl)-4-chloro-3-hydroxy-1H-indole-5,7-dicarbaldehyde (4c).*** A yellow solid, mp: decomposed at 268.9–272.5°C; IR (KBr) 3540, 3352, 3030, 2839, 1670, 1585, 1465, 1030, 902, 814, 633 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 11.63 (s, 1H, NH, Exchanged with $D_2O$), 10.47 (s, 1H, CHO), 10.38 (s, 1H, CHO), 8.74 (s, broad, 1H, OH, Exchanged with $D_2O$), 8.18 (s, 1H, CH), 7.97 (d, $J$ = 8.4 Hz, 2H, CH), 7.35 (d, $J$ = 8.35 Hz, 2H, CH) ppm; $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 192.5, 189.5, 136.7, 135.4, 134.7, 132.2, 130.2, 129.6, 127.7, 126.7, 124.9, 122.0, 121.4, 119.9 ppm; Anal. Calcd. for $C_{16}H_9BrClNO_3$: C, 50.76; H, 2.40; N, 3.70. Found: C, 50.82; H, 2.53; N, 3.66.

***2-Biphenyl-4-yl-4-chloro-3-hydroxy-1H-indole-5,7-dicarbaldehyde (4d).*** A yellow solid, mp: decomposed at 204.1–205.9°C; IR (KBr) 3561, 3419, 3033, 2922, 2857, 1670, 1598, 1468, 1427, 1029, 901, 840, 766, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 11.60 (s, 1H, NH, Exchanged with $D_2O$), 10.49 (s, 1H, CHO), 10.40 (s, 1H, CHO), 8.82 (s, 1H, OH, Exchanged with $D_2O$), 8.17 (s, 1H, CH), 8.12 (d, $J$ = 7.1 Hz, 2H, CH), 7.83 (d, $J$ = 7.0 Hz, 2H, CH), 7.76 (d, $J$ = 5.8 Hz, 2H, CH), 7.49 (m, 2H, CH), 7.39 (m, 1H, CH) ppm; $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 192.6, 189.4, 140.5, 140.0, 136.6, 134.6, 134.4, 132.3, 130.9, 130.7, 129.7, 129.3, 128.4, 127.7, 127.3, 124.8, 122.1, 119.8 ppm; Anal. Calcd. for $C_{22}H_{14}ClNO_3$: C, 70.31; H, 3.75; N, 3.73. Found: C, 70.51; H, 3.68; N, 3.75.

***7-(4-Bromophenyl)-5-methyl-4-oxo-4,6-dihydro-pyrano [2,3-c]pyrrole-3-carbaldehyde (6b).*** In addition to 2-(4-bromophenyl)-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbalde-hyde **4c**, 5-methyl-4-oxo-7-phenyl-4,6-dihydro-pyrano[2,3-c]pyrrole-3-carbaldehyde **6b** was obtained in the case of 4-bromoacetophenone. Ratio of **4c**/**6a** was obtained 68/32, according to $^1H$ NMR spectrum of the mixture of **4c** and **6a**. This product

**Scheme 3**



was characterized only in mixture with **4c** using $^1$H NMR spectrum and eliminate from mixture with washing of solid with warm 85% ethanol. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.75 (s, 1H, NH, Exchanged with $D_2O$), 10.43 (s, 1H, CHO), 8.63 (s, 1H, CH), 7.57 (d, $J$ = 8.2 Hz, 2H, CH), 7.36 (d, $J$ = 8.2 Hz, 2H, CH), 2.5 (s, 3H, $CH_3$) ppm.

***4-Chloro-2-phenyl-5,7-bis-phenyliminomethyl-1H-indol-3-ol (14).*** To mixture of 4-chloro-3-hydroxy-2-phenyl-1*H*-indole-5,7-dicarbaldehyde **4a**. (0.2 mmol) and 3 drops of concentrate $H_2SO_4$ in boiling ethanol (5 mL), was added Aniline **13** (0.4 mmol), and stirred at the same temperature for the 5 min. Then the heat was removed and solution was cooled to room temperature and product was obtained as pale yellow crystals in 85% yield by filtration and washing with 5 mL of ethanol. mp: decomposed at 173.6–175.1°C; IR (KBr) 3559, 3053, 2849, 2585, 2060, 1677, 1557, 1497, 1321, 1015, 741, 685, 606 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.34 (s, 1H, NH, Exchanged with $D_2O$), 9.20 (s, 1H, HC=NPh), 9.05 (s, 1H, HC=NPh), 8.52 (s, 1H, OH, Exchanged with $D_2O$), 8.00 (d, $J$ = 7.55 Hz, 1H, CH), 7.5–7.04 (m, 15H, CH) ppm; Anal. Calcd. for $C_{28}H_{20}ClN_3O$: C, 74.74; H, 4.48; N, 9.34. Found: C, 74.68; H, 4.47; N, 9.21.

***4-Chloro-5,7-bis-[(2,4-dinitrophenyl)hydrazonomethyl]-2-phenyl-1H-indol-3-ol (16).*** To the solution of 2,4-dinitrophenylhydrazine **15** (0.6 mmol) and 3 drops of concentrate $H_2SO_4$ in mixture of ethanol/water (3/2 mL), was added the hot solution of 4-chloro-3-hydroxy-2-phenyl-1*H*-indole-5,7-dicarbaldehyde **4a** (0.2 mmol) in ethanol (5 mL), and stirred for the 5 min. Then solution was cooled to room temperature and product was obtained as dark purple solid in 83% yield by filtration and washing with 5 mL of mixture of ethanol/water (3/2 mL). mp: 326.8–328.5°C. Don't soluble in solvents such as DMSO-$d_6$, Aceton-$d_6$ and *etc*. for taking NMR spectra. IR (KBr) 3539, 3428, 3270, 3087, 1613, 1508, 1422, 1329, 1208, 1131, 920, 827, 734, 597 cm$^{-1}$; Anal. Calcd. for $C_{28}H_{18}ClN_9O_9$: C, 50.96; H, 2.75; N, 19.10. Found: C, 51.09; H, 2.64; N, 18.93. In comparing of IR spectrum of **16** with IR spectrum of **4a**, peak of the C—H of the aldehyde group at 2850 cm$^{-1}$ for **4a** was eliminated in **16** IR spectrum, and the C=O peak of **4a** at 1673 cm$^{-1}$ was replaced with C=N peak of **16** at 1613 cm$^{-1}$.

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## REFERENCES AND NOTES

[1] Saxton, J. E. Nat Prod Rep 1997, 14, 559.

[2] (a) Lounasmaa, M.; Tolvanen, A. Nat Prod Rep 2000, 17, 175; (b) Faulkner, D. J. Nat Prod Rep 1999, 16, 155.

[3] (a) Kam, T.-S.; Choo, Y.-M. Helv Chim Acta 2004, 87, 991; (b) Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. J Org Chem 2005, 70, 2555; (c) Van Zandt, M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrova, T.; Mitschler, A.; Podjarny, A. D. J Med Chem 2005, 48, 3141; (d) Takayama, H.; Tsutsumi, S. I.; Kitajima, M.; Santiarworn, D.; Liawruangrath, B.; Aimi, N. Chem Pharm Bull 2003, 51, 232; (e) Humphrey, G. R.; Kuethe, J. T. Chem Rev 2006, 106, 2875; (f) Stolc, S.; Snirc, V.; Majekova, M.; Gasparova, Z.; Gajdosikova, A.; Stvrtina, S. Cell Mol Neurobiol 2006, 26, 1493; (g) Takayama, H.; Misawa, K.; Okada, N.; Ishikawa, H.; Kitajima, M.; Hatori, Y.; Murayama, T.; Wongseripipatana, S.; Tashima, K.; Matsumoto, K.; Horie, S. Org Lett 2006, 8, 5705; (h) Kuethe, J. T. Chimia 2006, 60, 543; (i) Hopkins, C. R.; O'Neil, S. V.; Laufersweiler, M. C.; Wang, Y.; Pokross, M.; Mekel, M.; Evdokimov, A.; Walter, R.; Kontoyianni, M.; Petrey, M. E.; Sabatakos, G.; Roesgen, J. T.; Richardson, E.; Demuth, T. P. Bioorg Med Chem Lett 2006, 16, 5659; (j) Pruss, R.; Jamot, L.; Drouot, C. FR 2,885,905, 2005; Chem Abstr 2007, 146, 27812; (k) Froissant, J.; Marguet, F.; Olivier-Bandini, A.; Puech, F. PCT Int Appl. WO 2,006,111,648, 2006; Chem Abstr 2006, 145, 455025; (l) Yasuma, T.; Ujikawa, O.; Iwata, H. PCT Int Appl. WO 2,006,112,549, 2006; Chem Abstr 2006, 145, 454930; (m) Heinrich, T.; Blaukat, A.; Staehle, W.; Greiner, H.; Kordowicz, M. Ger Offen DE 102,005,019,094, 2006; Chem Abstr 2006, 145, 45499; (n) Tietze, L. F.; Major, F. Eur J Org Chem 2006, 10, 2314; (o) Bischoff, H.; Dittrich-Wengenroth, E.; Wuttke, M.; Heckroth, H.; Thielemann, W.; Woltering, M.; Otteneder, M. PCT Int Appl. WO 2,004,005,253, 2004; Chem Abstr 2004, 140, 93922.

[4] (a) Sekar, N. Colourage 2003, 50, 65; (b) Diwu, Z.; Zhang, J.; Tang, Y. US Pat. 2,006,223,076, 2006; Chem Abstr 2006, 145, 392008.

[5] (a) Cacchi, S.; Fabrizi, G. Chem Rev 2005, 105, 2873; (b) Zeni, G.; Larock, R. C. Chem Rev 2004, 104, 2285; (c) Joule, J. A. In Science of Synthesis;Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; Vol. 10, pp 361–652; (d) Sundberg, R. J. Indoles; Academic Press: London, 1996; (e) Gilchrist, T. L. J Chem Soc Perkin Trans 1 2001, 2491; (f) Gribble, G. W. J Chem Soc Perkin Trans 1 2000, 1045; (g) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. J Am Chem Soc 2002, 124, 15168; (h) Kamijo, S.; Yamamoto, Y. Angew Chem Int Ed Engl 2002, 41, 3230; (i) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. Angew Chem Int Ed Engl 2002, 41, 4732; (j) Smith, A. B.; Kanoh, N.; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. J Am Chem Soc 2003, 125, 8228; (k) Siebeneicher, H.; Bytschkov, I.; Doye, S. Angew Chem Int Ed Engl 2003, 42, 3042; (l) Shimada, T.; Nakamura, I.; Yamamoto, Y. J Am Chem Soc 2004, 126, 10546; (m) Willis, M. C.; Brace, G. N.; Holmes, I. P. Angew Chem Int Ed Engl 2005, 44, 403; (n) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. Angew Chem Int Ed Engl 2005, 44, 606; (o) Herzon, S. B.; Myers, A. G. J Am Chem Soc 2005, 127, 5342; (p) Dunetz, J. R.; Danheiser, R. L. J Am Chem Soc 2005, 127, 5776; (q) Taber, D. F.; Tian, W. J Am Chem Soc 2006, 128, 1058; (r) Tokuyama, H.; Fukuyama, T. Chem Rec 2002, 2, 37; (s) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. Eur J Org Chem 2002, 2671; (t) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. Angew Chem Int Ed Engl 2000, 39, 2488; (u) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. J Am Chem Soc 2002, 124, 4628; (v) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. Org Lett 2003, 5, 1899; (w) Fukuda, T.; Akashima, H.; Iwao, M. Tetrahedron 2005, 61, 6886; (x) Kaspar, L. T.; Ackermann, L. Tetrahedron 2005, 61, 11311; (y) Schmidt, A. M.; Eilbracht, P. J Org Chem 2005, 70, 5528; (z) Smith, A. B., III; Kürti, L.; Davulcu, A. H. Org Lett 2006, 8, 2167; (aa) Linnepe née Köhling, P.; Schmidt, A. M.; Eilbracht, P. Org Biomol Chem 2006, 4, 302; (bb) Sridharan, V.; Perumal, S.; Avendaño, C.; Menéndez, J. C. Synlett 2006, 91; (cc) Kearney, A. M.; Vanderwal, C. D. Angew Chem Int Ed Engl 2006, 45, 7803; (dd) Zhao, J.; Hughes, C. O.; Toste, F. D. J Am Chem Soc 2006, 128, 7436; (ee) Barluenga, J.; Jiménez-Aquino, A.; Valdés, C.; Aznar, F. Angew Chem Int Ed Engl 2007, 46, 1529; (ff) Trost, B. M.; McClory, A. Angew Chem Int Ed Engl 2007, 46, 2074; (gg) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. Org Lett 2007, 9, 2601; (hh) Sanz, R.; Castroviejo, M. P.; Guilarte, V.; Pérez, A.; Fañanás, F. J. J Org Chem 2007, 72, 5113.

[6] Riley, H. A.; Gray, A. R. Org Synth 1943, 2, 509.

[7] Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. J Org Chem 2008, 73, 2090.

[8] (a) Jutz, C. Adv Org Chem 1976, 9, 225; (b) Seshadri, S. J Sci Ind Res 1973, 32, 128; (c) Chatterjee, A.; Biswas, K. M. J Org Chem 1973, 38, 4002; (d) Sayah, B.; Léon, N. P.; Milet, A.; Guindet, J. P.; Vallée, Y. J Org Chem 2001, 66, 2522.

[9] Jones, G.; Stanforth, S. P. Org React 2000, 56, 355.

[10] Marson, C. M. Tetrahedron 1992, 48, 3659.

[11] (a) Meth-Cohn, O. Heterocycles 1993, 35, 539; (b) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. Org Lett 2007, 9, 2421; (c) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. J Org Chem 2007, 72, 8593; (d) Beccalli, E. M.; Marchesini, A. J Org Chem 1987, 52, 3426; (e) Guzman, A.; Romero, M. J Org Chem 1990, 55, 5793; (f) Shrestha, S.; Hwang, S. Y.; Lee, K. H.; Cho, H. Bull Korean Chem Soc 2005, 26, 1138; (g) Asokan, C. V.; Anabha, E. R.; Thomas, A. D.; Jose, A. M.; Lethesh, K. C.; Prasanth, M.; Krishanraj, K. U. Tetrahedron Lett 2007, 48, 5641; (h) Ali, M. M.; Sana, S.; Tasneem, Rajanna, K. C.; Saiprakash, P. K. Synth Commun 2002, 32, 1351; (i) Lacova, M.; Loos, D.; Furdik, M.; Matulova, M.; El-Shaaer, H. M. Molecule 1998, 3, 149; (j) Chen, C. H.; Reynolds, G. A. J Org Chem 1979, 44, 3144; (k) Sivaprasad, G.; Sridhar, R.; Perumal, P. T. J Heterocycl Chem 2006, 43, 389; (l) Kumar, K. H.; Perumal, P. T. Chem Lett 2005, 34, 1346; (m) Sridhar, R.; Sivaprasad, G.; Perumal, P. T. J Heterocycl Chem 2004, 41, 405; (n) Selvi, S.; Perumal, P. T. Synth Commun 2001, 31, 2199.

[12] (a) Abramov, M. A.; Dehaen, W. Synthesis 2000, 1529; (b) Smeets, S.; Asokan, C. V.; Motmans, F.; Dehaen, W. J Org Chem 2000, 65, 5882.

[13] (a) Sabitha, G. Aldrichimica Acta 1996, 29, 13; (b) Nohara, A.; Umetani, T.; Sanno, Y. Tetrahedron Lett 1973, 22, 1995; (c) Nohara, A.; Umetani, T.; Sanno, Y. Tetrahedron 1974, 30, 3553; (d) Klutchko, S.; Kaminsky, D.; Von Strandtmann, M. US Pat. 4,098,799, 1978; Chem Abstr 1979, 90, 22813c.

[14] Thomas, A. D.; Asokan, J.; Asokan, C. V. Tetrahedron 2004, 60, 5069.

# $SnCl_2 \cdot 2H_2O$-Catalyzed One-Pot Synthesis of 4(3*H*)-Quinazolinones from Anthranilic Acid, Ortho Esters, and Amines under Solvent Free Conditions

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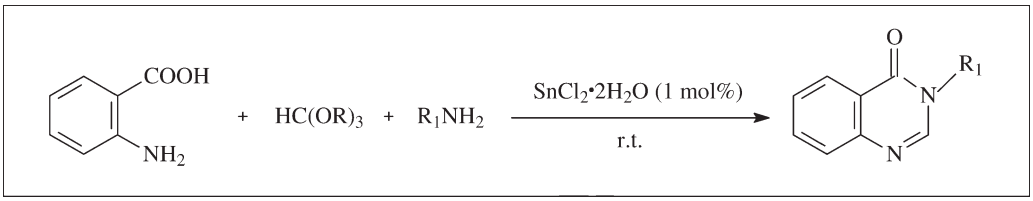


A simple, efficient, and green procedure for the one-pot synthesis of 4(3*H*)-quinazolinones by three components condensation of anthranilic acid, ortho esters, and amines in the presence of $SnCl_2 \cdot 2H_2O$ has been developed. The reaction occurred within short reaction time at room temperature under solvent-free conditions to afford the title products in excellent yields.

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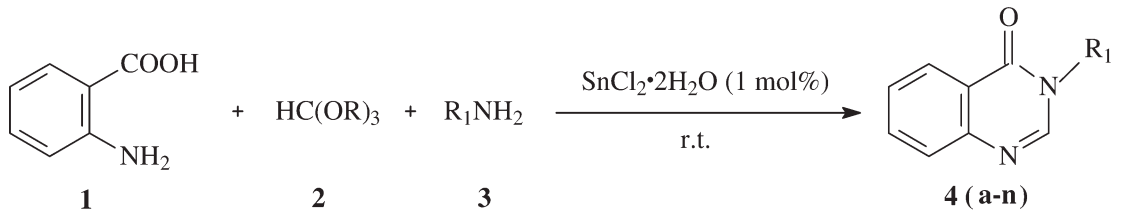
## INTRODUCTION

It has been more than a century since the initial studies on 4(3*H*)-quinazolinones [1], and they are well-known as important fused heterocycles because of their pharmacological and therapeutic properties such as antimalarial, antitumor, anticonvulsant, antiinflammatory, fungicidal, and antimicrobial activities [2]. Moreover, the 4(3*H*)-quinazolinone moiety is found in several bioactive natural products [3]. Because of the importance of 4(3*H*)-quinazolinones different strategies for their synthesis have been described in the literature: (a) cyclocondensation of anthranilamide with aryl, alkyl, or heteroaryl aldehydes in refluxing ethanol [4]; (b) poly(ethylene glycol) supported by aza-Wittig reaction [5]; (c) intramolecular cyclization of fluorine-containing *S*-ethyl *N*-benzoylisothioureas [6]; (d) cyclocondensation of 2-fluorobenzoyl chlorides with 2-amino-*N*-heterocycles [7]; (e) copper-catalyzed cascade reactions of the substituted 2-halobenzoic acids with amidines [8]; (f) reaction of polymer-bound isothiourea with isatoic anhydride [9]; (g) reaction of anthranilic acids and ammonium or triethylammonium *N*-aryl-dithiocarbamates [10].

Multicomponent reactions (MCRs) are especially attractive synthesis strategies due to the fact that the products are formed in a single step and also the diversity could be achieved simply by varying the reacting components. In this type of reaction, at least three easily accessible components are reacted to form a single product, which incorporates essentially all of the atoms of the starting materials. MCRs are highly flexible, chemoselective, convergent, and atom efficient processes. Therefore, very efficient way to access heterocycles is by using MCRs in the past decade. Several groups have reported MCRs preparation methods for synthesis of 4(3*H*)-quinazolinones from anthranilic acid, orthoesters, and amines using $NaHSO_4$ or Amberlyst-15 [11], Yb(III)-resin [12], $Yb(OTf)_3$ [13], $Bi(TFA)_3$-[nbp]$FeCl_4$ ionic liquid [14], $La(NO_3)_3 \cdot 6H_2O$ or *p*-toluenesulfonic acid [15], Keggin-type heteropolyacid under microwave irradiation [16], and $SiO_2$—$FeCl_3$ [17] *etc*. However, some of these methods associated with certain drawbacks such as expensive catalyst, high temperature (60–80°C), long reaction time (20 h), and using harmful organic solvent. In addition, aniline having strong electron-withdrawing substitutes, *e.g*., Cl and $NO_2$, gave generally no products at room temperature in previous reports. Therefore, it is desirable to develop green and efficient methods for the synthesis of 4(3*H*)-quinazolinones.

During the course of our study on Lewis acid–catalyzed organic reactions, we found that stannous chloride, as an inexpensive and commercially available catalyst, can catalyze one-pot three components Mannich-type reaction efficiently [18]. As an extension of our study on efficient synthesis of 4(3*H*)-quinazolinones, we reported here a one-pot MCR of anthranilic acid **1**, orthoesters **2**, and primary amines **3** in the presence of 1 mol % $SnCl_2 \cdot 2H_2O$ at room temperature without solvent (Scheme 1). Most products were formed within several minutes in excellent yields.

**Scheme 1**




**1** **2** **3** **4 (a-n)**

## RESULTS AND DISCUSSION

First, a controlled experiment of an anthranilic acid, a triethyl orthoformate, and an aniline in the absence of catalyst was investigated. The result showed that only 5% product was obtained after 1 h. However, various 4(3*H*)-quinazolinones **4** were prepared efficiently using anthranilic acid **1**, trimethyl or triethyl orthoformate **2**, and different substituted aryl amines or alkyl amine **3** in the presence of $SnCl_2 \cdot 2H_2O$ at room temperature without solvent (Table 1). All condensations mediated by $SnCl_2 \cdot 2H_2O$ proceeded smoothly. Anilines carrying either electron-donating or electron-withdrawing groups all afford high yields. Steric hindrance seems to have no effects on the efficiency of this transformation. The reaction could tolerate different functional groups, such as alkyl, halogen, and nitro present in the anilines. The products derived from triethyl orthoformate were formed in somewhat higher yields than those from trimethyl orthoformate. Furthermore, trimethyl orthoformate required a comparatively longer reaction time. The condensation yield with primary aliphatic amines was lower than those with aniline derivatives.

A mechanism for this reaction has also been postulated as shown in Scheme 2. The first step in this reaction involves the $SnCl_2 \cdot 2H_2O$ catalyzed formation of imidic ester **5**, which stabilized by $Sn^{2+}$. The imidic ester **5** may be very prone to react with an aryl amine **3**,

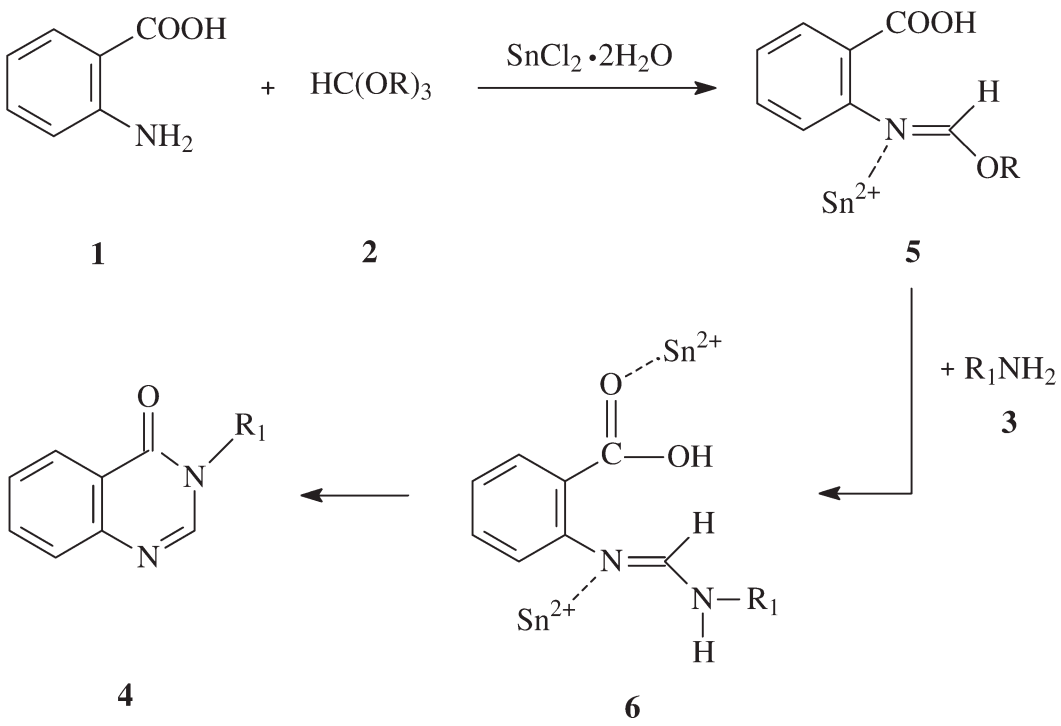
**Table 1**

Preparation of 4(3*H*)-quinazolinones **4**(**a**–**n**) catalyzed by $SnCl_2 \cdot 2H_2O$.[a]

| Product (**4**) | R | $R_1$ | Time (h) | Isolated yield (%) | Mp (°C) Found | Mp (°C) Reported |
|---|---|---|---|---|---|---|
| **4a** | Et | H | 0.4 | 91 | 141–143 | 139–140 [13] |
| **4b** | Et | 2-Me | 1.1 | 93 | 154–156 | – |
| **4c** | Et | 3-Me | 3 | 97 | 137–139 | 136–137 [13] |
| **4d** | Et | 4-Me | 0.2 | 91 | 150–151 | 146–147 [13] |
| **4e** | Et | 2-MeO | 0.5 | 97 | 152–154 | – |
| **4f** | Et | 4-MeO | 0.5 | 96 | 138–140 | – |
| **4g** | Et | 2-Cl | 0.1 | 81 | 119–120 | – |
| **4h** | Et | 4-Cl | 0.2 | 84 | 122–124 | – |
| **4i** | Et | 4-Br | 0.1 | 91 | 149–150 | – |
| **4j** | Et | 2-$NO_2$ | 0.1 | 61 | 151–153 | 156–158 [13] |
| **4k** | Et | 3-$NO_2$ | 0.3 | 93 | 152–154 | 154–156 [13] |
| **4l** | Et | 4-$NO_2$ | 0.2 | 86 | 167–169 | 165–166 [13] |
| **4m** | Et | 4-COOH | 0.1 | 64 | 240–242 | – |
| **4n** | Et | $PhCH_2$ | 0.1 | 56 | 154–155 | – |
| **4a** | Me | H | 4 | 82 | 139–141 | 139–140 [13] |
| **4b** | Me | 2-Me | 3 | 96 | 154–156 | – |
| **4c** | Me | 3-Me | 7 | 45 | 137–139 | 136–137 [13] |
| **4d** | Me | 4-Me | 1 | 87 | 149–150 | 146–147 [13] |
| **4e** | Me | 2-MeO | 2.2 | 91 | 152–154 | – |
| **4f** | Me | 4-MeO | 1 | 94 | 138–140 | – |
| **4g** | Me | 2-Cl | 0.2 | 80 | 118–120 | – |
| **4h** | Me | 4-Cl | 0.7 | 51 | 123–125 | – |
| **4i** | Me | 4-Br | 0.3 | 86 | 148–150 | – |
| **4j** | Me | 2-$NO_2$ | 7 | 50 | 152–154 | 156–158 [13] |
| **4k** | Me | 3-$NO_2$ | 0.1 | 92 | 152–153 | 154–156 [13] |
| **4l** | Me | 4-$NO_2$ | 0.1 | 80 | 166–168 | 165–166 [13] |
| **4m** | Me | 4-COOH | 0.1 | 51 | 240–242 | – |
| **4n** | Me | $PhCH_2$ | 0.1 | 51 | 154–155 | – |

[a] The structures of the products were determined from spectral and analytical data (IR, $^1H$ NMR and elemental analysis).

**Scheme 2**




thus leading to the amidine intermediate **6**. Then, amidine intermediate **6** activated by $Sn^{2+}$ cyclized to form the quinazolinone **4**. A similar mechanism had also been described by Wang *et al*. [13].

In conclusion, we have demonstrated a simple and efficient one-pot three components coupling condensation from an anthranilic acid, orthoesters, and primary amines in the presence of $SnCl_2 \cdot 2H_2O$ for the preparation of 4(3*H*)-quinazolinones. The mild and solvent-free conditions, short reaction time (0.1–7 h), excellent yields (45–97%), inexpensive, nontoxic, and commercially available catalysts, and simple workup make it a useful process for the synthesis of 4(3*H*)-quinazolinones.

## EXPERIMENTAL

Melting points were determined using RY-1 micromelting point apparatus and were uncorrected. Infrared spectra were recorded on Scimitar 2000 series Fourier Transform instrument of VARIAN. $^1$H NMR spectra were recorded on Bruker ARX-500 spectrometer in DMSO-$d_6$ using TMS as an internal standard. Elemental analyzes were performed on EA 2400II elemental analyzer (Perkin–Elmer).

**General procedure for the synthesis of 4(3*H*)-quinazolinones.** To a mixture of anthranilic acid (10 mmol), an orthoester (12 mmol), and an amine (12 mmol), $SnCl_2 \cdot 2H_2O$ (0.1 mmol) was added. The mixture was stirred at room temperature for an appropriate time (Table 1). The reaction was monitored by TLC. After completion, the solid obtained was crystallized in ethanol. The pure products were identified by IR, $^1$H NMR, and elemental analysis. The spectral properties of some representative 4(3*H*)-quinazolinones are given below:

***3-(2-Methylphenyl)quinazolin-4(3H)-one (4b).*** White solid. IR (KBr): 1687, 1594, 1489 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.56 (s, 1H), 8.31 (d, $J$ = 7.2 Hz, 1H), 7.75–7.52 (m, 2H), 7.23–7.07 (m, 5H), 2.31 (s, 3H). Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.26; H, 5.12; O, 6.77. Found: C, 76.35; H, 5.10; O, 6.72.

***3-(2-Methoxyphenyl)quinazolin-4(3H)-one (4e).*** White solid. IR (KBr): 1681, 1595, 1457 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.36 (s, 1H), 8.21 (d, $J$ = 7.7 Hz, 1H), 7.45 (d, $J$ = 6.8 Hz, 1H), 7.25 (t, $J$ = 7.0 Hz, 1H), 7.08–7.03 (m, 2H), 6.94 (t, $J$ = 7.1 Hz, 1H), 6.78 (d, $J$ = 8.2 Hz, 1H), 6.53 (t, $J$ = 7.3 Hz, 1H), 3.85 (s, 3H). Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.80; O, 12.68. Found: C, 71.34; H, 4.82; O, 12.72.

***3-(4-Methoxyphenyl)quinazolin-4(3H)-one (4f).*** White solid. IR (KBr): 1715, 1591, 1454 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.54 (s, 1H), 8.05 (d, $J$ = 7.5 Hz, 1H), 7.54–7.48 (m, 2H), 7.16 (t, $J$ = 7.5 Hz, 1H), 6.97 (dd, $J$ = 8.5, 9.5 Hz, 4H), 3.76 (s, 3H). Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.80; O, 12.68. Found: C, 71.51; H, 4.77; O, 12.64.

***3-(2-Chlorophenyl)quinazolin-4(3H)-one (4g).*** Yellow solid. IR (KBr): 1667, 1602, 1414 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.57 (s, 1H), 8.02 (d, $J$ = 7.7 Hz, 1H), 7.73–7.70 (m, 2H), 7.61 (t, $J$ = 7.6 Hz, 1H), 7.25–7.16 (m, 2H), 6.76 (d, $J$ = 8.0 Hz, 1H), 6.53 (t, $J$ = 7.2 Hz, 1H). Anal. Calcd. for $C_{14}H_9ON_2Cl$: C, 65.51; H, 3.53; O, 6.23; N, 10.91. Found: C, 65.42; H, 3.55; O, 6.24; N, 10.93.

***3-(4-Chlorophenyl)quinazolin-4(3H)-one (4h).*** Pale yellow solid. IR (KBr): 1672, 1616, 1485 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.52 (s, 1H), 7.71–7.68 (m, 2H), 7.24–7.20 (m, 2H), 6.75 (d, $J$ = 7.4 Hz, 2H), 6.52 (d, $J$ = 7.2 Hz, 2H). Anal.

Calcd. for $C_{14}H_9ON_2Cl$: C, 65.51; H, 3.53; O, 6.23; N, 10.91. Found: C, 65.43; H, 3.52; O, 6.25; N, 10.95.

***3-(4-Bromophenyl)quinazolin-4(3H)-one (4i).*** White solid. IR (KBr): 1713, 1587, 1443 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 8.55 (s, 1H), 8.01 (d, $J$ = 7.7 Hz, 1H), 7.60 (t, $J$ = 7.5 Hz, 1H), 7.46–7.44 (m, 4H), 7.18 (d, $J$ = 7.5 Hz, 2H). Anal. Calcd. for $C_{14}H_9ON_2Br$: C, 55.84; H, 3.01; O, 5.31; N, 9.30. Found: C, 55.77; H, 3.01; O, 5.32; N, 9.33.

***3-(4-Carboxylphenyl)quinazolin-4(3H)-one (4m).*** White solid. IR (KBr): 1701, 1593, 1484 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 10.49 (s, 1H), 8.34 (s, 1H), 7.92–7.88 (m, 3H), 7.71 (t, $J$ = 8.5 Hz, 2H), 7.63 (d, $J$ = 5.5 Hz, 1H), 7.31 (d, $J$ = 8.5 Hz, 1H), 6.56 (d, $J$ = 5.5 Hz, 1H). Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.67; H, 3.79; O, 18.03. Found: C, 67.76; H, 3.78; O, 18.00.

***3-Benzylquinazolin-4(3H)-one (4n).*** White solid. IR (KBr): 1678, 1621, 1459 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 8.52 (s, 1H), 8.00 (d, $J$ = 7.5 Hz, 1H), 7.54–7.47 (m, 2H), 7.41–7.36 (m, 4H), 7.32 (t, $J$ = 6.8 Hz, 1H), 7.13 (t, $J$ = 7.0 Hz, 1H), 4.61 (s, 2H). Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.26; H, 5.12; O, 6.77. Found: C, 76.35; H, 5.10; O, 6.74.

## REFERENCES AND NOTES

[1] Weddige, A. J Prakt Chem 1887, 36, 141.

[2] (a) Takaya, Y.; Chiba, T.; Tanitsu, M.; Murata, K.; Kim, H. S.; Wataya, Y.; Oshima, Y. Parasitol Int 1998, 47, 380; (b) Cao, S. L.; Feng, Y. P.; Jiang, Y. Y.; Liu, S. Y.; Ding, G. Y.; Li, R. T. Bioorg Med Chem Lett 2005, 15, 1915; (c) Kornet, M. J.; Varia, T.; Beaven, W. J Heterocycl Chem 1983, 20, 1553; (d) Yadav, M. R.; Shirude, S. T.; Parmar, A.; Balaraman, R.; Giridhar, R. Chem Heterocycl Compd 2006, 42, 1038; (e) Hu, Y. G.; Yang, S. J.; Ding, M. W. Phosphorus Sulfur Silicon 2004, 179, 1933; (f) Bahadur, S.; Saxena, M. Arch Pharm (Weinheim) 1983, 316, 964.

[3] (a) Ablondi, F.; Gordon, S.; Morton, J., II; Williams, J. H. J Org Chem 1952, 17, 14; (b) Koepfli, J. B.; Mead, J. F.; Brockman, J. A. J Am Chem Soc 1947, 69, 1837.

[4] Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. Tetrahedron Lett 2004, 45, 3475.

[5] Xie, C.; Li, H. X.; Liu, M. G.; Ding, M. W. Chin Chem Lett 2008, 19, 505.

[6] Layeva, A. A.; Nosova, E. V.; Lipunova, G. N.; Trashakhova, T. V.; Charushin, V. N. J Fluorine Chem 2007, 128, 748.

[7] Deetz, M. J.; Malerich, J. P.; Beatty, A. M.; Smith, B. D. Tetrahedron Lett 2001, 42, 1851.

[8] Liu, X. W.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. Angew Chem Int Ed Engl 2009, 48, 348.

[9] Yang, R. Y.; Kaplan, A. Tetrahedron Lett 2000, 41, 7005.

[10] Lakhan, R.; Srivastava, M. J Chem Sci 1993, 105, 11.

[11] Das, B.; Banerjee, J. Chem Lett 2004, 33, 960.

[12] Jiang, Z. D.; Chen, R. F. Synth Commun 2005, 35, 503.

[13] Wang, L. M.; Xia, J. J.; Qin, F.; Qian, C. T.; Sun, J. Synthesis 2003, 1241.

[14] Khosropour, A. R.; Mohammadpoor-Baltork, I.; Ghorbankhani, H. Tetrahedron Lett 2006, 47, 3561.

[15] Narasimhulu, M.; Mahesh, K. C.; Reddy, T. S.; Rajesh, K.; Venkateswarlu, Y. Tetrahedron Lett 2006, 47, 4381.

[16] Ighilahriz, K.; Boutemeur, B.; Chami, F.; Rabia, C.; Hamdi, M.; Hamdi, S. M. Molecules 2008, 13, 779.

[17] Chari, M. A.; Mukkanti, D. S. K. Catal Commun 2006, 7, 787.

[18] Wang, M.; Song, Z. G.; Wan, X.; Zhao, S. Monatsh Chem 2009, 140, 1205.

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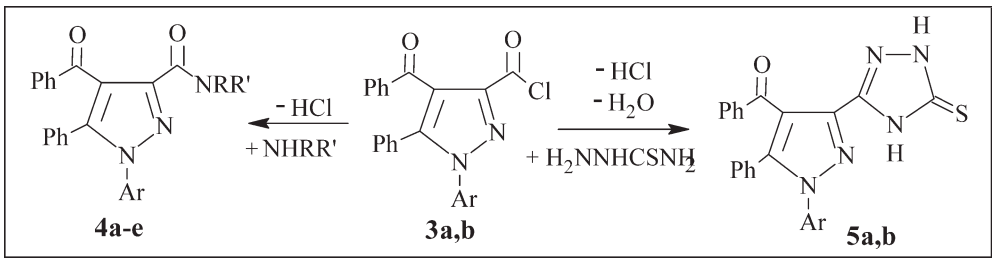


The 1*H*-pyrazole-3-carboxylic acids **2** were converted via reactions of their acid chlorides **3** with some semi- and thiosemicarbazide derivatives into the corresponding new phenylsemi- and thiosemicarbazides **4a–e**, **6**, 5-(pyrazol-3-yl)-4*H*-1,2,4-triazol-3-thiones **5a**,**b**, and 2-(pyrazol-3-yl)-1,3,4-thiadiazol **7** derivatives, in good yields (45-97%, respectively). The reactions of **4a,c,e** with *Lawesson* reagent lead to the products **6** and **7** formation. The structures of these newly synthesized compounds were determined from the IR, $^{1}$H- and $^{13}$C-NMR spectroscopic data and elemental analyses.

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## INTRODUCTION

2,3-Furandiones in general are considered as convenient and versatile synthons in heterocyclic synthesis [1,2]. A convenient method for their synthesis, the mechanism of reactions, and semiempirical (AM1 and PM3) and *ab initio* (DFT) calculations on the interaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) with several semicarbazones, ureas, thioureas, and anilides have been reported recently [3–7]. The reactions of 2,3-furandione **1** and various hydrazines or hydrazones result in new pyrazole-3-carboxylic acids, pyrazolopyridazinones, and some of their derivatives. The pyrazole carboxylic acids can be easily transformed into the corresponding acid chloride, ester, or amide derivatives by the general chemical procedures [8–13]. Pyrazole derivatives are generally well-known nitrogen containing heterocycles, and various procedures have been developed for their syntheses [14–17].

Pyrazole derivatives are very important organic compounds because they are widely used in pharmaceuticals and agrochemicals. Their excellent control activities in regard to various plant diseases are studied [18,19]. They can also be used as antifungal [20], antibacterial [21], antimicrobial [22,23], and anti-inflammatory agents [24–28]. The possible biological properties of the pyrazol, pyridazinone, pyrazolopyridazinone [29], and oxazin derivatives make it attractive to study these compounds.

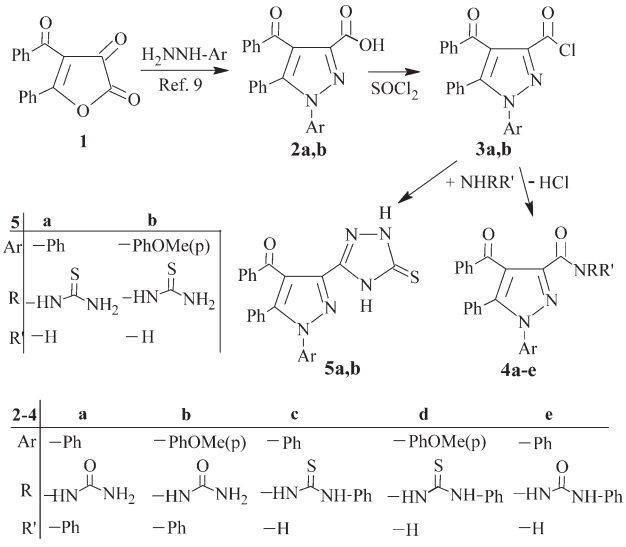
In view of these important properties, we decided both to prove reproducibility of the reaction of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid (**2a**) and -acid chloride (**3a**) with some semi- and thiosemicarbazide derivatives and to extend our investigations related to preparing new heterocycles, which include the pyrazole ring in their structure. Here, we report the chemical behavior of **3** toward various semi- and thiosemicarbazides (see Scheme 1). As a result of these reactions, new phenylsemi- and thiosemicarbazides **4a–e**, **6**, 5-(substituted pyrazol-3-yl)-4*H*-1,2,4-triazol-3-thiones **5a**,**b**, and 2-(substituted pyrazol-3-yl)-1,3,4-thiadiazol **7** derivatives were synthesized, and their structures were identified by spectroscopic and elemental analyses.

## RESULTS AND DISCUSSION

Treatment of the yellow furandione **1** with arylhydrazines under reflux in benzene for 1–6 h, the corresponding white coloured 1*H*-pyrazole-3-carboxylic acids **2** [8] were obtained. The compounds **2** can easily be transformed into the corresponding 1*H*-pyrazole-3-carboxylic acid chloride **3** by usual chemical procedures [9]. Substituted 2,3-furandione **1**, -acid **2** and -acid chloride **3**, which are used as an important initial materials in the synthesis of the target heterocycles, were prepared using the literature procedures (**2b** and **3b** were synthesized by us, yet) [1,8,9,15] (see Scheme 1).

The compounds **3** treatment with various semi- and thiosemi-carbazide derivatives in boiling benzene or xylene gave the corresponding new structures **4**,**5** as main

**Scheme 1**

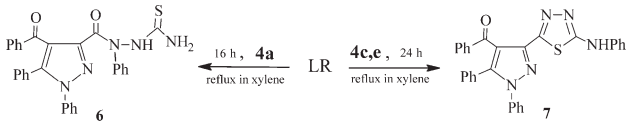



product. The progress of the reactions was monitored by thin-layer chromatography until complete consumption of the starting materials. The compounds **4a–e**, **5a**,**b** were obtained in excellent yields (70–97%), except **5a** (45%), after evaporation of the organic solvents and recrystallization from proper solvent (like methanol or butanol, see Experimental part). The reaction of the compound **3b** with 1-phenylsemicarbazide led to the formation of **4b**, under reflux in xylene for 8 h, in 76% yield without opening the pyrazole ring. To make the reaction selective, we had to determine its parameters, in other words, the reaction pathway, leading to such results. The excellent yield of the reaction can be explained by the chemical behavior of the compound **3** toward H-active nucleophiles, such as semi- and thiosemicarbazides. It should start with a nucleophilic attack of the nitrogen atoms' lone pair electrons of the semicarbazide to the antibonding (π*) orbital at the carbonyl carbon at C3 position of the pyrazol ring. Simultaneous attack of the other nitrogen atoms of the semicarbazide to the carbonyl carbon of the **3** could form some by-products. We assume that the reaction occurs under thermodynamic control. The by-products formed in this way are removed when the raw products are treated with diethyl ether. Previously, analogs reactions have been reported with hydrazines, ureas, diamines, aminophenols, and the corresponding open chain compounds [9–13]. In the IR spectrum of compound **4b**, the ═NH absorption bands were observed between 3480 and 3300 $cm^{-1}$, and the C═O absorption was at 1682 $cm^{-1}$. The $^1$H-NMR signals were found at δ equal to 9.09 ppm (s, 1H, NH), 7.68–6.92 (m, 19H, ArH), 6.20 (b, 2H, $NH_2$), and 3.77 ppm (s, 3H, $OCH_3$), and $^{13}$C NMR signals at δ such as 190.56 (t, PhCO), 159.98, 158.23 (two s, C═O), 159.50 (C─$OCH_3$), 144.28, 143.45 (C-3, C-5), 118.40 (C-4), and 55.90 ppm (q, $OCH_3$). Finally, the elemental analysis data along with spectroscopic data (details see Experimental) confirm the structure of **4b**.

Interaction of the pyrazole-3-carboxylic acid chlorides **3** with some semi- and thiosemicarbazide derivatives at reflux results in the corresponding new products **4a–e**. Surprisingly, using thiosemicarbazide in reaction with **3**, the 5-(substituted pyrazol-3-yl)-4*H*-1,2,4-triazol-3-thione derivatives **5a**,**b** were obtained exclusively. At this point, the reaction of **3** with thiosemicarbazide in boiling benzene for 4 h with no catalytic amounts of pyridine or triethylamine gave the product **5a**, which was obtained in 65% yield by recrystallizing from *n*-butanol (see Scheme 1). The moderate to good yield of the reaction can be explained by the chemical behavior of acid chlorides, similar to the behavior of the compound **3** toward *N*-nucleophiles [8–13]. The formation of **5** can easily be explained by a nucleophilic attack on the carbonyl group of the acid chloride **3**. It appears, that this process can be followed by elimination of a molecule of hydrogen chloride, and finally, loss of a molecule of water, to give **5**, whose formation is confirmed by TLC using authentic specimens of **5** and strongly supported by the results of all analytical and spectroscopic measurements. A Beilstein test did not give a green colour for compound **5**. The IR spectrum of **5a** showed characteristic absorption bands between 3500 and 2900 $cm^{-1}$ (b, NH), and at 1662 $cm^{-1}$ (s, CO). The $^1$H-NMR signals were found to be at δ equal to 10.49 (b, 1H, NH), 9.34 (b, 1H, NH), 7.77–7.08 ppm (m, 15H, ArH), and the $^{13}$C-NMR signals at δ such as 191.70 (t, PhC═O), 159.84 (C═S), 154.68–114.88 (arom. C's), 144.27, 143.66 (C-3, C-5), and 123.08 ppm (C-4).

To examine, if that kind of chemistry can be extended to somewhat modified systems, several attempts to change functional groups in **4** have now been made, e.g. transformation of carbonyl groups into the corresponding C═S-moieties using the *Lawesson* reagent [2,4-bis-(4-methoxyphenyl) 1,3,2,4-dithiadiphosphetane-2,4-disulfide] [30–33]. According to the usual experimental procedures applied to achieve sulfurization of carbonyls with aid of the Lawesson reagent (LR) [30–33], the phenylsemicarbazide derivatives **4a**, **4c,** or **4e** and LR were refluxed in dry xylene on an oil bath for 16 or 24 h, thus, forming a yellow solution. After cooling, white coloured crystals (**6**) or yellow needles (**7**) could be obtained in moderate yields (39–20%). Surprisingly, the outcome of these experiments did not follow the expected routes, but novel, potential, and biologically active pyrazole derivated heterocycles were obtained from those reactions as shown in Scheme 2.

**Scheme 2**




## CONCLUSION

This article reported the facile synthesis of new phenylsemi- and thiosemicarbazides **4a–e**, **6**, 5-(substituted pyrazol-3-yl)-4*H*-1,2,4-triazol-3-thiones **5a**,**b**, and 2-(substituted pyrazole-3-yl)-1,3,4-thiadiazol **7** derivatives from the nucleophilic substitution or recyclization of a pyrazole-3-carbonyl chlorides **3** with various semi- and thiosemicarbazides. The products were easily purified and obtained with a good yield and characterized by spectroscopic techniques as well as microanalyses. All newly synthesized compounds are soluble in most of organic solvents, but their limited solubility in most of inorganic solvents could be a drawback for subsequent applications. However, it may happen these compounds possess interesting biological properties [18–29] that would deserve further investigations. These functionalized products are amenable to further transformations, and we anticipate that they may have important applications in medicinal and synthetic organic chemistry.

## EXPERIMENTAL

Melting points are uncorrected and recorded on Electrothermal 9200 digital melting point apparatus. Microanalyses were performed on a Leco-932 CHNS-O Elemental Analyser. A Jasco 460 Plus FTIR and a Shimadzu FTIR-8400 model spectrophotometers were used for IR spectra (in the range of 400–4000 $cm^{-1}$ region), using KBr pellets or ATR techniques. The $^1$H-and $^{13}$C-NMR spectra were measured with Bruker 300 MHz and Bruker Avance III 400 MHz spectrometers and the chemical shifts were recorded in ppm units. After completion of the reactions, solvents were evaporated with rotary evaporator (Buchi RE model 111). The reactions were followed by TLC using DC Alufolien Kieselgel 60 $F_{254}$ Merck and Camag TLC lamp (254/366 nm). Solvents and all other chemical reagents were purchased from Merck, Sigma, Aldrich and Fluka and used directly without further purification. Solvents were dried by refluxing with the appropriate drying agents and distilled before use.

**4-Benzoyl-5-phenyl-1-*p*-methoxyphenyl-1*H*-pyrazole-3-carboxylic acid (2b).** A mixture of furandione **1** (0.28 g, 1 mmol) and 4-methoxyphenylhydrazine hydrochloride (0.17 g, 1 mmol) was refluxed in 30 mL of dry benzene for 6 h by adding 2–3 drops pyridine. After cooling, the precipitate was filtered off and treated with dry ether to give a crude solid that was recrystallized from methanol. The yield 0.25 g (63%) of **2b**, mp 232°C; IR (ATR): 3400–2400 (b, OH, COOH), 3065, 3030 (arom. CH), 2951–2897 (aliph. CH), 1674 (s br, CO's), 1604–1464 (phenyl and pyrazole rings C⋯C, C⋯N), 1248 $cm^{-1}$ (C—O); $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.69–6.81 (m, 14H, ArH), 3.86 ppm (s, 3H, $OCH_3$); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 183.34 (t, PhC=O), 170.15 (s, COOH), 159.75 (MeO—Ph), 158.75 (N—Ph), 143.90, 143.12 (C-3, C-5), 139.82 (C—Ph), 134.99, 134.25, 132.03, 130.51, 128.90, 128.63, 128.44, 128.13, 128.10, 127.60, 127.28, 127.25 (C—Ph), 116.50 (s, C-4), 114.02, 114.00 (C—Ph), 55.53 ppm (q, $OCH_3$). Anal. Calcd. for $C_{24}H_{18}N_2O_4$ (398.41): C, 72.35; H, 4.55; N, 7.03. Found: C, 72.13; H, 4.72; N, 6.94.

**4-Benzoyl-5-phenyl-1-*p*-methoxyphenyl-1*H*-pyrazole-3-carbonyl chloride (3b).** Compound **2b** (0.40 g, 1 mmol) and thionyl chloride (1 mL, 13.8 mmol) were refluxed on a steam bath for 6 h. After cooling, the crude precipitate formed was filtered off and recrystallized from xylene or toluene, yield 0.31 g (68%), mp 177°C; IR (ATR): 3060, 3013 (arom. CH), 2967–2870 (aliph. CH), 1761, 1648 (s, CO), 1595–1454 (phenyl and pyrazole rings C⋯C, C⋯N), 1250 $cm^{-1}$ (C—O); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 7.80–6.74 (m, 14H, ArH), 3.78 ppm (s, 3H, $OCH_3$). $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 191.35 (t, $J$ = 4.4 Hz, PhCO), 162.75 (s, COCl), 159.61 (MeO—Ph), 143.44, 142.58 (C-3, C-5), 138.15 (C—Ph), 133.81, 132.05, 130.08, 129.59, 129.49, 129.06, 128.83, 128.30, 127.75, 127.60 (C—Ph), 122.97 (s, C-4), 114.60 (C—Ph), 55.90 ppm (q, $OCH_3$). Anal. Calcd. for $C_{24}H_{17}N_2O_3Cl$ (416.86): C, 69.15; H, 4.11; N, 6.72. Found: C, 69.23; H, 4.29; N, 6.60.

**1-[(4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl]-1-phenylsemicarbazide (4a).** Acid chloride **3a** (0.39 g, 1 mmol) and 1-phenylsemicarbazide (0.15 g, 1 mmol) were refluxed in xylene on an oil bath for 2 h. After cooling, the crude precipitate that formed was filtered off and recrystallized from methanol, yield 0.44 g (88%) of **4a**, mp 232–233°C; IR (KBr): 3488, 3334, 3256 (NH⇄OH and $NH_2$), 3057 (aromatic CH), 1713, 1658 (s, CO), 1597–1452 $cm^{-1}$ (C⋯C, C⋯N); $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 9.10 (s, 1H, NH), 7.58–7.10 (m, 20H, ArH), 6.19 ppm (b, 2H, $NH_2$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 190.50 (t, $J$ = 4.3 Hz, PhCO), 159.13 (s, C=O), 158.21 (C=O), 155.83 (N—Ph), 143.42, 142.54 (C-3, C-5), 138.95 (C—Ph), 134.52, 133.18, 132.11, 131.86, 130.53, 129.59, 129.03, 128.82, 128.67, 128.56, 128.26, 126.08 (C—Ph), 122.51, 119.94 ppm (C-4). Anal. Calcd. for $C_{30}H_{23}N_5O_3$ (501.54): C, 71.84; H, 4.62; N, 13.96. Found: C, 72.03; H, 4.79; N, 13.64.

**1-[(4-Benzoyl-5-phenyl-1-*p*-methoxyphenyl-1*H*-pyrazol-3-yl) carbonyl]-1-phenylsemicarbazide (4b).** Acid chloride **3b** (0.42 g, 1 mmol) and 1-phenylsemicarbazide (0.15 g, 1 mmol) were refluxed in xylene on an oil bath for 8 h. After evaporation, the oily residue obtained was treated with dry ether. The crude product formed was filtered off and recrystallized from a mixture of benzene-cyclohexane (1:3), yield 0.40 g (76%) of **4b**, mp 129°C; IR (ATR): 3480, 3383, 3309 (NH⇄OH and $NH_2$), 3065, 2912, 2849 (arom. and aliph. CH), 1682 (s br, CO's), 1590–1447 (C⋯C, C⋯N), 1248 $cm^{-1}$ (C—O); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 9.09 (s, 1H, NH), 7.68–6.92 (m, 19H, ArH), 6.20 (b, 2H, $NH_2$), 3.77 ppm (s, 3H, $OCH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 190.56 (t, $J$ = 4.2 Hz, PhCO), 159.98 (s, C=O), 159.50 (MeO—Ph), 158.23 (C=O), 155.30 (N—Ph), 144.28, 143.45 (C-3, C-5), 141.15 (C—Ph), 138.17, 134.21, 132.10, 131.93, 130.55, 130.08, 129.49, 128.92, 128.76, 128.15, 127.96, 127.59, 126.79 (C—Ph), 124.91, 118.40 (C-4), 116.61 (C—Ph), 55.90 ppm (q, $OCH_3$). Anal. Calcd. for $C_{31}H_{25}N_4O_4$ (517.55): C, 71.94; H, 4.87; N, 10.83. Found: C, 72.03; H, 4.77; N, 10.68.

**1-[(4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl]-4-phenylthiosemicarbazide (4c).** Acid chloride **3a** (0.30 g, 0.8 mmol) and 4-phenylthiosemicarbazide (0.13 g, 0.8 mmol) were refluxed in benzene for 1 h. After cooling, the crude precipitate that formed was filtered off and recrystallized from *n*-butanol to give 0.27 g of **4c** (68%), mp 250–251°C; IR (KBr): 3393, 3209 (NH⇄OH ve NH), 3065 (arom. CH), 2415 (w, tautomeric SH), 1674 (CO), 1610–1460 (C⋯C, C⋯N), 1360 $cm^{-1}$ (C=S); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 12.61 (s, 1H, NH⇄SH), 10.02 (b, 1H, NH), 9.72 (b, 1H, NH), 7.54–6.92 ppm (m, 20H, ArH); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 191.50 (t, $J$ = 4.4 Hz, PhCO), 161.63 (C=S), 158.26 (C=O, amide), 156.60 (N—Ph), 145.17, 142.56 (C-3, C-5 exchangeable), 140.24 (C—Ph), 138.86, 137.06, 133.96, 130.46, 129.11, 128.99, 128.91, 128.60, 128.18, 127.87, 127.71, 126.13 (C—Ph), 123.17 (C-4), 117.08, 116.88 ppm (C—Ph). Anal. Calcd. for $C_{30}H_{23}N_5O_2S$ (517.60): C, 69.61; H, 4.48; N, 13.53; S, 6.19. Found: C, 69.88; H, 4.80; N, 13.91; S, 6.00.

**1-[(4-Benzoyl-5-phenyl-1-*p*-methoxyphenyl-1*H*-pyrazol-3-yl) carbonyl]-4-phenylthiosemicarbazide (4d).** Acid chloride **3b** (0.42 g, 1 mmol) and 4-phenylthiosemicarbazide (0.17 g, 1 mmol) were refluxed in xylene for 6 h. After evaporation, the oily residue obtained was treated with dry ether. The crude product formed was filtered off and recrystallized from *n*-butanol to give 0.38 g of **4d** (70%), mp 202°C; IR (ATR): 3400–3100 (NH⇄OH and NH), 3065, 2966, 2873 (C—H), 2450 (w, tautomeric SH), 1674 (s br, CO's), 1604–1475 (C⋯C, C⋯N), 1370 $cm^{-1}$ (C=S); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 12.59 (s, 1H, NH⇄SH), 10.39 (b, 1H, NH), 9.96 (t, 1H, NH), 7.74–6.92 (m, 19H, ArH), 3.76 ppm (s, 3H, $OCH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 191.30 (t, $J$ = 4.2 Hz, PhCO), 160.06 (C=S), 159.85 (MeO—Ph), 159.61 (C=O, amide), 156.62 (N—Ph), 144.07, 142.19 (C-3, C-5 exchangeable), 140.68 (C—Ph), 138.15, 137.63, 134.74, 133.63, 132.19, 131.03, 130.17, 129.58, 129.22, 128.85, 128.56, 128.33, 128.13, 127.85, 127.77, 126.39 (C—Ph), 122.09 (C-4), 117.86, 116.88, 114.52 (C—Ph), 55.90 ppm (q, $OCH_3$). Anal. Calcd. for $C_{31}H_{25}N_4O_3S$ (533.62): C, 69.77; H, 4.72; N, 10.50; S, 6.01. Found: C, 69.85; H, 4.80; N, 10.32; S, 6.14.

**1-[(4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl]-4-phenylsemicarbazide (4e).** Acid chloride **3a** (0.30 g, 0.8 mmol) and 4-phenylsemicarbazide (0.15 g, ∼0.8 mmol) were refluxed in benzene for 4 h. After cooling, the crude precipitate was filtered off and recrystallized from *n*-butanol, yield 0.40 g (97%) of **4e**, mp 219°C; IR (KBr): 3435, 3329 (NH⇄OH), 3060 (arom. CH), 1696, 1641 (s, CO), 1601–1478 $cm^{-1}$ (C⋯C, C⋯N); $^1$H-NMR (300 MHz, $CDCl_3$/DMSO-$d_6$): δ 9.79 (s, 1H, NH), 8.37 (s, 1H, NH), 7.99 (s, 1H, NH), 7.71–6.85 ppm (m, 20H, ArH); $^{13}$C-NMR (75 MHz, $CDCl_3$/DMSO-$d_6$): δ 190.26 (t, $J$ = 4.3 Hz, PhCO), 159.51, 154.52 (HNC=O), 143.16, 142.70 (C-3, C-5), 138.48, 137.87, 137.09, 132.21, 128.87, 128.46, 128.21, 127.88, 127.76, 127.68, 127.47, 126.96, 124.65 (C—Ph), 121.37, 121.18, 117.62 ppm (C-4). Anal. Calcd. for $C_{30}H_{23}N_5O_3$ (501.54): C, 71.84; H, 4.62; N, 13.96. Found: C, 71.47; H, 4.77; N, 14.21.

**5-(4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-3-thione (5a).** Acid chloride **3a** (0.50 g, 1.3 mmol) and thiosemicarbazide (0.12 g, 1.3 mmol) were refluxed in benzene for 4 h. After cooling, the crude precipitate was filtered off and recrystallized from *n*-butanol, yield 0.36 g (65%) of **5a**, mp 208°C; IR (KBr): 3600–2900 $cm^{-1}$ (b, NH, peak max.: 3468, 3339, 3182), 3055 (arom. CH), 1662 (s, CO), 1602–1497 (C⋯N, C⋯C), 1367 $cm^{-1}$ (C=S); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 10.49 (b, 1H, NH), 9.34 (b, 1H, NH), 7.77–7.08 ppm (m, 15H, ArH); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 191.70 (t, $J$ = 4.5 Hz, PhCO), 159.84 (C=S), 154.68 (N—Ph), 144.27, 143.66, 143.25 (C-3, C-5 or C-5′ exchangeable), 140.23 (C—Ph), 139.21, 138.18, 136.39, 135.24, 133.67, 132.26, 131.75, 130.41, 129.68, 129.31, 128.91, 128.27, 127.74, 125.32 (C—Ph), 123.08 (C-4), 117.18, 114.88 ppm (C—Ph). Anal. Calcd. for $C_{24}H_{17}N_5OS$ (423.49): C, 68.07; H: 4.05; N: 16.54; S: 7.57. Found: C, 67.90; H, 4.25; N, 16.40; S. 7.30.

**5-(4-Benzoyl-5-phenyl-1-*p*-methoxyphenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-3-thione (5b).** Acid chloride **3b** (0.50 g, 1.2 mmol) and thiosemicarbazide (0.11 g, 1.2 mmol) were refluxed in xylene for 8 h. After cooling, the crude precipitate was filtered off and recrystallized from a mixture of carbon tetrachloride and cyclohexane (1:3), yield 0.45 g (83%) of **5b**, mp 140°C; IR (ATR): 3320, 3156 (NH), 3057, 2935 (C—H), 2450 (w, tautomeric SH), 1670 (s, CO), 1598–1452 (C⋯C, C⋯N), 1362 $cm^{-1}$ (C=S); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 12.58 (s, 1H, NH⇄SH), 10.36 (b, 1H, NH), 7.76–6.92 (m, 14H, ArH), 3.76 ppm (s, 3H, $OCH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 191.30 (t, $J$ = 4.6 Hz, PhCO), 161.93 (C=S), 159.81 (MeO—Ph), 156.63 (N—Ph), 144.07, 143.47, 142.21 (C-3, C-5 or C-5′ exchangeable), 140.68 (C—Ph), 138.15, 137.87, 134.73, 133.82, 132.19, 131.87, 130.32, 129.74, 129.28, 128.86, 128.33, 127.85, 126.39 (C—Ph), 122.10 (C-4), 116.80, 114.60, (C—Ph), 55.93 ppm (q, $OCH_3$). Anal. Calcd. for $C_{25}H_{19}N_5O_2S$ (453.52): C, 66.21; H: 4.22; N: 15.44; S: 7.07. Found: C, 66.08; H, 4.25; N, 15.15; S. 7.33.

**1-[(4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl]-1-phenylthiosemicarbazide (6). 4a** (0.50 g, 1.1 mmol) and LR (0.54 g, 1.3 mmol) were refluxed in xylene on an oil bath for 16 h. Than the solvent was evaporated and remaining oily residue was treated with dry diethyl ether to give a crude product that was recrystallized from xylene. Yield 0.20 g (39%) of **6**, mp 263°C; IR (KBr): 3600–2950, (b, NH, peak max.: 3446, 3220, 3196), 3055 (arom. CH), 1690, 1637 (CO), 1594–1472 (C⋯C, C⋯N), 1364 $cm^{-1}$ (C=S); $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.80 (d, 1H, NH), 7.77 (d, 1H, NH), 7.66–6.86 (m, 20H, ArH and 1H, NH). Anal. Calcd. for $C_{30}H_{23}N_5O_2S$ (517.60): C, 69.61, H, 4.48, N, 13.53, S, 6.19. Found: C, 69.47, H: 4.63; N: 13.76, S: 6.04.

**5-Anilino-2-(4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)-1,3,4-thiadiazol (7). 4e** (0.50 g, 1 mmol) and LR (0.54 g, 1.3 mmol) were refluxed in xylene on an oil bath for 24 h. Than the solvent was evaporated and remaining oily residue was treated with dry diethyl ether to give a crude product that was recrystallized from xylene. Yield 0.11 g (20%) of **7**, mp 323°C; IR (KBr): 3196 (NH), 3058 (arom. CH), 1640 (CO), 1594–1491 $cm^{-1}$ (C⋯C, C⋯N); $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 14.27 (s, 1H, NH), 7.46–6.97 ppm (m, 20H, ArH);$^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 175.44 (t, $J$ = 4.2 Hz, PhCO), 149.00 (N=C—S), 148.60 (S—C—NH), 141.60, 139.21, 137.65, 133.98, 131.07, 130.10, 129.93, 129.51, 129.25, 129.17, 128.84, 128.74, 128.58, 128.26, 128.08, 127.92, 126.96, 126.42, 126.06, 111.49 ppm (arom. C's). Anal. Calcd. for $C_{30}H_{21}N_5OS$ (499.59): C, 72.12; H, 4.24; N, 14.02; S, 6.42. Found: C, 72.40; H, 4.50; N, 13.80; S, 6.71.

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## REFERENCES AND NOTES

[1] Ziegler, E.; Eder, M.; Belegratis, C.; Prewedourakis, E. Monatsh Chem 1967, 98, 2249.

[2] Review: Kollenz, G.; Heilmayer, W. Trends in Heterocycl Chem 1993, 3, 379.

[3] Altural, B.; Akçamur, Y.; Sarıpınar, E.; Yıldırım, I.; Kollenz, G. Monatsh Chem 1989, 120, 1015.

[4] Yıldırım, I.; Sarıpınar, E.; Güzel, Y.; Patat, S.; Akçamur, Y. J Mol Struct 1995, 334, 165.

[5] Yıldırım, I.; Tezcan, M.; Güzel, Y.; Sarıpınar, E.; Akçamur, Y. Turk J Chem 1996, 20, 27.

[6] Yıldırım, I.; Ilhan, I. O. J Heterocycl Chem 1997, 34, 1047.

[7] Yıldırım, I.; Kandemirli, F. Heteroat Chem 2004, 15/1, 9.

[8] Akçamur, Y.; Penn, G.; Ziegler, E.; Sterk, H.; Kollenz, G.; Peters, K.; Peters, E. M.; von Schnering, H. G. Monatsh Chem 1986, 117, 231.

[9] Akçamur, Y.; Şener, A.; Ipekoğlu, A. M.; Kollenz, G. J Heterocycl Chem 1997, 34, 221.

[10] Şener, A.; Kasımoğulları, R.; Şener, M. K.; Bildirici, I; Akçamur, Y. J Heterocycl Chem 2002, 39, 869.

[11] Yildirim, I.; Kandemirli, F.; Akçamur, Y. J Mol Struct 2005, 738, 275.

[12] Yildirim, I.; Kandemirli, F.; Demir, E. Molecules 2005, 10, 559 and references therein.

[13] Yildirim, I.; Kandemirli, F. Struct Chem 2006, 17, 241.

[14] Dinçer, M.; Ozdemir, N.; Yildirim, I.; Demir, E.; Işık, S. Acta Cryst E 2004, 60, 946.

[15] Yildirim, I.; Ozdemir, N.; Akçamur, Y.; Dinçer, M.; Andac, O. Acta Cryst E 2005, 61, 256.

[16] Joule, J. A.; Mills, K.; Smith, G. F. Heterocyclic Chemistry, 3rd ed.; Chapman & Hall: London, UK, 1995; Chapter 22, pp 402–405.

[17] Elguero, J. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, pp 167–302.

[18] Sing, S. P. Heterocycles 1990, 31, 855.

[19] Sternbach, L. M. Prog Drug Res 1978, 22, 229.

[20] Jaiswal, N.; Jaiswal, R.; Barthwal, J.; Kishor, K. Indian J Chem 1981, 20B, 252.

[21] Küçükgüzel, S. G.; Rollas, S.; Erdeniz, H.; Kiraz, M.; Ekinci, A. C.; Vidin, A. J Med Chem 2000, 35, 761.

[22] Dias, L. R. S.; Alvim, M. J.; Freitas, A. C. C.; Barreiro, E. J.; Miranda, A. L. P. Pharm Acta Helv 1994, 69, 163.

[23] Lyga, J. W.; Patera, R. M.; Plummer, M. J.; Halling, B. P.; Yuhas, D. A. Pestic Sci 1994, 42, 29.

[24] Genoin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. J Med Chem 2000, 43, 1034.

[25] Badawey, E.; El-Ashmawey, I. M. Eur J Med Chem 1998, 33, 349.

[26] Tewari, A. K.; Mishra, A. Bioorg Med Chem 2001, 9, 715.

[27] Akbas, E.; Berber, I.; Sener, A.; Hasanov, B. Il Farmaco 2005, 60, 23.

[28] Rostom, S. A. F.; Shalaby, M. A.; El-Demellawy, M. A. Eur J Med Chem 2003, 38, 959.

[29] Bildirici, I.; Şener, A.; Tozlu, I. Med Chem Res 2007, 16, 418 and references therein.

[30] Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S. O. Bull Soc Chim Belg 1978, 87, 223.

[31] Scheibye, S.; Shabana, R.; Lawesson, S. O.; Romming, C. Tetrahedron 1982, 38, 993.

[32] Boeglin, D.; Cantel, S.; Martinez, J.; Fehrentz, J.-A. Tetrahedron Lett 2003, 44, 459.

[33] Thompson, M. J.; Heal, W.; Chen, B. Tetrahedron Lett 2006, 47, 2361.

# Reactions with Hydrazonoyl Halides 62: Synthesis and Antimicrobial Evaluation of Some New Imidazo [1,2-*a*]pyrimidine, Imidazo [1,2-*a*]pyridine, Imdazo [1,2-*b*]pyrazole, and Quinoxaline Derivatives



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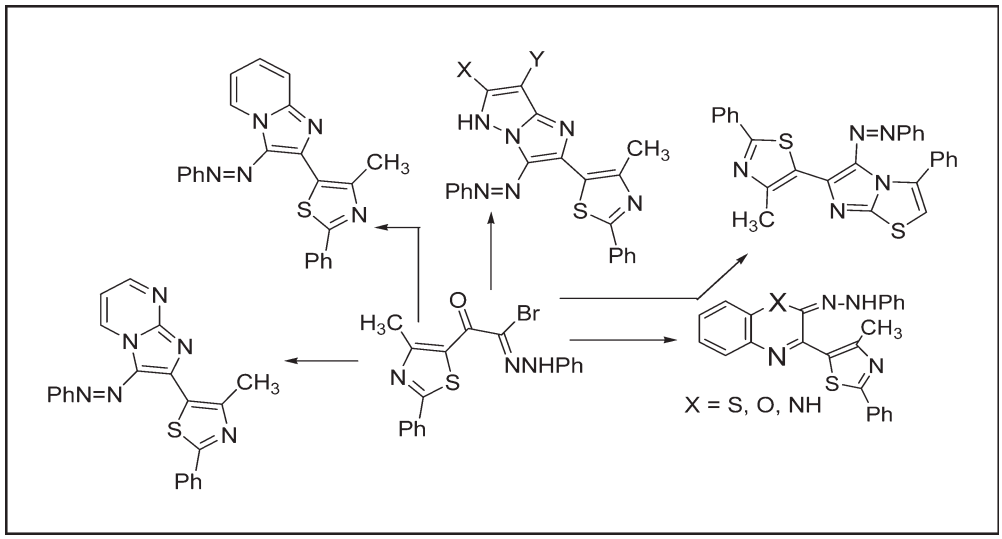


3-Arylazo-2-(4-methyl-2-phenylthiazol-5-yl)imidazo[1,2-*a*]pyrimidine, 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-phenylazoimidazo[1,2-*a*]pyridine, 3-arylazo-2-(4-methyl-2-phenylthiazol-5-yl)-6-phenyl-5*H*-imidazo[1,2-*b*]pyrazole, 6-(4-methyl-2-phenyl-thiazol-5-yl)-5-phenylazo3-phenyl-imidazo[2,1-*b*]thiazole, 3-(4-methyl-2-phenylthiazol-5-yl)-2-phenylhydrazino-(1*H*)-quinoxaline, 3-(4-methyl-2-phenylthiazol-5-yl)- 2-phenylazoquinoxaline, 3-(4-methyl-2-phenylthiazol-5-yl)-2-phenylhydrazinobenzo-[1,4] thiazine, 3-(4-methyl-2-phenyl-thiazol-5-yl)-2-phenylhydrazinobenzo[1,4]oxazine, and 3-(4-methyl-2-phenyl-thiazol-5-yl)-2-phenylazo-1*H*-pyrido[2,3-*b*]pyrazine derivatives were synthesized *via* reaction of 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-oxo-*N*-arylethanehydrazonoyl bromide with each of 2-aminopyrimidine, 2-aminopyridine, 3-aminopyrazoles, 2-amino-4-phenylthiazole, *o*-phenylenediamine, *o*-aminothiophenol, *o*-aminophenol, or 2, 3-diaminopyridine, respectively. All structures of the newly synthesized compounds were elucidated by elemental analysis, spectral data, and alternative synthetic route whenever possible. The entire newly synthesized compounds are tested toward different microorganisms.

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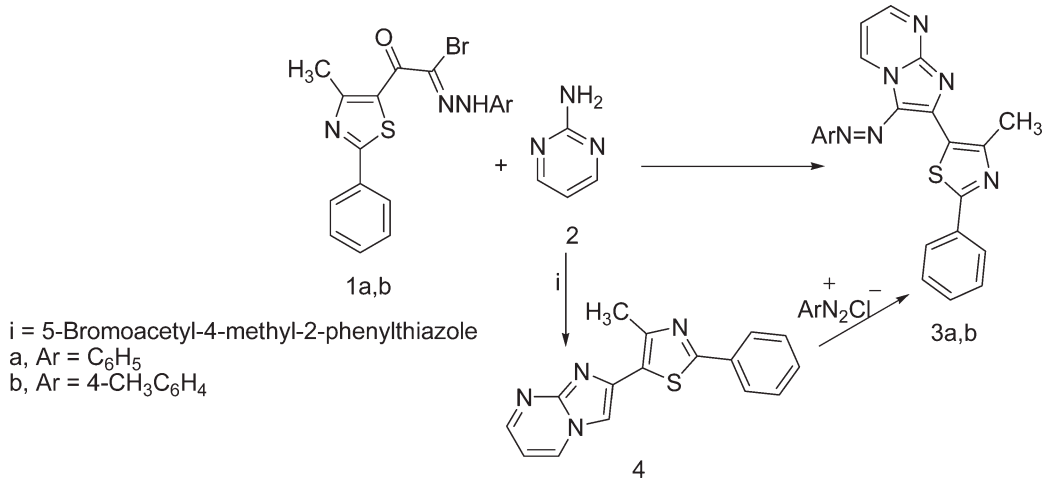
## INTRODUCTION

Our continuous interest in the chemistry of hydrazonoyl halides [1–9] originates from our persistent trials to obtain pyridines, pyrimidines, pyridazines, and their analogs. The importance of such compounds lies in their diverse pharmaceutical activities, namely antibacterial [10,11], antidiabetic [12], anti-HIV [13], antiviral [14,15], and analgesic activities. We report herein the reactivity of 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-oxo-*N*-arylethanehydrazonoyl bromides toward 2-aminopyrimidine, 2-aminopyridine, 3-aminopyrazoles, 2-amino-4-phenylthiazole, *o*-phenylenediamine, *o*-aminothiophenol, *o*-aminophenol, and 2,3-diaminopyridine.

## RESULTS AND DISCUSSION

Treatment of 2-aminopyrimidine (**2**) with the appropriate 2-(4-methyl-2-phenylthiazol-5-yl)-2-oxo-*N*-arylethanehydrazonoyl bromide (**1a**, **b**) in ethanol gave 3-arylazo-2-(4-methyl-2-phenylthiazol-5-yl)imidazo[1,2-*a*] pyrimidine (**3a**, **b**) in a good yield (Scheme 1). Structure **3** was elucidated by elemental analysis, spectral

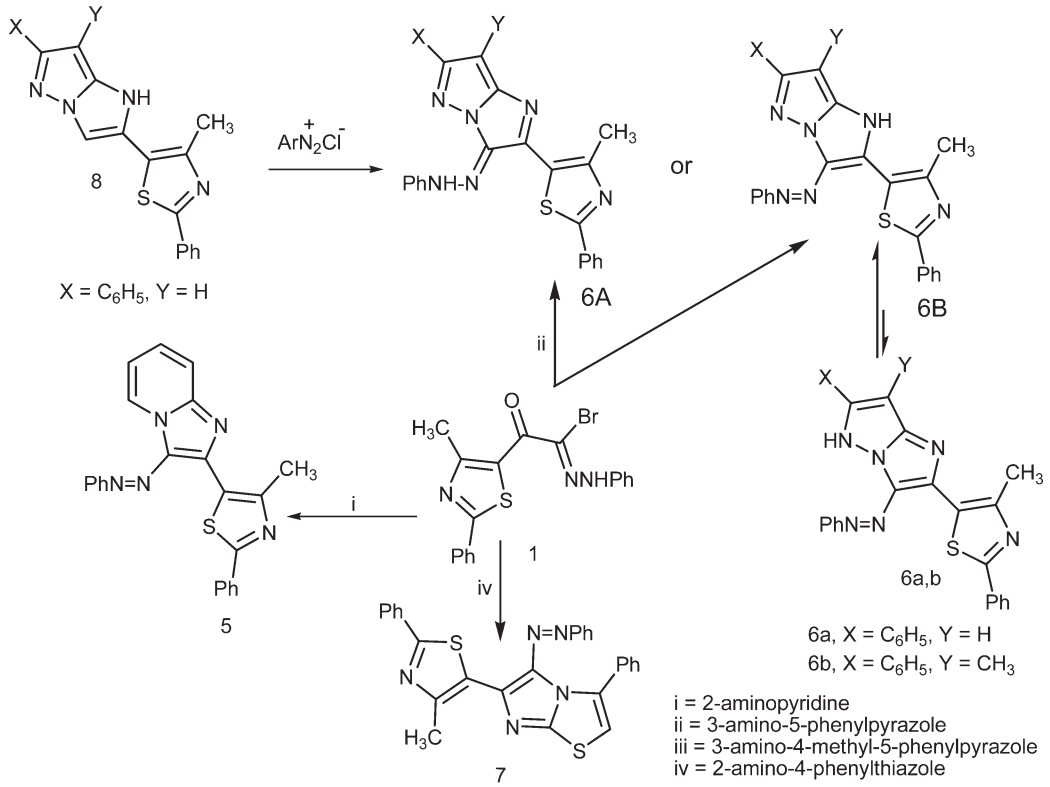
**Scheme 1**



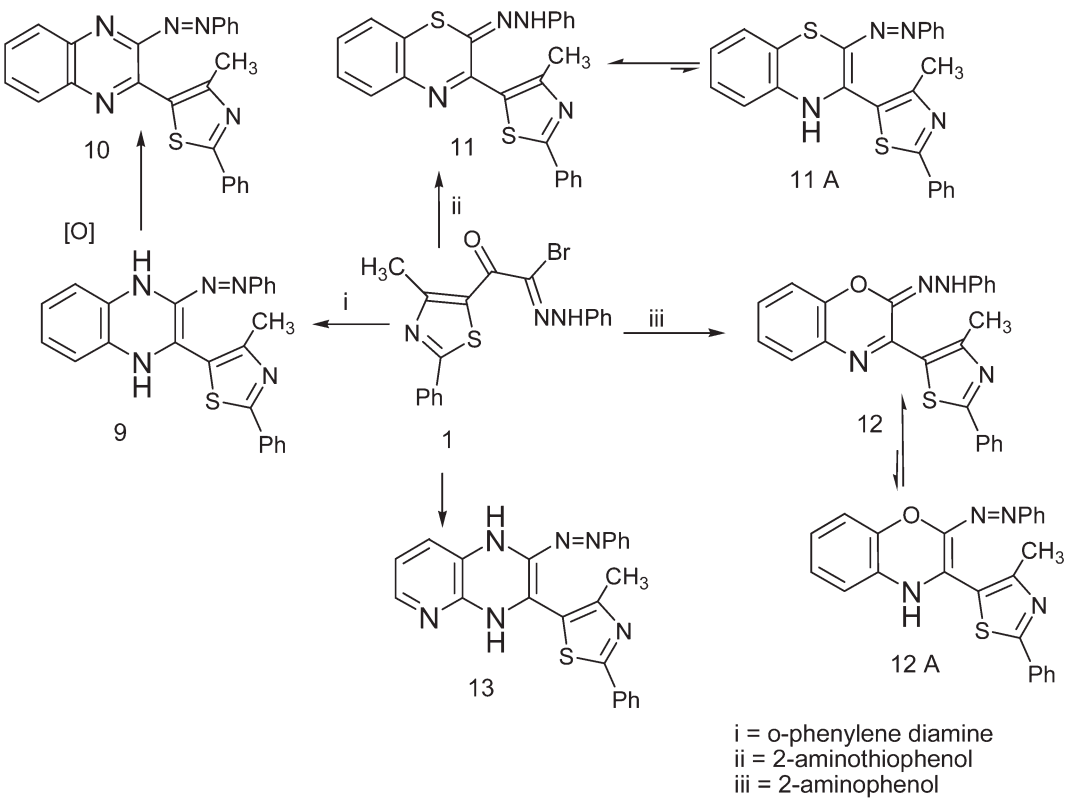

data, and alternative synthesis. $^1$H-NMR spectrum of **3a** showed signals at $\delta = 2.46$ (s, 3H, 4-methylthiazole), 6.86–6.70 (t, 3H, pyrimidine H-5), 7.36–7.37 (d, 2H, ArH), 7.62–7.67 (m, 3H, ArH), 7.70–7.81 (m, 3H, ArH), 8.53–8.54 (d, 1H, pyrimidine H-4), 8.65–8.66 (d, 1H, pyrimidine H-6). Its IR (cm$^{-1}$) spectrum revealed bands at 3060, 2923 (CH), 1645 (C=N), 1599 (C=C), 1321 ($CH_3$), and no band between 1800 and 1650 cm$^{-1}$ attributed the absence of carbonyl group. Thus, treatment of 2-(4-methyl-2-phenylthiazol-5-yl)imidazo[1,2-*a*]pyrimidine (**4**), which was synthesized *via* reaction of 2-aminopyrimidine with 2-bromo-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanone, with the appropriate arenediazonium chloride in ethanolic sodium acetate gave a product identical in all aspects (mp., mixed mp., and spectra) with **3a** and **3b**, respectively.

Analogously, the appropriate 2-aminopyridine, 3-amino-5-phenylpyrazole, 3-amino-4-methyl-5-phenylpyrazole, or 2-

**Scheme 2**



**Scheme 3**




amino-4-phenylthiazole was reacted with 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-oxo-*N*-phenylethanehydrazonoyl bromide (**1a**) in boiling ethanol gave 3-phenylazo-2-(4-methyl-2-phenylthiazol-5-yl)imidazo[1,2-*a*]pyridine (**5**), 3-phenylazo-2-(4-methyl-2-phenyl-thiazol-5-yl)-6-phenyl-5*H*-imidazo [1,2-*b*]pyrazole (**6a**), 2-(4-methyl-2-phenyl-thiazol-5-yl)-5-methyl-6-phenyl-3-phenylazo-5*H*-imidazo[1,2-*b*]pyrazole (**6b**), and 6-(4-methyl-2-phenyl-thiazol-5-yl)-5-phenylazo3-phenylimidazo[2,1-*b*]thiazole (**7**), respectively (Scheme 2).

Structures **5**–**7** were elucidated by elemental analyses, spectral data, and alternative synthetic route. Thus, treatment of 2-(4-methyl-2-phenylthiazol-5-yl)-6-phenyl-1*H*-imidazo[1,2-*b*]pyrazole (**8**), which was synthesized from 2-bromo-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanone with 3(5)-amino-5(3)-phenylpyrazole in boiling ethanol, with benzenediazonium chloride in ethanolic sodium acetate solution gave product identical in all aspects (mp., mixed mp., and spectra) with **6a**.

Attention was then turned to the tautomeric structure of the product **6a** as they can exist in the tautomeric hydrazone form **A** or phenylazoenamine form **B** (Scheme 2). Unfortunately, their spectra (IR and $^1$H-NMR) were not of too much help to decide the actual tautomeric form of the compound in question. This problem was solved by examining UV spectrum and M.O. calculation. The electronic absorption of compound **6a** in ethanol was also compatible with the azo form **B**. The product exhibits in ethanol two bands at $\lambda_{nm} = 315$ (log $\varepsilon =$ 3.3416) and 466 (log $\varepsilon = 4.1734$). Such an absorption pattern is similar to that of typical azo-form [16,17]. M.O. calculation using HyperChem semi-empirical method AM1, for structure **6A**, showed $E = -6034.948$ kcal/mol and heat formation = 365.522 kcal/mol, for structure **6B** showed $E = -6096.498$ kcal/mol and heat formation = 303.972 kcal/mol, and for structure **6a**, $E = -6113.009$ kcal/mol and heat formation = 287.460 kcal/mol. These results indicted that the structure **6a** was more compatible tautomeric form.

Treatment of **1a** with *o*-phenylenediamine in boiling ethanol under reflux gave 3-(4-methyl-2-phenylthiazol-5-yl)-2-phenylhydrazino-(1*H*)-quinoxaline (**9**). Structure **9** was confirmed by elemental analysis, spectral data, and its oxidation with hydrogen peroxide in acetic acid to afford 3-(4-methyl-2-phenyl-thiazol-5-yl)-2-phenylazoquinoxaline (**10**) (Scheme 3).

Analogously, treatment of **1a** with the appropriate of each of 2-aminothiophenol, 2-aminophenol, or 2,3-diaminopyridine gave 3-(4-methyl-2-phenyl-thiazol-5-yl)-2-phenylhydrazinobenzo[1,4]thiazine (**11**), 3-(4-methyl-2-phenyl-thiazol-5-yl)-2-phenylhydrazinobenzo[1,4]oxazine (**12**), and 1-(1,4-dihydro-3-(4-methyl-2-phenylthiazol-5-yl)-2-phenylazopyrido[2,3-*b*]pyrazine (**13**), respectively. Structures **11A** and **12A** were ruled out according to UV spectra. Thus, UV spectra of **11** and **12** exhibit

**Table 1**

Response of various microorganisms to some synthesized compounds *in vitro* culture.

| Comp no. | *S. aureus* | *B. subitis* | *E. coli* | *Ps. aeruginosa* | *C. albicans* |
|---|---|---|---|---|---|
| **3a** | ≥1600 | ≥800 | ≥800 | ≥400 | ≥400 |
| **3b** | ≥1600 | ≥800 | ≥800 | ≥800 | ≥400 |
| **4** | ≥1600 | ≥400 | ≥800 | ≥800 | ≥800 |
| **5** | ≥800 | ≥800 | ≥800 | ≥400 | ≥800 |
| **6a** | ≥800 | ≥800 | ≥400 | ≥800 | >800 |
| **6b** | ≥1600 | ≥800 | ≥800 | ≥400 | ≥400 |
| **7** | ≥1600 | ≥400 | ≥800 | ≥800 | ≥800 |
| **8** | ≥1600 | ≥800 | ≥800 | ≥800 | ≥400 |
| **9** | ≥1600 | ≥400 | ≥800 | ≥400 | ≥800 |
| **10** | ≥1600 | ≥400 | ≥400 | ≥800 | ≥800 |
| **11** | ≥1600 | ≥800 | ≥800 | ≥800 | ≥400 |
| **12** | ≥1600 | ≥400 | ≥400 | ≥400 | ≥800 |
| **13** | ≥1600 | ≥400 | ≥800 | ≥400 | ≥800 |
| **DMSO** | >1600 | >400 | >800 | >800 | >400 |
| Ciprofloxacin | ≤100 | ≤25 | ≤25 | 400 | ≥800 |
| Triflucan | ≥800 | ≥800 | ≥800 | ≥800 | ≤25 |

$\lambda_{max}$ = 357 (log ε = 4.022) and 345 (log ε = 2.716), whereas spectrum of **13** exhibits two bands at $\lambda_{max}$ = 345 (log ε = 4.0177) and 466 (log ε = 4.6467).

**Antimicrobial screening.** Ten selected compounds were screened for their antimicrobial activity using five selected standard isolates, which have been chosen as representative examples of different types of microorganisms as follows: Gram-positive both nonsporulated bacteria as *Staphylococus aureus* and sporulated as *Bacillus subtilis*, Gram-negative as *Escherichia coli* and *Pseudomonas aeruginosa*, and a fungus as *Candida albicans*.

***Method: Agar dilution technique.*** The appropriate volume of membrane filtered stock solution of 0.05 g/5 mL of each compound was prepared by the twofold dilution method to obtain the concentrations: 400, 200, 100, 50, and 25 μg/mL [18]. The volumes were added to the molten LB agar (about 50°C). After mixing, the media were allowed to harden and dry by placing in an incubator at 37°C for 10 min. Plates containing serial dilutions of each compound were inoculated with a sterile multiinoculator onto the surface of the agar medium so that the final inoculum of each isolate on the agar surface was in the order of $10^4$–$10^5$ CFU/spot. Ciprofloxacin and triflucan were used as positive controls and the solvent, dimethylsulfoxide (DMSO), as negative control. Minimum inhibitory concentrations (MICs) were read after 18 h incubation at 37°C for bacteria and 25°C for fungus. The MIC is reported as the lowest concentration of the compound that prevents the growth of visible colonies. The obtained MICs of 10 representative examples are presented in Table 1.

As shown in Table 1, there is variability in the susceptibilities of the different organisms to the different compounds. *S. aureus* was the most resistant organism. Some compounds showed antibacterial activity, whereas others showed antifungal activity.

## EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FTIR 8201 PC Spectrophotometer. $^1$H-NMR and $^{13}$C-NMR spectra were recorded in $CDCl_3$ solution on a Varian Mercury 300 MHz spectrometer, and chemical shifts are expressed as δ using TMS as an internal reference. The ultraviolet spectrum was recorded using Shimadzu UV–vis 1601 PC double beam spectrophotometer. Mass spectra were recorded on a GC-MS QP1000. Elemental analyses were carried out at the Micro analytical center of Cairo University. The hydrazidoyl bromides **1**(**a**, **b**) were prepared as previously reported [19].

**General procedure for the synthesis of (3a, b), (5), (6a, b), (7), (9), (11), (12), and (13).** A mixture of the appropriate hydrazonoyl bromide **1a**, **b** (5 mmol), the appropriate 2-aminopyrimidine, 2-aminopyridine, 3-amino-5-phenylpyrazole, 3-amino-4-methyl-5-phenylpyrazole, 2-amino-4-phenylthiazole, *o*-phenylenediamine, 2-aminothiophenol, 2-aminophenol or 2,3-diaminopyridine (6 mmol), and triethylamine (0.5 g, 0.75 mL, 5 mmol) in ethanol (25 mL) was heated under reflux for 3 h and then cooled. The solid precipitated was collected, washed with water, and then crystallized from the appropriate solvent to give **3**(**a**, **b**), **5**, **6**(**a**, **b**), **7**, **8**, **11**–**13**, respectively.

***3-Phenylazo-2-(4-methyl-2-phenylthiazol-5-yl)imidazo[1,2-a]pyrimidine (3a).*** This compound was obtained as violet crystals (DMF-EtOH), mp > 300°C, yield (69%); IR ($cm^{-1}$): 3060, 2923 (CH), 1623 (C=N), 1599 (C=C), 1321 ($CH_3$). $^1$H-NMR $(CD_3)_2SO$: δ = 2.46 (s, 3H, 4-methylthiazole), 7.07–7.13 (t, 3H, *J* = 5.6 Hz, pyrimidine H-5), 7.49–7.51 (d, 2H, *J* = 4.0 Hz, ArH), 7.94–7.97 (m, 3H, ArH), 8.27 (m, 3H, ArH), 8.56–8.58 (d, 1H, *J* = 4.0 Hz, pyrimidine H-4), 8.95–

8.98 (d, 1H, $J$ = 4.0 Hz, pyrimidine H-6). $^{13}$C-NMR: δ = 14.71 ($CH_3$), 110.64, 156.19, 160.11 (thiazole), 113.45, 120.45, 145.78 (imidazole), 122.04, 125.11, 127.31, 129.21, 130.12, 131.18, 135.20, 154.68 (aromatic carbons), 108.12, 134.45, 152.67 (pyrimidine). Anal. Calcd. for $C_{22}H_{16}N_6S$ (396.46): C, 66.72; H, 4.07; N, 21.20; S, 8.09. Found: C, 66.60; H, 4.00; N, 21.40; S, 8.20.

***3-[4-Methylphenylazo)-2-(4-methyl-2-phenylthiazol-5-yl)imidazo[1,2-a]pyrimidine (3b).*** This compound was obtained as red crystals (AcOH), mp 272–74°C, yield (66%); IR ($cm^{-1}$): 3060, 2968 (CH), 1625 (C=N), 1599 (C=C), 1321 ($CH_3$). $^1$H-NMR $(CD_3)_2SO$: δ = 2.46 (s, 3H, 4-methylthiazole), 2.53 (s, 3H, 4-$CH_3C_6H_4$), 6.86–6.70 (t, 3H, pyrimidine H-5), 7.36–7.37 (d, 2H, ArH), 7.62–7.67 (m, 3H, ArH), 7.70–7.81 (m, 2H, ArH), 8.53–8.54 (d, 1H, pyrimidine H-4), 8.65–8.66 (d, 1H, pyrimidine H-6). Anal. Calcd. for $C_{23}H_{18}N_6S$ (410.49): C, 67.30; H, 4.42; N, 20.47; S, 7.81. Found: C, 67.55; H, 4.53; N, 20.12; S, 7.68.

***2-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)-3-phenylazoimidazo[1,2-a]pyridine (5).*** This compound was obtained as violet crystals (DMF/EtOH), mp 223–26°C, yield (55%); $^1$H-NMR $(CD_3)_2SO$: δ = 2.46 (s, 3H, 4-methylthiazole), 6.85 (t, 1H, pyridine H-5), 7.15 (d, 1H, pyridine H-3), 7.37 (t, 1H, pyridine H-4), 7.62–7.84 (m, 10 H, ArH), 8.78 (d, 1H, pyridine H-6). $^{13}$C-NMR: δ = 14.85 ($CH_3$), 111.21, 155.71, 160.32 (thiazole), 111.62, 121.45, 144.10 (imidazole), 122.10, 125.00, 126.58, 128.84, 130.54, 131.10, 136.24, 154.44 (aromatic carbon), 112.12, 117.89, 123.77, 126.28 (pyridine). Anal. Calcd. for $C_{23}H_{17}N_5S$ (395.48): C, 69.85; H, 4.33; N, 17.71; S, 8.11. Found: C, 69.70; H, 4.09; N, 17.55; S, 8.00.

***3-Phenylazo-2-(4-methyl-2-phenylthiazol-5-yl)-6-phenyl-5H-imidazo[1,2-b]pyrazole (6a).*** This compound was obtained as red crystals (DMF/EtOH), mp > 300°C, yield (89%); IR ($cm^{-1}$): 3424 (NH), 1633 (C=N), 1607 (C=C). $^1$H-NMR: δ = 2.46 (s, 3H, 4-methylthiazole), 6.19 (s, 1H, pyrazole H-4), 7.36–7.91 (m, 16 H, ArH and NH proton). Anal. Calcd. for $C_{27}H_{20}N_6S$ (460.55): C, 70.41; H, 4.38; N, 18.25; S, 6.96. Found: C, 70.40; H, 4.02; N, 18.41; S, 7.02.

***2-(4-Methyl-2-phenyl-thiazol-5-yl)-5-methyl-6-phenyl-3-phenylazo-5H-imidazo[1,2-b]pyrazole (6b).*** This compound was obtained as red crystals (DMF/EtOH), mp > 300°C, yield (67%); $^1$H-NMR: δ = 2.46 (s, 3H, 4-methylthiazole), 2.50 (s, 3H, 4-$CH_3C_6H_4$), 6.15 (s, 1H, pyrazole H-4), 7.36–8.10 (m, 14H, ArH), 8.42 (s, br., 1H, NH). $^{13}$C-NMR: δ = 14.45 ($CH_3$), 21.21 ($CH_3$), 83.89, 142.67, 159.14 (pyrazole), 108.00, 122.45 (imidazole, 114.23, 160.45, 163.57 (thiazole), 122.12, 122.57, 128.42, 129.23, 130.12, 134.45, 139.57, 153.38 (aromatic carbons). Anal. Calcd. for $C_{28}H_{22}N_6S$ (474.58): C, 70.86; H, 4.67; N, 17.71; S, 6.76. Found: C, 71.14; H, 4.73; N, 17.66; S, 6.66.

***6-(4-Methyl-2-phenyl-thiazol-5-yl)-5-phenylazo3-phenylimidazo[2,1-b]thiazole (7).*** This compound was obtained as red crystals (AcOH), mp > 300°C, yield (80%); $^1$H-NMR: δ = 2.46 (s, 3H, 4-methylthiazole), 7.24 (s, 1H, thiazole H-5), 7.36–7.97 (m, 15H, ArH), $^{13}$C-NMR: δ = 13.57 ($CH_3$), 14.57 ($CH_3$), 103.25, 111.23, 126.32, 158.74, 159.62, 145.43 (thiazole rings), 114.25, 120.85 (imidazole), 122.12, 125.42, 127.61, 128.08, 130.24, 131.75, 135.28, 155.35 (aromatic carbons). Anal. Calcd. for $C_{27}H_{19}N_5S_2$ (477.60): C, 67.90; H, 4.01; N, 14.66; S, 13.43. Found: C, 67.80; H, 4.96; N, 14.30; S, 13.07.

***3-(4-Methyl-2-phenylthiazol-5-yl)-2-phenylazo-(1H)-quinoxaline (9).*** This compound was obtained as orange crystals (EtOH), mp 240–42°C, yield (80%); IR ($cm^{-1}$): 3399 (NH), 3047, 2964 (CH), 1632 (C=N), 1605 (C=C). $^1$H-NMR: δ = 2.57 (s, 3H, 4-methylthiazole), 7.08–7.89 (m, 14H, ArH), 8.92 (s, br., 1H, NH), 9.22 (s, br., 1H, NH). Anal. Calcd. for $C_{24}H_{19}N_5S$ (409.51): C, 70.93; H, 4.68; N, 17.10; S, 7.83. Found: C, 70.50; H, 4.56; N, 17.39; S, 7.70.

***3-(4-Methyl-2-phenyl-thiazol-5-yl)-2-phenylhydrazinobenzo[1,4]thiazine (11).*** This compound was obtained as shiny green crystals (DMF/EtOH), mp 280–82°C, yield (89%); IR: 3422 (NH), 3058, 2982 (CH), 1655 (C=N), 1602 (C=C). $^1$H-NMR: δ = 2.62 (s, 3H, 4-methylthiazole), 7.18–8.29 (m, 14H, ArH), 13.09 (s, br., 1H, NH). MS: 426 (4.98%), 384 (11%), 360 (16%), 354 (59%), 319 (17.8%), 302 (38%), 372 (18%), 270 (100%), 226 (15%), 212 (22%), 196 (12%), 148 (54.9%), 122 (27%), 94 (23%), 63 (20%). Anal. Calcd. for $C_{24}H_{18}N_4S_2$ (426.56): C, 67.58; H, 4.25; N, 13.13; S, 15.03. Found: C, 67.90; H, 4.55; N, 13.33; S, 15.21.

***3-(4-Methyl-2-phenyl-thiazol-5-yl)-2-phenylhydrazinobenzo[1,4]oxazine (12).*** This compound was obtained as yellow crystals (DMF/EtOH), mp 202–204°C, yield (72%); IR ($cm^{-1}$): 3422 (NH), 2924 (CH), 1634 (C=N), 1602 (C=C). $^1$H-NMR: δ = 2.59 (s, 3H, 4-methylthiazole), 7.18–8.29 (m, 14H, ArH), 9.32 (s, br., 1H, NH). $^{13}$C-NMR: δ = 15.57 ($CH_3$), 112.32, 158.85, 162.10 (thiazole), 129.23, 139.53, 144.71, 150.82 (oxazine), 115.24, 118.35, 119.85, 127.45, 128.68, 129.28, 130.30, 130.45, 13.90, 133.72, 143.68 (aromatic carbons). Anal. Calcd. for $C_{24}H_{18}N_4OS$ (410.49): C, 70.22; H, 4.42; N, 13.56; S, 7.81. Found: C, 70.44; H, 4.56; N, 13.72; S, 7.65.

***3-(4-Methyl-2-phenyl-thiazol-5-yl)-2-phenylhydrazino-1H-pyrido[2,3-b]pyrazine (13).*** This compound was obtained as red crystals (DMF/EtOH), mp > 300°C, yield (70%); IR ($cm^{-1}$): 3382 (NH), 3060, 2969 (CH), 1632 (C=N), 1595 (C=C). $^1$H-NMR: δ = 2.56 (s, 3H, 4-methylthiazole), 7.18–8.35 (m, 13H, ArH), 10.51 (s, br., 2H, NH). MS: 409 (4.9%), 308 (22.8%), 228 (10.5%), 213 (22.4%), 205 (17.8%), 183 (16%), 182 (100%), 179 (14.6%), 153 (16.5%), 140 (77%), 125 (14%), 124 (20%). Anal. Calcd. for $C_{23}H_{18}N_6S$ (410.49): C, 67.30; H, 4.42; N, 20.47; S, 7.81. Found: C, 67.11; H, 4.10; N, 120.12; S, 7.55.

**General procedure for the synthesis of 4 and 8.** A mixture of 2-bromo-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanone [20] (1.48 g, 5 mmol) and 2-aminopyrimidine (0.48 g, 6 mmol) or 2-amino-4-phenylthiazole (0.56 g, 6 mmol) in ethanol (25 mL) was heated under reflux for 3–4 h. The resulting solid was neutralized with sodium bicarbonate solution, collected by filtration, and then was crystallized from ethanol to give **4** and **8**, respectively.

***2-(4-Methyl-2-phenylthiazol-5-yl)imidazo[1,2-a]pyrimidine (4).*** This compound was obtained as yellow crystals (EtOH), mp 223–26°C, yield (62%); IR ($cm^{-1}$): 3060.3, 2928 (CH), 1655 (C=N), 1599 (C=C), 1369 ($CH_3$). $^1$H-NMR: δ = 2.46 (s, 3H, 4-methylthiazole), 6.91 (d, 1H, pyrimidine H-5), 7.62 (t, 2H, ArH), 7.68 (t, 1H, ArH), 7.76 (d, 2H, ArH), 7.91 (s, 1H, imidazole H-4), 8.50 (d, 1H, pyrimidine H-6), 8.57 (d, 1H, pyrimidine H-4). $^{13}$C-NMR: δ = 13.85 ($CH_3$), 114.21, 150.71, 160.82 (thiazole), 111.62, 124.45, 149.10 (imidazole), 125.00, 126.58, 131.10, 136.24 (phenyl), 110.12, 135.77, 151.28 (pyrimidine). MS: 293 (8.8%), 292 (30%), 202 (19.9%), 203 (10%), 188 (22.9), 144 (15.9), 92 (7.1%), 66 (10.6%). Anal. Calcd. for $C_{16}H_{12}N_4S$ (292.36): C, 65.73; H, 4.14; N, 19.16; S, 10.97. Found: C, 65.90; H, 4.33; N, 19.02; S, 10.70.

***2-(4-Methyl-2-phenylthiazol-5-yl)-6-phenyl-1H-imidazo[1,2-b]pyrazole (8).*** This compound was obtained as orange crystals (DMF), mp 244–47°C, yield (60%); $^1$H-NMR $(CD_3)_2SO$: δ = 2.46 (s, 3H, 4-methylthiazole), 6.15 (s, 1H, pyrazole H-4), 7.40 (s, 1H, imidazole H-4), 7.45–7.92 (m, 10H, ArH), 8.42 (s, br., 1H, NH). Anal. Calcd. for $C_{21}H_{16}N_4S$ (356.44): C, 70.67; H, 4.52; N, 15.72; S, 9.00. Found: C, 70.55; H, 4.31; N, 15.50; S, 9.07.

***Alternative synthesis of 3a, b and 6a.*** A solution of the appropriate arenediazonium chloride (10 mmol) was added dropwise to a stirred solution of the appropriate reactant (**4**, **8**) (10 mmol) in ethanol (50 mL) containing sodium acetate trihydrate (1.3g, 10 mmol) at 0–5°C. The reaction mixture was stirred for 3 h at 0°C, the resulting solid was collected and crystallized from ethanol to give **3**(**a**, **b**) and **6a**, respectively.

***3-(4-Methyl-2-phenyl-thiazol-5-yl)-2-phenylazoquinoxaline (10).*** A mixture of compound **9** (0.5 g) in ethanol (20 mL) and hydrogen peroxide (3 mL, 30%) was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, the resulting solid was collected and recrystallized to give **10**. This compound was obtained as red crystals (DMF/EtOH), mp > 300°C, yield (78%); $^1$H-NMR $(CD_3)_2SO$: δ = 2.46 (s, 3H, 4-methylthiazole), 7.26–8.13 (m, 14H, ArH). $^{13}$C-NMR: δ = 15.57 ($CH_3$), 109.58, 162.11, 167.00 (thiazole), 138.32, 139.54, 146.61, 145.45 (pyrazine), 124.12, 125.54, 126.28, 129.23, 129.65, 129.89, 132.52, 133.21, 154.94 (phenyl groups). Anal. Calcd. for $C_{24}H_{117}N_5S$ (407.49): C, 70.74; H, 4.21; N, 17.19; S, 7.87. Found: C, 70.90; H, 4.31; N, 17.33; S, 7.60.

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## REFERENCES AND NOTES

[1] Abdelhamid, A. O.; Afif, M. A. Phosphorus Sulfur Silicon Relat Elem, Part 61 2008, 183, 2703.

[2] Rateb, N. M.; Abdelhamid, A. O. Heteroat Chem 2004, 15, 107.

[3] Abdelhamid, A. O.; Sayed, A. R.; Zaki, Y. H. Phosphorus Sulfur Silicon Relat Elem 2007, 182, 1447.

[4] Abdelhamid, A. O.; Ismail, Z. H.; Abdel-Aziem, A. J Chem Res 2007, 609.

[5] Shawali, A. S.; Edrees, M. M. Arkivoc 2006, 9, 292.

[6] Shawali, A. S.; Mosselhi, M. A. N. J Heterocycl Chem 2003, 40, 725.

[7] Abdelhamid, A. O.; El-Ghandour, A. H.; Hussein, A. M.; Zaki, Y. H. J Sulfur Chem 2004, 25, 329.

[8] Abdelhamid, A. O.; Alkhodshi, M. A. M. J Heterocycl Chem 2005, 42, 527.

[9] Abdelhamid, A. O.; Al-Atoom, A. A. Synth Commun 2006, 36, 97.

[10] Nussbaumer, P.; Petranyi, G., Stutz, A. J Med Chem 1991, 34, 65.

[11] Broom, N. J. P.; Elder, J. S.; Hannan, P. C. T.; Pons, J. E.; O'Hanlon, P. J.; Walker, G.; Wilson, J.; Woodall, P. J. J Antibiot 1995, 48, 1336.

[12] Nakanishi, M.; Imamura, H.; Maruyama, Y.; Hoshino, H. J Pharm Soc Jpn 1970, 90, 272.

[13] Briel, D. Pharmazie 1955, 50, 675.

[14] Yamaguchi, M.; Maruyama, N.; Koga, T.; Kamei, K.; Akima, M.; Kuroki, M.; Hamana, M.; Ohi, N. Chem Pharm Bull 1995, 43, 236.

[15] Boyd, R. E.; Press, J. P.; Rasmussen, C. R.; Raffa, R. B.; Codd, E. E.; Connelly, C. D.; Martinez, Q. S.; Li, R. P.; Lewis, M. A.; Almond, B. J. J Med Chem 2001, 44, 863.

[16] Shawali, A. S.; Harb, N. M. S.; Badahdah, K. O. J Heterocycl Chem 1985, 22, 1397.

[17] Shawali, A. S.; Mosselhi, M. A. M.; Farghaly, T. A. J Chem Res 2007, 479.

[18] El-Helby, A. A. J Pharm Sci 2001, 27, 375.

[19] Abdelhamid, A. O.; Abed, N. M.; Al-Fayez, F. M. Phosphorus Sulfur Silicon Relat Elem 2000, 156, 35.

[20] Prakash, O.; Tyagi, D. S.; Sangal, D. S. J Indian Chem Soc 1981, 57, 1136.

# A Novel Synthetic Route to Synthesize 2,4,8, 10-Tetraoxaspiro[5.5]-Undecane from Formaldehyde under Hydrothermal Conditions

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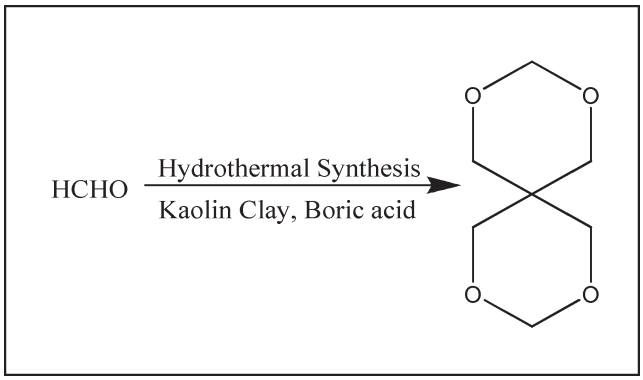


We report here the hydrothermal synthesis of 2,4,8,10-tetraoxaspiro[5.5]-undecane by using formaldehyde, the only precursor, in the presence of kaolin clay and boric acid. The reported method is the simplest one to synthesize the aforementioned product.

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## INTRODUCTION

The spectacular nature of the hydrothermal systems provides a great deal of new synthetic routes in innovative, unconventional, as well as safest ways. This is exemplified by a number of novel synthetic discoveries in the realm of hydrothermal synthesis [1,2]. Also, a novel method for the translation of sodium hydrogen carbonate into phenol depicts that hydrothermal reaction routes have diverse applications [2]. Not only this but the hydrothermal synthesis also provides intriguing clues to the origin of life [1,3]. Furthermore, such kind of synthetic routes occupy a special place because of their pollution free nature. Also, the reactions take place safely within closed systems and do not need expensive materials as used in normal organic synthesis. Here, we present a simplest route to synthesize 2,4,8,10-tetraoxaspiro[5.5]-undecane **(1)** under the simplest hydrothermal conditions and demonstrate the versatility of the hydrothermal techniques.

Compound **1** is a very important synthetic precursor of many organic compounds. It has multifarious applications, from simple organic synthesis to medicines. One derivative, like 3,9-bis(2-hydrazidoethyl)-**1**, is used as a curing agent to produce a sufficient amount of cured epoxy resin [4]. Many derivatives of **1** are used as stabilizers for polyolefins and other polymers [5]. Similarly the binary blends of the acrylate rubber and chlorinated polypropylene give dynamic mechanical properties with 3,9-bis[1,1-dimethyl-2{β-(3-*tert*-butyl-4-hydroxy-5-methylphenyl)-propionyloxy}ethyl]-1 [6] and 3,9-di-2-furyl-1 type compounds serve as important intermediates in the synthesis of pesticides [7]. Moreover, its derivatives serve as prominent parts of many patents, *i.e*., 3,9-bis[2-{3-(3-*tert*-butyl-4-hydroxy-5-methylphenyl) propionyloxy}-1,1-dimethylethyl]-1 is used in the synthesis of high quality antioxidants for many polymers [8,9], 3,9-bis [1,1-dimethyl-2-{β-(3-*tert*-butyl-4-hydroxy-5-methylphenyl)propionyl-oxy}ethyl]-1 serves as an oxidant in the synthesis of molding materials with excellent properties [10], while its many derivatives serve as essential components to bestow excellent chemical makeup for decorating ceramics [11]. Its derivatives enjoy a special place in the field of medicine and surgery, *e.g*., -1-3,9-dipropamine(11′) is used in the synthesis of anti-inflammatory drug derivatives like pyrimidine and bispyrimidine [12] derivatives, 3,9-diethylidene-1 has potential applications in dental surgery [13], 3,9-dimethylene-1, is used in the synthesis of biodegradable polymers for the controlled release of paracetamol [14]. 1 has been synthesized in many ways, but the most remarkable

synthetic routes are achieved by the transacetalization of triols [15]. Here, we report the hydrothermal synthesis of **1** by using formaldehyde as the only starting reagent, by using a mixture of boric acid and kaolin as catalyst, hence it presents the simplest route to synthesize the intended product.

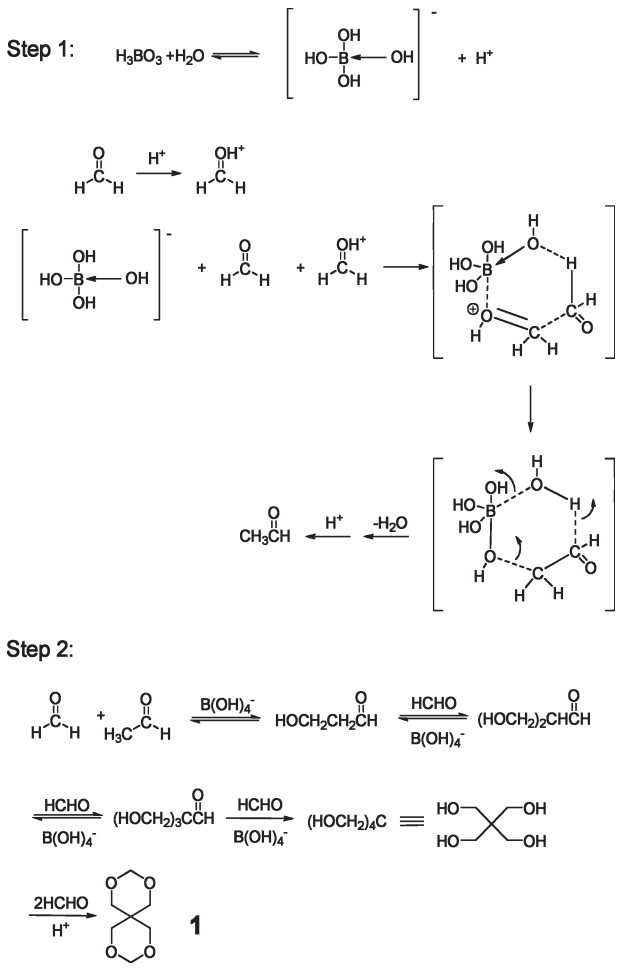
## RESULTS AND DISCUSSION

Compound **1** was successfully synthesized. The yield of the reaction was 0.4%. The proposed mechanism for the reaction is described in the Scheme 1.

In the first step (Step 1) of Scheme 1, boric acid hydrolyzes and reacts with formaldehyde which results in the protonation of formaldehyde and another molecule of formaldehyde to form acetaldehyde through a cyclic transition state. In the second step (Step2), this acetaldehyde molecule further undergoes a series of mechanistic steps, to form the product.

Many parameters influence this reaction pathway, *i.e.*, temperature, pH, presence of catalysts. We have found that with any change in anyone of the above described parameters, the reaction fails to occur. Moreover, all of these parameters facilitate the synthesis of **1**. We were interested to know the effect of temperature on our pathway. Hence, we performed the reaction below 100°C. Most interestingly, we found that temperature window of 80–90°C gives a series of small open chained oxygenated products like carbon dioxide, formic acid *etc*. Also, temperature exceeding 100°C, causes degradation and decomposition of the product, implying that the above described method to synthesize **1** is only feasible at 100°C. The presence of catalyst mixture (boric acid and kaolin) is also essential, which is mainly responsible for the condensation, cyclization and stabilization of the formaldehyde units. Similarly, the reaction time and pH are also critical factors for the reaction.

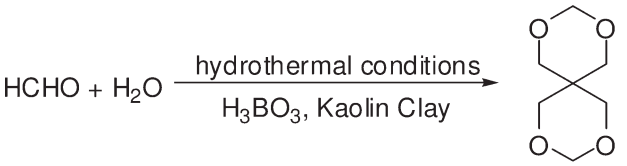
**Scheme 1.** Mechanism of reaction.




## EXPERIMENTAL

In our synthesis, 2 mL formaldehyde and 12 mL doubly distilled water [16] were added into each steel alloy (Fe-Cr-Ni, alloy GB1220-92) autoclaves with a filling capacity of 90% and recrystallized boric acid and kaolin clay (0.1 g each) were also added into the reaction mixture of each of the autoclaves. The final pH of the reaction mixture was nearly 3. The autoclaves were then sealed tightly and placed in the ovens at a temperature range from 100–200°C for 3 days. However, the reaction was successful at 100°C. After 3 days the autoclaves were taken out and analyzed.

The reaction can be written as follows:




## CHARACTERIZATION BY GC-MS

The product was identified and characterized by the GC-MS (Thermo Co.). Figure 1 shows the GC-MS of product as well as that of standard.

## CONCLUSIONS

As discussed above, in our synthesis, the presence of boric acid and kaolin was essential. Our experiment clearly proves that hydrothermal synthesis provides unique reaction pathways, which in other ways are very difficult to obtain [1,2]. Moreover, in similar ways, many other polymerization reactions can be obtained by utilizing simple precursors [2]. Also, we synthesized our product without using any harmful or expensive reagent.

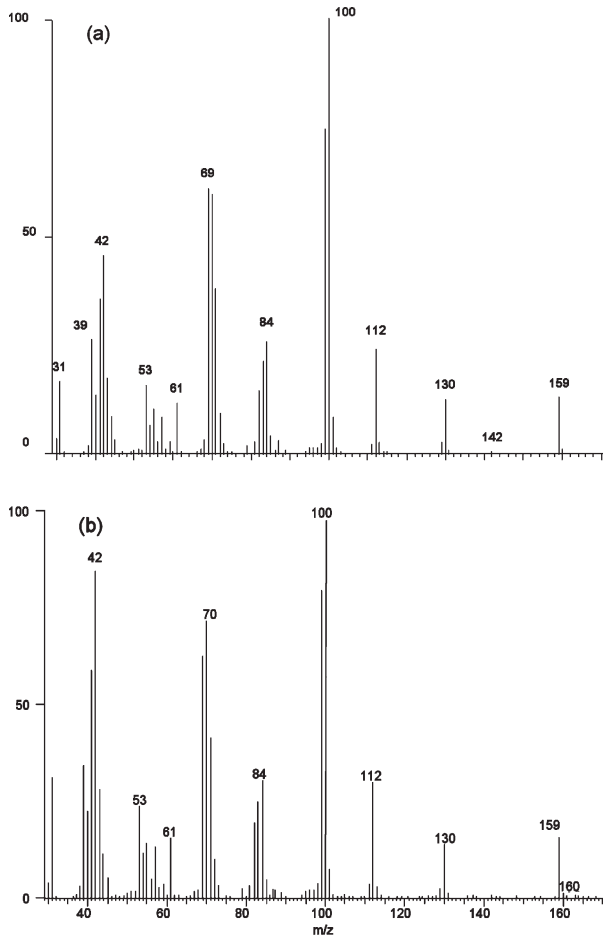



**Figure 1.** (a) Shows the GCMS of the standard (b) shows the GCMS of the product.

As we know that the progress of today's society depends on the synthesis and development of the advanced materials, which need consumption of energy as well as utilization of very toxic solvents and other chemicals. This all can play havoc with the environment and life. In addition, it is well known that our earth is a closed system with limited resources for use. This provokes an urge of recycling the materials in safest ways, *i.e*., to ensure maximum recycling at the expense of minimum energy.

Finally, our synthetic route to synthesize 1 clearly proves that hydrothermal routes of synthesis enjoy an important position in the field of synthetic chemistry and a very likely candidate for recycling of waste and conversion of industrial waste (like formaldehyde, carbon monoxide, carbon dioxide, *etc*.) into useful products and the most likely candidate to promote ''Green Chemistry''.

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## REFERENCES AND NOTES

[1] Feng, S.; Xu, R. Acc Chem Res 2001, 34, 239.

[2] Tian, G.; Yuan, H.; Mu, Y.; He, C.; Feng, S. Org Lett 2007, 9, 2019.

[3] Feng, S.; Tian, G.; He, C.; Yuan, H.; Mu, Y.; Wang, Y.; Wang, L. J Mater Sci 2008, 43, 2418.

[4] Yukuta, T.; Ohashi, T. U.S. Pat. 3,968,084 (1976).

[5] Fruhstorfer, W.; Nameny, I.; Baumer, W.; Dennler, B. U.S. Pat. 3,621,034 (1971).

[6] Wu, C.; Otani, Y.; Namiki, N.; Emi, H.; Nitta, K.-h. Polym J 2001, 33, 322.

[7] Lin, J.; Jian, F.-F. Acta Cryst 2008, 64, 2130.

[8] Kimura, K. U.S. Pat. 20,070,129,280 (2007).

[9] Ikuo, T.; Hirotaka, I. U.S. Pat. 20,050,233,142 (2005).

[10] Kashio, M. U.S. Pat. 20,090,005,530 (2009).

[11] Tang, R. H.; Zhang, Y.; Morales, R. W.; Wang, A. E.; Hart, D. P. U.S. Pat. 20,060,235,111 (2006).

[12] Sham, M. S.; Shubhi, J.; Monica, D.; Rakesh, S.; Ram, R. Bioorg Med Chem 2007, 15, 3334.

[13] Schwach-Abdellaoui, K.; Loup, P. J.; Vivien-Castioni, N.; Mombelli, A.; Baehni, P.; Barr, J.; Heller, J.; Gurny, R. AAPS Pharm Sci 2002, 4, 4.

[14] Qi, M.; Li, X.; Yang, Y.; Zhou, S. Eur J Pharm Biopharm 2008, 70, 445.

[15] Gras, J.-L.; Nouguier, R.; Mchich, M. Tetrahedron Lett 1987, 28, 6601.

[16] Before further proceeding, GC-MS of the HCHO was taken and it indicated no organic contamination. Water was also doubly distilled and boric acid was recrystallized twice. Kaolin clay was also free of any organic contamination.

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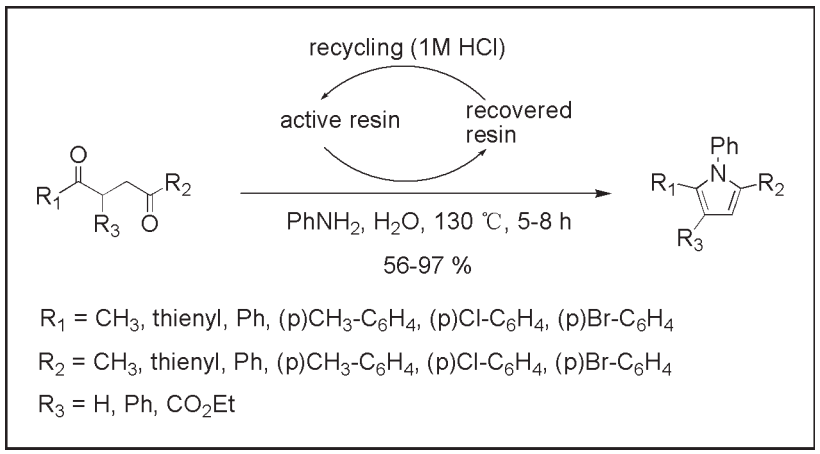


Cationic exchange resin has been utilized for the first time as a novel and recyclable heterogeneous catalyst for the synthesis of *N*-substituted pyrroles from variety of 1,4-diketones and aniline. This simple synthesis has been accomplished with excellent yields. The recovered catalyst can be reused for subsequent runs with only a gradual decrease in activity.

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## INTRODUCTION

Pyrrole rings have great importance in organic chemistry as they can be found in several natural products [1], organic materials [2], and bioactive molecules [3]. Especially, substituted pyrroles present antibacterial [4], antiviral [5], anti-inflammatory, and antioxidant activities [6]. One of the most important approaches to pyrrole synthesis is the Paal–Knorr reaction, which involves the reaction of 1,4-dicarbonyl compounds and their masked equivalents with primary amines. Generally, the most used conditions include *p*-TsOH in toluene or benzene [7], AcOH/methanol [8], $TiCl_4$ in toluene [5a], $Ti(OPr)_4$ in benzene [9], $Bi(OTf)_3$/[bmim]$BF_4$ [10], $Bi(NO_3)_3$ in $CH_2Cl_2$ [11]. However, some of these methods often suffer from certain drawbacks, such as hazardous organic solvents, metals, and high costs. As the increase environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents and metals. Therefore, the development of green and facile methods for the synthesis of pyrroles is desirable. Besides, on the other hand, reactions in water have recently attracted significant attention because water is a cheap, safe, and nontoxic solvent [12]. In addition, if aqueous reactions can be efficiently mediated by heterogeneous catalysts that can be recycled and reused, the result will be nearly ideal processes in terms of both greeness and simplicity [13]. Therefore, we wish to report a high-yielding and straightforward synthesis of *N*-substituted pyrroles using water as solvent and a cationic exchange resin as a recyclable heterogeneous catalyst.

## RESULTS AND DISCUSSION

In our initial investigation, the condensation of aromatic 1,4-dione (**5a**) with two equivalents of aniline was carried out in 1 *M* HCl aqueous at reflux for 24 h. To our surprise, it gave furan **5d** in 100% yield instead of

**Scheme 1.** Condensation of **5a** with 2 equivalents of aniline under different reaction conditions.

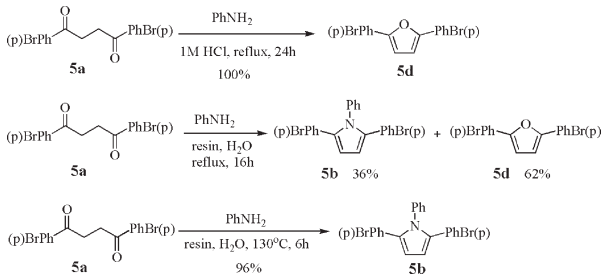
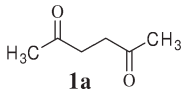
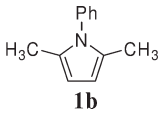
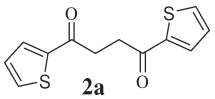
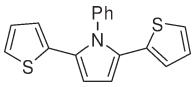
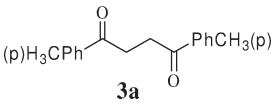
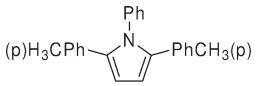
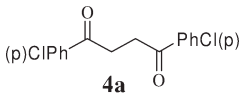
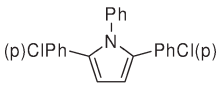
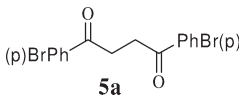
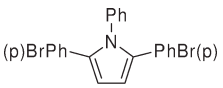
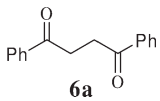
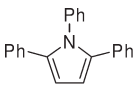
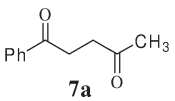
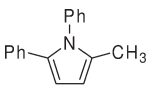
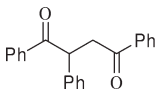
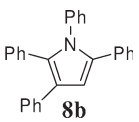
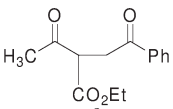
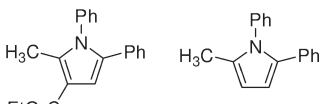


**Table 1**

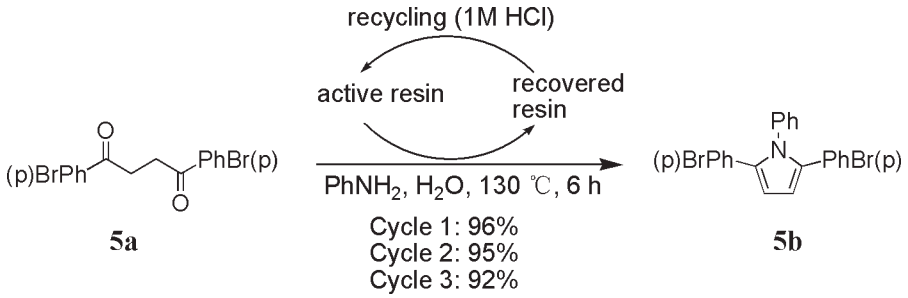
Condensation of 1,4-diketones and aniline into pyrroles using cationic exchange resin in water.[a]

| Entry | 1,4-Diketone | Pyrrole | Time (h) | Yield (%)[b] | Ref. |
|---|---|---|---|---|---|
| 1 |  **1a** |  **1b** | 5 | 85 | [14] |
| 2 |  **2a** |  **2b** | 8 | 95 | [15] |
| 3 |  **3a** |  **3b** | 6 | 96 | [16] |
| 4 |  **4a** |  **4b** | 6 | 95 | [16] |
| 5 |  **5a** |  **5b** | 6 | 96 | [16] |
| 6 |  **6a** |  **6b** | 6 | 94 | [16] |
| 7 |  **7a** |  **7b** | 5 | 87 | [14] |
| 8 |  **8a** |  **8b** | 6 | 97 | [17] |
| 9 |  **9a** |  **9b** **7b** | 6 | **9b**: 56, **7b**: 34 | [14,18] |

[a] For a typical experimental procedure see Ref. [19].
[b] Refers to yield of isolated product after flash chromatography.

pyrrole **5b** (Scheme 1). Then, the reaction was performed in acidic Dowex 50 W × 8-200 (1.7 meq $mL^{-1}$) cationic exchange resin in water at reflux for 16 h, which provided pyrrole **5b** in 36% yield accompanied by furan **5d** in 62% yield. It suggested that the presence of cationic exchange resin can facilitate the pyrrole condensation, while 1 *M* HCl aqueous only catalyzed the formation of furan. To improve the reaction rate and to observe the effect of temperature on the condensation, the reaction was carried out in a sealed tube at increased temperature. Higher temperatures than 140°C led to thermal decomposition of the resin. We therefore set the reaction at

**Scheme 2.** Recovery of the cationic exchange resin for recycling and use in subsequent Paal–Knorr pyrrole synthesis.




130°C; the starting material **5a** was consumed in 6 h. We pleasurably found that the reaction exclusively provided the *N*-substituted pyrrole **5b** in excellent yield of 96%. It seems that the higher temperature favors the formation of pyrrole in the presence of resin in water.

Encouraged by this new finding, we further investigated the reaction by using wide range of diketone compounds. The condensation of substituted 1,4-diketones and aniline proceeded smoothly and gave the corresponding pyrroles in good to excellent yields in water in the presence of cationic exchange resin (Table 1). The reactions were carried out in sealed tubes at 130°C. In this manner, the reactions can be run as a batch in sealed tubes within an oven without stirring. The reactions were complete in 5–8 h, and the two equivalents of amine were used to afford a valuable increase of the yields. To assess the generality of the method, variety of 1,4-dicarbonyl compounds including aromatic and aliphatic, di- and tri-substituted 1,4-dicarbonyl compounds were subjected to the condensation with aniline to give the corresponding pyrrole derivatives. When the 1,4-diphenyl-1,4-diones (**3–6a**, entries 3–6) were used, The excellent yields of 94–96% were obtained. Triphenyl 1,4-dione (**8a**, entry 8) gave the best yield of 97%. Nevertheless, methyl substituted 1,4-diones (**1a** and **7a**, entries 1 and 7) provided the products in slightly decreased yields (85 and 87%, respectively). Although 1,4-di(thienyl)butane-1,4-dione (**2a**, entry 2) required longer reaction time, the product was received in excellent yield of 95%. Interestingly, when ethyl 2-acetyl-4-oxo-4-phenylbutanoate (**9a**, entry 9) was submitted to the reaction conditions described earlier, the corresponding ester substituted pyrrole **9b** was obtain in 56% yield, accompanied by decarboxylated product pyrrole **7b** in 34% yield.

Finally, to verify that the solid catalyst could be recycled, the resin was recovered from the condensation between **5a** and aniline by filtration, reactivated it by treatment with a small amount of 1 *M* HCl [13] and used it in subsequent cyclizations. The reaction was performed three times using the same resin, and only a small decrease in the isolated yield of **5b** was observed. (Scheme 2).

## CONCLUSION

In summary, a new catalytic protocol to synthesize pyrroles by Paal–Knorr condensation in water has been developed. Compared to previous reported methods, the present procedure avoids the use of metals and organic solvents, and instead employs cationic exchange resin as a cheap and readily available heterogeneous catalyst that is easily removed from the product mixture, which can be recycled and reused. This method has great potential for future application.

**Acknowledgments.** Financial support from 2007 Select Project in Scientific and Technological Activities for Returned Scholars of The State Personnel Ministry and the High-Tech Training Fund of Southwest University (XSGX0601) is gratefully acknowledged.

### REFERENCES AND NOTES

[1] Lindel, T.; Breckle, G.; Hochgürtel, M.; Volk, C.; Grube, A.; Köck, M. Tetrahedron Lett 2004, 45, 8149.

[2] (a) Novák, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. Chem Rev 1997, 97, 207; (b) Higgins, S. J. Chem Soc Rev 1997, 26, 247.

[3] Snyder, L. B.; Meng, Z.; Mate, R.; D'Andrea, S. V.; Marinier, A.; Quesnelle, C. A.; Gill, P.; DenBleyker, K. L.; Fung-Tomc, J. C.; Frosco, M. B.; Martel, A.; Barrett, J. F.; Bronson, J. J. Bioorg Med Chem Lett 2004, 14, 4735.

[4] (a) Dannhardt, G.; Kiefer, W.; Krämer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. Eur J Med Chem 2000, 35, 499; (b) Ragno, R.; Marshall, G. R.; Santo, R. D.; Costi, R.; Massa, S.; Rompei, R.; Artico, M. Bioorg Med Chem 2000, 8, 1423; (c) Unverferth, K.; Engel, J.; Höfgen, N.; Rostock, A.; Günther, R.; Lankau, H. J.; Menzer, M.; Rolfs, A.; Liebscher, J.; Müller, B.; Hofmann, H. J. J Med Chem 1998, 41, 63.

[5] (a) Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Forli, S.; Rovini, M.; Cappelli, A.; Manetti, F.; Botta, M.; Sautebin, L.; Rossi, A.; Pergola, C.; Ghelardini, C.; Vivoli, E.; Makovec, F.; Anzellotti, P.; Patrignani, P.; Anzini, M. J Med Chem 2007, 50, 5403; (b) Harrak, Y.; Rosell, G.; Daidone, G.; Plescia, S.; Schillaci, D.; Pujol, M. D. Bioorg Med Chem 2007, 15, 4876.

[6] Lehuédé, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfonf, J.-M. Eur J Med Chem 1999, 34, 991.

[7] Cihanera, A.; Algıb, F. Electrochim Acta 2008, 54, 665.

[8] Fu, L.-F.; Gribble, G. W. Tetrahedron Lett 2008, 49, 3545.

[9] Yu, S.-X.; Quesne, P. W. L. Tetrahedron Lett 1995, 36, 6205.

[10] Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K. Tetrahedron Lett 2004, 45, 5873.

[11] Banik, B. K.; Banik, I.; Renteriaa, M.; Dasgupta, S. K. Tetrahedron Lett 2005, 46, 2643.

[12] (a) Li, C. J. Chem Rev 2005, 105, 3095; (b) Lindstrom, U. M. Chem Rev 2002, 102, 2751.

[13] Aplander, K.; Hidestal, O.; Katebzadeh; K.; Lindstrom, U. M. Green Chem 2006, 8, 22.

[14] Surya, K. D. Synth Commun 2008, 38, 2768.

[15] Just, P. E.; Chane-Ching, K. I.; Lacaze, P. C. Tetrahedron 2002, 58, 3467.

[16] Periasamy, M.; Srinivas, G.; Bharathi, P. J Org Chem 1999, 64, 4204.

[17] Anita, E. M.; Ashwin, R. B.; Andrea M. Z.; Karl A. S. J Org Chem 2006, 71, 5715.

[18] Girolamo, C.; Gaetano D.; Anna, M. A.; Giuseppe, P.; Enrico A. Heterocycles 1986, 24, 3403.

[19] Typical experimental procedure for the synthesis of N-substituted pyrroles. To a mixture of 1,4-diphenylbutane-1,4-dione (**6a**) (133 mg, 0.56 mmol) in $H_2O$ (3 mL) was added cationic exchange resin (1.63 g, Dowex 50 W $\times$ 8-200) and aniline (0.12 mL, 1.12 mmol). The reaction mixture was heated at 130°C in a sealed tube for 6 h within an oven without stirring. After cooling to room temperature, the catalyst was filtered off and washed with diethyl ether. The filtrate was extracted with diethyl ether. The combined extracts were washed with water, brine, dried ($Na_2SO_4$), and filtered. The solvents were removed and purified by flash chromatography (petroleum ether/$CH_2Cl_2$ 2:1) to give compound **6b** (155 mg, 94% yield), identical to that previously reported [16].

# Biological Importance of the Indole Nucleus in Recent Years: A Comprehensive Review



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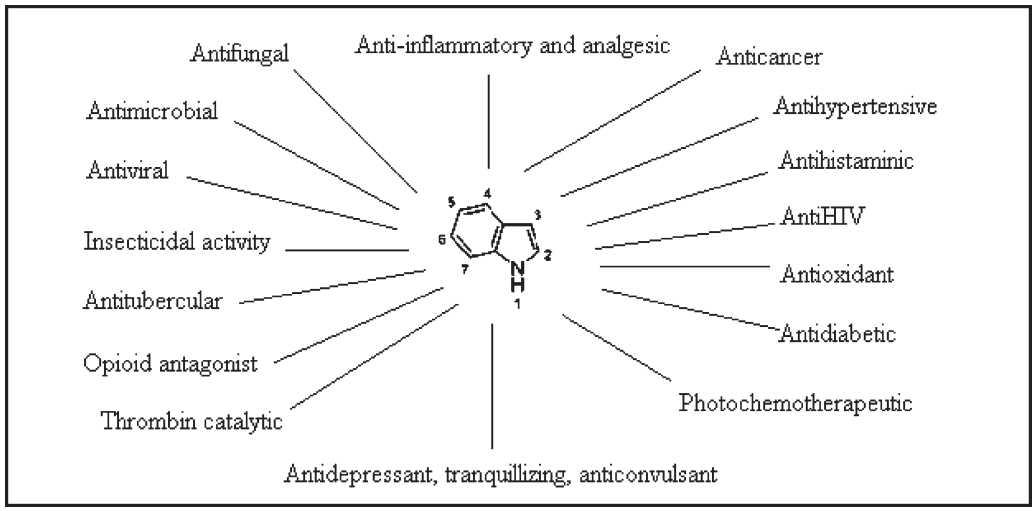


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## INTRODUCTION

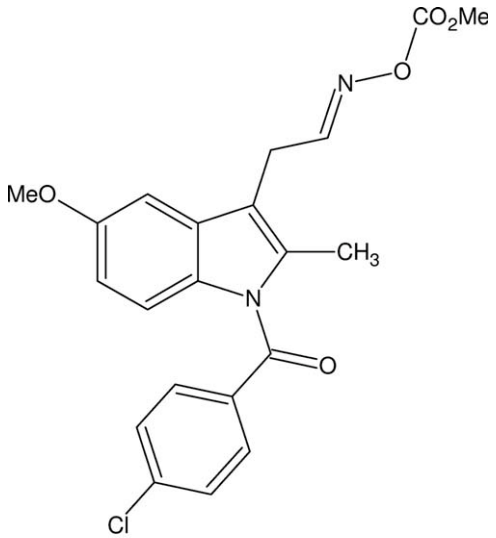
Heterocyclic compounds are those cyclic compounds in which one or more of the ring carbons are replaced by another atom. The non-carbon atoms in such rings are referred to as ''heteroatoms.'' Such bicyclic heterocyclic compounds containing pyrrole ring with benzene ring fused to α,β-position are known as Indoles. Indole has a benzene ring and pyrrole ring sharing one double bond. It is a heterocyclic system with 10 electrons from four double bonds and the lone pair from the nitrogen atom.

Indole is an important heterocyclic system because it is built into proteins in the form of amino acid tryptophan, because it is the basis of drugs like indomethacin and because it provides the skeleton of indole alkaloids—biologically active compounds from plants including strychnine and LSD.

The incorporation of indole nucleus, a biologically accepted pharmacophore in medicinal compounds (Table 1), has made it versatile heterocyclic possessing wide spectrum of biological activities (Table 2). In the present study, we have made an attempt to collect biological properties of imidazole nucleus reported in the new millennium.

## BIOLOGICAL ACTIVITIES OF INDOLE NUCLEUS

**Anti-inflammatory and analgesic activity.** Abele *et al*. synthesized isatin and indole oximes and carried out the chemical reactions and biological activities of the synthesized compounds where the compound (**1**) was found to be most active analgesic and anti-inflammatory agent [1].




**(1)**

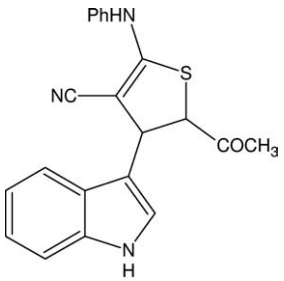
Radwan *et al*. carried out the synthesis and biological evaluation of 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents. They reported 3-(3-indolyl) thiophene derivative (**2**) as a

**Table 1**

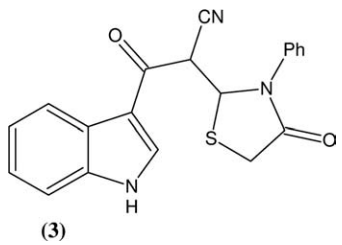
Various biological activities of compounds possessing indole nucleus are as follows.

| S. No. | Biological activities | References |
|---|---|---|
| 1. | Anti-inflammatory and analgesic | [1–5] |
| 2. | Antifungal | [1,6] |
| 3. | Antimicrobial | [7,8] |
| 4. | Insecticidal activity | [1,9] |
| 5. | Anticancer | [1,10–13] |
| 6. | 5-Lipoxygenase inhibitors | [14] |
| 7. | AntiHIV | [1,15] |
| 8. | Antioxidant | [16,17] |
| 9. | Antitubercular | [1,18] |
| 10. | Antiviral | [1] |
| 11. | Plant growth regulator | [1] |
| 12. | Antidepressant, tranquillizing, anticonvulsant | [1,19] |
| 13. | Cardiovascular activity | [1,20] |
| 14. | Antihypertensive | [1] |
| 15. | Antihistaminic | [21] |
| 16. | Opioid antagonist | [22] |
| 17. | Photochemotherapeutic activity | [23] |
| 18. | Antidiabetic activity | [24] |
| 19. | LXR receptor agonist | [25] |
| 20. | ACAT inhibitor | [26] |
| 21. | IL-1 inhibitors | [27] |
| 22. | $LTB_4$ production inhibitor | [28] |
| 23. | Steroid 5α-reductase inhibitor | [29] |
| 24. | Glycoprotein IIb\IIIa inhibitor | [30] |
| 25. | Thrombin catalytic activity | [31] |
| 26. | Peroxisome proliferator-activated receptor agonist | [32] |
| 27. | Cytosolic phospholipase A2α inhibitors | [33] |
| 28. | Galanine $GAL_3$ receptor antagonist | [34] |
| 29. | Selective CB2 receptor agonist | [35] |
| 30. | Selective dopamine agonist | [36,37] |

potent anti-inflammatory compound whereas thiazolidine-4-one derivative (**3**) exhibit analgesic activity [2].

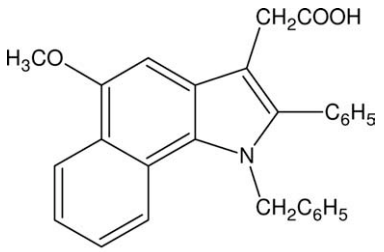



**(2)**



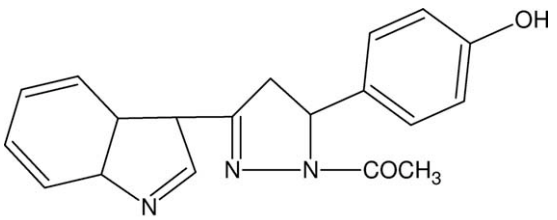

**(3)**

Kalaskar *et al*. synthesized indole-3-acetic acids and evaluated them for their *in vivo* anti-inflammatory activity. The compound 1,2-disubstituted-5-methoxyindole/benz(g)indole-3-acetic acid (**4**) showed significant activity [3].




**(4)**

The synthesis and anti-inflammatory activity of heterocyclic indole derivatives was performed by Rani *et al*. The compound **(5)** was found to be most potent (inhibition of oedema at 50 μg/Kg dose) [4].




**(5)**

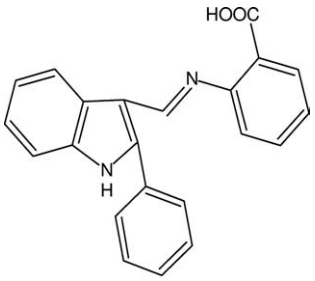
Amir *et al*. carried out synthesis and anti-inflammatory activity of various indole and indazole derivatives where the compounds 2-Phenyl-3-(2′-carboxyphenyliminomethyl)-

**Table 2**

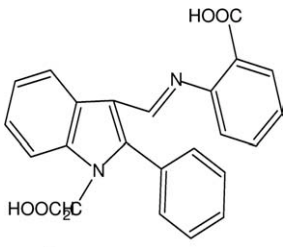
Importance of indole derivatives in medicinal chemistry.

| S.No. | Indole derivative | Biological activity |
|---|---|---|
| 1. | Indomethacin | Anti-inflammatory and analgesic |
| 2. | Fendosal | Analgesic |
| 3. | Etodolac | Antiarthritis |
| 4. | Sumatriptan | Antimigraine |
| 5. | Besipirdine | Nootropic |
| 6. | Noratriptan | CNS stimulant |
| 7. | Pindolol | Antihypertensive |
| 8. | Indolmycin | Antibiotic |
| 9. | Indigo carmine | As a dye in functional kidney test and in milk testing |
| 10. | Adrenochrome | Hemostatic |

indole (**6**) and 2-phenyl-3-(2′-carboxyphenyliminomethyl)-indol-1-acetic acid (**7**) were found to be most potent [5].

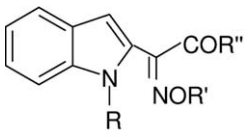



**(6)**



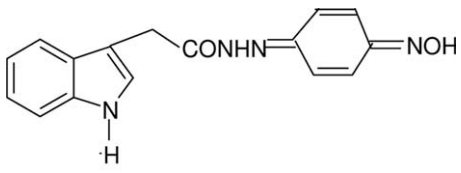

**(7)**

**Antifungal activity.** Some of the isatin and indole oximes synthesized by Abele *et al*. were found to be exhibiting high fungicidal activity where the oxime derivates of 2-substituted indoles **(8)** and 3-substituted indoles **(9)** demonstrated significant antifungal activity [1].



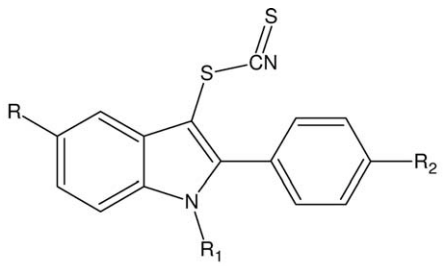

R,R' = Alkyl
R'' = OAlk, SAlk, NHAlk, NAlk

**(8)**



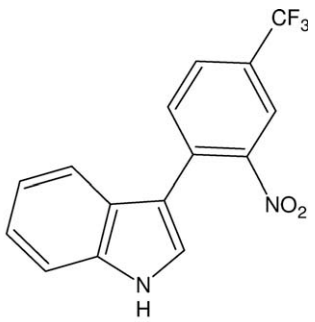

**(9)**

A series of S-(indolyl-3)diethyl dithiocarbamates was synthesized and evaluated for their activity by Skii *et al*. The compounds (**10a–e**) were found to be exhibiting highest antifungal activity [6].



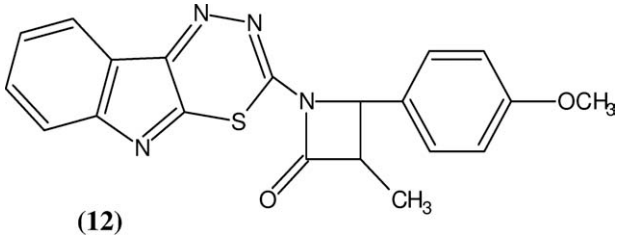

**10a:** R= $R_1$ = $R_2$ = H
**10b**: R = H, $R_1$ =$CH_2$Ph
**10c**: R = $R_2$ = H, $R_1$ = Ph
**10d**: R = $R_1$ = H, $R_2$ = Br
**10e**: R = $R_2$ = Br, $R_1$ = H

**Antimicrobial activity.** The synthesis and antibacterial activity of some substituted 3-(aryl) and 3-(heteroaryl) indoles were reported by Hiari *et al*. The most active compound was reported to be 3-(4-trifluoromethyl-2-nitrophenyl) indole **(11)** exhibiting MIC $\approx$ 7 μg/$cm^3$ against *Escherichia coli* and *Staphylococcus aureus* [7].

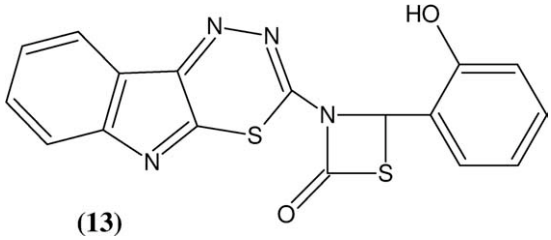



**(11)**

Panwar *et al*. synthesis substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents. The compounds (**12**) and (**13**) were found to exhibit most inhibitory effect against *E. coli* and *S. aureus* [8].

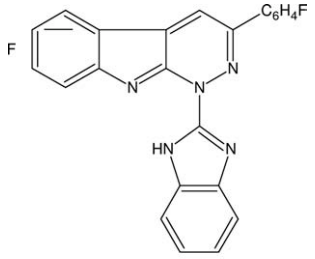



**(12)**




**(13)**

**Insecticidal activity.** Sharma *et al*. investigated the insecticidal activity of synthesized novel indole derivatives. The compounds **(14)** and **(15)** exhibited promising results against *Spodoptera liture* (eighth instar larvae) and *Jeliothis armigera* [9].



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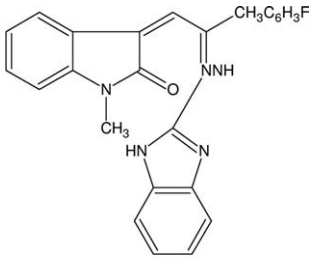
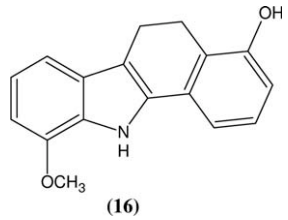
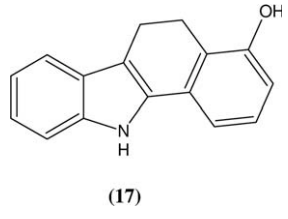


**(15)**

**Anticancer activity.** The series of various tricyclic and tetracyclic indoles synthesized by Hong *et al*. were evaluated for their anticancer activity where the compounds **16, 17, 18,** and **19** were found to exhibit highest *in vitro* activity against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) cell lines [10].



**(16)**



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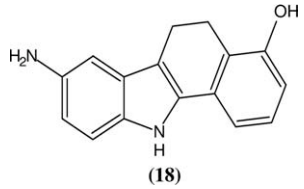
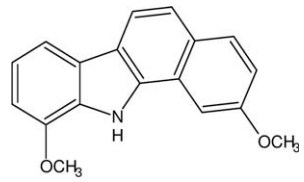
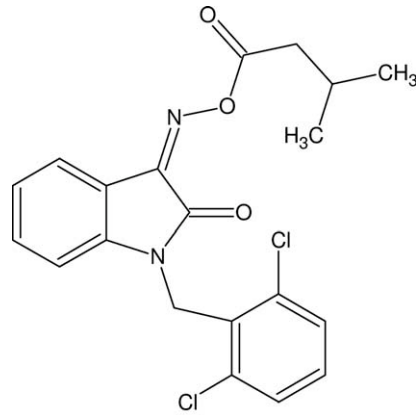


**(18)**



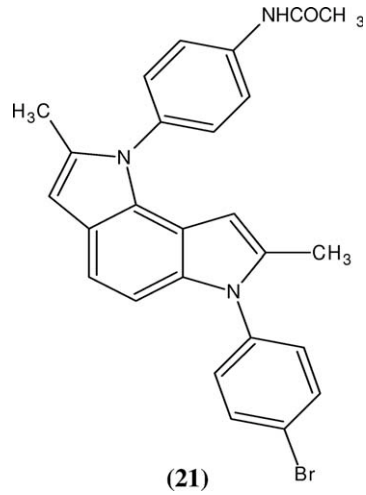
**(19)**

The compound **(20)** synthesized by Abele *et al*. was reportedly showing highest anticancer activity [1].



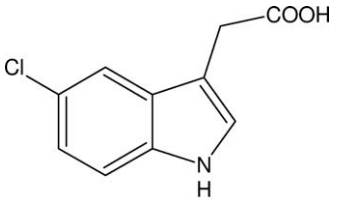
**(20)**

Garcia *et al*. synthesized pyrrolo[2,3-e] indole derivatives and evaluated them for possible *in vitro* cytotoxic activity. The most active compound was found to be (**21**), which shows best result in PC-3 (prostate) cell line [11].



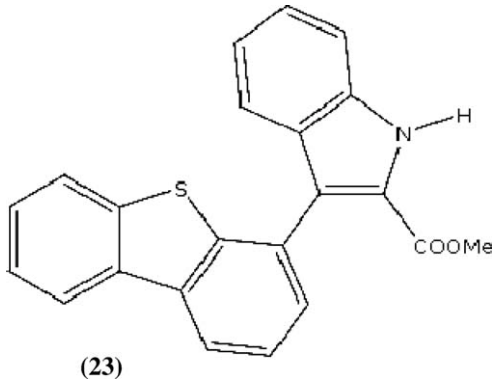
**(21)**

A series of halogenated indole-3-acetic acids as oxidatively activated prodrugs with potential for targeted cancer therapy were reported by Rossiter *et al*. These derivatives were oxidized by horse radish peroxidase (HRP) and toxicity against V79 Chinese hamster lung fibroblasts was determined and the compound (**22**) was found to possess highest cytotoxicity and it was the best drug for targeted cancer therapy [12].



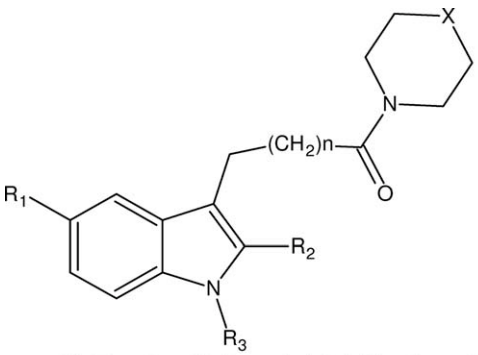

**(22)**

Queiroz *et al*. studied the inhibitory activity of the heteroarylindoles and of the phenylbenzothienoindole on the growth of human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer). The results showed that the methyl 3-(dibenzothien-4-yl)indole-2-carboxylate (**23**) had most potent growth inhibitory activity in all the tumor cell lines tested (with $GI_{50}$ values ranging from11 to 17 μ*M*) [13].



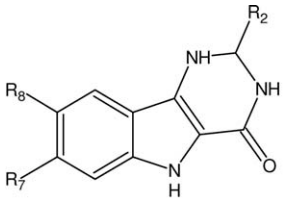

**(23)**

**Lipoxygenase inhibitor.** Zheng *et al*. synthesized a series of indole derivatives as possible 5-lipoxygenase inhibitors. In all, four compounds **24, 25, 26,** and **27** exhibited the most potent inhibitory activity with $IC_{50}$ values ranging from 0.74 μ*M* to 3.17 μ*M* [14].

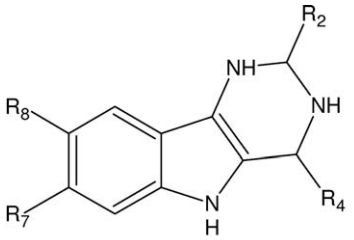



**24**: $R_1 = R_2 = H$, $R_3$ = 3, 4-Dichlorobenzyl, X = O, n = 0
**25**: $R_1$ = Cl, $R_2 = CH_3$, $R_3$ = Benzyl, X = O, n = 2
**26**: $R_1 = R_2 = R_3 = H$, X = BocN, X = O, n = 2
**27**: $R_1 = R_2 = H$, $R_3$ = Benzyl, X = NH, n = 2

**HIV inhibitors.** The analogs of pyrimido[5,4-b]indoles were synthesized and biologically evaluated by Merino *et al*. for their possible HIV inhibitory activity. The derivative **(28)** formed by substitution at position 2 in analog-I and derivative **(29)** at position 2, 4 in analog II (formed in 65% and 64% maximum yield) were reported to be the inhibitors of wild and mutant HIV-1 RT types in an ''*in vitro*'' recombinant HIV-1 RT screening assay as well as anti-infectives in $HLT4lacZ\text{-}1_{IIIB}$ cells [15].



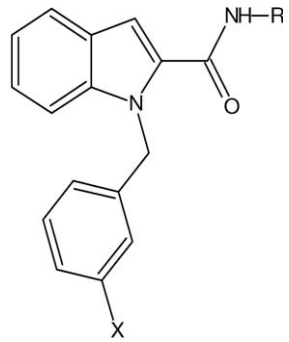

**Analog I**
**28**: $R_2$ = methyl-N-[4-(2′-methoxyphenyl)]piperazinyl, $R_7 = R_8 = H$



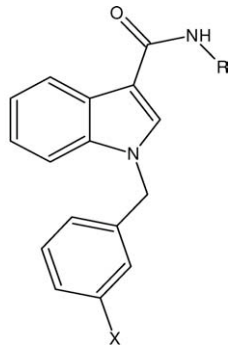

**Analog II**
**29:** $R_2$ = 2′-pyridyl, $R_4$ = N-morpholinyl, $R_7 = R_8 = H$

**Antioxidant activity.** A series of indole derivatives were synthesized and biologically evaluated by Enien *et al*., and found that Indole-2 and 3-carboxamides were having antioxidant properties by Chemoluminesence and Electron spin resonance spin trapping. They further reported that the derivatives **30** and **31** have strongest scavenging effect on $OH^-$ radicals, *i.e*., quenching >30%

and the derivatives **31** and **32** have strongest effect on scavenging of superoxide radicals [16].

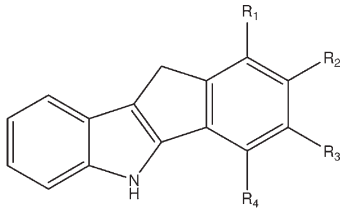


Indole-2-carboxamide
**30**: X=H, R=Phenyl



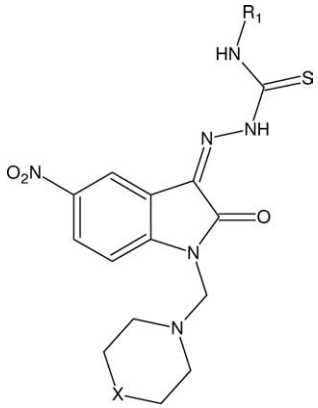
Indole-3-carboxamide
**31:** X=H, R=Thiazolyl
**32:** X=F, R=Thiazolyl

Talaz *et al*. described the synthesis of 5,10-dihydroindeno[1,2-b]indoles containing substituents such as methoxy, hydroxyl, and halogen (F, Cl, and Br) on indeno part and their antioxidant activity and radical scavenging activities were assessed by various *in vitro* assays and compared with the activities of synthetic and standard antioxidant compounds. The compounds **(33)** and **(34)** were found to have maximum $Fe^{3+}$–$Fe^{2+}$ reducing ability whereas compound **(35)** was found to have maximum $Cu^{2+}$–$Cu^{+}$ reducing ability [17].

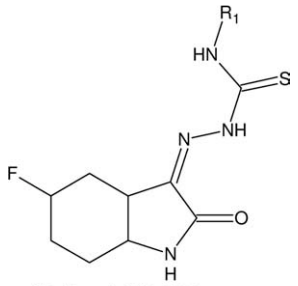


**33**: $R_1$=OMe, $R_2$= H, $R_3$= H, $R_4$= OMe
**34**: $R_1$=OH, $R_2$= OH, $R_3$= H, $R_4$= H
**35**: $R_1$=OH, $R_2$= H, $R_3$= H, $R_4$= OH

**Antituberculosis activity.** A new series of 1H-indole-2,3-dione derivatives were synthesized and evaluated for *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* H37Rv by Karali *et al*. Among the tested compounds, 5-nitro-1H-indole-2,3-dione-3-thiosemicarbazones and its 1-morpholinomethyl (**36, 37, 38,** and **39**) derivatives exhibited significant inhibitory activity with MIC values $\geq$ 75% [18].

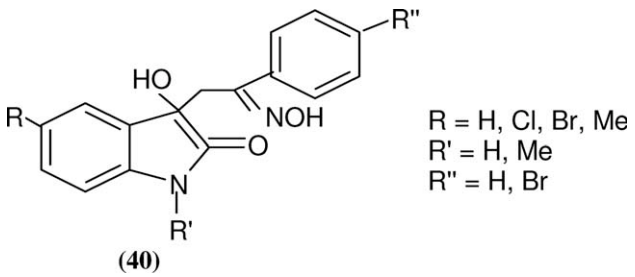


**36:** $R_1 = CH_3$
**37:** $R_1 = C_6H_5$
**38:** $R_1 = 4\text{-}CH_3C_6H_4$



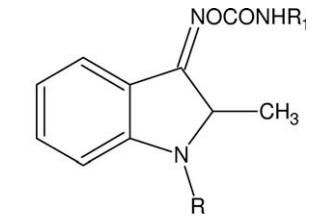
**39:** $R_1 = 4\text{-}CH_3C_6H_4$

Among the series of isatin and indole oximes synthesized and evaluated by Abele *et al*., the highest broad spectrum antibacterial activity was exhibited by oxime derivatives of 2-indolinone **(40)** against *M. tuberculosis* [1].



**(40)**

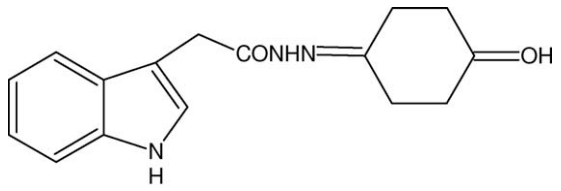
**Antiviral activity.** The indole oxime, carbamoyl derivative of indole-3-oxime **(41),** exhibited the most potent antiviral activity among the isatin and indole oximes synthesized by Abele *et al*. [1].



**(41)**

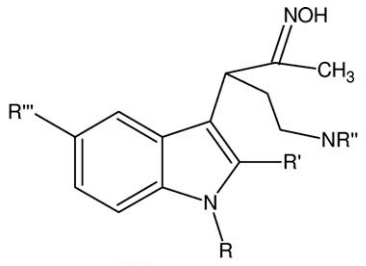
R = H, methyl, ethyl
$R_1$ = methyl, phenyl

**Plant growth regulator.** The 3-substituted indole **(42)** was reported to be a plant growth regulator by Abele *et al*. among the various isatin and indole oximes synthesized and evaluated by them [1].



**(42)**

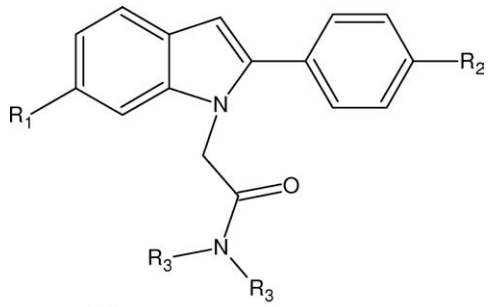
**Antidepressant, tranquillizing, and anticonvulsant activity.** The oxime of indole aminoketone **(43)** exhibited high antidepressant activity among the isatin and indole oximes synthesized and evaluated for their biological activity by Abele *et al*. [1].



**(43)**

R = H R' = H, methyl R'' = methyl, ethyl R''' = H, Cl, OMe

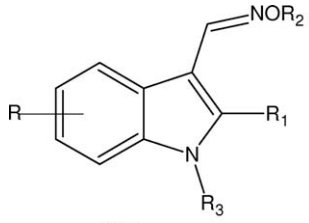
A series of N-substituted indoles were synthesized by Falco *et al*., and afterwards, *in vitro* screening and *in vivo* spontaneous motor activity in mice had revealed molecules with good *in vitro* affinities for the $\alpha_1$-subunit of $GABA_A$ receptor and potent *in vivo* induction of sedation and **(44)** was found most potent compounds [19].



**(44)**

$R_1 = R_2$ = methyl, $R_3$ = propyl

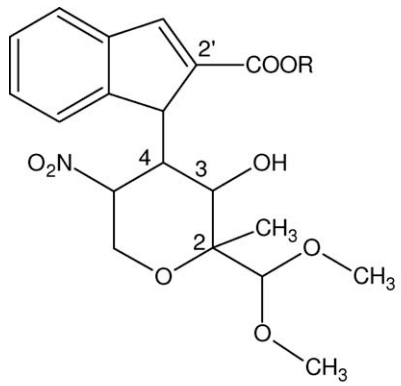
**Cardiovascular activity.** The isatin oxime **(45)** exhibited the highest antiarrhythmic activity among the isatin and indole oximes synthesized by Abele *et al*. [1].



**(45)**

R = H, Alkyl, OH, Halogen, $NO_2$, $NH_2$
$R_1$ = Halogen, OH, SH, $NH_2$
$R_2$ = H, Alkyl, Ar
$R_3$ = H

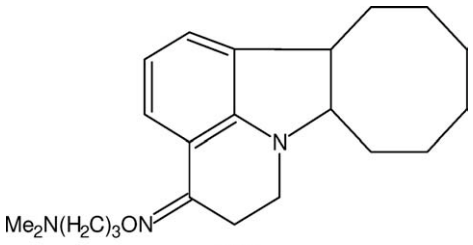
A number of benzopyranyl indoline and indole analogs were synthesized and evaluated for Cardioselective anti-ischemic ATP-sensitive potassium channel ($K_{ATP}$) opener activity by Lee *et al*. The compounds **(46)** and **(47)** showed the best cardioprotective activity [20].



**46**: (2-S, 3-R, 4-S, 2'-S) = R= Ethyl
**47**: (2-R, 3-S, 4-R, 2'-R) = R= Ethyl

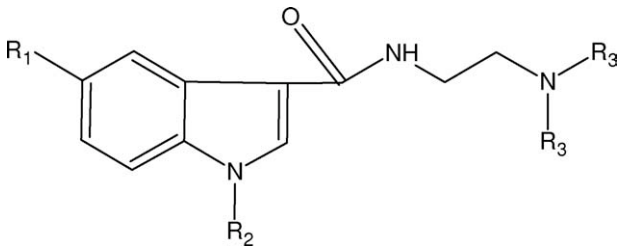
**Antihypertensive activity.** Among the various isatin and indole oximes reported by Abele *et al*., compound

(**48**), a tetracyclic derivatives of indole oximes, was found to have hypotensive activity lowering the blood pressure in rats by 28% [1].



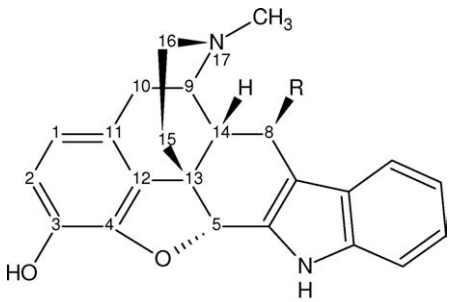

**(48)**

**Antihistaminic activity.** A number of indole amide derivatives bearing a side chain, in which the indole ring replaces the isoster benzimidazole nucleus typical of some well known antihistamines, were prepared and tested for the antihistaminic activity by Battaglia *et al*. The most active compounds **49, 50, 51, 52, 53,** and **54** were tested *in vivo* for their ability to antagonize histamine induced cutaneous vascular permeability in rats [21].



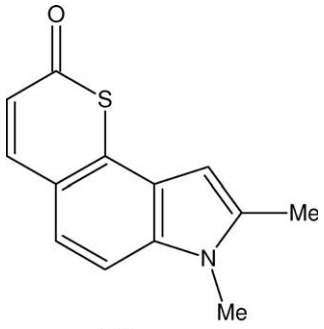

| Compound No. | $R_1$ | $R_2$ | $R_3$-N-$R_3$ |
|---|---|---|---|
| **49** | H | $CH_2C_6H_5$ | $CH_3/CH_3$ |
| **50** | H | $CH_2C_6H_5$ | Piperidine |
| **51** | H | $CH_2C_6H_4$-p-F | $CH_3/CH_3$ |
| **52** | H | $CH_2C_6H_4$-p-F | Piperidine |
| **53** | H | $CH_2C_6H_4$-p-Cl | $CH_3/CH_3$ |
| **54** | H | $CH_2C_6H_4$-p-Cl | Piperidine |

**Opioid antagonist.** The synthesis and biological activity of 8β-substituted hydromorphone indole derivatives were carried out by Yu *et al*. The compound 6,7-dehydro-4,5α-epoxy-8β-methyl-6,7,2′,3′-indolomorphinan **(55)** was found to be a δ antagonist with submolar affinity (0.7 n*M*) for the opioid receptor, and to have good δ-selectivity (μ/δ = 322 n*M*) [22].



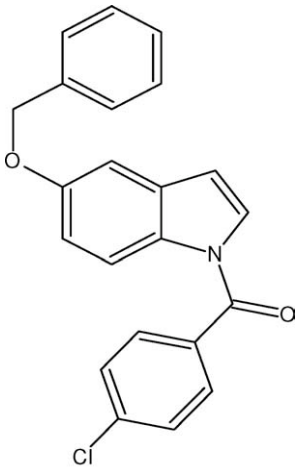

**(55)**

**Photochemotherapeutic activity.** The synthesis and photochemotherapeutic activity of thiopyrano[2,3-e]indol-2-ones was performed by Barraja *et al*., wherein the compound thiopyrano[2,3-e]-indol-2-ones **(56)** showed the maximum phototoxicity on two cultured cell lines: HL-60 and LoVo [23].



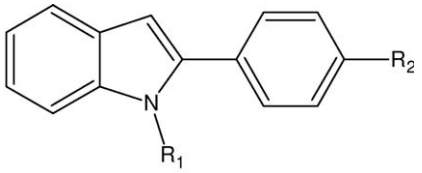

**(56)**

**Antidiabetic activity.** Some of the indole derivatives were evaluated for their insulin sensitizing and glucose lowering effects by Li *et al*. The indole derivative **(57)** showed increase in activity of PPARγ agents, which shows decreased serum glucose and contributing to antidiabetic activity [24].



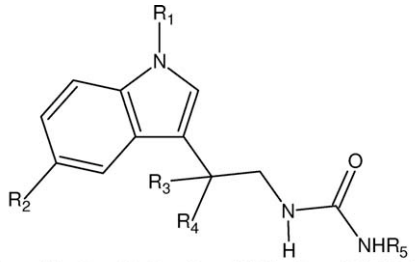

**(57)**

**LXR receptor agonist.** A series of 2-Aryl-*N*-acyl indole derivatives was synthesized and biologically evaluated as liver X receptor (LXR) agonists by Kher *et al*. The compound **(58)** was found to be most active with $EC_{50} = 0.012$ μ*M* [25].



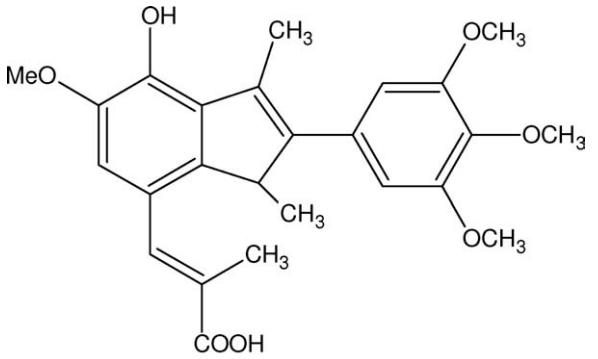
**(58)**
$R_1 = COPh$, $R_2 = (CH_2)_2CN$

**ACAT inhibitors (hypocholestrolemic activity).** The indole derivatives synthesized by Bellemin *et al*., were evaluated for their hypocholestrolemic activity. The compounds **(59)** and **(60)** were found to be most effective ACAT inhibitor with $ED_{25}$ values of 0.098 and 0.063 mg/Kg, respectively [26].



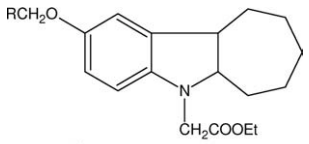
**(59):** $R_1 = CH_3$, $R_2 = H$, $R_3 = R_4 = (CH_2)_4$, $R_5 = 2,6\text{-}(i\text{-}Pr)_2C_6H_3$
**(60):** $R_1 = (CH_3)_2N(CH_2)_2$, $R_2 = H$, $R_3 = R_4 = (CH_2)_4$, $R_5 = 2,6\text{-}(i\text{-}Pr)_2C_6H_3$

**IL-1 inhibitors.** Among the series of hydroxyindole derivatives synthesized and evaluated for IL-1 generation inhibitors by Tanaka *et al*., the compound **(61)** was found to be potent inhibitors of IL-1 generation with IL-1α = 6.4 μ*M* and IL-2 = 8.6 μ*M* [27].

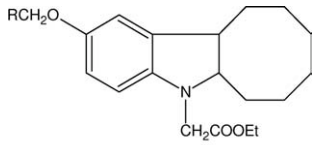


**(61)**

**$LTB_4$ production inhibitor.** The compounds **(62)** and **(63)** exhibited the highest inhibitory activity against $LTB_4$ production among the series of novel thiopyrano[3,2-b] and cycloalkeno[1,2-b]indole derivatives synthesized and evaluated by Caubere *et al*. [28].

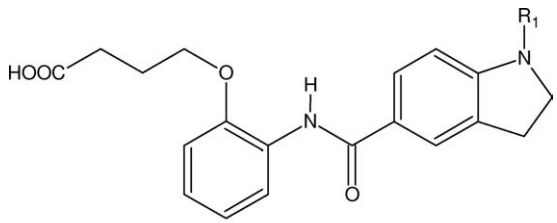


**(62)**
R = 2-quinolyl

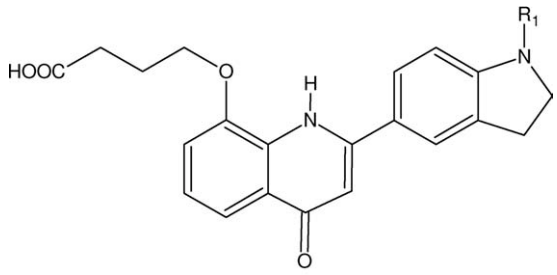


**(63)**
R = 2-quinolyl

**Steroid 5α-reductase inhibitor.** A class of indole and benzimidazole derivatives were synthesized and evaluated for their inhibitory activity against rat prostatic 5α-reductase by Takami *et al*. The compounds **(64)** and **(65)** were found to be showing most potent inhibitory activity against rat prostatic 5α-reductase with $IC_{50} = 9.6 \pm 1.0$ n*M* and $19 \pm 6.2$ n*M*, respectively [29].

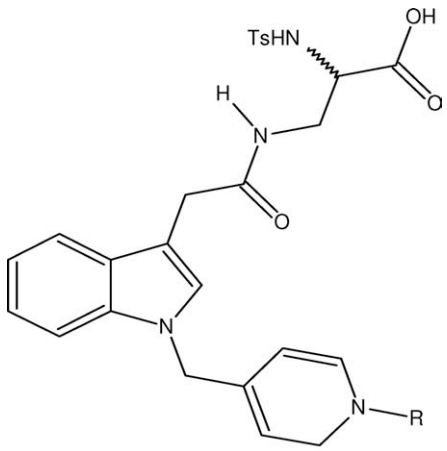


**(64)**
$R_1$ = 4, 4′-dipropylbenzhydryl



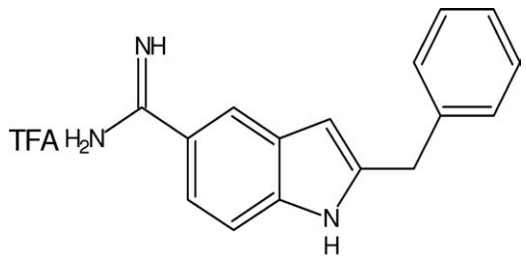
**(65)**
$R_1$ = 4-isobutyl-α-methylbenzyl

**Glycoprotein IIb\IIIa inhibitors.** Grumel *et al*. synthesis 1,3-disubstituted indole derivatives as glycoprotein IIb/IIIa antagonists wherein the compound **(66)** was found to exhibit highest Glycoprotein IIb/IIIa inhibitory activity with $IC_{50} = 4.5$ μ*M* [30].



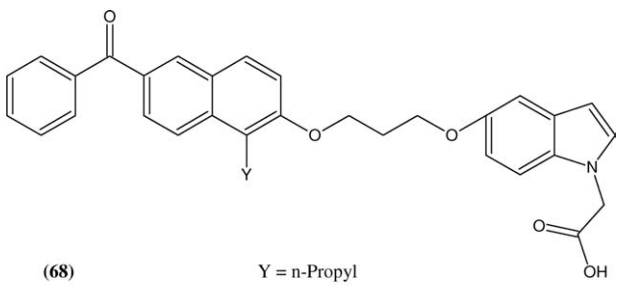

**(66)**
R = H, HCl

**Thrombin catalytic activity.** The substituted 5-amide indoles were evaluated as inhibitors of thrombin catalytic activity by Iwanowicz *et al*. The compound **(67)** was found to be the most potent inhibitor of thrombin catalytic activity with an inhibition constant, $K_i = 260$ n*M* [31].




**(67)**

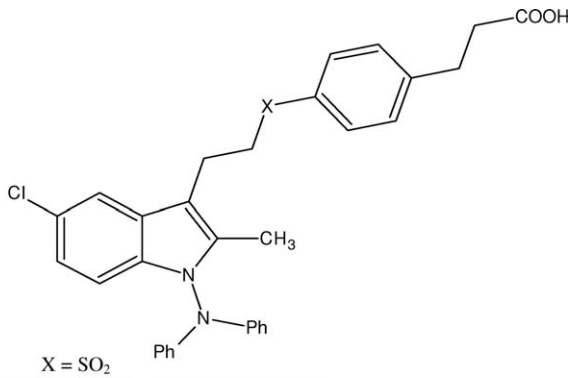
**Peroxisome proliferator-activated receptor agonist.** A series of indole based PPAR agonist were synthesized and biologically evaluated by Mahindroo *et al*. [32]. The compound **(68)** was found to be most potent PPAR agonist with $IC_{50} = 0.050$ μ*M* and $EC_{50} = 0.070$ μ*M*.




**(68)** Y = n-Propyl

**1.2.27 Cytosolic Phospholipase A2α inhibitors**

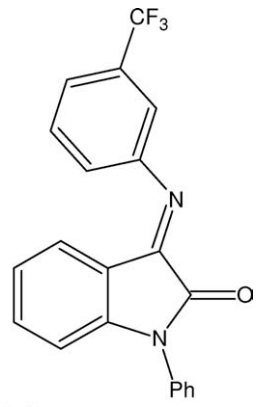
**Cytosolic phospholipase A2α inhibitors.** The potential of indole nucleus as Cytosolic Phospholipase A2α inhibitors was evaluated by Mckew *et al*. The compound **(69)** was found to be most potent $IC_{50} = 0.5$ μ*M* in the GLU assay and $IC_{50} = 0.8$ μ*M* in the rat whole blood assay [33].




**(69)** X = $SO_2$

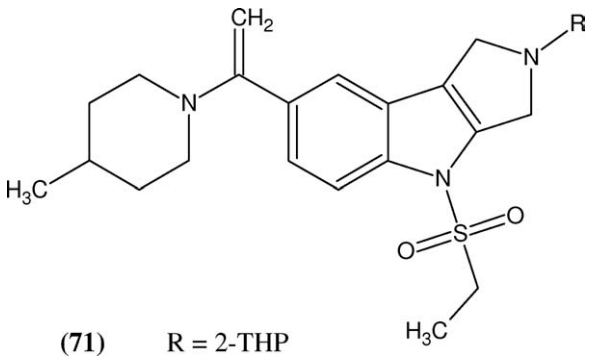
**1.2.28 Galanine $GAL_3$ receptor antagonist**

**Galanine $GAL_3$ receptor antagonist.** A series of 3-arylimino-2-indolones were reported to be as Galanine $GAL_3$ receptor antagonists by Konkel *et al*. The compound **(70)** was found to be most potent antagonist with $K_b = 29$ n*M* [34].



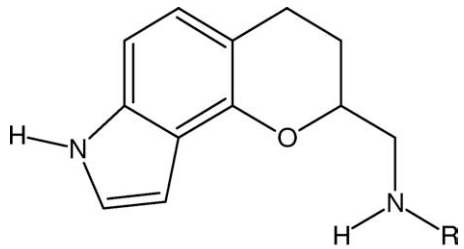

**(70)**

**Selective CB2 receptor agonist.** The preparation and evaluation of a class of CB2 receptor agonist based on a 1,2,3,4-tetrahydropyrrolo[3,4-b] indole moiety were reported by Page *et al*. The compound **(71)** showed to be most potent CB2 receptor agonist [35].



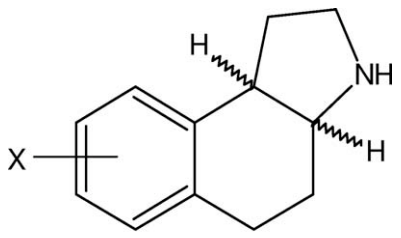
**(71)** R = 2-THP

**Selective dopamine agonist.** A series of 2-(aminomethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indole and indole-8-one derivatives were synthesized and evaluated by Mewshaw *et al*. The compound **(72)** was found to be most potent agonist [36].



**(72)** R = Benzyl

The class of cis- and trans-2,3,3a,4,5,9b-hexahydro-1H-binz[e]indoles synthesized by Song *et al*. were evaluated for dopamine $D_2$ and $D_3$ receptor binding affinity. The cis-diastereoisomer **(73)** was found to be more potent among the synthesized compounds [37].



**(73)** X = 8-OH

## REFERENCES AND NOTES


[1] Abele, E.; Abele, R.; Dzenitis, O.; Lukevics, E. Chem Heterocycl Compd 2003, 39, 3.

[2] Radwan, M. A. A.; Ragab, E. A.; Sabry, N. M.; Shenawy, S. M. E. Bioorg Med Chem 1997, 15, 3832.

[3] Kalaskar, G. P.; Girisha, M.; Purohit, M. G.; Thippeswamy, B. S.; Patil, B. M. Indian J Heterocycl Chem 2007, 16, 325.

[4] Rani, P.; Srivastava, V. K.; Kumar, A. Eur J Med Chem 2004, 39, 449.

[5] Amir, M.; Dhar, N.; Tiwari, S. K. Indian J Chem 1997, 36B, 96.

[6] Skii, N. M. P.; Magedov, I. V.; Drozd, V. N. Chem Heterocycl Compd 1997, 33, 1475.

[7] Panwar, H.; Verma, R. S.; Srivastava, V. K.; Kumar, A. Indian J Chem 2006, 45B, 2099.

[8] Hiari, Y. M. A.; Qaisi, A. M.; Abadelah, M. M.; Voelter, W. Monatshefte Fur Chemie 2006, 137, 243.

[9] Sharma, K.; Jain, R.; Joshi, K. C. Indian J Heterocycl Chem 1992, 1, 189.

[10] Hong, B. C.; Jiang, Y.; Chang, Y.; Lee, S. J Chin Chem Soc 2006, 53, 647.

[11] Garcia, L. C.; Martinez, R. Eur J Med Chem 2002, 37, 261.

[12] Rossiter, S.; Folkes, L. K.; Wardman, P. Bioorg Med Chem Lett 2002, 12, 2523.

[13] Queiroz, M. R. P.; Abreu, A. S.; Carvalho, M. S. D.; Ferreira, P. M. T.; Nazareth, N.; Nascimento, M. S. Bioorg Med Chem 2008, 16, 5584.

[14] Zheng, M.; Zheng, M.; Ye, D.; Deng, Y.; Qiu, S.; Luo, X.; Chen, K.; Liu, H.; Jiang, H. Bioorg Med Chem Lett 2007, 17, 2414.

[15] Merino, I.; Monge, A.; Font, M.; Irujo, J. J. M.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J. J.; Sarobe, P.; Borrás, F. Il Farmaco 1999, 54, 255.

[16] Enein, H. Y. A.; Kruk, I.; Lichszteld, K.; Michalska, T.; Kiadna, A.; Marczynski, S.; Olgen, S. Luminescence 2004, 19, 1.

[17] Talaz, O.; Gulcin, I.; Goksu, S.; Saracoglu, N. Bioorg Med Chem 2009, 17, 6583.

[18] Karali, N.; Gursoy, A.; Kandemirli, F.; Shvets, N.; Kaynak, F. B.; Ozbey, S.; Kovalishyn, V.; Dimoglo, A. Bioorg Med Chem 2007, 15, 5888.

[19] Falco, J. L.; Pique, M.; Gonalez, M.; Buira, I.; Mendez, E.; Terencio, J.; Perez, C.; Princep, M.; Palomer, A.; Guglietta, A. Eur J Med Chem 2006, 41, 985.

[20] Lee, S.; Yi, K. Y.; Kim, S. K.; Suh, J.; Kim, N. J.; Yoo, S. E.; Lee, B. H.; Sao, H. W.; Kim, S. O.; Lim, H. Eur J Med Chem 2003, 38, 459.

[21] Battaglia, S.; Boldrini, E.; Settimo, F. D.; Dondio, G.; Motta, C. L.; Marini, A. M.; Primofiore, G. Eur J Med Chem 1999, 34, 93.

[22] Yu, H.; Prisizano, T.; Dersch, C. M.; Marcus, J.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Bioorg Med Chem 2002, 12, 165.

[23] Barraja, P.; Sciabica, L.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G.; Disaro, S.; Basso, G.; Viola, G.; Dall'Acqua, F. Bioorg Med Chem Lett 2005, 15, 2291.

[24] Li, Y. Y.; Wu, H. S.; Tang, L.; Feng, C. R.; Yu, J. H.; Li, Y.; Yang, Y. S.; Yang, B.; He, Q. J Pharmacol Res 2007, 56, 335.

[25] Kher, S.; Lake, K.; Sircar, I.; Pannala, M.; Bakir, F.; Zapf, J.; Xu, K.; Zhang, S. H.; Liu, J.; Morera, L.; Sakurai, N.; Jack, R.; Cheng, J. F. Bioorg Med Chem 2000, 17, 4442.

[26] Bellemin, R.; Decerprit, A.; Festal, D. Eur J Med Chem 1996, 31, 123.

[27] Tanaka, M.; Kaneko, T.; Akamatsu, H.; Okita, M.; Chiba, K.; Obaishi, H.; Yamatsu, I. Eur J Med Chem 1995, 39, 449.

[28] Caubere, C. K.; Caubere, P.; Pfeiffer, B.; Manechez, D.; Renard, P. Eur J Med Chem 1999, 34, 51.

[29] Takami, H.; Kishibayashi, N.; Ishii, A.; Kumazawa, T. Bioorg Med Chem 1998, 6, 2441.

[30] Grumel, V.; Merour, J. Y.; Lesur, B.; Giboulot, T.; Frydman, A.; Guillaumet, G. Eur J Med Chem 2002, 37, 45.

[31] Iwanowicz, E. J.; Lau, W. F.; Lin, J.; Roberts, M.; Seiler, S. M. Bioorg Med Chem Lett 1996, 6, 1339.

[32] Mahindroo, N.; Wang, C. C.; Liao, C. J.; Tsai, C. H.; Chen, X.; Lyu, P. C.; Chao, Y. S.; Wu, S. Y.; Hsieh, H. P. J Med Chem 2006, 49, 1212.

[33] Mckew, J. C.; Foley, M. A.; Thakker, P.; Sum, F. E.; Tam, S.; Wu, K.; Shen, W. H.; Zhang, W.; Gonzalez, M.; Liu, S.; Mahadeven, A.; Sard, H.; Clark, J. D. J Med Chem 2006, 49, 135.

[34] Konkel, M. J.; Lagu, B.; Boteju, L. W.; Jimenez, H.; Noble, S.; Walker, M. W.; Koirnberg, B. E.; Gregory, T.; Pugsley, T. A.; Zoski, K.; Wise, L. D. J Med Chem 2006, 49, 3757.

[35] Page, D.; Yang, H.; Brown, W.; Walpole, C.; Fleurent, M.; Gaudreault, F.; Onge, S. S. Bioorg Med Chem Lett 2007, 17, 6183.

[36] Mewshaw, R. E.; Marquis, K. L.; Shi, X.; Stack, G.; Wasik, T.; Scerni, R.; Couprt, J.; Andree, T. H. Tetrahedron 1998, 54, 7081.

[37] Song, X.; Crider, A. M.; Cruse, S. F.; Ghosh, D.; Stevens, C. K.; Liang, L.; Varming, A. Eur J Med Chem 1999, 34, 487.

# Selectivity of *N*-Aroyl-*N*′-arylthioureas towards 2-(1,3-Dioxo-1*H*-inden-2(3*H*)-ylidene)malononitrile. New Synthesis of (*Z*)-*N*-((*E*)-4-Amino-1-aryl-5-cyano-6-oxo-1*H*-indeno[1,2-*d*][1,3]-thiazepin-2(6*H*)-ylidene)-4-arylamides of Antitumor and Antioxidant Activities

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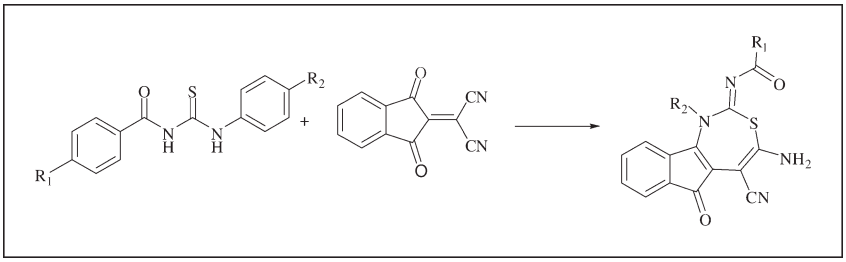

The reaction between *N*-aroyl-*N*′-arylthioureas with 2-(1,3-dioxoindan-2-ylidene)malononitrile furnished indeno[1,2-*d*][1,3]thiazepines in 70–85% yields. The mechanism of the products' formation is discussed. Some of the products showed effective antitumor and antioxidant activities. The results revealed that compound indenothiazepine derivative showed a high inhibition of the cell growth of Hep-G2 cells is compared with the growth of untreated control cells, as concluded from their low $IC_{50}$ value 21.73 μ*M*. On the other hand, two indenothiazepine derivatives have an effective antioxidant activity with $SC_{50}$ values of 62.5 m*M* and 87.4 m*M*, respectively.

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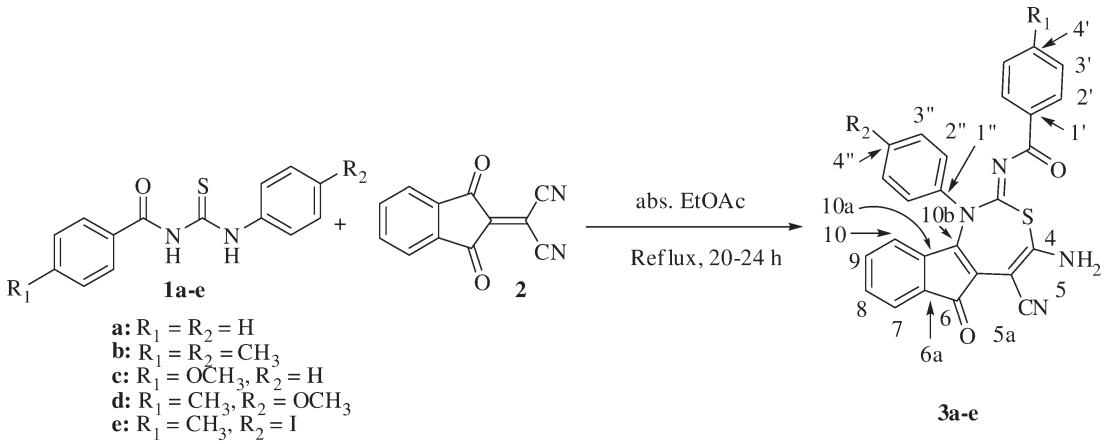
## INTRODUCTION

The importance of *N*-aroyl-*N*′-arylthioureas is found largely in heterocyclic syntheses. Many of these substrates have interesting biological activities and are used as a rich source for materials for development of agrochemical and pharmaceutical products [1]. Additionally, it was known that the reaction of amidinothioureas, imidoylthioureas, thioacylamidines, amidino-thioureas, *o*-methyl-1-aryl-2-thioisobiurets, and 1-aryl-isodithiobiurets with diethyl azodicarboxylate gave the corresponding thiadiazoles by the oxidative cyclic S—N bond formation [2]. A series of 3-alkyl-5-methylene-2-arylimino-1,3-thiazolidin-4-ones were obtained from the reaction of *N*-alkyl-*N*′-arylthioureas with dimethyl but-2-ynedioate [3]. Hyrazino-thioureas, such as 1-acylthiosemicarbazides reacted with phenyl propiolate in acetic acid under reflux to afford triazolothiazines [3]. In light of the aforementioned, it appears that the reaction pathways of substituted thioureas vary from one reagent to another. Our synthetic program uses cycloadditions as efficient methods of preparation of novel heterocycles, rather than those suffering from low yields because of the multiple steps described in their preparation [4]. Aly *et al*. [5] reported the synthesis of a series of 1,3-thiazines by the reaction of *N*-aroyl-*N*′-substituted thioureas with ethyl propiolate, dimethyl but-2-ynedioate, and (*E*)-1,4-diphenyl-but-2-ene-1,4-dione. Herein we report on our findings for the synthesis of various novel thiazepines, during the reaction of various *N*-aroyl-*N*′-aryl-thioureas **1a–e** [6] with 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)-malononitrile (**2**).

## RESULTS AND DISCUSSION

**Chemistry.** Scheme 1 outlines the reaction of **1a–e** with **2** in dry ethyl acetate under $N_2$ atmosphere. The

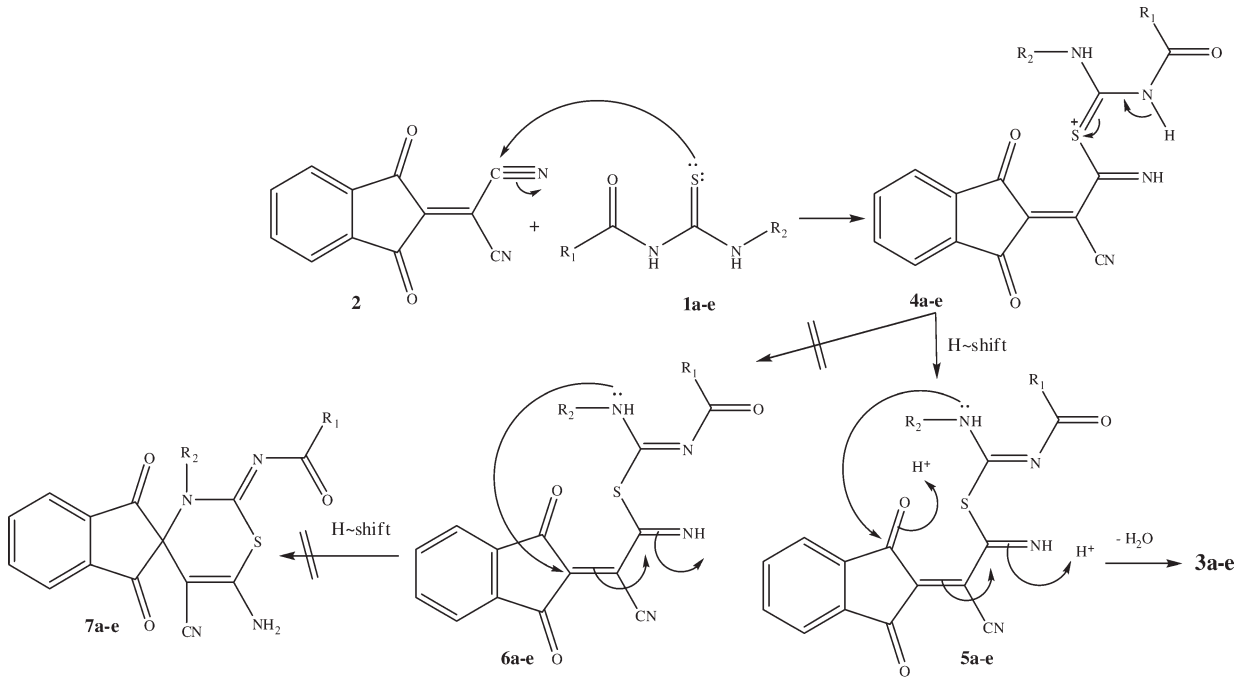
**Scheme 1.** Reactions of aroyl thioureas **1a–e** with **2**; synthesis of (*Z*)-*N*-((*E*)-4-amino-1-aryl-5-cyano-6-oxo-1*H*-indeno[1,2-*d*][1,3]thiazepin-2(6*H*)-ylidene)-4-arylamides **3a–e**. **3a**: 75%; **3b**: 80%; **3c**: 85%; **3d**: 82%; **3e**: 70%.




reaction proceeded to yield, after chromatographic purification and recrystallization, compounds **3a–e** (70–85%). We chose *N*-aroyl-*N*′-arylthioureas **1a–e** having aryl groups with electron donating and withdrawing substituents on the benzene ring to examine their effect on the course of reaction. The structure of **3a–e** was established on the basis of mass, IR, $^{1}$H NMR, $^{13}$C NMR spectra, and elemental analyses. Mechanistically, the formation of compounds **3a–e** can be explained as because of addition of the sulfur atom nonbonded pair of **1a–e** to the nitrile group in **2** (Scheme 2). The formed intermediate **4** undergoes a hydrogen shift to give **5**. Cyclization then occurs *via* addition of the NH lone-pair to the carbonyl group, followed by elimination of water, to give the stable heterocyclic compounds **3a–e**. The NMR spectra excluded the formation of *spiro*-indolothiazines **7a–e**, but all the data are consistent with indeno[1,2-*d*][1,3]thiazepines **3a–e** (Scheme 2).

Compounds **3a–e** show IR absorptions at $\nu = 3120–3350$, 2222–2200, 1733–1665, and 1649–1595 cm$^{-1}$ corresponding to the $NH_2$, nitrile, carbonyl, and azomethine groups, respectively. The spectra are strikingly similar: clearly the products are of the same general type, and share some substructures. The spectra show

**Scheme 2.** Suggested mechanism of the reaction of **1a–e** with **2**.



local symmetry only in the aryl rings, which can apparently rotate about their axes; the indanedione-derived substructures show individual signals for each proton and each carbon, requiring these substructures to lack the plane of symmetry present in **2** and the alternative products **7a–e**. Each $^1$H NMR spectrum showed a broad, 2H signal near $\delta_H = 8.20$ ppm, which gives no heteronuclear multiple quantum coherence (HMQC) or heteronuclear single quantum coherence (HSQC) correlation, suggesting that these protons are not attached to carbon. In **3e**, the *p*-tolyl C—$CH_3$ group is distinctive at $\delta_H = 2.31$ and $\delta_C = 21.2$ ppm. The proton signal at $\delta_H = 2.31$ ppm gives heteronuclear multiple bond correlation correlation (HMBC) correlation with one of the signals at $\delta_C = 143.3$ ppm, which is assigned as C-4′. The C—$CH_3$ $^1$H signal gives COSY correlation with $\delta_H = 7.21$ ppm, and C-4′ gives HMBC correlation with $\delta_H = 7.69$ ppm; these correlations suggest that $\delta_H = 7.21$ and 7.69 ppm are H-3′ and H-2′, respectively. These signals showed HMQC correlation with $\delta_C = 129.0$ and 129.3 ppm, respectively. The *p*-toluamide carbonyl at $\delta_C = 175.2$ ppm gives HMBC with $\delta_H = 7.69$ but not 7.21 ppm, which is consistent with the foregoing. The spectra of **3b** contain signals identical to those just described within $\delta_H = 0.02$, $\delta_C = 0.07$ ppm, and $J = 0.1$ Hz; these signals are assigned to the toluamide substructure of **3b**. In the HMBC spectrum of **3b**, correlation is observed between H-3′ and $\delta_C = 132.6$ not 133.3 ppm; therefore, the former is assigned as C-1′. By analogy with the chemical shifts of **3e**, $\delta_C = 132.6$ is assigned as C-1′, and $\delta_C = 143.3$ ppm is assigned as C-4′. Similarly, in **3c** the methoxy group is distinctive at $\delta_H = 3.77$ and $\delta_C = 55.4$ ppm. This proton signal gives HMBC correlation with a signal at $\delta_C = 163.0$ ppm, which is assigned as C-4′. C-4′ gives HMBC correlation with proton signals at $\delta_H = 7.75$ and 6.91 ppm, which thus must be H-2′ and H-3′. The amide carbonyl at $\delta_C = 174.6$ gives HMBC correlation with $\delta_H = 7.75$ ppm, which leads to assignment of this proton signal as H-2′. By elimination, $\delta_H = 6.91$ ppm must be H-3′. H-2′ and H-3′ give HSQC correlation with $\delta_C = 132.6$ and 113.7 ppm, which therefore are assigned as C-2′ and C-3′, respectively. H-3′ gives HMBC correlation with the nonprotonated carbon at $\delta_C = 127.4$ ppm, which is assigned as C-1′. The signals at $\delta_C = 115.0$–116.0 ppm are assigned as nitrile carbons [7]. The carbons at $\delta_C = 136.6$, 132.2, 125.5, and 125.0 give HMQC correlation with proton signals at $\delta_H = 7.76$, 7.76, 7.98, and 6.69 ppm, again with little variation in the chemical shifts.

The most distinctive of these proton signals is that at $\delta_H = 6.69$ ppm, which is a doublet in **3b** and **3c**, suggesting that it is one of the end protons of the four-spin system (either H-7 or H-10). For the moment arbitrarily assigning this proton as H-10, the attached carbon (HMQC: $\delta_C = 125.0$ ppm) is assigned as C-10. H-10 also gives COSY correlation with one of the two unresolved protons at $\delta_H = 7.76$ ppm, which therefore is H-8, 9. These protons give HMQC correlation with the carbons at $\delta_C = 136.6$ and 132.2 ppm. The latter carbons give HMBC correlation to H-10; the former does not. C-9 is two bonds from H-10, C-8 is three bonds away; as three-bond C—H couplings usually give stronger HMBC correlations than two-bond couplings, $\delta_C = 132.2$ ppm is assigned as C-8 and $\delta_C = 136.6$ ppm is assigned as C-9. C-9 gives HMBC correlation with the signal at $\delta_H = 7.98$ ppm, which thus is assigned as H-7 and its attached carbon ($\delta_C = 125.5$ ppm) as C-7. In **3b**, H-7 appears as a double of doublet with large and small coupling constants ($J = 6.6$, 1.4 Hz), as expected in this position. The remaining $^{13}$C signals are those at $\delta_C = 193.2$, 170.2, 165.9, 143.4, 133.4, 105.0, 70.9, and 53.1 ppm. The remaining carbon atoms are C-6, 2, 4, 10a, 6a, 10b, 5a. and 5; they are assigned in the order stated. In **3b** and **3c**, the signal at $\delta_C = 105.2$ ppm gives HMBC correlation to H-10, so it was assigned as C-10b. Also in **3b** and **3c**, the signal at $\delta_C = 143.5$ ppm gives HMBC correlation to H-7 and either H-8 or H-9; this is expected for C-10a, as which this signal is therefore assigned. In **3e** and **3b**, the signal at $\delta_C = 53.2$ ppm gives HMBC correlation to the remaining proton signal at $\delta_H = 8.22$ ppm, which has an integral of 2H, and gives no HMQC correlation in any of the compounds; its only other HMBC correlation is in **3b** to $\delta_C = 165.9$. This idea is consistent with chemical-shift simulation using ChemNMR, which predicts for **3b** that C4, 5, and 5a will resonate at $\delta_C = 152$, 9, and 107.0 ppm, respectively.

The most surprising thing here is the predicted chemical shift of C-5, which is unusually far upfield for an $sp^2$-hybridized carbon. The rationale would be that the electron density at C-5 is higher than normal, due to resonance donation by the nitrogen on C-4. However, the assigned experimental shifts are very close to those of 1,1-dimethoxyethene, and enamines behave similarly to enol ethers (Fig. 1). The $\delta_C$ values for C-4 and C-5 are in accordance with the observed trends in the $\delta_C$ values in push–pull system in alkenes [8]. It is consistent with these assignments, however, that the amine protons give HMBC correlation to C-4 and C-5. The remaining upfield signal at $\delta_C = 70.9$ ppm is assigned as C-5a.

**Biological section.**

***Anticancer activity.*** The cytotoxicity testing of compounds **3b–d** was carried out using solid tumor (Hep-G2) cells, which were treated with different doses of the tested compounds and submitted to MTT assay [9]. The yellow tetrazolium salt is reduced by mitochondrial enzyme succinate dehydrogenase, present in living cells, to form insoluble purple formazan crystals, which are solubilized by the addition of detergent. The relative viable cells were determined by the amount of MTT

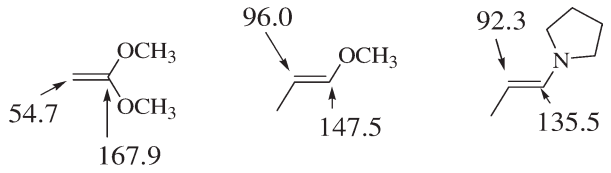



**Figure 1.** Assigned chemical shift values of the carbon signals in 1,1-dimethoxyethene and enamines.

converted to the insoluble formazan crystals. The data were expressed as the mean percentage of the viable cells as compared with the respective control cultures treated with solvent. Half-maximal growth inhibitory concentration ($IC_{50}$) values were calculated from the line equation of the dose-dependent curve of each compound. Compound **3b** resulted in a high inhibition of the cell growth of Hep-G2 cells compared with the growth of untreated control cells, as concluded from the $IC_{50}$ value of 21.73 μ*M*. on the other hand, compounds **3c**,**d** led to insignificant change in the growth of Hep-G2 cells as indicated from their $IC_{50}$ values (>100 μ*M*). Results are represented as percentage of control untreated cells as shown in Figures 2–4.

**Antioxidant activity.** 1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable nonphysiological radical, which could provide a relative figure of the radical scavenging activity of the tested compounds [10]. The DPPH assay showed that **3c** possessed no scavenging activity to DPPH with high $SC_{50}$ values (>100 μ*M*) compared with the scavenging activity ($SC_{50}$ 8.41) of the well-known antioxidant (ascorbic acid); on the other hand, compounds **3b** and **3d** had effective antioxidant activity with $SC_{50}$ values of 62.5 and 87.4 μ*M*, respectively (Fig. 5).

## EXPERIMENTAL

**Chemistry: General methods.** *N*-Aroyl-*N*′-arylthioureas **1a–e** were prepared according to literature [6], whereas 2-(1,3-dioxoindan-2-ylidene)-malononitrile (**2**) was prepared according to literature [8]. IR spectra were measured of KBr pellets; absorption frequencies (ν) are stated in $cm^{-1}$. NMR spectra were measured in DMSO-$d_6$ solution, at 400.13 MHz for $^1H$ and 100.6 MHz for $^{13}C$; chemical shifts are stated in ppm (δ), and coupling constants are stated in Hz.

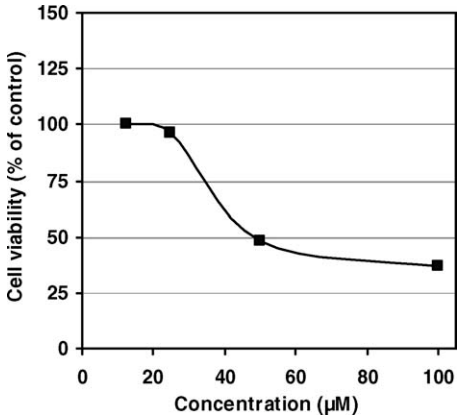



**Figure 3.** The effect of compound **3c** on the growth of Hep-G2 cells. As measured by MTT assay. As measured by MTT assay. Results are represented as percentage of control untreated cells.

**Chemistry**

***Reaction between N-aroyl-N′-arylthioureas 1a–e and 2-(1,3-dioxo-1H-inden-2(3H)-ylidene)malononitrile (CNIND, 2).*** To a solution of **2** (0.208 g, 1 mmol) in dry ethyl acetate (10 mL) a solution of **1a–e** (1 mmol) in dry ethyl acetate (10 mL) was added over 10 min at room temperature with stirring. The reaction mixture was continued with stirring at refluxing temperature for 24–20 h. The reaction mixture was concentrated and the residue was separated by preparative TLC (silica gel) using toluene:ethyl acetate (2:1) as eluant. The major zones were extracted with acetone. The isolated products **3a–e** were recrystallized from the stated solvents.

***(Z)-N-(E)-4-Amino-5-cyano-6-oxo-1-phenyl-1H-indeno[1,2-d][1,3]thiazepin-2(6H)-ylidene)benzamide (3a).*** Yellowish white crystals (DMF/$H_2O$, 10:1), 336 mg (75%), m.p. 257–259°C. IR: 3284, 3123 (m, $NH_2$), 3048–3000 (m, Ar-CH), 2989–2913 (m, aliph.-CH), 2213 (s, CN), 1729, 1667 (s,

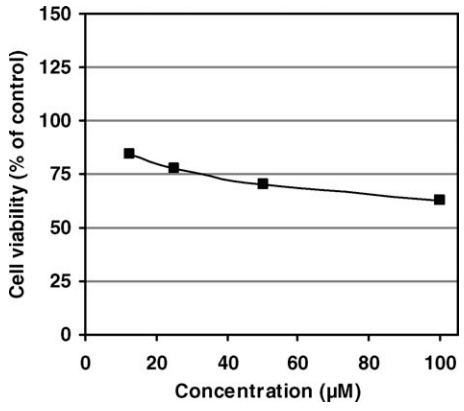



**Figure 2.** The effect of compound **3b** on the growth of Hep-G2 cells. As measured by MTT assay. Results are represented as percentage of control untreated cells.

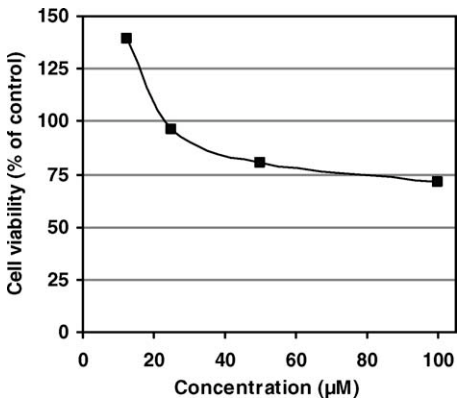



**Figure 4.** The effect of **3d** on the growth of Hep-G2 cells. As measured by MTT assay. Results are represented as percentage of control untreated cells.

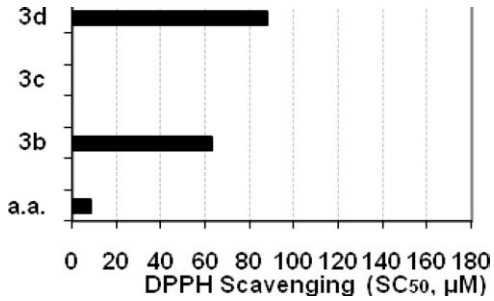



**Figure 5.** The antioxidant activity of **3b**, **3c,** and **3d** was investigated using DPPH assay. The results are represented as $SC_{50}$ values (μM) as (Mean± S.E, $n = 4$).

C=O), 1649, 1602 (s, C=N). $^1$H NMR: 8.21 (bs, 2H; $NH_2$), 7.97 (dd, $J = 6.8, 1.6$, 1H; H-7), 7.92–7.29 (m, 10H; Ar-H), 6.63 (d, $J = 6.5$, 1H; H-10). $^{13}$C NMR: 193.2 (C-6), 175.3 (benzamide C=O), 170.3 (C-2), 165.7 (C-4), 142.9 (C-10a), 136.7 (C-4′), 136.2 (C-9), 134.7 (C-1′), 134 (C-1″), 133.5 (C-6a), 131.8 (C-8), 129.9 (C-2′), 128.7 (C-3′), 127.6 (C-3″), 125.5 (C-7), 125.4 (C-10), 125.1 (C-2″), 124.6 (C-4″), 116.3 (CN), 104.9 (C-11), 70.9 (C-5a), 54.1 (C-5). FAB MS: m/z (%) = 448 [$M^+$] (22). Anal. Calcd. for $C_{26}H_{16}N_4O_2S$ (448.10): C, 69.63; H, 3.60; N, 12.49; S, 7.15. Found: C, 69.79; H, 3.49; N, 12.52; S, 7.28.

***(Z)-N-(E)-4-Amino-5-cyano-1-(4-methylphenyl)-6-oxo-1H-indeno[1,2-d][1,3]thiazepin-2(6H)-ylidene)-4-methylbenzamide (3b).*** Yellowish white crystals (DMF/$H_2O$, 10:1), yield = 381 mg (80%), m.p. 271–272°C. IR (KBr): 3295, 3120 (w, m, $NH_2$), 3070–3000 (m, Ar-CH), 2990–2910 (m, aliph.-CH), 2210 (s, CN), 1733, 1669 (s, s, C=O), 1645, 1608 (s, s, C=N). $^1$H NMR: 8.22 (bs, 2H; $NH_2$), 7.98 (dd, $J = 6.6, 1.4$, 1H; H-7), 7.75 (t, $J = 5.7$, 2H; H-8,9), 7.7 (d, $J = 8.1$, 2H; H-2′), 7.43 (d, $J = 8.2$, 2H; H-3″), 7.33 (bd, $J = 7.2$, 2H; H-2″), 7.19 (d, $J = 8.0$, 2H; H-3′), 6.61 (d, $J = 6.8$, 1H; H-10), 2.47 (s, 3H; H-4a″), 2.3 (s, 3H; H-4a′). $^{13}$C NMR: 193.4 (C-6), 175.2 (benzamide C=O), 170.1 (C-2), 165.9 (C-4), 143.6 (C-10a), 143.2 (C-4′), 139.1(C-4″), 136.5 (C-9), 133.7 (C-1″), 133.3 (C-6a), 132.6 (C-1′), 132.3 (C-8), 129.9 (C-3″), 129.2 (C-2′), 129.1 (C-2″), 129.0 (C-3′), 125.4 (C-7), 125.0 (C-10), 116.0 (CN), 105.3 (C-11), 70.6 (C-5a), 53.2 (C-5), 21.1 (C-4a′), 20.9 (C-4a″). MS (70 eV): m/z (%) = 476 [$M^+$] (24), 449 (23), 342 (14), 284 (12), 183 (10), 149 (20), 119 (100), 91 (40), 65 (18). Anal. Calcd. for $C_{28}H_{20}N_4O_2S$ (476.55): C, 70.57; H, 4.23; N, 11.76; S, 6.73. Found: C, 70.69; H, 4.29; N, 11.52; S, 6.58.

***(Z)-N-(E)-4-Amino-5-cyano-6-oxo-1-phenyl-1H-indeno[1,2-d][1,3]thiazepin-2(6H)-ylidene)-4-methoxybenzamide (3c).*** Yellowish white crystals (acetone), yield = 407 mg, (85%), m.p. 270–271°C. IR (KBr): 3350, 3150 (w, $NH_2$), 3050–3013 (m, Ar-CH), 2996–2923 (m, aliph.-CH), 2200 (s, CN), 1727, 1665 (s, C=O), 1608 (s, C=N). $^1$H NMR: 8.22 (bs, 2H; $NH_2$), 7.97 (d, $J = 7.4$, 1H; H-7), 7.75 (d, $J = 8.4$, 2H; H-2′), 7.71–7.68 (m, 2H; H-8,9), 7.63 (bs, 3H; H-3″,4″), 7.45 (bs, 2H; H-2″), 6.91 (d, $J = 8.7$, 2H; H-3′), 6.57 (d, $J = 7.5$, 1H; H-10), 3.77 (s, 3H; $OCH_3$). $^{13}$C NMR: 193.4 (C-6), 174.6 (benzamide C=O), 169.6 (C-2), 165.9 (C-4), 163 (C-4′), 143.5 (C-10a), 136.5 (C-9), 136.4 (C-1″), 133.5 (C-6a), 132.6 (C-2′), 131.4 (C-8), 129.6 (C-2″), 129.5 (C-4″), 129.4 (C-3″), 127.4 (C-1′), 125.4 (C-7), 125.0 (C-10), 116.0 (CN), 113.7 (C-3′), 105.2 (C-11), 70.8 (C-5a), 55.4 ($OCH_3$), 53.2 (C-5). MS (70 eV): m/z (%) = 478 [$M^+$] (24), 451 (20), 387 (13), 285 (20), 119 (100), 91 (32), 65 (14). Anal. Calcd. for $C_{27}H_{18}N_4O_3S$ (478.52): C, 67.77; H, 3.79; N, 11.71; S, 6.70. Found: C, 67.97; H, 3.70; N, 11.79; S, 6.85.

***(Z)-N-(E)-4-Amino-5-cyano-1-(4-metoxylphenyl)-6-oxo-1H-indeno[1,2-d][1,3]thiazepin-2(6H)-ylidene)-4-methylbenzamide (3d).*** Yellowish white crystals (DMF/$H_2O$, 10:1), yield = 404 mg, (82%), m.p. 278–280°C. IR (KBr): 3296, 3132 (m, $NH_2$), 3048–3011 (m, Ar-CH), 2992–2914 (m, aliph.-CH), 2212 (s, CN), 1731, 1670 (s, C=O), 1645, 1605 (s, C=N). $^1$H NMR: 8.21 (bs, 2H; $NH_2$), 7.98 (d, $J = 8.5$, 1H; H-7), 7.78 (t, $J = 6.7$, 2H; H-8,9), 7.72 (d, $J = 8.0$, 2H; H-2′), 7.35 (bs, 2H; H-2″), 7.21 (d, $J = 8.0$, 2H; H-3′), 7.16 (d, $J = 8.2$, 2H; H-3″), 6.65 (d, $J = 5.1$, 1H; H-10), 3.89 (s, 3H; $OCH_3$), 2.31 (s, 3H; C—$CH_3$). $^{13}$C NMR: $\delta_C$ 193.4 (C-6), 175.2 (benzamide C=O), 170.3 (C-2), 165.9 (C-4), 159.6 (C-4″), 143.6 (C-4′), 143.2 (C-10a), 136.5 (C-9), 133.4 (C-6a), 132.5 (C-8), 132.3 (C-1″), 130.7 (C-2″), 129.3 (C-2′), 129.0 (C-3′), 128.7 (C-1′), 125.4 (C-7), 125.1 (C-10), 116.0 (C-3″), 114.5 (CN), 105.4 (C-11), 70.5 (C-5a), 55.5 ($OCH_3$), 53.2 (C-5), 21.1 (C—$CH_3$). MS (70 eV): m/z (%) = 492 [$M^+$] (25), 465 (10), 342 (12), 300 (18), 266 (14), 208 (12), 183 (20), 165 (36), 119 (100), 91 (34), 65 (12). Anal. Calcd. for $C_{28}H_{20}N_4O_3S$ (492.55): C, 68.28; H, 4.09; N, 11.37; S, 6.51. Found: C, 68.00; H, 4.12; N, 11.20; S, 6.45.

***(Z)-N-(E)-4-amino-5-cyano-1-(4-iodophenyl)-6-oxo-1H-indeno[1,2-d][1,3]thiazepin-2(6H)-ylidene)-4-methylbenzamide (3e).*** Yellowish white crystals (ethyl acetate), yield = 412 mg (70%), m.p. 294–295°C. IR (KBr): 3275, 3150 (m, $NH_2$), 3063–3013 (m, Ar-CH), 2988–2917 (m, aliph.-CH), 2202 (s, CN), 1732, 1669 (s, C=O), 1643, 1605 (s, C=N). $^1$H NMR: 8.22 (bs, 2H; $NH_2$), 7.99 (d, $J = 8.2$, 2H; H-2″), 7.98–7.94 (m, 1H; H-7), 7.76–7.72 (m, 2H; H-8,9), 7.69 (d, $J = 7.7$, 2H; H-2′), 7.28 (d, $J = 7.6$, 2H; H-3″), 7.21 (d, $J = 7.7$, 2H; H-3′), 6.69–6.65 (m, 1H; H-10), 2.31 (s, 3H; C—$CH_3$). $^{13}$C NMR: 193.2 (C-6), 175.2 (benzamide C=O), 170.2 (C-2), 165.9 (C-4), 143.4 (C-10a), 143.3 (C-4′), 138.3 (C-2″), 136.6 (C-9), 136.1 (C-1″), 133.4 (C-6a), 132.6 (C-1′), 132.2 (C-8), 131.5 (C-3″), 129.3 (C-2′), 129.0 (C-3′), 125.5 (C-7), 125.0 (C-10), 115.9 (CN), 105.0 (C-11), 96.2 (C-4″), 70.9 (C-5a), 53.1 (C-5), 21.2 (C—$CH_3$). MS (70 eV): m/z (%) = 588 [$M^+$] (12), 119 (100), 91 (12), 65 (11). Anal. Calcd. for $C_{27}H_{17}IN_4O_2S$ (588.42): C, 55.11; H, 2.91; N, 9.52; S, 5.45. Found: C, 55.24; H, 2.88; N, 9.28; S, 5.30.

**Biological section**

***Cell culture.*** Human hepatocellular carcinoma (HepG2) cells were routinely cultured in Dulbeco's Modified Eagle's Medium. Media were supplemented with 10% fetal bovine serum, 2 mM L-glutamine, containing 100 units/mL penicillin G sodium, 100 units/mL streptomycin sulphate, and 250 ng/mL amphotericin B. Cells were maintained at subconfluency at 37°C in humidified air containing 5% $CO_2$. For subculturing, monolayer cells were harvested after trypsin/EDTA treatment at 37°C. Cells were used when confluence had reached 75%. Tested samples were dissolved in dimethyl sulphoxide (DMSO). All cell culture material was obtained from Cambrex BioScience (Copenhagen, Denmark). All chemicals were obtained from Sigma/Aldrich, USA, except mentioned. All experiments were repeated three times, unless mentioned.

*Cytotoxicity assay*. Cytotoxicity of tested samples was measured using the MTT cell viability assay. MTT (3-[4,5-

dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide) assay is based on the ability of active mitochondrial dehydrogenase enzyme of living cells to cleave the tetrazolium rings of the yellow MTT and form a dark blue insoluble formazan crystals, which is largely impermeable to cell membranes, resulting in its accumulation within healthy cells. Solubilization of the cells results in the liberation of crystals, which are then solubilized. The number of viable cells is directly proportional to the level of soluble formazan dark blue color. The extent of the reduction of MTT was quantified by measuring the absorbance at 570 nm [9].

*Reagents preparation.* MTT solution: 5 mg/mL of MTT dissolved in 0.9% NaCl. Acidified isopropanol: 0.04 N HCl in absolute isopropanol.

*Procedure.* Cells ($0.5 \times 10^5$ cells/well) in serum-free media were plated in a flat bottom 96-well microplate, and treated with 20 μL of different concentrations of each tested compound for 20 h at 37°C in a humidified 5% $CO_2$ atmosphere. After incubation, media were removed and 40 μL MTT solution/well were added and incubated for an additional 4 h. MTT crystals were solubilized by adding 180 μL of acidified isopropanol/well, and the plate was shaken at room temperature, followed by photometric determination of the absorbance at 570 nm using a microplate ELISA reader. Triplicate repeats were performed for each concentration and the average was calculated. Data were expressed as the percentage of relative viability compared with the untreated cells compared with the vehicle control, with cytotoxicity indicated by <100% relative viability.

*Calculations.* Percentage of relative viability was calculated using the following equation:

$$[\text{Absorbance of treated cells}/\text{Absorbance of control cells} \times 100$$

Then the half maximal inhibitory concentration $IC_{50}$ was calculated from the equation of the dose-response curve.

**Antioxidant activity (scavenging of DPPH).** DPPH is a stable deep violet radical because of its unpaired electron. In the presence of an antioxidant radical scavenger, which can donate an electron to DPPH, the deep violet color decolorizes to the pale yellow nonradical form [10]. The change of color and the subsequent fall in absorbance are monitored spectrophotometrically at $\nu = 520$ nm.

***Reagents preparation.*** Ethanolic DPPH: 0.1 m*M* DPPH/absolute ethanol. Standard ascorbic acid solution: Serial dilutions of ascorbic acid in concentrations ranging from 0 to 2.5 μ*M* in distilled water. A standard calibration curve was plotted using serial dilutions of ascorbic acid in concentrations ranging from 0 to 2.5 μ*M* in distilled water.

*Procedure.* In a flat bottom 96 well-microplate, a total test volume of 200 μL was used. In each well, 20 μL of different concentrations (0–100 μg/mL final concentration) of tested compounds were mixed with 80 μL of ethanolic DPPH were mixed and incubated for 30 min at 37°C. Triplicate wells were prepared for each concentration and the average was calculated. Then photometric determination of absorbance at 515 nm was done using a microplate ELISA reader.

*Calculations.* The half-maximal scavenging capacity ($SC_{50}$) values for each tested compounds and ascorbic acid was estimated *via* two competitive dose curves.

$$\text{Abs}_{50} \text{ of ascorbic acid} = (\text{Abs}_{100} - \text{Abs}_0)/2$$

$SC_{50}$ of ascorbic acid was calculated using the curve equation. $SC_{50}$ of each compound was determined using the curve equation using $Abs_{50}$ of ascorbic acid.

## REFERENCES AND NOTES

[1] Danilkina, N. A.; Mikhailov, L. E.; Ivin, B. A. Russ J Org Chem 2006, 42, 783.

[2] Kihara, Y.; Kabashima, S.; Uno, K.; Okawara, T.; Yamasaki, T.; Furukawa, M. Synthesis 1970, 1020.

[3] Danilkina, N. A.; Mikhailov, L. E.; Ivin, B. A. In the 3rd Euro-Asian Heterocyclic Meeting "Heterocycles in Organic and Combinatorial Chemistry" (EAHM-2004), Novosibirsk, Russia, September 12–17, 2004.

[4] (a) Aly, A. A. Org Biomol Chem 2003, 1, 756; (b) Aly, A. A. Tetrahedron 2003, 59, 1739; (c) Aly, A. A.; Ehrhardt, S.; Hopf, H.; Dix, I.; Jones, P. G. Eur J Org Chem 2006, 335; (d) Hopf, H.; Aly, A. A.; Swaminathan, V. N.; Ernst, L.; Dix, I.; Jones, P. G. Eur J Org Chem 2005, 68; (e) Aly, A. A.; Hopf, H.; Ernst, L.; Dix, I.; Jones, P. G. Eur J Org Chem 2006, 3001; (f) Aly, A. A.; Hopf, H.; Dix, I.; Jones, P. G. Tetrahedron 2006, 62, 4498.

[5] Aly, A. A.; Ahmed, E. Kh.; El-Mokadem, K. M. J Heterocycl Chem 2007, 44, 1431.

[6] Sarkis, G. Y.; Faisal. E. D. J Heterocycl Chem 1985, 22, 137.

[7] Breitmaier, E.; Voelter, W. Carbon-13 NMR Spectroscopy, 3rd ed.; VCH: Weinheim, 1987, 242.

[8] Gewald, K.; Schindler, R. S. Prakt Chem 1990, 332, 223.

[9] Hansen, M. B.; Nielsen, S. E.; Berg, K. J Immunol Methods 1989, 119, 203.

[10] Van Amsterdam, F. T. M.; Roveri, A.; Maiorino, M.; Ratti, E.; Ursini, F. Free Radic Biol Med 1992, 12, 183.

# Synthesis of 14-Aryl-14*H*-dibenzo[*a*,*j*]xanthenes Catalyzed by Acyclic Acidic Ionic Liquids



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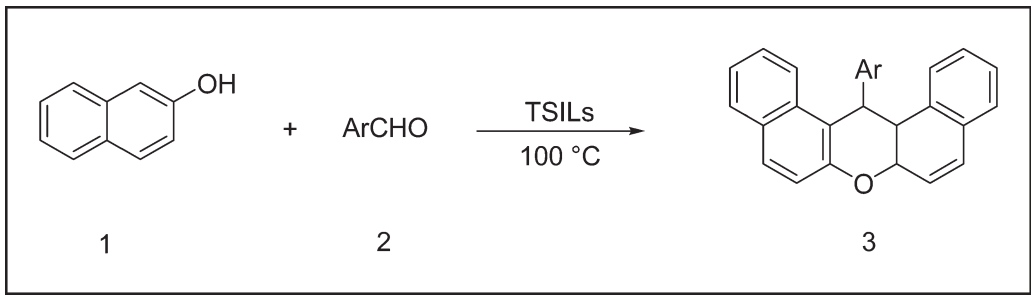


Some recyclable acyclic $SO_3H$-functionalized ionic liquids have been used as novel catalysts for the synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes *via* the one-pot condensation of β-naphthol and aromatic aldehydes in aqueous medium. The condensation reaction was accomplished successfully with various aromatic aldehydes with good to excellent yields ranged from 86 to 96% within 5–30 min. After the reaction, the products could simply be separated from the catalysts by filtration. When separated from the reaction mixture, the catalysts could be recycled and reused for several times without noticeably reducing catalytic activity. The methodology gives the advantages of high yields, short reaction time, and easy work-up procedure.

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## INTRODUCTION

The synthesis of xanthenes derivatives is of much importance because of their wide range of biological and pharmaceutical properties, such as antiviral, and anti-inflammatory activities as well as efficacy in photodynamic therapy [1,2]. Furthermore, these compounds can be used as dyes [3], pH-sensitive fluorescent materials for visualization of bimolecular [4] and used in laser technologies [5]. Recently, many synthetic methods for synthesis of these compounds have been reported by the condensation of aldehydes with β-naphthol in the presence of *p*-toluenesolfonic acid [6], sulfamic acid [7], fluoroboric acid/silica-gel [8], cellulose sulfuric acid [9], zirconium(iv) oxide chloride [10], $CBr_4$ [11], molecular ionine [12], heteropoly acid [13], silica sulfuric acid [14], Amberlyst-15 [15], and cyanuric chloride [16] as catalysts. However, the search for the new readily available and green catalysts is still being actively pursued.

With the increasing public concern over environmental degradation and future resources, it is of great importance for chemists to come up with new approaches that are less hazardous to human health and environment. Being used in large amounts and are usually volatile liquids, the solvents used in organic synthesis are high on the list of environmental pollutants. For overcoming these problems; one approach is to use the water as the green medium, another approach is to develop new processes involving the solvent-free conditions. In recent years, ionic liquids have been emerged as a powerful alternative to conventional molecular organic solvents because of their particular properties, such as undetectable vapor pressure, wide liquid range, as well as ease of recovery and reuse, and making them a greener alternative to volatile organic solvents. Combining the useful characteristics of solid acids and mineral acids, Brønsted acidic task-specific ionic liquids (TSILs) are designed to replace traditional mineral liquid acids, such as sulfuric acid and hydrochloric acid in chemical processes [17]. Such acidic TSILs have dual role (solvent and catalyst) in organic reactions [18–21]. In fact, the use of Brønsted-acidic TSILs as catalysts is an area of ongoing activity; however, development and exploration of acidic TSILs are currently in the preliminary stage.

We are especially interested in developing the potential use of efficient, simple, and inexpensive TSILs

**Table 1**

Synthesis of 14-phenyl-14*H*-dibenzo[*a*,*j*]xanthenes catalyzed by acidic ionic liquids.[a]

| Entry | Catalyst | TSILs (mol %)[b] | Time (min) | Yields (%)[c] |
|---|---|---|---|---|
| 1 | – | – | 180 | – |
| 2 | [TMPSA][$HSO_4$] | 1 | 60 | 80 |
| 3 | [TMPSA][$HSO_4$] | 3 | 30 | 86 |
| 4 | [TMPSA][$HSO_4$] | 5 | 5 | 93 |
| 5 | [TMPSA][$HSO_4$] | 7 | 5 | 94 |
| 6 | [TMPSA][$HSO_4$] | 9 | 5 | 95 |
| 7 | [TMPSA][$HSO_4$] | 15 | 5 | 94 |
| 8 | [TEPSA][$HSO_4$] | 5 | 5 | 90 |
| 9 | [TBPSA][$HSO_4$] | 5 | 5 | 92 |
| 10 | [TMBSA][$HSO_4$] | 5 | 5 | 94 |
| 11 | [TEBSA][$HSO_4$] | 5 | 5 | 93 |
| 12 | [PyPSA][$HSO_4$] | 5 | 5 | 91 |
| 13 | [MIMPSA][$HSO_4$] | 5 | 5 | 93 |
| 14 | [bmim][$HSO_4$] | 5 | 30 | 85 |

[a] 5 mmol benzaldehyde, 10 mmol β-naphthol, water is used as a solvent.
[b] Molar ratio of TSILs to benzaldehyde.
[c] Isolated yields.

catalysts. In our previous work, some novel and relatively cheap $SO_3H$-functional halogen-free acidic ionic liquids that bear an alkane sulfonic acid group in an acyclic trialkylammonium cation have been synthesized and their catalytic activity for acid-catalyzed reactions have also been investigated [22–24]. In continuation of our work in studying acid-catalyzed reactions in ionic liquids, we report here the synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes in acidic ionic liquids.

## RESULTS AND DISCUSSION

For the beginning of this study, benzaldehyde and β-naphthol were used as the model reactants to compare the catalytic performance of the TSILs. As shown in Table 1, nearly no xanthenes could be detected in the absence of ionic liquids (entry 1), which indicated that the catalyst was absolutely necessary for this condensation reaction. All the prepared eight TSILs proved to be very active, leading to 86–95% yield of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes in the presence of 5% TSILs (entries 4, 8–14). In addition, ionic liquids containing the shorter length of alkyl chain are relatively cheaper. Further, the better immiscibility of the resulted xanthenes with the shorter length of alkyl chain should facilitate the separation in work-up procedure. Hence, [TMPSA][$HSO_4$] should be the best catalyst for this condensation among the five acyclic TSILs, and the optimized reaction conditions were presented in Table 1 (entry 4).

**Table 2**

Reusing of the ionic liquid [TMPSA][$HSO_4$].[a]

| Entry | Run | Isolated yield (%) |
|---|---|---|
| 1 | Fresh | 93 |
| 2 | 1 | 94 |
| 3 | 2 | 93 |
| 4 | 3 | 91 |
| 5 | 4 | 92 |
| 6 | 5 | 90 |
| 7 | 6 | 90 |

[a] 5 mmol benzaldehyde, 10 mmol β-naphthol, 0.25 mmol catalyst, 100°C, 5 min.

Compared with the traditional methods, use of volatile solvents and catalysts, which is complex, and time and energy consuming, and environmentally malign, the easy recycling is an attractive property of the TSILs for the environmental protection and economic reasons. So, the recycling performance of [TMPSA][$HSO_4$] in the same model condensation reaction was subsequently explored. After the reaction, the products were isolated from the catalytic system by filtration, the catalyst was reused in the next run directly without further

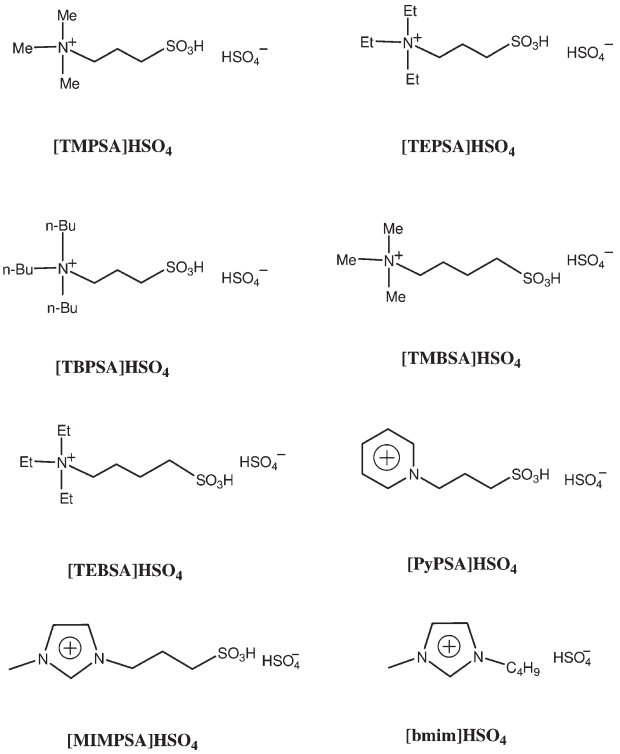
**Table 3**

Synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes catalyzed by [TMPSA][$HSO_4$].[a]

| Entry | Ar | Product | Time (min) | m.p. (°C) [lit.] | Yields (%)[b] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **3a** | 5 | 184–185 [8] | 93 |
| 2 | *o*-$ClC_6H_4$ | **3b** | 10 | 213–215 [6] | 92 |
| 3 | *p*-$ClC_6H_4$ | **3c** | 5 | 286–288 [6] | 96 |
| 4 | 2,4-$ClC_6H_3$ | **3d** | 10 | 228–229 [10] | 95 |
| 5 | *p*-$FC_6H_4$ | **3e** | 5 | 238–239 [6] | 95 |
| 6 | *o*-$NO_2C_6H_4$ | **3f** | 10 | 213–215 [8] | 90 |
| 7 | *m*-$NO_2C_6H_4$ | **3g** | 10 | 211–212 [6] | 91 |
| 8 | *p*-$NO_2C_6H_4$ | **3h** | 5 | 310–312 [8] | 95 |
| 9 | *p*-$CH_3C_6H_4$ | **3i** | 10 | 227–229 [6] | 92 |
| 10 | *p*-$CH_3OC_6H_4$ | **3j** | 30 | 202–204[6] | 86 |

[a] 5 mmol benzaldehyde, 10 mmol β-naphthol, 0.25 mmol catalyst, 100°C.
[b] Isolated yields.

**Scheme 1**




purification. As shown in Table 2, the catalyst can be reused at least six times without appreciable decrease in yield and reaction rate, and the yield ranged from 94–90%.

The condensation reactions of other substituted benzaldehydes and β-naphthol in the presence of [TMPSA][$HSO_4$] were accomplished under the optimized reaction conditions described above and the results are presented in Table 3. It can easily be seen that all aromatic aldehydes with either electro-withdrawing or electro-donating substituents, such as nitro and methoxy groups gave reasonable to good yields ranged from 85–96% with 30 min. However, aromatic aldehydes with electron-withdrawing group are more actively than that with electro-donation one. Their physical properties were determined and structures were confirmed by $^1$H NMR spectral data.

In conclusion,, it was demonstrated that some readily available, economic TSILs have been used as recyclable catalysts for the condensation of benzaldehydes and β-naphthol to synthesis 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes. The merit of this methodology is that it is simple, high efficient, and eco-friendly.

## EXPERIMENTAL

Melting points were determined on X-6 microscope melting apparatus. $^1$H NMR spectra were recorded on Bruker DRX300 (300 or 500 MHz) and $^{13}$C NMR spectra on Bruker DRX300 (75.5 MHz) spectrometer. Mass spectra were obtained with automated FININIGAN Trace Ultra-Trace DSQ GC/MS spectrometer. All chemicals (AR grade) were commercially available and used directly without further purification.

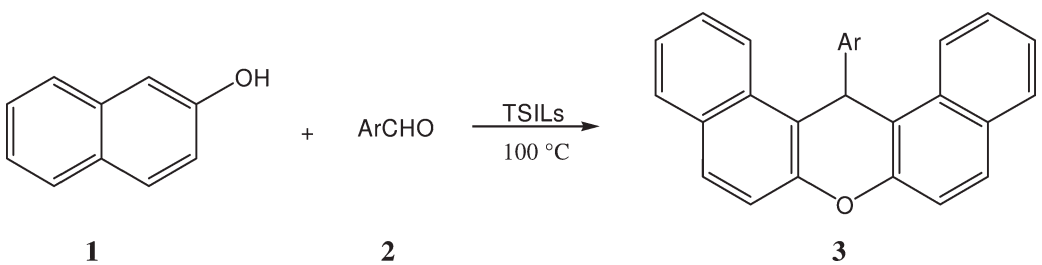
**Synthesis of $SO_3$H-functional halogen-free acidic ionic liquid (TSILs).** All acyclic $SO_3$H-functionalized halogen-free acids, such as [TMPSA][$HSO_4$], [TEPSA][$HSO_4$] were synthesized according to our previous methods [18], the pyridine, imidazole-based $SO_3$H-functionalized ionic liquids for comparison were obtained according to reported methods [16]. The structures of TSILs were analyzed by $^1$H NMR, $^{13}$C NMR, and MS spectral data (Scheme 1).

**The selected spectral data for $SO_3$H-functionalized halogen-free TSILs.** ***N,N,N-trimethyl-N-propanesulfonic acid ammonium hydrogen sulfate [TMPSA][HSO4].*** $^1$H NMR (300 MHz, $D_2O$): δ 3.22 (t, $J$ = 7.2 Hz, 2H, N—$CH_2$—C—C—$SO_3$), 2.90 (s, 9H, N—$CH_3$), 2.73 (t, $J$ = 7.8 Hz, 2H, N—C—C—$CH_2$—$SO_3$), 1.99 (m, 2H, N—C—$CH_2$—C—$SO_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 65.00, 52.51, 47.89, 18.85. MS (*m*/*z*): 279.05 ($M^+$), 182.14(100).

***N,N,N-triethyl-N-propanesulfonic acid ammonium hydrogen sulfate [TEPSA][HSO4].*** $^1$H NMR (300 MHz, $D_2O$): δ 3.22–3.05 (m, 8H, (6H + 2H), N—$CH_2$—$CH_3$, N—$CH_2$—C—C—$SO_3$), 2.85 (t, $J$ = 7.2 Hz 2H, N—C— C—$CH_2$—$SO_3$), 1.97 (m, 2H, N—C—$CH_2$—C—$SO_3$), 1.12 (t, 9H, N—C—$CH_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 56.00, 52.95, 48.34, 18.93, 8.04. MS (*m*/*z*): 321.05 ($M^+$), 322.05, 320.15, 194.05(100).

***N,N,N-tributyl-N-propanesulfonic acid ammonium hydrogen sulfate [TBPSA][HSO4].*** $^1$H NMR (500 MHz, $D_2O$): δ 3.28(t, 2H, $J$ = 4.0 Hz, N—$CH_2$—C—C—$SO_3$), 3.13(t, 6H, $J$ = 8.5 Hz, N—$CH_2$—C—C—$CH_3$), 2.85(t, 2H, $J$ = 7.0 Hz, N—C—C—$CH_2$—$SO_3$), 2.03 (m, 2H, N—C—$CH_2$—C—$SO_3$), 1.56 (m, 6H, N—C—$CH_2$—C—$CH_3$), 1.27 (m, 6H, N—C—C—$CH_2$—$CH_3$), 0.84 (t, 9H, $J$ = 7.5 Hz, N—C—C—C—$CH_3$).

**Scheme 2**




**1** **2** **3**

$^{13}$C NMR (75.5 MHz, $D_2O$): δ 58.49, 50.66, 48.42, 23.93, 20.36, 19.16, 14.46. MS (*m*/*z*): 405.29 ($M^+$), 406.28, 404.28(100).

***N,N,N-trimethyl-N-butanesulfonic acid ammonium hydrogen sulfate [TMBSA][HSO$_4$].*** $^1$H NMR (300 MHz, $D_2O$): δ 3.24 (t, $J$ = 8.4 Hz, 2H, N—$CH_2$—C—C—C—$SO_3$), 2.99 (s, 9H, N—$CH_3$), 2.85 (t, $J$ = 7.5 Hz, 2H, N—C—C—C—$CH_2$—$SO_3$), 1.82 (m, 2H, N—C—$CH_2$—C—C—$SO_3$), 1.70 (m, 2H, N—C—C—$CH_2$—C—$SO_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 66.15, 53.16, 50.31, 21.46, 19.93. MS (*m*/*z*): 293.36 ($M^+$), 196.39(100).

***N,N,N-triethyl-N-butanesulfonic acid ammonium hydrogen sulfate [TEBSA][HSO$_4$].*** $^1$H NMR (300 MHz, $D_2O$): δ 3.15 (q, $J$ = 7.2 Hz, 6H, N—$CH_2$—$CH_3$), 3.07 (t, $J$ = 8.4 Hz, 2H, N—$CH_2$—C—C—C—$SO_3$), 2.82 (t, $J$ = 7.2 Hz, 2H, N—C—C—C—$CH_2$—$SO_3$), 1.68 (m, 4H, N—C—$C_2H_4$—C—$SO_3$), 1.11 (m, $J$ = 7.2 Hz, 9H, N—$CH_2$—$CH_3$). $^{13}$C NMR (75.5 MHz, $D_2O$): δ 56.21, 52.85, 50.32, 21.50, 20.20, 6.90. MS (*m*/*z*): 335.35 ($M^+$), 208.36(100).

**General procedure for the synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes derivatives.** In a typical experiment, to a round-bottomed flask charged with β-naphthol (10 mmol) **1**, aldehyde (5 mmol) **2** in 5 mL of water was added to acidic ionic liquid (0.25 mmol) under stirring. The mixture was then stirred for a certain time at 100°C (Scheme 2). On completion (monitored by TLC), the precipitated crude product was collected by filtration and recrystallized from ethanol (95%) to afford pure 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes **3**. The filtrate containing ionic liquid could be reused directly in the next run without further purification. The products were identified by IR, $^1$H NMR, and physical data (m.p.) with those reported in the literatures.

**The selected data for chalcone 3a.** ***14-Phenyl-14H-dibenzol[a,j]xanthene (3a, $C_{27}H_{18}O$).*** Colorless crystals; m.p. 184–185°C; IR (KBr, $cm^{-}1$): 3074, 3020, 2886, 1622, 1591, 1513, 1455, 1430, 1401, 1251, 1152, 1078, 1028, 962, 857, 827, 743, 700. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.46 (s, 1H, CH), 6.96 (t, $J$ = 7.2 Hz, 1H, Ar-H), 7.12 (t, $J$ = 7.2 Hz, 2H, Ar-H), 7.36–7.58 (m, 8H, Ar-H), 7.74–7.81 (m, 4H, Ar-H), 8.37 (d, $J$ = 8.4 Hz, 2H, Ar-H).

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## REFERENCES AND NOTES

[1] Jamison, J. M.; Krabill, K.; Hatwalkar, A. Cell Biol Int Rep 1990, 14, 1075.

[2] Chibale, K.; Visser, M.; Schalkwyk, D. V.; Smith, P. J.; Saravanamuthu, A.; Fairlamb, A. H. Tetrahedron 2003, 59, 2289.

[3] Bhowmik, B. B.; Ganguly, P. Spectrochim Acta A 2005, 61, 1997.

[4] Knight, C. G.; Stephens, T. Biochem J 1989, 258, 683.

[5] Ahmad, M.; King, T. A.; Cha, B. H.; Lee, J. J Phy D App Phy 2002, 35, 1473.

[6] Khosropour, A. R.; Khodaei, M. M.; Moghannian, H. Synlett 2005, 6, 955.

[7] Rajitha, B.; Kumar, B. S.; Reddy, Y. T.; Reddy, P. N.; Sreenivasulu, N. Tetrahedron Lett 2005, 46, 8691.

[8] Liu, Y. H.; Tao, X. Y.; Lei, L. Q.; Zhang, Z. H. Synth Commun 2009, 39, 580.

[9] Madhav, J. V.; Reddy, Y. T.; Reddy, P. N.; Reddy, M. N.; Kuarm, S.; Crooks, P. A.; Rajitha, B. J Mol Catal A Chem 2009, 304, 85.

[10] Mosaddegh, E.; Islami, M. R. Org Prep Proced Int 2008, 40, 586.

[11] Raju, B. C.; Pradeep, D. V. S.; Reddy, P. P.; Rao, J. M. Lett Org Chem 2008, 5, 450.

[12] Mohamed, A. P.; Vaderapura, P. J. Bioorg Med Chem Lett 2007, 17, 621.

[13] Mostafa, M. A.; Mozhdeh, S.; Ayoob, B. App Catal A Gen 2007, 323, 242.

[14] Hamid, R. S.; Majid, G.; Asadollah, H. Dyes Pigm 2008, 76, 564.

[15] Ko, S.; Yao, C. F. Tetrahedron Lett 2006, 47, 8827.

[16] Mohammad, A. B.; Majid, M. H.; Gholam, H. M. Catal Commun 2007, 8, 1595.

[17] Welton, T. Coord Chem Rev 2004, 248, 2459.

[18] Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H., Jr. J Am Chem Soc 2002, 124, 5962.

[19] Fang, D.; Zhou, X. L.; Ye, Z. W.; Liu, Z. L. Ind Eng Chem Res 2006, 45, 7982.

[20] Gong, K.; Fang, D.; Wang, H. L.; Liu, Z. L. Dyes Pigm 2009, 80, 30.

[21] Shen, J.; Wang, H.; Lium, H.; Sun,Y.; Liu, Z. J Mol Catal A Chem 2007, 280, 24.

[22] Fang, D.; Luo, J.; Zhou, X. L.; Liu, Z. L. Catal Lett 2007, 116, 76.

[23] Fang, D.; Luo, J.; Zhou, X. L.; Ye, Z. W.; Liu, Z. L. J Mol Catal A Chem 2007, 274, 208.

[24] Fang, D.; Shi, Q. R.; Cheng, J.; Gong, K.; Liu, Z. L. App Catal A Gen 2008, 345, 158.

# Construction of 3,4-Dihydro-1,2-diazete Ring through 4π Electron Cyclization of 4-Hydroxy-2-oxo-2*H* Chromene-3-carbaldehyde [(1*E*)-arylmethylene] Hydrazone



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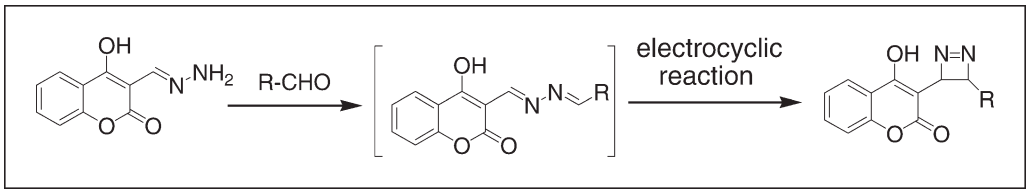


A new, short and efficient synthesis of 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one is described in which the 3,4-dihydro-1,2-diazete ring is constructed from arylmethylene hydrazone by 4π electron cyclization as per electrocyclic reaction.

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## INTRODUCTION

Nitric oxide (NO) has been recognized as an important cellular mediator with diverse biological functions [1,2] including treatment for the respiratory, cardiovascular, infective, and other several diseases [3]. Derivatives of 3,4-dihydro-1,2-diazete-1,2-dioxide have recently been investigated as NO donors *in vitro* and *in vivo* and found to be highly effective vasodilators [4]. 1,2-Diazetine *N*,*N*-dioxides (diazetine dioxides) are a class of strained four-membered ring azo dioxide heterocycles. Although the first report of a diazetine dioxide was as early as 1971, only a handful of such compounds are currently known [5–9]. Diazetine dioxides have been used as highly effective low-energy triplet quenchers in photochemical reactions [10] and have been recently investigated for their biological activity as potent vasorelaxant and antiaggregant agents [7–9,11]. One of the more intriguing aspects of the reactivity of diazetine dioxides is their tendency to liberate 2 equiv of nitric oxide (NO) upon decomposition to yield the corresponding alkene [5,7]. It is the production of the biologically active molecule NO that has suggested the possibility of using diazetine dioxides as pharmaceutical agents [7,11]. The mechanism by which NO is liberated still remains a question [12,13]. Despite the marked pharmaceutical application of diazetidines [14], isosteric diazetenes [15], 1,2-dihydro-1,2-diazetenes [16], and 3,4-dihydro-1,2-dihydro-1,2-diazetenes [17] derivatives, their conjugation with heterocyclic compounds is less studied.

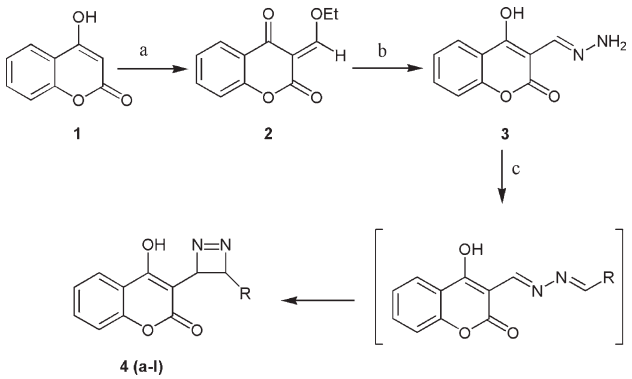
Coumarin and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity [18–26]. Many of these compounds have proved to be active as antitumor [18,19], antibacterial [20,21], antifungal [22–24], anticoagulant [25], and anti-inflammatory [26]. In addition, these compounds are used as additives to food and cosmetics [27], dispersed fluorescent and laser [28].

The potential pharmaceutical utility of 1,2-diazete derivatives and 4-hydroxy coumarin derivatives prompted us to synthesize new 3,4-dihydro-1,2-diazete derivatives incorporated with 4-hydroxy coumarin framework **4**(**a**–**l**).

## RESULTS AND DISCUSSION

The synthesis of 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives **4**(**a**–**l**) is shown in Scheme 1. The precursor 4-hydroxy coumarin **1** was prepared by following the literature methods [29]. A mixture of **1** and triethyl orthoformate containing catalytic amount of *p*-toluene sulfonic acid (PTSA) was subjected to microwave irradiation at 240 W for 2 min to obtain 3-ethoxymethylene-3*H*-2,4-dione (**2**) in moderate yield (∼60%). The hydrolysis of **2** with $K_2CO_3$ resulted into 4-hydroxy coumarin-3-carbaldehyde [30]. Subsequent treatment of the **2** with hydrazine hydrate at ambient temperature afforded 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde- hydrazone (**3**) in excellent yield (∼90%). It was found that the reaction did not require any solvent or external heating. When hydrazone **3** reacted with various aldehydes at 100°C in DMSO containing con. HCl as a catalyst, 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives

**Scheme 1.** Reagents and conditions: (a) Triethyl orthoformate. Microwave irradiation at 240 W, 2 min; (b) $NH_2NH_2 \cdot H_2O$, r.t., Stirr.; (c) R-CHO, DMSO, con. HCl, 100°C, 30 min.




**4a–l** were obtained in good yield (Table 1). One can envisage that the intermediates 4-hydroxy-2-oxo-2*H* chromene-3-carbaldehyde (arylmethylene) hydrazones underwent 4π electron cyclization to form a four membered 1,2-diazete ring system incorporates with 4-hydroxy coumarin nucleolus **4a–l** (Scheme 1). The formation of 1,2-diazete ring system was confirmed by IR, Mass, $^1$H NMR, and $^{13}$C NMR spectral study.

The IR spectrum of **4a** exhibited O—H stretching vibration peak in the range of 3200–3400 $cm^{-1}$ and C=O Stretching vibration of coumarin at 1690 $cm^{-1}$ indicating the presence of hydroxyl group. The $^1$H NMR spectrum of compound **4a** displayed the hydroxyl proton at 14.04 δ ppm as a singlet. Two methine protons of diazete ring were observed at 8.8 and 8.6 δ ppm. The downfield chemical shift of these protons compared with simple 1,2-diazete ring system (4–5 δ ppm reported by G. W. Breton *et al*. [31] and 8.69 δ ppm reported by Yutaka Ishida *et al*. [32]) may be attributed to their conjugation with coumarin and phenyl ring system attached with the diazete structure. Moreover, the chemical shift of methine proton was also compared with that of compound **3** (7.19 δ ppm) also supporting the formation of diazete framework. The assignment of relative stereochemistry of both methine protons can be carried out based on coupling constant. The larger values of derived coupling constants place both protons in trans position. The mass spectrum of **4a** showed three signals $M^+$+1, $M^+$, and $M^+$-$N_2$ at 294, 293, and 264, respectively. Extrusion of $N_2$ from compound in the mass spectra reveals the existence of the cyclic product, which is in accordance with the assigned structure of **4a**.

The mechanism involved in the formation of 1,2-diazete ring follows the electrocyclic reaction. Arylmethylene hydrazone is a conjugated chain containing 4π electron system which undergoes 4π electron cyclization as per pericyclic reaction (Scheme 2).

**Table 1**

Physical properties of the synthesized compounds **4(a–l)**.

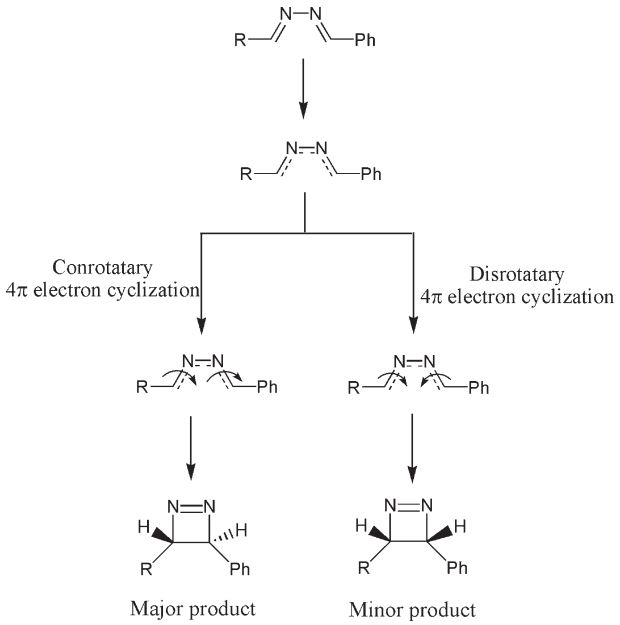
| Entry | Product | R | Yield (%)[a] | Mp (°C) |
|---|---|---|---|---|
| 1 | **4a** | Ph | 75 | 230–232 |
| 2 | **4b** | 4-$CH_3$-$C_6H_4$ | 71 | 214–216 |
| 3 | **4c** | 4-$OCH_3$-$C_6H_4$ | 76 | 206–208 |
| 4 | **4d** | 3,4-di-$OCH_3$-$C_6H_4$ | 85 | 218–220 |
| 5 | **4e** | 2,5-di-$OCH_3$-$C_6H_4$ | 79 | 210–212 |
| 6 | **4f** | 2-Cl-$C_6H_4$ | 65 | 212–214 |
| 7 | **4g** | 4-F-$C_6H_4$ | 65 | 206–208 |
| 8 | **4h** | 2-OH-$C_6H_4$ | 70 | 210–212 |
| 9 | **4i** | 4- $NO_2$-$C_6H_4$ | 80 | 214–216 |
| 10 | **4j** | 4-*N*,*N*-di-$CH_3$-$C_6H_4$ | 60 | 204–206 |
| 11 | **4k** | 3-Pyridyl | 62 | 228–230 |
| 12 | **4l** | 2-Furyl | 58 | 214–216 |

[a] Isolated yields after purification.

## CONCLUSIONS

In summary, novel 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives (**4a–l**) were prepared from 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde hydrazone and various aldehydes in DMSO *via* electrocyclic reaction through 4π electron cyclization. The pharmacological study of all compounds is currently under investigation.

**Scheme 2.** Plausible mechanism of 4π electron cyclization.



## EXPERIMENTAL

Melting points were determined on electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 $F_{254}$ (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. $^1$H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Fluka, Sigma Aldrich, Merck, and Rankem and used without further purification.

**3-Ethoxymethylene-3*H*-chromene-2,4-dione (2).** A mixture of 6.2 mmol of 4-hydroxycoumarin (1.0 g, 6.2 mmol), triethyl orthoformate (7 mL), and *p*-toluenesulfonic acid monohydrate (0.02 g) was placed in a 50 mL beaker. The beaker was covered with a stem-less funnel and irradiated in the microwave oven for 2 min at 240 W. The resultant residue was cooled to room temperature, the solvent was decanted, and the residue was crystallized in chloroform to give pure yellow crystals. Yield: 0.81 g (60%); mp 140–141°C.

**4-Hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde hydrazone (3).** 3-(Ethoxymethylene)-3*H*-chromene-2,4-dione (**2**, 2.18 g, 10 mmol) was stirred at room temperature with excess 50% hydrazine hydrate for about 10–15 min. The solid separated out was filtered and crystallized from chloroform to give **3**, yield: 1.83 (90%); mp 138–140°C. IR (KBr): 3528, 3245, 1689, 1545; $^1$H NMR (400 MHz, DMSO) δ 8.47 (s, 1H, OH), 7.98 (m, 1H, ArH), 7.55 (m, 1H, ArH), 7.23 (m, 2H, ArH), 7.19 (s, 1H, =CH), 5.88 (s, 2H, $NH_2$); MS(EI): 204 ($M^+$).

**General procedure for the synthesis of 4-hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (4a).** A mixture of equimolar amount of 4-hydroxy-2-oxo-2*H*-chromene-3-carbaldehyde hydrazone **3** and benzaldehyde was dissolved in DMSO containing catalytic amount of con. HCl and heated at 100°C for 30 min with stirring. The reaction mixture was allowed to attain room temperature. The separated solid was filtered off and washed with methanol. The crude product obtained was recrystallized from chloroform to give 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (**4a**) as a yellow solid. Yield 75%; mp 230–232°C; IR (KBr) 3200, 1690 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 14.04 (s, 1H, OH), 8.80 (d, $J$ = 12.36 Hz, 1H, CH), 8.67 (d, $J$ = 15.52 Hz, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.45–7.39 (m, 3H, Ar), 7.26–7.17 (m, 2H, Ar); MS(EI) 292 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.78; H, 4.25; N, 9.45.

Compounds **4b–l** were prepared by following the same procedure as described for **4a**.

**4-Hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (4a).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3200, 1690 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.04 (s, 1H, OH), 8.80 (d, $J$ = 12.36 Hz, 1H, CH), 8.67 (d, $J$ = 15.52 Hz, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.45–7.39 (m, 3H, Ar), 7.26–7.17 (m, 2H, Ar); MS(EI) 292 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.78; H, 4.25; N, 9.45.

**4-Hydroxy-3-[4-(4-methylphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4b).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3190, 1690 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.14 (s, 1H, OH), 8.95 (d, $J$ = 12.12 Hz, 1H, CH), 8.60 (d, $J$ = 31.64 Hz, 1H, CH), 8.05 (t, 1H, Ar), 7.69 (d, 2H, Ar), 7.67 (t, 1H, Ar), 7.64–7.60 (m, 4H, Ar), 2.42 (s, 3H, $CH_3$); MS(EI) 306 $[M]^+$. Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.51; H, 4.54; N, 9.05.

**4-Hydroxy-3-[4-(4-methoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4c).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3140, 1716 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.86 (d, $J$ = 12.48 Hz, 1H, CH), 8.70 (d, $J$ = 10.08 Hz, 1H, CH), 8.02 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.62 (t, 1H, Ar), 7.31–7.23 (m, 2H, Ar), 7.00–6.98 (m, 2H, Ar), 3.86 (s, 3H, $OCH_3$); MS(EI) 322 $[M]^+$. Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.11; H, 4.24; N, 8.58.

**3-[4-(3,4-Dimethoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4d).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3210, 1699 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.88 (d, $J$ = 12.30 Hz, 1H, CH), 8.64 (d, $J$ = 14.42 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.82 (d, 2H, Ar), 7.59 (t, 1H, Ar), 7.48–7.20 (m, 3H, Ar), 3.88 (s, 6H, $OCH_3$); MS(EI) 352 $[M]^+$. Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.61; H, 4.49; N, 7.81.

**3-[4-(2,5-Dimethoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4e).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3235, 1687 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.96 (d, $J$ = 2.64 Hz, 1H, CH), 8.90 (d, $J$ = 12.4 Hz, 1H, CH), 8.03 (t, 1H, Ar), 7.91 (d, 2H, Ar), 7.62 (t, 1H, Ar), 7.44 (t, 1H, Ar), 7.30 (t, 1H, Ar); 7.26 (t, 1H, Ar), 3.88 (s, 6H, $OCH_3$); MS(EI) 352 $[M]^+$. Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.59; H, 4.71; N, 7.84.

**3-[4-(2-Chlorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4f).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3221, 1702 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.80 (d, $J$ = 12.28 Hz, 1H, CH), 8.68 (d, $J$ = 18.06 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.61 (t, 1H, Ar), 7.43–7.49 (m, 3H, Ar), 7.22–7.27 (m, 1H, Ar); MS(EI) 326 $[M]^+$. Anal. Calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.37; H, 3.26; N, 8.47.

**3-[4-(4-Fluorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4g).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3088, 1716 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.81 (d, $J$ = 12.58 Hz, 1H, CH), 8.73 (d, $J$ = 10.02 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.74 (d, 2H, Ar), 7.58 (t, 1H, Ar), 7.44–7.49 (m, 2H, Ar), 7.23–7.26 (m, 2H, Ar); MS(EI) 310 $[M]^+$. Anal. Calcd. for $C_{17}H_{11}FN_2O_3$: C, 65.81; H, 3.57; N, 9.03. Found: C, 65.73; H, 3.51; N, 9.12.

**4-Hydroxy-3-[4-(2-hydroxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4h).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3400, 3259, 1696 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO) δ 14.09 (s, 1H, OH), 9.57 (s, 1H, OH), 8.79 (d, $J$ = 12.30 Hz,

1H, CH), 8.66 (d, $J$ = 11.38 Hz, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.46–7.39 (m, 2H, Ar), 7.25–7.17 (m, 2H, Ar); MS(EI) 308 $[M]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.12; H, 4.06; N, 8.94.

**4-Hydroxy-3-[4-(4-nitrophenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (4i).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3490, 1697 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO) δ 14.07 (s, 1H, OH), 8.81 (d, $J$ = 12.18 Hz, 1H, CH), 8.68 (d, $J$ = 15.55 Hz, 1H, CH), 7.99 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.56 (t, 1H, Ar), 7.48–7.57 (m, 3H, Ar), 7.23–7.21 (m, 1H, Ar); MS(EI) 337 $[M]^+$. Anal. Calcd. for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.47; H, 3.18; N, 12.55.

**3-{4-[4-(Dimethylamino)phenyl]-3,4-dihydro-1,2-diazet-3-yl}-4-hydroxy-2*H*-chromen-2-one (4j).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3209, 1719 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO) δ 14.10 (s, 1H, OH), 8.87 (d, $J$ = 12.28 Hz, 1H, CH), 8.71 (d, $J$ = 14.68 Hz, 1H, CH), 8.02 (t, 1H, Ar), 7.75 (d, 2H, Ar), 7.60 (t, 1H, Ar), 7.40–7.32 (m, 2H, Ar), 7.27–7.23 (m, 2H, Ar), 2.97 (s, 6H, $N(CH)_2$); MS(EI) 335 $[M]^+$. Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.88; H, 5.03; N, 12.64.

**4-Hydroxy-3-(4-pyridin-3-yl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (4k).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3235, 1699 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO) δ 14.10 (s, 1H, OH), 8.80 (d, $J$ = 12.96 Hz, 1H, CH), 8.65 (d, $J$ = 14.93 Hz, 1H, CH), 7.95 (t, 1H, Ar), 7.74 (d, 2H, Ar), 7.58 (t, 1H, Ar), 7.14–6.81 (m, 4H, Pyr.); MS(EI) 293 $[M]^+$. Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.37; H, 3.59; N, 14.15.

**3-[4-(2-Furyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (4l).** This compound was obtained according to the earlier general procedure; Yellow solid; IR (KBr): 3266, 1689 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO) δ 14.08 (s, 1H, OH), 8.78 (d, $J$ = 11.08 Hz, 1H, CH), 8.64 (d, $J$ = 15.34 Hz, 1H, CH), 7.90 (t, 1H, Ar), 7.70 (d, 2H, Ar), 7.54 (t, 1H, Ar), 6.98–6.69 (m, 3H, Fur.); MS(EI) 282 $[M]^+$. Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92. Found: C, 63.78; H, 3.41; N, 9.84.

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## REFERENCES AND NOTES

[1] Bredt, D. S.; Snyder, S. H. Annu Rev Biochem 1994, 63, 175.

[2] Schmit, H.; Walter, U. Cell 1994, 78, 919.

[3] Lehmann, J. Expert Opin Ther Pat 2000, 10, 559.

[4] Utepbergenov, D. I.; Khramtsov, V. V.; Vlassenko, L. P.; Markel, A. L.; Mazhukin, D. G.; Tikhonov, A.Y.; Volodarsky, L. B. Biochem Biophys Res Commun 1995, 214, 1023.

[5] Singh, P.; Boocock, D. G. B.; Ullman, E. F. Tetrahedron Lett 1971, 42, 3935.

[6] White, D. K.; Greene, F. D. J Am Chem Soc 1978, 100, 6760.

[7] Severina, I. S.; Belushkina, N. N.; Grigoryev, N. B. Biochem Mol Biol Int 1994, 33, 957.

[8] Kirilyuk, I. A.; Utepbergenov, D. I.; Mazhukin, D. G.; Fechner, K.; Mertsch, K.; Khramtsov, V. V.; Blasig, I. E.; Haseloff, R. J Med Chem 1998, 41, 1027.

[9] Khramtsov, V. V.; Utepbergenov, D. I.; Woldman, Ya. Yu.; Vlassenko, L. P.; Markel, A. L.; Kiriljuk, I. A.; Grigor'ev, I. A.; Mazhukin, D. G.; Tikhonov, A. Ya.; Volodarsky, L. B. Biochemistry (Moscow) 1996, 61, 1223.

[10] (a) Ullman, E. F.; Singh, P. J. J Am Chem Soc 1972, 94, 5077; (b) Singh, P. J.; Ullman, E. F. J Am Chem Soc 1976, 98, 3018.

[11] (a) Wang, G. P.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J Chem Rev 2002, 102, 1091; (b) Yelinova, V. I.; Bobko, A. A.; Mazhukin, D. G.; Markel, A. L.; Khramtsov, V. V. Russ J Bioorg Chem 2003, 29, 395; (c) Utepbergenov, D. I.; Khramtsov, V. V.; Vlassenko, L. P.; Markel, A. L.; Mazhukin, D. G.; Tikhonov, A. Ya.; Voldarsky, L. B. Biochem Biophys Res Commun 1995, 214, 1023; (d) Severina, I. S.; Ryaposova, I. K.; Volodarsky, L. B.; Mozhuchin, D. C.; Tichonov, A. Ya.; Schwartz, G. Ya.; Granik, V. G.; Grigoryev, D. A.; Grigoryev, N. B. Biochem Mol Biol Int 1993, 30, 357.

[12] (a) Greene, F. D.; Gilbert, K. E. J Org Chem 1975, 40, 1409; (b) Singh, P. J Org Chem 1975, 40, 1405.

[13] Snyder, J. P.; Heyman, M. L.; Suciu, E. N. J Org Chem 1975, 40, 1395.

[14] Zahradnik, M. The Production and Application of Fluorescent Brightening Agent; Wiley, 1992.

[15] Moore, J. A. In Chemistry of Heterocyclic compounds; Weissberger, A., Ed.; Interscience: New York, 1964; Vol. 19 II, p 916.

[16] Nunn, E. E.; Warrener, R. N. J Chem Soc Chem Commun 1972, 818.

[17] Effenberger, F.; Maier, R. Angew Chem Int Ed 1966, 5, 416.

[18] (a) Raev, L.; Voinov, E.; Ivanov, I.; Popov, D. Pharmazie 1990, 45, 696; (b) Raev, L.; Voinov, E.; Ivanov, I.; Popov, D. Chem Abstr 1990, 114, 74711B.

[19] Nofal, Z. M.; El-Zahar, M.; Abd El-Karim, S. Molecules 2000, 5, 99.

[20] El-Agrody, A. M.; Abd El-Latif, M. S.; El-Hady, N. A.; Fakery, A. H.; Bedair, A. H. Molecules 2001, 6, 519.

[21] Pratibha, S.; Shreeya, P. Indian J Chem 1999, 38B, 1139.

[22] Patonay, T.; Litkei, G. Y.; Bognar, R.; Erdei, J.; Misztic, C. Pharmazie 1984, 39, 86.

[23] Shaker, R. M. Pharmazie 1996, 51, 148.

[24] El-Farargy, A. F. Egypt J Pharm Sci 1991, 32, 625.

[25] Manolov, I.; Danchev, N. D. Eur J Med Chem Chim Ther 1995, 30, 531.

[26] Emmanuel-Giota, A. A.; Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. J Heterocycl chem 2001, 38, 717.

[27] Kennedy, R. O.; Thornes, R. D. Counarins: Biology, Applications and Mode of Action; Wiley, 1997.

[28] Emeleus, H. J.; Hurst, G. L. J Chem Soc 1962, 3276.

[29] Stahmann, M. A.; Wolff, I.; Link, K. P. J Am Chem Soc 1943, 65, 2285.

[30] Rad-Moghadam, K.; Mohseni, M. Monatsh chem 2004, 135, 817.

[31] Breton, G. W.; Shugart, J. H.; Hughey, C. A.; Perala, S. M.; Hicks, A. D. Org Lett 2001, 3, 3185.

[32] Ishida, Y.; Donnadieu, B.; Bertrand, G. Proc Natl Acad Sci USA 2006, 103, 13585.

# Synthesis of Some New Pyridones, Fused Pyrimidines, and Fused 1,2,4-Triazines



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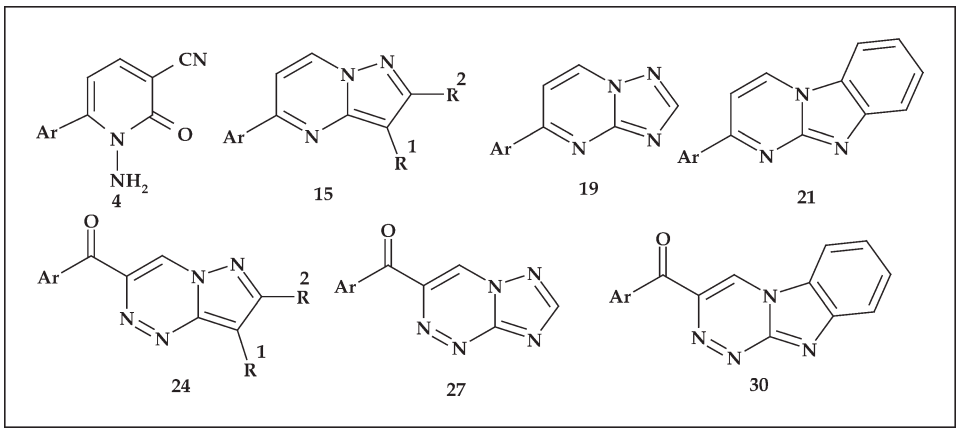


Cyclocondensation of hydrazides, 3-aminopyrazoles, 3-amino-1,2,4-triazole, 2-aminobenzoimidazole, pyrazole-3-diazonium salts, 1,2,4-triazol-3-diazonium salt, or benzoimidazole-2-diazonium salt with sodium salt of 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one gave 2-pyridones, pyrazolo[1,5-*a*]pyrimidines, triazolo[1,5-*a*]pyrimidine, benzo[4,5]imidazo[1,2-*a*]pyrimidine, (pyrazolo[5,1-*c*][1,2,4]triazin-3-yl)-methanone, [1,2,4]triazolo[5,1-*c*][1,2,4]triazin-3-yl-methanone, or benzo[4,5]imidazo[2,1-*c*] [1,2,4]triazin-3-yl-methanone derivatives, respectively, which will be tested for anti-tumor and anti-cancer activates.

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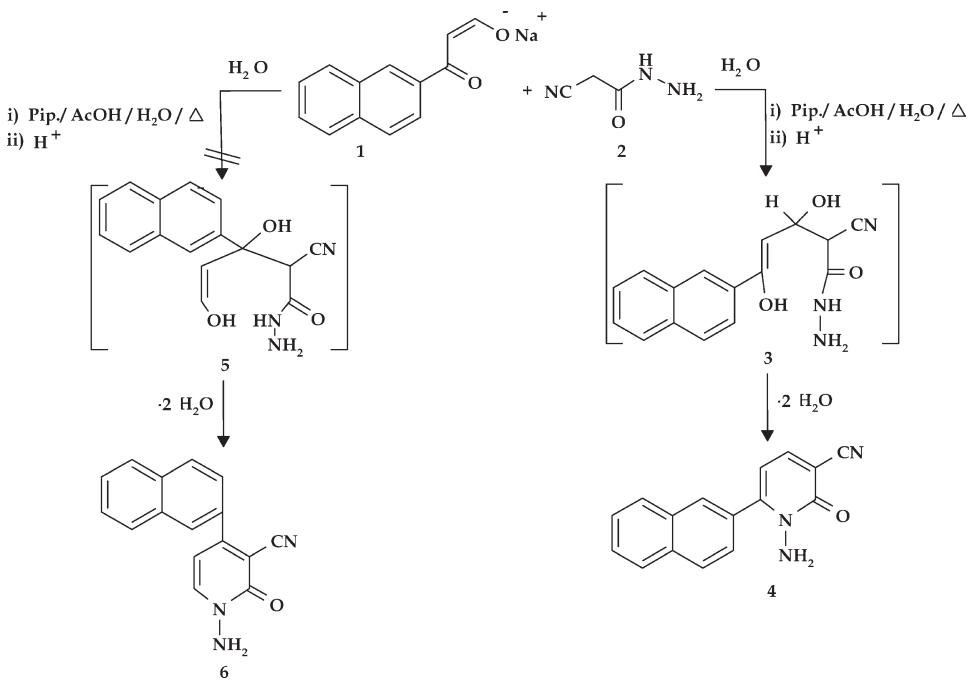
## INTRODUCTION

Chemotherapeutic anticancer agents continue to be an active area of research at many companies and research centers [1–3]. So that, pyridine, pyrazolopyrimidine, and trazine derivatives have received considerable attention due to their wide range of applications in chemotherapy, such as anti-inflammatory, anti-tumor, anti-mycobacterial, anti-fungal, and anti-viral activities [4–6]. Recently, it has been reported that many pyridine and pyrazolopyrimidine derivatives showed strong cytotoxicity against several human cancer cell lines [6–9]. Pyrazolo[4,3-*d*]pyrimidine and pyrazolo[1,5-*a*]pyrimidine derivatives were reported to be inhibitors of tyrosine kinase and cyclin-dependent kinases (CDK) which are involved in mediating the transmission of mitogenic signals and numerous other cellular events [3,10–15], including cell proliferation, migration, differentiation, metabolism, and immune response. It was also found that many of these derivatives may block proliferation of various cancer cell lines [16]. In view of these reports and in continuation with the previous work, here a successful trial for synthesizing new derivatives of pyridones, pyrazolo[1,5-*a*]pyrimidines, triazolo[1,5-*a*]pyrimidine, imidazo[1,2-*a*]pyrimidine, pyrazolo[5,1-*c*]triazine, triazolo[5,1-*c*]triazine, and imidazo [2,1-*c*]triazine derivatives which will be tested for anti-tumor and anti-cancer activates are reported.

## RESULTS AND DISCUSSION

As a part of our program directed for the development of efficient and simple procedures for the synthesis of antimetabolites [17–19], we have recently reported different and successful approaches for the synthesis of 2-pyridones [17,19]. The synthesized compounds act as intermediates for synthesis of deazafolic acid ring system and deazapyrimidine nucleosides, which reported to be significantly active, both *in vitro* and *in vivo* [20,21]. They also act as inhibitor of dihydrofolate reductase [22], cytotoxicity against various experimental tumors as potential as methotrexate [23,24], and one of the most effective antimetabolites currently used in treatment of various solid tumors [25,26]. This prompted our interest to the synthesis and study of the chemistry of this class of compounds [17,18]. Although *N*-amino-2-pyridones have proved to be useful synthetic intermediates, there are few procedures for their preparation and they are usually obtained in low yield by the reaction of hydrazine with 2-pyridones [27,28]. I have reported in this part, one step synthesis of 2-pyridones from the reaction

**Scheme 1**



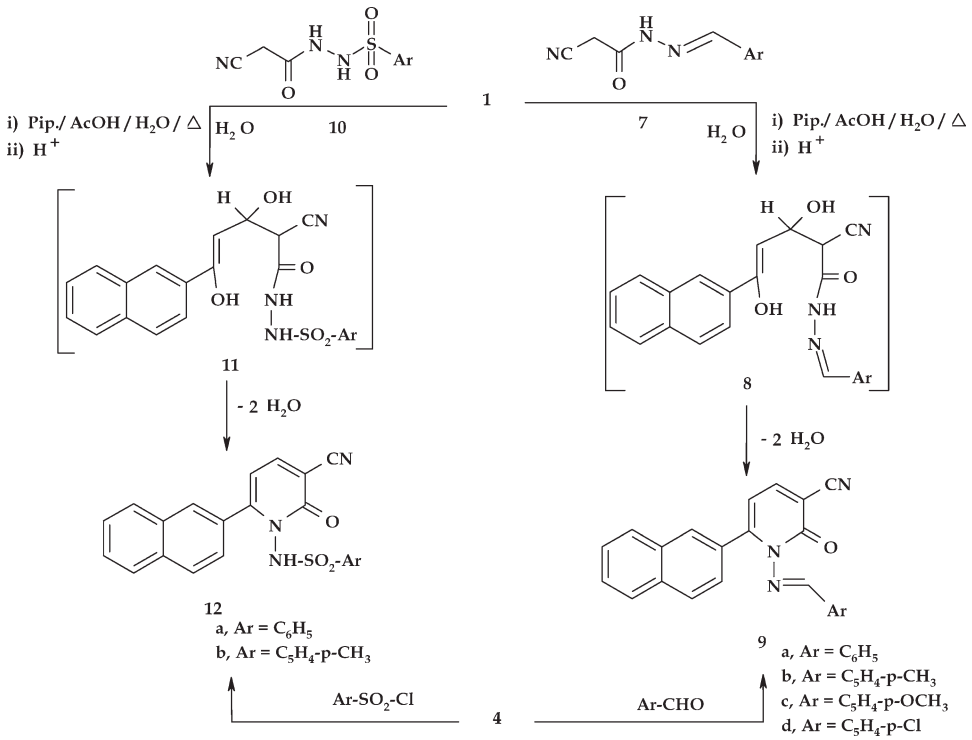
of 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **1** with different hydrazides. Thus, it has been found that salt **1** reacted with cyanoacetic acidhydrazide **2** to give a trisubstituted 2-pyridone. Two modes of cyclization are feasible, giving a 1,2,3,6- or 1,2,3,4-tetrasubstituted products, as outlined in Scheme 1. First, initial attack by a methylene carbanion takes place at the formyl group of the salt **1** and subsequent Michael cyclization followed by elimination of two moles of water to give the 1,2,3,6-trisubstituted product **4**. Second, initial nucleophilic attack by the methylene carbon takes place at the ketonic group, followed by cyclization and elimination of water giving 1,2,3,4-trisubstituted isomer **6**. In fact, only one isomer was obtained, which was suggested to be **4** due to the fact that initial attack of the active methylene carbon at the unhindered formyl group leading to **4** being much more probable than attack at the hindered and electronically disfavored ketonic group [29]. Spectral studies did not allow us to distinguish between structures **4** and **6**. $^1$H-NMR for the product revealed the absence of $CH_2$ and the presence of 2-naphthyl protons from $\delta = 7.54$–8.66 ppm whereas the amino group has two protons at $\delta = 2.70$ ppm in solution. No significant amounts of the alternative regioisomers could be detected. To establish structure of the product, the crystal structure of a similar previous work has been reported [19,29,30]. The X-ray analysis of this work confirms the exclusive presence of the regioisomer **4** [29].

The reaction of sodium salts of 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **1** with arylidenecyanoacetohydrazide **7** and arylsulfonylcyanoacetohydrazide **10** derivatives represents a novel, one step, synthesis of *N*-arylideneamino- and *N*-arylsulphonylamino-2-pyridones, respectively. Thus, it has been found that, salt **1** reacted with arylidenecyanoacetohydrazide **7** to give *N*-arylideneamino-2-pyridones **9,** whereas **1** reacted with arylsufonylcyanoacetohydrazide **10** to give *N*-arylsulfonylamino-2-pyridones **12**. The structure of compound **12b** was established on the basis of its elemental analysis and spectral data (IR, $^1$H-NMR, and MS). Thus, the mass spectra of **12b** was compatible with the molecular formula $C_{23}H_{17}N_3O_3S$ ($M^+$ 415) and the $^1$H-NMR showed a signal at $\delta = 2.35$ ppm assigned for methyl group. Moreover, both **7** and **12** can be obtained from the reaction of **4** with aldehydes or arylsufonylchlorides, respectively, as shown in Scheme 2.

Analogously, treatment of sodium 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **1** with appropriate amounts of 3-aminopyrazoles **13** [31], in the presence of piperidine acetate afforded pyrazolo[1,5-*a*]pyrimidines **15**. Structure of the product **15b** was confirmed by elemental analysis and spectral data (IR, $^1$H–NMR, and MS). The mass spectra of **15b** was compatible with the molecular formula $C_{23}H_{17}N_3$ ($M^+$ 335) and $^1$H NMR for the product revealed the presence of a $CH_3$ protons at $\delta = 2.41$ ppm and methine H of pyrazole at $\delta = 6.22$ ppm and methine 2H of pyrimidine at $\delta = 8.52$ and 8.78 ppm in solutions as shown in Figure 1.

The reaction seemed to proceed via initial nucleophilic attack by the exocyclic amino group of

**Scheme 2**




aminopyrazoles **13** at the ketonic group, which formed *in situ* from salt **1** with water, followed by cyclization and elimination of two moles of water to give the products **15** Scheme 3. It has been suggested that the formation of the alternative isomeric products **17** is based on the initial attack of endocyclic amino group at the ketonic group. The latter suggestion is excluded due to the higher nucleophilicity of the exocyclic primary amino group than the endocyclic amino group which previously reported [17,29,30].

Similarly, treatment of sodium 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **1** with 3-amino-1,2,4-triazole or 2-aminobenzoimidazole in the presence of piperidine acetate afforded 5-(naphthalen-2-yl)[1,2,4]triazolo[1,5-*a*]pyrimidine **19** or 2-(naphthalen-2-yl)benzo[4,5]imidazo[1,2-*a*]pyrimidine **21**, respectively, Scheme 4. The structure of **19** was confirmed by elemental analysis and spectral data (IR, $^1$H–NMR, and MS). The mass spectra of **19** was compatible with the molecular formula $C_{15}H_{10}N_4$ ($M^+$ 246) and $^1$H NMR for the product revealed the presence methine H of triazole at $\delta = 8.27$ ppm and methine 2H of pyrimidine at $\delta = 7.54$ and 8.52 ppm.

Finally, the reaction of sodium 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **1** with pyrazole-3-diazonium salts **22**, 1,2,4-triazol-3-diazonium salt **25,** or benzoimidazole-2-diazonium salt **28** in the presence of piperidine acetate afforded naphthalen-2-yl-(pyrazolo[5,1-*c*][1,2,4] triazin-3-yl)-methanone derivatives **24,** naphthalene-2-yl-[1,2,4]triazolo[5,1-*c*][1,2,4]triazin-3-yl-methanone **27,** or benzo[4,5] imidazo[2,1-*c*][1,2,4]triazin-3-yl-naphthalen-2-yl-methanone **30,** respectively, Scheme 5. The structure of **24** was confirmed by elemental analysis and spectral data (IR, $^1$H-NMR, and MS). The mass spectra of **24a** was compatible with the molecular formula $C_{22}H_{14}N_4O$ ($M^+$ 350) and IR for the product revealed the presence carbonyl group at 1,665 cm$^{-1}$.

## EXPERIMENTAL

All melting points are uncorrected IR spectra were obtained (KBr disk) on a Perkin Elmer 11650 FT-IR instrument. The $^1$H-NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2$ SO using $Si(CH_3)_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

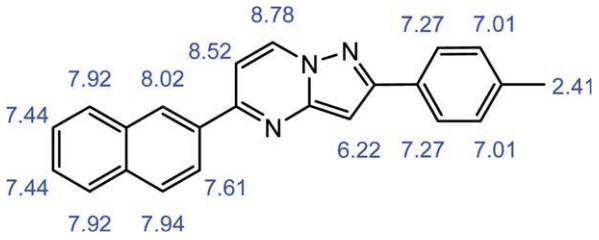
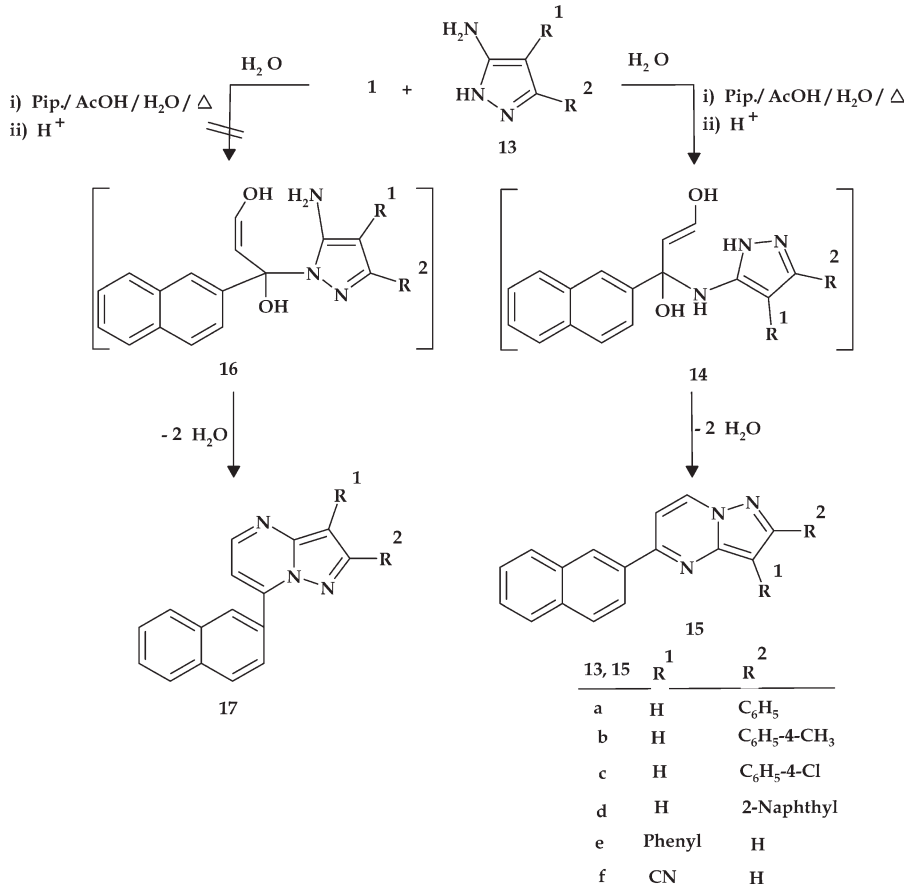


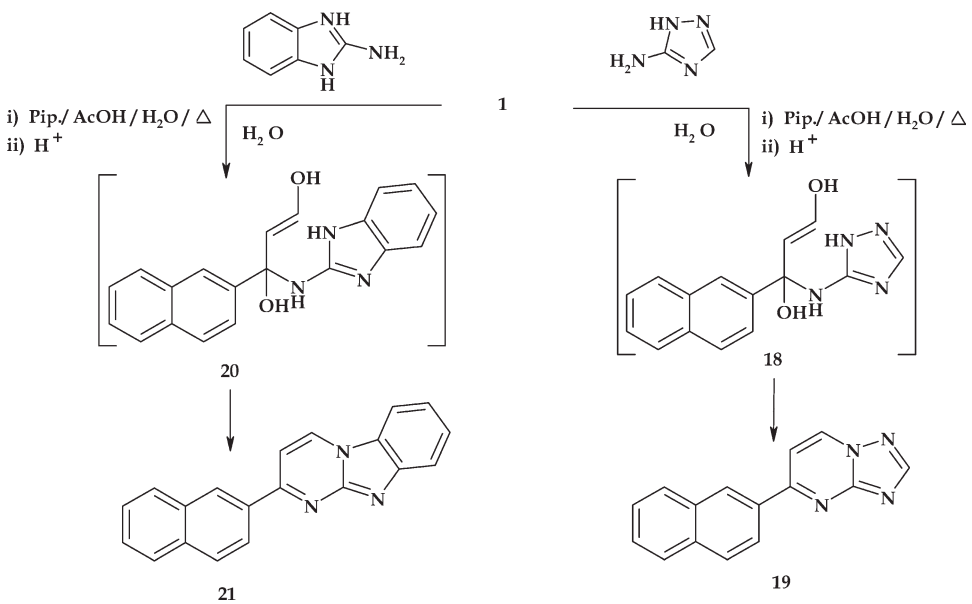

**Figure 1.** $^1$H NMR δ values for **15b.**

**Scheme 3**

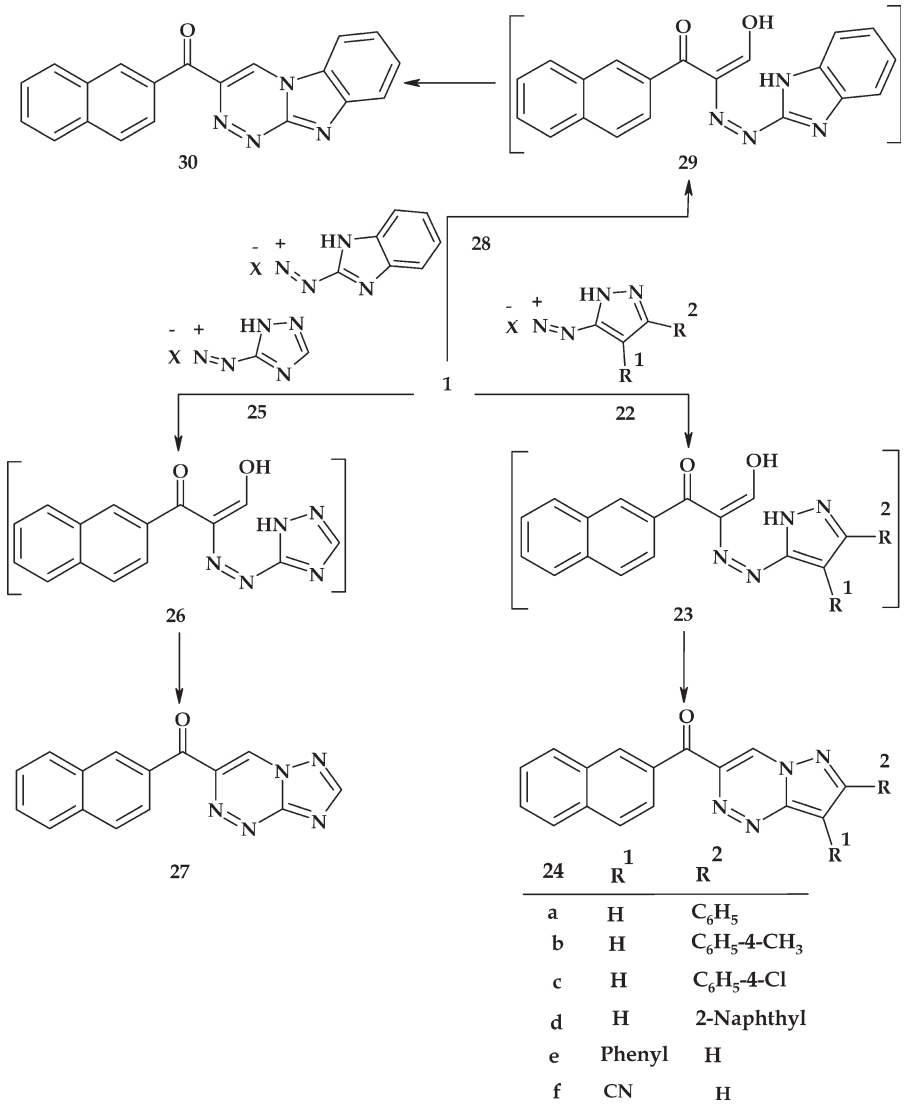



| 13, 15 | $R^1$ | $R^2$ |
|---|---|---|
| a | H | $C_6H_5$ |
| b | H | $C_6H_5$-4-$CH_3$ |
| c | H | $C_6H_5$-4-Cl |
| d | H | 2-Naphthyl |
| e | Phenyl | H |
| f | CN | H |

**Scheme 4**



**Scheme 5**




**2-Pyridones (4), (9a–d), (12a,b), Pyrazolo[1,5-*a*]pyrimidines (15a–f), Triazolo[1,5-*a*]pyrimidine (19), Benzo[4,5]imidazo[1,2-*a*]pyrimidine (21), (pyrazolo [5,1-*c*][1,2,4] triazin-3-yl)-methanones (24a–f), [1,2,4] Triazolo[5,1-*c*] [1,2,4]triazin-3-yl-methanone (27), or Benzo[4,5] imidazo [2,1-*c*][1,2,4]triazin-3-yl-methanone (30).** ***General method (A).*** A mixture of 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **1** (0.01 mole), cyanoacitic acidhydrazide **2**, arylidenecyanoacetohydrazides **7,** arylsulfonylcyanoacetohydrazides **10**, 3-aminopyrazoles **13**, 3-amino-1,2,4-triazole, 2-aminobenzoimidazole, pyrazole-3-diazonium salts **19,** 1,2,4-triazol-3-diazonium salts **22,** or benzoimidazole-2-diazonium salts **25** (0.01 mole) in piperidine acetate (1 mL), {pipridine + acetic acid + $H_2O$}, and $H_2O$ (3 mL) was refluxed for 5 min. Acetic acid (1.5 mL) was added to the hot solution and the performed solid product was filtered off and recrystallized from ethanol.

***Method (B) for preparation of 2-pyridones (9a–d) or (12a,b).*** An equimolar amount of aldehydes or arylsulfonylchlorides was added to a cold solution of compounds **4** in pyridine. The mixture was stirred for 12h and then poured over ice-water mixture and neutralized with dil. HCl. The formed solid product was filtered off to produce 2-pyridones **9** or **12**, respectively.

***2-Pyridone (4).*** Yellow crystals from EtOH, (yield 72%), m.p. 278–280°C, $\nu_{max}/cm^{-1}$ (KBr) 3388 and 3168 ($NH_2$), 3043 (CH, aromatic), 2210.9 (CN), 1643 (CO); $^1$H-NMR (300 MHz, DMSO-d6): $\delta$ = 2.49 (s, 2H, $NH_2$), 7.54–8.73 (m, 9H, aromatic); m/z 261 (Calcd for $C_{16}H_{11}N_3O$ (261.29):C, 73.55; H, 4.24; N, 16.08%. Found: C, 73.37; H, 4.36; N, 15.92%).

***2-Pyridones (9a–d).*** *9a.* Pale yellow crystals from EtOH, (yield 74%), m.p. 235°C, $\nu_{max}/cm^{-1}$ (KBr) 3048 (CH, aromatic), 2206.3 (CN), 1662 (CO); $^1$H-NMR (300 MHz, DMSO-d6): δ = 6.13–7.71 (m, 14H, aromatic), 8.10 (s, 1H, =CH); m/z 349 (Calcd for $C_{23}H_{15}N_3O$ (349.40): C, 79.07; H, 4.33; N, 12.03%. Found: C, 79.16; H, 4.14; N, 12.12%).

*9b.* Pale yellow crystals from EtOH, (yield 79%), m.p. 230°C, $\nu_{max}/cm^{-1}$ (KBr) 3033 (CH, aromatic), 2198.3 (CN), 1675 (CO); $^1$H-NMR (300 MHz, DMSO-d6): δ = 2.35 (s, 3H, $CH_3$), 6.27–7.70 (m, 13H, aromatic), 8.07 (s, 1H, =CH); m/z 363 (Calcd for $C_{24}H_{17}N_3O$ (363.42): C, 79.32; H, 4.72; N, 11.56%. Found: C, 79.38; H, 4.64; N, 11.62%).

*9c.* Pale yellow crystals from EtOH, (yield 77%), m.p. 220°C, $\nu_{max}/cm^{-1}$ (KBr) 3064 (CH, aromatic), 2208.3 (CN), 1671 (CO); $^1$H-NMR (300 MHz, DMSO-d6): δ = 3.76 (s, 3H, $CH_3$), 6.29–7.73 (m, 13H, aromatic), 8.09 (s, 1H, =CH); m/z 379 (Calcd for $C_{24}H_{17}N_3O_2$ (379.42): C, 75.98; H; 4.52; N, 11.07%. Found: C, 75.92; H; 4.61; N, 11.12%).

*9d.* Pale yellow crystals from EtOH, (yield 71%), m.p. 200°C, $\nu_{max}/cm^{-1}$ (KBr) 3051 (CH, aromatic), 2199.1 (CN), 1661 (CO); $^1$H-NMR (300 MHz, DMSO-d6): δ = 6.31-7.72 (m, 13H, aromatic), 8.12 (s, 1H, =CH); m/z 383 (Calcd for $C_{23}H_{14}ClN_3O$ (383.84): C, 71.97; H, 3.68; Cl, 9.24; N, 10.95%. Found: C, 72.03; H, 3.64; Cl, 9.31; N, 11.02%).

***2-Pyridones (12a,b).*** *12a.* Pale yellow crystals from EtOH, (yield 73%), m.p. 220°C, $\nu_{max}/cm^{-1}$ (KBr) 3350 (NH), 3061 (CH, aromatic), 2208.1 (CN), 1666 (CO); $^1$H-NMR (300 MHz, DMSO-d6): δ = 2.0 (s, 1H, NH), 6.13–7.93 (m, 14H, aromatic); m/z 401 (Calcd for $C_{22}H_{15}N_3O_3S$ (401.45): C, 65.82; H, 3.77; N, 10.47; S, 7.99%. Found: C, 65.93; H, 3.65; N, 10.54; S, 8.05%).

*12b.* Pale yellow crystals from EtOH, (yield 75%), m.p. 290°C, $\nu_{max}/cm^{-1}$ (KBr) 3361 (NH), 3064 (CH, aromatic), 2210.1 (CN), 1664 (CO); $^1$H NMR (300 MHz, DMSO-d6): δ = 2.1 (s, 1H, NH), 2.35 (s, 3H, $CH_3$), 6.15–7.94 (m, 13H, aromatic); MS: m/z = 415 (2.56, M), 345 (36.34%), 280 (53.54%), 238 (85.33%), 234 (39.34%), 121 (80.65%), 92 (90.54%), 69 (100%); (Calcd for $C_{23}H_{17}N_3O_3S$ (415.47): C, 66.49; H, 4.12; N, 10.11; S, 7.72%. Found: C, 66.52; H, 4.07; N, 10.21; S, 7.80%).

***Pyrazolo[1,5-a]pyrimidines (15a–f).*** *15a.* Colorless crystals from EtOH, (yield 78%), m.p. 210°C, $\nu_{max}/cm^{-1}$ (KBr) 3073 (CH, aromatic); $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.53 (s, 1H), 7.22–7.89 (m, 13H, aromatic), 8.50 (d, 1H); m/z 321 (Calcd for $C_{22}H_{15}N_3$ (321.38): C, 82.22; H, 4.70; N, 13.07%. Found: C, 82.20; H, 4.77; N, 13.13%).

*15b.* Colorless crystals from EtOH, (yield 75%), m.p. 194°C, $\nu_{max}/cm^{-1}$ (KBr) 3082 (CH, aromatic); $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, $CH_3$), 6.21 (s, 1H), 7.01–8.05 (m, 11H, aromatic), 8.52 (d, 1H), 8.78 (d, 1H); m/z 335 (Calcd for $C_{23}H_{17}N_3$ (335.41): C, 82.36; H, 5.11; N, 12.53%. Found: C, 82.27; H, 5.04; N, 12.56%).

*15c.* Colorless crystals from EtOH, (yield 71%), m.p. 225°C, $\nu_{max}/cm^{-1}$ (KBr) 3051 (CH, aromatic); $^1$H-NMR (300 MHz, $CDCl_3$): δ = 6.23 (s, 1H), 7.02–8.02 (m, 11H, aromatic), 8.57 (d, 1H), 8.75 (d, 1H); m/z 355 (Calcd for $C_{22}H_{14}ClN_3$ (355.83): C, 74.26; H, 3.97; Cl, 9.96; N, 11.81%. Found: C, 74.15; H, 4.05; Cl, 9.87; N, 11.90%).

*15d.* Colorless crystals from EtOH, (yield 82%), m.p. 220°C, $\nu_{max}/cm^{-1}$ (KBr) 3062 (CH, aromatic); $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.53 (s, 1H), 7.22–7.89 (m, 14H, aromatic), 8.51 (d, 1H), 8.78 (d, 1H); m/z 371 (Calcd for $C_{26}H_{17}N_3$ (371.45): C, 84.07; H, 4.61; N, 11.31%. Found: C, 84.16; H, 4.52; N, 11.36%).

*15e.* Colorless crystals from EtOH, (yield 73%), m.p. 190°C, $\nu_{max}/cm^{-1}$ (KBr) 3073 (CH, aromatic); $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.89 (m, 12H, aromatic), 8.12 (d, 1H), 8.51 (s, 1H), 8.62 (d, 1H); m/z 321 (Calcd for $C_{22}H_{15}N_3$ (321.38): C, 82.22; H, 4.70; N, 13.07%. Found: C, 82.26; H, 4.65; N, 13.02%).

*15f.* Colorless crystals from EtOH, (yield 75%), m.p. 225°C, $\nu_{max}/cm^{-1}$ (KBr) 3053(CH, aromatic), 1223 (CN); $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.89 (m, 7H, aromatic), 7.60 (d, 1H), 8.15 (s, 1H), 8.51 (d, 1H); m/z 270 (Calcd for $C_{17}H_{10}N_4$ (270.30): C, 75.54; H, 3.73; N, 20.73%. Found: C, 75.51; H, 3.82; N, 20.80%).

***Triazolo[1,5-a]pyrimidine (19).*** Colorless crystals from EtOH, (yield 72%), m.p. 210°C, $\nu_{max}/cm^{-1}$ (KBr) 3053(CH, aromatic); $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.89 (m, 7H, aromatic), 7.52 (d, 1H), 8.27 (s, 1H), 8.50 (d, 1H); m/z = 246 (Calcd for $C_{15}H_{10}N_4$ (246.27): C, 73.16; H, 4.09; N, 22.75%. Found: C, 73.19; H, 4.13; N, 22.64%).

***Benzo[4,5]imidazo[1,2-a]pyrimidine (21).*** Colorless crystals from EtOH, (yield 78%), m.p. 230°C, $\nu_{max}/cm^{-1}$ (KBr) 3053(CH, aromatic); $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.89 (m, 11H, aromatic), 7.52 (d, 1H), 8.50 (d, 1H); m/z 295 (Calcd for $C_{20}H_{13}N_3$ (295.35): C, 81.34; H, 4.44; N, 14.23%. Found: C, 81.39; H, 4.38; N, 14.27%).

***(Pyrazolo[5,1-c][1,2,4]triazin-3-yl)-methanones (24a–f).*** *24a.* Colorless crystals from AcOH, (yield 75%), m.p. 210°C, $\nu_{max}/cm^{-1}$ (KBr) 3073 (CH, aromatic), 1665 (CO); $^1$H NMR (300 MHz, DMSO-d6): δ = 6.53 (s, 1H), 7.22–8.22 (m, 12H, aromatic), 9.56 (s, 1H); m/z 350 (Calcd for $C_{22}H_{14}N_4O$ (350.38): C, 75.42; H, 4.03; N, 15.99%. Found: C, 75.45; H, 4.12; N, 16.04%).

*24b.* Colorless crystals from AcOH, (yield 73%), m.p. 194°C, $\nu_{max}/cm^{-1}$ (KBr) 3082 (CH, aromatic), 1665 (CO); $^1$H NMR (300 MHz, DMSO-d6): δ = 2.35 (s, 3H, $CH_3$), 6.21 (s, 1H), 7.12–8.22 (m, 11H, aromatic),

9.46 (s, 1H); m/z 364 (Calcd for $C_{23}H_{16}N_4O$ (364.41): C, 75.81; H, 4.43; N, 15.37%. Found: C, 75.87; H, 4.52; N, 15.41%).

*24c.* Colorless crystals from AcOH, (yield 71%), m.p. 225°C, $\nu_{max}/cm^{-1}$ (KBr) 3051 (CH, aromatic), 1663 (CO); $^1H$ NMR (300 MHz, DMSO-d6): $\delta$ = 6.53 (s, 1H), 7.22–7.86 (m, 11H, aromatic), 9.42 (s, 1H); m/z 384 (Calcd for $C_{22}H_{13}ClN_4O$ (384.83): C, 68.67; H, 3.41; Cl, 9.21; N, 14.56%. Found: C, 68.53; H, 3.36; Cl, 9.30; N, 14.62%).

*24d.* Colorless crystals from AcOH, (yield 79%), m.p. 220°C, $\nu_{max}/cm^{-1}$ (KBr) 3062 (CH, aromatic), 1654(CO); $^1H$ NMR (300 MHz, DMSO-d6): $\delta$ = 6.53 (s, 1H), 7.32–8.22 (m, 14H, aromatic), 9.46 (s, 1H); m/z 400 (Calcd for $C_{26}H_{16}N_4O$ (400.44): C, 77.99; H, 4.03; N, 13.99%. Found: C, 78.05; H, 4.11; N, 14.04%).

*24e.* Colorless crystals from AcOH, (yield 77%), m.p. 226–230°C, $\nu_{max}/cm^{-1}$ (KBr) 3073 (CH, aromatic), 1646 (CO); $^1H$ NMR (300 MHz, DMSO-d6): $\delta$ = 7.22–7.89 (m, 12H, aromatic), 8.40 (s, 1H), 9.46 (s, 1H); MS: m/z = 350 (34.57%, $M^+$ 1), 350 (100%, M), 321 (9.27%), 154 (85.33%), 126 (58.26%), 100 (3.93%), 69 (4.95%), 55 (8.15%) (Calcd for $C_{22}H_{14}N_4O$ (350.38): C, 75.42; H, 4.03; N, 15.99%. Found: C, 75.37; H, 4.06; N, 15.92%).

*24f.* Colorless crystals from AcOH, (yield 77%), m.p. 225°C, $\nu_{max}/cm^{-1}$ (KBr) 3064(CH, aromatic), 1653 (CO), 1221 (CN); $^1H$ NMR (300 MHz, DMSO-d6): $\delta$ = 7.32–8.22 (m, 7H, aromatic), 7.63 (s, 1H), 9.36 (s, 1H); m/z 299 (Calcd for $C_{17}H_9N_5O$ (299.29): C, 68.22; H, 3.03; N, 23.40%. Found: C, 68.15; H, 3.23; N, 23.64%).

***[1,2,4]Triazolo[5,1-c][1,2,4]triazin-3-yl-methanone (27)*** Color-less crystals from AcOH, (yield 74%), m.p. 260°C, $\nu_{max}/cm^{-1}$ (KBr) 3053(CH, aromatic), 1665 (CO); $^1H$ NMR (300 MHz, DMSO-d6): $\delta$ = 7.32–8.21 (m, 7H, aromatic), 8.27 (s, 1H), 9.46 (s, 1H); m/z = 275 (Calcd for $C_{15}H_9N_5O$ (275.27): C, 65.45; H, 3.30; N, 25.44%. Found: C, 65.36; H, 3.22; N, 25.51%).

***Benzo[4,5] imidazo[2,1-c][1,2,4]triazin-3-yl-methanone (30)*** Colorless crystals from AcOH, (yield 76%), m.p. 230°C, $\nu_{max}/cm^{-1}$ (KBr) 3053(CH, aromatic), 1665 (CO); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.32–8.22 (m, 11H, aromatic), 9.45 (s, 1H); m/z 324 (Calcd for $C_{20}H_{12}N_4O$ (324.34): C, 74.06; H, 3.73; N, 17.27%. Found: C, 74.13; H, 3.67; N, 17.32%).

## REFERENCES AND NOTES


[1] Bridges, A. J. Chem Rev 2001, 101, 2541.

[2] Wang, J. D.; Miller, K.; Boschelli, D. H.; Ye, F.; Wu, B.; Floyd, M. B.; Powell, D. W.; Wissner, A.; Weber, J. M.; Boschelli, F. Bioorg Med Chem Lett 2000, 10, 2477.

[3] Shenone, S.; Bruno, O.; Bondavalli, F.; Ranise, A.; Mosti, L.; Menozzi, G.; Fossa, P.; Donnini, S.; Santoro, A.; Ziche, M.; Manetti, F.; Botta, M. Eur J Med Chem 2004, 39, 939.

[4] Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Micky, J. A.; Abdel-Megeid, F. M. E. Biorg Med Chem 2008, 16, 7102.

[5] Shaheen, F.; Badashah, A.; Gielen, M.; Gieck, C.; Jamil, M.; de Vos, D. J Organometallic Chem 2008, 693, 1117.

[6] Son, J.; Zhao, L.; Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Ch. Jeong, T.; Jeong, B.; Lee, C.; Lee, E. Eur J Med Chem 2008, 43, 675.

[7] Zhao, L. X.; Sherchan, J.; Park, J. K.; Jhang, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E. S. Arch Pharm Res 2006, 29, 1091.

[8] Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E. S. Bioorg Med Chem 2007, 15, 4351.

[9] Cesarini, S.; Spallarossa, A.; Ranise, A.; Schenone, S.; Rosano, G.; La Colla, P.; Sanna, G.; Bernardetta, B.; Loddo, R. Eur J Med Chem 2009, 44, 1106.

[10] Kim, D. C.; Lee, Y. R.; Yang, B.; Shin, K. J.; Kim, D. J.; Chung, B. Y.; Yoo, K. H. Eur J Med Chem 2003, 38, 525.

[11] Shenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Fossa, P.; Mosti, L.; Menozzi, G.; Carraro, F.; Naldini, A.; Bernini, C.; Manetti, F.; Botta, M. Bioorg Med Chem Lett 2004, 14, 2511.

[12] Morisi, R.; Celano, M.; Tosi, E.; Schenone, S.; Navarra, M.; Ferretti, E.; Costante, G.; Durante, C.; Botta, G.; D'Agostino, M.; Brullo, C.; Filetti, S.; Botta, M.; Russo, D. J Endocrinol Invest 2007, 30, RC31.

[13] Angelucci, A.; Schenone, S.; Gravina, G. L.; Muzi, P.; Festuccia, C.; Vicentini, C.; Botta, M.; Bologna, M. Eur. J. Cancer 2006, 42, 2838.

[14] Farley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebben, A. J.; Rutledge, R. Z. R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. Bioorg Med Chem Lett 2002, 12, 2767.

[15] Farley, M. E.; Rubino, R. S.; Hoffman, W. F.; Hambaugh, S. R.; Arrington, K. L.; Hungate, R. W.; Bilodeau, M. T.; Tebben, A. J.; Rutledge, R. Z.; Kendall, R. L.; McFall, R. C.; Huckle, W. R.; Coll, K. E.; Thomas, K. A. Bioorg Med Chem Lett 2002, 12, 3537.

[16] Krystof, V.; Moravcova, D.; Paprskarova, M.; Barbier, P.; Peyrot, V.; Hlobikova, A.; Havlicek, L.; Stramd, M. Eur J Med Chem 2006, 41, 1405.

[17] Ahmed, O. M.; Mohamed, M. A.; Ahmed R. R.; Ahmed, S. A. Eur J Med Chem 2009, 44, 3519.

[18] Ahmed, S. A.; El-Ghandour, A. H. H.; Abdelhamid, A. O.; Mohamed, M. A.; Mohamed, B. M. J Chem Res 2008, 1, 26.

[19] Elgemeie, G. H.; Elghandour, A. H.; Elzanate A. M.; Mohamed, M. A. Mansora Sci Bull 2004, 31.

[20] Temple, C.; Elliot, R. D.; Montgomery, J. A. J Org Chem 1982, 47, 761.

[21] Taylor, E. C.; Palmer, D. C.; George, T. J.; Fletcher, S. R.; Tseng, C. P.; Horrion, P. J.; Beardsley G. P. J Org Chem 1983, 48, 4852.

[22] Stone, S. R.; Montgomery, J. A.; Morrision, J. F. Biochem Pharmcol 1974, 33, 175.

[23] Grivsky, E. M.; Lee, S.; Sigel, S. W.; Durch, D. S.; Nichol, C. A. J Med Chem 1980, 23, 327.

[24] Ensminger, W. D.; Grindey, G. B.; Hoglind, J. A. In Advances in Cancer Chemotherapy; Rosowsky, A., Ed.; Marcel Dekker: New York, 1976; 1, p 61.

[25] DeGraw, J. I.; Christine, P. H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. J Med Chem 1990, 33, 673.

[26] Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. J Med Chem 1985, 28, 914.

[27] Katritzky, A. R. Handbook of Heterocyclic Chemistry; Pergmon Press: Elmsford, NY, 1985.

[28] Rees, C. W.; Yelland, M. J Chem Soc Perkin Trans 1, 1972, 77.

[29] Elgemeie, G. H.; Mohamed, M. A.; Jones, P. G. Acta Crystallogr E 2002, 58, 1293.

[30] Ahmed, S. A.; Hussein, A. M.; Hozayen, W. G. M.; El-Ghandour, A. H. H.; Abdelhamid, A. O. J Heterocyclic Chem 2007, 44, 803.

[31] David, M. D.; Amy, H.; Steven, M.; James, R.; Anderow, J. Tetrahedron 2004, 60, 90.

# Synthesis of Imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and Benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones with the Aid of Low-Valent Titanium Reagent



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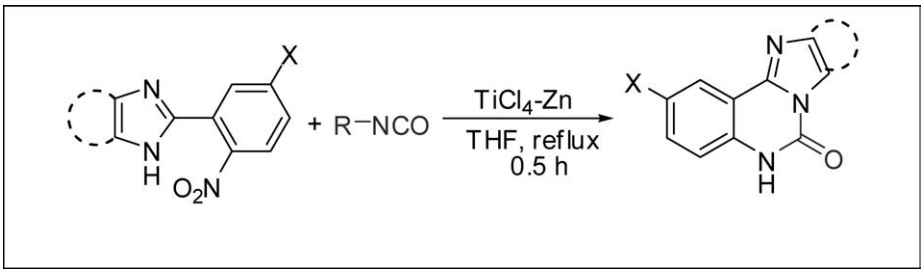


A short and facile synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones was accomplished in good yields *via* the novel reductive cyclization of 2-(2-nitrophenyl)-imidazoles or 2-(2-nitrophenyl)benzoimidazoles with isocyanates promoted by low-valent titanium reagent.

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## INTRODUCTION

Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling of carbonyl compounds, and are attracting increasing interest in organic synthesis [1]. Many other functional groups can also be coupled [2]. Recently, we have reported the low-valent titanium induced intermolecular reductive coupling reaction of carboxylic derivatives with aromatic ketones [3], the intramolecular reductive coupling reaction of 4,4-dicyano-1,3-diaryl-1-butanone [4], the cyclodimerization of α,β-unsaturated ketones [5], and the intramolecular reductive coupling reaction of ketomalononitriles [6].

A literature survey reavealed that quinazolinones show antihypertonic, antirheumatic, antiana-phylactic, antiasthmatic, tranquilizing, neuro-stimulating, and benzodiazepine binding activity [7,8]. For example, 3-substituted quinazolinones, such as SGB-1534 (**1**) [9] and ketanserin (**2**) have been found to have antihypertensive activities mediated *via* α-adrenoceptor and serotonic receptor anatgonism, respectively. Addition of a (2-methoxyphenyl)piperazine side chain at the 2- or 3-position of the angular tricyclic 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system of SGB-1534 resulted in the formation of potent antihypertensive agents such as 2-[[4-(2-methoxyphenyl)-piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**3**) and 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**4**) that selectively antagonized the $\alpha_1$-adrenoceptor [10]. (Fig. 1).

The synthesis of quinazolinones is well studied, and recent development in combinatorial chemistry made the preparation of large number of quinazolinones in a short time possible. Sequential cyclizations of 2-isothio- cyanatobenzonitrile and 2-isocyanatobenzonitrile with α-aminoketones resulted 6*H*-imidazo[1,2-*c*]quinazolinones with high yields [11]. A series of 2-[(substituted- phenylpiperazin-1-yl)methyl]- and 2-[(substitutedphenyl-piperidin-1-yl)methyl]-2,3-dihydroimidzao[1,2-*c*]quinazolin-5(6*H*)-ones were synthesized by bromo-cyclization with NBS in THF at room temperature [10,12]. But many of these still suffer from drawbacks such as drastic conditions, unsatisfactory yields, long-reaction time, high temperature, complex manipulation, and inaccessible starting materials.

Therefore, the development of more efficient methods for the preparation of this kind of compounds is still an active ongoing research area, and there is scope for further improvement toward milder reaction conditions and improved yields. In recent years, our interest has been focused on the synthesis of quinazolines uing low-valent titanium reagent. We have previously reported the synthesis of quinazolines [13], quinazoline-2,4-diones [14], imidazo[1,2-*c*]quinazolines [15], 2-thioxoquinazolinones, imidazo[1,2-*c*]quinazolin-5-amines, and benzimidazo[1,2-*c*] quinazolin-5-amines [16] by the reaction of nitro-

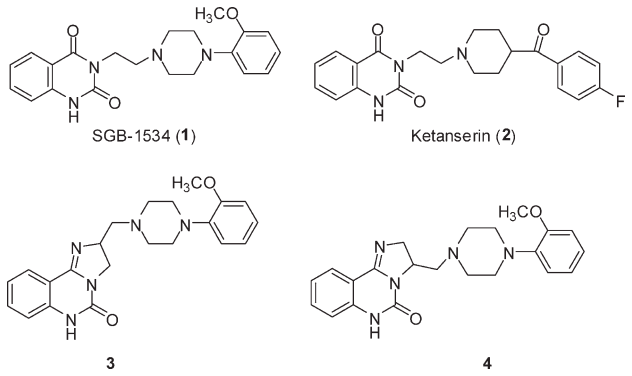



**Figure 1.** SGB-1534 (**1**), Ketanserin (**2**).

compounds with orthoformates, triphosgene, aldehydes, ketones, and isothiocyanates, respectively, induced by low-valent titanium reagent.

As our earlier works goes, herein, we wish to describe a method induced by low-valent titanium reagent for the preparation of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-one using 2-(2-nitrophenyl)imidazole, 2-(2-nitrophenyl)benzoimidazole and isocyanates as starting materials.

## RESULTS AND DISCUSSION

On the basis of our previous experience, we selected 2-(2-nitrophenyl)-4,5-diphenyl-1*H*-imidazoles **1a** and the 1-isocyanato-4-methylbenzene **2a** as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, we briefly examined the effect of different temperatures and low-valent titanium systems. The results obtained from these experiments indicated that the reaction temperatures had a significant influence on the success of this reaction. To our delight at refluxed the reaction proceeded smoothly in high yield (entry 3). To further evaluate the influence of low-valent titanium system, this reaction was carried out with different low-valent titanium reagents. From the results it is obvious that the best system is $TiCl_4$/Zn.

Having established an optimal condition for the protocol, we performed a more detailed examination of the substrates. Thus, the behavior of a variety of substrates, which include different isocyanates as well as different

**Table 1**

Optimization for the reductive cyclization reaction.

| Entry | Temperature (°C) | $TiCl_4$/M | Isolated yield (%) |
|---|---|---|---|
| 1 | r.t. | $TiCl_4$/Zn | 42 |
| 2 | 40 | $TiCl_4$/Zn | 55 |
| 3 | reflux | $TiCl_4$/Zn | 89 |
| 4 | reflux | $TiCl_4$/Fe | 34 |
| 5 | reflux | $TiCl_4$/Mg | 48 |

2-(2-nitrophenyl)imidazoles or 2-(2-nitrophenyl) benzoimidazoles was examined.

First of all, we performed the reaction of a variety of 2-(2-nitrophenyl)imidazoles **1** and isocyanates **2** via $TiCl_4$/Zn system in anhydrous THF (Scheme 2, Table 2).

Furthermore, treatment of 2-(2-nitrophenyl)benzoimidazoles **4** and isocyanates **2** with $TiCl_4$/Zn in anhydrous THF under the same reaction conditions, the reductive cyclization products benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones **5** were obtained in good yields (Scheme 3). The results are summarized in Table 3.

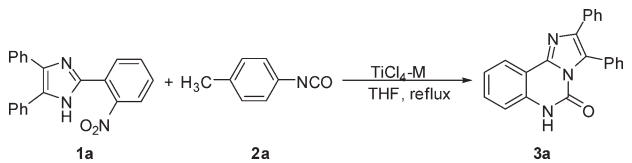
As shown in Table 1 and Table 2, for series of **1** and **2**, either the aromatic ring containing weak electron-withdrawing groups (such as halides) or electron-donating groups (such as alkyl group), reacted well to give the corresponding products **3** in high yields under the same reaction conditions. So we concluded that no obvious effects from the electronic or nature of the aromatic ring substrates were observed in the above reactions.

Because the nitro compounds are easy to be reduced to amines by low-valent titanium reagent [17], we think this reaction may proceed through the intermediate amine **6**. As shown in Scheme 4, the nitro compound was reduced by low-valent titanium to generate amine **6**, which was then reacted with isocyanates to give intermediate **7**. Finally, the expected products **3** were produced by addition and elimination.

All the products were characterized by $^1$H-NMR and IR.

In conclusion, a series of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones were synthesized induced by low-valent titanium reagent ($TiCl_4$/Zn). The process was carried out only

**Scheme 1**




**Scheme 2**

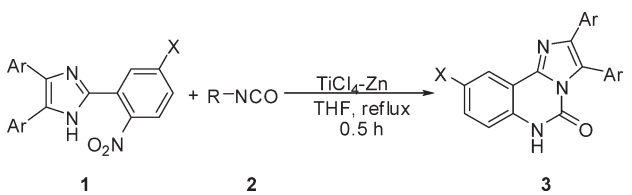


**Table 2**

The synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones **3**.

| Compd. | Ar | X | R | Yield/%[a] |
|---|---|---|---|---|
| **3a** | Ph | H | 4-$CH_3C_6H_4$ | 89 |
| **3b** | Ph | Cl | 4-$CH_3C_6H_4$ | 85 |
| **3c** | 4-$CH_3C_6H_4$ | Cl | 4-$CH_3C_6H_4$ | 88 |
| **3d** | 4-$CH_3OC_6H_4$ | Cl | 4-$ClC_6H_4$ | 92 |
| **3e** | 4-$BrC_6H_4$ | H | 4-$ClC_6H_4$ | 83 |

[a] Isolated yield.

one step to generate diversity on the imidazo[1,2-c]quinazolines. The yields are higher and the reaction times are shorter than the protocol we reported earlier [14]. The short reaction times (0.5 h) and simple reaction conditions make this protocol attractive.

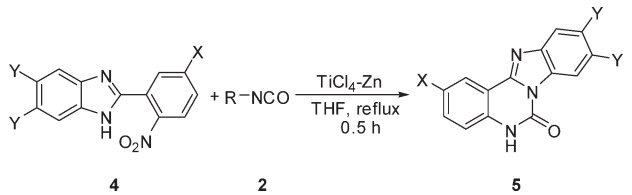
## EXPERIMENTAL

THF was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under $N_2$ atmosphere. Melting points are uncorrected. IR spectra were recorded on Tensor 27 spectrometer in KBr with absorptions in $cm^{-1}$. $^1$H-NMR spectra were determined on NMRststem-300 MHz or UNITY INOVA 400 MHz spectrometer in DMSO-$d_6$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS.

**General procedure for the synthesis of 3 and 5 is represented as follows.** $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (0.384 g, 6 mmol) in freshly distilled anhydrous THF (10 mL) at r.t. under a dry $N_2$ atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. and a solution of 2-(2-niteophenyl)imidazole or 2-(2-nitrophenyl) benzoimidazole (1 mmol) and isocycanates (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 30 min under $N_2$. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous $Na_2SO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

***2,3-Diphenylimidazo[1,2-c]quinazolin-5(6H)-one (3a): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3160, 1706, 1596, 1553, 1480, 1443, 1378, 1335, 803, 779, 749, 702 $cm^{-1}$.

**Scheme 3**




4 2 5

**Table 3**

The synthesis of benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones **5**.

| Compd. | X | Y | R | Yield/%[a] |
|---|---|---|---|---|
| **5a** | H | H | 4-$ClC_6H_4$ | 90 |
| **5b** | H | Cl | 4-$ClC_6H_4$ | 81 |
| **5c** | H | $CH_3$ | 4-$CH_3C_6H_4$ | 87 |
| **5d** | Cl | H | 4-$CH_3C_6H_4$ | 89 |

[a] Isolated yield.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 7.23–7.29 (m, 3H, ArH), 7.33–7.37 (m, 2H, ArH), 7.43–7.47 (m, 7H, ArH), 7.55–7.59 (m, 1H, ArH), 8.26 (d, $J$ = 8.0 Hz, 1H, ArH), 11.75 (s, 1H, NH).

***9-Chloro-2,3-diphenylimidazo[1,2-c]quinazolin-5(6H)-one (3b): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3160, 1706, 1596, 1553, 1480, 1443, 1378, 1335, 803, 779, 749, 702 $cm^{-1}$.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 7.23–7.25 (m, 3H, ArH), 7.34–7.36 (m, 1H, ArH), 7.43–7.45 (m, 7H, ArH), 7.92–7.94 (m, 1H, ArH), 8.16–8.17 (m, 1H, ArH), 11.84 (s, 1H, NH).

***9-Chloro-2,3-di(4-methylphenyl)imidazo[1,2-c]quinazolin-5(6H)-one (3c): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3220, 1706, 1598, 1551, 1480, 1443, 1370, 1334, 1280, 1234, 1073, 813, 797, 749, 760 $cm^{-1}$.

$^1$H-NMR (300 MHz, DMSO-$d_6$) δ: 2.24 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$), 7.05 (d, $J$ = 7.8 Hz, 2H, ArH), 7.19–7.35 (m, 7H, ArH), 7.55–7.59 (m, 1H, ArH), 8.15 (d, $J$ = 2.1 Hz, 1H, ArH), 11.79 (s, 1H, NH).

***9-Chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5(6H)-one (3d): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3210, 1703, 1614, 1594, 1554, 1520, 1491, 1366, 1330, 1287, 1246, 1171, 1037, 828, 750, 740 $cm^{-1}$.

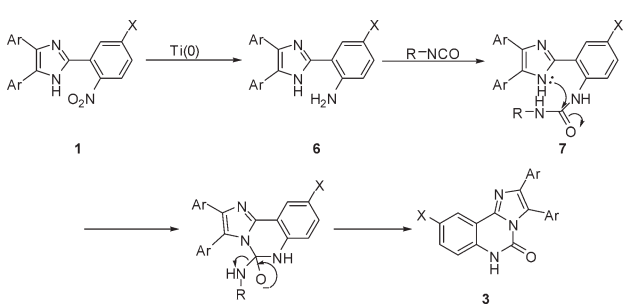
$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 3.73 (s, 3H, $CH_3O$), 3.33 (s, 3H, $CH_3O$), 6.85 (d, $J$ = 8.8 Hz, 2H, ArH), 6.99 (d, $J$ = 8.4 Hz, 2H, ArH), 7.34–7.36 (m, 3H, ArH), 7.42 (d, $J$ = 8.8 Hz, 2H, ArH), 7.58 (d, $J$ = 8.8 Hz, 1H, ArH), 8.16 (s, 1H, ArH), 11.79 (s, 1H, NH).

***2,3-Bis(4-bromophenyl)imidazo[1,2-c]quinazolin-5(6H)-one (3e): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3227, 3172, 3073, 1709, 1594, 1572, 1550, 1492, 1478, 1392, 1072, 959, 744, 727, 694 $cm^{-1}$.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 7.33–7.41 (m, 6H, ArH), 7.49–7.51 (m, 2H, ArH), 7.53–7.57 (m, 1H, ArH), 7.61–7.63 (m, 2H, ArH), 8.22 (d, $J$ = 8.0 Hz, 1H, ArH), 11.79 (s, 1H, NH).

***Bezimidazo[1,2-c]quinazolin-6(5H)-one (5a): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3150, 3077, 2916,

**Scheme 4**

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2849, 1722, 1614, 1592, 1541, 1479, 1450, 1427, 1382, 1330, 1292, 1226, 1148, 928, 756, 699 $cm^{-1}$.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 7.34–7.50 (m, 4H, ArH), 7.62–7.66 (m, 1H, ArH), 7.84 (d, $J$ = 7.6 Hz, 1H, ArH), 8.29 (d, $J$ = 7.6 Hz, 1H, ArH), 8.35 (d, $J$ = 8.0 Hz, 1H, ArH), 11.95 (s, 1H, NH).

***9,10-Dichlorobenzimidazo[1,2-c]quinazolin-6(5H)-one (5b): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3156, 3089, 2928, 1713, 1626, 1614, 1547, 1510, 1480, 1415, 1392, 1324, 1300, 1267, 1232, 1209, 1160, 1099, 877, 867, 779, 748, 713, 688 $cm^{-1}$.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 7.35–7.39 (m, 2H, ArH), 7.66–7.69 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.25 (d, $J$ = 8.0 Hz, 1H, ArH), 8.42 (s, 1H, ArH), 12.12 (s, 1H, NH).

***9,10-Dimethylbenzimidazo[1,2-c]quinazolin-6(5H)-one (5c): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3156, 3066, 2975, 2913, 2842, 1720, 1624, 1596, 1551, 1511, 1479, 1455, 1380, 1344, 1291, 1230, 1159, 994, 914, 878, 744, 665 $cm^{-1}$.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 2.38 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 7.33–7.38 (m, 2H, ArH), 7.61–7.64 (m, 2H, ArH), 8.12 (s, 1H, ArH), 8.27 (d, $J$ = 8.0 Hz, 1H, ArH), 11.91 (s, 1H, NH).

***2-Chlorobenzimidazo[1,2-c]quinazolin-6(5H)-one (5d): white solid, m.p. >300°C (Lit [14] >300°C).*** IR (KBr) ν: 3204, 3037, 2922, 1712, 1611, 1551, 1476, 1436, 1385, 1328, 1238, 1167, 1146, 1110, 1081, 1059, 1008, 939, 911, 881, 825, 758, 714, 687 $cm^{-1}$.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ: 7.35–7.37 (m, 1H, ArH), 7.41–7.49 (m, 2H, ArH), 7.63–7.66 (m, 1H, ArH), 7.82–7.84 (m, 1H, ArH), 8.17–8.18 (m, 1H, ArH), 8.30–8.32 (m, 1H, ArH), 12.04 (s, 1H, NH).

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## REFERENCES AND NOTES

[1] McMurry, J. E. Chem Rev 1989, 89, 1513.

[2] (a) McMurry, J. E.; Fleming, M. P. J Org Chem 1976, 41, 896; (b) McMurry, J. E. Acc Chem Res 1983, 16, 405; (c) Lenoir, D. Synthesis 1989, 883; (d) Fürstner, A.; Bogdanovi, B. Angew Chem Int Ed Engl 1996, 35, 2443; (e) Zhou, L. H.; Tu, S. J.; Shi, D. Q.; Dai, G. Y. W.; Chen, X. Synthesis 1998, 851; (f) Mariappan, P.; Gadthula, S.; Surisetti, S. Tetrahedron Lett 2001, 42, 7123.

[3] Shi, D. Q.; Chen, J. X.; Chai, W. Y.; Chen, W. X.; Kao, T. Y. Tetrahedron Lett. 1993, 34, 2963.

[4] Shi, D. Q.; Mu,L. L.; Lu, Z. S.; Dai, G. Y. Synth Commun 1997, 27, 4121.

[5] Zhou, L. H.; Shi, D. Q.; Dai, G. Y.; Chen, W. X. Tetrahedron Lett 1997, 38, 2729.

[6] Shi, D. Q.; Rong, L. C.; Shi, C. L.; Zhuang, Q. Y.; Wang, X. S.; Tu, S. J.; Hu, H. W. Synthesis 2005, 717.

[7] Francis, J. E.; Cash, W. D.; Barbaz, W. D.; Bernard, P. S.; Lovell, R. A.; Mazzenga, G. C.; Friedmann, R. C.; Hyun, J. L.; Braunwalder, A. F.; Loo, P. S.; Bennett, D. A. J Med Chem 1991, 34, 281.

[8] (a) Cianci, C.; Chung, T. D. Y.; Menwell, N.; Putz, H.; Hagen, M.; Colonno, R. J.; Krystal, M. Antiviral Chem Chemother 1996, 7, 353; (b) Gineinah, M. M.; Ismaiel, A. M.; El-Kerdawy, M. M. J Het Chem 1990, 27, 723; (c) Liu, K. C.; Hu, M. K. Arch Pharm (Weinheim) 1986, 319, 188; (d) Kottke, K.; Kuehmstedt, H.; Graefe, I.; Wehlau, H.; Knocke, D. DD 253623 (1988), Chem Abstr 1988, 109, 17046; (e) Kathawala, F.; Hardtmann, G. E. Ger Offen 2,146,076 (1972), Chem Abstr 1972, 77, 48501; (f) Kathawala, F.; Hardtmann, G. E. Ger Offen 2,261,095 (1971), Chem Abstr 1973, 79, 66385.

[9] (a) Nagano, H.; Takagi, M.; Kubodera, N.; Matsunaga, I.; Nabat, H.; Ohba, Y.; Sakai, K.; Hata, S. I.; Uchida, Y. Eur. Pat. 89065,1983, ChugaiPharmaceutical Co., Ltd; Chem Abstr 1984, 100, 6547. (b) Imagawa, J.; Sakai, K. Eur J Pharmacol 1986, 131, 257.

[10] Chern, J. W.; Yen, M. H.; Lu, G. Y.; Shiau, C. Y.; Lai, Y. J.; Chan, C. H. J Med Chem 1993, 36, 2196.

[11] Langer, P.; Bodtke, A. Tetrahedron Lett 2003, 44, 5965.

[12] Chern, J. W.; Tao, P. L.; Wang, K. C.; Gutcait, A.; Liu, S. W.; Yen, M. H.; Chien, S. L.; Rong J. K. J Med Chem 1998, 41, 3128.

[13] Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. Tetrahedron Lett 2003, 44, 3199.

[14] Shi, D. Q.; Dou, G. L.; Li, Z. Y.; Ni, S. N.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Tetrahedron 2007, 63, 9764.

[15] Shi, D. Q.; Wang, J. X.; Shi, C. L.; Rong, L. C.; Zhuang, Q. Y.; Hu, H. W. Synlett 2004, 1098.

[16] Dou, G. L.; Wang, M. M.; Shi, D. Q. J Comb Chem 2009, 11, 151.

[17] Ceorge, J.; Chandraseharan, S. Synth Commun 1983, 13, 495–499.

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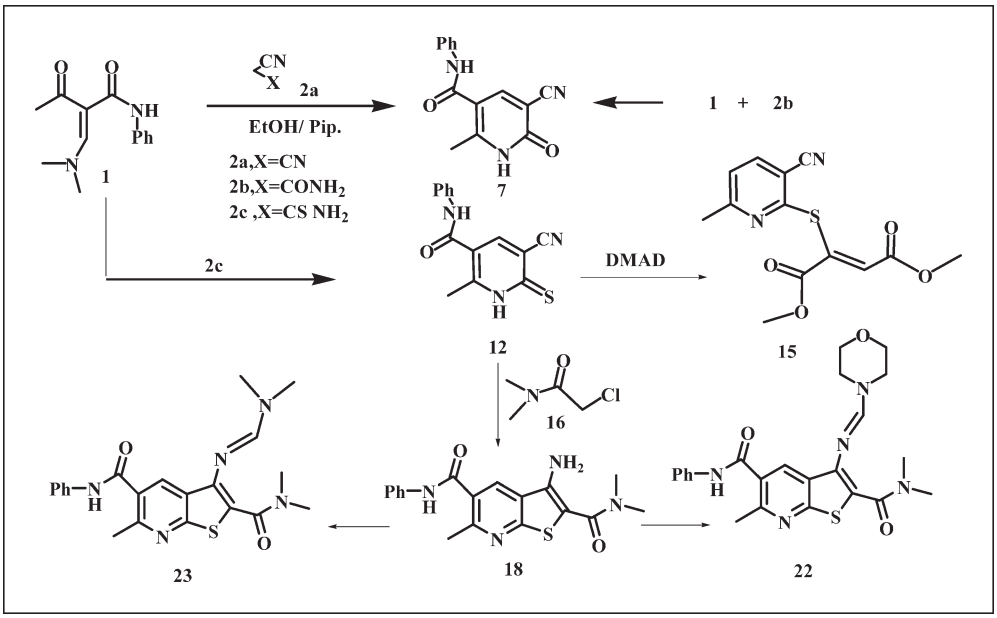


2-Dimethylaminomethylene-3-oxo-*N*-phenylbutyramide **1** reacts with malononitrile **2a** to afford the pent-2-enedioic acid 1-amide 5-phenylamide derivative **6**, which could be cyclized to give the 6-methyl-pyridone derivative **7**. Compound **1** reacts with cyanoacetamide **2b** to afford the same pyridone **7** and with cyanothioacetamide **2c** to afford the analogous pyridinethione **12**. Compound **12** reacts with DMAD to afford the pyridine derivative **15** and with *N*,*N*-dimethylchloroacetamide **16** to afford the thieno[2,3-d]pyridine derivative **18**. Compound **18** reacts with morpholine-4-carboxaldehyde **19**, *N*,*N*-diemthylformamide **20**, and 2,5-dimethoxy-tetrahydrofuran **21** to afford the fully aromatic thieno[2,3-d]pyridine derivatives **22**, **23**, and **24**, respectively.

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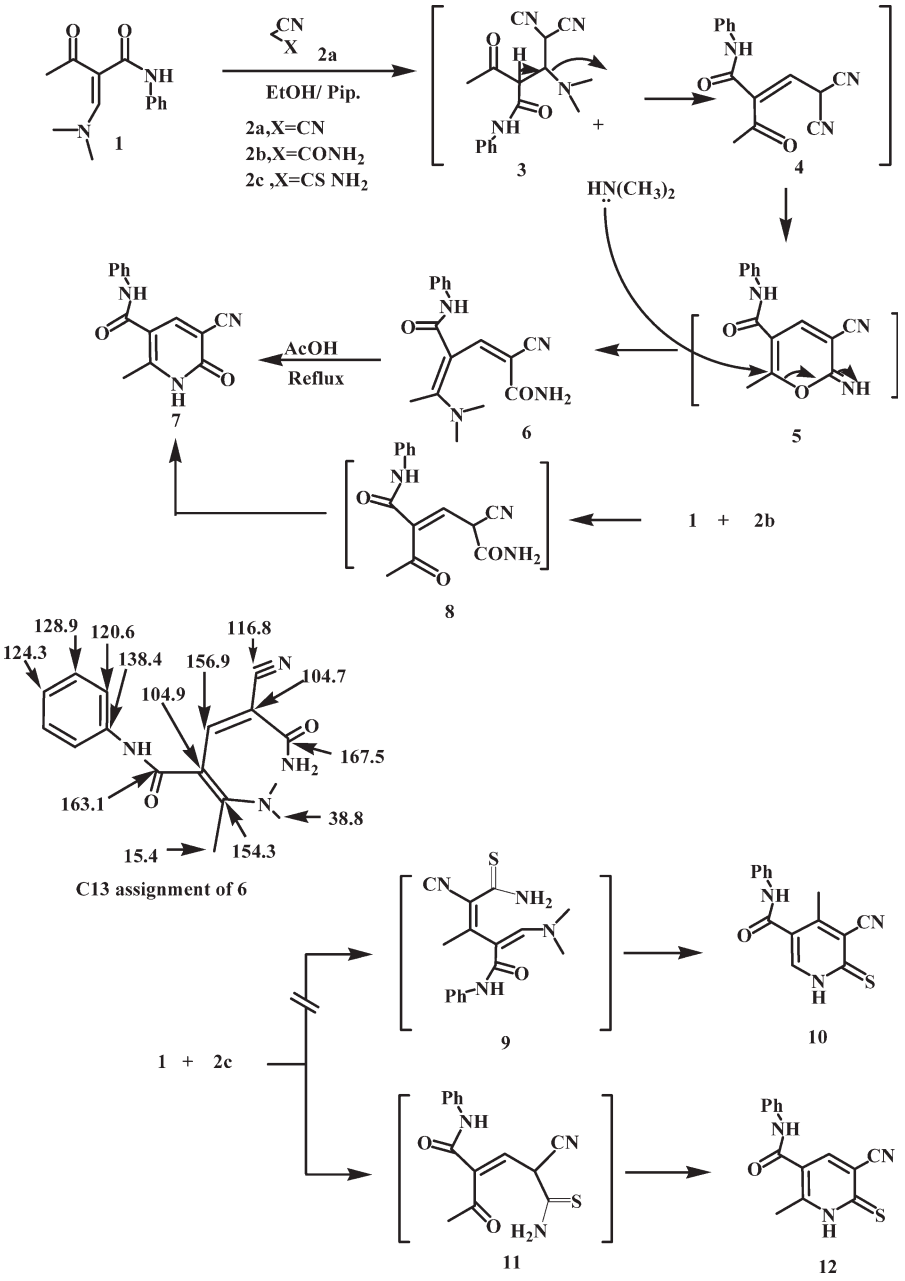
## INTRODUCTION

In the past 2 decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals [1–5]. Some functionally substituted pyridine and pyridone derivatives posses marked pharmaceutical activities such as anti HIV-1 reverse transcriptase agents, calcium channel blockers, anticongestive heart failure agents, and antagonists of P2 receptors for neurotransmitters [6–12]. The reaction of enaminones with active methylene nitriles represents one of the strategies for the preparation of 2-1*H*-pyridone [13–15]. Thus, some functionally substituted 2-1*H*-pyridone derivatives were required for biological activity studies. 2-Dimethylaminomethylene-3-oxo-*N*-phenylbutyramide (obtained from the reaction of acetoacetanilide with DMFDMA according to the literature method [16]) seemed a suitable synthone for the synthesis of the required 2-1*H*–pyridone derivatives through its reaction with active methylene reagents.

## RESULTS AND DISCUSSION

Thus, the enaminone compound **1** was prepared and allowed to react with the active methylene compounds **2a-c** (Scheme 1) according to the method reported earlier by us [17]. The reaction of **1** with malononitrile **2a** afforded a yellow crystalline solid of mp.197°C. The IR spectrum of this product showed absorption bands at $\upsilon_{max}$ = 2217, 1665, and 1656 $cm^{-1}$ corresponding to a cyano and two amide carbonyl functions. The mass spectrum of this product showed a molecular ion peak

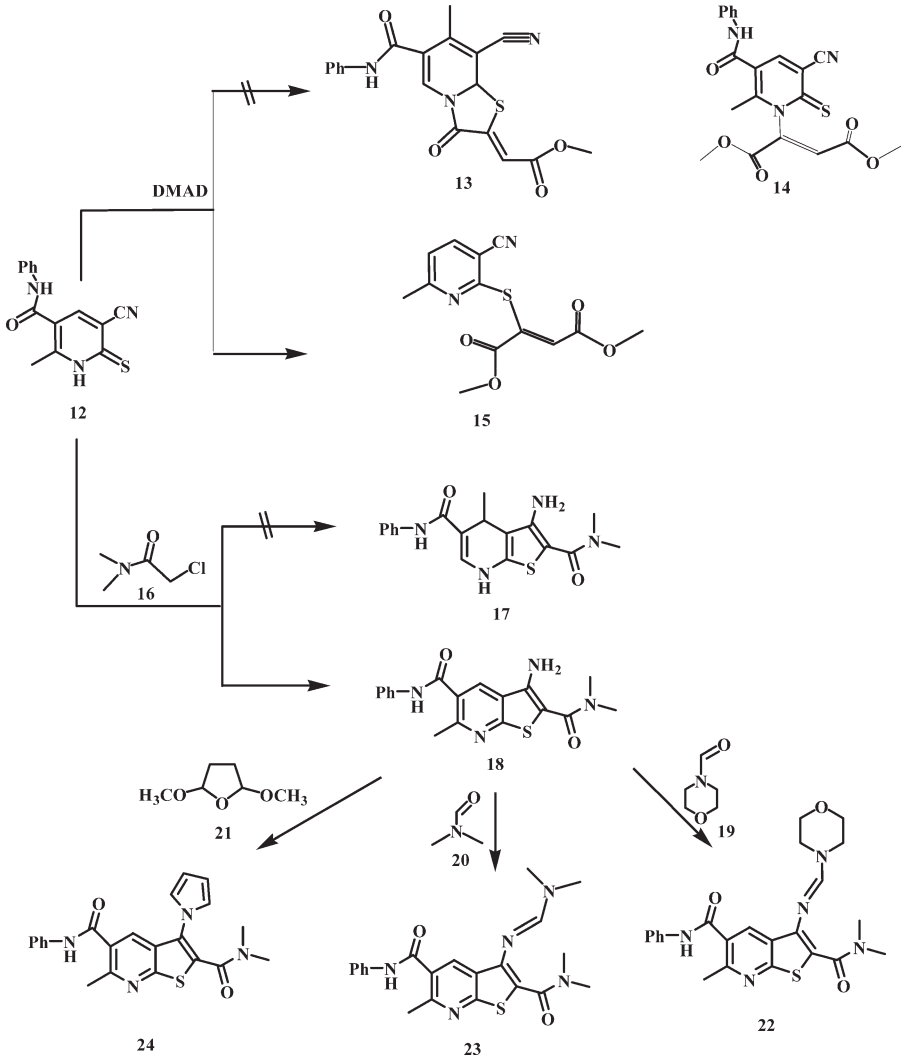
**Scheme 1.** Preparation of compounds **6**, **7**, and **12**.




at $m/z = 298$, which corresponds to the molecular formula $C_{16}H_{18}N_4O_2$ (M. Wt. 298.34). The $^1$H NMR spectrum of this product revealed a singlet (3H) at 1.69 corresponding to a methyl group, a singlet (6H) at 2.75 corresponding to the N($CH_3$)$_2$ groups, a singlet (1H) at 7.15 due to the =C*H* proton, a $D_2O$ exchangeable singlet at 8.35 (1H) attributable to an NH, beside an aromatic multiplet at 7.24–7.55 (7H, Ph+$NH_2$). Based on these data and on the analogy with our previous reported work [17], the 2-Cyano-4-(1-dimethylamino-ethylidene)-pent-2-enedioic acid 1-amide 5-phenylamide **6** was assigned to this product.

The formation of **6** from the reaction of **1** with **2a** is assumed to take place *via* the sequence shown in Scheme 1. The active methylene of malononitrile undergoes addition to the double bond of **1** to afford the intermediate **3**, followed by elimination of dimethyl amine to afford 2-acetyl-4,4-dicyanobut-2-enoic acid phenylamide **4** that directly undergoes ring closure *via* its enolized form to afford the iminopyran intermediate **5**. This newly formed iminopyran is attacked by the dimethyl amine (still present in the reaction medium) and undergoes ring opening to afford **6**. The ring opening of iminopyran under the effect ammonia and amines is well

**Scheme 2.** Preparation of compounds **15**, **18**, **22**, **23**, and **24**.




established in the literature [14,17]. The $^{13}C$ NMR data of this product are in complete agreement with structure **6** (*cf*. Scheme 1 and Experimental).

Compound **6** could be readily cyclized *via* elimination of dimethyl amine upon reflux in acetic acid to afford yellow crystals of mp. 217–219°C.

The $^{1}H$ NMR spectrum of **7** revealed the disappearance of the N$Me_2$ signal and the presence of a singlet integrated for 1H at $\delta = 8.65$, which is attributed to the C4-H, beside the other signals as expected (*cf*. Experimental). The 2-1*H*-pyridinone derivative structure **7** was assigned to this product based on the analytical and spectral data, and compound **7** has been previously described in the literature from other route, mp. 216–218°C [18].

The reaction of **1** with cyanoacetamide **2b** afforded the same 2-1*H*-pyridinone **7**. It is assumed that **2b** followed the same addition elimination sequence to afford the intermediate **8** (analogous to **4** in the above sequence) that undergoes directly the cyclization *via* elimination of water without passing through the iminopyran step, as the amide group is already present. The identity of the products obtained from the reactions of **1** with either **2a** or **2b** was deduced from the typical melting points and spectral data. A similar result has been previously observed [17].

The reaction of compound **1** with cyanothioacetamide **2c** was reported earlier to afford the pyridinthione **10** (No. **3** in the original article [19]) *via* the intermediate **9** (Number **2** in the original article). The author of ref. 19 incorrectly assumed that the reaction proceeds *via* a Knoevenagel condensation between the carbonyl group of **1** and the active methylene of **2c** to afford **9** (his **2**). On the basis of our aforementioned results, we have reinvestigated this reaction. This reaction of **1** and **2c** was found to follow the same pathway as that of **1** with **2b** to afford the intermediate **11** (analogous to **8**; Scheme 1) *via* the addition–elimination sequence, which

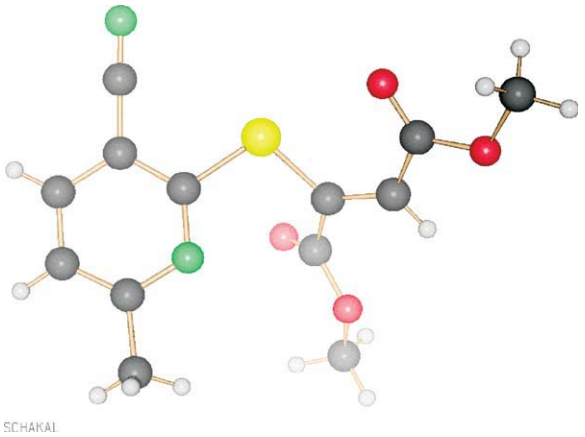



**Figure 1.** X-ray crystallographic structure of **15**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

then undergoes cyclization *via* loss of water to afford the pyridinethione **12**. The melting point, analytical, and spectral data of our product are the same as those reported in [19]; however, the $^{13}C$ NMR data reported in [19] are wrong; the phenyl carbons should appear as four signals and not six as reported, and the whole spectrum showed only 12 signals.(*cf.* experimental).

The incorrect assignment in [19] leads to the pyridinethione **10** (his **3**) with the methyl group in the 4-position, whereas the correct structure is **12** carrying the methyl group in the 6-position. This has serious consequences for some other reactions described in this article. For example, all the reactions depicted in his Scheme 2 are all based on the imaginary presence of the methyl group in position-4 and are all vagaries.

The reaction of this pyridinethione **12** with dimethyl acetylenedicarboxylate was claimed to afford the thiazolopyridine derivative **13** (Scheme 2) (number **9** in the original article [19]). The formation of this thiazolopyridine seemed doubtful as the pyridinethione has only one proton on its nitrogen, so how the thiazole ring is formed while still retaining one hydrogen on C-2. Furthermore, the $^{13}C$ NMR data given to **13** (his **9**) cited only 10 carbons (excluding the repeated values for the aromatic carbons), while it should reveal 17 carbons. Based on all these discrepancies, we decided to reinvestigate this reaction.

Compound **12** was allowed to react with dimethyl acetylenedicarboxylate (DMAD) in chloroform (the same reaction conditions reported in [19]) to afford after recrystallization and purification on column with silica gel using pentane/ethyl acetate (3:1) as eluent a white crystalline product of mp. 126°C (Lit. mp. of compound **13** in Scheme 2 (his **9**); >300°C [19]). The mass spectrum of this product showed $m/z = 292$ [$M^+$]. From this molecular mass and the elemental analysis data (*cf.* experimental), we could calculate a molecular formula $C_{13}H_{12}N_2O_4S$ for this product, which is not applicable to **13** (old **9**) or **14** (assuming that the NH adds to the C≡C in DMAD). The IR spectrum of this product showed two carbonyl absorption at $\upsilon_{max} = 1712$ and 1710 assignable to two ester CO, a cyano absorption band at 2220 $cm^{-1}$ and no bands that could be assigned to the amide CO. The $^1H$ and $^{13}C$ NMR showed a pattern that could not be justified to either of the structures **13** (reported **9** [19]) or **14** (*cf.* experimental). From the presence of two ester carbonyl absorption bands and the presence of two methyl signals in the $^1H$ and $C^{13}$ NMR spectra, we got the impression that a Michael addition took place from either the NH in the pyridinethione or the SH in the tautomer mercapto pyridine to the activated C≡C of DMAD, and from the absence of the amide carbonyl absorption band in the IR spectrum and the presence of two doublets at $\delta = 7.36$ and 8.22 ppm with $j = 8.56$ Hz in the $^1H$ NMR spectrum, we got the impression that the amide group was eliminated either in the form of phenyl isocyanate or *via* hydrolysis of the amide linkage followed by decarboxylation. Thus, structure **15** was suggested to this product. This structure actually fulfills all the requirements of all the available data. However, it was mandatory to have an X-ray crystallographic picture for this compound. Fortunately, the X-ray picture [20,21] came exactly in complete agreement with our imagination; (see Fig. 1 and the experimental). It shows clearly the attachment of S to the DMAD, the absence of the anilide group, and also shows the methyl group at the 6-position of the pyridine ring (the *p*-position to the cyano group) which is a further proof to our suggested mechanism (*cf.* Scheme 1).

Compound **12** reacts also with *N,N*-dimethyl chloroacetamide **16** under the same reaction conditions described in ref. 19 to afford the fully aromatic thieno[2,3-*b*]pyridine derivative **18** rather than the claimed dihydro-derivative **17** (his **11** [19]). It should be stated that the $^1H$ NMR data reported for compound **17** (old **11**) are completely applicable to our compound **18** (*cf.* experimental part).

Compound **18** was allowed to react with morpholine-4-carboxaldehyde **19**, *N,N*-diemthylformamide **20**, and 2,5-dimethoxy-tetrahydrofuran **21** under the same reaction conditions described in ref. 19 to afford products very similar to those described (his numbers **15**, **16**, and **17** in his Scheme 4); however, the obtained products were found to be the fully aromatic thieno[2,3-*b*]pyridine derivatives **22**, **23**, and **24**, respectively (*cf.* Scheme 2). It should be stated also that the $^1H$ NMR data reported in reference [19] for compounds **22**, **23**, and **24** (Scheme 2; numbers **15**, **16**, and **17** in his Scheme 4) are completely not applicable to their assigned structures.

## EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as

KBr pellets on a Perkin Elmer 1430 spectrophotometer. The $^1$H NMR and $^{13}$C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-$d_6$ using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Micro-analytical Center at Cairo University. X-ray data [20] were collected using a Bruker Nonius 5622 diffractometer and were corrected by SADABS factors and emperical absorption. The structure was solved by direct methods and expanded using Fourier technique. SCHAKAL 99 program system was used in the graphic representation of the structure [21]. The nonhydrogen atoms are refined anisotropically and the hydrogen atoms were refined according to theoretical models. X-ray crystallography, elemental and spectral data of compound **15** were made in the Institute of Organic Chemistry, TU-Dresden, Germany.

**2-Cyano-4-(1-dimethylamino-ethylidene)-pent-2-enedioic acid 1-amide 5-phenylamide 6.** To a mixture of 2-dimethylaminomethylene-3-oxo-*N*-phenylbutyramide **1** (2.32 g; 10 mmol) and malononitrile **2a** (0.66 g; 10 mmol) in ethanol (15 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid product thus precipitated was collected by filtration and recrystallized from dioxan to give yellow crystals, yield (2.23 g, 75%); mp 197–198°C (Dioxan); $\upsilon_{max}$ = 3435–3284 ($NH_2$ and NH), 2217 (CN), 1665, and 1656 cm$^{-1}$ (2 CO); MS: *m*/*z* = 298 [M$^+$]; $\delta_H$ = 1.69 (s, 3H, $CH_3$), 2.75 (s, 6H, $2CH_3$), 7.15 (s, 1H, CH), 7.10–7.65 (m, 7H, Ph+$NH_2$), 8.35 (s, 1H, NH). $\delta_C$ = 15.4 (q), 38.8 (q), 104,7 (s), 104,9 (s), 116,8 (s), 120.6 (d), 124.3 (d), 128.9 (d), 138.4 (s), 154.3 (s), 156.9 (d), 163.1 (s), 167.5 (s).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: (298.34): C, 64.41; H, 6.08; N, 18.78. Found: C, 64.45; H, 6.10; N, 18.90.

**Synthesis of 5-cyano-2-methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid phenyl amide 7.** ***Method A: Cyclization of compound 6.*** Compounds **6** (2.98 g, 10 mmol) was refluxed in ethanolic sodium ethoxide (15 mL) for 30 min. The solvent was reduced to one third of its volume under reduced pressure and left to cool overnight. The solid precipitate that appeared was collected by filtration and crystallized from ethanol to afford **7** as yellow crystals, yield (2.15 g, 85%), mp. 219–220°C.

***Method B: The reaction of 2-dimethylaminomethylene-3-oxo-N-phenylbutyramide 1 with cyanoacetamide 2b.*** To a mixture of **1** (2.32 g, 10 mmol) and cyanoacetamide **2b** (0.84 g, 10 mmol) in ethanol (20 mL) was added a catalytic amount of piperidine (5 drops). The reaction mixture was refluxed for 6 h and then left to cool to room temperature. The contents of the flask were poured onto ice-cold water and acidified with few drops of conc. HCl till just neutral (pH paper). The precipitated solid product was filtered off, washed thoroughly with cold water, dried, and recrystallized from ethanol/DMF (4:1) to give **7** as yellow crystals, yield (1.97 g, 78%); mp. 217–219°C (Lit. mp. 216–218°C [18]); $\upsilon_{max}$ = 3382, 3275 (NH), 2235 (CN), and 1657 and 1638 cm$^{-1}$ (2CO); MS: *m*/*z* = 253 [M$^+$]; $\delta_H$ = 2.63 (s, 3H, $CH_3$), 7.12–7.68 (m, 5H, Ph), 7.82 (br.s., 1H, NH), 8.65 (s, 1H, H-4), 10.60 (br.s., 1H, NH). $\delta_C$ = 16.48 (q), 104.66 (s), 112.65 (s), 116.15 (s), 121.05 (d), 124.57 (d), 128.65 (d), 138.45 (s), 145.6 (s), 153.95 (d), 159.86 (s), 164.55 (s).

Anal. Calcd. *for* $C_{14}H_{11}N_3O_2$: (253.26): C, 66.40; H, 4.38; N, 16.59. Found: C, 66.45; H, 4.47; N, 16.70.

**5-Cyano-2-methyl-6-thioxo-1,6-dihydro-pyridine-3-carboxylic acid phenylamide 12.** A mixture of compound **1** (2.32 g, 10 mmol) and cyanothioacetamide **2c** (1.0 g, 10 mmol) in ethanol (25 mL) with sodium ethoxide catalyst was refluxed for 30 min. After cooling down, the reaction mixture was poured onto cold water and acidified with dil. HCl. The precipitated solid product thus formed was collected by filtration and recrystallized from ethanol to afford **12** as yellow crystals, Yield (1.94 g, 72%), mp. 225–227°C (lit. 235°C [19]), $\upsilon_{max}$ = 3345, 3228 (NH), 2215 (CN), and 1658 cm$^{-1}$ (CO); MS: *m*/*z* = 269 [M$^+$]; $\delta_H$ = 1.74 (s, 3H, $CH_3$), 7.05–7.68 (m, 5H, Ph), 8.15 (s, 1H, H-4), 9.25 (br.s., 1H, NH), 13.92 (br.s., 1H, NH). $\delta_C$ = 185.65 (s), 167.46 (d), 163.85 (s), 143.15 (s), 135.26 (s), 128.66 (d), 124.25 (d), 120.38 (d), 116.24 (s), 116.58 (s), 107.47 (s), 15.42 (q).

Anal. Calcd for $C_{14}H_{11}N_3OS$: (269.32): C, 62.43; H, 4.12; N, 15.60. Found: C, 62.45; H, 4.18; N, 15.70.

**2-(3-Cyano-6-methylpyridin-2-ylsulfanyl)-but-2-enedioic acid dimethyl ester 15.** To a suspension of **12** (2.69 g, 10 mmol) in 15 mL of chloroform was added (2.13 g, 15 mmol) dimethyl acetylenedicarboxylate (DMAD) and a catalytic amount of triethylamine. The reaction mixture was stirred at room temperature for 3h. The precipitated solid formed after evaporation of the solvent was collected and recrystallized from methanol and then purified by flash chromatography using a column with silica gel (10 cm height with 2 cm$^2$ diameter) using pentane/ethyl acetate (3:1) as eluent to afford compound **15** as yellow crystals, yield (2.29 g, 65%), mp. 125–126°C (lit. >300°C [19]), $\upsilon_{max}$ = 2220 (CN), 1712 and 1710 (2 ester CO); MS: *m*/*z* = 292 [M$^+$]; $\delta_H$ = 2.47 (s, 3H, $CH_3$), 3.62 (s, 3H, $CH_3$), 3.78 (s, 3H, $CH_3$), 6.98 (s, 1H, olefin H), 7.36 (d, 1H, *j* = 8.65 Hz, H-5); 8.22 (d, 1H, *j* = 8.56 Hz, H-4). $\delta_C$ = 24.04 (q), 52.00 (q), 52.50 (q), 104.46 (s), 115.57 (s), 121.24 (d), 127.82 (d), 139.63 (s), 142.16 (d), 157.74 (s), 162.85 (s), 163.85 (s), 163.93 (s).

X-ray crystallographic data: Colourless crystals, $C_{13}H_{12}N_2O_4S$ ($M_r$ = 292.31 g mol$^{-1}$), monoclinic, space group $P2_1/c$ (No. 14), *a* = 8.950(2) Å, *b* = 21.930(4) Å, *c* = 7.337(2) Å, α[$^O$] = 90.00, β[$^O$] = 104.48 (3), γ[$^O$] = 90.00; *V*[Å$^3$] = 1394.3 (6), *Z* = 4, $D_{calc.}$ = 1.392 g cm$^{-3}$, *F*(000) = 608e, μ($M_o$ $K_\alpha$) = 0.246 nm$^{-1}$; the final difference Fourier ρ = 0.29 (−0.21) e Å$^{-3}$.crystal dimensions = 0.33 × 0.17 × 0.08 mm. Max. resolution [sin θ/λ]$_{max}$ = 0.64 Å$^{-1}$/ 99.8%. Data were collected using a Bruker Nonius area detector at T[°C] = −75 (2), with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) using the CCD data collection and SADABS absorption correction method; min 90.5%; max 98.1%. No. of independent reflections are 3043 were counted with observed reflections 2415. $R_{av}$ = 0.071. The final *R* and $R_W^2$ = 0.040 and 0.098, respectively.

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: (292.31): C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.01; H, 3.86; N, 9.73; S, 10.88.

**3-Amino-6-methyl-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 18.** To a solution of **12** (2.69 g, 10 mmol) in methanol (25 mL) was added *N*,*N*-dimethyl chloroacetamide **16** (1.22 g, 10 mmol) followed by few drops of sodium methoxide. The reaction mixture was refluxed for 1 h and then left to cool to room temperature. The mixture was then poured onto ice-cold water and acidified by few drops of dil. HCl till just neutral. The precipitated solid product was filtered off and recrystallized from methanol to afford

compound **18** as yellow crystals, yield (2.4 g, 68%), mp. 221–222°C (lit. 220°C [19]), $\upsilon_{max}$ = 3445, 3328 ($NH_2$ and NH), 1680 and 1668 (2CO) $cm^{-1}$; MS: *m*/*z* = 354 [$M^+$]; $\delta_H$ = 2.32 (s, 3H, $CH_3$), 3.54 (s, 6H, $2CH_3$), 7.05–7.80 (m, 7H, Ph+$NH_2$), 8.22 (s, 1H, H-4), 9.35 (br.s., 1H, NH).

Anal. Calcd for $C_{18}H_{18}N_4O_2S$: (354.43): C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 60.92; H, 5.15; N, 15.87; S, 9.25.

**The reaction of compound 18 with morpholine-4-carboxaldehyde 19, *N*,*N*-diemthylformamide 20, and 2,5-dimethoxy-tetrahydrofuran 21 (general procedure).** To a solution of **18** (3.54 g; 10 mmol) in 20 mL of phosphorus oxychloride was added each of **19**, **20**, or **21**. The reaction mixture was refluxed for 2 h in each case, left to cool to room temperature, and then poured onto ice-cold water and neutralized with ammonia. The precipitated solids thus formed were filtered off and recrystallized from the proper solvent to afford **22**, **23**, and **24**, respectively.

**6-Methyl-3-[(morpholin-4-ylmethylene)-amino]-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 22.** Yellow crystals, Yield (3.16 g; 70%), mp. 279–281°C (EtOH/DMF) (lit. 280°C [19]), $\upsilon_{max}$ = 3385, 3258 (NH), 1675 and 1668 $cm^{-1}$ (2CO); MS: *m*/*z* = 451 [$M^+$]; $d_H$ = 2.25 (s, 3H, $CH_3$), 3.05 (t, 4H, $2CH_2$), 3.29 (s, 6H, $2CH_3$), 3.72 (t, 4H, $2CH_2$), 7.05–7.60 (m, 6H, Ph + olefin H), 8.22 (s, 1H, H-4), 9.34 (br.s., 1H, NH).

Anal. Calcd. for $C_{23}H_{25}N_5O_3S$: (451.54): C, 61.18; H, 5.58; N, 15.51; S, 7.10. Found: C, 61.25; H, 5.68; N, 15.57; S, 7.23.

**3-(Dimethylamino-methyleneamino)-6-methyl-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 23.** Coffee brown crystals, yield (2.66 g; 65%), mp. 272–273°C (dioxan) (lit. 275°C [19]), $\upsilon_{max}$ = 3442, 3328 (NH), 1678, and 1669 $cm^{-1}$ (2CO); MS: *m*/*z* = 409 [$M^+$]; $d_H$ = 2.23 (s, 3H, $CH_3$), 2.55 (s, 6H, $2CH_3$), 3.15 (s, 6H, $2CH_3$), 7.05–7.55 (m, 6H, Ph + olefin H), 8.28 (s, 1H, H-4), 9.31 (br.s., 1H, NH).

Anal. Calcd for $C_{21}H_{23}N_5O_2S$: (409.50): C, 61.59; H, 5.66; N, 17.10; S, 7.83. Found: C, 61.72; H, 5.73; N, 17.25; S, 7.98.

**6-Methyl-3-pyrrol-1-yl-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 24.** Yellow crystals, Yield (2.9 g; 72%), mp. 312–313°C (EtOH/DMF) (lit. >300°C [19]), $\upsilon_{max}$ = 3435, 3329 (NH), 1676, and 1667 $cm^{-1}$ (2CO); MS: *m*/*z* = 404 [$M^+$]; $d_H$ = 2.24 (s, 3H, $CH_3$), 3.05 (s, 6H, $2CH_3$), 6.12–7.68 (m, 9H, Ph + pyrrole H), 8.25 (s, 1H, H-4), 9.33 (br.s., 1H, NH).

Anal. Calcd for $C_{22}H_{20}N_4O_2S$: (404.48): C, 65.33; H, 4.98; N, 13.85; S, 7.93. Found: C, 65.37; H, 4.85; N, 13.72; S, 8.13.

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## REFERENCES AND NOTES

[1] Abdelrazek, F. M.; Michael, F. A.; Mohamed, A. E. Arch Pharm Chem life Sci (Weinheim) 2006, 339, 305.

[2] Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Arch Pharm Chem Life Sci (Weinheim) 2007, 340, 543.

[3] Abdelrazek, F. M.; Ghozlan, S. A.; Michael, F. A. J Heterocycl Chem 2007, 44, 63.

[4] Abdelrazek, F. M.; Mohamed, A. M. Afinidad 2008, 65, 56.

[5] Abdelrazek, F. M.; Metwally, N. H. Synth Commun 2009, 39, 4088.

[6] Deshang, P.; Cipolina, J. A.; Lowmoster, N. K. J Org Chem 1988, 53, 1356.

[7] Worbel, J.; Li, Z.; Dietrich, A.; McCaleb, M.; Mihan, B.; Serdy, J.; Sullivan, D. J Med Chem 1998, 41, 1084.

[8] Troschutz, R.; Karger, A. J Heterocycl Chem 1997, 34, 1147.

[9] Robertson, R. M.; Robertson, D. In The Pharmacological Basis of Therapeutics, Goodman and Gilman's, 9th ed.; Gillman, A. G., consulting ed.; Mc Graw-Hill Health Professions Divisions: New York, 1996; p 759.

[10] Farah, A. E.; Alousi, A. A. Life Sci 1978, 22, 543.

[11] Svetlik, J.; Pronayova, N.; Hanas, V. J Heterocycl Chem 2000, 37, 395.

[12] Bremner, D. H.; Dunn, A. D.; Wilson, K. A.; Sturrock, K. R.; Wishart, G. Synthesis 1997, 494.

[13] Torres, M.; Gil, S.; Parra, M. Curr Org Chem 2005, 9, 1757 (Review).

[14] Abdelrazek, F. M.; Michael, F. A. J Heterocycl Chem 2006, 43, 7.

[15] Yermolayev, S. A.; Gorobets, N. Y.; Lukinova, E. V.; Shishkin, O. V.; Shishkina, S. V.; Desenko, S. M. Tetrahedron 2008, 64, 4649.

[16] Abu Elmaati, T. M.; Said, S. B.; Abu Elenein, N. S.; Sofan, M. A.; Khodeir, M. N. Pol J Chem 2002, 76, 945.

[17] Abdelrazek, F. M.; Elsayed, A. N. J Heterocycl Chem 2009, 46, 949.

[18] Deyanov, A. B.; Konshin, M. E. Chem Heterocycl Compd 2004, 40, 452; (Translated from: *Khimiya Geterotsiklicheskikh Soedinenii* 2004, No.4, 547 Plenum Publishing Corporation).

[19] Abu Elmaati, T. M. J Heterocycl Chem 2004, 41, 947.

[20] Crystallographic data (excluding structure factors) for the structure **15** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 746861. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[21] Keller, E. SCHAKAL 99, A Computer Program for the Graphic Representation of Molecular and Crystallographic Models; Universität Freiburg: Freiburg, Germany, 1999.

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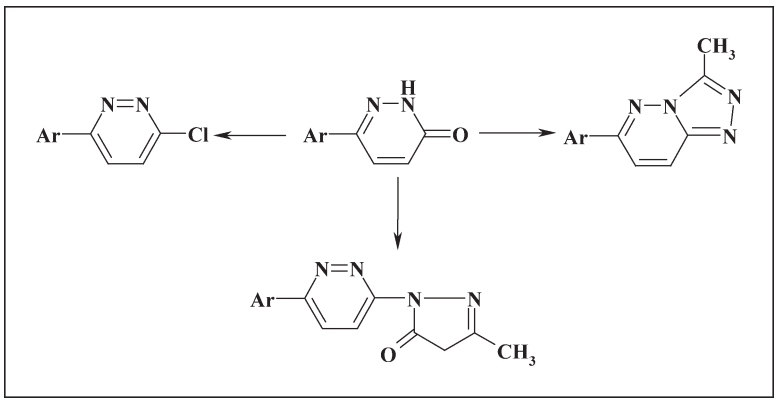


Synthesis of new heterocyclic compounds containing the pyridazinone moiety, which have a valuable biological activities, has been achieved through the nucleophilic addition of benzylamine to 4-(*p*-substituted phenyl)-4-oxo-2-butenoic acid **1a,b**, followed by cyclocondensation of the adducts **2a,b** to the corresponding pyridazin-3-one derivatives **3a,b**. The behavior of the latter compounds toward different nucleophilic and electrophilic reagents was investigated. The structures of the newly synthesized compounds were elucidated by elemental analysis and spectroscopic data.

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## INTRODUCTION

A large number of pyridazinone derivatives were reported to exhibit insecticidal [1–5], herbicidal [2,6], antiallergenic [7], antihypertensive [8], analgesic [9], anti-inflammatory [10], and bacteriocidal activities [11]. This prompted us to synthesize a new series of heterocyclic pyridazinone derivatives through the reaction of 4-(*p*-bromophenyl) or 4-(*p*-methylphenyl)-4-oxo-2-butenoic acid **1a,b** [12] with benzylamine in dry benzene and yielded the addition products **2a,b**. The latters were reacted with hydrazine hydrate in ethanol to give the unexpected pyridazin-3-one derivatives **3a,b,** respectively, rather than the expected 4,5-dihydropyridazin-3(2*H*)-one derivatives **4a,b**. The products **3** were used for synthesis of some important heterocyclic compounds through their conversion to the corresponding 3-chloropyridazine derivatives **7a,b**, which act as a key factor in synthesis of different heterocyclic pyridazine derivatives.

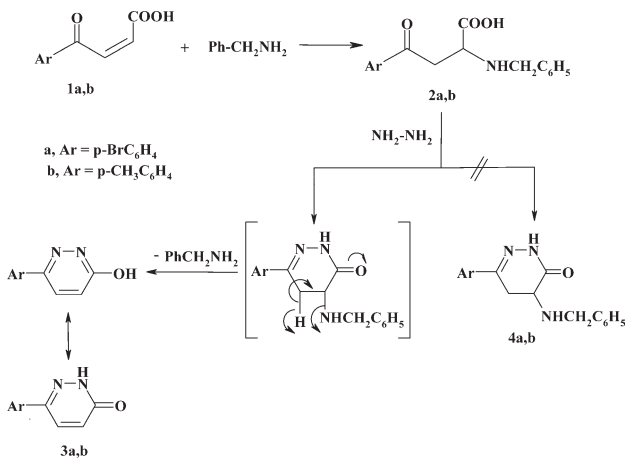
## RESULTS AND DISCUSSION

The reaction of 4-(*p*-bromo- and *p*-methylphenyl)-4-oxo-2-butenoic acid **1a,b** and benzylamine in dry benzene gave 4-(*p*-bromo- and tolyl)-4-oxo-2-(benzylamino)butanoic acid **2a,b**. Condensation of the acid derivatives **2a,b** with hydrazine hydrate in boiling ethanol afforded the unexpected 6-(*p*-substituted phenyl)pyridazin-3(2*H*)-one **3a,b** with the fission of the benzylamino group in position 4 and aromatization of the pyridazine ring [13,14] (Scheme 1).

Thus, structure of compound **2b** is supported by its correct elemental analysis, and its mass spectrum which revealed the molecular ion peak at $m/z = 297$ ($M^+$ 2.5%) for the molecular formula $C_{18}H_{19}NO_3$. Also, the structure of compounds **3** were elucidated by their elemental analysis and spectroscopic data. Thus, the $^1H$ NMR (DMSO) of compound **3a** showed signals at $\delta =$ 7.25–8.14 ppm (6H, m, Ar—H and —CH=CH— of pyridazine ring) and 8.98 (broad s, 1H, NH). Its mass spectrum showed molecular ion peak at $m/z = 252$ ($M^+ +1$, 24.2%) corresponding to the molecular formula $C_{10}H_7N_2OBr$.

In contrast, condensation of **2a,b** with hydroxylamine hydrochloride in boiling pyridine yielded the corresponding 3-(*p*-substituted phenyl)-4,5-dihydro-5-(benzylamino)-1,2-oxazin-6-ones **5a,b** with no fission of the benzylamino group. In support for the products **5a,b**, the acid **2b** was easily dehydrated in boiling acetic

**Scheme 1**

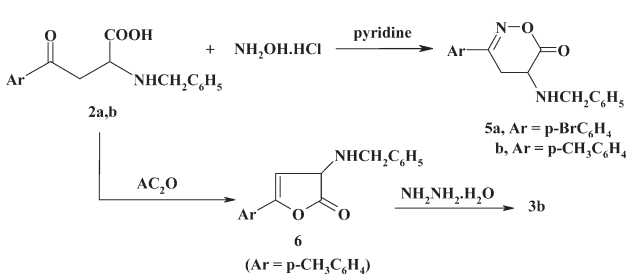



anhydride or heated at its melting point to yield 3-(benzylamino)-5-(4-methylphenyl)furan-2(3*H*)-one **6** (Scheme 2).

The structure of the oxazin-6-one derivative **5a** was confirmed by its correct elemental analysis and spectroscopic data. The IR of **5a** showed bands at 1683 $cm^{-1}$ (C=O), 1588 $cm^{-1}$ (C=N), and at 3287 $cm^{-1}$ (NH). Its mass spectrum showed a molecular ion peaks at $m/z$ = 359 ($M^+$, 7.7%) coincident with the molecular formula $C_{17}H_{15}N_2O_2Br$. The structure of the furanone derivative **6** was established by its correct elemental analysis, and its IR spectrum which showed a strong absorption at 1771 $cm^{-1}$ characteristic for the C=O of the five membered lactone ring and a band at 3195 $cm^{-1}$due to NH. The mass spectrum revealed the molecular ion peak at $m/z$ = 279 ($M^+$, 34.30%) for the molecular formula $C_{18}H_{17}NO_2$ and the base peak at $m/z$ = 106 (100%). Also, the structure of **6** was further established by its hydrolysis with hot alkali to the corresponding acid **2b**. In addition, the reaction of compound **6** with hydrazine hydrate in boiling ethanol gave the pyridazinone **3b,** which was identified by m.p. and mixed m.p. determination.

The keto-enol tautomerism in the pyridazinone ring is elucidated by the formation of its chloroderivative by the reaction of pyridazinones **3a,b** with nucleophilic

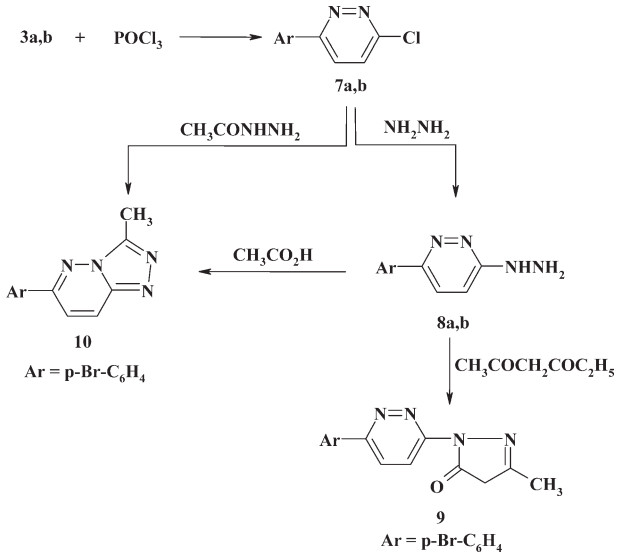
**Scheme 2**



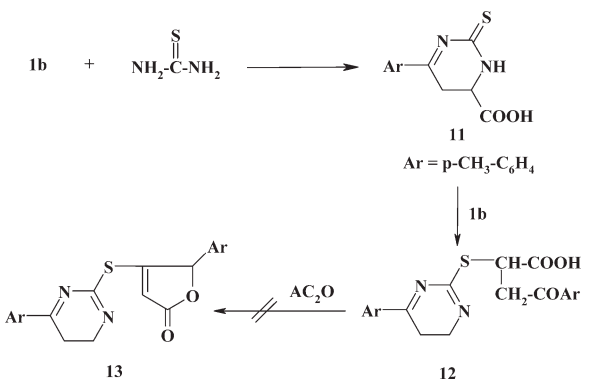

reagents like phosphorus oxychloride to give 3-chloropyridazines **7a,b** [15] which act as a key intermediate for the formation of different fused heterocyclic compounds which may have biological activities [16]. Thus, derivatives **7a,b** were submitted to react with hydrazine hydrate in boiling butanol to afford the corresponding hydrazine derivatives **8a,b** in good yield. On treatment of compound **8a** with ethylacetoacetate in boiling ethanol, 2-[6-(4-bromophenyl)pyridazin-3-yl]-5-methyl-2,4-dihydro-3H-pyrazol-3-one **9** was afforded. On the other hand, when compound **8a** was refluxed with acetic acid, the corresponding 6-(4-bromophenyl)-3-methyl[1,2,4]-triazolo[4,3-*b*]pyridazine **10** [17] was produced. The latter compound could be also obtained via the condensation of the chloropyridazine derivative **7a** with acetylhydrazine in boiling butanol (Scheme 3).

The structure of the compound **9** was confirmed by its elemental analysis and spectroscopic data. Thus, the IR of the compound showed absorption bands at 1643 $cm^{-1}$ (C=O) and at 1582 $cm^{-1}$ (C=N). The $^1$H NMR (DMSO) exhibited signals at δ = 2.04 ppm (s, 3H, $CH_3$); 2.23 (s, 2H, $CH_2$), 7.41–8.42 (m, 6H, Ar'H). The mass spectrum revealed the molecular ion peak at $m/z$ = 332 ($M^+$ +1, 100%) corresponding to the molecular formula $C_{14}H_{11}N_4OBr$. The structure of compound **10** was also elucidated by elemental analysis and spectroscopic data (IR, $^1$H NMR, and Ms). Thus, the $^1$H NMR of **10** showed signals at δ = 1.98 ppm (s, 3H, $CH_3$) and at 7.00–8.23 (m, 6H, $C_6H_4$, HC=CH). On the other hand, butenoic acid derivative **1b** was found to react with thiourea in boiling ethanol to give 6-(4-methylphenyl)-2-thioxo-2,3,4,5-tetrahydro-pyrimidine-4-carboxylic acid **11**. As a point of interest, the addition of the carboxylic acid **11** to another molecule of **1b** in dry benzene

**Scheme 3**



**Scheme 4**




containing a catalytic amount of pipredine has been achieved to afford the corresponding oxobutanoic acid derivative **12** but with cleavage of the carboxylic group of the pyridazine ring. An attempt to cyclize compound **12** through the dehydration with boiling acetic anhydride to afford the corresponding furanone derivative **13** has been failed (Scheme 4).

The structures of the compounds **11** and **12** were confirmed by their elemental analysis and spectroscopic data. Thus, the IR of the compound **11** showed bands at 3242 $cm^{-1}$ (NH), 1678 (C=O), and at 1491 (C=S). Its mass spectrum revealed the molecular ion peak at $m/z$ = 248 ($M^+$, 29.5%) related to the molecular formula $C_{12}H_{12}N_2O_2S$. The structure of **12** was also proved by its correct elemental analysis and spectroscopic data. The IR of the compound showed the absence of the band related to the NH group and exhibited bands at 1682 $cm^{-1}$ (C=O), and 1642 (C=O), and at 1355 (C—S—C). The mass spectrum of the compound revealed the molecular ion peak at $m/z$ = 394 ($M^+$, 4.0%) corresponding to the molecular formula $C_{22}H_{22}N_2O_3S$.

## EXPERIMENTAL

The Infrared spectra were recorded on a BRUKER IFS-25 FT-IR spectrophotometer using KBr at the region 400–4000 $cm^{-1}$, $^1H$ and $^{13}C$ on a BRUKER AVANCE/200 ULTRA-SHLIELD™ transform instrument using TMS as internal standard, Mass spectra were obtained with an Shimad 24 GCMS-QP 1000EX., Elemental analyses were determined on FISONS instruments DP200 series 2 and Euro EA3000 series Euro Vector. Elemental analyses for (CHNS) of all compounds are in accordance with the theoretical values within (0.4%) error. All melting points were uncorrected. Compounds **1a,b** were synthesized according to the literature procedure [18,19]. Compounds **3a,b**, **7a,b,** and **8a,b** could be obtained through other procedures [20,21].

**Synthesis of 2-(benzylamino)-4-(4-bromo- (methyl)-phenyl)-4-oxobutanoic acid 2a,b.** A mixture of compounds **1a,b** (0.01 mol) was refluxed with an equimolar amount of benzylamine for 3 h in 50 mL dry benzene. The reaction mixture was cooled and left at room temperature over night to precipitate the products as pale yellow needles. The solid products were collected and recrystallized from ethanol.

***2a.*** Pale yellow (76%), m.p. 177°C, $\nu_{max}/cm^{-1}$ (KBr) 3292 (NH), 1677 and 1651 (C=O); $m/z$ 362 (Calcd. for $C_{17}H_{16}NO_3Br$: C, 56.35; H, 4.42; N, 3.87% Found: C, 56.02; H, 4.41; N, 3.62%).

***2b.*** Pale yellow (67%), m.p. 187°C, $\nu_{max}/cm^{-1}$ (KBr) 3289 (NH), 1671 and 1655 (C=O); $^1H$ NMR (DMSO) $\delta$ = 1.98 ppm (s, 3H, $CH_3$), 2.26 (s, 2H, C—$CH_2$), 2.45 (s, 2H, N—$CH_2$) 3.42 (s, 1H, CH), 7.22–8.14 (m, 9H, ArH), 9.10 (s, 1H, NH), and 12.21 (s, 1H, COOH); $m/z$ 297 (Calcd. for $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71% Found: C, 72.50; H, 6.41; N, 4.62%).

**Synthesis of 6-(4-bromo-(methyl)phenyl)pyridazin-3(2*H*)-one 3a,b.** Equivalent amounts of **2a,b** (0.01 mol) and hydrazine hydrate were refluxed in 50 mL ethanol for 10 h. The reaction mixture was concentrated and left to precipitate the products, which were filtered off to give yellow crystals of **3a,b**.

***3a.*** Yellow (87%), m.p. 195°C, $\nu_{max}/cm^{-1}$ (KBr) 3311 (NH) and 1648 (C=O); $^1H$ NMR (DMSO) $\delta$ = 7.25–8.14 ppm (6H, m, Ar—H and —CH=CH— of pyridazine ring) and 8.98 (broad s, 1H, NH); $m/z$ 252 (Calcd. for $C_{10}H_7N_2OBr$: C, 47.80; H, 2.78; N, 11.15% Found: C, 47.55; H, 2.41; N, 11.00%).

***3b.*** Yellow (88%), m.p. 227°C, $\nu_{max}/cm^{-1}$ (KBr) 3294 (NH), 1648 (C=O); $m/z$ 186 (Calcd. for $C_{11}H_{10}N_2O$: C, 70.96; H, 5.37; N, 15.05% Found: C, 70.48; H, 5.66; N, 15.22%).

**Synthesis of 5-(benzylamino)-3-(4-bromo-(methyl)-phenyl)-4,5-dihydro-6*H*-1,2-oxazin-6-one 5a,b.** A mixture of **2a,b** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in 20 mL pyridine was refluxed for 6 h. The reaction mixture was cooled and poured onto ice/HCl mixture. The obtained solid was collected by filtration and recrystallized from suitable solvent.

***5a.*** Pale brown (68%), m.p. 140°C, from benzene, $\nu_{max}/cm^{-1}$ (KBr) 3287 (NH), 1683 (C=O), 1588 (C=N); $m/z$ 359 (Calcd. for $C_{17}H_{15}N_2O_2Br$: C, 56.82; H, 4.18; N, 7.79% Found: C, 56.99; H, 4.42; N, 8.02.00%).

***5b.*** White (64%), m.p. 250°C, from EtOH, $\nu_{max}/cm^{-1}$ (KBr) 3289 (NH), 1684 (C=O), 1588 (C=N); $^1H$ NMR (DMSO) $\delta$ = 1.99 ppm (s, 3H, $CH_3$), 2.32 (s, 2H, C—$CH_2$), 2.58 (s, 2H, N—$CH_2$), 3.11 (s, 1H, CH), 7.00–8.24 (m, 9H, ArH), 9.14 (s, 1H, NH); $m/z$ 294 (Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.46; H, 6.12; N, 9.52% Found: C, 73.26; H, 6.41; N, 9.50%).

**Synthesis of 3-(benzylamino)-5-(4-methylphenyl)furan-2(3*H*)-one 6.** Compound 2b (0.01 mol) was refluxed in 50 mL acetic anhydride for 8 h. The solution was concentrated over water bath and kept to separate the solid product which was collected and recrystallized from acetic acid.

***6.*** White (64%), m.p. 155°C, $\nu_{max}/cm^{-1}$ (KBr) 3195 (NH), 1771 (C=O), $^1H$ NMR (DMSO) $\delta$ = 1.84 ppm (s, 3H, $CH_3$), 2.11 (s, 2H, $CH_2$), 2.89–3.15 (s, 2H, 2CH), 6.98–8.01 (m, 9H, ArH), 8.99 (s, 1H, NH); $m/z$ 279 (Calcd. for $C_{18}H_{17}NO_2$: C, 77.42; H, 6.09; N, 5.01% Found: C, 77.11; H, 6.21; N, 4.89%).

**Synthesis of 3-(4-bromo- (methyl)phenyl)-6-chloropyridazine 7a,b.** A mixture of the pyridazinones **3a,b** (0.01 mol) and $POCl_3$ (10 mL) was heated in water bath for 4 h. After cooling, the reaction mixture was poured onto a mixture of ice/

water. The precipitate was collected by filtration, and the solid product was recrystallized from methanol.

***7a.*** Brown (77%), m.p. 199°C, $\nu_{max}/cm^{-1}$ (KBr) 1612 (C=N), (Calcd. for $C_{10}H_6N_2ClBr$: C, 44.56; H, 2.24; N, 10.39% Found: C, 44.24; H, 2.22; N, 10.41.00%).

***7b.*** Gray (65%), m.p. 165C, $\nu_{max}/cm^{-1}$ (KBr) 1612 (C=N), *m/z* 204 (Calcd. for $C_{11}H_9N_2Cl$: C, 64.56; H, 4.43; N, 13.69% Found: C, 64.68; H, 4.18; N, 13.22%).

**Synthesis of 3-(4-bromo- (methyl)phenyl)-6-hydrazinopyridazine 8a,b.** A mixture of compounds **7a,b** (0.01 mol) and hydrazine hydrate (0.015 mol) was refluxed for 6 h in *n*-butanol (50 mL), and the solid obtained was collected and recrystallized from suitable solvent.

***8a.*** Pale brown (75%), m.p. 184°C, from MeOH, $\nu_{max}/cm^{-1}$ (KBr) 3319–3199 (NH, $NH_2$), *m/z* 265 (Calcd. for $C_{10}H_9N_4Br$: C, 45.30; H, 3.42; N, 21.13% Found: C, 45.00; H, 3.69; N, 20.98%).

***8b.*** Yellow (71%), m.p. 155°C, from EtOH, $\nu_{max}/cm^{-1}$ (KBr) 3314–3195 (NH, $NH_2$), *m/z* 200 (Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98% Found: C, 66.02; H, 6.11; N, 27.68%).

**Synthesis of 2-[6-(4-bromophenyl)pyridazin-3-yl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 9.** A mixture of equivalent amounts of compound **8a** (0.01 mol) and ethylacetoacetate in 50 mL ethanol was refluxed for 6 h. The reaction mixture was concentrated to separate the solid product, filtered off, and recrystallized from ethanol.

***9.*** White (62%), m.p. 235°C, $\nu_{max}/cm^{-1}$ (KBr), 1643 (C=O), 1582 (C=N); $^1$H NMR (DMSO) $\delta$ = 2.04 (s, 3H, $CH_3$), 2.23 (s, 2H, $CH_2$), 7.41–8.22 (m, 6H, ArH); *m/z* 331 (Calcd. for $C_{14}H_{11}N_4OBr$: C, 50.77; H, 3.35; N, 16.92% Found: C, 50.25; H, 3.45; N, 16.65%).

**Synthesis of 6-(4-bromophenyl)-3-methyl[1,2,4]triazolo[4,3-b]pyridazine 10.** ***Method A.*** A mixture of **8a** (0.01 mol) and acetic acid (30 mL) was refluxed for 8 h. The reaction mixture was left to cool, and the precipitated solid product was collected by filtration and recrystallized from ethanol.

***Method B.*** A mixture of **8a** (0.01 mol) and acetohydrazide (0.01 mol) was refluxed for 5 h in absolute ethanol (20 mL). The reaction mixture was diluted by water, collected by filtration, and recrystallized from ethanol.

***10.*** Brown (56%), m.p. 212°C, $^1$H NMR (DMSO) $\delta$ = 1.98 ppm (s, 3H, $CH_3$), 7.00–8.23 (m, 6H, $C_6H_4$, HC=CH); *m/z* 289 (Calcd. for $C_{12}H_9N_4Br$: C, 49.85; H, 3.14; N, 19.38%. Found: C, 49.95; H, 3.33; N, 19.01%).

**Synthesis of 6-(4-methylphenyl)-2-thioxo-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid 11.** Compound **1b** (0.01 mol) was refluxed with thiourea (0.01 mol) in 30 mL acetic acid for 3 h. The reaction mixture was cooled, left at room temperature over night, and filtered off to give pale yellow needles of the product that was recrystallized from ethanol.

***11.*** Yellow (64%), m.p. 250°C, $\nu_{max}/cm^{-1}$ (KBr) 3242 (NH), 1678 (C=O), 1491 (C=S); $^1$H NMR (DMSO) $\delta$ = 2.12 ppm (s, 3H, $CH_3$), 2.23 (s, 2H, $CH_2$), 3.34 (s, 1H, CH), 6.88–7.81 (m, 4H, ArH), 8.78 (s, 1H, NH), 12.41 (s, 1H, COOH); *m/z* 248 (Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91%. Found: C, 58.24; H, 5.01; N, 11.28; S, 12.84%).

**Synthesis of 4-(4-methylphenyl)-2-{[6-(4-methylphenyl)-4,5-dihydropyrimidin-2-yl]thio}-4-oxobutanoic acid 12.** A mixture of **1b** (0.01 mol) and compound **11** (0.01 mol) was refluxed in dry benzene (30 mL) containing few drops of pipredine for 6 h. The solution was evaporated and the product was collected and recrystallized from ethanol.

***12.*** Pale yellow (58%), m.p. 183°C, $\nu_{max}/cm^{-1}$ (KBr) 1682, 1642 (2C=O), 1355 (C—S—C); $^1$H NMR (DMSO) $\delta$ = 2.11 ppm (s, 6H, $2CH_3$), 2.12–2.35 (broad s, 6H, $3CH_2$), 3.11 (d, 1H, CH), 6.94–8.23 (m, 8H, ArH), 12.44 (s, 1H, COOH); *m/z* 394 (Calcd. for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10; S, 8.13%. Found: C, 67.11; H, 5.33; N, 6.99; S, 8.00%).

## REFERENCES AND NOTES

[1] Meki, N.; Lomioka, H.; Fujumot, K.; Jmahese, T.; Mekya, K. Jpn Kokau Tokkyo Jpo2 1990, 45, 471; Chem Abstr 1990, 113, 54361.

[2] Ywan, B.; Liu, C.; Lian Gaodeng, G. Xuexws Huaxue Xuebao 1989, 10, 543; Chem Abstr 1990, 112, 158175.

[3] Bettarini, F.; Lapuzzi, L.; Massimini, S.; Castoro, P.; Capriale, V. Eur. Pat. Appl. Ep. 391390(CL CO 7D 23716) 1990; Chem Abstr 1991, 114, 12239.

[4] Snmez, M.; Berber, I.; Akbaş, E. Eur J Med Chem 2006, 41, 101.

[5] Freud, W.; Hawprecht, G.; Wuozer, B.; Westphslen, K. O.; Weyer, M. Ger. Offen. DE 3807896 (CL CO 7D 237/14) 1989; Chem Abstr 1990, 113, 23935.

[6] Wriede, V.; Wuerzer, B.; Meyer, N.; Westphalen, K. O. Ger. Offen DE 3825468 (CL CO 7D 237/22), 1990; Chem Abstr 1990, 113, 23936.

[7] Barlogova, S.; Guint, J. Cesk Hyg 1975, 20, 5.

[8] Bergmann, R.; Gericke, R. J Med Chem 1990, 33, 492.

[9] Schoen, W. Eur. Pat. Appl. EP 347987(CL CO 7K 5/02), 1989; Chem Abstr 1991, 114, 229391.

[10] Blaschhe, H.; Straissing, H.; Fillier, H.; Enznhofer, R. Eur. Pat. Appl. E. P. 372305(CL CO 7D 403/12), 1990; Chem Abstr 1990, 113, 231393.

[11] Rabat, C.; Coudert, P.; Tronche, P.; Bastide, J.; Bastide, P.; Privat, A. M. Chem Pharm Bull 1989, 37, 2832.

[12] Baddar, F. G.; El-Habashi, A.; Fateen, A. K. J Chem Soc 1965, 3342.

[13] Juranic, Z.; Stevaic, L.; Dra kulic, B.; Stano, T.; Kovic, J.; Radularic, S.; Juranic, I. J Serb Chem Soc 1990, 64, 505.

[14] El-Mobayad, M.; Sayed, G. H.; El-Shekeil, A. G.; Abd El-Ghani, E. Indian J Chem Sect B 1990, 29, 72.

[15] El-Mobayad, M.; Sayed, G. H.; El-Shekeil, A. G.; Abd El-Ghani, E. Egypt J Chem 1991, 34, 73.

[16] Juralg, Z.; Sterovic, L. J.; Drokulic, B.; Stano Jkovic, T.; Radulovic, S.; Jurovic, I. J Serb Chem Soc 1999, 64, 505.

[17] Wasfy, A. F.; Arief, M. H.; Amine, M. S.; Donia, S. G.; Aly, A. A.; Z Nat forsch 2002, 57b, 668.

[18] Cromwell, N. H.; Cook, K. E.; Greger, P. L. J Am Chem Soc 1965, 78, 4416.

[19] Dixon, S.; Gregory, H.; Wiggins, L. F. J Chem Soc 1949, 2139.

[20] Ji, J. G.; Li, T.; Mortell, K. H.; Schrimpf, M. R.; Nersesian, D. L.; Pan, L. P. PCT W.O. Pat. 2006065233, 2006.

[21] Cao, L. H.; Wang, C. F.; Tao, J. Chin J Organic Chem 2006, 26, 1686.

# Synthesis, Antioxidant and Antimicrobial Activity of Novel Benzene-1,4-diamine-bis-dioxaphosphepine-6λ$^5$ Iminophosphoranes



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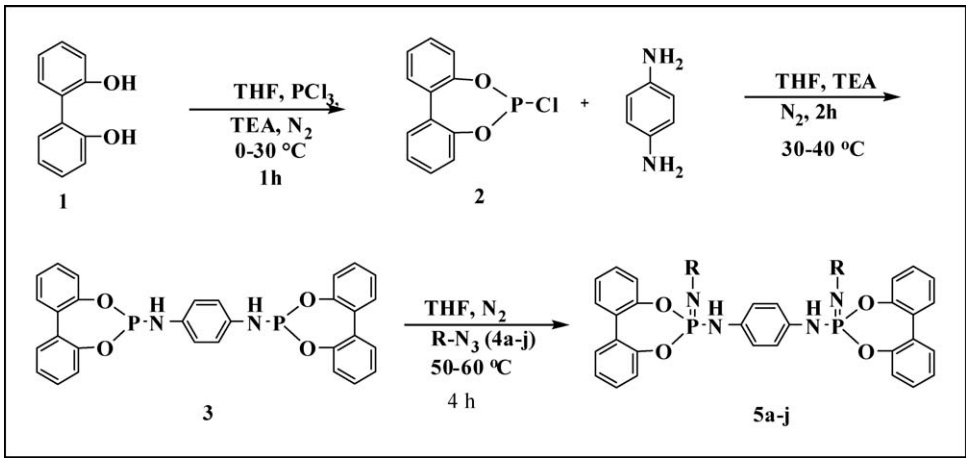


A new class of novel benzene-1,4-diamine-bis-dioxaphosphepine-6λ$^5$ iminophosphoranes (**5a–j**) were synthesized by the reaction of 6-chlorodibenzo[*d,f*][1,3,2]dioxaphosphepine (**2**) with 1,4-diaminobenzene to form bis-dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-yl-benzene-diamine (**3**). Its subsequent reaction with different alkyl/aryl azides (**4a–j**) in tetrahydrofuran at 50–60°C under inert atmosphere yielded title compounds. Their structures were established by elemental analysis, IR, $^1$H, $^{13}$C, $^{31}$P NMR, and mass spectral studies. All the title compounds were screened for antioxidant properties and found to exhibit potent *in vitro* antioxidant and antimicrobial activity

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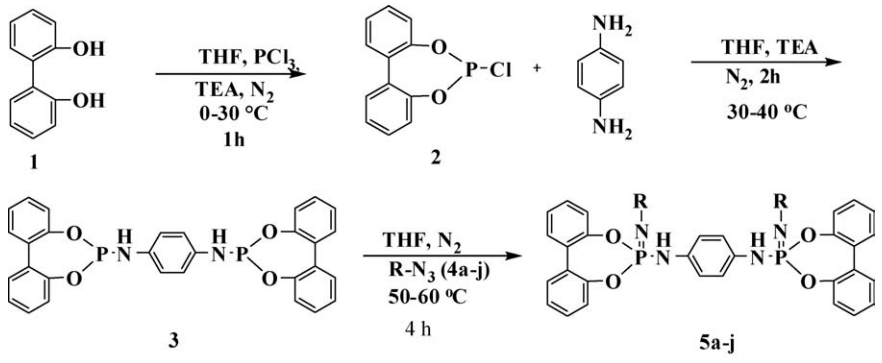
## INTRODUCTION

In recent years, the detailed mechanism of antioxidant action of organophosphorus compounds and their relationships between chemical structure and antioxidant activity have been comprehensively studied, in spite of their great practical importance. Depending on their structure and scavenging activity, phosphites and phosphonates may act as both primary and secondary antioxidants [1,2]. Reactive oxygen species (ROS) are produced by univalent reduction of dioxygen to superoxide anion which in turn disproportionate to $H_2O_2$ and $O_2$ spontaneously. The ROS are believed to play a major role in the inflammatory process in rheumatoid arthritis (RA) and contribute to the destruction of cartilage and bone [3,4]. The most important ROS implicated in inflammatory tissue injury are superoxide radical ($O_2^{\bullet -}$), hydrogen peroxide ($H_2O_2$), hydroxyl radical ($HO^{\bullet}$), and hypochlorous acid ($HOCl^{\bullet}$). In the inflammed joint, these ROS can be produced by macrophages, neutrophils, and chondrocytes [5]. The inflammed rheumatoid joint also undergoes a hypoxia–reperfusion cycle, which results in ROS generation [6]. Antioxidants may have a therapeutic role in RA by suppressing the inflammation. As our synthesized compounds are contrast in the structure to bisphosphonates, the aim of this study was to investigate the *in vitro* antioxidant profile of different bis-iminophosphoranes. To the best of our knowledge the antioxidant profile of different bis-iminophosphranes has not yet been systematically studied.

## RESULTS AND DISCUSSION

Cyclization of 2,2′-dihyroxybiphenyl (**1**) with phosphorus trichloride at 0°C under dry and inert conditions in the presence of triethylamine (TEA) in tetrahydrofuran (THF) afforded the corresponding 6-chlorodibenzo[*d,f*][1,3,2]dioxaphosphepine (**2**). Reaction of **2** with 1,4-diaminobenzene led to bis dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-yl]-1,4-benzenediamine (**3**). Further reac-

**Scheme 1**




| Entry | R | Entry | R |
|---|---|---|---|
| 5a | $CH_3$ | 5f | $CH_2$-$CH(CH_3)_2$ |
| 5b | $CH_2$-$CH_3$ | 5g | $CH{=}CH_2$ |
| 5c | $CH_2$-$CH_2CH_3$ | 5h | $CH_2$-$CH{=}CH_2$ |
| 5d | $CH_2$-$(CH_2)_2$-$CH_3$ | 5i | $CH_2$-$C_6H_5$ |
| 5e | $CH(CH_3)_2$ | 5j | $CH_2$-$C_6H_4$-$NO_2$(4) |

tion of **3** with different organic azides **4a–j** in dry THF at 50–60°C led to **5a–j** in high yields (Scheme 1). The reactions were monitored by thin layer chromatography (TLC). The chemical structures of **5a–j** were confirmed by elemental analysis and spectral data (IR, $^1$H, $^{13}$C, $^{31}$P NMR, and mass spectra).

Characteristic IR absorptions were observed for C—N, P=N, and NH in the regions 1010–1081, 1206–1265, and 3280–3410 cm$^{-1}$, respectively [7]. The aromatic hydrogens resonated as multiplets at δ 6.45–7.99, the P—NH proton chemical shift appeared as a singlet at δ 3.75–5.20. The chemical shifts of other aliphatic hydrogens and carbon-13 **5a–j** appeared in the expected region [8]. $^{31}$P NMR chemical shifts were observed in the region δ 4.25–9.20 [7]. LCMS of **5a**, **5b**, **5e**, **5g**, **5i**, and **5j** gave molecular ion peaks and diagnostic daughter ions at their expected m/z values.

The radical scavenging capacity of **5a–j** was evaluated by using methods such as 1,1-diphenyl-2-picryl hydrazyl (DPPH) and nitric oxide scavenging activity. **5j** showed appreciable antioxidant activity. Because of —$NO_2$ substituents which affect the electron and hydrogen donating capacities, appears to be useful in inducing antioxidant activity. As —$NO_2$ is highly withdrawing moiety, thereby electron density around phosphonate moiety decrease and increases affinity toward oxygen derived free radicals and mobilizes ROS to be scavenged out of living system.

## EXPERIMENTAL

All melting points were determined in open capillary tubes on Mel-Temp apparatus and are uncorrected. Microanalyses were performed at the Central Drug Research Institute, Lucknow, India. Infrared spectra ($\nu_{max}$ in cm$^{-1}$) were recorded as KBr pellets on a Perkin-Elmer 283 double beam spectrophotometer. $^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded on AMX 400 MHz spectrophotometer operating at 400 MHz for $^1$H NMR, 100 MHz for $^{13}$C NMR, and 161.9 MHz for $^{31}$P NMR, using DMSO-$d_6$ as solvent. The $^1$H and $^{13}$C NMR chemical shifts were referenced to Tetra Methyl Silane (TMS) and $^{31}$P NMR chemical shifts to 85% $H_3PO_4$.

**Typical experimental procedure.**

***Preparation of alkyl azides.*** In a dry 100-mL round-bottomed flask fitted with dropping funnel, calcium chloride guard tube, sodium azide (0.64 g, 0.01 mole), and 10 mL of dry THF were placed and stirred. Alkyl/aryl bromide (0.01 mole) in 10 mL of dry THF was added to it at room temperature. Temperature of the reaction mixture was raised to 40–45°C and stirred for 4 h. After cooling to room temperature, it was filtered to remove sodium bromide. The filtrate containing alkyl/aryl azide was used for the next step reaction.

***N1,N4 Bis[6-(alkyl/arylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepine-6yl]benzene-1,4-diamine 5a–j.*** A solution of slight excess of phosphorus trichloride (0.43 g, 0.005 mole) in dry THF (25 mL) under nitrogen atmosphere, was added dropwise to a well-stirred solution of 2,2′-dihydroxybiphenyl(**1**) (0.930 g, 0.005 mole) and TEA (1.4 g, 0.01 mole) in dry THF(20 mL) at 0°C. After the addition, the temperature of the reaction mixture was slowly raised and kept at 25–30°C for 1 h. The reaction progress was monitored by TLC. The mixture was filtered to remove triethylamine hydrochloride and the filtrate was rota-evaporated. The residue-6-chlorodibenzo[*d,f*][1,3,2]dioxaphosphepine (**2**) was used for the next step.

To the intermediate **2** in dry THF (20 mL), 1,4-diaminobenzene (0.548 g, 0.05 mole) was added at 10°C in the presence of TEA at nitrogen atmosphere in dry THF. After the addition,

the reaction mixture was brought to 30–40°C and stirred for 2 h to complete the reaction. It was treated with alkyl/aryl azides (0.01 mole) in THF at 50–60°C and stirred for 4 h to complete the reaction. The progress of the reaction was monitored by TLC (ethyl acetate:hexane, 2:8) analysis. After completion of the reaction, solvent was removed in a rota-evaporator to get crude products. The residue was purified by column chromatography on silicagel (80–120 mesh) using petroleum ether-ethylacetate (8:2) as eluant. It was recrystallized from 2-propanol to afford pure (**5a–j**).

*N1,N4-Bis[6-(methylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5a).* Yield 65%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.81–7.96 (20H, m, Ar-H), 3.78 (2H, s, NH), 0.88 (6H, s, $CH_3$); $^{13}$C NMR data: 131.01 (C-1, C-11), 117.61 (C-2, C-10), 127.5 (C-3, C-9), 112.5 (C-4, C-8), 120.0 (C-12, C-13), 151.6 (C-14, C-15), 132.0 (C′-1, C′-4), 114.5 (C′-2, C′-3, C′-5, C′-6), 21.4 ($CH_3$-N); $^{31}$P NMR data: δ 6.75; IR (KBr) cm$^{-1}$: 3385 (P—NH), 1208 (P—N), 1045 (N—C); LCMS *m/z*: 595 ($M^+$ + 1); Anal. Calcd. for $C_{32}H_{28}N_4O_4P_2$: C, 64.65; H, 4.75; N, 9.42. Found C, 64.60; H, 4.68; N, 9.36.

*N1,N4-Bis[6-(ethylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5b).* Yield 68%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.88–7.90 (20H, m, Ar-H), 3.95 (2H, s, NH), 1.88–2.01 (4H, m, $CH_2$), 1.22 (6 H, t, $J$ = 11.5 Hz, -$CH_3$); $^{31}$P NMR data: δ 7.78; IR (KBr) cm$^{-1}$: 3280 (P—NH), 1225 (P=N), 1055 (N—C); LCMS *m/z*: 626 ($M^+$ + 1); Anal. Calcd. for $C_{34}H_{32}N_4O_4P_2$: C, 65.59; H, 5.18; N, 9.00. Found C, 65.51; H, 5.09; N, 8.95.

*N1,N4-Bis[6-(propylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5c).* 65%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.76–7.70 (20H, m, Ar-H), 4.51(2H, s, NH), 1.60 (4H, t, $J$ = 9.5 Hz, —$CH_2$—$CH_2$—$CH_3$), 1.33–1.34 (4H, m, $CH_2$—$CH_2$—$CH_3$), 0.98 (6H, t, $J$ = 10.3 Hz, —$CH_2$—$CH_2$—$CH_3$); $^{31}$P NMR data: δ 5.25; IR (KBr) cm$^1$: 3350 (P—NH), 1220 (P=N), 1010 (N—C); Anal. Calcd. for $C_{36}H_{36}N_4O_4P_2$: C, 66.46; H, 5.58; N, 8.61. Found C, 66.40; H, 5.51; N, 8.55.

*N1,N4-Bis[6-(butylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5d).* Yield 69%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.80–7.82 (20H, m, Ar-H), 5.25 (2H, s, NH), 1.51 (4H, t, $J$ = 6.8 Hz, —$CH_2$—$CH_2$—$CH_3$), 1.23–1.40 (8H, m, $CH_2$—$CH_2$—$CH_2$—$CH_3$), 0.95 (6H, t, $J$ = 10.9 Hz, —$CH_2$—$CH_2$—$CH_2$—$CH_3$); $^{31}$P NMR data: δ 8.10; IR (KBr) cm$^{-1}$: 3410 (P—NH), 1265 (P=N), 1025 (N—C); Anal. Calcd. for $C_{38}H_{40}N_4O_4P_2$: C, 67.25; H, 5.94; N, 8.26. Found C, 67.20; H, 5.86; N, 8.18.

*N1, N4-Bis[6-(vinylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene- diamine (5e).* Yield 73%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.45–7.52 (20H, m, Ar-H), 5.05 (2H, t, $J$ = 11 Hz, CH=$CH_2$), 4.22 (4H, d, $J$ = 5.3 Hz, $CH_2$=CH), 3.82 (2H, s, NH); $^{13}$C NMR data: 128.0 (C-1, C-11), 118.7 (C-2, C-10), 127.4 (C-3, C-9), 113.1 (C-4, C-8), 125.7 (C-12, C-13), 151.0 (C-14, C-15), 145.0 (N-CH), 117.4 (CH=$CH_2$), 132.2 (C′-1, C′-4), 114.8 (C′-2, 3,5); $^{31}$P NMR data: δ 6.59; IR (KBr) cm$^1$: 3392 (P—NH), 1209 (P=N), 1081 (N—C); LCMS *m/z*: 618 ($M^+$); Anal. Calcd for $C_{34}H_{28}N_4O_4P_2$: C, 66.02; H, 4.56; N, 9.06. Found C, 65.96; H, 4.51; N, 9.01.

*N1,N4-Bis[6-(isopropylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5f).* Yield 70%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.91–7.79 (20H, m,Ar-H), 4.35 (2H, s, NH), 2.81–2.98 (2H, m, CH), 1.16 (12H, d, $J$ =10.2Hz, CH—$CH_3$); $^{13}$C NMR data: 131.2 (C-1, C-11), 116.3 (C-2, C-10), 130.3 (C-3, C-9), 113.0 (C-4, C-8), 126.3 (C-12, C-13), 154.0 (C-14, C-15), 132.0 (C′-1, C′-4), 115.6 (C′-2, C′-3, C′-5, C′-6), 30.6 (CH-N),16.6 ($CH_3$); $^{31}$P NMR data: δ 4.25; IR (KBr) cm$^{-1}$: 3370 (P—NH), 1216 (P=N), 1043 (N—C); Anal. Calcd for $C_{36}H_{36}N_4O_4P_2$: C,66.46; H, 5.58; N, 8.61. Found C, 66.40; H, 5.51; N, 8.56.

**Table 1**

DPPH radical scavenging activity of **5a–j**.

| Compound | $IC_{50}$ (μg/mL) |
|---|---|
| **5a** | 19 |
| **5b** | 19 |
| **5c** | 14 |
| **5d** | 13 |
| **5e** | 25 |
| **5f** | .13 |
| **5g** | 16 |
| **5h** | 15 |
| **5i** | 13 |
| **5j** | 11 |
| **BHT** | 72.50 |

*N1,N4-Bis[6-(isobutylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5g).* Yield 72%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.79–7.81 (20H, m, Ar-H), 4.18 (2H, s, NH), 1.52–1.91 (2H, m, CH—$CH_2$), 1.28 (4H, d, $J$ = 5.4 Hz, $CH_2$—CH), 1.15 (12H, t, $J$ = 10.2 Hz, CH—$CH_3$); $^{13}$C NMR data: 131.6 (C-1, C-11), 118.7 (C-2, C-10), 128.4 (C-3, C-9), 114.8 (C-4, C-8), 125.7 (C-12, C-13), 155.0 (C-14, C-15), 127.4 (C′-1, C′-4), 117.3 (C′-2, C′-3, C′-5, C′-6), 35.0 (CH), 29.0 (N—$CH_2$), 19.2 (CH—$CH_3$); $^{31}$P NMR data: δ 9.20; IR (KBr) cm$^{-1}$: 3357 (P—NH), 1206 (P=N), 1058 (N—C); LCMS *m/z*: 678 ($M^+$); Anal. Calcd. for $C_{38}H_{40}N_4O_4P_2$: C,67.25; H, 5.94; N, 8.26. Found C, 67.19; H, 5.90; N, 8.21.

*N1,N4-Bis[6-(allylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine(5h).* Yield 71%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.80–7.99 (20H, m, Ar-H), 5.71 (2H, m, CH), 5.02–5.10 (4H,m, CH2),4.10 (2H, s, NH) 2.10 (4H, d, $J$ = 5.2Hz, N—$CH_2$); $^{31}$P NMR data: δ 9.10; IR (KBr) cm$^{-1}$: 3290 (P—NH), 1210 (P=N), 1029 (N—C); Anal. Calcd. for $C_{36}H_{32}N_4O_4P_2$: C, 66.87; H, 4.99; N, 8.66. Found C, 66.80; H, 4.92; N, 8.60.

*N1,N4-Bis[6-(benzylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5i).* Yield 75%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.80–7.96 (30H, Ar-H), 3.75 (2H, s, NH), 2.01 (4H, s, $CH_2$-Ar); $^{13}$C NMR data: 128.4 (C-1, C-11), 118.7 (C-2, C-10), 127.4 (C-3, C-9), 114.8 (C-4, C-8), 125.7 (C-12, C-13), 155.0 (C-14, C-15), 136.2 (C′-1, C′-4), 117.3 (C′-2, C′-3, C′-5, C′-6), 140.1 (C″-1), 130.1 (C″-2, C″-6), 128.2 (C″-3, C″-5), 125.8 (C″-4), 28.09 ($CH_2$-Ar); $^{31}$P NMR data: δ 4.94; IR (KBr) cm$^{-1}$: 3390 (P—NH), 1244.9 (P=N), 1045 (N—C); LCMS *m/z*: 746 ($M^+$); Anal. Calcd for $C_{44}H_{36}N_4O_4P_2$: C, 70.77; H, 4.86; N, 7.50. Found C, 70.71; H, 4.81; N, 7.45.

*N1,N4-Bis[6-(nitrobenzylimino)-6λ$^5$-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl]-1,4-benzene-diamine (5j).* Yield 71%, viscous liquid; $^1$H NMR (DMSO-$d_6$): δ 6.80–7.92 (28H, m,

**Table 2**

Nitric oxide scavenging activity of **5a–j**.

| Name of the compound | $IC_{50}$ (μg/mL) |
|---|---|
| **5a** | 20 |
| **5b** | 22 |
| **5c** | 35 |
| **5d** | 29 |
| **5e** | 55 |
| **5f** | 24 |
| **5g** | 25 |
| **5h** | 22 |
| **5i** | 26 |
| **5j** | 14 |
| **BHT** | 357.14 |

Ar-H), 4.20 (2H, s, NH), 2.15 (4H, s, Ar-$CH_2$); $^{31}$P NMR data: δ 5.25; IR (KBr) $cm^{-1}$: 3390 (P—NH), 1225 (P=N), 1020 (N—C); LCMS *m/z*: 808 ($M^+$ +1); Anal. Calcd. for $C_{44}H_{34}N_6O_8P_2$: C, 63.16; H, 4.10; N, 10.04. Found C, 63.11; H, 4.05; N, 9.99.

## ANTIOXIDANT ACTIVITY

**DPPH radical scavenging activity.** The hydrogen or electron donation abilities of title compounds were measured from the bleaching of the purple color methanol solution of DPPH [9]. This spectrophotometric assay uses the stable radical DPPH as a reagent. One milliter of various concentrations of the title compounds (20, 40, 60, 80, and 100 μg/mL) in methanol were added to 4 mL of 0.004% methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was red against blank at 517 nm.

**Table 3**

Antibacterial activity of **5a–j**.

| | Zone of inhibition/mm | | | | | |
|---|---|---|---|---|---|---|
| | *Staphylococcus aureus* | | | *Escherichia coli* | | |
| Compd. | 100 (ppm[a]) | 50 (ppm[a]) | 25 (ppm[a]) | 100 (ppm[a]) | 50 (ppm[a]) | 25 (ppm[a]) |
| **5a** | 11 | 8 | 6 | 12 | 8 | 4 |
| **5b** | 8 | 6 | – | 10 | 7 | 5 |
| **5c** | 10 | 8 | 6 | 12 | 8 | 4 |
| **5d** | 6 | 5 | 4 | 12 | 6 | 6 |
| **5e** | 14 | 9 | 5 | 14 | 12 | 8 |
| **5f** | 13 | 11 | 8 | 13 | 11 | 7 |
| **5g** | 7 | 4 | – | 9 | 8 | 4 |
| **5h** | 10 | 8 | 5 | 10 | 6 | 5 |
| **5i** | 12 | 10 | 8 | 10 | 6 | 4 |
| **5j** | 11 | 8 | 5 | 12 | 8 | 6 |
| [b]***Penicillin*** | 9 | 6 | – | 12 | 8 | – |

[a] In DMF
[b] Reference compound.

**Table 4**

Antifungal activity[a] of **5a–j**.

| | Zone of inhibition/mm | | | | | |
|---|---|---|---|---|---|---|
| | *Aspergillus niger* | | | *Helminthosporium oryzae* | | |
| Compd. | 100 (ppm[a]) | 50 (ppm[a]) | 25 (ppm[a]) | 100 (ppm[a]) | 50 (ppm[a]) | 25 (ppm[a]) |
| **5a** | 9 | 7 | 5 | 11 | 6 | 5 |
| **5b** | 10 | 8 | 4 | 11 | 9 | 5 |
| **5c** | 12 | 9 | 6 | 12 | 10 | 7 |
| **5d** | 11 | 10 | 8 | 14 | 10 | 4 |
| **5e** | 10 | 7 | 5 | 12 | 8 | 7 |
| **5f** | 11 | 5 | 3 | 12 | 10 | 9 |
| **5g** | 8 | 6 | 4 | 9 | 8 | 4 |
| **5h** | 9 | 8 | 6 | 11 | 9 | 5 |
| **5i** | 12 | 11 | 9 | 13 | 12 | 8 |
| **5j** | 8 | 9 | 6 | 9 | 7 | 4 |
| [b]***Griseofulvn*** | 12 | 10 | 5 | 12 | 10 | 5 |

[a] In DMF.
[b] Reference compound.

The antioxidant activity of these compounds was expressed as $IC_{50}$ (Inhibition concentration, 50%) of **5j** which showed highest DPPH scavenging activity with 11 μg/mL when compared with other compounds (Table 1). The percent of inhibition of free radical production from DPPH was calculated by using the following equation. Butylated hydroxyl toluene (BHT) was used as a standard reference compound.

$$I = \frac{[(A_{\text{control}}) - (A_{\text{sample}})]}{\text{Blank}} 100 \quad (1)$$

where, $A_{\text{control}}$ is absorbance of the control.

Control reaction containing the entire reagent except the test compound.

$A_{\text{sample}}$ is absorbance of the test compound.

**Nitric oxide scavenging activity.** Nitric oxide scavenging activity was measured by slightly modified methods of Green *et al*. and Marcocci *et al*. [10]. Nitric oxide radicals were generated from sodiumnitropruside. One milliliter of sodiumnitroprusside (m*M*) and 1.5 mL of phosphate buffer saline (0.2*M*, $p_H$ 7.4) were added to the different concentrations (20, 40, 60, 80, and 100 μg) of the extract and incubated for 150 min at 25°C. After incubation, 1 mL of the reaction mixture was treated with 1 mL of Griess reagent (1% Sulfanilamide, 2% of $H_3PO_4$ and 0.1% naphthylethylene diamine dihydro chloride).

Absorbance was measured at 546 nm. **5j** showed highest DPPH scavenging activity with 14 mg/mL when compared with other compounds (Table 2). Butylated

hydroxy toluene was added as a standard. The percent of inhibition (I %) was calculated by using the following equation:

$$I = \frac{[(A_{\text{control}}) - (A_{\text{sample}})]}{\text{Blank}} 100 \qquad (2)$$

**Antibacterial activity.** Antibacterial activity of all the title compounds (**5a–j**) was assayed [11] against *Staphylococcus aureus* ATCC-25923 (Gram positive) and *Escherichia coli* ATCC-25922 (Gram-negative) at three different concentrations (100, 50, and 25 ppm) in DMF (Table 3). The compounds were diluted in DMF for bioassay. Solvent control was included although no antibacterial activity has been noted in the solvent employed. Penicillin G (Hi-media) controls (20 $\mu g/mL^1$) were included to compare with compounds (**5a–j**). All samples were tested in triplicate and average results were recorded.

**Antifungal activity.** The compounds (**5a–j**) were screened for their antifungal activity (Table 4) against *Aspergillus niger* and *Helminthosporium oryzae* species along with standard fungicide Griseofulvin at three different concentrations (100, 50, and 25 ppm) in DMF [12] All the compounds (**5a–j**) exhibited moderate to high antifungal activity when compared with that of the reference compound. The majority of the compounds exhibited high activity against fungi.

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## REFERENCES AND NOTES

[1] Schwetlick, K. In Mechanisms of Polymer of Degradation and Stabillisation; Elsevier Applied Science: London, 1990; p23.

[2] Schwetlick, K. Pure Appl Chem 1983, 55, 1629.

[3] Tiku, M. L.; Liesch, J. B.; Robertson, F. M. J Immunol 1990, 145, 690.

[4] Bax, B. E.; Alam, A. S.; Banerji, B.; Bax, C. M.; Bevis, P. J.; Stevens, C. R.; Moonga, B. S.; Blake, D. R.; Zaidi, M. Biochem Biophys Res Commun 1992, 183, 1153.

[5] Bauerova, K.; Bezek, A. Gen Physiol Biophys 1999, 18, 15.

[6] Edmonds, S. E.; Blake, D. R.; Morris, C. J.; Winyard, P. G. J Rheumatol 1993, 37, 26.

[7] Mohan, Ch.; Hari Babu, B.; Nagaraju, C.; Suresh Reddy, C.; Janardhan Reddy, V. J Heterocycl Chem 2008, 45, 1337.

[8] Haranath, P.; Sreedhar Kumar, V.; Suresh Reddy, C.; Nagaraju, C.; Devendranath Reddy, C. Synth Commun 2007, 37, 1697.

[9] Okhawa, H.; Ohishi, N.; Yagi, K. Anal Biochem 1979, 95, 351.

[10] Privalle, C.; Talarico, T.; Keng, T.; DeAngelo, J. Free Radical Biol Med 2000, 28, 1507.

[11] Vincent, J. C.; Vincent, H. W. Proc Soc Exp Biol Med 1994, 55, 162.

[12] Benson, H. J. Microbiological Applications, 5th ed.; W.C. Brown Publications: Boston, MA, 1990; p 156.

# 2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde as a New Synthon for the Synthesis of Fused Ring Heterocycles *via* Intramolecular 1,3-Dipolar Cycloaddition Reactions



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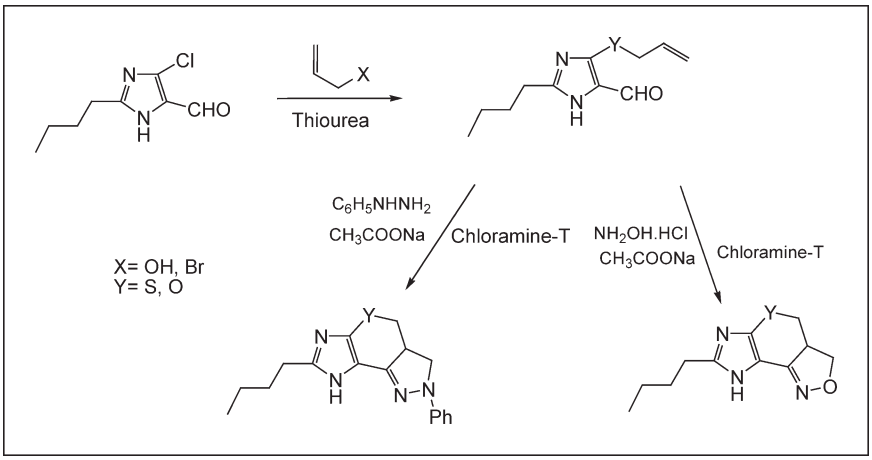


The title compound 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde was transformed into tricyclic heterocycles by substituting the chlorine atom by an unsaturated thiolate or alkoxide and then converting aldehyde function into 1,3-dipole. Chloramine-T was used as an efficient reagent for the generation of 1,3-dipoles, which resulted the formation of fused ring heterocycles *via* intramolecular 1,3-dipolar cycloaddition reaction. The method is very useful for the construction of many biologically active fused heterocycles.

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## INTRODUCTION

The intramolecular 1,3-dipolar cycloaddition is a powerful method for the construction of fused ring heterocycles [1,2]. In particular intramolecular nitrile oxide cycloaddition results dihydroisoxazole derivatives, which are precursors for γ-amino alcohols, β-hydroxy ketones and derivatives, useful in the synthesis of natural products [3]. Similarly intramolecular nitrile imine cycloaddition results 2-pyrazoline derivatives.

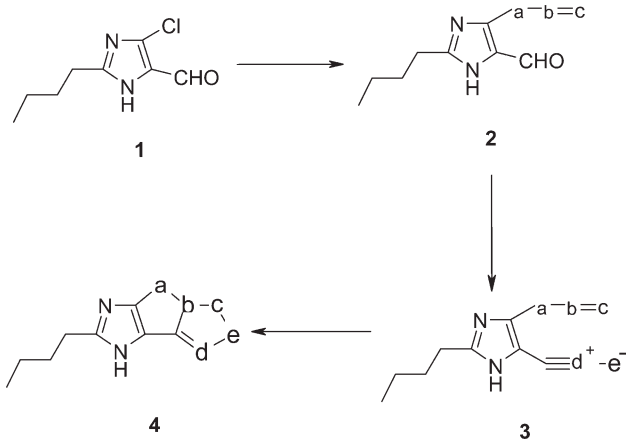
In our previous report, we have used chloramine-T for the generation of nitrile oxide [4], nitrile imine [5], nitroso alkene [6], and azoalkene [7] which are useful intermediates for the synthesis of biologically active 2-isoxazolines, 2-pyrazolines, 1,2-oxazines, and pyridazines, respectively. 2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde **1**, a key intermediate for the synthesis of Losartan a nonpeptide angiotensin antagonist, which is an orally active antihypertensive drug [8], and also shows broad spectrum of activity [9–10]. Compounds of these types are interesting starting materials for intramolecular cycloaddition reaction due to the presence of chloro and formyl groups ortho to each other. The chlorine atom can be easily substituted by nucleophiles **2** and the formyl function is suitable for conversion into series of 1,3-dipoles. The final step is the intramolecular cycloaddition of dipole and dipolarophile **3** to give the fused ring system **4** (Scheme 1).

## CHEMISTRY

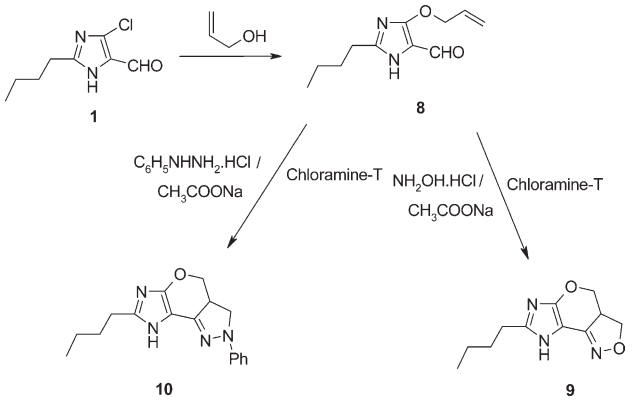
The starting compound 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde was synthesized by literature procedure [9]. Substitution of chloro group with allyl thiols furnished 2-butyl-5-(allylsulfanyl)imidazole-4-carbaldehyde. This compound could be transformed into the tricyclic heterocycles by converting the aldehyde function into 1,3-dipoles (Scheme 2). Similarly, substitution with allyl alcohol furnished the 2-butyl-5-(allyloxyl)imidazole-4-carbaldehyde which could be transformed into corresponding tricyclic heterocycles by converting the aldehyde function into 1,3-dipoles (Scheme 3).

The aldehyde **5** was converted into the oxime and then oxidized with chloramine-T to give nitrile oxide,

**Scheme 1**



**Scheme 3**

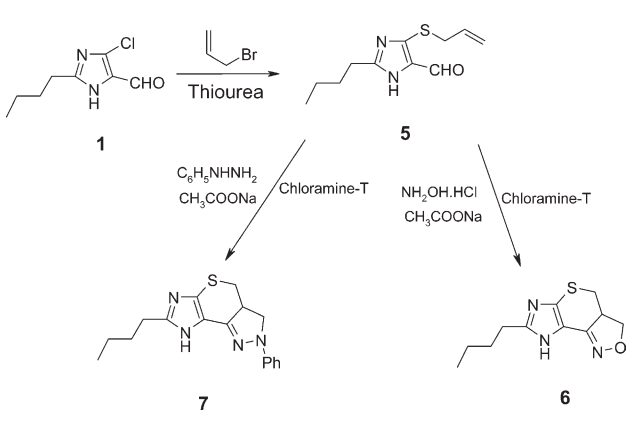


which undergoes intramolecular cycloaddition to form dihydroisoxazole **6**. The aldehyde **5** was converted to phenyl hydrazone and then oxidized with chloramine-T to give nitrile imine, which on intramolecular cycloaddition results pyrazole derivative **7**. The aldehyde **5** was prepared by substituting chloro group of aldehyde **1** with allyl thiol, generated by basic decomposition of the allyl isothiourea salt. Similarly, compounds **9** and **10** are synthesized to form aldehyde **1** by substituting chloro group with allyl alcohol.

## RESULTS AND DISCUSSION

$^1$H NMR, $^{13}$C NMR, IR, and elemental analyses characterized all the synthesized compounds. $^1$H NMR of aldehyde **5** showed a doublet at δ 3.89 for two protons due to $CH_2S$ group and two multiplets at δ 4.9–5.02 and 5.62–5.71 are due to vinylic $CH_2$ and vinylic CH groups, respectively. Aldehydic proton was observed at δ 9.63 and a broad singlet at δ 11.7 is due to NH group of imidazole ring. $^{13}$C NMR showed peak at δ 116.2 and 131.9 due to vinylic $CH_2$ and vinylic CH groups, respectively. The aldehydic carbon was observed at δ 184.2.

**Scheme 2**



$^1$H NMR of isoxazoline **6** showed multiplet at δ 2.92–2.98 for one proton due to CH group. A multiplet at δ 3.15–3.23 is due to $CH_2S$ group and a multiplet at δ 3.92–4.01 is due to $CH_2$ group of isoxazoline ring. $^{13}$C NMR showed doublet at δ 33.3 due to CH group. A triplet at δ 44.4 may be due to carbon of $CH_2S$ group and triplet at δ 63.3 is due to $CH_2$ group of isoxazoline ring. All other substituents are observed in the expected region. The moderate yield of 67% is obtained starting from aldehyde **5** because the intermediate impure oxime was taken directly for next step without purification. The yield of isoxazoline **6** can be improved by purifying the oxime.

$^1$H NMR of pyrazoline **7** showed multiplet at δ 2.85–2.92 for one proton due to CH group. A doublet was observed at δ 3.10 is due to $CH_2S$ group and a multiplet at δ 3.86–3.92 is due to $CH_2$ group of pyrazolines ring. The aromatic protons are observed in the region δ 6.85–7.12. In $^{13}$C NMR a triplet at δ 32.5 may be due to carbon of $CH_2S$ group and a triplet at δ 56.1 may be due to $CH_2$ group of isoxazoline ring. A doublet at δ 46.9 indicates the presence of CH group. All other substituents are observed in the expected region. The moderate yield of 65% is obtained starting from aldehyde **5**. The yield of pyrazoline **7** can be improved by purifying the intermediate phenyl hydrazone.

$^1$H NMR of aldehyde **8** showed a doublet at δ 4.79 for two protons due to $CH_2O$ group and two multiplets at δ 5.22–5.31 and 5.60–5.69 are due to vinylic $CH_2$ and vinylic CH groups, respectively. Aldehydic proton was observed at δ 9.89 and a broad singlet at δ 11.59 is due to NH group of imidazole ring. $^{13}$C NMR showed peak at δ 117.0 and 134.9 due to vinylic $CH_2$ and vinylic CH groups, respectively. The aldehydic carbon was observed at δ 182.1.

$^1$H NMR of isoxazoline **9** showed multiplet at δ 2.96–3.0 for one proton due to CH group. A doublet δ 4.16 is due to $CH_2O$ group and a multiplet at δ 3.96–4.04 is due to $CH_2$ group of isoxazoline ring. $^{13}$C NMR showed doublet at δ 44.3 due to CH group. A triplet at δ 73.3 may be due to carbon of $CH_2O$ group and triplet at δ 62.1 is due to $CH_2$ group of isoxazoline ring. All other substituents are observed in the expected region.

$^1$H NMR of pyrazoline **10** showed multiplet at δ 2.80–2.86 for one proton due to CH group. A multiplet at δ 3.76–3.83 is due to $CH_2$ group of pyrazolines ring. A doublet was observed at δ 4.22, which is due to $OCH_2$ group. The aromatic protons are observed in the region δ 6.85–7.12. $^{13}$C NMR showed doublet at δ 44.2 due to CH group. A triplet at δ 52.1 may be due to $CH_2$ group of isoxazoline ring and a triplet at δ 71.3 is due to $OCH_2$ group. All other substituents are observed in the expected region.

## CONCLUSIONS

In conclusion, we have demonstrated that 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde can be used for intramolecular 1,3-dipolar cycloaddition by substituting chloro group with unsaturated nucleophiles and converting the aldehyde function into 1,3-dipole. Chloramine-T is found to be an efficient reagent for the generation of 1,3-dipole. Other compounds possessing a halogen and aldehyde group at ortho position are also potential candidates for carrying out similar reactions.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. $^{13}$C NMR spectra were measured on Jeol 400 (100 MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used, s = singlet, d = doublet, t = triplet, and m = multiplet. Infrared (IR) spectra were recorded on Shimadzu 8300 IR spectrometer. Elemental analyses were obtained on a Vario-EL instrument. Thin layer chromatography (TLC) was done with precoated silica gel G plates.

**2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde 1 [7].** The aldehyde **1** was synthesized by literature procedure [9]. $^1$H NMR $CDCl_3$: δ 0.92 (t, $J$ = 7.5 Hz, 3H, $CH_3$), 1.32 (m, 2H, $CH_2$), 1.64 (m, 2H, $CH_2$), 2.61 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 9.32 (s, 1H, CHO), 11.89 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.2 (q), 23.2 (t), 28.1 (t), 30.1 (t), 128.2 (s), 144.1 (s), 158.8 (s), 179.2 (d). IR (KBr pellets $cm^{-1}$) ν 3409, 3070, 2969, 2827, 1672, 1459. Anal. Calcd for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; N, 15.01%. Found: C, 51.38; H, 5.98; N, 15.10%.

**5-Allylsulfanyl-2-butyl-3*H*-imidazole-4-carbaldehyde 5.** A solution of allyl bromide (4.87 g, 40.24 mmol) and thiourea (3.08 g, 40.52 mmol) in ethanol (50 mL) were refluxed for 1 h. Ethanolic NaOH solution (3.2 g, 50 mL) was then added and the reaction mass was refluxed for 1 h. The aldehyde **1** (5.0 g, 26.9 mmol) was added to the mixture, which was then refluxed for 2 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 50 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed to give crude oil which was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **5** as a pale yellow oil (4.10 g, 68%). $^1$H NMR $CDCl_3$: δ 0.94 (t, 3H, $CH_3$), 1.33 (m, 2H, $CH_2$), 1.64 (m, 2H, $CH_2$), 2.60 (t, 2H, $CH_2$), 3.89 (d, 2H, $CH_2S$), 4.9–5.02 (m, 2H, vinylic $CH_2$), 5.62 (m, 1H,vinylic CH), 9.63 (s, 1H, CHO), 11.70 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.4 (q), 23.0 (t), 28.4 (t), 32.1 (t), 39.2 (t), 118.2 (t), 131.9 (d), 139.8 (s), 147.2 (s), 157.8 (s), 181.2 (d). IR (KBr pellets $cm^{-1}$) ν 3410, 2949, 2816, 1669, 1461. Anal. Calcd. for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49%. Found: C, 58.96; H, 7.10; N, 12.44%.

**7-Butyl-3a,4-dihydro-3*H*,8*H*-2-oxa-5-thia-1,6,8-triaza-as-indacene 6.** A solution of aldehyde **5** (2.0 g, 8.92 mmol) in ethanol (20 mL) was warmed with aqueous $NH_2OH.HCl$ (0.92 g 13.33 mmol) and $CH_3COONa$ (1.10 g, 13.40 mmol) for 1 h. Ethanol was removed under vacuum and the residue was extracted with ethyl acetate (2 × 25 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed. The resultant residue was dissolved in ethanol (20 mL), chloramine-T (3.0 g, 10.67 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 25 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **6** as a pale yellow oil (1.41 g, 67%). $^1$H NMR $CDCl_3$: δ 0.92 (t, 3H, $CH_3$), 1.32 (m, 2H, $CH_2$), 1.64 (m, 2H, $CH_2$), 2.61 (t, 2H, $CH_2$), 2.92–2.98 (m, 1H, CH), 3.15–3.23 (m, 2H, $CH_2$), 3.92–4.01 (m, 2H, $CH_2$), 11.79 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.0 (q), 23.4 (t), 28.4 (t), 32.5 (t), 33.3 (d), 44.4 (t), 69.3 (t), 111.3 (s), 136.2 (s), 148.8 (s), 156.1 (s). IR (KBr pellets $cm^{-1}$) ν 3416, 2981, 1590, 1421, 1220, 1151. Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.67; H, 6.37; N, 17.71%. Found: C, 55.59; H, 6.41; N, 17.78%.

**7-Butyl-2-phenyl-2,3a,4,8-tetrahydro-3*H*-5-thia-1,2, 6,8-tetraaza-as-indacene 7.** A solution of aldehyde **5** (2.0 g, 8.92 mmol) in ethanol (20 mL) was warmed with aqueous phenyl hydrazine hydrochloride (1.93 g, 13.40 mmol) and $CH_3COONa$ (1.10 g, 13.41 mmol) for 1 h. The reaction mass was cooled and the solid formed was filtered. The solid was dissolved in ethanol (20 mL), chloramine-T (3.0 g, 10.67 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 25 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 8:2) to give **7** as a yellow oil (1.81 g, 65%). $^1$H NMR $CDCl_3$: δ 0.95 (t, $J$ = 7.5 Hz, 3H, $CH_3$), 1.35 (m, 2H, $CH_2$), 1.69 (m, 2H, $CH_2$), 2.65 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 2.85–2.92 (m, 1H, CH), 3.10–3.15 (d, 2H, $CH_2$), 3.86–3.92, (m, 2H, $CH_2$), 6.85–6.95 (m, 3H, ArH), 7.12 (t, 2H, ArH),

11.77 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.1 (q), 23.6 (t), 28.9 (t), 30.7 (t), 32.5 (t), 46.9 (d), 56.1 (t), 110.3 (s), 112.9 (d), 118.1 (d), 119.9(s), 129.8 (d), 134.1 (s), 144.8 (s), 151.1 (s), 153.6 (s). IR (KBr pellets $cm^{-1}$) ν 3411, 3012, 2956, 1643, 1319, 1014. Anal. Calcd. for $C_{17}H_{20}N_4S$: C, 65.35; H, 6.45; N, 17.93%. Found: C, 65.45; H, 6.40; N, 17.90%.

**5-Allyoxy-2-butyl-3*H*-imidazole-4-carbaldehyde 8.** A mixture of aldehyde **1** (5 g, 26.9 mmol), allyl alcohol (2.34 g, 40.3 mmol), and potassium *tert*-butoxide (3.61 g, 32.23 mmol) in tetrahydrofuran (50 mL) were stirred at room temperature for 4 h. The reaction mass was diluted with diethyl ether (25 mL) and the solid was filtered. The filtrate was evaporated and the residue was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **8** as a pale yellow oil (4.02 g, 72%). $^1$H NMR $CDCl_3$: δ 0.92 (t, $J$ = 7.5 Hz, 3H, $CH_3$), 1.30 (m, 2H, $CH_2$), 1.65 (m, 2H, $CH_2$), 2.65 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 4.79 (d, $J$ = 7.0 Hz, 2H, $CH_2S$), 5.22–5.41 (m, 2H, vinylic $CH_2$), 5.60–5.69 (m, 1H, vinylic CH), 9.89 (s, 1H, CHO), 11.59 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.8 (q), 23.0 (t), 28.4 (t), 32.1 (t), 76.2 (t), 118.2 (t), 122.2 (s), 134.9 (d), 149.8 (s), 155.8 (s), 182.1 (d). IR (KBr pellets $cm^{-1}$) ν 3422, 2959, 2856, 1669, 1641, 1215. Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 63.44; H, 7.74; N, 13.45%. Found: C, 63.49; H, 7.70; N, 13.40%.

**7-Butyl-3a,4-dihydro-3*H*,8*H*-2,5-dioxa-1,6,8-triaza-as-indacene 9.** A solution of aldehyde **8** (1.0 g, 4.80 mmol) in ethanol (10 mL) was warmed with aqueous $NH_2OH.HCl$ (0.50 g 7.24 mmol) and $CH_3COONa$ (0.60 g, 7.30 mmol) for 1 h. Ethanol was removed under vacuum and the residue was extracted with ethyl acetate (2 × 10 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed. The resultant residue was dissolved in ethanol (10 mL), chloramine-T (1.62 g, 5.76 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 20 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **9** as a pale yellow oil (0.65 g, 61%). $^1$H NMR $CDCl_3$: δ 0.92 (t, 3H, $CH_3$), 1.32 (m, 2H, $CH_2$), 1.64 (m, 2H, $CH_2$), 2.61 (t, 2H, $CH_2$), 2.96–3.0 (m, 1H, CH), 3.92–4.04 (m, 2H, $CH_2$), 4.16 (d, 2H, $CH_2$), 11.80 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.0 (q), 23.4 (t), 29.4 (t), 31.5 (t), 44.3 (d), 58.4 (t), 73.3 (t), 109.3 (s), 136.2 (s), 149.8 (s), 157.1 (s). IR (KBr pellets $cm^{-1}$) ν 3410, 2952, 1638, 1598, 1220, 1100. Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99%. Found: C, 59.61; H, 6.89; N, 19.04%.

**7-Butyl-2-phenyl-2,3a,4,8-tetrahydro-3*H*-5-oxa-1,2,6, 8-tetraaza-as-indacene 10.** A solution of aldehyde **8** (1.0 g, 4.8 mmol) in ethanol (10 mL) was warmed with aqueous phenyl hydrazine hydrochloride (1.03 g, 7.15 mmol) and $CH_3COONa$ (0.60 g, 7.31 mmol) for 1 h. The reaction mass was cooled and the solid formed was filtered. The solid was dissolved in ethanol (10 mL), chloramine-T (1.62 g, 5.76 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 20 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried ($Na_2SO_4$), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 8:2) to give **10** as a yellow oil (0.90 g, 63%). $^1$H NMR $CDCl_3$: δ 0.93 (t, $J$ = 7.5 Hz, 3H, $CH_3$), 1.33 (m, 2H, $CH_2$), 1.66 (m, 2H, $CH_2$), 2.64 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 2.88–2.93 (m, 1H, CH), 3.86–3.92 (m, 2H, $CH_2$), 4.08–4.15, (m, 2H, $CH_2$), 6.90–7.05 (m, 3H, ArH), 7.24 (t, 2H, ArH), 11.75 (bs, 1H, NH). $^{13}$C NMR $CDCl_3$: δ 13.2 (q), 23.8 (t), 29.2 (t), 30.9 (t), 44.2 (d), 52.4 (d), 71.3 (t), 114.3 (s), 112.0 (d), 117.4 (d), 129.2 (d), 132.1 (s), 144.8 (s), 149 (s), 153.1 (s). IR (KBr pellets $cm^{-1}$) ν 3396, 3026, 2990, 1635, 1235. Anal. Calcd. for $C_{17}H_{20}N_4O$: C, 68.90; H, 6.80; N, 18.90%. Found: C, 68.99; H, 6.71; N, 18.84%.

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## REFERENCES AND NOTES

[1] Padwa, A. In 1,3-Diploar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, p 227.

[2] Wade, P. A. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 1111.

[3] Kozikowski, A. P. Acc Chem Res 1984, 17, 410.

[4] Gaonkar, S. L.; Lokanatha Rai, K. M.; Prabhuswamy, B. Med Chem Res 2007, 15, 407.

[5] Lokanatha Rai, K. M.; Hassner, A. Synth Commun 1989, 19, 2799.

[6] Gaonkar, S. L.; Lokanatha Rai, K. M. J Heterocycl Chem 2005, 42, 877.

[7] Gaonkar, S. L.; Lokanatha Rai, K. M. Tetrahedron Lett 2005, 46, 5969.

[8] Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, P. C.; Yoo, S. W.; Timmermans, P. B. M. W. M. J Med Chem 1991, 34, 2525.

[9] Gaonkar, S. L.; Lokanatha Rai, K. M.; Suchetha Shetty, N. Med Chem Res 2009, 18, 221.

[10] Kumar, C. A.; Swamy, S. N.; Gaonkar, S. L.; Basappa; Salimath, B. P.; Rangappa, K. S. Med Chem 2007, 3, 269.

# Synthesis of New 4-Oxo-thiazolidine-5-ylidenes of Antitumor and Antioxidant Activities

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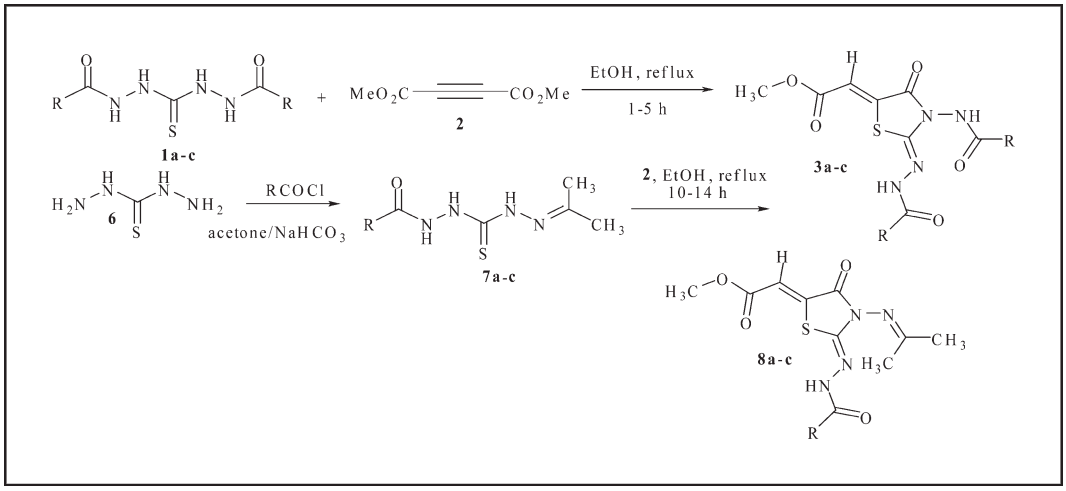


Reaction of diacyl thiocarbohydrazides with dimethyl but-2-ynedioate in refluxing ethanol led to 4-oxa-thiazolidine-5-ylidene-acetates in good yields. Reaction of the newly prepared *N*-(2-(propan-2-ylidene) hydrazine-carbonothioyl)arylhydrazides with dimethyl but-2-ynedioate gave the corresponding (*Z*)-methyl-2-arylhydrazide-4-oxo-3-(propan-2-ylideneamino)thiazolidine-5-ylidene)-acetates. The mechanism is discussed. Antitumor and antioxidant activities have been also investigated.

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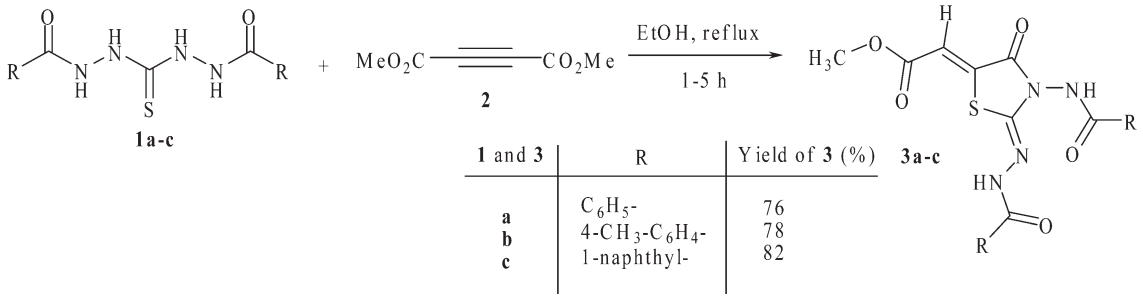
## INTRODUCTION

The development of simple synthesis routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Recent report has shown that various *N*-ethyl hydrazine-carbothioamides can undergo different cyclization reactions to give five member heterocycles, which showed a general stimulation effect on B cell's response [1]. Thiazolidine-4-one ring systems are known to possess antibacterial [2,3], antituberculosis [4–6], antiviral [7–14], anticancer [15–18], and antioxidant [19]. In view of the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared. 4-Phenyl-thiosemicarbazide reacts smoothly with dimethyl but-2-ynedioate in the presence of aldehydes or ketones under solvent free conditions to produce highly functionalized thiazolidine-4-ones [20]. The reaction of thioureas with acetylenic esters has been reported to give a thiazolin-4-one, an imidazolinthion, or a 1,3-thiazin-4-one [21]. Recent reports by Aly *et al*. [22] demonstrated that the reaction of *N*-aroyl thioureas with of dimethyl but-2-ynedioate under reflux in acetic acid yielded the corresponding 1,3-thizinones. Additionally, diethyl maleate reacts with *N*-substituted-hydrazino-carbothioamides to form ethyl [1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates [23]. Reaction proceeds *via* bicyclization and oxidation processes [23]. Whilst 2,3-diphenylcyclopropenone reacts with ylidene-*N*-phenylhydrazine-carbothioamides to form the pyrrolo[2,1-*b*]-1,3,4-oxadiazoles *via* formal [2 + 3]cycloaddition [24]. On the other side, we reported on one pot synthesis of 1,3-thiazin-2-ylidene-substituted hydrazides *via* one-pot reaction of *N*-substituted-hydrazino-carbothioamides with 1,4-diphenylbut-2-

**Scheme 1.** Synthesis of new 1,3-thiazolidine-4-ones **3a–c**.




| 1 and 3 | R | Yield of 3 (%) |
|---|---|---|
| a | $C_6H_5$- | 76 |
| b | 4-$CH_3$-$C_6H_4$- | 78 |
| c | 1-naphthyl- | 82 |

yne-1,4-dione [25]. On the basis of aforementioned encouraged results, we investigate the reaction of acyl thiocarbohydrazides with dimethyl but-2-ynedioate. Moreover antitumor and antioxidant activities of the isolated products have been investigated.

## RESULTS AND DISCUSSION

**Chemistry.** We have now reacted diacyl thiocarbohydrazides **1a–c** [26] with dimethyl but-2-ynedioate (**2**); the reactions gave mainly the corresponding (*Z*)-methyl-2-[(*Z*)-3-aroylamido-2-(2-arylhydrazono)]-4-oxa-thiazolidine-5-ylidene)-acetates (**3a–c**, Scheme 1). For structure prevalent, we choose one derivative identified as **3b** and investigate its NMR in comparative with its expected regioisomers **3bI–III** (Fig. 1). As IR and $^{13}C$ NMR did not reveal any absorbance of the C=S group. Moreover, the five C=S in $^{13}C$ chemical shifts are all too far upfield for a C=S. Therefore the upfield five carbon signals in the $^{13}C$ NMR spectra of compound 3b must represent three carbon signals of four C=O and one for the C=N carbon (see the EXPERIMENTAL SECTION). Accordingly the structure of the regioisomer **3bI** is excluded. The magnitude of the coupling constant ($J$ = 5.2 Hz) further argues that ring carbonyl (C-4) and vinylic-proton are mutually *cis*. Under gated decoupling, the ring carbonyl (C-4) couples to vinylic-proton with $J$ = 5.2 Hz, a value which requires a three- not two-bond coupling as depicted in structures **3b** and **3bIII** and excluded the formation of other regioisomers (**3bI** and **3bII**). It was reported, if the coupling constant for the vinylic-proton and endocyclic carbon atom in a condensation product is about ~5 Hz (*vicinal*-coupling), this product has a five-membered ring; if the coupling constant approaches a value of 1 Hz (*geminal*-coupling), the product should be assigned six-membered thiazine structure [27,28]. Most of the C—H coupling constants are within conventional ranges [29], except that the $J_{C-H}$ values for C-2′ and C-3′ are unusually small for benzenes. Presumably this arises from restricted rotation. In compound **3b** there are two *p*-toluoyl units, one slightly broadened, which is presumably due to restricted rotation. Toluamide rotation and NH exchange are independent processes, which in general occur at different rates. The methoxyl protons are distinctive at $\delta_H$ = 3.81; this signal gives HMQC correlation with the attached carbon at $\delta_C$ = 52.7 and HMBC correlation with the ester carbonyl at $\delta_C$ = 165.6. The signal ($\delta_C$ = 160.9) giving HMBC correlation to vinylic-H ($\delta_H$ = 6.96) is assigned as C-4. The carbon ($\delta_C$ = 116.8) giving HMQC correlation to vinylic-H is assigned as

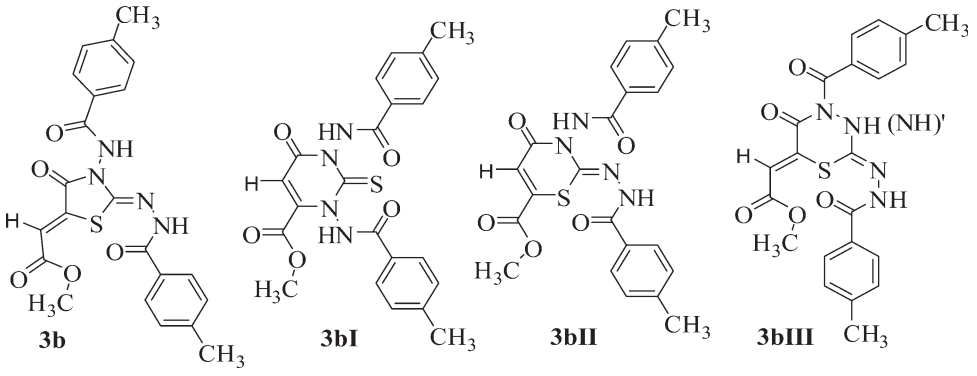



**Figure 1.** Structure of some commercial triazolopyrimidine-2-sulfonamide herbicides.

**Table 1**

NMR spectroscopic data of compound **3b**.

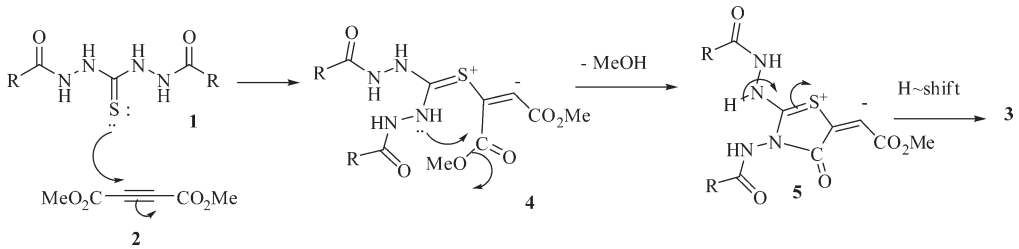
| | COSY | HMQC | HMBC | Assignment |
|---|---|---|---|---|
| $^1$H NMR (ppm) | | | | |
| 11.67 (bs; 1H) | 11.34 | | | benzamido-NH |
| 11.34 (bs; 1H) | 11.67 | | | hydrazono-NH |
| 7.88 (d, $J$ = 7.7; 2H) | 7.39 | | | H-2′ |
| 7.77 (bd, $J$ = 6.4; 2H) | 7.31 | | | H-2″ |
| 7.39 (d, $J$ = 8.0; 2H) | 7.88 | | | H-3′ |
| 7.31 (bd, $J$ = 6.1; 2H) | 7.77 | | | H-3″ |
| 6.96 (s; 1H) | | | | vinylic-H |
| 3.81 (s; 3H) | | | | $OCH_3$ |
| 2.41 (s; 3H) | | | | benzamido-$CH_3$ |
| 2.37 (s; 3H) | | | | hydrazono-$CH_3$ |
| $^{13}$C NMR (ppm) | | | | |
| 165.6 (q, $J$ = 4.3) | | | 3.81 | ester C=O |
| 164.3 (dt, $J_d$ = 8.6, $J_t$ = 4.2) | | | 7.88 | benzamido-C=O |
| 163.4 (b) | | | 11.34 | hydrazono-C=O |
| 160.9 (d, $J$ = 5.2) | | | 6.96 | C-4 |
| 152.0 (b) | | | 11.34 | C-2 |
| 143.0 (q, $J$ = 7.5) | | | 7.88, 2.41 | C-4′ |
| 141.8 (bq) | | | 7.77, 2.37 | C-4″ |
| 137.5 (s) | | | 6.96 | C-5 |
| 129.8 (t, $J$ = 7.7) | | | | C-1′ |
| 129.2 (ddq, $J_d$ = 165.8, 5.5; $J_q$ = 5.5) | | 7.39 | 7.39, 2.41 | C-3′ |
| 128.9 (bd, $J$ = 136.9) | | 7.31 | 2.37 | C-3″ |
| 127.8 (t, $J$ = 7.6) | | | | C-1″ |
| 127.7 (dd, $J$ = 160.9, 6.4) | | 7.88 | 7.88 | C-2′ |
| 127.5 (bd, $J$ = 136.3) | | 7.77 | | C-2″ |
| 116.8 (d, $J$ = 173.7) | | 6.96 | | vinylic-CH |
| 52.7 (q, $J$ = 148.2) | | 3.81 | | $OCH_3$ |
| 21.0 (tq, $J_t$ = 4.9, $J_q$ = 126.7) | | 2.41 | 7.39 | benzamido-$CH_3$ |
| 20.9 (tq, $J_t$ = 4.9, $J_q$ = 126.7) | | 2.37 | | hydrazono-$CH_3$ |

vinylic-CH. One other carbon ($\delta_C$ = 137.5) gives HMBC correlation to vinylic-H, and is assigned as C-5. The benzamido- and hydrazono-C=O appear distinctively at $\delta_C$ = 164.3 and 163.4, respectively. They give HMBC correlation to the ortho protons on the attached tolyl rings at $\delta_H$ = 7.88 and 7.77, respectively.

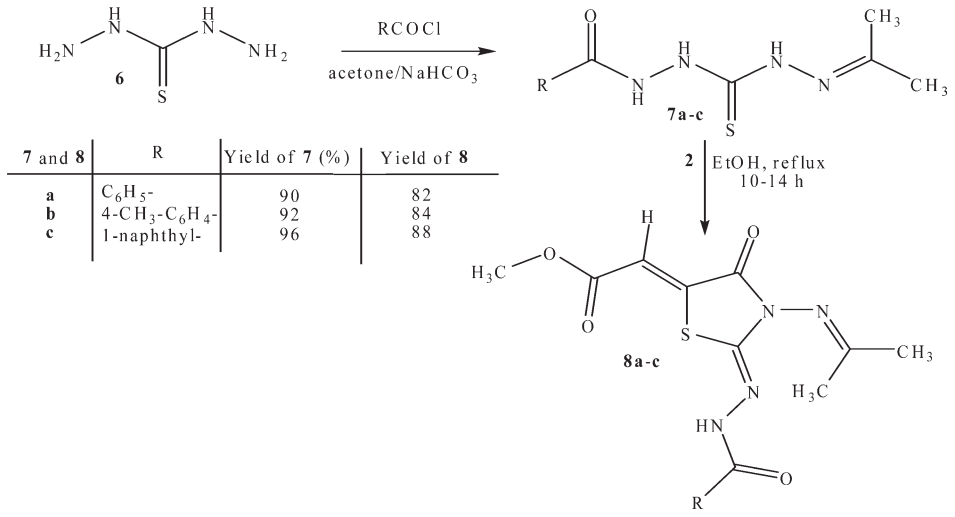
The signals at $\delta_C$ = 143 and 141.8 give HMBC correlation with the *ortho* protons and $CH_3$ ($\delta_H$ = 7.88, 2.41 and 7.77, 2.37) are assigned as C-4′ and C-4″, respectively. The assignment of distinctive hydrogen and carbon signals and their δ values as well as the corresponding coupling constants of compound **3b** are as shown in Table 1.

On the basis of well established chemistry of electrophilic acetylenes [21], it is reasonable to assume that compounds **4** resulted from the initial conjugate addition of the sulfur atom of **2** to the acetylenic ester. Then, the ester group of intermediate **4** was attacked by the amino moiety to yield **5** by elimination of methanol molecule (Scheme 2). Hydrogen shift is then proposed to be

**Scheme 2.** Plausible mechanism of 1,3-thiazolidine-4-ones **3a–c**.



**Scheme 3.** Synthesis of 1,3-thiazolidine-4-ones **8a–c**.




| 7 and 8 | R | Yield of 7 (%) | Yield of 8 |
|---|---|---|---|
| a | $C_6H_5$- | 90 | 82 |
| b | 4-$CH_3$-$C_6H_4$- | 92 | 84 |
| c | 1-naphthyl- | 96 | 88 |

occurred in **5** to produce the stable heterocycle **3** (Scheme 2). Previously it was reported that thiocarbohydrazide (**6**) condensed with acetone to form the corresponding mono-condensed products [30] likewise in case of **7a–c** (Scheme 3). Herein we reacted compound **2** with aroyl chlorides in presence of acetone. The reaction proceeds successfully to give compounds **7a–c** in good yields (Scheme 3). Interestingly, on reacting the newly prepared compounds **7a–c** with dimethyl but-2-ynedioate ethyl ester (**2**), the reaction gave the corresponding thiazolidines **8a–c** in good yields (Scheme 3).

In compound **8a**, the $^1$H NMR spectrum showed the two methyl protons are distinctive at $\delta_H = 2.06$ and 1.94; this signals gives HMQC correlation with the attached carbon at $\delta_C = 25.0$ and 18.7 and HMBC correlation with the carbon at $\delta_C = 168.9$ which is assigned as $C(CH_3)_2$. The methoxyl protons are distinctive at $\delta_H = 3.87$; this signal gives HMQC correlation with the attached carbon at $\delta_C = 52.6$ and HMBC correlation with the ester carbonyl at $\delta_C = 166.1$. The signal ($\delta_C = 162.1$) giving HMBC correlation to vinylic-H ($\delta_H = 6.96$) is assigned as C-4. The carbon ($\delta_C = 117.3$) giving HMQC correlation to vinylic-H is assigned as vinylic-CH. One other carbon ($\delta_C = 139.4$) gives HMBC correlation to vinylic-H, and is assigned as C-5. The benzoyl C=O appear at $\delta_C = 166.0$ gives HMBC correlation with *ortho* protons at ($\delta_H = 7.91$).

**Biological section.**

***Cytotoxicity against Hep-G2 cells.*** Using MTT assay, we studied the effect of the compounds on the proliferation of human hepatocellular carcinoma after 48 h incubation. Incubation of Hep-G2 cell line with gradual doses of the compounds led to insignificant change in the growth of Hep-G2 cells as indicated from their $IC_{50}$ values (>100 μ*M*), except, compound **3c**, which resulted in a high inhibition of the cell growth of Hep-G2 cells compared with the growth of untreated control cells, as concluded from their low $IC_{50}$ value 36.14 μ*M*. However, compounds **8a** and **3b** represents a moderate antitumor agent against Hep-G2 cells. Figure 2 shows the effect of compounds **3a–c** and **8a,b** on the growth of Hep-G2 cells. As measured by MTT assay, results are represented as percentage of control untreated cells.

***Antioxidant activity.*** DPPH is a stable nonphysiological, radical, which could provide a relative figure of the radical scavenging activity of the tested compounds. The DPPH assay showed that some of the tested compounds possessed no scavenging activity to DPPH with high $SC_{50}$ values (>100 μ*M*) compared to the scavenging activity ($SC_{50}$ 8.41) of the well-known antioxidant (ascorbic acid, A.A), except compounds **3b**, **3c**, and **8a** which

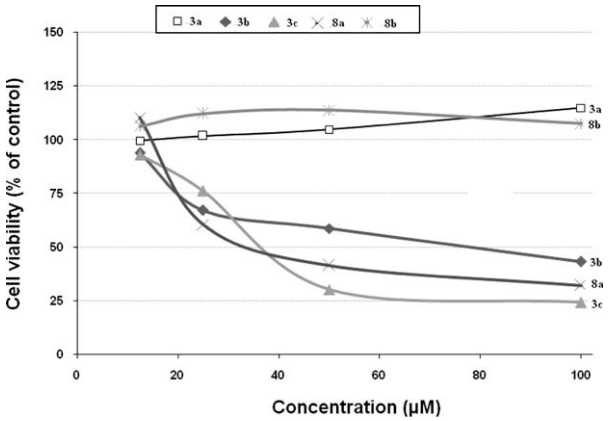



**Figure 2.** The effect of compounds **3a,c** and **8a,b** on the growth Hep-G2 cells. As measured by MTT assay. Results are represented as percentage of control untreated cells.

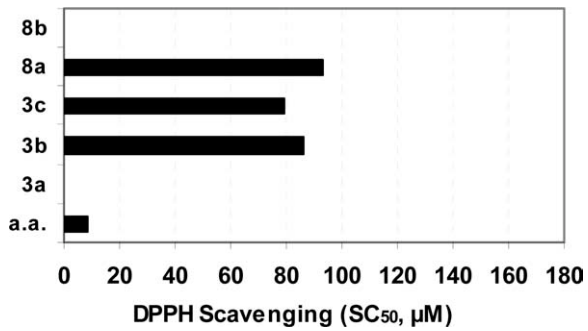



**Figure 3.** The antioxidant activity of **3b**, **3c**, and **8a** was investigated using DPPH assay. The results are represented as $SC_{50}$ values (μM) as (mean ± SE, $n = 4$)

had effective antioxidant activity with $SC_{50}$ values of 86.4, 79.2, and 92.8 μ*M*, respectively (Fig. 3).

## EXPERIMENTAL

**Chemistry.** TLC analysis was performed on analytical Merck 9385 silica aluminium sheets (Kiselgel 60) with $PF_{254}$ indicator. Melting points were determined on Stuart electrothermal melting point apparatus and were uncorrected. The IR spectra were recorded as KBr disks on Shimadzu-408 infrared spectrophotometer, Faculty of Science, El-Minia University. The NMR spectra were measured using Bruker AV-400, Florida Institute of Technology, USA. Chemical shifts were expressed as δ (ppm) with tetramethylsilane as internal reference. The samples were dissolved in chloroform-$d_6$ and/or dimethyl sulphoxide (DMSO)-$d_6$, s = singlet, d = doublet, dd = doublet of doublet, and t = triplet. Mass spectra were recorded on Varian MAT 312 instrument in E1 mode (70 eV), Technische Universität Braunschweig, Germany. Elemental analyses were performed using Varian Elementary device in National Research Center (Dokki, Giza, Egypt).

***Materials.*** Dimethyl but-2-ynedioate (**2**) and thiocarbohydrazide (**6**) were bought from Fluka. Diaroyl thiocarbohydrazides **1a–c** were prepared according to the literature [26].

***Reactions between diaroyl thiocarbohyhydrazides 1a–c with 2.*** An equal mixture of **1a–c** (1 mmol) and **2** (0.142 g, 1 mmol) was heated at reflux in absolute ethanol for 1–5 h (the reaction was followed by TLC analysis). The solvent was evaporated under vacuum and the obtained yellow precipitates were dissolved in dichloromethane and applied on column chromatography (dichloromethane, silica gel). The obtained products **3a–c** were recrystallized from the stated solvents.

*(Z)-Methyl-2-[(Z)-3-benzamido-2-(2-benzoylhydrazono)-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (**3a**).* Yellow crystals (toluene), yield = 323 mg (76%), m.p. 261–263°C. IR (potassium bromide): ν = 3240, (NH), 3070–3010 (Ar-CH), 2985–2875 (aliph.-CH), 1742, 1696, 1663 (C=O), 1618 (C=N) $cm^{-1}$. $^1H$ NMR (400.13 MHz, DMSO-$d_6$): $\delta_H$ = 11.78 (b, s, 1H, benzamido-NH), 11.44 (b, s, 1H, hydrazino-NH), 7.99 (d, 2H, H-2′, $J$ = 7.5 Hz), 7.87 (d, 2H, H-2″, $J$ = 7.0 Hz), 7.71 (t, 1H, H-4′, $J$ = 7.4 Hz), 7.61 (t, 3H, H-3″,4″, $J$ = 7.4, 7.7 Hz), 7.53 (t, 2H, H-3′, $J$ = 7.2 Hz), 6.98 (s, 1H, vinylic-H), 3.81 (s, $OCH_3$) ppm. $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): $\delta_C$ = 165.6 (2 benzoyl C=O), 164.5 (C-4), 160.8 (ester C=O), 151.9 (C-2), 137.4 (C-5), 132.8 (C-4′), 132.6 (C-1′), 131.7 (C-4″), 130.6 (C-1″), 128.7 (C-3′), 128.4 (C-3″), 127.7 (C-2′), 127.5 (C-2″), 116.9 (vinylic-CH), 52.7 ($OCH_3$) ppm. MS (70 eV, EI); *m/z* (%) = 424 [M+] (24), 312 (20), 283 (32), 281 (100), 138 (20), 104 (63), 91 (25), 77 (96), 69 (24), 57 (14), 51 (24). *Anal*. Calcd. for $C_{20}H_{16}N_4O_5S$ (424.43): C, 56.60; H, 3.80; N, 13.20; S, 7.55. Found: C, 56.50; H, 3.82; N, 13.28; S, 7.86.

*(Z)-Methyl-2-[(Z)-3-(4-methylbenzamido)-2-(2-(4-methylbenzoyl)-hydrazono)-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (**3b**).* Yellow crystals (methanol), yield = 353 mg (78%), m.p. 270–271°C. IR (potassium bromide): ν = 3070–3005 (Ar-CH), 2990–2850 (aliph.-CH), 1740, 1680, 1640 (C=O), 1612 (C=N) $cm^{-1}$. The NMR: Table 1. MS (70 eV, EI); *m/z* (%) = 452 [$M^+$] (24), 375 (18), 343.23 (30), 119 (100), 91 (27), 65 (30). *Anal*. Calcd. for $C_{22}H_{20}N_4O_5S$ (452.48): C, 58.40; H, 4.46; N, 12.38; S, 7.09. Found: C, 58.38; H, 4.63; N, 12.43; S, 7.23.

*(Z)-Methyl-2-[(Z)-3-(1-napthamido)-2-(2-(1-naphthoyl)hydrazono)-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (**3c**).* Yellow crystals (methanol), yield = 430 mg (82%), m.p. 259–260°C. IR (potassium bromide): ν = 3240, (NH), 3035–3005 (Ar-CH), 2985–2910 (aliph.-CH), 1740, 1691, 1670, 1953 (C=O), 1610 (C=N) $cm^{-1}$. $^1H$ NMR (400.13 MHz, DMSO-$d_6$): $\delta_H$ = 11.81 (b, s, 1H, napthamido-NH), 11.70 (b, s, 1H, hydrazino-NH), 8.55 (d, 1H, H-8′, $J$ = 8.1 Hz), 8.22 (d, 1H, H-8″, $J$ = 6.4 Hz), 8.17 (d, 1H, H-4′, $J$ = 7.8 Hz), 8.12 (d, 1H, H-4″, $J$ = 8.0 Hz), 8.06–7.95 (m, 2H, H-3′,3″), 7.89 (d, 1H, H-2′, $J$ = 6.2 Hz), 7.78 (d, 1H, H-2″, $J$ = 6.6 Hz), 7.69 (d, 2H, H-5′,5″, $J$ = 7.4 Hz), 7.64–7.56 (m, 4H, H-6′,7″, 6″,7″), 7.02 (s, 1H, vinylic-H), 3.84 (s, $OCH_3$) ppm. $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): $\delta_C$ = 166.9 (napthamido-C=O), 165.7 (ester-C=O), 165.1 (C=O), 160.6 (C-4), 147.8 (C-2), 137.6 (C-5), 133.2 (C-8a′), 133.1 (C-4a′), 132.3 (C-8a″), 131.2 (C-4′), 130.8 (C-1′), 130.5 (C-4″), 130 (C-3′), 129.8 (C-3″), 128.3 (C-4a″), 128.2 (C-1″), 127.4 (C-7′), 127.0 (C-7″), 126.6 (C-6′, C-6″), 126.4 (C-2′), 126.2 (C-2″), 126.1 (C-8′), 125.4 (C-8″), 124.9 (C-5′, C-5″), 116.8 (vinylic-CH), 52.7 ($OCH_3$) ppm. MS (FAB, 70 eV); *m/z* (%) = 524 [$M^+$] (100). *Anal*. Calcd. for $C_{28}H_{20}N_4O_5S$ (524.55): C, 64.11; H, 3.84; N, 10.68; S, 6.11. Found: C, 63.87; H, 3.95; N, 10.73; S, 6.21.

***Synthesis of N-(2-propan-2-ylidene)-hydrazine-carbonothioyl)arylhydrazides 7a–c.*** To a suspension solution of **6** (0.106 g, 1 mmol) and $NaHCO_3$ (0.126 g, 1.5 mmol) in dry acetone (20 mL) was stirred at room temperature, the corresponding acid chloride (1 mmol) in dry acetone (5 mL) was added dropwise over a period of 20 min. The reaction mixture was stirred for further continued 3 h at room temperature then at refluxing temperature for 15 min. The reaction mixture was filtered and the salt precipitate was washed three times with chloroform (20 mL). The solvent of the filtrate was removed under vacuum. The obtained precipitate was then washed three times with 0.1*N* HCl (5 mL) followed by three times with water (30 mL). The obtained products **7a–c** were recrystallized from glacial acetic acid.

*4-Methyl-N-(2-propan-2-ylidene)hydrazinecarbono-thionyl)-benzamide (**7a**).* White crystals, yield = 225 mg (90%), m.p. 172–174°C. IR (potassium bromide): ν = 3230–3315 (NH), 3041–3009 (Ar-CH), 2981–2915 (aliph.-CH), 1674 (C=O), 1617 (C=N), 1365 (C=S) $cm^{-1}$. $^1H$ NMR (400.13 MHz, chloroform-$d_3$): $\delta_H$ = 9.98 (b, s, 1H, NH-2), 9.76 (b, s, 1H, NH-1), 9.24 (b, s, 1H, NH-3), 7.92 (d, 2H, H-2, $J$ = 7.8 Hz),

7.57 (t, 1H, H-4, $J$ = 7.5 Hz), 7.41 (t, 2H, H-3, $J$ = 7.5 Hz), 1.97 (s, 3H, $CH_3^a$), 1.89 (s, 3H, $CH_3^b$) ppm. $^{13}$C NMR (100.6 MHz, chloroform-$d_3$): $\delta_C$ = 132.8 (C-4), 131.5 (C-1), 128.6 (C-3), 128.4 (C-2), 24.8 ($CH_3^a$), 19.4 ($CH_3^b$) ppm. MS (70 eV, EI); $m/z$ (%) = 250 [$M^+$] (40), 105 (100), 77 (42), 56 (31). *Anal*. Calcd. for $C_{11}H_{14}N_4OS$ (250.32): C, 52.78; H, 5.64; N, 22.38; S, 12.81. Found: C, 53.03; H, 5.50; N, 22.54; S, 12.97.

*4-Methyl-N-(2-(propan-2-ylidene)hydrazine-carbonothioyl)-benzohydrazide (**7b**)*. White crystals, yield = 243 mg (92%), m.p. 179–181°C. IR (potassium bromide): ν = 3234–3321 (NH), 3033–3005 (Ar-CH), 2978–2914 (aliph.-CH), 1679 (C=O), 1619 (C=N), 1359 (C=S) cm$^{-1}$. $^1$H NMR (400.13 MHz, chloroform-$d_3$): $\delta_C$ = 9.96 (b, s, 1H, NH-2), 9.72 (b, s, 1H, NH-1), 9.44 (b, s, 1H, NH-3), 7.83 (d, 2H, H-2, $J$ = 7.6 Hz), 7.23 (d, 2H, H-3, $J$ = 7.6 Hz), 2.33 (3H, Ar-$CH_3$), 1.96 (s, 3H, $CH_3^a$), 1.90 (s, 3H, $CH_3^b$) ppm. $^{13}$C NMR (100.6 MHz, chloroform-$d_3$): $\delta_C$ = 176.4 (C=S), 164.7 (benzoyl C=O), 156.5 (C(CH3)2), 143.4 (C-4), 132.8 (C-1), 129.4 (C-3), 127.6 (C-2), 24.9 ($CH_3^a$), 21.5 (Ar-$CH_3$), 19.6 ($CH_3^b$) ppm. MS (70 eV, EI); $m/z$ (%) = 264 [$M^+$] (30), 119 (100), 91 (32), 56 (27). *Anal*. Calcd. for $C_{12}H_{16}N_4OS$ (264.35): C, 54.52; H, 6.10; N, 21.19; S, 12.13. Found: C, 54.63; H, 6.23; N, 21.41; S, 12.27.

*4-Methyl-N-(2-(propan-2-ylidene)hydrazine-carbono-thioyl)-naphthamide (**7c**)*. White crystals, yield = 288 mg (96%), m.p. 181–183°C. IR (potassium bromide): ν = 3242–3316 (NH), 3030–3012 (Ar-CH), 2981–2919 (aliph.-CH), 1669 (C=O), 1624 (C=N), 1341 (C=S) cm$^{-1}$ $^1$H NMR (400.13 MHz, chloroorm-$d_3$): $\delta_H$ = 10.7 (b, s, 1H, NH-3), 10 17 (b, s, 1H, NH-1), 10.11 (b, s, 1H, NH-2), 9.0 (d, 1H, H-8, $J$ = 8.1 Hz), 8.05 (d, 1H, H-2, $J$ = 7.4 Hz), 7.98 (d, 1H, H-4, $J$ = 8.0 Hz), 7.91 (d, 1H, H-5, $J$ = 8.0 Hz), 7.79 (dd, 1H, H-7, $J$ = 7.7, 7.5 Hz), 7.55 (dd, 1H, H-H-6, $J$ = 7.6, 7.4 Hz), 7.48 (t, 1H, H-3, $J$ = 8.0 Hz), 1.98 (s, 3H, $CH_3^a$), 1.91 (s, 3H, $CH_3^b$) ppm. $^{13}$C NMR (100.6 MHz, chloroform-$d_3$): $\delta_C$ = 76.4 (C=S), 165.3 (napthoyl C=O), 159.7 (N=C($CH_3$)$_2$), 137.2 (C-4), 136.8 (C-4a), 133.5 (C-1), 132.4 (C-2), 131.6 (C-8a), 131.1 (C-3), 129.3 (C-5), 129.2 (C-7), 128.6 (C-8), 127.8 (C-6), 25.1 ($CH_3^a$), 19.9 ($CH_3^b$) ppm. MS (70 eV, EI); $m/z$ (%) = 300 [$M^+$] (36), 155 (100), 127 (23), 56 (19). *Anal*. Calcd. for $C_{15}H_{16}N_4OS$ (300.38): C, 59.98; H, 5.37; N, 18.65; S, 10.67. Found: C, 59.73; H, 5.23; N, 18.41; S, 10.47.

***Reactions between aroyl thiocarbohyhydrazides 7a–c with 2.*** As previously mentioned before: an equal mixture of **7a–c** (1 mmol) and 2 (0.142 g, 1 mmol) was heated at reflux in absolute ethanol for 10–14 h (the reaction was followed by TLC analysis). The solvent was evaporated under vacuum. The obtained products were then dissolved in dichloromethane and applied on column chromatography (dichloromethane, silica gel). The obtained pure products were recrystallized from the stated solvents.

*(Z)-Methyl-2-[(Z)-2-(2-benzoylhydrazono)-4-oxo-3-(propan-2-ylideneamino)-1,3-thiazolidin-5-ylidene]-acetate (**8a**)*. Yellow crystals (methanol), yield = 296 mg (82%), m.p. 216–218°C. IR (potassium bromide): ν = 3235 (NH), 3063–3015 (Ar-CH), 2995–2905 (aliph.-CH), 1736, 1698, 1672 (C=O), 1642, 1608 (C=N) cm$^{-1}$. $^1$H NMR (400.13 MHz, chloroform-$d_3$): $\delta_H$ = 8.30 (b, s, 1H, hydrazino-NH), 7.91 (d, 2H, H-2′, $J$ = 7.6 Hz), 7.60 (t, 1H, H-4′, $J$ = 7.4 Hz), 7.49 (t, 2H, H-3′, $J$ = 7.6 Hz), 6.96 (s, 1H, vinylic-H), 3.87 (s, $OCH_3$), 2.06 (s, $CH_3^a$), 1.94 (s, $CH_3^b$) ppm. $^{13}$C NMR (100.6 MHz, chloroform-$d_3$): $\delta_C$ = 168.9 (C(CH3)2), 166.1 (ester C=O), 166 (benzoyl C=O), 162.1 (C-4), 152.5 (C-2), 139.4 (C-5), 133 (C-4′), 130.9 (C-1′), 128.9 (C-3′), 127.7 (C-2′), 117.3 (vinylic-CH), 52.6 ($OCH_3$), 25.0 ($CH_3^a$), 18.7 ($CH_3^b$) ppm. MS (70 eV, EI); $m/z$ (%) = 360 [$M^+$] (30), 217 (28), 105 (100), 77 (32), 56 (20). *Anal*. Calcd. for $C_{16}H_{16}N_4O_4S$ (360.39): C, 53.32; H, 4.47; N, 15.55; S, 8.90. Found: C, 53.50; H, 4.50; N, 15.34; S, 8.97.

*(Z)-Methyl-2-[(Z)-2-(2-(4-methylbenzoyl)-hydrazono)-4-oxo-3-(propan-2-ylidene-amino)-1,3-thiazolidin-5-ylidene]-acetate (**8b**)*. Yellow crystals (methanol), yield = 315 mg (84%), m.p. 245–247°C. IR (potassium bromide): ν = 3200 (NH), 3070–3019 (Ar-CH), 2976–2873 (aliph.-CH), 1735, 1695, 1665 (C=O), 1645, 1607 (C=N) cm$^{-1}$. $^1$H NMR (400.13 MHz, chloroform-$d_3$): $\delta_H$ = 8.45 (b, s, 1H, hydrazino-NH), 7.80 (d, 2H, H-2′, $J$ = 8.0 Hz), 7.27 (d, 2H, H-3′, $J$ = 7.9 Hz), 6.93 (s, 1H, vinylic-H), 3.86 (s, $OCH_3$), 2.41 (benzoyl $CH_3$), 2.04 (s, $CH_3^a$), 1.92 (s, $CH_3^b$) ppm. $^{13}$C NMR (100.6 MHz, chloroform-$d_3$): $\delta_C$ = 168.9 (N=C($CH_3$)$_2$), 166.1 (ester C=O), 165.3 (benzoyl C=O), 162.2 (C-4), 152.6 (C-2), 143.7 (C-4′), 139.5 (C-5), 129.5 (C-3′), 128.0 (C-1′), 127.7 (C-2′), 117.2 (vinylic-CH), 52.5 ($OCH_3$), 25.0 ($CH_3^a$), 21.6 (benzoyl $CH_3$) 18.7 ($CH_3^b$) ppm. MS (70 eV, EI); $m/z$ (%) = 374 [$M^+$] (24), 275 (18), 119 (100), 91 (17), 56 (12). *Anal*. Calcd. for $C_{17}H_{18}N_4O_4S$ (374.41): C, 54.53; H, 4.85; N, 14.96; S, 8.56. Found: C, 54.24; H, 5.07; N, 14.82; S, 8.67.

*(Z)-Methyl-2-[(Z)-2-(2-(1-napthoyl)hydrazono)-4-oxo-3-(propan-2-ylideneamino)-1,3-thiazolidin-5-ylidene]-acetate (**8c**)*. Yellow crystals (methanol), yield = 361 mg (88%), m.p. 224–225°C. IR (potassium bromide): ν = 3064–3006 (Ar-CH), 2968–2879 (aliph.-CH), 1729, 1698, 1671 (C=O), 1648, 1612 (C=N) cm$^{-1}$. $^1$H NMR (400.13 MHz, chloroform-$d_3$): $\delta_H$ = 9.60 (b, s, 1H, hydrazino-NH), 9.14 (d, 1H, H-8′, $J$ = 8.4 Hz), 8.23 (d, 1H, H-2′, $J$ = 7.2 Hz), 7.95 (d, 1H, H-4′, $J$ = 8.0 Hz), 7.82 (d, 1H, H-5′, $J$ = 8.1 Hz), 7.65 (dd, 1H, H-7′, $J$ = 7.7, 7.5 Hz), 7.51 (dd, 1H, H-6′, $J$ = 7.5, 7.3 Hz), 7.49 (t, 1H, H-3′, $J$ = 7.9 Hz), 6.95 (s, 1H, vinylic-H), 3.94 (s, $OCH_3$), 2.07 (s, $CH_3^a$), 1.96 (s, $CH_3^b$) ppm. $^{13}$C NMR (100.6 MHz, chloroform-$d_3$): $\delta_C$ = 169.3 (N=C(CH3)2), 167.4 (ester C=O), 167.2 (napthoyl C=O), 164.7 (C-4), 153.9 (C-2), 141.2 (C-4′), 140.3 (C-5), 134.6 (C-4′a), 133.2 (C-2′), 132.5 (C-8′$^a$), 131.3 (C-1′), 130.2 (C-5′), 129.6 (C-7′), 128.8 (C-8′), 128.1 (C-6′), 127.8 (C-3′), 118.3 (vinylic-CH), 52.8 ($OCH_3$), 25.5 ($CH_3^a$), 19.3 ($CH_3^b$) ppm. MS (70 eV, FAB); $m/z$ (%) = 410 [$M^+$] (100). *Anal*. Calcd. for $C_{20}H_{18}N_4O_4S$ (410.45): C, 58.53; H, 4.42; N, 13.65; S, 7.81. Found: C, 58.28; H, 4.67; N, 13.82; S, 7.67.

**Biological section.**

***Cell culture.*** Human hepatocellular carcinoma (HepG2) cells were routinely cultured in Dulbeco's Modified Eagle's Medium. Media were supplemented with 10% fetal bovine serum, 2 m*M* L-glutamine, containing 100 units/mL penicillin G sodium, 100 units/mL streptomycin sulphate, and 250 ng/mL amphotericin B. Cells were maintained at subconfluency at 37°C in humidified air containing 5% $CO_2$. For subculturing, monolayer cells were harvested after trypsin/EDTA treatment at 37°C. Cells were used when confluence had reached 75%. Tested samples were dissolved in DMSO. All cell culture material was obtained from Cambrex BioScience (Copenhagen,

Denmark). All chemicals were from Sigma/Aldrich, except mentioned. All experiments were repeated three times, unless mentioned.

*Cytotoxicty assay*. Cytotoxicity of tested samples was measured using the MTT cell viability assay. MTT (3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide) assay is based on the ability of active mitochondrial dehydrogenase enzyme of living cells to cleave the tetrazolium rings of the yellow MTT and form a dark blue insoluble formazan crystals which is largely impermeable to cell membranes, resulting in its accumulation within healthy cells. Solubilization of the cells results in the liberation of crystals, which are then solubilized. The number of viable cells is directly proportional to the level of soluble formazan dark blue color. The extent of the reduction of MTT was quantified by measuring the absorbance at 570 nm [31].

*Reagents preparation*. MTT solution: 5 mg/mL of MTT in 0.9% NaCl. Acidified isopropanol: 0.04*N* HCl in absolute isopropanol.

*Procedure*. Cells ($0.5 \times 10^5$ cells/well) in serum-free media were placed in a flat bottom 96-well microplate and treated with 20 μL of different concentrations of each tested compound for 20 h at 37°C, in a humidified 5% $CO_2$ atmosphere. After incubation, media were removed and 40 μL MTT solution/well were added and incubated for an additional 4 h. MTT crystals were solubilized by adding 180 μL of acidified isopropanol/well and plate was shacked at room temperature, followed by the photometric determination of the absorbance at 570 nm using microplate ELISA reader. Triplicate repeats were performed for each concentration and the average was calculated.

Data were expressed as the percentage of relative viability compared with the untreated cells compared with the vehicle control, with cytotoxicity indicated by <100% relative viability.

*Calculations*. Percentage of relative viability was calculated using the following equation: [Absorbance of treated cells/Absorbance of control cells)] × 100.

Then the half maximal inhibitory concentration IC50 was calculated from the equation of the dose response curve.

***Antioxidant activity (scavenging of DPPH).*** 1,1-Diphenyl-2-picrylhydrazyl is a stable deep violet radical due to its unpaired electron. In the presence of an antioxidant radical scavenger, which can donate an electron to DPPH, the deep violet color decolorize to the pale yellow nonradical form [32]. The change in colorization and the subsequent fall in absorbance are monitored spectrophotometrically at $\nu = 520$ nm.

*Reagents preparation*. Ethanolic DPPH: 0.1 m*M* DPPH/absolute ethanol, standard ascorbic acid solution. Serial dilutions of ascorbic acid in concentrations ranging from 0–2.5 μ*M* in distilled water. A standard calibration curve was plotted using serial dilutions of ascorbic acid in concentrations ranging from 0–2.5 μ*M* in distilled water.

*Procedure*. In a flat bottom 96-well microplates, a total test volume of 200 μL was used. In each well, 20 μL of different concentrations (0–100 μg/mL final concentration) of tested compounds were mixed with 180 μL of ethanolic DPPH and incubated for 30 min at 37°C. Triplicate wells were prepared for each concentration and the average was calculated. Then, the photometric determination of absorbance at $\nu = 515$ nm was done using microplate ELISA reader.

*Calculations*. The half-maximal scavenging capacity ($SC_{50}$) values for each tested compounds and ascorbic acid was estimated via two competitive dose curves.

Abs50 of ascorbic acid = (Abs100 − Abs0)/2.

$SC_{50}$ of ascorbic acid was calculated using the curve equation.

$SC_{50}$ of each compound was determined using the curve equation using Abs50 of ascorbic acid.

## REFERENCES AND NOTES

[1] Mavrova, A. T.; Wesselinova, D.; Tsenov, Y. A.; Denkova, P. Eur J Med Chem 2009, 44, 63.

[2] Andres, C. J.; Bronson, J. J.; D'Andrea, S. V.; Deshpande, M. S.; Falk, P. J.; Grant-Young, K. A.; Harte, W. E.; Ho, H.; Misco, P. F.; Robertson, J. G.; Stock, D.; Sun, Y.; Walsh, A. W. Bioorg Med Chem Lett 2000, 10, 715.

[3] Bonde, C. G.; Gaikwad, N. J. Bioorg Med Chem 2004, 12, 2151.

[4] Karalı, N.; Gürsoy, A.; Kandemirli, F.; Shvets, N.; Kaynak, F. B.; Özbey, S.; Kovalishyn, V.; Dimoglo, A. Bioorg Med Chem 2007, 15, 5888.

[5] Küçükgüzel, Ş. G.; Oruç, E. E.; Rollas, S.; Şahin, F.; Özbek, A. Eur J Med Chem 2007, 37, 197.

[6] Küçükgüzel, Ş. G.; Kocatepe, A.; De Clercq, E.; Şahin, F.; Güllüce, M. Eur J Med Chem 2006, 41, 353.

[7] Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Höltje, H. D.; Höltje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappalà, M. J Med Chem 2002, 45, 5410.

[8] Barreca, M. L.; Chimirri, A.; De Luca, L.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappalà, M.; Balzarini, J.; De Clercq, E.; Pannecouque, C.; Witvrouw, M. Bioorg Med Chem Lett 2001, 11, 1793.

[9] Rao, A.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. Farmaco 2003, 58, 115.

[10] Barreca, M. L.; Chimirri, A.; De Clercq, E.; De Luca, L.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappalà, M. Farmaco 2003, 58, 259.

[11] Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. Antiviral Res 2004, 63, 79.

[12] Rawal, R.; Yenamandra, S. P.; Katti, S. B.; De Clercq, E. Bioorg Med Chem 2005, 13, 6771.

[13] Kaushik-Basu, N.; Bopda-Waffo, A.; Talele, T. T.; Basu, A.; Chen, Y.; Küçükgüzel, Ş. G. Front Biosci 2008, 13, 3857.

[14] Rawal, R.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. Bioorg Med Chem 2007, 15, 1725.

[15] Ramla, M. M.; Omar, M. A.; Tokuda, H.; El-Diwani, H. I. Bioorg Med Chem 2007, 15, 6489.

[16] Ottanà, R.; Carotti, S.; Maccari, R.; Landini, I.; Chiricosta, G.; Caciagli, B.; Vigorita, M. G.; Mini, E. Bioorg Med Chem Lett 2005, 15, 3930.

[17] Gududuru, V.; Hurh, E.; Dalton, J. T.; Miller, D. D. J Med Chem 2005, 48, 2584.

[18] Gududuru, V.; Hurh, E.; Dalton, J. T.; Miller, D. D. Bioorg Med Chem Lett 2004, 14, 5289.

[19] Clemens, J. A.; Ho, P. P.; Panetta, J. A. Stroke 1991, 22, 1048.

[20] Yavari, I.; Hosseini, N.; Moradi, L. Mon Chem 2008, 139, 133.

[21] George, M. V.; Khetan, S. K.; Gupta, R. K. Adv Heterocycl Chem 1976, 19, 273.

[22] Aly, A. A.; Ahmed, E. K.; El-Mokadam, K. M. J Heterocycl Chem 2007, 44, 1431.

[23] Aly, A. A.; Hassan, A. A.; Ibrahim, Y. R.; Abdel-Aziz, M. J Heterocycl Chem 2009, 46, 687.

[24] Aly, A. A.; Hassan, A. A.; Ameen, M. A.; Brown, A. B. Tetrahedron Lett 2008, 49, 4060.

[25] Aly, A. A.; Hassan, A. A.; Ibrahim, Y. R. J Chem Res 2008, 699.

[26] Li, Z.; Zhao, Y.; Yang, J. Phosphorus Sulfur Silicon Relat Elem 2007, 182, 79.

[27] Danilkina, N. A.; Mikhailov, L. E.; Ivin, B. A. Russ J Org Chem 2006, 42, 783.

[28] Vögeli, U.; von Philipsborn, W.; Nagarajan, K.; Nair, M. D. Helv Chim Acta 1978, 61, 607.

[29] (a) Breitmaier, E.; Voelter, W. Carbon-13 NMR Spectroscopy, 3rd ed.; VCH: Weinheim, 1987; p 134. (b) Pretsch, E.; Bühlmann, P.; Badertscher, M. Structure Determination of Organic Compounds, 4th ed.; Springer: Berlin, 2009; p 80, 93.

[30] Dvorko, M.; Albanov, A.; Chipanina, N.; Sherstyannikova, L.; Samoilov, V.; Komarova, T.; Glotova, T. Chem Heterocycl Compd 2006, 42, 1421.

[31] Hansen, M. B.; Nielsen, S. E.; Berg, K. J Immunol Methods 1989, 119, 203.

[32] Van Amsterdam, F. T.; Roveri, A.; Maiorino, M.; Ratti, E.; Ursini, F. Free Radical Biol Med 1992, 12, 183.

# Synthesis of Crown Compounds Containing a 1,3,4-Oxadiazole Moiety: Microwave-Assisted Synthesis



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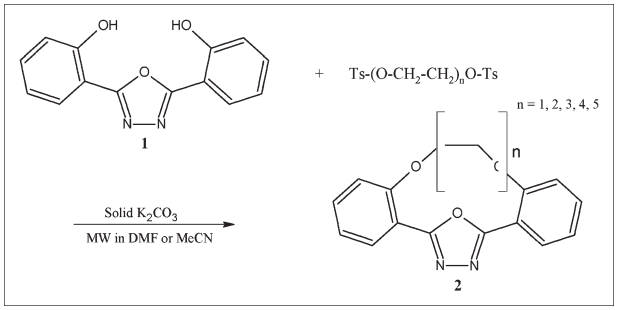


New macrocyclic polyether compounds containing a 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole moiety are quickly prepared by a nucleophilic substitution reaction involving ethylene glycol ditosylate or polyethylene glycol ditosylate and a biphenol, the 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole, with solid anhydrous potassium carbonate as a base under microwave irradiation (monomode and multimode). The structures of new macrocyclic polyether compounds were confirmed by $^{1}H$, $^{13}C$ NMR, mass spectrometry, and elemental analysis.

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## INTRODUCTION

The design and synthesis of artificial hart mimics possessing specific weak interactions and complexation properties to ion and neutral molecules has inspired many scientists during the past decades [1,2]. The Pedersen's [3] synthesis of crown ethers and the demonstrated ability of these molecules to chelate cations launched a whole search for further novel polyether macrocyclic structures that promote similar recognition phenomena [4]. The 1,3,4-oxadiazole ring is very rigid and as for the crown compounds containing a 1,3,4-thiadiazole moiety [5], the macrocyclic polyether containing it has potentially planar conformation [6]. A synthesis of such compounds containing 1,3,4-oxadiazole moiety has been previously effectuated by condensation of ethylene glycol or polyethylene glycol derivatives with the 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole by direct displacement reaction of halide with the bisphenolate and using the classical heating process. This synthesis requires long reaction time, and poor yields were obtained [7]. No macrocyclic compounds were found when we tried the heterocyclisation of the 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole with ethylene glycol ditosylate or polyethylene glycol ditosylate under classical heating using a previously described procedure [5]. In this article we report the microwave-assisted synthesis of crown compounds containing a 1,3,4-oxadiazole moiety.

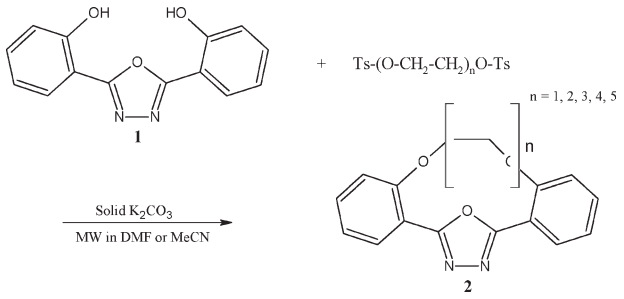
## RESULTS AND DISCUSSION

Macrocyclic compounds **2a–d** were prepared by a nucleophilic substitution reaction involving a glycol ditosylate with the bisphenoloxadiazole (1) (Scheme 1). This reaction was easily achieved by microwave irradiation and the macrocycles **2a–d** were obtained in moderate yields and excellent state of purity as in ref. 6 (Table 1).

A good achievement of this synthesis requires longer times (9 h) under irradiation using multimode microwave reaction compared with monomode one (2 h). However, no reaction product has been isolated using classical conventional heating.

To understand the pathway mechanisms that occur in the nucleophilic substitution reaction for cyclization of ditosyl polyether, quantum calculations at density functional theory (DFT) level were performed with thiadiphenol, both in vacuum and acetonitrile solvent, using polarized continuum method (PCM) method. The obtained results in the case of 1,3,4-thiadiazole moiety

**Scheme 1.** Synthesis of marcocyclic compounds containing a 1,3,4-oxadiazole moiety.




are analyzed in term of electronic energy of the calculated molecule conformations [6].

Specific microwave effect was observed in this reaction, the polarity is increased during the reaction from the ground state toward the transition state, and the stabilization of the transition state is more effective than that of the ground state (Scheme 2), this result in an enhancement of reactivity by a decrease in the activation energy [8].

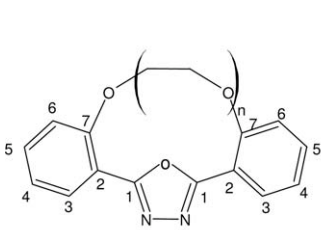
Using the monomode irradiation process, the notable enhancement in the yields of the crown compounds synthesis, and the shorter time of the reaction, can be explained by the fact that the microwaves are focused through a wave guide on the reaction vessel. The power density is, therefore, higher than using a multimode microwave apparatus.

## EXPERIMENTAL

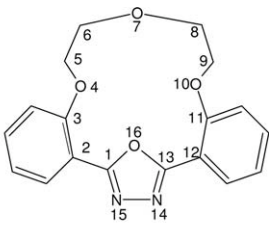
Melting points were determined with on an IA 9000 series electrothermal apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker F.T. AC 300 spectrometer (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) using chloroform-$d_1$ ($CDCl_3$) as solvent. Matrix-assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the macrocyclic polyether compounds **2a–d**. Elemental analyses were performed by the elemental analysis service of CNRS, Vernaison, France. All starting materials were of reagent grade and used as purchased.

**General procedure for the synthesis of macrocycles 2a–d.** A mixture of 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole **1** (0.75 g, 2.95 mmoles), anhydrous potassium carbonate (1.65 g, 12 mmoles), and ethylene glycol ditosylate or polyethylene glycol ditosylate (2.78 mmoles) in 30 mL of a nonprotic polar solvent, such as DMF or acetonitrile, was introduced into a fluoropolymeric cylindrical flask placed in a MARS5 XP-1500 PLUS CEM multimode microwave and irradiated for 9 h (300 W) at 150°C or irradiated for 2 h (150 W) in a CEM monomode microwave in DMF at 150°C with vigorous stirring. The precipitate was heated under reflux with 20 mL of aqueous potassium hydroxide solution for 1 h to destroy the unreacted tosylate, oxadiazole derivative **1**, or the open-chain intermediate of **2**. After cooling, the crude product was filtered, washed with water, recrystallized from ethanol, and dried under high vacuum. Yields, melting points, and results of the elemental analysis (C, H, and N) for compounds **2a–d** were given in Table 1.

The general formula of the parent macrocyclic compound with corresponding numbering scheme is given later. Localization of the methylene groups in the polyether macrocycle has been made using the International Union of Pure and Applied Chemistry rules concerning the different bicyclic systems.




Numbering used for the Localization of aromatic carbon




Example of the numbering used for the bicyclic systems (**2a**)

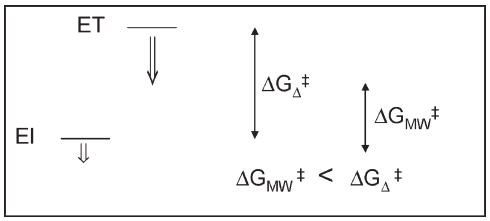
***2,3,11,12-Dibenzo-4,7,10,16-tetraoxa-14,15-diazabicyclo[11.2.1]-hexadeca-13,15-diene (2a).*** $^1$H NMR ($CDCl_3$): δ (ppm) 3.95–3.99 (m, 4H, $CH_2$ (6) and $CH_2$ (8)), 4.26–4.29 (m, 4H, $CH_2$ (5) and $CH_2$ (9)), 7.01 (d, $J$ = 8.6 Hz, 2H, 6-H), 7.08 (dd, $J$ = 7.7 Hz, 2H, 4-H), 7.48 (dd, $J$ = 7.9 Hz, 2H, 5-H), 8.11 (d, $J$ = 7.7 Hz, 2H, 3-H). $^{13}$C NMR ($CDCl_3$): δ (ppm) 61.5 ($CH_2$ (5) and $CH_2$ (9)), 63.4 ($CH_2$ (6) and $CH_2$ (8)), 110.8 ($C_6$),

**Table 1**

Physical and analytical data of compounds **2a–d**.

| Compound | Yield (%) | | Mp (°C) | Molecular formula | Analysis (%) found/calcd. | | |
|---|---|---|---|---|---|---|---|
| | Monomode (2 h) | Multimode (9 h) | | | C | H | N |
| **2a** (n = 2) | 47 | 36 | 175 | $C_{18}H_{16}N_2O_4$ | 66.52 | 5.10 | 8.71 |
| | | | | | 66.66 | 4.97 | 8.64 |
| **2b** (n = 3) | 51 | 33 | 200 | $C_{20}H_{20}N_2O_5$ | 65.01 | 5.63 | 7.84 |
| | | | | | 65.21 | 5.47 | 7.60 |
| **2c** (n = 4) | 42 | 30 | 185 | $C_{22}H_{24}N_2O_6$ | 63.95 | 6.06 | 6.82 |
| | | | | | 64.07 | 5.87 | 6.79 |
| **2d** (n = 5) | 39 | 27 | 187 | $C_{24}H_{28}N_2O_7$ | 62.98 | 6.33 | 6.27 |
| | | | | | 63.15 | 6.18 | 6.14 |

**Scheme 2**




113.5 ($C_4$), 122.5 ($C_2$), 127.2 ($C_3$), 138.6 ($C_5$), 150.1 ($C_7$), 163.4 ($C_1$-oxadiazole). MALDI-TOF-MS: *m*/*z* 325 (M +1).

***2,3,14,15-Dibenzo-4,7,10,13,19-pentaoxa-17,18-diazabicyclo[14.2.1]nonadeca-16,18-diene (2b).*** $^1$H NMR ($CDCl_3$): δ (ppm) 3.54 (s, 4H, CH2 (8) and $CH_2$ (9)), 3.87–3.91 (m, 4H, $CH_2$ (6) and $CH_2$ (11)), 4.24–4.28 (m, 4H, $CH_2$ (5) and $CH_2$ (12)), 7.04 (d, $J$ = 8.3 Hz, 2H, 6-H), 7.08 (dd, $J$ = 8.0 Hz, 2H, 4-H), 7.49 (dd, $J$ = 8.0 Hz, 2H, 5-H), 7.90 (d, $J$ = 7.6 Hz, 2H, 3-H). $^{13}$C NMR ($CDCl_3$): δ (ppm) 60.3 ($CH_2$ (5) and $CH_2$ (12)), 62.7 ($CH_2$ (8) and $CH_2$ (9)), 73.2 ($CH_2$ (6) and $CH_2$ (11)), 108.1 ($C_6$), 114.5 ($C_4$), 121.3 ($C_2$), 126.3 ($C_3$), 138.3 ($C_5$), 152.8 ($C_7$), 164.0 ($C_1$-oxadiazole). MALDI-TOF-MS: *m*/*z* 369 (M + 1).

***2,3,17,18-Dibenzo-4,7,10,13,16,22-hexaoxa-20,21-diazabicyclo[17.2.1]docosa-19,21-diene (2c).*** $^1$H NMR ($CDCl_3$): δ (ppm) 3.61–3.68 (m, 8H, $CH_2$ (8, 9, 11, and 12)), 4.11 (t, $J$ = 5.6 Hz, 4H, $CH_2$ (6) and $CH_2$ (14)), 4.33 (t, $J$ = 5.6 Hz, 4H, $CH_2$ (5) and $CH_2$ (15)), 7.04 (d, $J$ = 8.6 Hz, 2H, 6-H), 7.13 (dd, $J$ = 7.5 Hz, 2H, 4-H), 7.45 (dd, $J$ = 7.8 Hz, 2H, 5-H), 8.53 (d, $J$ = 8.5 Hz, 2H, 3-H). $^{13}$C NMR ($CDCl_3$): δ (ppm) 60.3 ($CH_2$ (5) and $CH_2$ (15)), 61.4 ($CH_2$ (6) and $CH_2$ (14)), 63.1 ($CH_2$ (8) and $CH_2$ (12)), 64.0 ($CH_2$ (9) and $CH_2$ (11)), 108.8 ($C_6$), 115.4 ($C_4$), 123.1 ($C_2$), 128.72 ($C_3$), 135.0 ($C_5$), 153.4 ($C_7$), 165.5 ($C_1$-oxadiazole). MALDI-TOF-MS: *m*/*z* 413 (M + 1).

***2,3,20,21-Dibenzo-4,7,10,13,16,19,25-heptaoxa-23,24-diazabicyclo[20.2.1]pentacosa-22,24-diene (2d).*** $^1$H NMR ($CDCl_3$): δ (ppm) 3.56 (s, 4H, $CH_2$ (11) and $CH_2$ (12)), 3.56–3.78 (m, 8H, $CH_2$ (9), $CH_2$ (14), $CH_2$ (17) and $CH_2$ (18)), 4.09 (t, $J$ = 5.1 Hz, 4H, $CH_2$ (6) and $CH_2$ (17)), 4.38 (t, $J$ = 5.1 Hz, 4H, $CH_2$ (5) and $CH_2$ (18)), 7.08 (d, $J$ = 7.5 Hz, 2H, 6-H), 7.13 (dd, $J$ = 6.7 Hz, 2H, 4-H), 7.44 (dd, $J$ = 7.0 Hz, 2H, 5-H), 8.54 (d, $J$ = 8.4 Hz, 2H, 3-H). $^{13}$C NMR ($CDCl_3$): δ (ppm) 60.8 ($CH_2$ (5) and $CH_2$ (18)), 62.6 ($CH_2$ (6) and $CH_2$ (17)), 64.1 ($CH_2$ (8) and $CH_2$ (15)), 64.1 ($CH_2$ (9, 11, 12 and 14), 108.9 ($C_6$), 114.9 ($C_4$), 122.0 ($C_2$), 126.5 ($C_3$), 138.8 ($C_5$), 152.7 ($C_7$), 164.7 ($C_1$-oxadiazole). MALDI-TOF-MS: *m*/*z* 457 (M + 1).

## REFERENCES AND NOTES

[1] Lehn, J. M. Angew Chem Int Ed Eng 1988, 27, 89.

[2] Cram, D. J. Angew Chem Int Ed Eng 1988, 27, 1009.

[3] Pedersen, C. J. J Am Chem Soc 1967, 89, 7017.

[4] (a) Bradshaw, J. S.; Chamberlin, D. A.; Harrison, P. E.; Wilson, B. E.; Arena, G.; Dalley, N. K.; Lamb, J. D.; Izatt, R. M. J Org Chem 1985, 50, 3065; (b) Bradshaw, J. S.; Nielsen, R. B.; Tse, P. K.; Arena, G.; Wilson, B. E.; Dalley, N. K.; Lamb, J. D.; Christensen, J. J.; Izatt, R. M. J Heterocyclic Chem 1986, 23, 361; (c) Bradshaw, J. S.; McDaniel, C. W. B.; Skidmore, D.; Nielsen, R. B.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. J Heterocyclic Chem 1987, 24, 1085; (d) Elshani, S.; Apgar, P.; Wang, S.; Wai, C. M. J Heterocyclic Chem 1994, 31, 1271; (e) Yang, J.; Li, Z. T.; Hua, W. T. Youji Huaxue 2001, 21, 467; (f) Hegmann, T.; Neumann, B.; Wolf, R.; Tschierske, C. J Mat Chem 2005, 15, 1025.

[5] Lebrini, M.; Bentiss, F.; Lagrenée, M. J Heterocyclic Chem 2004, 41, 419.

[6] Lebrini, M.; Bentiss, F.; Vezin, H.; Wignacourt, J. P.; Roussel, P.; Lagrenée, M. Heterocycles 2005, 65, 2847.

[7] Zhou, J. M.; Hua, W. T.; Yang, Q. C. Gaodeng Xuexiao Huaxue Xuebao 1996, 17, 1721.

[8] (a) Perreux, L.; Loupy, A. Tetrahedron 2001, 57, 9199; (b) Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. Euro J Org Chem 2002, 7, 1278.

# Novel 2-Hydrazino-pyrimidin-4(3*H*)-One Derivatives as Potential Dihydrofolate Reductase Inhibitors



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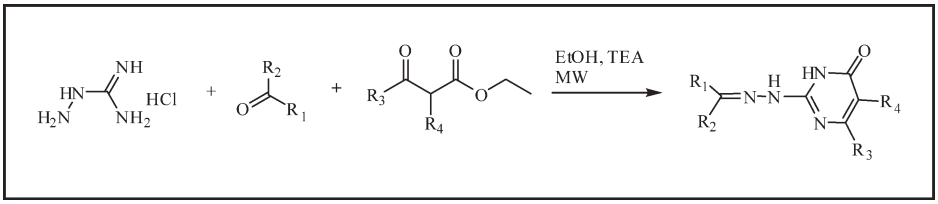


Novel substituted 2-hydrazino-pyrimidin-4(3*H*)-one derivatives were synthesized and examined for their antifolate activity against DHFR from *Pneumocystis carinii* (pc), *Toxoplasma gondii* (tg), *Mycobacterium avium* (ma), and rat liver (rl). A novel, simple, and feasible methodology was developed for the synthesis of the titled compounds. Amongst these, compound **8** 6-phenyl-2-(2-(1-(thiophen-2-yl) ethylidene)hydrazinyl) pyrimidin-4(3*H*)-one exhibited 17.74 μ*M* activity against pcDHFR.

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## INTRODUCTION

Dihydrofolate reductase (DHFR), a crucial enzyme required for the conversion of folic acid to dihydro and tetrahydro folic acid (a cofactor involved in one carbon transfer in purine and pyrimidine *de-novo* synthesis) has been successfully explored as a target for the treatment of various infective diseases. Opportunistic organisms such as *Pneumocystis carinii* (pc), *Toxoplasma gondii* (tg), and *Mycobacterium avium* (ma) cause life threatening infections in immunocompromised hosts. Majority of the DHFR inhibitors explored have a 2,4-diamino moiety on the aromatic/heteroaromatic ring as an important pharmacophoric feature which forms a crucial H-bonding interaction at the bottom of the active site in both microbial and human DHFR [1]. The structural requirements of potential DHFR inhibitors have been summarized in a recent review article [2]. Only few reports are found in literature for DHFR inhibitors lacking 2,4-diamino moiety on the pyrimidine/triazine nucleus.

Gschwend *et al*. screened a library of 50,000 compounds using the program DOCK to develop selective inhibitors towards *P. carinii* [3]. Several novel classes of compounds were identified as potential DHFR inhibitors, providing new avenues for lead optimization. The most potent compound (Threne Red Violet RH, Fig. 1) identified had $IC_{50}$ of 6.9 μ*M* towards the fungal enzyme.

This indicated that novel scaffolds could be designed inhibiting the folate pathway efficiently. In this light, virtual screening of ASINEX database using docking algorithm Glide was undertaken [4]. Crystal structure pcDHFR PDB ID: 1KLK, 2.30 Å resolution [5] was used for the docking studies. Initially, all compounds were docked using HTVS mode in Glide, top 10% hits from this study were again docked using SP (Standard precision mode). Finally, top 1% hits emerged from this study were redocked using XP (Extra precision mode). The scaffolds obtained from XP docking were used for novel inhibitor design.

Interestingly, in these virtual screening studies some of the new scaffolds lacking conventional 2,4-diamino pharmacophore, were also identified as hits but have not yet been reported as DHFR inhibitors. On the basis of the structural features of the new scaffolds obtained from virtual screening, 2-hydrazino-pyrimidin-4(3*H*)-one as the basic nucleus was chosen as a potential part of designed DHFR inhibitors.

The designed analogs were studied computationally to get an insight into the binding pattern of these compounds. When a 2-hydrazino-pyrimidin-4(3*H*)-one analog was superimposed on trimethoprim, in the active site of pcDHFR, conserved interactions were observed. It was also observed that the –NH of the pyrimidinone part forms hydrogen bonding with Ile123 in the active site of pcDHFR. The docking studies revealed that pyrimidinone part of the molecule is stabilized using van der Waals interactions with residues like Ile123, Ile10, Val11, Phe36, Glu32, Ile33, and Leu25. The bridge portion of the designed analogs are shown to form

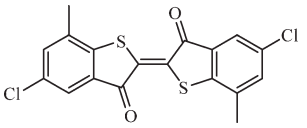


**Figure 1.** Hit identified from the study of Gschwend *et al.*

favorable interactions with Ile123, Thr61, whereas the distal part forms van der Waals interactions with Asn23, Ser64, Pro66, Ile65, Phe69, Leu72, and Phe36 in the active site of the enzyme. Pyrimidinone ring forms π-π stacking interactions with Phe36 (4.470 Å) at the bottom of the active site.

Substituted pyrimidin-4(3*H*)-one compounds have widespread biological activities [6]. However, to the best of our knowledge these types of molecules are not yet explored as DHFR inhibitors. Therefore, based on virtual screening and new scaffold design, synthesis and evaluation of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives against DHFR from various opportunistic microorganisms were undertaken.

## RESULTS AND DISCUSSION

The reported methods for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives involve acetic acid catalyzed condensation reaction of aromatic aldehydes with a cyclic intermediate of ethyl acetoacetate and semicarbazide [6,7]. Formic acid catalyzed condensation reaction of ketone with semicarbazide has also been reported [8].

However, reported methods for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives suffer from several disadvantages such as use of commercially unavailable cyclic intermediates as starting material, multi-step reactions which in turn make the process costly, lengthy, time consuming and also affect the yield and quality of the final products. Moreover, the use of acetic acid or formic acid [8], makes the workup cumbersome. Therefore, designing an efficient protocol using commercially available starting materials, involving easy workup procedure for the synthesis of these compounds was taken into consideration.

In the present work, initially a two step process was developed using conventional heating (Method 1). The first step involves condensation of ethanolic solution of substituted ketones with semicarbazide hydrochloride to yield a substituted semicarbazone using absolute ethanol as solvent.

In step II, the ethanolic solution of semicarbazone was treated with various β- ketoesters in presence of a base to yield the desired analogs as shown in Scheme 1. Various bases such as triethylamine, pyridine and ammonium acetate were explored for this step. Triethylamine was found to give good yields, in less time than other bases.

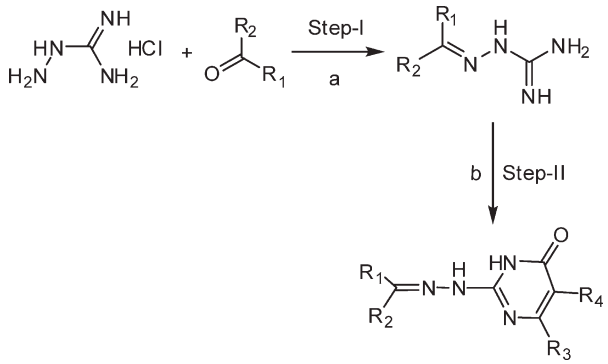
Microwave (MW) assisted synthesis is known to be advantageous over conventional reaction reported in literature; with respect to time, yield and workup procedures [9].

In this light, the above synthetic scheme was carried out using microwave irradiation (Method 2). Although steps I and II took many hours to complete under conventional heating (Method 1) no more starting materials could be detected after 10–20 min under microwave irradiation.

Encouraged by the results obtained using microwave method, a one pot microwave assisted method was also investigated.

In case of one pot microwave assisted reaction, an ethanolic solution of β-ketoester, semicarbazide hydrochloride and substituted ketone was subjected to microwave irradiation with intermittent addition of triethylamine. Appropriate workup procedures followed by column purification led to the isolation of the desired compound as shown in Scheme 2. Thus, a one step process using microwave irradiation without isolating the intermediate was developed (Method 3). Thereafter, all

**Scheme 1.** Method for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives. A, EtOH, reflux; b, TEA, EtOH, reflux.




**Scheme 2.** Microwave assisted one pot method for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-ones.

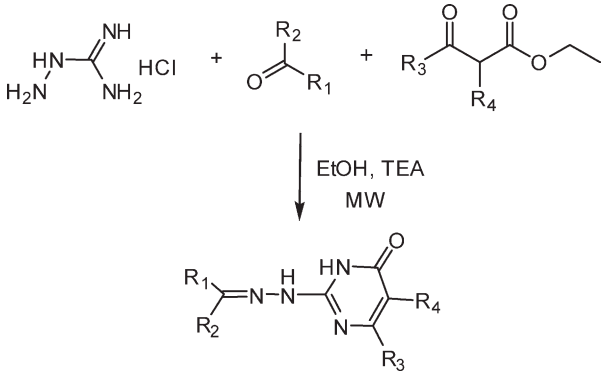
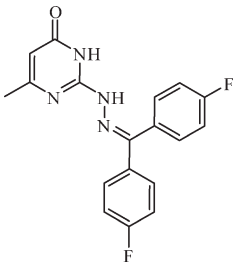
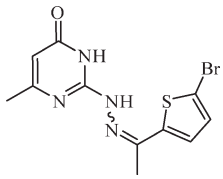
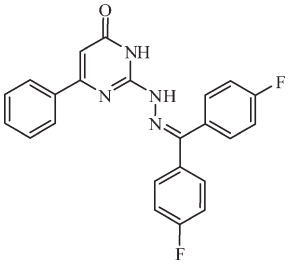
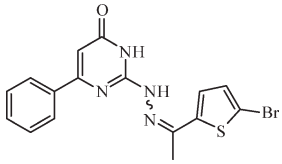
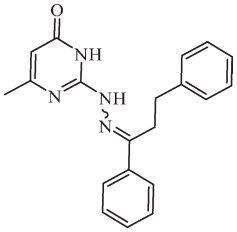
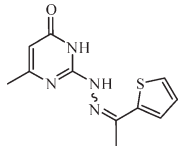
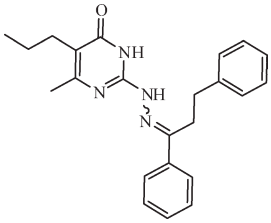
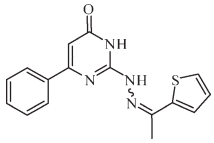


**Table 1**

List of synthesized 2-hydrazino-pyrimidin-4(3*H*)-one derivatives.

| No. | Structure | Mol. formula | No. | Structure | Mol. formula |
|---|---|---|---|---|---|
| 1 |  | $C_{18}H_{14}F_2N_4O$ | 5 |  | $C_{11}H_{11}BrN_4OS$ |
| 2 |  | $C_{23}H_{16}F_2N_4O$ | 6 |  | $C_{16}H_{13}BrN_4OS$ |
| 3 |  | $C_{20}H_{20}N_4O$ | 7 |  | $C_{11}H_{12}N_4OS$ |
| 4 |  | $C_{23}H_{26}N_4O$ | 8 |  | $C_{16}H_{14}N_4OS$ |

the compounds were synthesized using one pot microwave assisted method (Method 3).

The processes developed in this present work are feasible, simple, cost-effective and time saving.

The course of the reaction was monitored by thin layer chromatography (TLC) and the structures were confirmed by spectral data. The MS of all the compounds exhibited the molecular ion peak. $^1$H NMR spectra of 2-hydrazino-pyrimidin-4(3H)-one showed the presence of characteristic, $D_2O$ exchangeable –NH peaks at δ ranging from 7.0 to 8.0. All the other spectral data was found to be satisfactory. The list of synthesized compounds is given Table 1.

The synthesized compounds were evaluated for their ability to inhibit DHFR from pc, tg, ma, and rl using a continuous spectrophotometric assay measuring oxidation at 340 n*M* of NADPH at 37°C under conditions of saturating substrate and cofactor as previously described [10,11]. The results of this assay are given in Table 2, along with previously reported data for reference compounds [12].

The compound **5** showed 51.38 μ*M* activity against pcDHFR and 60.54 μ*M* activity against maDHFR. The Compound **8** also exhibited comparable potency as that of trimethoprim against pcDHFR. The Compound **6** exhibited micromolar potency against pc DHFR. However, the synthesized molecules were not selective.

In summary based on virtual screening experiments, 2-hydrazino-pyrimidin-4(3*H*)-one was designed as novel antifolate scaffold. An efficient, simple protocol was

**Table 2**

Dihydrofolate reductase inhibition by synthesized compounds.

| S. N. | Activity $IC_{50}$ ($\mu M$) | | | |
|---|---|---|---|---|
| | pc | tg | ma | rl |
| 1 | 138.102 (32) | 138.102 (28) | 138.102 (22) | 138.102 (35) |
| 2 | 10.313 (3) | 10.313 (0) | 10.313 (0) | 10.313 (9) |
| 3 | 12.515 (7) | 12.515 (4) | 12.515 (8) | 12.515 (0) |
| 4 | 126.036 | 12.401 (26) | 12.401 (22) | 20.208 |
| 5 | 13.294 (5) | 51.375 | 60.544 | 13.294 (58) |
| 6 | 88.833 | 95.949 | 126.981 | 58.674 |
| 7 | 19.130 (8) | 173.499 | 93.153 | 19.130 (58) |
| 8 | 17.740 | 14.209 (20) | 14.209 (19) | 14.766 |
| Trimethprim[a] | 12 | 2.80 | 0.30 | 180 |
| Piritrexim[a] | 0.013 | 0.0043 | 0.00061 | 0.0033 |
| Trimetrexate[a] | 0.042 | 0.01 | 0.0015 | 0.003 |

Inhibitory concentration ($IC_{50}$, $\mu M$) against rlDHFR, pcDHFR, tgDHFR and maDHFR by target compounds. Triplicate assays were performed as previously described [10,11].

Because of lack of solubility the exact $IC_{50}$ could not be determined for some compounds; hence maximum soluble concentration was used to determine % inhibition. Number in parentheses indicates percent inhibition obtained at that concentration. For e.g., 138.102 (32) indicates 32% inhibition at 138.102 $\mu M$ concentration.

[a] Data taken from reference [12].

developed for synthesis of these molecules. The synthesized compounds were evaluated against DHFR of opportunistic organisms. Some of the evaluated compounds showed appreciable antifolate activity, thus validating our methodology. Therefore, these compounds could act as good leads for novel antifolates. The results would be used for design and synthesis of analogs with improved potency and selectivity.

## EXPERIMENTAL

Melting points (mp) were recorded on Thermomik Compbell electronics, having oil-heating system and were uncorrected. The microwave reactions were carried out using CEM Focused Microwave System in monomode, Model Discover. Analytical thin-layer chromatography (TLC) was carried out on precoated plates $SiO_2$ (silica gel 60, F 254, Merck). $SiO_2$ (Silica gel 420, Merck) was used for column chromatography using CombiFlash® RETRIEVE® system. FTIR spectra were recorded on ''Buck scientific infrared spectroscopy M500 spectrophotometer'' using KBr pellets. All the NMR spectra were recorded on FT-NMR JEOL, 60 MHz or JEOL AL 300 MHz spectrometer with DMSO-*d6* or $CDCl_3$ as solvent using tetramethyl silane (TMS) as internal reference: s = singlet, d = doublet, t = triplet, q = quartet, m = mutiplet, bs = broad singlet. The mass spectrum was recorded on a Waters Q/TOF Micromass spectrometer.

**General procedure method 1 (method using conventional reflux) Step I: synthesis of semicarbazone.** Substituted ketone (13.7 mmol) and semicarbazide hydrochloride (13.7 mmol) were stirred in 30 mL absolute ethanol in a round bottom flask and the mixture was refluxed on a sand bath with vigorous stirring for 14–18 hrs. After the reaction commenced, ketones reacted with semicarbazide hydrochloride giving a base spot on TLC (in solvent system EtOAc:Hexanes = 9:1). The reaction mixture was then concentrated under reduced pressure and the obtained solid residue was partitioned between 50 mL water and 50 mL EtOAc:hexanes (1:9) to extract unreacted starting materials in organic layer. Aqueous layer was stirred for 5 min with solid sodium bicarbonate (3 g) leading to precipitation of solid semicarbazone which was then filtered and washed with water (3 × 50 mL). The obtained solid was recrystallized from 40 mL of MeOH. This gave pure semicarbazone in free base form which was used for the cyclization with β-ketoester.

**Representative example.** 2-(bis(4-fluorophenyl)methylene) hydrazinecarboximidamide: To the ethanolic solution of bis(4-fluorophenyl)methanone (3g, 13.7 mmol); semicarbazide hydrochloride (1.51 g, 13.7 mmol) was added according to step 1, to yield 2.87g (yield: 76.12%) of pure yellow colored semicarbazone product ((2-(bis(4-fluorophenyl)methylene) hydrazinecarboximidamide).

**Step II: Synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives.** The semicarbazone (6.16 mmol), the β-ketoester derivative (6.16 mmol) and triethylamine (3.08 mmol) as a catalyst were suspended in 30 mL absolute ethanol and the mixture was refluxed on a sand bath with stirring for 18–22 hrs. TLC showed a product spot ($R_f$ of 0.4–0.6 in the solvent system EtOAc:Hexanes (7:3)). The reaction mixture was concentrated under vacuum and was partitioned between EtOAc (25 mL) and water (25 mL). The organic layer was separated, and the aqueous layer was extracted further with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (75 mL), dried ($NaSO_4$), and concentrated in vacuo. Column purification using flash chromatography ($SiO_2$, 5 g, 15% EtOAc/hexanes) of the crude product yielded pure 2-hydrazino-pyrimidin-4(3H)-one derivatives.

**Representative example.** 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methylpyrimidin-4(3H)-one (**1**): The ethanolic solution of 2-(bis(4-fluorophenyl) methylene) hydrazinecarboximidamide (1 g, 3.6 mmol) was treated with ethylacetoacetate (0.47 g, 3.6 mmol) and triethyl amine (0.18 g, 1.8 mmol) according to step 2, to yield 0.521 g (yield: 42%) of 2-(2-(bis(4-fluorophenyl)methylene)hydrazinyl)-6-methyl pyrimidin-4(3H)-one as buff colored solid.

**Method 2: (method using microwave assisted reaction) Step I: Synthesis of semicarbazone.** A mixture of the ketone (13.7 mmol) and semicarbazide hydrochloride (13.7 mmol) suspended in 30 mL absolute ethanol. This reaction mixture was subjected to microwave irradiation at a power of 60 W, for 15 min (target temperature 100°C). After the completion of reaction the compounds were isolated and purified as described in step I of method 1.

**Representative example.** 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methylpyrimidin-4(3H)-one: To the ethanolic solution of bis(4-fluorophenyl)methanone (3 g, 13.7 mmol); semicarbazide hydrochloride (1.51 g, 13.7 mmol) was added according to step 1, to yield 3.2 g (yield: 85.13%) of pure yellow colored semicarbazone product ((2-(bis(4-fluorophenyl)methylene) hydrazinecarboximidamide).

**Step II: Synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives.** The semicarbazone (3.6 mmol), the β-ketoester derivative (3.6 mmol) and triethylamine (1.8 mmol) as a catalyst were suspended in 30 mL absolute ethanol. This reaction mixture was subjected to microwave irradiation at a power of 60 W, for 20 min (target temperature of 100°C). After the completion of reaction the compounds were isolated and purified as described in step II of method 1.

**Representative example.** 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methylpyrimidin-4(3H)-one (**1**): The ethanolic solution of 2-(bis(4-fluorophenyl) methylene) hydrazinecarboximidamide (1 g, 3.6 mmol) was treated with ethylacetoacetate (0.47 g, 3.6 mmol) and triethyl amine (0.18 g, 1.8 mmol) according to step 2, to yield 0.583 g (yield: 47%) of 2-(2-(bis(4-fluorophenyl)methylene)hydrazinyl)-6-methyl pyrimidin-4(3H)-one as buff colored solid.

**Method 3: (One pot microwave assisted method).** A mixture of ketone (27.5 mmol), semicarbazide hydrochloride (27.5 mmol) and β-ketoester (27.5 mmol) were suspended in 30 mL absolute ethanol. This reaction mixture was subjected to microwave irradiation with power of 60 W, for 10 min (target temperature 100°C). After 10 min triethylamine (13.75 mmol) was added in and reaction mixture was subjected to microwave irradiation at the power range of 100 W, for 15–20 min (target temperature 100°C). Most of the starting material consumed after this time, the reaction mixture was then concentrated under reduced pressure and partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted further with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (75 mL), dried ($NaSO_4$), and concentrated *in vacuo*. Column purification using flash chromatography ($SiO_2$, 5 g, 15% EtOAc/hexanes) of the crude product yielded pure 2-hydrazino-pyrimidin-4(3H)-one derivatives.

**Representative example.** 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methyl pyrimidin -4(3H)-one (**1**): To the ethanolic solution of bis(4-fluorophenyl)methanone (3 g, 13.7 mmol), aminoguanide hydrochloride (1.51 g, 13.7 mmol) and ethylacetoacetate (1.41 g, 13.7 mmol) triethyl amine (0.69 g, 6.85 mmol) was added according to reaction described above to yield 1.93 g (yield: 40.6%) of buff colored product.

***2-(2-(Bis(4-fluorophenyl)methylene)hydrazinyl)-6-methylpyrimidin-4(3H)-one (1)*** IR (KBr) major bands at: 3466, 1654, 1560, 1506, 1384, 1299, 1226, 1157 $cm^{-1}$; $^1$ H NMR: δ 1.99 (s, 3H, —CH3), 5.78 (s, 1H, Ar —CH), 7.01–7.67 (m, 8H, Ar –H), 9.64 (bs, 2H, ex —NH); $^{13}$C NMR: δ 23.01, 103.71, 115.33, 115.62, 116.91, 117.19, 127.80, 129.93, 130.03, 130.78, 130.90, 132.64, 151.93, 161.99, 163.99, 165.13, 165.32, 171.77; *m/z* $[M+1]^+$ 341, $[M+2]^+$ 342, $[M+3]^+$ 343.

***2-(2-(Bis(4-fluorophenyl)methylene)hydrazinyl)-6-phenylpyrimidin-4(3H)-one (2)*** This compound was obtained as a yellow colored solid in 20 % yield, mp: 235–237°C; IR (KBr) major bands at: 3473, 1654, 1607, 1498, 1383, 1223, 974, 844 $cm^{-1}$; $^1$ H NMR: δ 6.37 (s, 1H, Ar –H), 7.04–7.82 (m, 14H, Ar –H and ex —NH), 9.70 (bs, 1H, ex —NH); $^{13}$C NMR: δ 109.09, 114026, 115.51, 115.80, 117.25, 117.54, 126.87, 127.15, 128.69, 129.64, 129.75, 129.99, 130.52, 130.70, 130.82, 132.52, 136.79, 149.97, 151.72, 162.37, 163.40, 163.76, 165.31; *m/z* $[M+1]^+$403, $[M+2]^+$ 404, $[M+3]^+$ 405.

***2-(2-(1,3-Diphenylpropylidene)hydrazinyl)-6-methylpyrimidin-4(3H)-one (3)*** This compound was obtained as a buff colored solid in 40.24 % yield, mp: 152–154°C; IR (KBr) major bands at: 3468, 1648, 1492, 1378, 1119 $cm^{-1}$;$^1$ H NMR: δ 2.09 (s, 3H, —CH3), 2.87 (t, 2H, —CH2), 3.12 (t, 2H, —CH2), 5.73 (s, 1H, Ar-H), 7.26-7.72 (m, 11 H, Ar –H and ex —NH), 9.69 (bs, 1H, —NH); $^{13}$C NMR: δ 21.26, 29.41, 32.02, 103.42, 121.86, 126.27, 126.45, 126.64, 128.46, 128.65, 128.82, 128.88, 129.73, 129.88, 129.99, 136.37, 140.30, 162.11, 176.91; *m/z* $[M]^+$ 333, $[M+1]^+$ 334, $[M+2]^+$ 335.

***2-(2-(1,3-Diphenylpropylidene)hydrazinyl)-6-methyl-5-propylpyrimidin-4(3H)-one (4)*** This compound was obtained as a buff colored solid in 10 % yield, mp: 213–214°C; $^1$ H NMR: δ 1.90 (s, 3H, —$CH_3$), 2.18 (t, 3H, —$CH_3$), 2.45 (m, 4H, 2—$CH_2$), 2.78 (t, 2H, —$CH_2$), 3.21 (t, 2H, —$CH_2$), 7.20–8.00 (m, 9H, Ar—H), 10.40 (bs, 1H, ex —NH), 11.40 (bs, 1H, ex —NH).

***2-(2-(1-(5-Bromothiophen-2-yl)ethylidene)hydrazinyl)-6-methylpyrimidin-4(3H)-one (5)*** This compound was obtained as a light brown solid in 30 % yield, mp: 226–228°C; IR (KBr) major bands at: 3497, 1643, 1560, 1384, 1129, 828 $cm^{-1}$; $^1$ H NMR: δ 2.17 (s, 3H, —$CH_3$), 2.31 (s, 3H, —$CH_3$), 5.70 (s, 1H, Ar—H), 6.99–7.26 (m, 4H, Ar—H and ex —NH); $^{13}$C NMR: δ 21.21, 21.92, 103.18, 113.64, 114.42, 127.24, 130.32, 144.08, 147.18, 152.32, 176.68; *m/z* $[M]^+$ 327.

***2-(2-(1-(5-Bromothiophen-2-yl)ethylidene)hydrazinyl)-6-phenylpyrimidin-4(3H)-one (6)*** This compound was obtained as a buff colored solid in 43% yield, mp: 225–226°C; $^1$ H NMR: δ 2.12 (s, 3H, —$CH_3$), 6.10 (s, 1H, Ar—H), 6.96–6.97 (d, 1H, Ar—H), 7.091–7.099 (d, 1H, Ar—H), 7.219–7.228 (d, 1H, Ar—H), 7.358–7.365 (d, 1H, Ar—H), 7.477–7.489 (m, 1H, Ar—H), 8.016 (bs, 2H, ex —NH); *m/z* $[M]^+$ 389, $[M+2]^+$ 391.

***6-methyl-2-(2-(1-(thiophen-2-yl)ethylidene) hydrazinyl) pyrimidin-4(3H)-one (7)*** This compound was obtained as a light brown solid in 27 % yield, mp: 229–230°C; IR (KBr) major bands at: 3497, 1664, 1633, 1575, 1425, 1384 $cm^{-1}$; $^1$ H NMR: δ 2.17 (s, 3H, —$CH_3$), 2.37 (s, 3H, —$CH_3$), 5.69 (s, 1H, Ar—H), 7.03–7.34 (m, 3H, Ar—H), 9.24 (bs, 2H, ex —NH); $^{13}$C NMR: δ 21.40, 22.20, 103.13, 127.27, 127.43, 128.46, 142.60, 147.78, 152.27, 152.36, 177.02; *m/z* $[M+1]^+$ 249.

***6-Phenyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)pyrimidin-4(3H)-one (8)*** This compound was obtained as yellow colored solid in 20% yield, mp: 228–230°C; $^1$ H NMR: δ 2.27 (s, 3H, —$CH_3$), 6.30 (s, 1H, Ar—H), 7.04–7.79 (m, 10H, Ar—H and ex—NH); $^{13}$C NMR: δ 17.59, 101.31, 126.77, 126.87, 127.14, 127.23, 127.37, 127.44, 128.52, 128.64, 128.80, 130.44, 151.25, 152.10, 152.24, 167.55; *m/z* $[M+1]^+$ 311.

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## REFERENCES AND NOTES

[1] Bag, S.; Tawari, N. R.; Degani, M. S. QSAR & Combi Sci 2008, 28, 296.

[2] Gangjee, A.; Kurup, S.; Namjoshi, O. Curr Pharm Design 2007, 13, 609.

[3] Gschwend, D. A.; Sirawaraporn, W.; Santi, D. V.; Kuntz, I. D. Proteins 1997, 29, 59.

[4] Glide, Version 4.5, Schrödinger, LLC, New York, 2008.

[5] Cody, V.; Galitsky, N.; Luft, J.; Pangborn, W.; Rosowsky, A.; Queener, S. F. Acta Cryst D 2002, 58, 946.

[6] Szilágyi, L.; Illyés, T. Z.; Györgydeák, Z.; Szabó, G.; Karácsony, A. Arkivoc 2004, vii, 243.

[7] Bower, J. D.; Doyle, F. P. J Chem Soc 1957, 727.

[8] Cooper, M. J.; Hull, R.; Wardleworth, M. J Chem Soc Perkin Trans 1 1975, 1433.

[9] Bag, S.; Vaze, V. V.; Degani, M. S. J Chem Res 2006, 4, 267.

[10] Broughton, M. C.; Queener, S. F. Antimicrob Agents Chemother 1991, 35, 1348.

[11] Chio, L.C.; Queener, S. F. Antimicrob Agents Chemother 1993, 37, 1914.

[12] Gangjee, A.; Yang, J.; Queener, S. F. Bioorg Med Chem 2006, 14, 8341.

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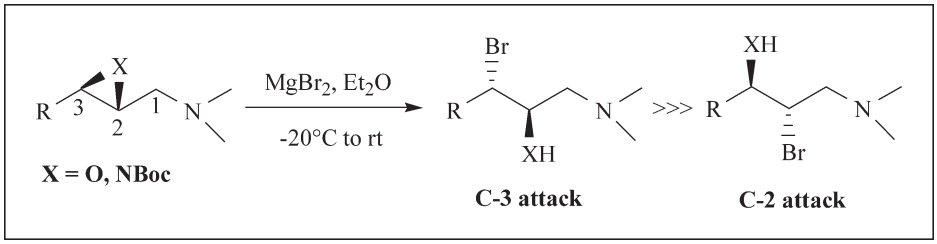


Regio- and stereo-controlled opening of 2,3-epoxy amines and 2,3-aziridine amines by the commercially available $MgBr_2$ is described. As reported, this new method could represent a general and useful approach for the preparation of promising intermediates. Moreover, in particular cases, the reaction evolves toward an interesting oxazolidin-2-one structure.

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## INTRODUCTION

The human immunodeficiency virus (HIV) is the causative agent of the acquired immunodeficiency syndrome (AIDS); the HIV-protease (PR) is one of the essential viral enzymes to its maturation and infectivity. Actually, synergy of the two RT and PR inhibitors represents the most efficacious therapy for the treatment of this disease called Highly Active Antiretroviral Therapy (HAART). All the same, the widespread diffusion of the disease and the development of numerous mutant resistant viruses to this therapy have prompted the research toward new and selective inhibitors of HIV-PR, see review [1].

In this field, we synthesized two analogues of Saquinavir **1**, where the anti stereochemistry of the hydroxyethylene isoster core (anti HEA) was substituted with a syn one, as shown in Figure 1 [2].

Among the methods already reported for obtaining syn amino alcohols, see review [3], certainly the multisteps strategy largely used by us consisting in (1) Sharpless AE of allylic alcohols, (2) regio- and stereoselective opening of oxirane ring with halides, (3) substitution of the halogen with azide, and (4) catalytic hydrogenation to amine, represents, despite the number of steps, a very general and flexible route to build up the chiral β-amino alcohols. Following up this approach, we considered the epoxy amine **3**, having the Saquinavir characteristic

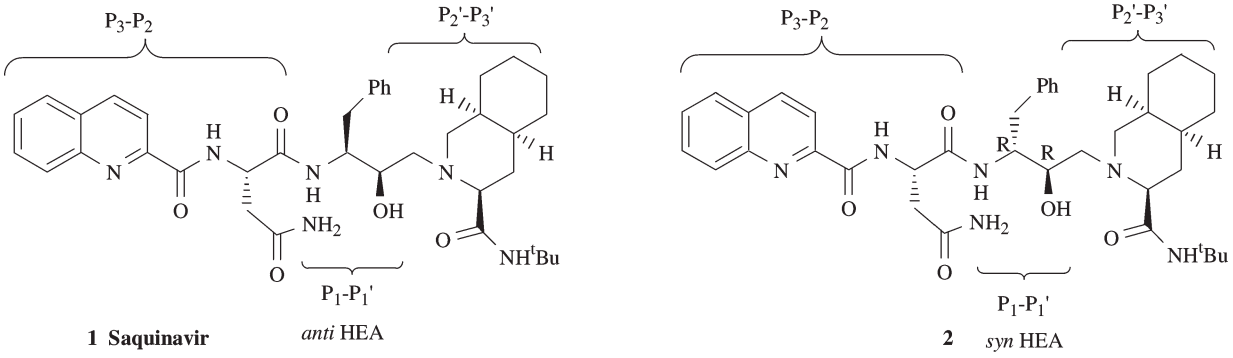
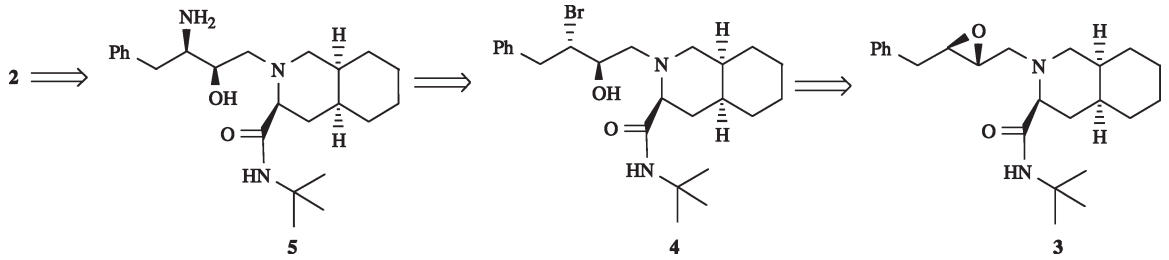



**Figure 1.** Saquinaver and *syn* HEA analog.

**Scheme 1**




residue (*S*,*S*,*S*)-decahydroisoquinoline-3-carboxylamide residue (DIQ) already introduced in the molecule, a straightforward precursor for our purpose. In fact, its stereo- and regioselective opening by halide, followed by steps (3) and (4), would have furnished the suitable syn amino alcohol **5**, as shown in retrosynthetic Scheme 1.

Apart from selected examples [4], to our best knowledge, the regio- and stereo-controlled opening of 2,3-epoxy amines by halides has never been exploited; therefore, we decided to better study this particular reactivity of these compounds.

## RESULTS AND DISCUSSION

During our studies, we have extensively investigated the metal halides-mediated opening of epoxy alcohols, esters (see review [5]), and aldehydes [6]. In every case, we established that the freshly prepared $MgI_2$, or the commercially available $MgBr_2$, as well as LiX/Amb15 system were able to direct the halide in C-3 position through a previously postulated chelated complex between the metal ($Mg^{2+}$, $Li^{+}$) and the two oxygen of the epoxide derivative. At this point, we hypothesized that also in the case of 2,3-epoxy amines, a possible chelate between metal, epoxide oxygen, and the nitrogen atom occurred, leading to a C-3 regioselective nucleophilic ring opening, Figure 2.

Our preliminary studies were restricted, for convenience, to racemic compounds; the 2,3-epoxy amines were synthesized in satisfactory yield from the corresponding 2,3-epoxy alcohols through the sequence described in Scheme 2: (1) transformation of the hydroxyl function in a good leaving group such as the mesilate (2) nucleophilic substitution with the suitable amine.

The prepared 2,3-epoxy amines were then submitted to the $MgBr_2$-mediated opening reaction employing dry $Et_2O$ as solvent at low temperature [7]. As shown in Table 1, the results confirmed our hypothesis: the nucleophilic attack of the bromine occurred preferentially in the C-3 position, as expected for chelation-controlled ring opening reactions. The regiochemistry of the products was assigned by spin–spin decoupling experiments carried out on the corresponding acetyl derivatives, whereas the anti stereochemistry was assigned in accordance with the $S_N2$ mechanism of the opening reaction.

As expected, the same reaction conditions applied to the 2,3-epoxy amine **3** afforded the desired bromoderivative **4**, in good yield and excellent regioselectivity (entry 5); the further elaboration of bromine carried out to our desired target, the syn amino alcohol **5**.

For the sake of completeness and for our interest on these compounds, the study was extended on 2,3-aziridine amines. Also in this case very few examples [8], regarding essentially aziridine-fused heterocycles, are already reported in literature. Likewise 2,3-aziridino alcohols [9], also for 2,3-aziridine amines, a cyclic chelate may be invoked to control the regioselectivity in the ring opening reaction by metal halides, Figure 3.

An expeditious sequence was employed to prepare the starting substrates, consisting on the direct introduction of the amines on C-1 position, followed by the usual transformation to the aziridine ring (Scheme 3) [10]. In this case, the chosen amines have been once again piperidine and, for our specific interest regarding the synthesis of D-*treo*-PDMP, morpholine [11].

When we submitted compounds **16–19** to $MgBr_2$ reaction, only one product was detected (Table 2); also

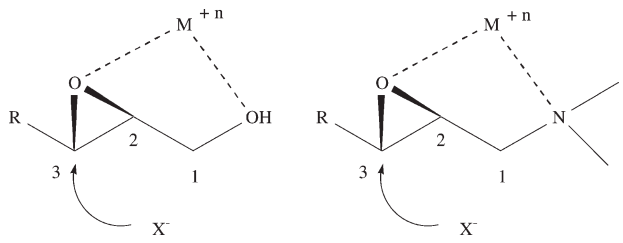
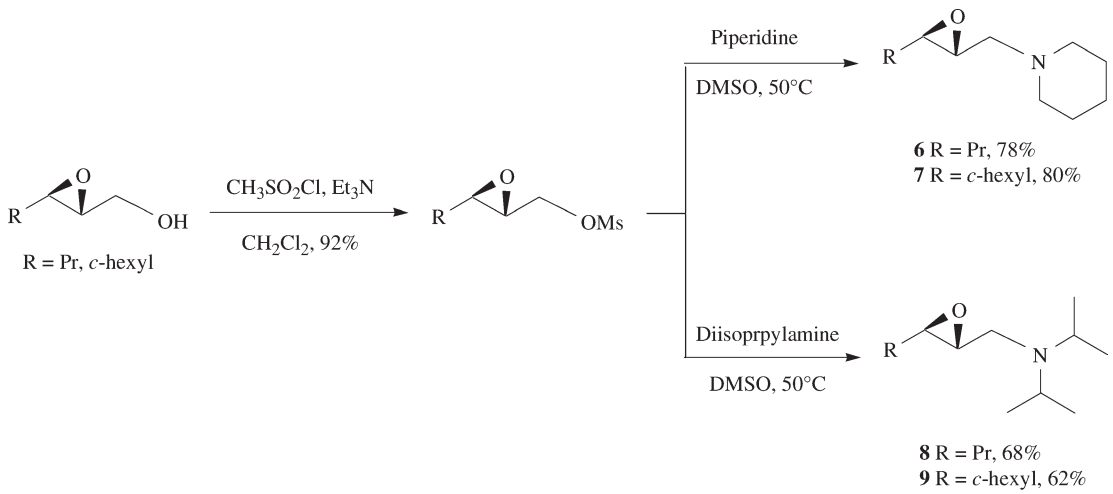
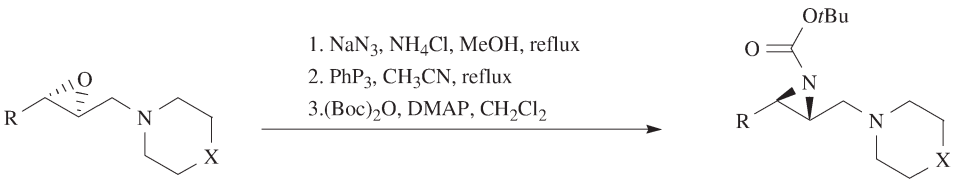



**Figure 2.** Possible cyclic chelate.

**Scheme 2**




**Scheme 3**

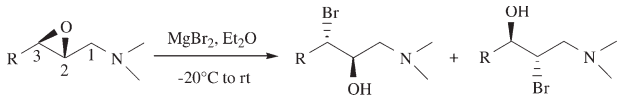


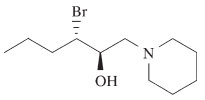
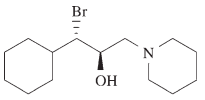
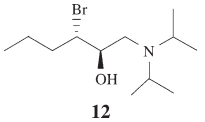
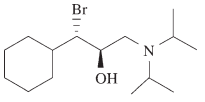

**6** R = Pr; X = $CH_2$, 92%
**14** R = Pr; X = O, 88%
**7** R = *c*-hexyl; X = $CH_2$, 93%
**15** R = *c*-hexyl; X = O, 91%

**16** R = Pr; X = $CH_2$, 72% from **6**
**17** R = Pr; X = O, 70% from **14**
**18** R = *c*-hexyl; X = $CH_2$, 69% from **7**
**19** R = *c*-hexyl; X = O, 73% from **15**

**Table 1**

Controlled opening of 2,3-epoxy amines.




| 2,3-Epoxy amine | Main haloderivative | Yield (%) | Ratio[a] C-3/C-2 |
|---|---|---|---|
| 6 |  **10** | 92 | 98:2 |
| 7 |  **11** | 65 | 90:10 |
| 8 |  **12** | 86 | 95:5 |
| 9 |  **13** | 69 | 90:10 |
| 3 | 4 | 68 | 95:5 |

[a] Regioisomeric ratio was determined by $^1$H NMR spectra.

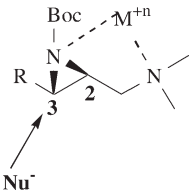



**Figure 3.** Possible cyclic chelate.

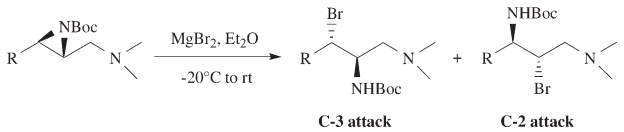
in this case, the ring opening occurred with an excellent C-3 regioselectivity (as demonstrated through spin–spin decoupling experiments), according to the proposed cyclic chelate model.

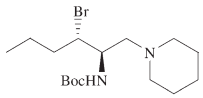
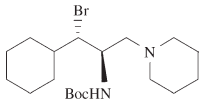
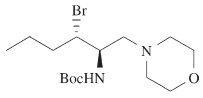
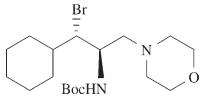
An unexpected behavior was observed when the C-3 position of the substrate was very reactive, as for **24** and **25**; in this case, the initial 3-bromo derivative underwent a rearrangement during the time (4–5 h), giving a new product, the physical data of which were in agreement with a 2-oxazolidinone structure (Scheme 4). This transformation could be explained through an intramolecular nucleophilic substitution of the bromine in benzylic and allylic position (Fig. 4).

In conclusion, the described new method represents a general and useful approach to the preparation of promising intermediates, due to the possible elaboration of the bromine [12]. Moreover, also when the reaction

**Table 2**

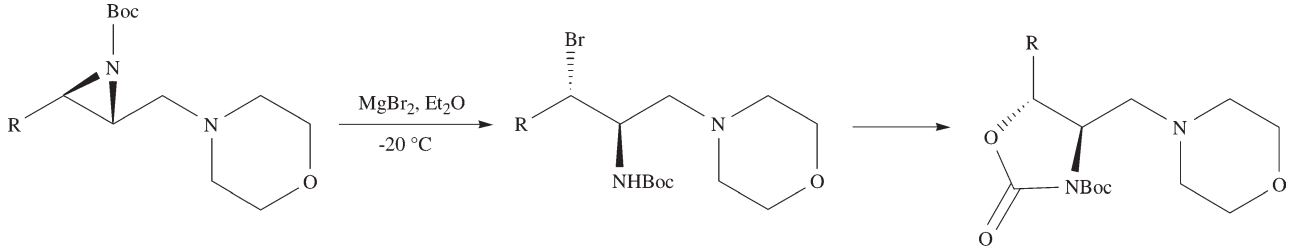
Controlled opening of 2,3-aziridine amines.




| 2,3-Aziridine amine | Main haloderivative | Yield (%) | Ratio[a] C-3/C-2 |
|---|---|---|---|
| 16 |  **20** | 81 | >95:5 |
| 17 |  **21** | 78 | >95:5 |
| 18 |  **22** | 78 | >95:5 |
| 19 |  **23** | 69 | >90:10 |

[a] Regioisomeric ratio was determined by $^1H$ NMR spectra.

**Scheme 4**




**24** R = Ph
**25** R = $CH_3CH$=CH

**26** R = Ph 86%
**27** R = $CH_3CH$=CH

**28** R = Ph 86%
**29** R = $CH_3CH$=CH

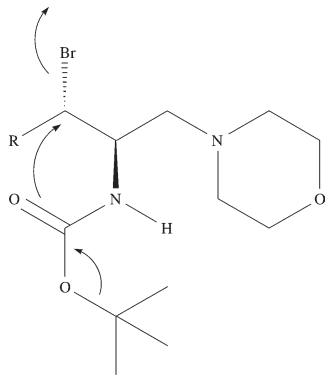



**Figure 4.** Proposed intramolecular cyclization.

evolves toward oxazolidin-2-ones, it could be of interest, considering the importance of oxazolidinones in the stereoselective synthesis of natural products and pharmaceuticals [13].

**Acknowledgments.** The authors thank MIUR (Ministry of University and Research, Rome) for partial financial support (PRIN 2005: Sintesi stereoselettiva e valutazione biologica di composti mirati all'attività antivirale).

## REFERENCES AND NOTES

[1] De Clercq, E. J Med Chem 2005, 48, 1297.

[2] Righi, G.; Ciambrone, S.; Bonini, C.; Campaner, P. Bioorg Med Chem 2008, 16, 902.

[3] Righi, G.; Bonini, C. Tetrahedron 2002, 58, 4981.

[4] (a) Epple, R.; Urbina, H. D.; Russo, R.; Liu, H.; Mason, D.; Bursulaya, B.; Tumanut, C.; Li, J.; Harris, J. L. Bioorg Med Chem Lett 2007, 17, 1254; (b) Robins, M. J.; Miles, R. W.; Samano, M. C.; Kaspar, R. L. J Org Chem 2001, 66, 8204; (c) Krow, G. R.; Lester, W. S.; Liu, N.; Yuan, J.; Hiller, A.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Cannon, K. J Org Chem 2001, 66, 1811; (d) Choi, D.; Yoo, B.; Colson, K. L.; Martin, G. E.; Kohn, H. J Org Chem 1995, 60, 3391.

[5] (a) Bonini, C.; Righi, G. Synthesis 1994,225 and references therein; (b) Bonini, C.; Federici, C.; Righi, G.; Rossi, L. J Org Chem 1995, 60, 4803; (c) Bonini, C.; Righi, G.; Rumboldt, G. J Org Chem 1996, 61, 3557; (d) Otsubo, K.; Inanaga, J.; Yamaguchi, M. Tetrahedron Lett 1987, 38, 4435.

[6] Bonini, C.; Chionne, A.; Righi, G. Eur J Org Chem 2000, 3127.

[7] Representative procedure for the ring opening of 2,3-three membered heterocyclic amines: To a cold (−20°C) stirred solution of 2,3-three membered heterocyclic amine (1 mmol) in $Et_2O$, $MgBr_2$ $Et_2O$ (516.5 mg, 2 mmol) was added. The mixture was stirred for 6 h (TLC monitoring) and then filtered through a pad of Celite. The filtrate was diluted with EtOAc, washed with saturated aq. NaCl, dried over Na2SO4, and then evaporated in vacuum. The crude mixture was purified by column chromatography (petroleum ether/ethyl acetate 7/3). (3S*,2R*)-3-Bromo-2-hydroxy-1-piperidine-hexane, 10. $^1$H NMR (200 MHz, $CDCl_3$): δ 4.31 (ddd, 1H, J 10.2 7.3 2.9 Hz, CHOH); 3.97 (ddd, 1H, J 9.2 7.3 2.9 Hz, CHBr); 3.41 (dd, 1H, J 13.2, 2.2 Hz, $CH_AN$); 3.35–2.99 (m, 6H, $CH_BN$+$2CH_2N$-piperidine+OH); 2.17–1.95 (m, 6H, $3CH_2$-piperidine); 1.93–1.15 (m, 4H, $2CH_2$); (t, 3H, J 7.3 Hz). $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 68.0; 61.1; 58.1; 54.2; 36.1; 22.5; 21.3; 20.1;13.0. HR-MS (ES Q-TOF) Calcd for $C_{11}H_{23}BrNO$ $(M+H)^+$: 264.0963 Found 264.0968. (1R*,2S*)-2-Bromo-1-(1′-methylpiperidinyl)-pentyl carbamic acid *t*-butyl ester, 20. $^1$H NMR (200 MHz, $CDCl_3$): δ 5.17–4.98 (bs, 1H, NHBoc); 4.48–4.34 (m, 1H, CHNHBoc); 3.88–3.67 (m, 1H, CHBr); 2.62–2.20 (m, 6H, $CH_2N$+$2CH_2N$-piperidine); 1.91–1.70 (m, 2H, $CH_2CHBr$); 1.5–1.18 (m, 8H, $CH_2$+$3CH_2$-piperidine); 1.44 (s, 9H, $C(CH_3)_3$); 0.93 (t, 3H, J 7.3 Hz, $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): δ 154.6; 78.7; 61.4; 60.7; 59.0; 53.9; 36.3; 28.3; 27.0; 24.5; 19.8; 12.9. HR-MS (ES Q-TOF) Calcd for $C_{16}H_{32}BrN_2O_2$ $(M+H)^+$: 363.1647 Found 363.1651. (2S,3R)-2-Bromo-2-phenyl-1-(1′-methylmorpholinyl) carbamic acid *t*-butyl ester, 26. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.54–7.23 (m, 5H); 5.38 (bd, 1H, J 4.4 Hz, NHBoc); 4.96 (d, 1H, J 6.6 Hz, CHBr); 4.36-4.08 (m, 1H, CHNH); 3.71 (t, 4H, J 4.4 Hz, $2CH_2O$-morpholine); 2.78–2.29 (m, 6H, $CH_2N$+$2CH_2N$-morpholine); 1.40 (s, 9H, $C(CH_3)_3$). Calcd for $C_{18}H_{28}BrN_2O_3$ $(M+H)^+$: 399.1283 Found 399.1288. (4R,5R)-4-Morpholin-4-ylmethyl-5-phenyl-oxazolidin-2-one, 28. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.52–7.29 (m, 5H); 5.96 (bs, 1H, NH); 5.22 (d, 1H, J 5.9 Hz, CHO); 3.91–3.78 (m, 1H, CHNH); 3.67 (t, 4H, J 4.4 Hz, $2CH_2O$-morpholine); 2.66–2.33 (m, 6H, $CH_2N$+$2CH_2N$-morpholine). $^{13}$C NMR (50 MHz, $CDCl_3$): δ 158,7; 138,5; 128,8; 125,6; 81,5; 66,6; 62,5; 57,4; 53,8. Calcd for $C_{19}H_{27}N_2O_5$ $(M+H)^+$: 363.1920 Found 363.1924.

[8] Hu, X. E. Tetrahedron Lett 2002, 43, 5315.

[9] Bonini, C.; Righi, G.; Franchini, T. Tetrahedron Lett 1998, 39, 2385.

[10] Tanner, D.; He, H. M.; Somfai, P. Tetrahedron 1992, 48, 6069.

[11] Manuscript in preparation.

[12] Since in our precedent studies, we have extensively used LiBr/Amb15 system to open 2-functionalized three membered heterocyclic rings in regioselective fashion, we decided to test it also in this contest. As expected, the reaction performed on compounds 3, 6, 7, 18, and 24 carried out to the same bromo derivatives obtained by $MgBr_2$.

[13] (a) Ager, D. J.; Prakash, I.; Schaad, D. R. Aldrichim Acta 1997, 30, 3; (b) Ahman, J. Target Heterocycl Syst 2001, 4, 341.

# A Convenient Racemic Synthesis of Two Isomeric Tetrahydropyridyl Alkaloids: Isoanatabine and Anatabine



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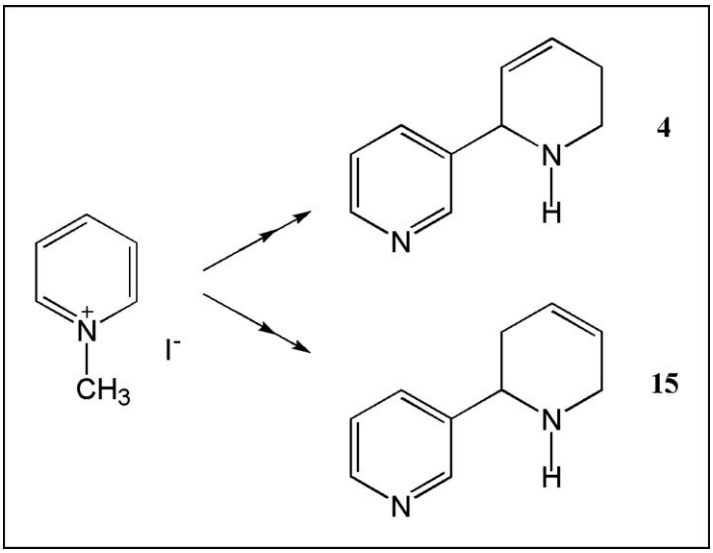



Anatabine is a major alkaloid in *Nicotiana tabacum* and its isomer, isoanatabine, was recently found in a marine worm. Reduction of 1-methylpyridinium iodide with sodium borohydride gave 1-methyl-3-piperideine, which was transformed with hydrogen peroxide into the *N*-oxide. Reaction of the *N*-oxide successively with trifluoroacetic anhydride and potassium cyanide gave 2-cyano-1-methyl-3-piperideine. Its reaction with 3-pyridylmagnesium chloride gave (±)-*N*-methyl-isoanatabine. This was transformed with *m*-chloroperbenzoic acid into the *N*-oxide which was *N*-demethylated with iron(II) sulfate, giving (±)-isoanatabine. The successive applications of literature procedures for the *N*-demethylation by decomposition of *N*-oxide contributed to the knowledge of the mechanism of this oxidative rearrangement. On the other hand, the reduction of 1-methylpyridinium iodide with sodium borohydride and with potassium cyanide present since the start of the reaction in a two layer ether-water system, gave 2-cyano-1-methyl-4-piperideine. This was transformed into (±)-anatabine by the same sequence of reactions used for the synthesis of (±)-isoanatabine.

*J. Heterocyclic Chem.*, **47**, 569 (2010).

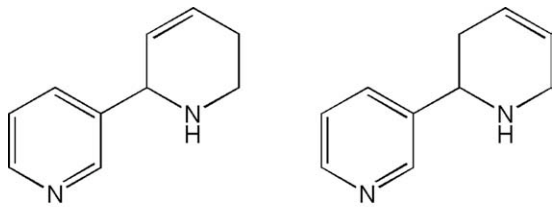
## INTRODUCTION

In fresh tobacco leaves of the *Nicotina tabacum* species, the alkaloid mixture consists of 93% (*S*)-nicotine, 3.9% (*S*)-anatabine, 2.4% (*S*)-nornicotine, 0.5% (*S*)-anabasine, and several other pyridine alkaloids which are detected in lower amounts [1]. (*S*)-Nicotine and several of its minor metabolites have potent modulatory effects on nicotinic acetylcholine receptors in the central and peripheral nervous systems. Thus, a variety of nicotinic agonists are being developed for the treatment of neurodegenerative and mental diseases [2]. As part of a search for biologically active compounds acting upon these receptors, we synthesized anatabine and isomeric isoanatabine (Scheme 1), found in a marine worm [3,4].

To our knowledge, only the procedure of Flann *et al*. has been published for the synthesis of (±)-isoanatabine, i.e., 2-(3-pyridyl)-3-piperideine [5] (Scheme 2). This multistep procedure starts with 3-butyn-1-ol and synthesized 1-amino-4-trimethylsilyl-but-3-ene. The condensation of the latter with 3-pyridinecarboxaldehyde gave the aldimine, which with trifluoroacetic acid cyclized by 1,2-addition to the imine group of the trimethylsilylated vinylcarbon, giving (±)-isoanatabine.

On the other hand, several procedures have been developed for the synthesis of anatabine, i.e., 2-(3-pyridyl)-4-piperideine (Scheme 3). In general, they start from a 3-substituted pyridine and the piperideine ring is constructed at the substituent moiety. Quan *et al*. started

**Scheme 1**




**Isoanatabine** **Anatabine**

from 3-formylpyridine [6]. The formyl group was transformed with ethyl carbamate into diethyl *N*,*N*′-(3-pyridylmethyl)-biscarbamate. With boron trifluoride etherate, the biscarbamate was decomposed by heating in benzene into an intermediate imine which cyclized with 1,3-butadiene (Diels Alder reaction), giving the *N*-ethoxycarbonyl-anatabine and, after hydrolysis, (±)-anatabine.

Deo and Crooks started from 3-(aminomethyl)-pyridine [7]. This was transformed with benzophenone into a ketimine. Its reaction with LDA gave the carbanion of the activated methylene, which was then monoalkylated with *cis*-1,4-dichloro-2-butene. Hydrolysis made free the 1-amino group which cyclized by reaction with the 5-chloro substituent of the pent-3-ene, giving (±)-anatabine.

Felpin *et al*. synthesized (*S*)-anatabine starting with the asymmetric addition of (+)-B-allyl-diisopinocampheylborane to 3-formylpyridine, giving the enantiomerically pure alcohol [8]. This was successively transformed into the mesylate, azide, and amine. The amino group previously transformed into carbamate was alkylated with allylbromide. Metathesis with the Grubb's ruthenium catalyst cyclized the two allyl groups into the *N*-carbamate protected (*S*)-anatabine, which was then deprotected.

Balasubramanian and Hassner synthesized (*S*)-anatabine starting from 3-pyridinecarboxaldehyde [9]. Its condensation with (*S*)-*p*-toluenesulfinamide gave an enantiomerically pure imine. After the enantioselective 1,2-addition to its imino group of the 4-carbanion of *cis*-1-hydroxy-4-phenylsulfonyl-but-2-ene (the dianion of which being obtained with LiHMDS), the amino group was deprotected. The Mitsunobu cyclization of the 1,5-unsaturated aminoalcohol generated the phenylsulfonyl substituted (*S*)-anatabine. Reductive elimination of the phenylsulfonyl substituent gave (*S*)-anatabine.

Ayers *et al*. synthesized (*S*)-anatabine starting with 3-(aminomethyl)-pyridine [10]. Its condensation with (+)-2-hydroxy-3-pinanone in the presence of boron trifluoride diethyl etherate gave an enantiomerically pure ketimine. The carbanion (generated with LDA) of the methylene α to the nitrogen of the imine group was enantioselectively monoalkylated with *cis*-1-bromo-4-(tetrahydropyran-2-yloxy)-but-2-en. The 4-tetrahydropyran and 2-hydroxy-3-pinanone groups were removed. The Mitsunobu cyclization of the unsaturated 1,5-aminoalcohol gave (*S*)-anatabine. The use of (−)-2-hydroxy-3-pinanone ketimine gave (*R*)-anatabine by the same procedure.

On the other hand, (*R*)-anatabine was synthesized starting with 1-(2,4-dinitrobenzene-1-yl)-pyridinium chloride and (*R*)-phenylglycinol [11].

The addition of lithium aluminum hydride to pyridine gives lithium tetrakis(*N*-dihydropyridyl)aluminate (LDPA) [12a]. The addition at 0°C of water to the solution of LDPA in pyridine, gives a mixture of 1,4-, 1,2-, and 2,5-dihydropyridines in a ratio of 26:37:38 [12b]. By conducting this hydrolysis under an atmosphere of oxygen, Yang and Tanner obtained (±)-anatabine with a yield of 59% [12c].

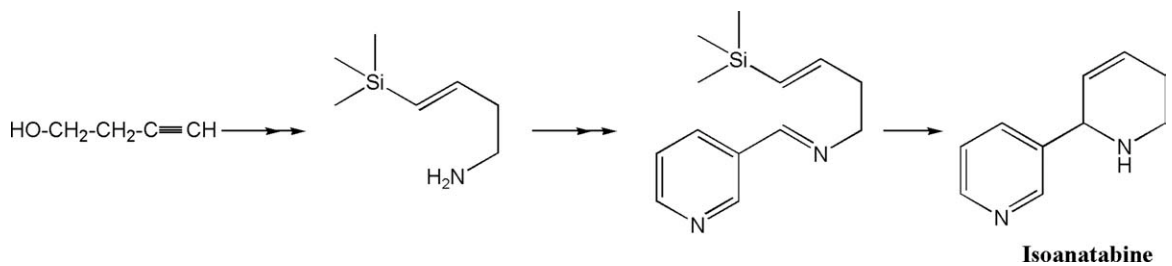
In this work, a short procedure has been developed for the synthesis of (±)-isoanatabine starting with 1-methylpyridinium iodide. By modifying the first reduction step, this procedure has been extended to the synthesis of (±)-anatabine.

## RESULTS AND DISCUSSION

### Synthesis of (±)-isonanatabine

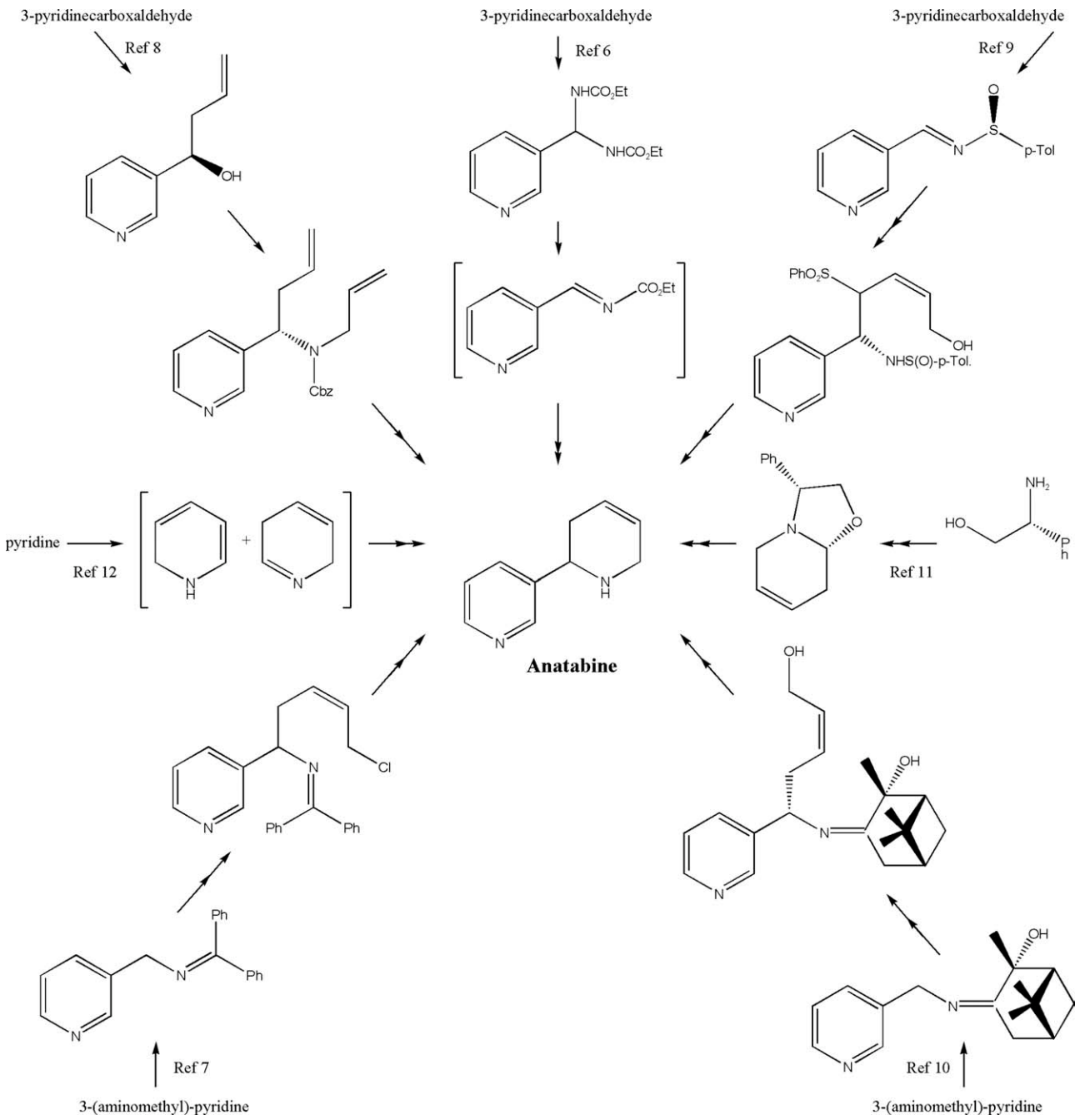
***Synthesis of (±)-N-methyl-isoanatabine 3a and (±)-N-benzyl-isoanatabine 3b.*** Reaction of pyridine with methyl iodide in acetone gave 1-methylpyridinium iodide (Scheme 4). According to a described procedure, the reaction of 1-methylpyridinium iodide with sodium borohydride in methanol yielded 1-methyl-3-piperideine, which was not isolated [13]. Oxidation with hydrogen

**Scheme 2**

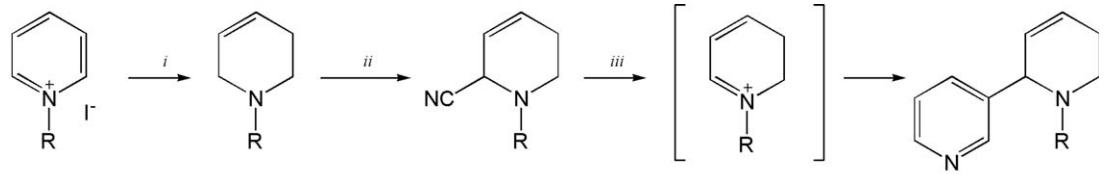



**Isoanatabine**

**Scheme 3**



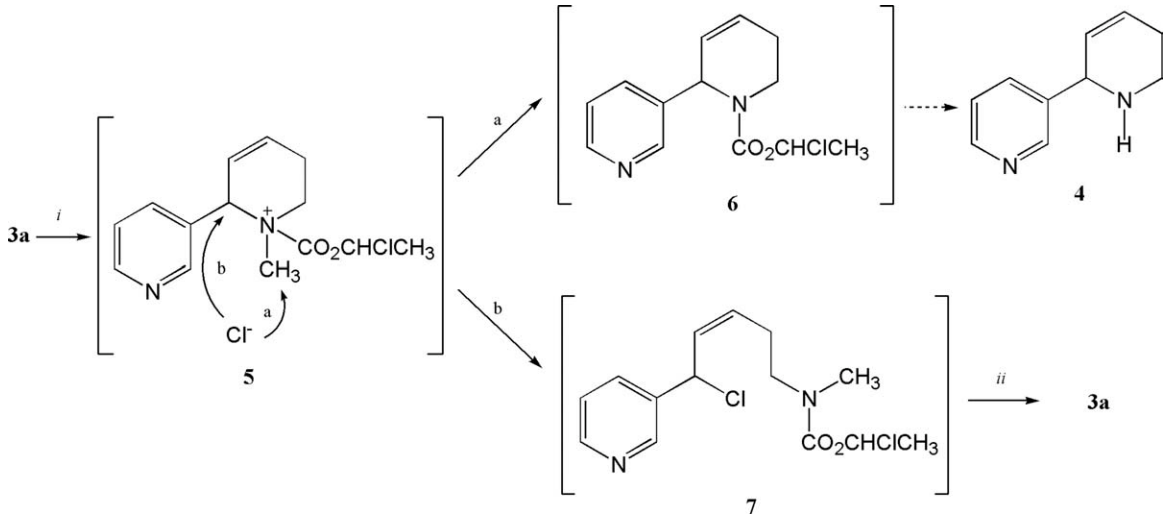

**Scheme 4.** Reagents and conditions: (*i*, *ii*) see refs. [13] and [14]. (*iii*) 3-PyrMgCl, THF/$Et_2O$, −10°C to rt, 16 h for **3a** (yield: 77%); 0°C to rt, 16 h for **3b** (yield: 67%).




**a**, R = $CH_3$
**b**, R = Bn

**1** **2** **3**

**Scheme 5.** Reagents and conditions: (*i*) ACE-Cl, 1,2-dichloroethane, reflux, 16 h. (*ii*) 2.5% NaOH, EtOH/$H_2O$ (9:1), 0°C (1 h) to rt (24 h), 75%.




peroxide gave 1-methyl-3-piperideine *N*-oxide. The *N*-oxide in methylene chloride was treated with trifluoroacetic anhydride. After 1 h, an aqueous solution of potassium cyanide was added while the pH of the aqueous layer was maintained at 4, giving (±)-2-cyano-1-methyl-3-piperideine **1a**.

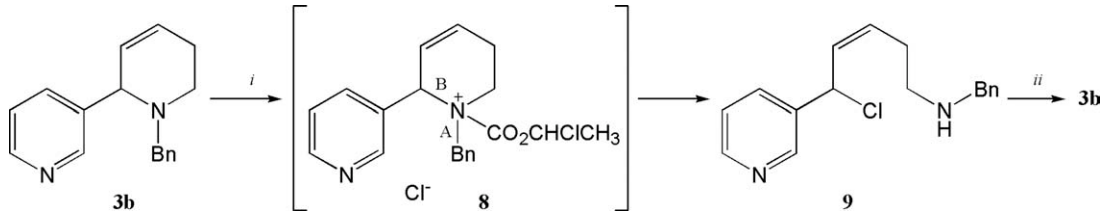
Alkylation of the α-amino nitrile **1a** with 3-pyridylmagnesium chloride (or 3-pyridylmagnesium bromide) was made according to the Bruylants reaction, i.e., the reaction of an α-tertiary-amino nitrile with a Grignard reagent [15]. The metal of the Grignard reagent probably mediates the formation of the conjugated iminium **2a**, on which subsequently adds the Grignard reagent. The stability and the reactivity of the iminium **2a** is the most likely reason why the Grignard reagent substitutes the CN in the α-aminonitrile **1a**, generating 1-methyl-2-(3-pyridyl)-3-piperideine **3a**, i.e., (±)-*N*-methyl-isoanatabine, rather than adding to it. The THF solution containing 5 equiv of the Grignard reagent was added at −10°C to a solution of the α-amino nitrile **1a**, also in THF. After stirring the mixture at room temperature overnight, **3a** was obtained with a yield of 77%. For the preparation of 3-pyridylmagnesium chloride, 1 equiv of 3-bromopyridine was added to 1 equiv of *i*-propylmagnesium chloride in THF at room temperature, and the mixture was stirred for 1 h [16].

The 3-pyridylmagnesium bromide was also used for the alkylation of α-amino nitrile **1a**. In this case, **3a** was obtained with a lower yield of 65%. The procedure previously described in the literature for the synthesis of 3-pyridylmagnesium bromide was modified [17]. The ratio of the reagents was changed and the reaction generating $MgBr_2$ was made in ether instead of THF, $MgBr_2$ being more soluble in ether than in THF as $MgBr_2$ forms a complex with ether. In this way, the transfer of the solution of $MgBr_2$ through a cannula under argon to the solution of 3-pyridyllithium was easier.

(±)-1-Benzyl-2-cyano-3-piperideine **1b** was synthesized according to the procedure of Bonin *et al*. [14]. This procedure is similar to the one used for the synthesis of **1a**, except for some modifications. Sodium borohydride was reacted with 1-benzyl-pyridinium bromide (obtained by reaction of benzyl bromide with pyridine in toluene [18]) in ethanol, giving the 1-benzyl-1,2,5,6-tetrahydropyridine, which was isolated with a yield of 75%. Its solution in dichloromethane was reacted with *m*-chloroperbenzoic acid, giving 1-benzyl-1,2,5,6-tetrahydropyridine-*N*-oxide isolated with a yield of 80%. To the solution of the *N*-oxide in dichloromethane was added trifluoroacetic anhydride; after 1 h at room temperature, an aqueous solution of potassium cyanide was added, during which the pH was maintained at 4. 1-Benzyl-2-cyano-3-piperideine **1b** was obtained with a yield of 57%. The subsequent alkylation of the α-amino nitrile **1b** with 3-pyridylmagnesium chloride was made according to the Bruylants reaction, generating (±)-1-benzyl-2-(3-pyridyl)-3-piperideine **3b**, i.e., (±)-*N*-benzyl-isoanatabine. The solution of the Grignard reagent in THF was added at 0°C to the solution of the α-amino nitrile **1b** in THF. The (±)-*N*-benzyl-isoanatabine **3b** was obtained with a yield of 67%.

***Attempts at N-demethylation and N-debenzylation by a chloroformate of the (±)-N-methyl- and (±)-N-benzyl-isoanatabines.*** To obtain (±)-isoanatabine **4**, the *N*-demethylation of **3a** was attempted by reacting **3a** with a chloroformate [19a]. The mixture of **3a** and 1 equiv of α-chloroethyl chloroformate (ACE-Cl) in 1,2-dichloroethane was refluxed for 16 h (monitored by TLC). After evaporation of the solvent, the residue was refluxed in methanol for 1 h, giving a mixture of unidentified

**Scheme 6.** Reagents and conditions: (*i*) ACE-Cl, $CH_2Cl_2$, 0°C to rt, 16 h. (*ii*) 2.5% NaOH, EtOH/$H_2O$ (9:1), 0°C (1 h) to rt, 5 h, 78%.




products. To solve the problem, the mixture of **3a** and ACE-Cl in 1,2-dichloroethane was refluxed for 16 h, but instead of the intermediate carbamate **6**, the *N*-[5-chloro-5-(pyridin-3-yl)-pent-3-enyl]-*N*-methyl-carbamic acid 1-chloro-ethyl ester **7** was isolated and analyzed (Scheme 5). Thereafter, **7** was treated with 2.5% sodium hydroxide in aqueous ethanol, and (±)-*N*-methyl-isoanatabine **3a** was recovered with a yield of 75% relative to the starting amount of **3a**.

The opening of the piperideine ring when **3a** is reacted with α-chloroethyl chloroformate can be explained by the intermediate formation of the quaternary ammonium salt **5** followed by the attack of the chloride ion at the benzylic carbon, following the pathway b instead of the attack at the methyl group (pathway a). This corresponds to the benzyl effect, i.e., the benzyl cleavage is preferred over the methyl loss on account of the great stability of the benzyl carbocation. The general rule indicates that the group that cleaves is the one that gives the most stable carbocation and the most reactive halide (e.g., benzyl or allyl); for simple alkyl groups, the smallest are the most readily cleaved [19]. A similar reactivity to that of **3a** is observed with nicotine. When nicotine is reacted with chloroformates, the pyrrolidine ring is opened and the δ-chlorocarbamates are obtained [20].

An assay was made for the *N*-debenzylation of **3b** by its reaction with α-chloroethyl chloroformate in dichloromethane at room temperature, as it is known that the benzyl group needs lower temperatures to be cleaved.

In the intermediate quaternary ammonium salt **8**, it was hoped that the breaking of the *N*-Bn (bond A) would be favored over the breaking of the *N*-(C-2 of the 3-piperideine) bond (bond B), generating (±)-isoanatabine **4** (Scheme 6). The reverse however occurred and 1-chloro-1-(3-pyridyl)-5-benzylamino-pent-2-ene **9** was formed. This could be due to the fact that the B bond breaking in **8** generates at the 2-C of the 3-piperideine a more stable carbocation because it is simultaneously a benzyl and allyl cation. The A bond breaking would generate a carbocation benzyl lacking the further allyl stabilization.

The treatment of **9** with 2.5% sodium hydroxide in aqueous ethanol permitted recovery of the starting (±)-*N*-benzyl-isoanatabine **3b** with a yield of 78%.

***Attempted N-debenzylation of (±)-N-benzyl-isoanatabine 3b with CAN.*** Yamaura *et al*. observed that the *N*-(4-methoxybenzyl) group on 2,5-piperazinediones can be oxidatively removed with $(NH_4)_2Ce(NO_3)_6$ (CAN), but not the unsubstituted benzyl group [21]. However, Bull *et al*. observed that the treatment of a range of *N*-unsubstituted benzyl tertiary amines with CAN at room temperature results in *N*-debenzylation to afford the corresponding secondary amine [22]. Therefore, the oxidative *N*-debenzylation of **3b** with CAN was assayed. A solution of **3b** and 2 equiv of CAN in 5:1 acetonitrile:water was stirred for 2 h at rt. Only the starting material **3b** was obtained. In another assay, 4 equiv of CAN were added to a solution of **3b** in 5:1 acetonitrile:water, and the solution was stirred 24 h at rt. Again only the starting **3b** was recovered. The concentration of CAN in the reaction mixture of each of these assays was greater than 0.25*M* as it is known that no oxidation is obtained at lower concentration [21]. A further assay was made with **3b** and 4 equiv of CAN, and stirring at 50°C overnight; isoanatabine **4** was not obtained but **3b** was completely transformed into a lot of unidentified products. The use of tetrahydrofuran instead of acetonitrile and higher concentrations of CAN at room temperature also led to the recovering of the starting (±)-*N*-benzyl-isoanatabine **3b**.

***N-Demethylation of the (±)-N-methyl-isoanatabine 3a by decomposition of its N-oxide 10 (nonclassical Polonovski reaction).*** Several possible methods for *N*-demethylation of **3a** were tested, starting from the *N*-oxide of **3a**, **10**. The *N*-oxide **10** was obtained by reaction of (±)-*N*-methyl-isoanatabine **3a** with *m*-chloroperoxybenzoic acid (1.1 equiv) in $CH_2Cl_2$ at 0°C to avoid the possible epoxidation of the double bond [23]. The usual work up, i.e., treatment of the reaction mixture by aq. NaOH to pH 10–11 and then extraction by $CHCl_3$ led to the isolation of the *N*-oxide only in low yield. The low yield was probably due to the high solubility of the *N*-oxide at basic pH. This problem was overcame by concentrating the reaction mixture and pouring the concentrate

over alumina and chromatographing. In this way, the (±)-*N*-methyl-isoanatabine-*N*-oxide **10** was obtained with a yield of 91% as a mixture of diastereomers in a 6:4 ratio (undefined stereochemistry). The diastereomers were not separated and were used in next step as a mixture.

The nonclassical Polonovski reaction for the *N*-demethylation of the *N*-oxide of (±)-*N*-methyl-isoanatabine **3a** was investigated [24a]. The desired reaction is the catalyzed decomposition of the tertiary amine *N*-oxide through an internal oxidation into the secondary amine, the *N*-methyl being oxidized to formaldehyde. When the reaction is catalyzed by an iron salt, the mechanism is believed to involve two successive one-electron transfers involving Fe(II)/Fe(III) redox reactions [24b,c]. Cations, free radicals and radical-cations ions stabilized as iminium ions and radicals, are considered as intermediates. Often the catalyst (the iron salt or complex, selenium dioxide, etc.) is engaged in stoichiometric amounts. The *N*-demethylation of the hydrochloride salts of the *N*-oxides of opiate alkaloids (codeine, codeine methyl ether, thebaine, thevinone, etc.) was realized with $FeSO_4 \cdot 7H_2O$ in methanol; the *N*-oxide of codeine gave norcodeine with a yield of 49%, in mixture with codeine, i.e., the product of *N*-deoxygenation [25]. When the same reaction was made using a porphyrin chelate of iron(II), the yield of norcodeine was increased to 91% [26]. The same reaction has been applied to the *N*-demethylation of the *N*-oxides of piperidines, benzomorphans, and morphinans using iron(II) chloride [27].

For the nonclassical Polonovski reaction of the *N*-oxides of tertiary amine catalyzed with iron salts in water or in nonpolar solvents, the ease of alkyl conversion to the corresponding carbonyl compound decreases in the order $C_6H_5CH_2 > CH_3 > RCH_2 > R_2CH$; this is the decreasing order for the ease of the breaking of the bond between the *N*-oxide nitrogen atom and one of the three alkyl groups linked to this nitrogen [24b,c]. This reactivity order for the rearrangement was assigned among others to the acidity of the protons on the carbon adjacent to the nitrogen atom; the greater stability of the intermediate benzyl carbocation, benzyl radical and benzyl radical-carbocation also explains the reactivity order and that benzyl cleavage is preferred over methyl loss (benzyl effect). For the *N*-demethylation of the *N*-oxides of opiates (codeine, codeine methyl ether, thebaine, thevinone, etc.) cited earlier, there was no benzyl group linked to the nitrogen atom; there was no competition from the benzyl effect and the *N*-demethylation was obtained with a good yield [25]. The *N*-oxide of *N*-methyl-isoanatabine and the *N*-oxide of the *N*-benzyl-isoanatabine are subjected to the benzyl effect. The failure of the trials for their *N*-demethylation and *N*-debenzylation with a chloroformate showed their high sensitivity to the benzyl effect and prompted to select assays able to avoid this benzyl effect.

Another secondary reaction that competes with the *N*-demethylation is the deoxygenation of the *N*-oxide, which is catalyzed by the iron salt or chelate. It generates back the tertiary amine from which was made the *N*-oxide. Moreover, the deoxygenation of the *N*-oxide may be accompanied by the oxidation (oxidative dehydrogenation) of the *N*-demethylated product or of the *N*-methylated one. Other secondary degradative reactions occur when the reaction temperature is too high.

Selective *N*-demethylation of the *N*-oxides of tertiary aminofumagillols to the corresponding secondary aminofumagillols has been made by heating the *N*-oxide with selenium dioxide in ethanol [28]. The *N*-oxides of tertiary aminofumagillols do not sustain the concurrence of the benzyl effect. However, they contain two epoxy and the α,β-unsaturated ester sensitive functionalities. These remained intact during the reaction.

Therefore, our first attempt at the *N*-demethylation of **10** by means of the nonclassical Polonovski reaction utilized $SeO_2$. A mixture of **10** and 1.5 equiv of $SeO_2$ in 95% ethanol was heated to reflux for 4 h under an atmosphere of argon. (±)-*N*-methyl-isoanatabine **3a** was formed with a yield of 65%, indicating that only *N*-deoxygenation occurred.

Several studies have been reported for the *N*-demethylation of the *N*-oxides of tertiary amines subjected to the benzyl effect, by means of their decomposition catalyzed by iron salts (generally engaged in stoichiometric amounts) in aqueous solutions containing large amounts of tartaric or citric acids (present as such or as their salts). The $FeSO_4$-catalyzed dealkylation of the *N*-oxide of *N*,*N*-dimethyl-benzylamine showed the importance of the benzyl effect relatively to the *N*-demethylation. When the *N*-oxide of *N*,*N*-dimethyl-benzylamine in an aqueous solution at pH 1–2 containing iron(II) sulfate was heated, benzaldehyde was produced with a yield of 85%, no *N*-demethylation being obtained [24b,c]. Under the same conditions at pH 1, the *N*-oxide of *N*,*N*-dimethyl-butylamine gave mainly formaldehyde and *N*-methyl-butylamine. On the other hand at pH 6–7, when the mixture in water of the *N*-oxide of *N*,*N*-dimethyl-benzylamine, L-(+)-tartaric acid and $FeSO_4 \cdot 7H_2O$ (or of $Fe(NO_3)_3 \cdot 9H_2O$) was heated, a mixture of formaldehyde (the product of *N*-demethylation) and benzaldehyde (2.3:1) was formed [24b,29]. At pH 6–7, the $Fe^{+2}/Fe^{+3}$ system is as a complex with the anion of tartaric acid. The *N*-oxide would occupy some coordination positions of this complex [30]. The rearrangement of the *N*-oxide would then occur at the coordination positions of the complex so the regioselectivity of the rearrangement would be directed by the geometry of the complex and thus by steric factors. This would explain the

production of formaldehyde and thus the *N*-demethylation, what did not occur when the iron ions were not chelated.

In previous experiments on the dealkylation of amine oxides, it was observed that reaction mixtures of iron (III) and tartaric or oxalic acid (reducing acids) generated iron(II) *in situ*, and that iron(II) was the initiator of the rearrangement [24b,c]. That iron(II) and not iron(III) was the initiator of the reaction was shown by experiments with iron(III) salts coordinated to nonreducing acids (sulfuric, succinic) [24b,c]. Under these conditions, the Polonovski reaction did not occur. When as little as 3% iron(II) sulfate was added to the reaction medium, secondary amine production began. On the other hand, iron(II) was converted to iron(III) during the course of the rearrangement; this was mainly due to the oxidation of iron(II) by the amine-oxide with formation of the tertiary amine (the secondary reaction of the amine-oxide: deoxygenation).

Noscapine (also called narcotine) has been converted by *N*-demethylation to nornarcotine in 35% overall yield *via* the noscapine *N*-oxide and in spite of the concurrence of a benzyl effect [31]. Therefore, the mixture of noscapine-*N*-oxide·HCl and iron(III) citrate, in water acidified to pH 1–2, was heated. Nicotine-*N*-oxide also suffers the competition of the benzyl effect during its *N*-demethylation by the nonclassical Polonovski reaction. A mixture in water at pH 6 of nicotine-*N*-oxide, $Fe(NO_3)_3$, L-(+)-tartaric acid and sodium carbonate was heated [32]. Nornicotine was obtained with a yield of 56%, besides several other alkaloids arising from the transformation of nicotine: myosmine (6.9%), *N*-methylmyosmine (2.1%), and nicotine (3.0%).

*N*-demethylation of (±)-*N*-methyl-isoanatabine **3a** by decomposition of its *N*-oxide **10** was attempted under the conditions used by Craig *et al*. for the *N*-demethylation of nicotine [32]. The pH of a mixture in water of **10**, 3 equiv of $Fe(NO_3)_3$, and 30 equiv of L-(+)-tartaric acid was adjusted to 6.3 by adding a solution of sodium carbonate. After heating at 80°C for 40 min, (±)-isoanatabine **4** was obtained but only with a low yield of 9%. The major compound isolated was the (±)*N*-methyl-anatabine **3a**, obtained with a yield of 49%, indicating that deoxygenation of the *N*-oxide was the main reaction.

The results obtained in the two preceding assays suggested that heating could induce the deoxygenation of **10** generating (±)-*N*-methyl-isoanatabine **3a**. Therefore, a method was searched for the decomposition of the *N*-oxide at room or lower temperature.

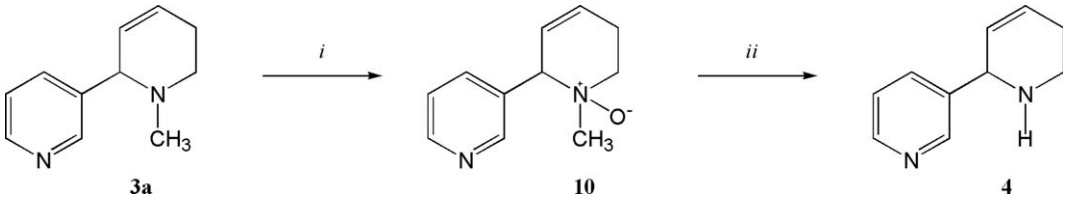
The secondary amine 5-dimethylamino-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine is a metabolite of a new vasopressin V2 receptor antagonist [33]. The *N*-demethylation of its *N*-oxide was sensitive to the competition from the benzyl effect. However, the *N*-demethylation of the *N*-oxide was obtained by stirring a mixture of *N*-oxide, meso-(tetraphenylporphinato)iron(III) chloride, Fe(TPP)Cl, and imidazole in dichloromethane at room temperature. The product of *N*-demethylation was obtained with a yield of 68%, accompanied by 25% of the deoxygenation product of the *N*-oxide. When imidazole was replaced by tetrazole, the secondary amine was produced with a yield of 86%, and the product of deoxygenation was no more detected. This showed the influence of the additives imidazole or tetrazole. They could make some association with the *N*-oxide and the iron porphyrin, orienting in this way the decomposition of the *N*-oxide toward the *N*-demethylation, and overcoming the benzyl effect. In the *N*-demethylation of the *N*-oxides of the *N*,*N*-dimethyl-benzylamine [24b,c] noscapine [31] and nicotine [32] cited earlier, the chelation of the iron ions by the tartaric and citric acids and their salts present in large excess, would explain the orientation by steric effects of the rearrangement of the *N*-oxide toward the *N*-demethylation. The increase of the yield of the *N*-demethylation of the *N*-dimethyl benzazepine *N*-oxide by the use of the additives imidazole or tetrazole corroborated that hypothesis.

Therefore, *N*-demethylation of (±)-*N*-methyl-isoanatabine **3a** was assayed in the conditions used by Kawano *et al*. [33]. The mixture of **10**, 1 equiv of Fe(TPP)Cl and 1 equiv of tetrazole in dichloromethane was stirred at room temperature during 16 h in the dark. The *N*-oxide **10** was recovered untransformed with a yield of 80%. The assay was repeated but without the addition of tetrazole; again the *N*-oxide **10** was recovered untransformed.

The *N*-demethylation of the galanthamine-*N*-oxide is sensitive to the competition from the benzyl effect [34]. However, the *N*-demethylation has been obtained with a yield of 76% by stirring at 10°C the *N*-oxide in methanol containing iron(II) sulfate. No cleavage at the benzylic carbon was observed. The selective demethylation of the galanthamine-*N*-oxide in the presence of iron salts indicated the preference for oxidation at the methyl center of the *N*-methyl substituted amine oxide. This is at the opposite of the general rule which gives the preference to the oxidation of the benzylic carbon. The bulky structure of galanthamine would induce the *N*-demethylation by a steric effect, the *N*-methyl being deprotected to oxidation outside of the bulky structure.

The *N*-demethylation of the *N*-oxide of the alkaloid glaucine suffers also from the competition of the benzyl effect [35]. However, the *N*-demethylation has been performed under the same conditions as for galanthamine without addition of a complexing agent. The *N*-oxide of glaucine was treated in methanol with iron(II) sulfate at 10°C. Norglaucine was formed with a yield of 52%. It

**Scheme 7.** Reagents and conditions: (*i*) *m*-CPBA, $CH_2Cl_2$, 0°C, 1.5 h, 91%. (*ii*) $FeSO_4 \cdot 7H_2O$, $CH_3OH$, 10°C, 1.5 h, 55%.




was accompanied by the formation for 13% of the product of the benzyl effect, which was further reduced. When the reaction temperature was 50°C or when the reagent was changed to ferrous chloride, only the product due to the benzyl effect was formed.

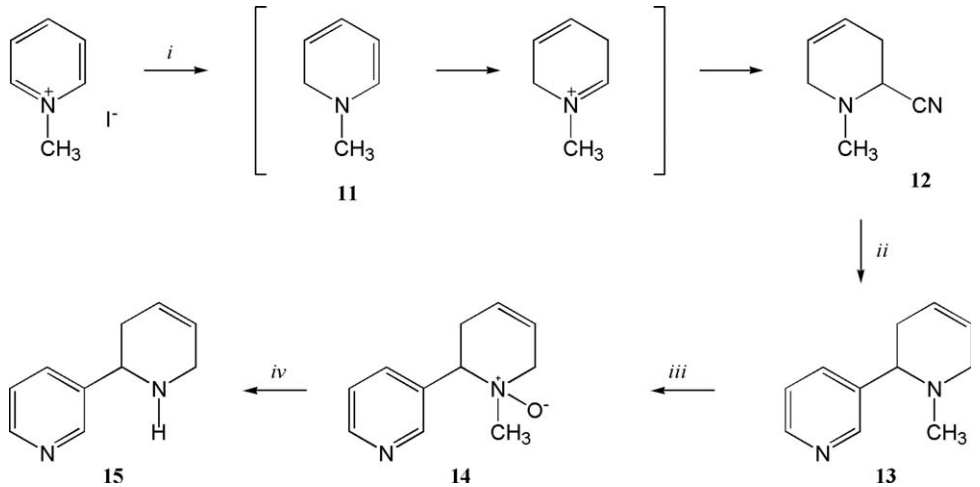
*N*-demethylation of the (±)-*N*-methyl-isoanatabine **3a** by decomposition of its *N*-oxide **10** was tested under the same conditions as the *N*-oxides of galanthamine [34] and glaucine [35] (Scheme 7). A mixture of **10** and 2 equiv of $FeSO_4 \cdot 7H_2O$ in methanol was stirred for 1.5 h at 10°C. The (±)-isoanatabine **4** was obtained with a yield of 55%. It was accompanied by the formation of 23% of (±)-*N*-methyl-isoanatabine **3a**, the product of deoxygenation. As with galanthamine and glaucine, the structure of the *N*-oxide **10** of isoanatabine would induce by a steric effect the *N*-demethylation without requiring an additive. The *N*-methyl would be more accessible to oxidation because of its greater exposure. For the *N*-demethylation by decomposition of the *N*-oxide, the search by the successive applications of described procedures thus contributes, by the analysis of the generated products, to the knowledge of the mechanism and of the experimental parameters orienting the selectivity of the oxidative rearrangement of the nonclassical Polonovski reaction.

**Synthesis of (±)-anatabine.** The procedure for the synthesis of (±)-isoanatabine **4** was extended to the synthesis of (±)-anatabine **15** (Scheme 8). (±)-2-Cyano-1-methyl-4-piperideine **12** is the isomer of (±)-2-cyano-1-methyl-3-piperideine **1a**. The sequence of transformations applied to compound **1a** for the synthesis of (±)-isoanatabine **4** could in principle be applied to **12** for the preparation of (±)-anatabine **15**. Therefore, a procedure for the synthesis of compound **12** was developed. Like for compound **1a** it started with the reduction of 1-methylpyridinium iodide with $NaBH_4$, but the experimental conditions were changed to obtain the double bond in the right position. A two phases solvent system was used [36]. To an aqueous solution of 4 equiv of potassium cyanide was added 1.5 equiv of hydrochloric acid at 0°C. This aqueous phase was layered with the same volume of ether. 1-Methylpyridinium iodide was added followed by 1.2 equiv of $NaBH_4$. After 5 h at room temperature, compound **12** was obtained with a yield of 95%.

The presence of the solution of potassium cyanide in water underlayering the ether phase since the beginning of the reduction of 1-methylpyridinium iodide by $NaBH_4$ permitted to limit the reduction to the formation of 1-methyl-1,2-dihydro-pyridine which in acidic condition was trapped by potassium cyanide, generating compound **12**.

The isomerization of (±)-2-cyano-1-methyl-4-piperideine **12** into (±)-2-cyano-1-methyl-3-piperideine **1a**

**Scheme 8.** Reagents and conditions: (*i*) $NaBH_4$, KCN, HCl, $H_2O/Et_2O$, 0°C to rt, 5 h, 95%. (*ii*) 3-PyrMgCl, THF, −10°C to rt, 16 h, 83%. (*iii*) *m*-CPBA, $CH_2Cl_2$, 0°C, 1.5 h, 88%. (*iv*) $FeSO_4 \cdot 7H_2O$, $CH_3OH$, 10°C, 3 h, 44%.



was attempted [37a,b]. If it succeeded, the aminonitrile **12** could be another starting point for the synthesis of (±)-isoanatabine **4**. The isomerization was attempted by heating **12** in 6*N* HCl. Thereafter, the solution was made basic by addition of potassium cyanide. However, the aminonitrile **12** was recovered untransformed.

The same sequence of transformations applied to compound **1a** for the synthesis of isoanatabine **4**, was applied to compound **12** for the preparation of anatabine **15**. The 3-pyridylmagnesium chloride was reacted with the α-amino nitrile **12** in THF, giving the *N*-methyl-anatabine **13** with a yield of 83%. Compound **13** was oxidized by *m*-CPBA in dichloromethane, giving the *N*-methyl-anatabine-*N*-oxide **14** with a yield of 88% as a mixture of two diastereomers in a 7:3 ratio. The diastereomers can be separated by chromatography on alumina.

The *N*-demethylation of **14** was made on the mixture of diastereomers by their decomposition at 10°C in methanol containing 2 equiv of $FeSO_4 \cdot 7H_2O$ leading to the anatabine **15** with a yield of 44%. It was accompanied by the formation of 44% of *N*-methyl-anatabine **13**, product of deoxygenation of the *N*-oxide **14** which could be recovered from the reaction mixture.

## EXPERIMENTAL

**General.** ESI-HRMS were performed on an Agilent 6210 TOF mass spectrometer. GC/CI analyses were performed on a Thermo Trace GC DSQ–Single Quadrupole. The $^1$H NMR spectra were recorded in $CDCl_3$ at 300 MHz with a Varian Mercury 300 and are reported in ppm from internal TMS on the δ scale. The $^{13}$C NMR spectra were recorded in $CDCl_3$ at 75.4 MHz with a Varian Mercury 300 instrument. The IR spectra were recorded with a Bruker Vector 22 instrument as films on a NaCl disk. Thin layer chromatography analyses (TLC) were performed with 0.20 mm Silica Gel 60, F-254 precoated plates (Selecto Scientific). Chromatographies were performed on silica gel columns (Fisher, Silica Gel Sorbent, 230–400 Mesh) using the flash technique or on alumina (Aluminoxid 90, Activity II–III, EMD).

***(±)-1-Methyl-2-(3-pyridyl)-3-piperideine: (±)-N-methyl-isoanatabine, 3a.*** 3-Bromopyridine (598 μL, 981 mg, 6.22 mmol) was added to *i*-PrMgCl (2*M*/THF, 3.11 mL, 6.22 mmol) in THF (1 mL) at room temperature under argon. After 2 h, the mixture was cooled at −10°C, then a solution of **1a** (152 mg, 1.24 mmol) in THF (2 mL) was added. The resulting reaction mixture was allowed to stir for 1 h at −10°C then left overnight at room temperature. After 16 h, water (5 mL) was added. Extraction with $CH_2Cl_2$ (3 × 10 mL), drying over magnesium sulfate and column chromatography using $CH_2Cl_2$/$CH_3OH/NH_3$ (95:5:1) as eluent afforded (±)-*N*-methyl-isoanatabine, **3a** (167 mg, 0.96 mmol, 77%). IR (NaCl): 3031, 2945, 2785, 1650, 1577, 1425, 1362, 1281, 1057, 850 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, 1H, $J$ = 2.4 Hz, ArH), 8.50 (dd, 1H, $J$ = 1.8, 4.8 Hz, ArH), 7.68 (dt, 1H, $J$ = 1.8, 7.8 Hz, ArH), 7.25 (ddd, 1H, $J$ = 0.6, 4.8, 7.8 Hz, ArH), 5.86 (m, 1H, C*H*=CH), 5.45 (dq, 1H, $J$ = 1.5, 9.9 Hz, CH=C*H*), 3.66 (app quintet, 1H, $J$ = 1.2 Hz, NC*H*Ar), 2.93 (m, 1H, NC$H_2$), 2.50 (m, 2 H, NC$H_2$ + C$H_2$—CH=CH), 2.12 (m, 1H, C$H_2$—CH=CH). $^{13}$C NMR (75.3 MHz, $CDCl_3$): δ 150.3 (CH), 149.0 (CH), 138.7 (C), 136.3 (CH), 129.3 (CH), 125.5 (CH), 123.8 (CH), 65.9 (CH), 51.9 ($CH_2$), 44.0 ($CH_3$), 26.2 ($CH_2$). ESI-HRMS: $m/z$ = 175.1244 (calculated for $[M + H]^+$: 175.1230); 197.1064 (calculated for $[M + Na]^+$: 197.1049); 371.2228 (calculated for $[2M + Na]^+$: 371.2206).

***(±)-1-Benzyl-2-(3-pyridyl)-3-piperideine: (±)-N-Benzyl-isoanatabine, 3b.*** 3-Bromopyridine (130 μL, 213 mg, 1.35 mmol) was added to *i*-PrMgCl (2*M*/THF, 675 μL, 1.35 mmol) in THF (1 mL) at room temperature under argon. After 2 h, the mixture was cooled at 0°C, then a solution of **1b** (51 mg, 0.26 mmol) in THF (1 mL) was added. The resulting reaction mixture was stirred overnight at room temperature. After 16 h, water (5 mL) was added. Extraction with $CH_2Cl_2$ (3 × 10 mL), drying over magnesium sulfate and column chromatography using $CH_2Cl_2/CH_3OH/NH_3$ (97:3:1) as eluent afforded **3b** (43 mg, 0.17 mmol, 67%). IR (NaCl): 3029, 2918, 2707, 1655, 1576, 1424, 1027, 849 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, 1H, $J$ = 2.1 Hz, ArH), 8.49 (dd, 1H, $J$ = 1.8, 4.8 Hz, ArH), 7.80 (dt, 1H, $J$ = 2.1, 7.8 Hz, ArH), 7.26 (ddd, 1H, $J$ = 0.6, 4.8, 7.8 Hz, ArH), 5.85 (m, 1H, C*H*=CH), 5.49 (dq, 1H, $J$ = 1.5, 9.9 Hz, CH=C*H*), 4.00 (app quintet, 1H, $J$ = 2.4 Hz, NC*H*Ar), 3.52 (d, $J$ = 13.5 Hz, 1H, C$H_2$ (Bn)), 3.43 (d, $J$ = 13.5 Hz, 1H, C$H_2$ (Bn)), 2.93 (m, 1H, NC$H_2$), 2.41–2.25 (m, 2H, NC$H_2$ + C$H_2$—CH=CH), 2.06 (bd, 1H, $J$ = 14.1 Hz, C$H_2$—CH=CH). $^{13}$C NMR (75.3 MHz, $CDCl_3$): δ = 150.4, 148.9, 139.4, 139.2, 136.3, 129.6, 128.8, 128.4, 127.1, 125.7, 123.8, 63.8, 59.0, 47.3, 25.9. ESI-HRMS: $m/z$ = 251.1567 (calculated for $[M + H]^+$: 251.1543); 273.1372 (calculated for $[M + Na]^+$: 273.1362).

**Assays of *N*-demethylation of (±)-*N*-methyl-isoanatabine 3a and *N*-debenzylation of (±)-*N*-benzyl-isoanatabine 3b with 1-chloroethyl chloroformate.**

***Attempted N-demethylation of (±)-N-methyl-isoanatabine 3a.*** 1-Chloroethyl chloroformate (80 μL, 106 mg, 0.74 mmol) was added at 0°C to a stirred solution of **3a** (107 mg, 0.61 mmol) in dry 1,2-dichloroethane (6 mL) under argon. The resulting mixture was heated to reflux for 16 h. The solvent was removed under reduced pressure to give the *N*-[5-chloro-5-(pyridin-3-yl)-pent-3-enyl]-*N*-

methyl-carbamic acid 1-chloro-ethyl ester (**7**). **7** was dissolved in 40 mL of 2.5% sodium hydroxide in aqueous ethanol (1:9) at 0°C; after 1 h at 0°C, the mixture was stirred at room temperature during 24 h. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to yield **3a** as yellow oil (80.3 mg, 0.46 mmol, 75%). *N*-[5-chloro-5-(pyridin-3-yl)-pent-3-enyl]-*N*-methyl-carbamic acid 1-chloro-ethyl ester (**7**): $^1$H NMR (300 MHz, $CDCl_3$): δ 9.06 (m, 1H, ArH), 8.83 (d, 1H, $J$ = 4.5 Hz, ArH), 8.54 (d, 1H, $J$ = 8.4 Hz, ArH), 8.05 (m, 1H, ArH), 6.89 (m, 1H, CH=CH), 6.74 (m, 1H, CH=CH), 6.57 (m, 1H, *CH*ClCH$_3$), 4.66 (app quint., 1H, NC*H*Ar), 3.49 (m, 2H, NC*H*$_2$), 2.99 (s, 3H, NCH$_3$), 2.21 (m, 2H, C*H*$_2$—CH=CH), 1.83 (d, 3H, $J$ = 5.7 Hz, CHCl*CH*$_3$). - $^{13}$C NMR (75.3 MHz, $CDCl_3$): δ 153.5 (CO), 153.3 (CO), 142.5 (CH), 139.4 (CH), 139.0 (CH), 137.0 (CH), 136.9 (CH), 136.2 (C), 127.3 (CH), 125.0 (CH), 124.8 (CH), 124.7 (CH), 124.1 (CH), 83.3 (CH), 58.4 (CH), 46.7 ($CH_2$), 45.9 ($CH_2$), 36.2 ($CH_2$), 35.6 ($CH_2$), 35.4 ($CH_2$), 34.7 ($CH_2$), 25.4 ($CH_3$), 25.1 ($CH_3$).

***Attempted N-debenzylation of (±)-N-benzyl-isoanatabine 3b.*** 1-Chloroethyl chloroformate (9 μL, 12 mg, 0.08 mmol) was added at 0°C to a stirred solution of **3b** (21 mg, 0.08 mmol) in dry dichloromethane (3 mL) under argon. The resulting mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure to give the 1-chloro-1-(3-pyridyl)-5-benzylamino-pent-2-en (**9**). Compound **9** was then stirred with 5 mL of 2.5% sodium hydroxide in aqueous ethanol (1:9) at 0°C; after 1 h at 0°C, the mixture was stirred at room temperature during 5 h. The mixture was extracted with dichloromethane (3 × 7 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to yield **3b** as a yellow oil (15.6 mg, 0.06 mmol, 78%). 1-Chloro-1-(3-pyridyl)-5-benzylamino-pent-2-en (**9**): $^1$H NMR (300 MHz, $CDCl_3$): δ 9.73 (bs, 1H, ArH), 9.32 (bs, 1H, ArH), 8.73 (bs, 1H, ArH), 8.03 (bs, 1 H, ArH), 7.74 (bs, 2 H, ArH), 7.35 (s, 3 H, Bn-H), 6.32 (bs, 1 H), 6.03 (bs, 1 H), 5.72 (bs, 1 H), 4.64 (bs, 2 H), 3.40 (bs, 1 H), 3.23 (bs, 1 H), 3.05 (m, 1 H), 2.42 (m, 1 H). The ESI-MS of **9** indicated polymeric material; this probably arised in the MS apparatus by the intermolecular substitution in **9** of the chlorine by the amino group. On the other hand, the GC-MS of **9** gave the MS spectrum of **3b**; at the temperature of the GC column oven (Rxi-5ms column, program: injector 200°C, detector 280°C, program: 40°C (1 min), 30°C/min to 280°C, 280°C (15 min); RT:12.08 min), **9** spontaneously cyclized into **3b** by the intramolecular substitution of the chlorine by the amino group.

**Assay for the *N*-debenzylation of (±)-*N*-benzyl-isoanatabine 3b with CAN (ammonium cerium (IV) nitrate).** To compound **3b** (37 mg, 0.15 mmol), dissolved in a 5:1 mixture of $CH_3CN$-$H_2O$ (2.4 mL), CAN (329 mg, 0.60 mmol) was added portionwise. After stirring 24 h at room temperature, the mixture was basified with an aqueous saturated solution of $NaHCO_3$ and then extracted with $CH_2Cl_2$. The organic phase was dried ($MgSO_4$), filtered, and concentrated *under vacuo* to obtain the starting compound **3b** (33 mg, 0.13 mmol, 88%).

***(±)-N-methyl-isoanatabine-N-oxide, 10.*** To a solution of **3a** (206 mg, 1.18 mmol) in $CH_2Cl_2$ (6 mL) at 0°C was added a solution of 70–75% aq. *m*-CPBA (320 mg, 1.3 mmol) in $CH_2Cl_2$ (11 mL). After stirring 1.5 h at 0°C under argon, the reaction mixture was concentrated *in vacuo* to a volume of 7 mL and then poured over alumina and chromatographed using $CH_2Cl_2$/$CH_3OH$ (95:5) as eluent to afford the *N*-oxide **10** as a mixture of two diastereomers in a 6:4 ratio (204 mg, 1.07 mmol, 91%). The diastereomers were not separated and were used in the next step as a mixture. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.76 (d, 0.6 H, $J$ = 1.8 Hz, ArH), 8.68 (dd, 0.6 H, $J$ = 1.8, 4.8 Hz, ArH), 8.64 (d, 0.4 H, $J$ = 1.5 Hz, ArH), 8.63 (dd, 0.4 H, $J$ = 1.5, 4.8 Hz, ArH), 8.10 (dt, 0.4 H, $J$ = 2.1, 7.8 Hz, ArH), 7.97 (dt, 0.6 H, $J$ = 1.8, 7.8 Hz, ArH), 7.40 (ddd, 0.6 H, $J$ = 0.6, 4.8, 7.8 Hz, ArH), 7.36 (ddd, 0.4 H, $J$ = 0.6, 4.8, 7.8 Hz, ArH), 6.18 (m, 1H, C*H*=CH), 5.84 (dq, 0.6 H, $J$ = 1.8, 10.2 Hz, CH=C*H*), 5.66 (dq, 0.4 H, $J$ = 2.1, 10.5 Hz, CH=C*H*), 5.07 (app quintet, 0.6 H, $J$ = 2.7 Hz, NC*H*Ar), 4.90 (app quintet, 0.4 H, $J$ = 2.4 Hz, NC*H*Ar), 3.60 (m, 1.2 H, NC*H*$_2$), 3.43 (m, 0.8 H, NC*H*$_2$), 3.19 (s, 1.2 H, NC*H*$_3$), 2.92 (m, 0.6 H, C*H*$_2$CH=CH), 2.75 (s, 1.8 H, NC*H*$_3$), 2.58 (m, 1H, C*H*$_2$CH=CH), 2.41 (m, 0.4 H, C*H*$_2$CH=CH). $^{13}$C NMR ($CDCl_3$): Major diastereomer, δ 151.5 (CH), 150.5 (CH), 139.0 (CH), 129.1 (C), 126.4 (CH), 123.8 (CH), 123.1 (CH), 76.4 (CH), 64.2 ($CH_2$), 51.1 ($CH_3$), 24.1 ($CH_2$). $^{13}$C NMR ($CDCl_3$): Minor diastereomer, δ 152.0 (CH), 150.1 (CH), 139.8 (CH), 129.3 (C), 126.3 (CH), 123.6 (CH), 122.9 (CH), 73.2 (CH), 61.9 ($CH_2$), 56.9 ($CH_3$), 23.2 ($CH_2$). ESI-HRMS: $m/z$ = 191.1192 (calculated for $[M + H]^+$: 191.1179); 213.1006 (calculated for $[M + Na]^+$: 213.0998); 381.2312 (calculated for $[2M + H]^+$: 381.2285); 403.2114 (calculated for $[2M + Na]^+$: 403.2104).

**Attempted *N*-demethylation of (±)-*N*-methyl-isoanatabine-*N*-oxide 10.** ***With selenium dioxide.*** To a stirred mixture of **10** (193 mg, 1.02 mmol) in 95% ethanol (10 mL) was added portionwise selenium dioxide (169 mg, 1.52 mmol) for 10 min. The mixture was heated to reflux for 4 h under an atmosphere of argon. The reaction was monitored by TLC. After 4 h, the starting material was still present. The mixture was

refluxed for 4 h more. The residue obtained by evaporation of the reaction mixture was purified by column chromatography through silica gel column, using $CH_2Cl_2/CH_3OH/NH_3$ (90:10:1) as eluent to give 115 mg (0.66 mmol, 65%) of **3a** and 19 mg (0.1 mmol, 10%) of **10**.

***With $FeSO_4 \cdot 7H_2O$.*** *N*-oxide **10** (95 mg, 0.50 mmol) was dissolved in MeOH (10 mL) and cooled at 10°C. $FeSO_4 \cdot 7H_2O$ (278 mg, 1 mmol) was added then the reaction mixture was stirred at 10°C for 1.5 h. Evaporation of the solvent afforded an orange solid, which was dissolved in 0.1*M* EDTA. Then, the pH was raised to 10 by addition of concentrated $NH_4OH$. The solution was extracted with $CHCl_3$ (3 × 20 mL), and the dried organic extracts over $MgSO_4$ were filtered and evaporated to yield a mixture of **4** and **3a** (2.3:1). These were separated by column chromatography on silica gel using $CH_2Cl_2/CH_3OH/NH_3$ (90:10:1) as an eluent. Pure (±)-isoanatabine (**4**) was obtained with a yield of 55% (44 mg, 0.28 mmol); pure (±)-*N*-methyl-isoanatabine (**3a**) was obtained with a yield of 23% (20 mg, 0.12 mmol). (±)-Isoanatabine (**4**): IR (NaCl): 3285, 3029, 2914, 2832, 1650, 1578, 1477, 1102, 1028, 716 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.59 (d, 1H, $J$ = 1.8 Hz, ArH), 8.51 (dd, 1H, $J$ = 1.5, 4.8 Hz, ArH), 7.70 (dt, 1H, $J$ = 1.5, 7.5 Hz, ArH), 7.25 (ddd, 1H, $J$ = 0.9, 5.1, 7.8 Hz, ArH), 6.01 (m, 1H, C*H*=CH), 5.71 (dq, 1H, $J$ = 1.8, 9.3 Hz, CH=C*H*), 4.52 (app quintet, 1H, $J$ = 2.7 Hz, NHC*H*Ar), 3.0 (m, 2 H, $NHCH_2$), 2.2 (m, 3 H, $CH_2$CH=CH + N*H*). $^{13}C$ NMR (75.3 MHz, $CDCl_3$): δ 149.7 (CH), 149.0 (CH), 139.3 (C), 135.6 (CH), 128.9 (CH), 127.6 (CH), 123.7 (CH), 56.2 (CH), 41.9 ($CH_2$), 25.7 ($CH_2$). ESI-HRMS: $m/z$ = 161.1087 (calculated for $[M + H]^+$: 161.1073); 183.0893 (calculated for $[M + Na]^+$: 183.0893).

***(±)-2-Cyano-1-methyl-4-piperideine, 12.*** To a stirred solution of potassium cyanide (5.45 g, 83.6 mmol) in water (11 mL) layered with ether (16 mL) was added a solution of 5*N* HCl (6.5 mL, 32.5 mmol). The mixture was stirred at 0°C, then 1-methylpyridinium iodide (5 g, 22.6 mmol) was added portionwise followed by $NaBH_4$ (1.03 g, 27.1 mmol). The stirring was continued for 5 h at room temperature. Water was added and the mixture was extracted with ether. The organic phases were combined, dried and evaporated to dryness. The resulting yellow oil was flash chromatographed on silica gel ($CH_2Cl_2/CH_3OH$ 95:5 + 1% conc. $NH_4OH$). This yielded **12** (2.62 g, 21.5 mmol, 95%) as a colorless oil. IR (NaCl): 3043, 2945, 2789, 2223, 1658, 1452, 1260, 1141, 1002, 793 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 5.74 (m, 2H, C*H*=C*H*), 3.81 (dd, 1H, $J$ = 1.5, 6 Hz, NC*H*CN), 3.24 (bd, 1H, $J$ = 16.5 Hz, $NCH_2$), 2.96 (bd, 1H, $J$ = 16.5 Hz, $NCH_2$), 2.69 (m, 1H, $CH_2$—CH=CH), 2.44 (s, 3H, $NCH_3$), 2.33 (m, 1H, $CH_2$—CH=CH). $^{13}C$ NMR (75.3 MHz, $CDCl_3$): δ 125.5 (CH), 120.9 (CH), 116.3 (CN), 51.2 (CH), 50.0 ($CH_2$), 43.6 ($CH_3$), 29.5 ($CH_2$). ESI-HRMS: $m/z$ = 123.0925 (calculated for $[M + H]^+$: 123.0917); 145.0745 (calculated for $[M + Na]^+$: 145.0736).

**Attempt of isomerization of 12 into 1a.** The amino nitrile **12** (52 mg, 0.43 mmol) in 1 mL of 6*N* HCl was heated at 80°C. After refluxing for 4 h, the mixture was cooled and enough aqueous sodium cyanide was added until the final solution was alkaline (pH 10). After stirring for 2 h, the mixture was extracted by $CH_2Cl_2$ (3 × 10 mL). The $CH_2Cl_2$ extracts were combined, dried over $MgSO_4$ and concentrated to yield the starting amino nitrile **12** (48 mg, 0.39 mmol, 92%).

**(±)-1-Methyl-2-(3-pyridyl)-4-piperideine: (±)-*N*-methyl-anatabine, 13.** 3-Bromopyridine (210 μL, 346 mg, 2.19 mmol) was added to *i*-PrMgCl (2*M*/THF, 1.1 mL, 2.19 mmol) in THF (1 mL) at room temperature under argon. After 2 h, the mixture was cooled at −10°C, then a solution of **12** (89 mg, 0.73 mmol) in THF (2 mL) was added. The resulting reaction mixture was allowed to stir for 1 h at −10°C then left overnight at room temperature. After 16 h, water (5 mL) was added. Extraction with $CH_2Cl_2$ (3 × 10 mL), drying over magnesium sulfate and column chromatography using $CH_2Cl_2/CH_3OH/NH_3$ (95:5:1) as eluent afforded (±)-*N*-methyl-anatabine **13** (106 mg, 0.61 mmol, 83%). IR (NaCl): 3034, 2985, 2910, 2773, 1666, 1577, 1427, 1321, 1258, 1051, 718 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.53 (d, $J$ = 2.1 Hz, 1H, ArH), 8.52 (dd, $J$ = 1.8, 5.1 Hz, 1H, ArH), 7.70 (dt, $J$ = 2.1, 7.8 Hz, ArH), 7.29 (ddd, 1H, $J$ = 0.6, 4.8, 7.8 Hz, ArH), 5.80 (m, 2H, C*H*=C*H*), 3.35 (m, 2H, $NCH_2$ + NC*H*Ar), 2.95 (m, 1H, $NCH_2$), 2.32 (m, 2H, $CH_2$—CH=CH), 2.07 (s, 3H, $NCH_3$). $^{13}C$ NMR (75.3 MHz, $CDCl_3$): δ 149.8 (CH), 149.0 (CH), 138.6 (C), 135.6 (CH), 125.5 (CH), 124.9 (CH), 123.9 (CH), 63.1 (CH), 55.2 ($CH_2$), 44.6 ($CH_3$), 35.3 ($CH_2$). ESI-HRMS: $m/z$ = 175.1223 (calculated for $[M + H]^+$: 175.1230).

**(±)-1-Methyl-2-(3-pyridyl)-4-piperideine-*N*-oxide: (±)-*N*-methyl-anatabine-*N*-oxide, 14.** To a solution of **13** (210 mg, 1.2 mmol) in $CH_2Cl_2$ (17 mL) at 0°C was added, in several portions, 70–75% aq. *m*-CPBA (327 mg, 1.33 mmol). After stirring 1.5 h at 0°C under argon, the reaction mixture was concentrated *in vacuo* to a volume of 3 mL and then poured over alumina and chromatographed using $CH_2Cl_2/CH_3OH$ (95:5) as eluent to afford the *N*-oxide **14** as a mixture of two diastereomers in a 7:3 ratio. The major diastereomer was isolated as a white solid and the minor diastereomer as an oil (combined 200 mg, 1.06 mmol, 88%). Major diastereomer, $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.68 (d, $J$ = 1.8 Hz, 1H, ArH), 8.64 (dd, $J$ = 1.5, 4.8 Hz, 1H, ArH), 8.40

(bd, $J$ = 7.8 Hz, 1H, ArH), 7.37 (dd, $J$ = 4.5, 8.1 Hz, 1H, ArH), 6.07 (m, 1H, CH=C*H*), 5.72 (m, 1H, CH=C*H*), 4.27 (dd, $J$ = 4.2, 10.8 Hz, 1H, NC*H*Ar), 4.16 (m, 1H, NC$H_2$), 3.92 (m, 1H, NC$H_2$), 3.24 (m, 1H, C$H_2$—CH=CH), 2.93 (s, 3H, NC$H_3$), 2.32 (m, 1H, C$H_2$—CH=CH). $^{13}$C NMR (75.3 MHz, $CDCl_3$): δ 150.9 (CH), 150.8 (CH), 137.8 (CH), 131.0 (C), 125.9 (CH), 123.7 (CH), 120.2 (CH), 71.4 (CH), 68.8 ($CH_2$), 58.6 ($CH_3$), 30.1 ($CH_2$). Minor diastereomer, $^1$H NMR (300 MHz, $CDCl_3$): δ 8.82 (d, $J$ = 2.1 Hz, 1H, ArH), 8.66 (dd, $J$ = 1.2, 4.8 Hz, 1H, ArH), 7.97 (dt, $J$ = 2.1, 8.1 Hz, 1H, ArH), 7.36 (dd, $J$ = 4.8, 8.1 Hz, 1H, ArH), 6.08 (m, 1H, CH=C*H*), 5.83 (m, 1H, CH=C*H*), 4.47 (m, 1H, NC*H*Ar), 4.15 (m, 1H, NC$H_2$), 3.97 (m, 1H, NC$H_2$), 2.98 (s, 3H, NC$H_3$), 2.31 (m, 2H, C$H_2$—CH=CH). $^{13}$C NMR (75.3 MHz, $CDCl_3$): δ 151.1 (CH), 150.8 (CH), 138.3 (CH), 129.7 (C), 124.9 (CH), 123.3 (CH), 121.9 (CH), 73.7 (CH), 68.5 ($CH_2$), 51.7 ($CH_3$), 29.1 ($CH_2$). ESI-HRMS (diastereomers): $m/z$ = 191.1176 (calculated for $[M + H]^+$: 191.1179); 213.0998 (calculated for $[M + Na]^+$: 213.0998); 381.2304 (calculated for $[2M + H]^+$: 381.2285); 403.2134 (calculated for $[2M + Na]^+$: 403.2104).

**(±)-2-(3-Pyridyl)-4-piperideine: (±)-Anatabine, 15.** A mixture of diastereomeric *N*-oxide **14** (171 mg, 0.9 mmol) was dissolved in MeOH (15 mL) and cooled at 10°C. $FeSO_4 \cdot 7H_2O$ (500 mg, 1.8 mmol) was added and the reaction mixture was stirred at 10°C for 3 h. Evaporation of the solvent afforded an orange solid which was dissolved in 0.1*M* EDTA (30 mL), then the pH was raised to 10 by addition of concentrated $NH_4OH$. The solution was extracted with $CHCl_3$ (3 × 30 mL), and the dried organic extracts over $MgSO_4$ were filtered and evaporated to yield a mixture of anatabine **15** and (±)-*N*-methyl-anatabine **13** (1:1). These were separated by flash column chromatography using $CH_2Cl_2/CH_3OH/NH_3$ (95:5:1) as eluent. Pure (±)-anatabine (**15**) was obtained in 44% yield (60 mg, 0.4 mmol); pure (±)-*N*-methyl-anatabine (**13**) was obtained with a yield of 44% (70 mg, 0.4 mmol). (±)-Anatabine **15**: IR (NaCl): 3280, 3031, 2916, 2830, 1655, 1578, 1427, 1311, 1100, 807 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, $J$ = 2.1 Hz, 1H, ArH), 8.52 (dd, $J$ = 1.8, 4.8 Hz, 1H, ArH), 7.73 (dt, $J$ = 2.1, 7.8 Hz, ArH), 7.27 (ddd, 1H, $J$ = 0.6, 5.1, 8.1 Hz, ArH), 5.84 (m, 2H, C*H*=C*H*), 3.90 (t, 1H, $J$ = 7.2 Hz, NC*H*Ar), 3.64 (bd, $J$ = 15.0 Hz, 1H, NC$H_2$), 3.49 (bd, $J$ = 15.0 Hz, 1H, NC$H_2$), 2.27 (m, 2H, C$H_2$—CH=CH). $^{13}$C NMR (75.3 MHz, $CDCl_3$): δ 148.9 (CH), 148.8 (CH), 140.1 (C), 134.3 (CH), 126.5 (CH), 125.3 (CH), 123.7 (CH), 55.5 (CH), 46.2 ($CH_2$), 34.1 ($CH_2$). ESI-HRMS: $m/z$ = 161.1084 (calculated for $[M + H]^+$: 161.1078).

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## REFERENCES AND NOTES

[1] Leete, E.; Mueller, M. E. J Am Chem Soc 1982, 104, 6440.
[2] Brennan, M. B. Chem Eng News 2000, 78, 23.
[3] Kem, W. R.; Scott, K. N.; Duncan, J. H. Experientia 1976, 32, 684.
[4] Kem, W. R.; Soti, F.; Rouchaud, A.; Rocca, J.; Johnson, J. IUPAC Mtg on Marine Natural Products; Prince Edward Island, 2008, p32.
[5] Flann, C.; Malone, T. C.; Overman, L. E. J Am Chem Soc 1987, 109, 6097.
[6] Quan, P. M.; Karns, T. K. B.; Quin, L. D. J Org Chem 1965, 30, 2769.
[7] Deo, N. M.; Crooks, P. A. Tetrahedron Lett 1996, 37, 1137.
[8] Felpin, F. X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. J Org Chem 2001, 66, 6305.
[9] Balasubramanian, T.; Hassner, A. Tetrahedron Asym 1998, 9, 2201.
[10] Ayers, J. T.; Xu, R.; Dwoskin, L. P.; Crooks, P. A. AAPS J 2005, 7, E752.
[11] Mehmandoust, M.; Marazano, C.; Das, B. C. J Chem Soc Chem Commun 1989, 1185.
[12] (a) Lansbury, P.T.; Peterson, J. O. J Am Chem Soc 1963, 85, 2236; (b) Tanner, D. D.; Yang, C.-M. J Org Chem 1993, 58, 1840; (c) Yang, C.-M.; Tanner, D. D. Can J Chem 1997, 75, 616.
[13] Grierson, D. S.; Harris, M.; Husson, H. P. J Am Chem Soc 1980, 102, 1064.
[14] Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H. P. J Org Chem 1984, 49, 2392.
[15] (a) Bruylants, P. Bull Soc Chim Belg 1924, 33, 467; (b) Agami, C.; Couty, F.; Evano, G. Org Lett 2000, 2, 2085; (c) Rouchaud, A.; Braekman, J.-C. Eur J Org Chem 2009, 2666.
[16] (a) Trecourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F., Queguiner, G. Tetrahedron Lett 1999, 40, 4339; (b) Lin, W.; Ilgen, F.; Knochel, P. Tetrahedron Lett 2006, 47, 1941; (c) Ren, H.; Knochel, P. Chem Commun 2006, 726; (d) Kloetzing, R. J.; Krasovskiy, A.; Knochel, P. Chem Eur J 2007, 13, 215.
[17] (a) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. J Med Chem 1987, 30, 871; (b) Cama, L. D.; Wildonger, K. J.; Guthikonda, R. N.; Ratcliffe, R. W.; Christensen, B. G. Tetrahedron 1983, 39, 2531.
[18] Passarella, D.; Favia R.; Giardini, A.; Lesma, G.; Martinelli, M.; Silvani, A.; Danieli B.; Efange, S. M. N.; Mash, D. C. Bioorg Med Chem 2003, 11, 1007.
[19] (a) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. J Org Chem 1984, 49, 2081; (b) Kapnang, H.; Charles, G. Tetrahedron Lett 1983, 24, 3233.
[20] Hootele, C.; Lenders, J. P. Chimia 1974, 28, 665.
[21] Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, G. Bull Chem Soc Jpn 1985, 58, 1413.
[22] (a) Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. J Chem Soc Perkin Trans 1 2002, 1858; (b) Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. J Chem Soc Perkin Trans 1 2001, 3106; (c) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. J Chem Soc Perkin Trans 1 2000, 3765.
[23] (a) Musina, L. A.; Shults, E. E.; Krichevskii, L. A.; Adekenov, S. M.; Shakirov, M. M.; Tolstikov, G. A. Russ Chem Bull Int Ed

2006, 55, 331; (b) Sashida, H.; Tsuchiya, T. Chem Pharm Bull 1984, 32, 4117.

[24] (a) Grierson, D. Org React 1990, 39, 85; (b) Ferris, J. P.; Gerwe, R. D.; Gapski, G. R. J Am Chem Soc 1967, 89, 5270; (c) Ferris, J. P.; Gerwe, R. D.; Gapski, G. R. J Org Chem 1968, 33, 3493.

[25] McCamley, K.; Ripper, J. A.; Singer, R. D.; Scammells, P. J. J Org Chem 2003, 68, 9847.

[26] Dong, Z.; Scammells, P. J. J Org Chem 2007, 72, 9881.

[27] Monkovic, I.; Wong, H.; Bachand, C. Synthesis 1985, 770.

[28] Lee, H. W.; Ahn, J. B.; Lee, J. H.; Kang, S. K.; Ahn, S. K.; Ha, D. C. Heterocycles 2006, 68, 915.

[29] Craig, J. C.; Mary, N. Y.; Wolf, L. J Org Chem 1964, 29, 2868.

[30] Craig, C. J.; Dwyer, F. P.; Glazer, A. N.; Horning, E. C. J Am Chem Soc 1961, 83, 1871.

[31] Aggarwal, S.; Ghosh, N. N.; Aneja, R.; Joshi, H.; Chandra, R. Helv Chim Acta 2002, 85, 2458.

[32] Craig, J. C.; Mary, N. Y.; Goldman, N. L.; Wolf, L. J Am Chem Soc 1964, 86, 3866.

[33] Kawano, Y.; Otsubo, K.; Matsubara, J.; Kitano, K.; Ohtani, T.; Morita, S.; Uchida, M. Heterocycles 1999, 50, 17.

[34] Mary, A.; Renko, D. Z.; Guillou, C.; Thal, C. Tetrahedron Lett 1997, 38, 5151.

[35] Huang, W. J.; Chen, C. H.; Singh, O. V.; Lee, S. L.; Lee, S. S. Synth Commun 2002, 32, 3681.

[36] Chapman, R. F.; Phillips, N. I. J.; Ward, R. S. Tetrahedron 1985, 41, 5229.

[37] (a) Fry, E. M. J Org Chem 1963, 28, 1869; (b) Fry, E. M. J Org Chem 1964, 29, 1647.

# Synthesis of Some Novel *N*-Alkyl/Acyl/Aroyl 2-(Chroman/6-bromochroman-2-yl)-1*H*-benzimidazoles Using Ionic Liquids and Their Antibacterial Activity

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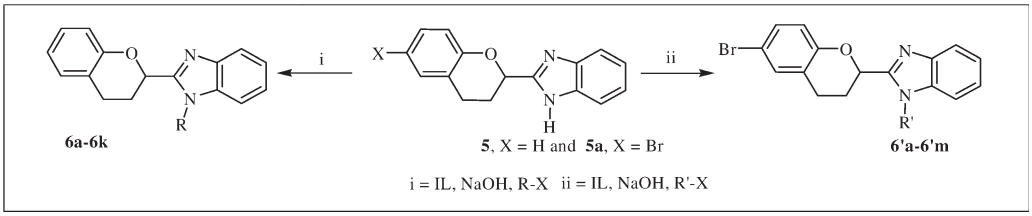


Synthesis of some novel *N*-substituted 2-(chroman/6-bromochroman-2-yl)-1*H*-benzimidazoles by the condensation of 3,4-dihydro-2*H*-chroman-2-carboxylic acid and 6-bromo-3,4-dihydro-2*H*-chroman-2-carboxylic acid with *o*-phenylenediamine in ionic liquid (IL) [bmim]$BF_4$ and subsequent reactions at the benzimidazole-NH with different types of electrophiles in ILs [bmim]$BF_4$ = 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]$PF_6$ = 1-butyl-3-methylimidazolium hexafluorophosphate and [buPy]$BF_4$ = butylpyridinium tetrafluoroborate in the presence of sodium hydroxide as a base have been reported. All the synthesized compounds were screened for their antibacterial activity. Some compounds exhibited promising antibacterial activity against *Staphylococcus aureus* and *Salmonella typhimurium* when compared to Cephalexin as a reference standard.

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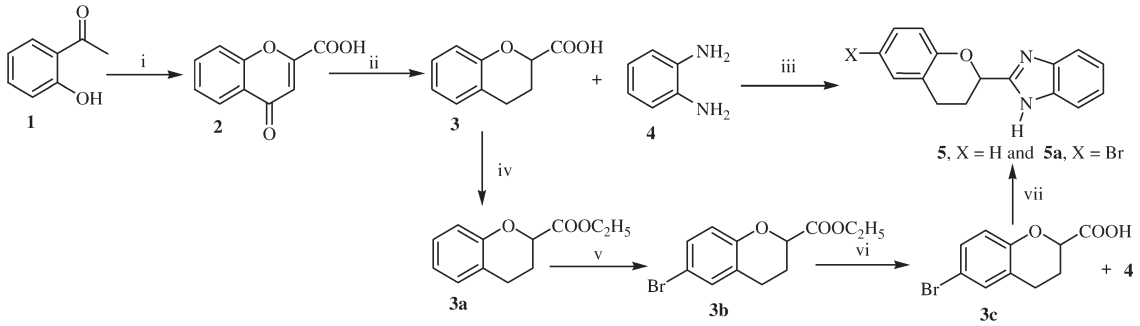
## INTRODUCTION

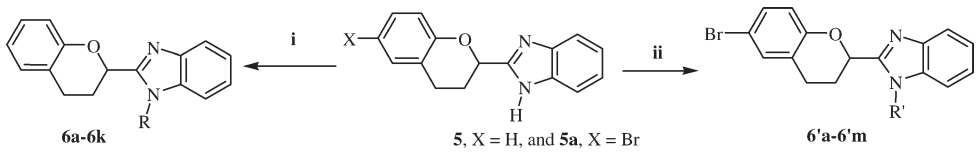
There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Of the wide variety of heterocyclic systems known till date, the nitrogen heterocycles are of great importance and benzimidazole is one amongst such important heterocycles because of its synthetic utility and broad spectrum of pharmacological activity [1–10]. Various substituted benzimidazoles are known to have varied biological activities and among these, 2-substituted benzimidazoles are found to be more potent [11]. The biological activities of benzimidazoles containing compounds have been well documented [12–13]. Despite their wide applicability, available routes for their synthesis are limited. The reported synthesis of benzimidazoles included reactions of aryl acid with *o*-phenylenediamine (OPDA) in conventional [14,15], microwave-assisted [16], and ionic liquids (ILs) [17] methods. The *N*-alkylation and acylation of benzimidazoles has been reported to be accomplished by treatment with an appropriate base such as sodium hydride, sodium hydroxide, potassium carbonate, pyridine, etc. followed by reaction of the resulting salt with an alkylating reagent in various solvents, e.g. acetone, acetonitrile, pyridine, DMF, THF, etc. [18–20].

In the rapidly developing field of synthetic organic chemistry, an efficient, simple, and highly selective synthetic method for widely used organic compounds from readily available reagents is one of the major challenges. ILs are proving to be increasingly promising as viable media not only for potentially 'green' synthesis and separations, but also for novel applications. The unique property set of the IL materials provides new options based on different chemical and physical properties. The room temperature ILs are of special interest as 'green' recyclable alternative to the classical molecular solvents in the synthetic organic chemistry [21–24]. ILs are the best choice for *N*-alkylation of heterocyclic compounds bearing an acidic hydrogen attached to nitrogen. The reports on great improvement in the yields and rates of reaction using ILs [25] prompted us to study the *N*-alkylation and acylation of benzimidazoles in ILs. Hence it was thought that it would be worthwhile to design and synthesize the *N*-substituted benzimidazoles in ILs under environment-friendly conditions and screen them for potential biological activity.

**Scheme 1.** Reagents, i) Diethyl Oxalate, NaOEt, aq.HCl ii) AcOH, $H_2$, Pd/C, 175psi iii) [bmim]$BF_4$, 100°C iv) Ethanolic-HCl v) AcOH, $Br_2$ vi) EtOH/NaOH vii) [bmim]$BF_4$,100°C



**Scheme 2**



i) IL, NaOH, R-X ii) IL, NaOH, R'-X

## RESULTS AND DISCUSSION

Compound **3** was synthesized according to literature procedure in good yield [26]. Condensation of 3,4-dihydro-2*H*-chroman-2-carboxylic acid **(3)** with OPDA **(4)** was carried out in IL [bmim]$BF_4$ at 100°C for 6 h to obtain compound **5** in excellent yield (scheme 1).

For the synthesis of compound **3c**, 3,4-dihydro-2*H*-chroman-2-carboxylic acid **(3)** was treated with ethanolic-HCl at 85°C for 3 h to afford the corresponding ethyl ester derivative **3a** in a reasonable yield. Compound **3a** was brominated using bromine in glacial acetic acid at 25°C for 2 h to obtain 6-bromo-3,4-dihydro-2*H*-chroman-2-carboxylic acid ethyl ester **(3b)**, which

**Table 1a**

Reaction conditions, physical and analytical data of synthesized compounds.

| Sr. No | Substrate | R/R′ | Ionic liquid | Reaction conditions | Product | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|---|---|
| 1 | **5** | $CH_3$—O—CO— | [bmim]$PF_6$ | 50°C, 3 h | **6a** | 75 | 132–133 |
| 2 | **5** | $C_2H_5$—O—CO— | [bupy]$BF_4$ | 50°C, 3 h | **6b** | 71 | 105–107 |
| 3 | **5** | $(CH_3)_2$—CH—$CH_2$—O—CO— | [bmim]$BF_4$ | 50°C, 3 h | **6c** | 77 | 90–92 |
| 4 | **5** | $C_6H_5$—O—CO— | [bmim]$PF_6$ | 50°C, 3 h | **6d** | 85 | 120–121 |
| 5 | **5** | $CH_3$—$SO_2$— | [bmim]$BF_4$ | 60°C, 2 h | **6e** | 82 | 190–192 |
| 6 | **5** | (*p*)—$CH_3$—$C_6H_4$—$SO_2$— | [buPy]$BF_4$ | 60°C, 2 h | **6f** | 73 | 172–173 |
| 7 | **5** | $C_6H_5$—$CH_2$— | [bmim]$BF_4$ | 75°C, 5 h | **6g** | 80 | 128–130 |
| 8 | **5** | (*p*)F—$C_6H_4$—$CH_2$— | [buPy]$BF_4$ | 75°C, 6 h | **6h** | 75 | 120–122 |
| 9 | **5** | (*p*)Br—$C_6H_4$—$CH_2$— | [bmim]$PF_6$ | 75°C, 5 h | **6i** | 76 | 155–157 |
| 10 | **5** | (*p*)$CH_3$—$C_6H_4$—$CH_2$— | [bmim]$BF_4$ | 75°C, 6 h | **6j** | 82 | 176–178 |
| 11 | **5** | (*p*)Tert.butyl—$C_6H_4$—$CH_2$— | [bmim]$BF_4$ | 75°C, 5 h | **6k** | 68 | 150–151 |
| 12 | **5a** | $CH_3$ | [bmim]$BF_4$ | 50°C, 5 h | **6′a** | 70 | 138–140 |
| 13 | **5a** | $C_2H_5$ | [bmim]$BF_4$ | 50°C, 5 h | **6′b** | 80 | 125–127 |
| 14 | **5a** | $CH_3$—O—CO— | [bmim]$PF_6$ | 50°C, 3 h | **6′c** | 73 | 140–141 |
| 15 | **5a** | $C_2H_5$—O—CO— | [buPy]$BF_4$ | 50°C, 3 h | **6′d** | 78 | 148–150 |
| 16 | **5a** | Isobutyl—O—CO— | [bmim]$BF_4$ | 50°C, 3 h | **6′e** | 75 | 120–121 |
| 17 | **5a** | $CH_3$—$SO_2$— | [bmim]$PF_6$ | 60°C, 2 h | **6′f** | 89 | 115–116 |
| 18 | **5a** | (*p*) $CH_3$—$C_6H_4$—$SO_2$— | [bupy]$BF_4$ | 60°C, 2 h | **6′g** | 86 | 140–141 |
| 19 | **5a** | $C_6H_5$—$CH_2$— | [bmim]$BF_4$ | 75°C, 5 h | **6′h** | 78 | 180–182 |
| 20 | **5a** | (*p*) F—$C_6H_4$—$CH_2$— | [buPy]$BF_4$ | 75°C, 6 h | **6′i** | 85 | 210–212 |
| 21 | **5a** | (*p*) Br—$C_6H_4$—$CH_2$— | [bmim]$PF_6$ | 75°C, 5 h | **6′j** | 80 | 178–180 |
| 22 | **5a** | (*p*) $CH_3$—$C_6H_4$—$CH_2$— | [bmim]$BF_4$ | 75°C, 6 h | **6′k** | 84 | 225–226 |
| 23 | **5a** | (*p*)Tert.butyl—$C_6H_4$—$CH_2$— | [bmim]$BF_4$ | 75°C, 5 h | **6′l** | 78 | 166–167 |
| 24 | **5a** | $C_6H_5$—O—CO— | [bmim]$BF_4$ | 50°C, 3 h | **6′m** | 82 | 170–172 |

**Table 1b**

Recycling of [bmim]$BF_4$ for the compound **6g**.

| Number of cycles | Yield (%) |
|---|---|
| 1 | 78 |
| 2 | 75 |
| 3 | 71 |

was further hydrolyzed in ethanol, sodium hydroxide, and 5*N* HCl to give 6-bromo-3,4-dihydro-2*H*-chroman-2-carboxylic acid **(3c)** as a brownish solid. Condensation of **3c** with **4** was carried out in IL [bmim]$BF_4$ at 100°C for 6 h yielded compound **5a** as a white solid.

The *N*-alkylation and acylation of **5** and **5a** with various electrophilic reagents in ILs to obtain the *N*-alkylated/acylated derivatives **6a-6k** and **6′a-6′m** (Scheme 2). The recovered IL was reused successfully with only a slight loss in yield (Table 1b). The structures of newly synthesized compounds were confirmed by IR, $^1$H NMR, $^{13}$C NMR, and mass spectrometry. The physical and spectral data of the compounds **6a-6k** and **6′a-6′m** is presented in experimental section. The synthesized compounds were tested for their antimicrobial activity against two different bacterial species namely, *Staphylococcus aureus* NCIM 5021 and *Salmonella typhimurium* NCIM 2501.

**Table 2**

Antibacterial activity of synthesized compounds **5, 5a, 6a–6k**, and **6′a–6′m** against *S. aureus* NCIM 5021.

| Compound No. | Concentration (μg/mL) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.1 | 1 | 10 | 100 | 200 | 500 | App. MIC |
| **5** | ++ | ++ | + | P | − | − | 10 |
| **6a** | ++ | + | + | P | − | − | 10 |
| **6b** | ++ | ++ | ++ | + | − | − | 100 |
| **6c** | ++ | ++ | + | + | − | − | 10 |
| **6d** | ++ | ++ | + | P | − | − | 10 |
| **6e** | ++ | ++ | ++ | + | − | − | 100 |
| **6f** | ++ | ++ | ++ | + | − | − | 100 |
| **6g** | ++ | ++ | + | P | − | − | 10 |
| **6h** | ++ | ++ | ++ | + | P | − | 100 |
| **6i** | ++ | ++ | + | + | − | − | 100 |
| **6j** | ++ | ++ | + | P | − | − | 10 |
| **6k** | ++ | ++ | ++ | + | − | − | 100 |
| **5a** | ++ | ++ | + | + | P | − | 10 |
| **6′a** | ++ | ++ | ++ | + | P | − | 100 |
| **6′b** | ++ | ++ | ++ | + | P | − | 100 |
| **6′c** | ++ | ++ | ++ | + | P | − | 100 |
| **6′d** | ++ | ++ | ++ | + | P | − | 100 |
| **6′e** | ++ | ++ | ++ | + | P | − | 100 |
| **6′f** | ++ | ++ | + | + | P | − | 10 |
| **6′g** | ++ | + | + | P | P | − | 1 |
| **6′h** | ++ | ++ | + | + | P | − | 10 |
| **6′i** | ++ | ++ | + | + | P | − | 10 |
| **6′j** | ++ | + | P | − | − | − | 1 |
| **6′k** | ++ | ++ | ++ | + | P | − | 100 |
| **6′l** | ++ | ++ | + | + | P | − | 10 |
| **6′m** | ++ | + | + | + | P | − | 1 |
| **Cephalexin** | + | − | − | − | − | − | 0.1 |

**Table 3**

Antibacterial activity of synthesized compounds **5, 5a, 6a–6k**, and **6′a–6′m** against *S. typhimurium* NCIM 2501.

| Compound No. | Concentration (μg/mL) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.1 | 1 | 10 | 100 | 200 | 500 | App. MIC |
| **5** | ++ | ++ | + | P | − | − | 10 |
| **6a** | ++ | ++ | + | + | − | − | 10 |
| **6b** | ++ | ++ | ++ | + | − | P | 100 |
| **6c** | ++ | ++ | ++ | + | − | − | 100 |
| **6d** | ++ | ++ | ++ | + | − | − | 100 |
| **6e** | ++ | ++ | ++ | + | − | − | 100 |
| **6f** | ++ | ++ | ++ | + | − | − | 100 |
| **6g** | ++ | ++ | + | P | − | − | 10 |
| **6h** | ++ | ++ | ++ | + | − | − | 100 |
| **6i** | ++ | ++ | ++ | + | − | − | 100 |
| **6j** | ++ | ++ | ++ | + | − | − | 100 |
| **6k** | ++ | ++ | + | P | − | − | 10 |
| **5a** | ++ | ++ | ++ | ++ | + | − | 200 |
| **6′a** | ++ | ++ | ++ | + | − | − | 100 |
| **6′b** | ++ | ++ | ++ | + | − | − | 100 |
| **6′c** | ++ | ++ | ++ | ++ | + | − | 200 |
| **6′d** | ++ | ++ | ++ | + | − | − | 100 |
| **6′e** | ++ | ++ | ++ | + | P | − | 100 |
| **6′f** | ++ | ++ | + | P | − | − | 10 |
| **6′g** | ++ | ++ | ++ | + | − | − | 100 |
| **6′h** | ++ | ++ | ++ | + | P | − | 100 |
| **6′i** | ++ | ++ | ++ | ++ | + | − | 200 |
| **6′j** | ++ | ++ | ++ | + | P | − | 100 |
| **6′k** | ++ | ++ | ++ | + | P | − | 100 |
| **6′l** | ++ | ++ | ++ | + | P | − | 100 |
| **6′m** | ++ | ++ | ++ | + | P | − | 100 |
| **Cephalexin** | + | − | − | − | − | − | 0.1 |

−, Total inhibition, no growth of organism; P, Poor growth compared to controls; +, Medium growth compared to controls; ++, Confluent growth, no inhibition.

## BIOLOGICAL ACTIVITY

All the compounds prepared herein were screened for their antibacterial activity against *Staphylococcus aureus* NCIM 5021 (Gram positive) and *Salmonella typhimurium* NCIM 2501 (Gram negative) bacterial strains. Cephalexin was used as a reference standard. Antibacterial activity result of compounds **5**, **5a, 6a-6k,** and **6′a-6′m** is summarized in Table 2 and 3. Some of the compounds found to have good antibacterial activity against *S. aureus*; however, they were found to have less activity against *S. typhimurium* when compared to Cephalexin as a reference standard.

## CONCLUSION

In conclusion, we have successfully synthesized a novel series of *N*-substituted 2-(chroman/6-bromo-chroman-2-yl)-1*H*-benzimidazole derivatives by the

condensation of 3,4-dihydro-2*H*-chroman-2-carboxylic acid and 6-bromo-3,4-dihydro-2*H*-chroman-2-carboxylic acid with OPDA and subsequent reactions at the benzimidazole-NH with different electrophilic reagents under different reaction conditions in ILs and tested for antibacterial activity. Some of the compounds **6′g**, **6′j**, 6′m showed the most potent inhibition at 1 μg/mL, where as compounds **5, 6a–6d**, **6g**, **6j** and **5a**, **6′f**, **6′h**, **6′i**, **6′l** were found to possess good activity at 10 μg/mL against *S. aureus* and compounds **5**, **6a**, **6g**, **6k**, **6′f** showed the good activity at 10 μg/mL, where as other compounds showed minimal activity against a *S. typhimurium*.

## EXPERIMENTAL

All the solvents were of commercial grade and OPDA, alkylating and acylating agents were obtained from Aldrich. Melting points were recorded on a MRVIS series, Lab India Instrument and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer in potassium bromide pellets unless otherwise stated. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury VX SWBB 300 MHz spectrometer. Elemental analysis was carried out on a PerkinElmer Series-II C H N S O Analyzer 2400. Chemical shifts are reported in ppm from internal tetramethylsilane (TMS) standard and are given δ units. The solvent for NMR spectra was $CDCl_3$ unless otherwise mentioned. Mass spectra were recorded on *hp* 1100 LC/MSD mass spectrometer (positive and negative APCI ion source, 50–200 V, nitrogen). ILs [bmim]$BF_4$, [bmim]$PF_6$, and [buPy]$BF_4$ were synthesized in the laboratory according to reported procedures [27].

**Synthesis of 6-bromo-3,4-dihydro-2*H*-chroman-2-carboxylic acid (3c).** A solution of (34 mmol) of **3a** dissolved in glacial acetic acid (50 mL) was cooled to 10–15°C. The compound **3a** was brominated by slowly adding a solution of bromine (33 mmol) in glacial acetic acid (25 mL). After the addition was complete, the solution was stirred at 25–30°C for 3 h. The reaction mass was then diluted with water (100 mL). The product was isolated by extraction with ethyl acetate (50 mL × 3). The ethyl acetate layer was washed with 5% aqueous sodium bicarbonate solution (50 mL × 2) and water (50 mL × 2). The ethyl acetate layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to obtain 6-bromo-3,4-dihydro-2*H*-chroman-2-carboxylic acid ethyl ester **(3b)**.

A solution of (67 mmol) of **3b** dissolved in ethanol (25 mL) was hydrolysed by 0.5*M* sodium hydroxide solution (25 mL) at 25–30°C for 1 h. The solution was concentrated to about its half volume and acidified with 5*N* hydrochloric acid. The resultant solid was filtered to give **3c,** 4.5 g, Yield 85%; mp 170–172°C; $^1$H NMR ($CDCl_3$) (300 MHz): δ 2.13–2.25 (m, 2H, $CH_2$), 2.29–2.37 (m, 1H, CH), 2.72–2.91 (m, 2H, $CH_2$), 4.79 (dd, 1H, $J$ = 7.8, 7.8 Hz, CH), 6.81 (d, 1H, $J$ = 9 Hz, Ar-H), 7.19–7.26 (m, 2H, Ar-H), 11.63 (s, 1H, COOH).

**Synthesis of 2-(chroman-2-yl)-1*H*-benzimidazole using IL (5).** A solution of (10 mmol) of **3** in IL [bmim]$BF_4$ (2 mL) and (12 mmol) of OPDA **(4)** was heated at 100°C for 6 h (as monitored by TLC). After 6 h the mixture was cooled to 25°C and diluted with water (10 mL). The product was extracted with ethyl acetate (10 mL × 2). The ethyl acetate layer was washed with 5*N* HCl (10 mL), 5% aqueous sodium bicarbonate solution (10 mL) and water (10 mL). The ethyl acetate layer was dried over sodium sulfate and evaporated under reduced pressure to afford crude product, which was recrystallized from ethyl acetate to obtain as a white solid compound **5**. After isolation of the product in ethyl acetate IL was in aqueous layer, which was further washed with ethyl acetate (10 mL) and dried under vacuum. The suspension was filtered to remove insoluble and the recovered IL was recycled.

**2-(Chroman-2-yl)-1*H*-benzimidazole (5).** mp 225–227°C; ir (KBr): 3434, 2950, 1487, 1231 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.20–2.35 (m, 2H, $CH_2$), 2.81–3.04 (m, 2H, $CH_2$), 5.47 (dd, $J$ = 8.6, 8.9 Hz, 1H, CH), 6.87–6.91 (m, 4H, Ar-H), 7.08–7.18 (m, 2H, Ar-H), 7.46 (d, $J$ = 7.4 Hz, 1H, Ar-H), 7.71 (d, $J$ = 7.6 Hz, 1H, Ar-H), 9.7 (bs, 1H, NH); ms: *m*/*z* 249.1 ($M^+$+1); Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.52; H, 5.52; N, 11.36.

**Synthesis of 2-(6-bromochroman-2-yl)-*1H*-benzimidazole using IL (5a).** A mixture of **3c** (10 mmol), OPDA **(4)** (12 mmol) and IL [bmim]$BF_4$ (2 mL) was heated to 100°C for 6 h (as monitored by TLC). The reaction mixture was then cooled to room temperature and diluted with water (10 mL). The product was extracted with ethyl acetate (10 mL × 2) and ethyl acetate layer was washed with 5*N* HCl (10 mL), 5% aqueous sodium bicarbonate solution (10 mL) and water (10 mL). The ethyl acetate layer was dried over sodium sulfate and solvent was evaporated under reduced pressure to obtain crude product, which was recrystallized from ethyl acetate to yield the pure compound **5a**. The IL was recovered by the procedure described earlier.

**2-(6-Bromochroman-2-yl)-*1H*-benzimidazole (5a).** mp 210–211°C; ir (KBr): 3428, 2919, 1476, 1232 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.26–2.38 (m, 2H, $CH_2$), 2.86–3.01 (m, 2H, $CH_2$), 5.46 (dd, $J$ = 8.7, 8.7 Hz, 1H, CH), 6.86 (d, $J$ = 9 Hz, 1H, Ar-H), 7.15–7.34 (m, 4H, Ar-H), 7.48 (d, $J$ = 6.9 Hz, 1H, Ar-H), 7.62 (d, $J$ = 6.9 Hz, 1H, Ar-H) 12.62 (bs, 1H, NH) ppm; $^{13}$C NMR (DMSO-$d_6$) (75 MHz): δ 23.36 ($CH_2$), 25.60 ($CH_2$), 72.25 (OCH), 111.77, 112.11, 119,01, 119.24, 121.64, 122.63, 125.01, 130.18, 132.18, 134.43, 142.95, 153.02, 153.23 (aromatic carbons) ppm; ms: *m*/*z* 329.32 ($M^+$+1); Anal. Calcd. for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.26; H, 3.75; N, 8.66.

**General procedure for the synthesis of compound 6′a-6′b using IL.** A solution (2 mmol) of **5a,** IL (2 mL), sodium hydroxide (4 mmol) and followed by the addition of respective alkylting reagents (3 mmol) at 25–30°C. After the addition was complete, the solution was heated to 50°C for 5 h (as monitored by TLC). The reaction mixture was then cooled to 25°C and diluted with water (10 mL). The product was extracted with ethyl acetate (10 mL × 2) and ethyl acetate layer was washed with water (10 mL × 2). The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure to obtain the corresponding *N*-substituted derivatives. The crude products were recrystallized from ethanol to give pure compounds **6′a** and **6′b,** respectively. The IL was recovered by the procedure described earlier.

***Methyl 2-(6-bromochroman-2-yl)-1H-benzimidazole (6′a).*** ir (KBr): 3435, 2948, 1474, 1231 cm$^{-1}$; 1H NMR (DMSO-$d_6$): δ 2.40–2.46 (m, 2H, $CH_2$), 2.97–3.01 (m, 2H, $CH_2$), 3.91

(s, 3H, $CH_3$), 5.63 (dd, $J$ = 8.1, 8.4 Hz, 1H, CH), 6.81(d, $J$ = 8.4 Hz, 1H, Ar-H), 7.28–7.35 (m, 4H, Ar-H), 7.59–7.66 (m, 2H, Ar-H) ppm; $^{13}$C NMR (DMSO-$d_6$) (75 MHz): δ 23.07 ($CH_2$), 23.59 ($CH_2$), 29.41 ($NCH_3$), 70.10 (CH), 108.11, 111.84, 117.24, 118.84, 121.01, 121.89, 122.08, 128.93, 130.95, 134.91, 140.60, 149.96, 151.55 (aromatic carbons) ppm; ms: $m/z$ 343.61 ($M^+$+1); Anal. Calcd. for $C_{17}H_{15}BrN_2O$: C, 59.49; H, 4.41; N, 8.56. Found: C, 59.38; H, 4.62; N, 8.32.

***Ethyl 2-(6-bromochroman-2-yl)-1H-brenzimidazole (6′b).*** ir (KBr): 3435, 2983, 1473, 1234 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 1.4 (t, $J$ = 6.9 Hz, 3H, $CH_3$), 2.42–2.50 (m, 2H, $CH_2$), 3.03–3.07 (m, 2H, $CH_2$), 4.41 (q, $J$ = 6.8 Hz, 2H, $CH_2$), 5.62 (dd, $J$ = 8.1, 8.3 Hz, 1H, CH), 6.78 (d, $J$ = 9 Hz, 1H, Ar-H), 7.24–7.36 (m, 4H, Ar-H), 7.61–7.67 (m, 2H, Ar-H) ppm; $^{13}$C NMR (DMSO-$d_6$) (75 MHz): δ 15.25 ($CH_3$), 24.25 ($CH_2$), 24.86 ($CH_2$), 39.23 ($NCH_2$), 71.24 (CH), 109.61, 113.08, 118.51, 120.24, 122.23, 123.12, 124.08, 130.22, 132.27, 135.11, 142.18, 150.80, 152.93 (aromatic carbons) ppm; ms: $m/z$ 357.66 ($M^+$+1); Anal. Calcd. for $C_{18}H_{17}BrN_2O$: C, 60.52; H, 4.80; N, 7.84. Found: C, 60.38; H, 4.97; N, 7.63.

**General procedure for the synthesis of compound (6a-6f, 6′c-6′g, and 6′m) using ILs.** To a solution of **5** and **5a** (2 mmol) in ILs (2 mL), pyridine (10 mmol), followed by the addition of appropriate acyl or arylsulfonyl chloride (3 mmol) were stirred (for reaction conditions, Table 1a). The reaction mixture was then cooled to 25°C and diluted with water (10 mL). The product was extracted with ethyl acetate (10 mL × 2), ethyl acetate layer was washed with 5% aqueous sodium bicarbonate solution (10 mL) followed by washed with water (10 mL). The ethyl acetate layer was dried over sodium sulfate and the solvent was evaporated to obtain the crude products, which were recrystallized from ethanol, to afford pure compounds (**6a-6f**), (**6′c-6′g** and **6′m**), respectively. The ILs was recovered by the procedure described earlier.

***Methyl 2-(chroman-2-yl)-1H-benzimidazole-1-carboxylate (6a).*** ir (KBr): 3453, 2922, 1759, 1455 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.40–2.51 (m, 2H, $CH_2$), 2.92–3.07 (m, 2H, $CH_2$), 4.13 (s, 3H, $CH_3$), 5.86 (dd, $J$ = 8.4, 8.6 Hz, 1H, CH), 6.87–6.94 (m, 2H, Ar-H), 7.12 (d, $J$ = 6.9 Hz, 2H, Ar-H), 7.37–7.38 (m, 2H, Ar-H), 7.82 (d, $J$ = 6.9, Hz, 1H, Ar-H), 7.95 (d, $J$ = 7.2 Hz, 1H, Ar-H); ms: $m/z$ 309.1 ($M^+$+1); Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.23; H, 5.35; N, 9.25.

***Ethyl 2-(chroman-2-yl)-1H-benzimidazole-1-carboxylate (6b).*** ir (KBr): 3453, 2972, 1744, 1455 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.53 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.40–2.51 (m, 2H, $CH_2$), 2.92–3.06 (m, 2H, $CH_2$), 4.57 (q, 2H, $CH_2$), 5.89 (dd, $J$ = 8.7 Hz, 1H, CH), 6.87–6.95 (m, 2H, Ar-H), 7.1 (d, $J$ = 6.9 Hz, 2H, Ar-H), 7.36–7.39 (m, 2H, Ar-H), 7.82 (d, $J$ = 8.1 Hz, 1H, Ar-H), 7.98 (d, 1H, $J$ = 6 Hz, Ar-H); ms: $m/z$ 323.1 ($M^+$+1); Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.92, H, 5.48; N, 8.85.

***Isobutyl 2-(chroman-2-yl)-1H-benzimidazole-1-carboxylate (6c).*** ir (KBr): 3272, 1738, 1456 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.57 (d, $J$ = 6.6 Hz, 6H, $CH_3$), 2.16–2.19 (m, 1H, CH), 2.44–2.52 (m, 2H, $CH_2$), 2.91–3.06 (m, 2H, $CH_2$), 4.32 (d, $J$ = 6.6 Hz, 2H, CH2), 5.91 (dd, $J$ = 8.1, 8.1 Hz, 1H, CH), 6.89–6.94 (m, 2H, Ar-H), 7.11 (d, $J$ = 6.6 Hz, 2H, Ar-H), 7.39 (m, 2H, Ar-H), 7.82 (d, $J$ = 6 Hz, 1H, Ar-H), 7.97 (d, $J$ = 5.7 Hz, 1H, Ar-H); ms: $m/z$ 351.2 ($M^+$+1); Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.86; H, 6.43; N, 8.10.

***Phenyl 2-(chroman-2-yl)-1H-benzimidazole-1-carboxylate (6d).*** ir (KBr): 3460, 2938, 1762 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.52–2.57 (m, 2H, $CH_2$), 2.99–3.05 (m, 2H, $CH_2$), 5.92 (dd, $J$ = 8.6, 8.7 Hz, 1H, CH), 6.86–6.97 (m, 2H, Ar-H), 7.12 (d, $J$ = 7.5 Hz, 2H, Ar-H), 7.26–7.52 (m, 7H, Ar-H), 7.87 (d, $J$ = 6.3 Hz, 1H, Ar-H), 8.09 (d, $J$ = 5.7 Hz ,1H, Ar-H); ms: $m/z$ 371.1 ($M^+$+1); Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.69; H, 4.78; N, 7.66.

***2-(Chroman-2-yl)-1-methanesulfonyl-1H-benzimidazole (6e).*** ir (KBr): 3436, 1583, 1489 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.59–2.69 (m, 2H, $CH_2$), 3.02–3.08 (m, 2H, $CH_2$), 3.56 (s, 3H, $CH_3$), 5.82 (dd, $J$ = 7.9, 8.1 Hz, 1H, CH), 6.76 (d, $J$ = 8.1 Hz, 2H, Ar-H), 6.89–6.94 (m, 2H, Ar-H), 7.41–7.44 (m, 2H, Ar-H), 7.82 (d, $J$ = 7.8 Hz, 1H, Ar-H), 7.97 (d, $J$ = 6.3 Hz, 1H, Ar-H); ms: $m/z$ 329.1 ($M^+$+1); Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.32; H, 4.80; N, 8.49.

***2-(Chroman-2-yl)-1-tosyl-1H-benzimidazole (6f).*** ir (KBr): 3399, 1485, 1374 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.41 (s, 3H, $CH_3$), 2.53–2.61 (m, 2H, $CH_2$), 2.96–3.10 (m, 2H, $CH_2$), 5.97 (dd, $J$ = 7.7, 7.9 Hz, 1H, CH), 6.7 (d, $J$ = 9 Hz, 1H, Ar-H), 6.88–6.93 (m, 1H, Ar-H), 7.08–7.15 (m, 2H, Ar-H), 7.3–7.40 (m, 4H, Ar-H), 7.76 (d, $J$ = 7.8 Hz, 1H, Ar-H), 7.97 (d, $J$ = 8.1 Hz, 2H, Ar-H), 8.05 (d, $J$ = 8.1 Hz, 1H, Ar-H); ms: $m/z$ 405.1 ($M^+$+1); Anal. Calcd. for $C_{23}H_{20}N_2O_3S$: C, 60.30; H, 4.98; N, 6.93. Found: C, 60.15; H, 5.20; N, 6.78.

***Methyl-2-(6-bromochroman-2-yl)-1H-benzimidazole-1-carboxylate (6′c).*** ir (KBr): 3434, 2926, 1753, 1481, 1357 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.42–2.52 (m, 2H, $CH_2$), 2.95–3.08 (m, 2H, $CH_2$), 4.13 (s, 3H, $CH_3$), 5.88 (dd, $J$ = 8.4, 8.4 Hz, 1H, CH), 6.83 (d, $J$ = 8.7 Hz, 1H, Ar-H), 7.19–7.4 (m, 4H, Ar-H), 7.80–7.95 (m, 2H, Ar-H) ppm; $^{13}$C NMR ($CDCl_3$) (75 MHz): δ 23.22 ($CH_2$), 23.87 ($CH_2$), 53.52 ($NCH_3$), 70.76 (OCH), 111.55, 113.68, 117.56, 119.39, 122.77, 123.47, 128.85, 130.66, 130.95, 131.31, 140.59, 149.28, 151.85, 152.26 (aromatic carbons) ppm; ms: $m/z$ 389.52 ($M^+$+1); Anal. Calcd. for $C_{18}H_{15}BrN_2O_3$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.94; H, 3.78; N, 7.34.

***Ethyl-2-(6-bromochroman-2-yl)-1H-benzimidazole-1-carboxylate (6′d).*** ir (KBr): 3436, 2945, 1745, 1480, 1330 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.51 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.45–2.50 (m, 2H, $CH_2$), 2.94–3.02 (m, 2H, $CH_2$), 4.58 (q, $J$ = 5.4 Hz, 2H, $CH_2$), 5.88, (dd, $J$ = 8.7 and 8.7 Hz, 1H, CH), 6.82 (d, $J$ = 8.4 Hz, 1H, Ar-H), 7.19–7.39 (m, 4H, Ar-H), 7.8–7.97 (m, 2H, Ar-H) ppm; $^{13}$C NMR (DMSO-$d_6$) (75 MHz): δ 13.1 ($CH_3$), 63.52 ($NCH_2$), 23.29 ($CH_2$), 24.94 ($CH_2$), 70.87 (OCH), 111.58, 113.78, 117.62, 119.44, 122.76, 123.43, 128.90, 130.71, 130.98, 131.52, 140.66, 148.78, 151.89, 152.29 (aromatic carbons) ppm; ms: $m/z$ 403.46 ($M^+$+1); Anal. Calcd. for $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98. Found: C, 56.70; H, 4.38; N, 7.15.

***Isobutyl-2-(6-bromochroman-2-yl)-1H-benzimidazole-1-carboxylate (6′e).*** ir (KBr): 3429, 2927, 1730, 1663, 1474 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 1.07 (d, $J$ = 6.6 Hz, 6H, $CH_3$), 1.50–1.58 (m, 1H, CH), 2.17–2.24 (m, 2H, $CH_2$), 2.98–3.04 (m, 2H, $CH_2$), 4.32 (d, $J$ = 6.6 Hz, 2H, $CH_2$), 5.9 (dd, $J$ = 8.9, 8.9 Hz, 1H, CH), 6.82 (d, $J$ = 8.4 Hz, 1H, Ar-H), 7.18–7.26 (m, 2H, Ar-H), 7.37–7.39 (m, 2H, Ar-H), 7.81 (d, $J$ = 7.8 Hz, 1H, Ar-H), 7.96 (d, $J$ = 6.6 Hz, 1H, Ar-H) ppm; $^{13}$C NMR ($CDCl_3$) (75 MHz): δ 19.21, 19.21, 24.38 ($CH_3$), 26.06 ($CH_2$), 27.81, 71.92 ($CH_3$), 74.46, 112.65, 114.80, 118.73, 120.59,

123.83, 124.52, 125.32, 129.98, 131.79, 132.59, 141.79, 150.10, 153.10, 153.38 (aromatic carbons) ppm; ms: *m/z* 429.51 ($M^+$+1); Anal. Calcd. for $C_{21}H_{21}BrN_2O_3$: C, 58.75; H, 4.93; N, 6.53. Found: C, 58.82; H, 4.83; N, 6.64.

***2-(6-Bromochroman-2-yl)-1-methanesulfonyl-1H-benzimidazole (6′f).*** ir (KBr): 3435, 3030, 2927, 1475, 1372 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.58–2.66 (m, 2H, $CH_2$), 2.96–3.04 (m, 2H, $CH_2$), 3.52 (s, 3H, $CH_3$), 5.8 (dd, *J* = 8.7, 8.9 Hz, 1H, CH), 6.65 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.18–7.44 (m, 4H, Ar-H), 7.82 (d, *J* = 5.4 Hz, 1H, Ar-H), 7.96 (d, *J* = 6.3 Hz, 1H, Ar-H) ppm; $^{13}C$ NMR (DMSO-$d_6$) (75 MHz): δ 24.25 ($CH_2$), 24.83 ($CH_2$), 42.62 ($SCH_3$), 70.69 (OCH), 113.32, 116.09, 117.88, 120.99, 124.17, 125.02, 126.03, 129.82, 130.11, 132.30, 141.04, 150.75, 152.76 (aromatic carbons) ppm; ms: *m/z* 409.23 ($M^+$+1); Anal. Calcd. for $C_{17}H_{15}BrN_2O_3S$: C, 50.13; H, 3.71; N, 6.88. Found: C, 50.30; H, 3.59; N, 7.11.

***2-(6-Bromochroman-2-yl)-1-tosyl-1H-benzimidazole (6′g).*** ir (KBr): 3432, 2938, 1474, 1370 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.41 (s, 3H, $CH_3$) 2.42–2.52 (m, 2H, $CH_2$), 2.92–3.01 (m, 2H, $CH_2$), 5.96 (dd, *J* = 8.4 and 8.4 Hz, 1H, CH), 6.56 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.18 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.26–7.42 (m, 4H, Ar-H), 7.76 (d, *J* = 6.9 Hz, 1H, Ar-H), 7.94 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.04 (d, *J* = 7.8 Hz, 2H, Ar-H) ppm; $^{13}C$ NMR ($CDCl_3$) (75 MHz): δ 21.70 ($CH_3$), 24.38 ($CH_2$), 26.08 ($CH_2$), 70.77 (OCH), 112.98, 113.78, 118.35, 120.95, 124.07, 124.94, 125.83, 127.29, 127.29, 130.04, 130.04, 130.09, 132.17, 132.91, 135.21, 141.46, 146.12, 151.62, 153.21 (aromatic carbons) ppm; ms: *m/z* 483.38 ($M^+$+1); Anal. Calcd. for $C_{23}H_{19}BrN_2O_3S$: C, 57.15; H, 3.96; N, 5.80. Found: C, 57.31; H, 3.85; N, 5.62.

**General procedure for the synthesis of compound (6g-6k and 6′h-6′l) using ILs.** A solution of (2 mmol) of **5** and **5a**, (4 mmol) of sodium hydroxide in ILs (2 mL), followed by the addition of appropriate (3 mmol) benzyl bromides at 25–30°C. After the addition was complete, the solution was heated to 75°C for 5–6 h (as monitored by TLC). The reaction mass was then cooled to 25°C and diluted with water (25 mL). The resultant solid was filtered and washed with water (10 mL) to afford crude products. The crude products were recrystallized from ethanol, to obtain pure compounds **6g-6k** and **6′h-6′l**, respectively. The aqueous layer contains the ILs, which was recovered as described earlier procedure.

***2-(Chroman-2-yl)-1-benzyl-1H-benzimidazole (6g).*** ir (KBr): 3432, 2930, 1583, 1487, 1232 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.55–2.63 (m, 2H, $CH_2$), 2.94–3.01 (m, 2H, $CH_2$), 5.36 (dd, *J* = 9.3, 9.4 Hz, 1H, CH), 5.62 (s, 2H, $CH_2$), 6.64 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.85–6.90 (m, 1H, Ar-H), 7.03–7.13 (m, 4H, Ar-H), 7.26–7.28 (m, 6H, Ar-H), 7.83 (d, *J* = 6, 6 Hz, 1H, Ar-H); ms: *m/z* 341.2 ($M^+$+1); Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.27; H, 5.82; N, 8.35.

***2-(Chroman-2-yl)-1-(4-fluorobenzyl)-1H-benzimidazole (6h).*** ir (KBr): 3454, 2945, 1485 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.56–2.60 (m, 2H, $CH_2$), 2.90–3.02 (m, 2H, $CH_2$), 5.35 (dd, *J* = 8.7, 9.0 Hz, 1H, CH), 5.58 (s, 2H, $CH_2$), 6.62 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.86–6.91 (m, 1H, Ar-H), 6.99–7.11 (m, 5H, Ar-H), 7.24–7.28 (m, 4H, Ar-H), 7.82 (d, *J* = 6.6 Hz, 1H, Ar-H); ms: *m/z* 360.2 ($M^+$+1); Anal. Calcd. for $C_{23}H_{19}FN_2O$: C, 77.08; H, 5.34; N, 7.82. Found: C, 77.26; H, 5.42; N, 7.68.

***2-(Chroman-2-yl)-1-(4-bromobenzyl)-1H-benzimidazole (6i).*** ir (KBr): 3432, 2926, 1584, 1459, 1231$cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.54–2.60 (m, 2H, $CH_2$), 2.99–3.04 (m, 2H, $CH_2$), 5.34 (dd, *J* = 7.8, 8.4 Hz, 1H, CH), 5.56 (s, 2H, $CH_2$), 6.59 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.88 (m, 2H, Ar-H), 6.99–7.11 (m, 2H, Ar-H), 7.19–7.31 (m, 4H, Ar-H), 7.42 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.83 (d, *J* = 7.2 Hz, 1H, Ar-H); ms: *m/z* 421.1 ($M^+$+1); Anal. Calcd. for $C_{23}H_{19}BrN_2O$: C, 65.88; H, 4.57; N, 6.68. Found: C, 65.98; H, 4.45; N, 6.78.

***2-(Chroman-2-yl)-1-(4-methylbenzyl)-1H-benzimidazole (6j).*** ir (KBr): 3431, 1582, 1456, 1230 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.31 (s, 3H, $CH_3$), 2.55–2.61 (m, 2H, $CH_2$), 2.91–3.01 (m, 2H, $CH_2$), 5.33 (dd, *J* = 7.5 Hz, 1H, CH), 5.57 (s, 2H, $CH_2$), 6.7 (d, *J* = 8.1 Hz, 1H, 5′ Ar-H), 6.86–6.90 (m, 1H, Ar-H), 7.01–7.11 (m, 6H, Ar-H), 7.30–7.32 (m, 3H, Ar-H), 7.82 (d, *J* = 7.2 Hz, 1H, Ar-H); ms: *m/z* 355.2 ($M^+$+1); Anal. Calcd. for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.19; H, 6.37; N, 8.11.

***2-(Chroman-2-yl)-1-(4-tert-butylbenzyl)-1H-benzimidazole (6k).*** ir (KBr): 3428, 2958, 1581, 1463 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.28 (s, 9H, *tert* butyl), 2.55–5.62 (m, 2H, $CH_2$), 2.97–3.01 (m, 2H, $CH_2$), 5.34 (dd, *J* = 9.1, 9.1 Hz, 1H, CH), 5.52–5.65 (s, 2H, $CH_2$), 6.63–6.66 (m, 1H, Ar-H), 6.85–6.90 (m, 1H, Ar-H), 7.03–7.10 (m, 3H, Ar-H), 7.26–7.31 (m, 6H, Ar-H), 7.82 (d, *J* = 6.2 Hz, 1H, Ar-H); ms: *m/z* 397.2 ($M^+$+1); Anal. Calcd. for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06. Found: C, 81.69; H, 7.31; N, 7.20.

***2-(6-Bromochroman-2-yl)-1-benzyl-1H-benzimidazole (6′h).*** ir (KBr): 3446, 2926, 1574, 1482, 1234 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.46–2.55 (m, 2H, $CH_2$), 2.94–3.01 (m, 2H, $CH_2$), 5.38 (dd, *J* = 7.2, 8.1 Hz, 1H, CH), 5.60 (s, 2H, $CH_2$), 6.47 (d, *J* = 9 Hz, 1H, Ar-H), 7.02–7.15 (m, 2H, Ar-H), 7.21–7.28 (m, 8H, Ar-H), 7.86 (d, *J* = 7.8 Hz, 1H, Ar-H) ppm; $^{13}C$ NMR ($CDCl_3$) (75 MHz): δ 22.99 ($CH_2$), 23.68 ($CH_2$), 46.54 ($NCH_2$), 70.08 (OCH), 108.89, 111.84, 117.25, 118.97, 121.24, 122.23, 122.73, 125.07, 125.07, 126.51, 127.57, 127.57, 128.87, 130.88, 134.55, 134.89, 140.74, 150.15, 151.41 (aromatic proton) ppm; ms: *m/z* 421.60 ($M^+$+1); Anal. Calcd. for $C_{23}H_{19}BrN_2O$: C, 65.88; H, 4.57; N, 6.68. Found: C, 65.70; H, 4.68; N, 6.77.

***2-(6-Bromochroman-2-yl)-1-(4-fluorobenzyl)-1H-benzimidazole (6′i).*** ir (KBr): 3435, 2928, 1605, 1484, 1227 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.54–2.58 (m, 2H, $CH_2$), 2.96–3.04 (m, 2H, $CH_2$), 5.38 (dd, *J* = 8.4, 8.4 Hz, 1H, CH), 5.56 (s, 2H, $CH_2$), 6.47 (d, *J* = 9 Hz, 1H, Ar-H), 6.96–6.99 (m, 2H, Ar-H), 7.12–7.22 (m, 3H, Ar-H), 7.26–7.44 (m, 4H, Ar-H), 7.85 (d, *J* = 9 Hz, 1H, Ar-H) ppm; $^{13}C$ NMR ($CDCl_3$) (75 MHz): δ 24.02 ($CH_2$), 24.72 ($CH_2$), 47.07 ($NCH_2$), 71.28 (OCH), 110.01, 113.17, 115.63, 115.92, 118.39, 120.29, 122.60, 123.57, 123.98, 128.03, 128.14, 130.18, 131.91, 132.22, 135.64, 142.03, 151.33, 152.62, 160.58 (aromatic carbons) ppm; ms: *m/z* 437.7 ($M^+$+1); Anal. Calcd. for $C_{23}H_{18}BrFN_2O$: C, 63.17; H, 4.15; N, 6.41. Found: C, 63.28; H, 4.31; N, 6.28.

***2-(6-Bromochroman-2-yl)-1-(4-bromobenzyl)-1H-benzimidazole (6′j).*** ir (KBr): 3444, 2932, 1574, 1480, 1234 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.51–2.57 (m, 2H, $CH_2$), 2.92–3.02 (m, 2H, $CH_2$), 5.36 (dd, *J* = 9, 9 Hz, 1H, CH), 5.54 (s, 2H, $CH_2$), 6.46 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.44 (d, *J* = 9 Hz, 2H, Ar-H), 6.97 (d, *J* = 7.8 Hz, 2H, Ar-H) 7.19 (m, 3H, Ar-H), 7.44 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.83 (d, *J* = 7.8 Hz, 1H, Ar-H) ppm; $^{13}C$ NMR ($CDCl_3$) (75 MHz): δ 23.95 ($CH_2$), 24.96 ($CH_2$), 47.11 ($NCH_2$), 71.13 (OCH), 109.81, 113.05, 118.19, 120.09, 121.48, 122.49, 123.45, 123.76, 127.88, 127.88, 129.96, 131.71,

131.71, 131.91, 134.97, 135.34, 141.74, 151.06, 152.34 (aromatic carbons) ppm; ms: *m*/*z* 499.64 ($M^+$+1); Anal. Calcd. for $C_{23}H_{18}Br_2N_2O$: C, 55.45; H, 3.64; N, 5.62. Found: C, 55.34; H, 3.76; N, 5.49.

***2-(6-Bromochroman-2-yl)-1-(4-methylbenzyl)-1H-benzimidazole (6′k).*** ir (KBr): 3427, 2929, 1513, 1262 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.32 (s, 3H, $CH_3$), 2.51–2.55 (m, 2H, $CH_2$), 2.94–3.0 (m, 2H, $CH_2$), 5.41 (dd, *J* = 8.6, 8.6 Hz, 1H, CH), 5.56 (s, 2H, $CH_2$), 6.55 (d, *J* = 8.7 Hz, 1H, Ar-H), 6.98–6.70 (m, 2H, Ar-H), 7.09–7.16 (m, 4H, Ar-H), 7.22–7.29 (s, 3H, Ar-H), 7.85 (d, *J* = 7.2 Hz, 1H, Ar-H) ppm; $^{13}C$ NMR ($CDCl_3$) (75 MHz): δ 21.16 ($CH_3$), 24.19 ($CH_2$), 24.88 ($CH_2$), 47.52 ($NCH_2$), 71.25 (OCH), 110.12, 112.99, 118.46, 119.9, 120.10, 122.35, 123.33, 123.93, 126.26, 129.39, 129.39, 130.04, 132.05, 132.97, 135.46, 137.46, 141.90, 151.28, 152.67 (aromatic carbons) ppm; ms: *m*/*z* 435.75 ($M^+$+1); Anal. Calcd. for $C_{24}H_{21}BrN_2O$: C, 66.52; H, 4.88; N, 6.46. Found: C, 66.40; H, 5.13; N, 6.58.

***2-(6-Bromochroman-2-yl)-1-(4-tert-butylbenzyl)-1H-benzi-midazole (6′l).*** ir (KBr): 3446, 2962, 1475, 1411, 1219 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.28 (s, 9H, *tert*. butyl), 2.50–2.54 (m, 2H, $CH_2$), 2.94–2.99 (m, 2H, $CH_2$), 5.36 (dd, *J* = 9.9 Hz, 1H, CH), 5.57 (s, 2H, $CH_2$), 7.02 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.11–7.13 (m, 1H, Ar-H), 7.21–7.29 (m, 8H, Ar-H), 7.85 (d, *J* = 7.8 Hz, 1H, Ar-H) ppm; $^{13}C$ NMR ($CDCl_3$) (75 MHz): δ 24.06 ($CH_2$), 24.75 ($CH_2$), 31.30, 31.30, 31.30 ($CH_3$), 34.51 (*tert*.butyl), 47.29 ($NCH_2$), 71.06, (OCH), 110.04, 112.90, 118.39, 120.05, 122.27, 123.25, 123.87, 125.56, 125.56, 125.91, 125.91, 129.91, 131.95, 133.03, 135.73, 141.86, 150.57, 151.24, 152.56 (aromatic carbons) ppm; ms: *m*/*z* 477.40 ($M^+$+1); Anal. Calcd. for $C_{27}H_{27}BrN_2O$: C, 68.21; H, 5.72; N, 5.89. Found: C, 68.10; H, 5.80; N, 6.10.

***Phenyl-2-(6-bromochroman-2-yl)-1H-benzimidazole-1-carboxylate (6′m).*** ir (KBr): 3435, 2925, 1766, 1475, 1355, 1232 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.50–2.54 (m, 2H, $CH_2$), 2.95–3.05 (m, 2H, $CH_2$), 5.60 (s, 2H, $CH_2$), 5.94 (dd, *J* = 9.0, 9.1 Hz, 1H, CH), 6.90 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.09–7.14 (m, 2H, Ar-H), 7.26–7.52 (m, 5H, Ar-H), 7.86–7.88 (m, 1H, Ar-H), 8.07–8.09 (m, 1H, Ar-H) ppm; ms: *m*/*z* 421.72 ($M^+$+1); Anal. Calcd. for $C_{23}H_{17}BrN_2O_3$: C, 61.48; H, 3.81; N, 6.23. Found: C, 61.58; H, 3.92; N, 6.31.

## REFERENCES AND NOTES

[1] Sheehan, D. J.; Hitchcock, C. A.; Sibley, C. M. Clin Microbiol Rev 1999, 12, 40.

[2] Kazimerczuk, Z.; Andrzejewska, M.; Klimesova, V. Eur J Med Chem 2005, 40, 203.

[3] Sukalovic, V.; Andric, D.; Roglic, G.; Sladjana, K. R.; Schratteholz, A.; Soski, V. Eur J Med Chem 2005, 40, 481.

[4] Mariana, B.; Mercedes, G. Mini Rev Med Chem 2005, 5, 409.

[5] Khalafi-Nezhad, A.; Soltani Rad, M. N.; Mohabatkar, H.; Ansari, Z.; Hemmateenejad, B. Bioorg Med Chem Lett 2003, 13, 1931.

[6] Bin, S.; Jincheng, H.; Qun, S.; Valenzano, K. J.; Lori, S.; Scott, N. Bioorg Med Chem Lett 2005, 15, 719.

[7] Li, Y.; Kataoka, M.; Tatsuta, M.; Yasoshima, K.; Yura, T.; Urbahns, K.; Kiba, A.; Yamamoto, N.; Gupta, J. B.; Hashimoto, K. Bioorg Med Chem Lett 2005, 15, 805.

[8] Garg, Y.; Samota, M. K.; Seth, G. Asian J Chem 2005, 17, 615.

[9] Teague, S. J.; Barber, S.; King, S.; Stein, L. Tetrahedron Lett 2005, 46, 4613.

[10] Hashimoto, K.; Tatsuta, M.; Yasoshima, K.; Shogase, Y.; Shimazaki, M.; Yura, T.; Li, Y.; Urbahns, K.; Yamamoto, N.; Gupta, J. B. Bioorg Med Chem Lett 2005, 15, 799.

[11] (a) Preston, P. N. Chem Rev 1974, 74, 279; (b) Preston, P. N. Merck Index 11th Edn. 1794.

[12] Preston, P. N.; In Benzimidazoles and Congeneric Tricyclic Compounds; Wiley Interscience: New York, 1980; Part 2, Chapter 10, pp 531.

[13] Daniel, L. A. Strategiies for Organic Drug Synthesis and Design; Wiley Interscience: 1998; p 300.

[14] Eaton, P. E.; Carlson, G. R.; Lee, J. T. J Org Chem 1973, 38, 4071.

[15] Phillips, M. A. J Chem Soc 1928, 172, 2393.

[16] Dubey, R.; Hari Narayana Moorthy, N. S. Chem Pharm Bull 2007, 55, 115.

[17] Maradolla M. B.; Allam S. K.; Mandha A.; Chandramouli G. V. P. Arkivoc 2008, 15, 42.

[18] Vinod Kumar, R.; Vaidya, S. D.; Siva Kumar, B. V.; Bhise U. N.; Bhirud S. B.; Mashelkar, U. C. Indian J Hetrocycl Chem 2005, 14, 197.

[19] Vaidya, S. D.; Siva Kumar, B. V.; Vinod Kumar, R.; Bhirud S. B.; Mashelkar, U. C. Euro J Med Chem 2008, 43, 986.

[20] Siva Kumar, B. V.; Vaidya, S. D.; Vinod Kumar, R.; Bhirud S. B.; Mane R. B. Euro J Med Chem 2006, 41, 599.

[21] Welton, T. Chem Rev 1999, 99, 2071.

[22] Wasserscheid, P.; Keim, W. Angew Chem Int Ed Engl 2000, 39, 3772.

[23] Sheldon, R. Chem Commun 2001, 1, 2399.

[24] Gordon, C. M. Appl Catal A 2001, 222, 101.

[25] Wasserscheid. P.; Welton, T., Eds. Ionic Liquids in Synthesis; VCH-Wiley: Weinheim, 2002.

[26] Connell, R. D. U. S. Pat.6,469,031 (2002).

[27] Owens, G. S.; Abu-Omer, M. M. J Mol Catal A 2002, 187, 211.

# Eco-Friendly, Solvent-Free Novel One-Pot, Three-Component Synthesis of Quinazolinones at Ambient Temperature Catalyzed by Silica Gel-Supported Phosphomolybdic Acid

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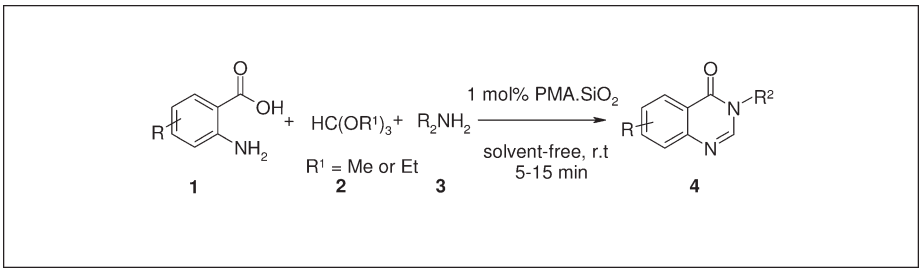


Silica gel supported Phosphomolybdic acid ($PMA.SiO_2$) catalyzes efficiently the one-pot three-component coupling reaction of anthranilic acid, orthoesters, and amines at room temperature to afford 4(3*H*)-Quinazolinones in high to excellent yields under solvent-free conditions. The supported catalyst can be recovered and reused.

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## INTRODUCTION

The demand for increasingly clean and efficient chemical syntheses is continuously becoming more urgent from both an economic and an environmental standpoint. Organic reactions under solvent-free conditions are advantageous because of enhanced selectivity and efficiency, ease of manipulation, and more importantly, toxic and often volatile solvents are avoided. These would be especially important during industrial production. Hence, the organic transformations under solvent-free conditions are attracting increasing attention.

Heteropoly acids are economically and eco-friendly green Lewis acids. Development of methods using heteropoly acids (HPAs) as catalysts for organic synthetic processes related to fine chemicals, such as flavors, pharmaceuticals, and food industries [1–4] have been under attention in the last decade. Heteropolyacids are more active catalysts than conventional inorganic and organic acids for various reactions in solution [5–11]. They are used as industrial catalysts for several liquid-phase reactions[12–15], such as alcohol dehydration [16], alkylation [17], or esterification [18] reactions. They are not corrosive and environmentally benign, presenting fewer disposal problems. Phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) belongs to the class of heteropoly acids. The supported HPAs are more active than typical solid acids and attracted much attention in organic synthesis owing to easy workup procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of the catalysts [19]. Supported reagents enhance their application in 'green synthesis'. Silica gel [17] is most commonly used as support, even though alumina, active carbon, and acidic ion-exchange resins are considered as suitable supports.

Natural products containing quinazolinone moiety possess a broad spectrum of biological properties, such as anticancer, antimalarial, anticonvulsant, analgesic, antihypertensive, antiviral, anti-tubercular, and anti-inflammatory activities [20–34]. Febrifugine and isofebrifugine natural products [35,36] containing 4(3*H*)quinazolinone scaffold have been used effectively against malarial fever in china for centuries (Fig. 1). Similarly, quinazolone containing compounds have been known as tyrosine kinase inhibitors [37,38], dihydrofolate reductase inhibitors [39], and tubulin polymerization inhibitors [40,41]. The interest in the quinazolone structural motif, led to a number of different synthetic methods to access this nucleus. The synthesis of 4(3*H*)-quinazolinone derivatives is achieved by cycloaddition reactions of anthranilic acid with imidates and imino halides [42–49]. The cyclization of cyano- and nitro- activated *o*-fluorobenzaldehydes with amidines and more recently, the

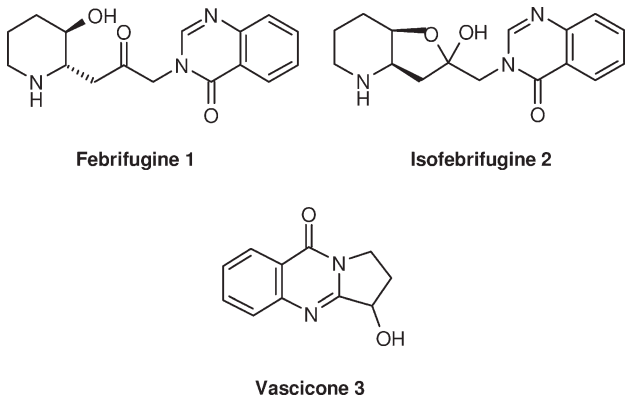



**Figure 1.** Quinazolinone moiety containing natural products.

condensation of fluoro substituted benzoyl chlorides with 2-amino-*N*-heterocycles represent one-pot approaches to quinazolines [50,51]. An intramolecular aza-Wittig type transformation of *o*-azidobenzamide derivatives has been employed as the key quinazolinone-forming step in the synthesis of the quinazoline alkaloid vasicinone [52]. Usually, 4*H*-3,1-benzaxazin-4-ones are valuable starting materials for the synthesis of these compounds [53]. Recently, 4(3*H*)-quinazolinones were prepared using $Bi(TFA)_3$-[nbp]$FeCl_4$ [54], $Yb(OTf)_3$ [55], $La(NO_3)_3.6H_2O$ [56], Silicagel/$FeCl_3$ [57], Silicagel/$NaHCO_3$ & Amberlist 15 [58]. Even-though, many reports appeared in the literature, some of these suffer from drawbacks, such as multi-step procedures, long reaction time, expensive reagents, low yields, harsh conditions, and cumber some product isolation.

As part of our program aimed at developing new green synthetic methodologies for the preparation of fine chemicals, we wish to report herein a remarkable catalytic activity of PMA for the one-pot synthesis of 4(3*H*)-quinazolinones.

## RESULTS AND DISCUSSIONS

Thus carrying out the reaction of anthranilic acid **1** with trimethyl/ethyl orthoformate **2** and primary amine **3** in1:1.2:1.2 mole ratio in the presence of 1 mol % of PMA.$SiO_2$ [59] at room temperature gave the desired 4(3*H*)-quinazolinone **4** in 98% yield (Scheme 1). The experimental procedure is simple and the reaction proceeds under solvent-free conditions. To expand the scope of this method, various 4(3*H*)-quinazolinones were synthesized under similar conditions in high to excellent yields. All the reactions proceeded efficiently at room temperature within 5–15 min in excellent yields under solvent-free conditions and all the products were characterized by NMR, IR and mass spectroscopy and also by comparison with authentic samples. As shown in Table 1, both aniline derivatives and benzyl amine reacted similarly under these reaction conditions without any difference to give the corresponding 4(3*H*)-quinazolinones in high yields. The present procedure does not require toxic or anhydrous organic solvents. The reaction is general, clean, rapid, and efficient. It is important to note that in the absence of catalyst the reaction did not yield the products and only the starting materials were isolated.

It is important to mention that in contrast to reported procedures, *m*-nitroaniline reacted at room temperature with anthranilic acid and trimethyl orthoformate to produce the product **4j** in 88% yield within 15 min, while many of the reports claim the reaction using aniline containing a nitro group requires heating at 60°C [54,56–58]. The one-pot reaction proceeded smoothly with the anilines containing electron-donating groups (such as methoxy and methyl) as well as containing electron-withdrawing groups (such as chloro, fluoro, and nitro).

In conclusion, we have demonstrated a three-component, one-pot procedure for the synthesis of 4(3*H*)-quinazolinones at ambient temperature using silica gel supported PMA. The noteworthy advantages of this method are mild solvent-free heterogeneous reaction conditions, improved yields, shorter reaction times, and operational simplicity, which make it a useful and attractive process for the synthesis of 4(3*H*)-quinazolinones. The supported catalyst can be recovered and reused.

## EXPERIMENTAL

All reactions were carried out under $N_2$ atmosphere and monitored by TLC on silica gel (60–120 mesh; Merck). IR spectra were recorded on a Thermo Nicolet Nexus-670 spectrometer; in *m*/*z*. $^1$H NMR spectra were recorded on Bruker (300/75 MHz) spectrometer in $CDCl_3$; δ in ppm, *J* in Hz. ESI Mass spectra were recorded on Agilent LC-MSD-Trap-SL apparatus; in *m*/*z*.

**General procedure for the preparation of Compound 4a.** To a mixture of anthranilic acid **1** (1 mmol), trimethyl or triethyl orthoformate **2** (1.2 mmol) and aniline **3a** (1.2 mmol), silicagel supported PMA [59] (0.01 mmol) was added. The reaction mixture was stirred at room temperature for 5 min. After completion of the reaction (monitored by TLC) 10 mL of $CH_2Cl_2$ was added to the reaction mixture and the catalyst

**Scheme 1**

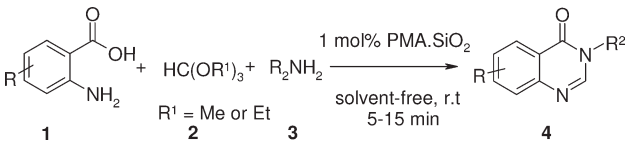
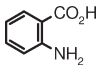
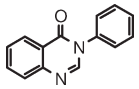
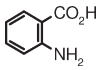
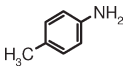
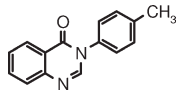
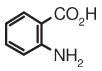
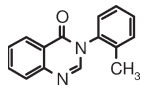
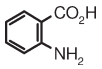
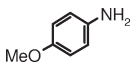
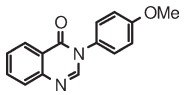
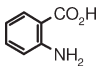
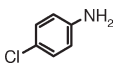
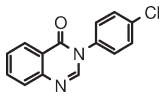
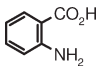
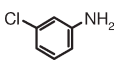
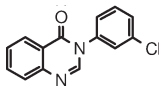
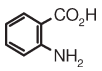
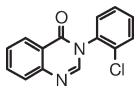
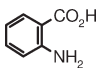
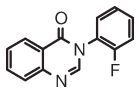
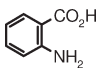
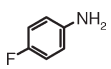
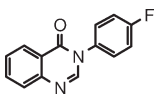
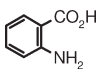
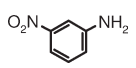
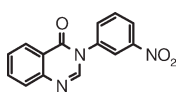
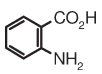
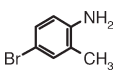
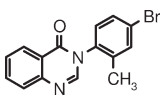
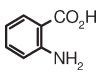
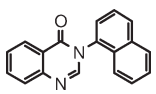
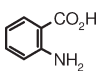
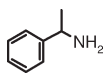
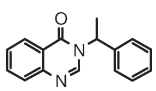
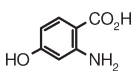


**Table 1**

PMA.$SiO_2$ catalyzed one-pot synthesis of 4(3*H*)-quinazolinones[a] at room temperature.

| Entry | Anthranilic acid | Amine | Quinazolinone | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|
| a |  |  |  | 5 | 98 |
| b |  |  |  | 5 | 98 |
| c |  |  |  | 5 | 96 |
| d |  |  |  | 5 | 95 |
| e |  |  |  | 8 | 95 |
| f |  |  |  | 8 | 94 |
| g |  |  |  | 8 | 94 |
| h |  |  |  | 10 | 92 |
| i |  |  |  | 10 | 92 |
| j |  |  |  | 15 | 88 |
| k |  |  |  | 8 | 95 |
| l |  |  |  | 8 | 90 |
| m |  |  |  | 5 | 91 |
| n |  |  |  | 8 | 95 |
| o |  |  |  | 10 | 92 |
| p |  |  |  | 10 | 92 |
| q |  |  |  | 6 | 94 |

[a] All products are characterized by NMR and Mass spectra.
[b] Yields refer to isolated pure products.

was recovered by filtration. The filtrate was washed with aq HCl (5%) (2 × 10 mL) followed by $H_2O$ (2 × 5 mL). The organic layer was dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure to get the crude product. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate 5:1 as eluent) to afford the pure product **4a** in 98% yield.

**Selected spectroscopic data.** ***Compound 4a.*** $^1$H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, 1H, $J$ = 10.9 Hz), 8.36 (s, 1H), 7. 49 (d, 1H, $J$ = 8.0 Hz), 7.39–7.23 (m,3H), 7.21–7.04 (m, 4H). IR (KBr): 1682, 1600, 1442, 1310, 753, 693 $cm^{-1}$. EIMS: *m*/*z* 223 ($M^+$+1).

***Compound 4b.*** $^1$H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, 1H, $J$ = 11.3 Hz), 8.31 (s, 1H), 7.41–7.35 (m, 1H), 7.15–7.05 (m, 2H), 7.00–6.95 (m, 3H), 2.32 (s, 3H). IR (KBr):1686, 1607, 1518, 1297, 815 $cm^{-1}$. EIMS: *m*/*z* 237 ($M^+$+1).

***Compound 4m.*** $^1$H NMR (300 MHz, $CDCl_3$): δ 8.31(d, 1H, $J$ = 8.0 Hz), 7.8 (s, 1H), 7.75–7.67 (m, 2H), 7.52–7.44 (m, 1H), 7.41–7.32 (m, 5H), 6.35 (q, 1H $J$ =7.3 Hz), 1.84 (d, 3H, $J$ = 7.3 Hz). IR (KBr):1674, 1605, 1474, 1383, 1248, 1160, 774, 700 $cm^{-1}$. EIMS: *m*/*z* 251 ($M^+$+1).

***Compound 4p.*** $^1$H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.32–7.18 (m, 3H), 7.08–6.95 (m, 5H). IR (KBr):1683, 1600, 1543, 1494, 1441, 1309, 753, 692 $cm^{-1}$. EIMS: *m*/*z* 268 ($M^+$+1).

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## REFERENCES AND NOTES

[1] Okuhara, T.; Mizuno, N.; Misono, M. Adv Catal 1996, 41, 113.

[2] Koepy, J. B.; Mead, J. F.; Brockman, J. A., Jr. J Am Chem Soc 1947, 69, 1837.

[3] Ablondi, F.; Gordon, S.; Morton, J. II; Williams, J. H. J Org Chem 1952, 17, 14.

[4] Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. Tetrahedron Lett 1999, 40, 2175.

[5] Tiofeeva, M. N.; Dimidov, A. V.; Kozhevnikov, I. V. J Mol Catal 1993, 79, 21.

[6] Drago, R. S.; Dias, J. A.; Maier, T. J Am Chem Soc 1997, 119, 7702.

[7] Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. J Med Chem 1990, 33, 161.

[8] Tereshima, K.; Shimamura, H.; Kawase, A.; Tanaka, Y.; Tanimura, T.; Kamisaki, T.; Ishizuka, Y.; Sato, M. Chem Pharm Bull 1995, 43, 2021.

[9] Kurogi, Y.; Inoue, Y.; Tsutsumi, K.; Nakamura, S.; Nagao, K.; Yohsitsugu, H.; Tsuda, Y. J Med Chem 1996, 39, 1443.

[10] Liverton, N. J.; Armstong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. Bioorg Med Chem Lett 1998, 8, 483.

[11] Gueyrard, D.; Gurnel, V.; Leoni, O.; Palmieri, S.; Rollin, P. Heterocycles 2000, 58, 827.

[12] Ono, Y.; Thomas, J. M.; Zamaraev, K. I., Eds.; Perspectives in Catalysis; Blackwell: London, 1992, p 341.

[13] Kozhevnikov, I. V.; Matveev, K. I. Appl Catal A 1983, 5(2), 135.

[14] Izumi, Y.; Urabe, K.; Onaka, A. Zeolite, Clay and Heteropolyacids in Organic Chemistry; VCH: Weinheim, Kodansha, Tokyo, 1992, p 99.

[15] Kozhevnikov, I. V. Catal Rev Sci Eng 1995, 37, 311.

[16] Misono, M.; Noriji, N. Appl Catal 1990, 64, 1.

[17] Izumi, Y.; Hasebe, R.; Urabe, K. J Catal 1983, 84, 402.

[18] Soeda, H.; Okuhara, T.; Misono, M. Chem Lett 1994, 909.

[19] Schwegler, M. A.; van Bekkum, H.; Munck, N. Appl Catal 1991,74.

[20] Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Thou, T. C. Science 1946, 103, 59.

[21] Martin, T. A.; Wheller, A. G.; Majewski, R. F.; Corrigan, J. R. J Med Chem 1964, 7, 2.

[22] Kurogi, Y.; Inoue, Y.; Tsutsumi, K.; Nakamura, S.; Nagao, K.; Yohsitsugu, H.; Tsuda, Y. J Med Chem 1966, 39, 1443.

[23] Ana, B.; Boteanu, S. Farmacia 1971, 19, 683.

[24] Dienei, J. B.; Dowalo, F.; Hoeven, H. V.; Bender, P.; Love, B. J Med Chem 1973, 16, 633.

[25] Ravishankar, C. H.; Devender Rao, A.; Bhaskar Rao, A.; Malla Reddy, V.; Sattur, P. B. Curr Sci 1984, 53, 1069.

[26] Chandrasekhar, V.; Raghurama Rao, A.; Malla Reddy, V. Indian Drugs 1986, 3, 24.

[27] Naithani, P. K.; Palit, G.; Srivastava, V. K.; Shankar, K. Indian J. Chem. 1989, 28B, 745.

[28] Dempcy, R. O.; Skibo, E. B. Bioorg Med Chem Lett 1993, 1, 39.

[29] Tereshima, K.; Shimamura, H.; Kawase, A.; Tanaka, Y.; Tanimura, T.; Kamisaki, T.; Ishizuka, Y.; Sato, M. Chem Pharm Bull 1995, 43, 2021.

[30] Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. Bioorg Med Chem Lett 1998, 8, 484.

[31] Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. Tetrahedron Lett 1999, 40, 2175.

[32] Gueyrard, D.; Gurnel, V.; Leoni, O.; Palmieri, S.; Rollin, P. Heterocycles 2000, 52, 827.

[33] Cao, S.-L.; Feng, Y.-P.; Jiang, Y.-Y.; Liu, S.-Y.; Ding, G.-Y.; Li, R.-T. Bioorg Med Chem Lett 2005, 5, 1915.

[34] Kunes, J.; Bazant, J.; pour, M.; Waisser, K.; slosarec, M.; Janota, J. Farmaco 2000, 55, 725.

[35] Kuehl, F. A., Jr; Spencer, C. F.; Folkers, K. J Am Chem Soc 1948, 70, 2091.

[36] Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. Tetrahedron Lett 1999, 40, 2175.

[37] Rewcastle, G. W.; Denny, W. A.; Bridges, A. J.; Zhou, H.; Cody, D. R.; McMichael, A.; Fry, D. W. J Med Chem 1995, 38, 3482.

[38] Bridges, A. J.; Zhon, H.; Cody, D. R.; Rewcastle, G.; McMichael, A.; Showalter, H. D. H.; Fry, D. W.; Kraker, A. J.; Denny, W. A. J Med Chem 1996, 39, 267.

[39] Rosowsky, A.; Mota, C. E.; Wright, J. E.; Queener, S. F. J Med Chem 1994, 37, 4522.

[40] Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. J Med Chem 1990, 33, 1721.

[41] Hour, M.-J.; Huans, L.-J.; Kuo, S.-C.; Xia, Y.; Bastow; Nakanishi, Y.; Hamel, E.; Lee, K. H. Med Chem 2000, 43, 4479.

[42] Onaka, T.; Tetrahedron Lett 1971, 46, 4387.

[43] Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. J Am Chem Soc 1977, 99, 2306.

[44] Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. Heterocycles 1985, 23, 2803.

[45] Sauter, F.; Frohlic, J.; Blasl, K.; Gewald, K. Heterocycles 1985, 40, 851.

[46] Majo, V. J.; Perumal, P. T. Tetrahedron Lett 1996, 37, 5015.

[47] Prasad, M.; Chen, L.; Repic, O.; Blacklock, T. J. Synth Commun 1998, 28, 2125.

[48] Connolly, D. J.; Guiry, P. J. Synlett 2001, 11, 1707.

[49] Wang, L.; Xia, J.; Qin, F.; Qian, C.; Sun, J. Synthesis 2003, 81, 1241.

[50] Kotsuki, H.; Sakai, H.; Morimoto, H.; Suenaga, H. Synlett 1999, 12, 1993.

[51] Deetz, J. M.; Malerich, J. P.; Beatty, A. M.; Smith, B. D. Tetrahedron Lett 2001, 42, 1851.

[52] Eguichi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamato, Y. J Org Chem 1996, 61, 7316.

[53] Bogest, M. T.; Gortner, R. A. J Am Chem Soc 1910, 32, 119.

[54] Khosropour, A. R.; Mohammadpoor-Baltork, I.; Ghorbankhani, H. Tetrahedron Lett 2006, 47, 3561.

[55] Wang, L.; Xia, J.; Qin, F.; Qian, C.; Sun, J. Synthesis 2003, 8, 1241.

[56] Narasimhulu, M.; Mahesh, K. C.; Reddy, T. S.; Rajesh, K.; Lu, Y. V. Tetrahedron Lett 2006, 47, 4381.

[57] Chari, M. A.; Shobha, D.; Mukkante, K. Catal commun 2006, 7, 787.

[58] Das, B.; Banerjee, J. Chem Lett 2004, 33, 960.

[59] Kishore Kumar, G. D.; Baskaran, S. J Org Chem 2005, 70, 4520.

# Stereoselective Synthesis of β-Amino Ketones Possessing β-[(2*H*-Pyran-2-one)-3-Yl]-β-chlorovinyl Moiety *via* Three-Component Direct Mannich-Type Reaction, Catalyzed with $ZrOCl_2 \cdot 8H_2O$

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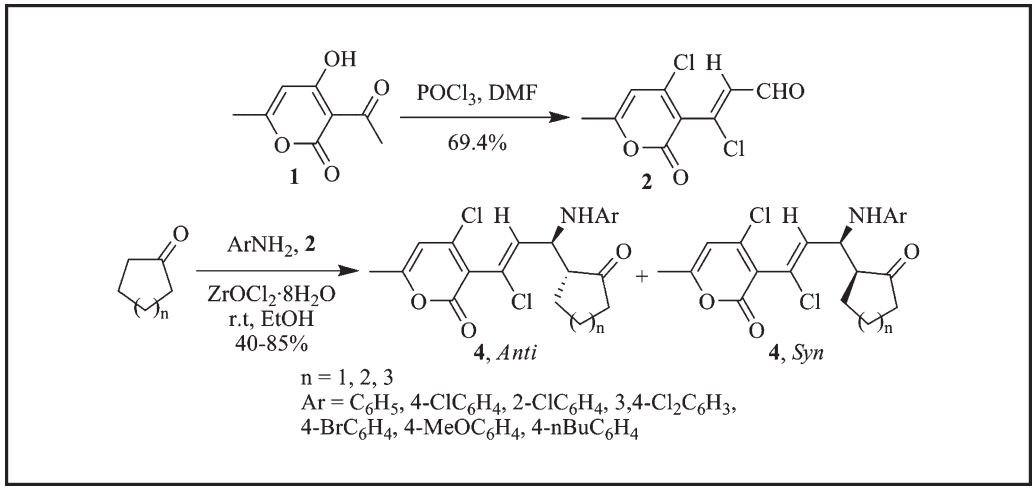


New *Z*-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein was synthesized starting from dehydroacetic acid using Vilsmeier–Haack reaction and efficiently used in three component direct Mannich-type reaction with different anilines, cyclic and acyclic ketones catalyzed with zirconium oxychloride ($ZrOCl_2 \cdot 8H_2O$) in ethanol at room temperature. Also, comenic aldehyde was used in direct Mannich-type reaction at the same conditions. The reaction proceeds rapidly and affords the corresponding β-amino ketones in good to high yields with moderate to high stereoselectivity.

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## INTRODUCTION

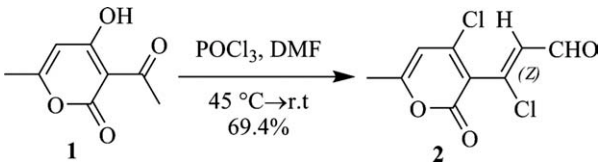
The Vilsmeier–Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds [1]. The reactions of aliphatic substrates [2], particularly carbonyl compounds [3] with chloromethylene iminium salts are highly versatile. One aspect of its importance is its reaction with a keto methylene group to produce β-chloroacroleins [4].

β-Amino carbonyl compounds are also attractive targets for chemical synthesis because of their wide utility as biologically active molecules [5]. The Mannich reaction is a classical method for preparation of the β-amino carbonyl compounds [5,6] and has been one of the most important basic reactions in organic chemistry for its use in natural product and pharmaceutical synthesis [7]. However, because of the drastic reaction conditions and long reaction times, the classical Mannich reaction is plagued by a number of serious disadvantages [6]. Therefore, catalytic Mannich reactions have been reported by several groups as an efficient method to prepare β-amino carbonyl compounds [8,9d].

Because of their easy availability [10] and low toxicity [11], Zr(IV) salts have recently attracted much attention as a catalyst for organic transformations [9]. To our knowledge, there have been only a few reports on the metal oxysalt-based organic reactions [12].

As part of our research on synthesis of pyrone derivatives[13], herein we report a simple and environmentally benign stereoselective synthesis of new β-amino ketones possessing β-[(2*H*-pyran-2-one)-3-yl]-β-chlorovinyl or 4-oxo-4*H*-pyran-2-yl moiety *via* direct Mannich-type reaction between *Z*-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein **2** or *O*-protected comenic aldehyde **10**, anilines and ketones at room temperature using $ZrOCl_2 \cdot 8H_2O$ as catalyst.

**Scheme 1.** Synthesis of *Z*-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein **2**.



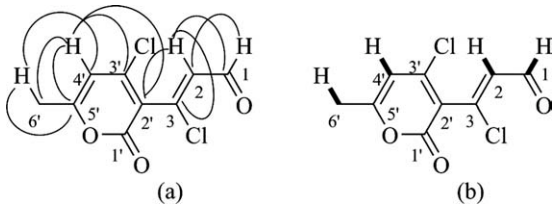




**Figure 1.** (a) HMBC correlations and (b) HMQC correlations for **2**.

## RESULTS AND DISCUSSION

A new β-chloroacrolein with 2*H*-pyran-2-one moiety **2** was synthesized from commercially available dehydroacetic acid **1** in 69.4% yield using Vilsmeier–Haack reaction as outlined in Scheme 1.

The structure of compound **2** was established from IR, $^1$H NMR, $^{13}$C NMR, 2D-NMRs (HMQC and HMBC), and mass spectral data and elemental analyses. The values of coupling constant $^3J$ of the proton signals of —ClC=C**H**—CO—**H** in the $^1$H NMR spectra equal to 6.8 Hz indicate that these atoms are located in the *s-cis* position [4h,i]. It was shown by the study of isomer composition of β-aryl-β-chloroacroleins, arising from aryl ketones [4j,k,o] and heteroaryl ketones [4o] in the reaction with Vilsmeier-Haack reagent, α-unsubstituted acroleins are obtained exclusively as a *Z* isomer. Therefore, **2** has *s-cis-Z*-configuration at the side chain. The HMBC spectral data of **2** [Fig. 1(a)] revealed long range correlations between the $H_1$ (δ 10.18) with $C_2$ (at δ 132.3); $H_2$ with $C_1$, $C_3$, and $C_{2'}$ (at δ 190.6, 142.8, and 120.1, respectively); $H_{4'}$ (δ 6.26) with $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ (at δ 120.1, 150.8, 164.1, and 20.4, respectively); $H_{6'}$ (δ 2.35) with $C_{4'}$ and $C_{5'}$ (at δ 107.1 and 164.1, respectively). There are no correlations between $C_{1'}$ (carbonyl group of α-pyrone ring) and protons. Also HMQC spectral data of **2** was shown in Figure 1(b) that revealed one bond correlation between $H_1$ (δ 10.18) with $C_1$ (δ 190.6); $H_2$ (δ 6.32) with $C_2$ (δ 132.3); $H_{4'}$ (δ 6.26) with $C_{4'}$ (δ 107.1); $H_{6'}$ (δ 2.35) with $C_{6'}$ (δ 20.4).

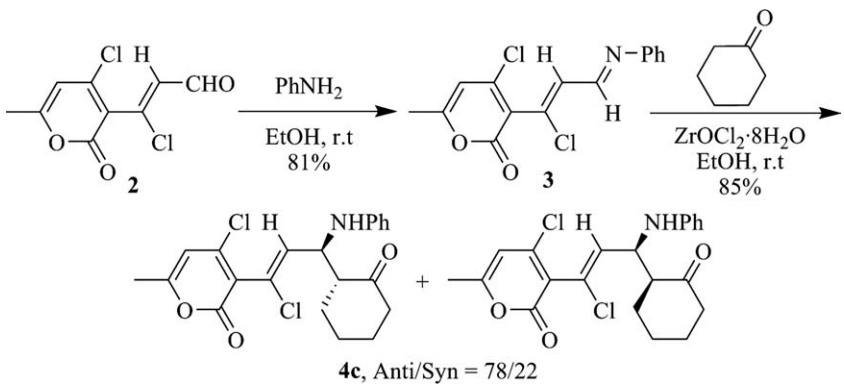
The $ZrOCl_2{\cdot}8H_2O$ catalyzed Mannich reaction was first studied with preformed imine **3**. As shown in Scheme 2, imine **3**, which was synthesized by reaction of **2** and aniline in EtOH at room temperature, was treated with cyclohexanone in the presence of catalytic amount of $ZrOCl_2{\cdot}8H_2O$ and Mannich adduct **4c** was isolated in 85% yield, with 78% anti selectivity.

Subsequently, a one-pot direct Mannich-type reaction of **2** with anilines and cyclic ketones were investigated (Scheme 3).

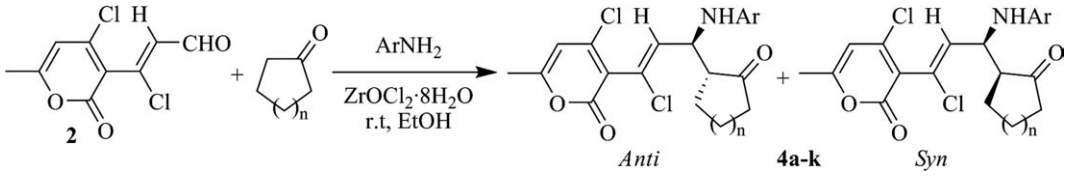
To examine the optimal conditions, Mannich reaction of **2** (1 mmol), aniline (1 equiv.), and cyclohexanone (2 equiv.), using $ZrOCl_2{\cdot}8H_2O$ as catalyst was carried out in different solvents such as acetonitrile, dichloromethane, ethanol, water, and solvent-free conditions. Ethanol was determined as a powerful solvent for high yield and anti selectivity of reaction and environmental acceptability. In dichloromethane, acetonitrile and under solvent-free conditions, in addition to Mannich adducts, side product **5** (Fig. 2), was obtained. In water, imine **3** was isolated as a sole product. Also 0.07 equiv. (7 mol %) of $ZrOCl_2{\cdot}8H_2O$ was determined as optimum amount of catalyst.

Eleven examples of the direct Mannich-type reaction of 2, anilines and cyclic ketones in ethanol are listed in Table 1. The reactions were performed by adding cyclic ketones (2 equiv.) to a mixture of the 2 (1 mmol) and anilines (1 equiv.) in ethanol in the presence of 0.07 equiv. of $ZrOCl_2{\cdot}8H_2O$ at room temperature to give the corresponding β-amino ketones 4a–k in 40–85% yields with moderate to high anti selectivity (Scheme 3).

**Scheme 2.** Synthesis of imine **3** and its Mannich reaction with cyclohexanone.



**Scheme 3.** One-pot Mannich-type reaction of **2**, anilines and cyclic ketones.



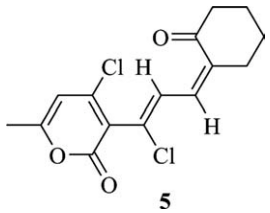




**Figure 2.** Structure of side product **5**.

According to the literature [8a,9d] anti/syn ratio was determined using $^1$H NMR spectra.

Exceptionally, in the case of cyclopentanone ($n = 1$), in addition to Mannich adducts **4a**,**b** the side product **6** was obtained. With increasing reaction time (over 2 h) the Mannich adducts **4a**,**b** were completely converted to **6** (Scheme 4). In the cases of cyclohexanone, product **4c** even after 24 h was not converted to adduct **5**. This can be attributed to more acidity of cyclopentanone protons in comparison with cyclohexanone ones. In the $^1$H NMR spectra of **5** and **6**, the values of coupling constant $^3J$ of the proton signals of —ClC=C**H**—C**H**= equal to 11.3 and 11.2 Hz, respectively, indicate that these atoms are located in the *s-trans* position.

Unexpectedly, from reaction of aliphatic amine such as *n*-butyl amine with **2** and cyclohexanone in the presence of $ZrOCl_2 \cdot 8H_2O$ in ethanol at room temperature, **5** was obtained as a sole product (Scheme 5). In fact, *n*-butyl amine acts as a base and aldol condensation was occurred instead of Mannich reaction.

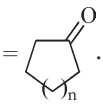
Also, direct Mannich-type reaction of **2** and anilines with acyclic ketones such as acetone and acetophenone catalyzed with $ZrOCl_2 \cdot 8H_2O$ was investigated at room temperature and corresponding β-amino ketones **7a–d** were obtained in good to high yields in short reaction time. The overall reaction is best formulated in Scheme 6.

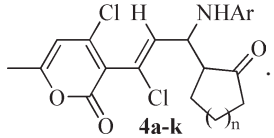
Methyl and Ethyl acetoacetate were also treated in the direct Mannich-type reaction with **2** and aniline, catalyzed with $ZrOCl_2 \cdot 8H_2O$ in ethanol at room temperature in 25 min, and interestingly corresponding dihydropyridines **8a**,**b** were isolated as sole products instead of Mannich adduct **9** (Scheme 7).

**Table 1**

Yields and selectivity of direct mannich-type reaction of β-[(2*H*-pyran-2-one)-3-yl]-β-chloroacrolein **2**, anilines, and cyclic ketones in the presence of $ZrOCl_2 \cdot 8H_2O$.

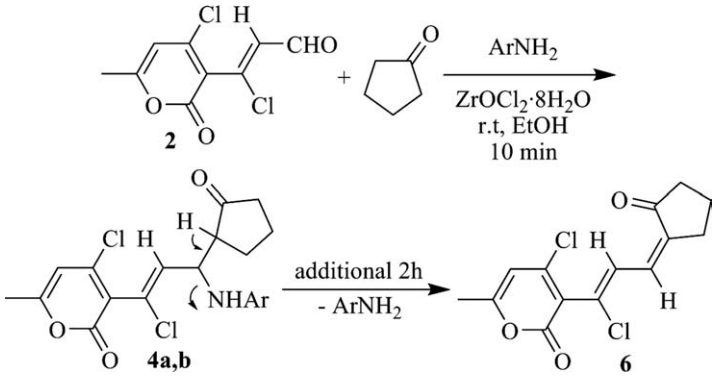
| Ketone[a] | $ArNH_2$ | Product[b] | Time (min) | Yield (%)[c] | Anti/Syn |
|---|---|---|---|---|---|
| $n = 1$ | $C_6H_5NH_2$ | **4a** | 10 | 40 | 63:37 |
| $n = 1$ | 4-$ClC_6H_4NH_2$ | **4b** | 10 | 55 | 70:30 |
| $n = 2$ | $C_6H_5NH_2$ | **4c** | 25 | 80 | 74:26 |
| $n = 2$ | 4-$ClC_6H_4NH_2$ | **4d** | 30 | 76 | 58:42 |
| $n = 2$ | 2-$ClC_6H_4NH_2$ | **4e** | 30 | 75 | 58:42 |
| $n = 2$ | 3,4-$Cl_2C_6H_3NH_2$ | **4f** | 30 | 85 | 33:67 |
| $n = 2$ | 4-$BrC_6H_4NH_2$ | **4g** | 30 | 80 | 70:30 |
| $n = 2$ | 4-$MeOC_6H_4NH_2$ | **4h** | 15 | 85 | 75:25 |
| $n = 2$ | 4-*n*$BuC_6H_4NH_2$ | **4i** | 20 | 78 | 80:20 |
| $n = 3$ | $C_6H_5NH_2$ | **4j** | 40 | 76 | 70:30 |
| $n = 3$ | 4-$ClC_6H_4NH_2$ | **4k** | 45 | 75 | 62:38 |

[a] Ketone =  .

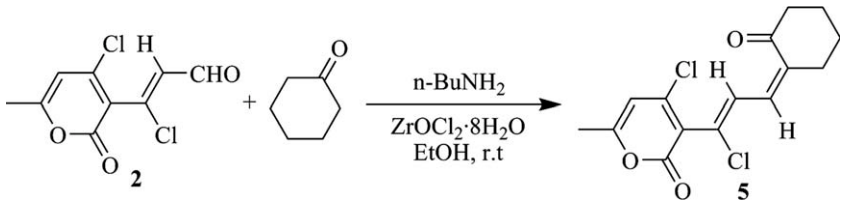
[b] Product = 


[c] Isolated yields.

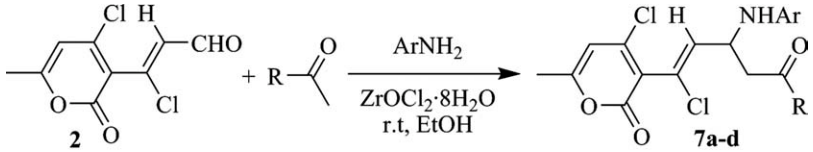
**Scheme 4.** Conversion of Mannich adducts **4a**,**b** to adduct **6**.




**Scheme 5.** Aldol reaction of **2** with cyclohexanone in the presence of *n*-$BuNH_2$/$ZrOCl_2 \cdot 8H_2O$.

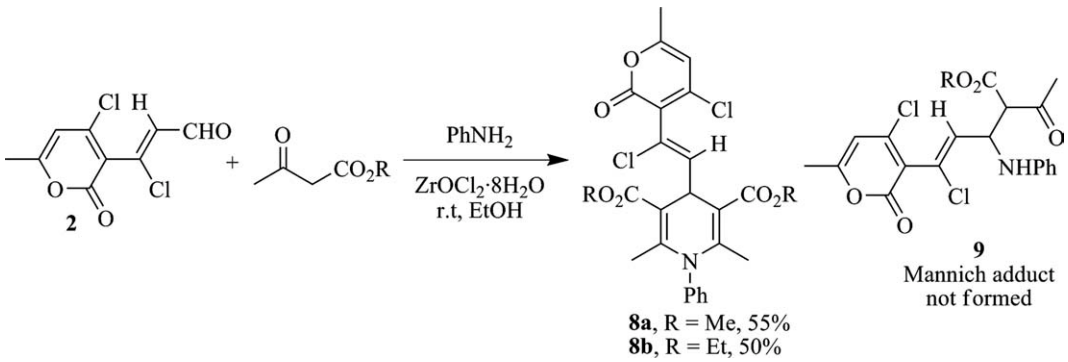



**Scheme 6.** Mannich reaction of **2**, anilines and acyclic ketones.



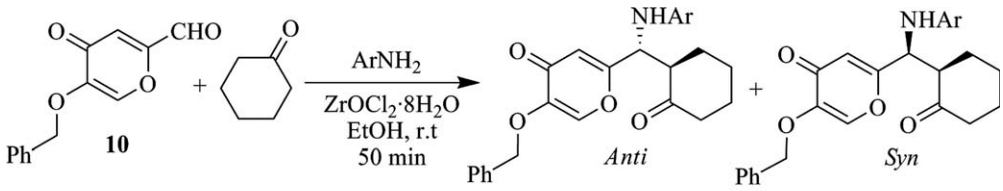

**7a** R = Me, Ar = $C_6H_5$, 10 min, 80%
**7b** R = Me, Ar = 4-$ClC_6H_4$, 10 min, 75%
**7c** R = Ph, Ar = $C_6H_5$, 90 min, 67%
**7d** R = Ph, Ar = 4-$ClC_6H_4$, 90 min, 65%

**Scheme 7.** Synthesis of new *N*-aryl dihydropyridines possessing β-[(2*H*-pyran-2-one)-3-yl]-β-chlorovinyl at $C_4$-position.




**8a**, R = Me, 55%
**8b**, R = Et, 50%

**Scheme 8.** Mannich-type reaction of comenic aldehyde **10**, anilines, and cyclohexanone.




**11a** Ar = $C_6H_5$, 88%, *Anti*/*Syn* = 40/60
**11b** Ar = 4-$ClC_6H_4$, 85%, *Anti*/*Syn* = 55/45
**11c** Ar = 3,4-$Cl_2C_6H_3$, 90% *Anti*/*Syn* = 75/25

Also, 5-(benzyloxy)-4-oxo-4*H*-pyran-2-carbaldehyde (*O*-protected comenic aldehyde) **10** was synthesized according to literature [14] and used in three component direct Mannich-type reaction with three different anilines and cyclohexanone. As shown in Scheme 8, $ZrOCl_2 \cdot 8H_2O$ efficiently catalyzed this reaction at room temperature and Mannich adducts **11a–c** were obtained in high yields with moderate stereoselectivity.

## CONCLUSIONS

In summary, new β-[(2*H*-pyran-2-one)-3-yl]-β-chloroacrolein was synthesized in good yield and was subjected to the three-component Mannich-type reaction with different anilines, cyclic and acyclic ketones, catalyzed with $ZrOCl_2 \cdot 8H_2O$ in ethanol. Moderate to good anti selectivity was observed in very short reaction times at room temperature. Similarly, Mannich-type reaction with protected comenic aldehyde was also investigated, and corresponding β-amino ketones were obtained in high yields with moderate to high stereoselectivity. Ethyl and methyl acetoacetate were also treated with aniline and β-[(2*H*-pyran-2-one)-3-yl]-β-chloroacrolein and interestingly corresponding dihydropyridines were synthesized instead of Mannich adduct.

## EXPERIMENTAL

**General.** All chemicals were purchased and used without any further purification. Melting points were determined on a Electrothermal MEL-TEMP apparatus (model 1202D) and are uncorrected. FTIR spectra were obtained with a Bruker Tensor 27 spectrometer. NMR spectra were recorded at 400 and 500 MHz for proton and at 100 and 125 MHz for carbon nuclei in $CDCl_3$. Elemental analyses were done by a Vario EL III, Elementar. The products were purified by PLC on silica gel by using hexane/acetone mixture as eluent. All compounds were characterized by their spectroscopic data and elemental analysis.

***Synthesis of Z-3-chloro-3-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)acrolein (2).*** $POCl_3$ (14.8 g, 96.4 mmol) was added dropwise to dimethylformamide (DMF) (24 mL) with stirring at 30–35°C. The mixture was stirred at 50°C for 1 h. Then a solution of dehydroacetic acid **1** (4 g, 19.4 mmol) in least amount of DMF was added dropwise with stirring to the reaction mixture. After that the mixture was stirred at 45–55°C for 2 h, kept over night at room temperature and poured into the water (200 mL). The obtained solution was left at room temperature. Yellowish brown crystals were filtered off and dried in air. β-[(2*H*-Pyran-2-one)-3-yl]-β-chloroacrolein **2** was obtained in 69.4% yield. Mp. 90–92°C; FTIR (KBr): 3081, 3030, 2968, 2927 (CH), 2864, 2746 ($CH_{Aldehyde}$), 1718, 1679, 1616, 1545, 1304, 1248, 1121, 837, 768 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 10.18 (d, $^3J$ = 6.8 Hz, 1H, CHO), 6.32 (d, $^3J$ = 6.8 Hz, 1H, $CH_{Vinyl}$), 6.26 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.35 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 190.6 ($C{=}O_{Aldehyde}$), 164.1, 158.5, 150.8, 142.8, 132.3, 120.1, 107.1, 20.4 ($CH_3$) ppm; Ms: m/z = 233 ($[M+H]^+$, 4%; $[M+H+2]^+$, 2.8%; $[M+H+4]^+$, 1.3%), 205 (25%), 189 (36%), 169 (30%), 43 (100%); Anal. Calcd. for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.60. Found: C, 46.56; H, 2.65.

***Synthesis of 4-chloro-3-[(1Z)-1-chloro-3-(phenylimino)-prop-1-enyl]-6-methyl-2H-pyran-2-one (3).*** β-[(2*H*-Pyran-2-one)-3-yl]-β-chloroacrolein **2** (1 mmol) was treated with Aniline (1 mmol) in ethanol (3 mL) at room temperature for 2 min. After completion of the reaction, mixture was poured into the water (20 mL). The resulting yellow solids were separated by filtration and dried in air. Imine **3** was obtained in 80.8% yield, Mp. 124–126°C; FTIR (KBr): 3100, 3020, 2967, 2922, 1717, 1684, 1625, 1542, 1266, 1154, 821, 764, 694 $cm^{-1}$; $^1H$ NMR (400MHz, $CDCl_3$): δ 8.62 (d, $^3J$ = 8.5 Hz, 1H, CH=N), 7.39–7.43 (m, 2H, $CH_{Ar}$), 7.22–7.30 (m, 3H, $CH_{Ar}$) 6.77 (d, $^3J$ = 8.5 Hz, 1H, $CH_{Vinyl}$), 6.24 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.33 (s, 3H, $CH_3$) ppm; $^{13}C$ NMR(100 MHz, $CDCl_3$): δ 161.9, 157.7, 155.7, 149.8, 149.3, 132.7, 131.6, 128.2, 126.0, 119.9, 119.3, 105.7, 18.8 ($CH_3$) ppm; Anal. Calcd. for $C_{15}H_{11}Cl_2NO_2$: C, 58.46; H, 3.60; N, 4.55. Found: C, 58.28; H, 3.91; N, 4.77.

**General procedure for Mannich-type reaction.** To a solution of β-[(2*H*-Pyran-2-one)-3-yl]-β-chloroacrolein **2** (1 mmol) in ethanol (5 mL) were added aniline (1 mmol), cyclohexanone (2 eq), and $ZrOCl_2 \cdot 8H_2O$ (0.022 g), successively at room temperature (20–25°C) and stirred for 25 min. After completion of the reaction, ethanol was evaporated under reduced pressure. The crude solid was dissolved in $CH_2Cl_2$ (10 mL) and catalyst was removed by filtration. Filtrate was washed with a 5% aqueous $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$, and concentrated to dryness. The crude mixture was purified by PLC on silica gel using hexane/acetone (20:3) to afford the final product. Specific detail was given for each compound.

***(Z)-4-Chloro-3-[1-chloro-3-(2-oxocyclopentyl)-3-(phenylamino)prop-1-enyl]-6-methyl-2H-pyran-2-one (4a).*** Anti/Syn: 63/37; Yellow solid; FTIR (KBr): 3381 (NH), 3055, 3020,

2939, 2865, 1734, 1722, 1626, 1546, 1505, 1305, 1260, 840, 750 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.13–7.18 (m, 2H, $CH_{Ar}$), 6.67–6.75 (m, 3H, $CH_{Ar}$), 6.10 (d, $^4J$ = 0.8 Hz, 0.63H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.05 (d, $^4J$ = 0.7 Hz, 0.37H, $CH_{\alpha\text{-Pyrone}}$, syn), 5.93 (d, $^3J$ = 8.7 Hz, 0.63H, $CH_{Vinyl}$, anti), 5.62 (d, $^3J$ = 9.3 Hz, 0.37H, $CH_{Vinyl}$, syn), 4.70 (dd, $^3J$ = 3.9 Hz, $^3J$ = 9.3 Hz, 0.37H, CH—N, syn), 4.53 (dd, $^3J$ = 7.1 Hz, $^3J$ = 8.6 Hz, 0.63H, CH—N, anti), 2.28 (s, 3H, $CH_3$, (anti and syn)), 2.06–2.35 (m, 7H, CH and $CH_{2\ Cyclopentanone}$, anti and syn); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 220.7, 218.7 ($C{=}O_{Cyclopentanone}$), 161.1, 161.0, 158.3, 149.1, 148.9, 145.5, 136.1, 133.4, 128.1, 128.0, 123.2, 122.9, 119.8, 117.5, 117.0, 113.4, 113.1, 105.5, 105.4, 52.7, 52.2, 51.4, 50.8, 38.5, 37.9, 25.9, 25.3, 19.9, 19.7, 18.9, 18.7 ppm; Anal. Calcd. for $C_{20}H_{19}Cl_2NO_3$: C, 61.24; H, 4.88; N, 3.57. Found: C, 60.93; H, 5.01; N, 3.68.

***(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-3-(2-oxocyclopentyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4b).*** Anti/Syn: 70/30; Yellow solid; FTIR (KBr): 3378 (NH), 3070, 3061, 2940, 2860, 1733, 1724, 1630, 1545, 1508, 1306, 1263, 857, 761 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.08–7.12 (m, 2H, $CH_{Ar}$, anti and syn), 6.62–6.66 (m, 1.4H, $CH_{Ar}$, anti), 6.59–6.61 (m, 0.6H, $CH_{Ar}$, syn), 6.11 (d, $^4J$ = 0.7 Hz, 0.7H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.07 (d, $^4J$ = 0.8 Hz, 0.3H, $CH_{\alpha\text{-Pyrone}}$, syn), 5.87 (d, $^3J$ = 8.7 Hz, 0.7H, $CH_{Vinyl}$, anti), 5.58 (d, $^3J$ = 9.4 Hz, 0.3H, $CH_{Vinyl}$, syn), 4.75–5.32 (s, br, 1H, NH, anti and syn), 4.63 (dd, $^3J$ = 3.3 Hz, $^3J$ = 8.9 Hz, 0.3H, CH—N, syn), 4.45 (dd, $^3J$ = 7.5 Hz, $^3J$ = 8.5 Hz, 0.7H, CH—N, anti), 1.85–2.46 (m, 7H, CH and $CH_{2\ Cyclopentanone}$, anti and syn), 2.25 (d, $^4J$ = 0.4 Hz, 2.1H, $CH_3$, anti), 2.23 (d, $^4J$ = 0.6 Hz, 0.9H, $CH_3$, syn). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 220.1, 219.3 ($C{=}O_{Cyclopentanone}$), 161.2, 161.0, 158.2, 158.1, 151.3, 150.1, 145.8, 136.6, 134.0, 128.8, 128.1, 124.1, 124.0, 119.6, 118.3, 118.1, 114.0, 113.8, 105.2, 52.4, 52.1, 51.1, 50.9, 38.6, 37.9, 26.1, 25.6, 20.3, 19.7, 18.3, 18.1 ppm; Anal. Calcd. for $C_{20}H_{18}Cl_3NO_3$: C, 56.29; H, 4.25; N, 3.28. Found: C, 56.01; H, 4.23; N, 3.59.

***(Z)-4-Chloro-3-[1-chloro-3-(2-oxocyclohexyl)-3-(phenylamino)prop-1-enyl]-6-methyl-2H-pyran-2-one (4c).*** Anti/Syn: 74/26; Pale yellow solid, FTIR (KBr): 3386 (NH), 3085, 3030, 2938, 2862, 1731, 1699, 1625, 1603, 1546, 1505, 1438, 1384, 1301, 1257, 1212, 795, 752, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.14–7.18 (m, 2H, $CH_{Ar}$), 6.68–6.73 (m, 3H, $CH_{Ar}$), 6.07 (d, $^3J$ = 9.3 Hz, 0.26H, $CH_{Vinyl}$, syn), 6.06 (d, $^4J$ = 0.8 Hz, 0.74H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.05 (d, $^4J$ = 0.7 Hz, 0.26H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.03 (d, $^3J$ = 8.4 Hz, 0.74H, $CH_{Vinyl}$, anti), 4.53 (dd, $^3J$ = 3.7 Hz, $^3J$ = 9.3 Hz, 0.26H, CH—N, syn), 4.48 (dd, $^3J$ = 4.8 Hz, $^3J$ = 8.4 Hz, 0.74H, CH—N, anti), 2.94 (dt, $^3J$ = 4.4 Hz, $^3J$ = 12.9 Hz, 0.26H, —COCH<, syn), 2.83–2.89 (m, 0.74H, —COCH<, anti), 2.23 (s, 3H, $CH_3$), 1.66–2.41 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 211.8 ($C{=}O_{Cyclohexanone}$), 160.9, 160.8, 158.2, 148.9, 146.1, 145.7, 136.8, 133.4, 128.0, 124.0, 122.6, 120.0, 119.6, 117.0, 116.9, 113.2, 112.8, 105.4, 105.3, 53.7, 53.6, 52.6, 52.5, 41.5, 41.3, 30.6, 29.6, 26.7, 25.9, 23.8, 23.4, 18.6 ppm; Anal. Calcd. for $C_{21}H_{21}Cl_2NO_3$: C, 62.08; H, 5.21; N, 3.45. Found: C, 62.07; H, 5.26; N, 3.69.

***(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4d).*** Anti/Syn: 58/42; Pale yellow solid, FTIR (KBr): 3393 (NH), 3095, 3042, 2935, 2864, 1729, 1697, 1623, 1548, 1498, 1439, 1238, 822 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.07–7.12 (m, 2H, $CH_{Ar}$), 6.57–6.62 (m, 2H, $CH_{Ar}$), 6.07 (d, $^4J$ = 0.7 Hz, 0.58H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.06 (d, $^4J$ = 0.8 Hz, 0.42H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.03 (d, $^3J$ = 9.3 Hz, 0.42H, $CH_{Vinyl}$, syn), 5.98 (d, $^3J$ = 8.4 Hz, 0.58H, $CH_{Vinyl}$, anti), 4.77 (s, br, 1H, NH), 4.45 (dd, $^3J$ = 3.7 Hz, $^3J$ = 9.3 Hz, 0.42H, CH—N, syn), 4.39 (dd, $^3J$ = 4.6 Hz, $^3J$ = 8.4 Hz, 0.58H, CH—N, anti), 2.91 (dt, $^3J$ = 4.5 Hz, $^3J$ = 12.8 Hz, 0.42H, —COCH<, syn), 2.80–2.85 (m, 0.58H, —COCH<, anti), 2.23 (s, 3H, $CH_3$), 1.65–2.42 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 212.0, 211.9 ($C{=}O_{Cyclohexanone}$), 161.3, 160.9, 158.2, 149.1, 148.7, 144.3, 140.4, 138.4, 137.8, 132.9, 128.1, 127.0, 126.9, 126.7, 124.4, 121.5, 120.1, 117.1, 114.3, 105.7, 105.3, 53.5, 52.7, 41.5, 40.9, 30.4, 29.5, 26.5, 25.9, 23.8, 23.7, 18.8, 18.7 ppm; Anal. Calcd. for $C_{21}H_{20}Cl_3NO_3$: C, 57.23; H, 4.57; N, 3.18. Found: C, 57.12; H, 4.62; N, 3.43.

***(Z)-4-Chloro-3-[1-chloro-3-(2-chlorophenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4e).*** Anti/Syn: 58/42; Pale yellow solid, FTIR (KBr): 3384 (NH), 3092, 2937, 2865, 1733, 1703, 1625, 1595, 1550, 1504, 1438, 1244, 848, 743 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.20–7.23 [2 × d, 7.22 (d, $^3J_{ortho}$ = 7.9 Hz, 0.42H, $CH_{Ar}$, syn), 7.21 (d, $^3J_{ortho}$ = 7.9 Hz, 0.58H, $CH_{Ar}$, anti)], 7.10–7.16 (m, 1H, $CH_{Ar}$), 6.82 (dd, $^4J_{meta}$ = 1.2 Hz, $^3J_{ortho}$ = 8.3 Hz, 0.42H, $CH_{Ar}$, syn), 6.77 (dd, $^4J_{meta}$ = 1.2 Hz, $^3J_{ortho}$ = 8.2 Hz, 0.58H, $CH_{Ar}$, anti), 6.60–6.65 (m, 1H, $CH_{Ar}$), 6.07 (d, $^4J$ = 0.9 Hz, 0.58H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.06 (d, $^4J$ = 0.9 Hz, 0.42H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.05 (d, $^3J$ = 9.4 Hz, 0.42H, $CH_{Vinyl}$, syn), 6.02 (d, $^3J$ = 8.4 Hz, 0.58H, $CH_{Vinyl}$, anti), 5.49 (s, br, 1H, NH), 4.57 (dd, $^3J$ = 3.5 Hz, $^3J$ = 9.3 Hz, 0.42H, CH—N, syn), 4.50 (dd, $^3J$ = 4.5 Hz, $^3J$ = 8.4 Hz, 0.58H, CH—N, anti), 2.94–3.00 (m, 0.42H, —COCH<, syn), 2.86–2.92 (m, 0.58H, —COCH<, anti), 2.23 (d, $^4J$ = 0.8 Hz, 3H, $CH_3$), 1.67–2.43 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 211.5, 211.4 ($C{=}O_{Cyclohexanone}$), 161.0, 160.9, 158.2, 149.0, 148.8, 142.2, 141.9, 136.2, 133.0, 128.0, 126.7, 124.4, 122.9, 119.6, 119.1, 117.0, 116.9, 112.2, 111.8, 105.5, 105.4, 53.6, 52.7, 52.3, 41.54, 41.52, 30.8, 29.5, 26.8, 25.9, 23.8, 23.6, 18.7 ppm; Anal. Calcd. for $C_{21}H_{20}Cl_3NO_3$: C, 57.23; H, 4.57; N, 3.18. Found: C, 57.40; H, 4.69; N, 3.50.

***(Z)-4-Chloro-3-[1-chloro-3-(3,4-dichlorophenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4f).*** Anti/Syn: 33/67; Pale yellow solid, FTIR (KBr): 3395 (NH), 3048, 2934, 2863, 1730, 1702, 1621, 1546, 1488, 1439, 1249, 844, 796, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.16–7.20 [2 × d: 7.19 (d, $^3J_{ortho}$ = 8.7 Hz, 0.33H, $CH_{Ar}$, anti), 7.18 (d, $^3J_{ortho}$ = 8.7 Hz, 0.67H, $CH_{Ar}$, syn)], 6.80 (d, $^4J_{meta}$ = 2.4 Hz, 0.33H, $CH_{Ar}$, anti), 6.78 (d, $^4J_{meta}$ = 2.6 Hz, 0.67H, $CH_{Ar}$, syn), 6.50–6.56 (m, 1H, $CH_{Ar}$), 6.09 (s, 0.33H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.08 (s, 0.67H, $CH_{\alpha\text{-Pyrone}}$, syn), 5.97–6.01 [2 × d: 5.99 (d, $^3J$ = 9.4 Hz, 0.67H, $CH_{Vinyl}$, syn), 5.98 (d, $^3J$ = 8.4 Hz, 0.33H, $CH_{Vinyl}$, anti)], 5.12 (s, br, 1H, NH), 4.41 (dd, $^3J$ = 3.7 Hz, $^3J$ = 9.3 Hz, 0.67H, CH—N, syn), 4.37 (dd, $^3J$ = 4.8 Hz, $^3J$ = 8.5 Hz, 0.33H, CH—N, anti), 2.84–2.93 (m, 1H, —COCH<,anti+syn), 2.24 (s, 3H, $CH_3$), 1.62–2.43 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 212.1, 212.0 ($C{=}O_{Cyclohexanone}$), 161.2, 161.1, 158.3, 158.2, 149.2, 148.9, 145.2, 132.3, 131.7, 131.6, 129.5, 129.4, 125.0, 119.9, 119.6, 119.5, 114.5, 112.9, 105.5, 105.4, 53.3, 53.2, 52.7, 41.5, 30.8, 29.4, 26.7, 25.8, 23.7, 23.5, 18.8 ppm; Anal. Calcd. for $C_{21}H_{19}Cl_4NO_3$: C, 53.08; H, 4.03; N, 2.95. Found: C, 53.01; H, 4.38; N, 3.21.

***(Z)-3-(3-(4-Bromophenylamino)-1-chloro-3-(2-oxocyclohexyl)prop-1-enyl)-4-chloro-6-methyl-2H-pyran-2-one (4g).*** Anti/Syn: 70/30; Pale yellow solid, FTIR (KBr): 3390 (NH), 3093, 2935, 2864, 1729, 1698, 1627, 1592, 1549, 1493, 1300, 820 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.21–7.25 (m, 2H, $CH_{Ar}$), 6.51–6.57 (m, 2H, $CH_{Ar}$), 6.08 (d, $^4J$ = 0.6 Hz, 0.7H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.07 (d, $^4J$ = 0.5 Hz, 0.3H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.03 (d, $^3J$ = 9.3 Hz, 0.3H, $CH_{Vinyl}$, syn), 5.98 (d, $^3J$ = 8.4 Hz, 0.7H, $CH_{Vinyl}$, anti), 4.45 (dd, $^3J$ = 3.6 Hz, $^3J$ = 9.3 Hz, 0.3H, CH—N, syn), 4.38 (dd, $^3J$ = 4.5 Hz, $^3J$ = 8.3 Hz, 0.7H, CH—N, anti), 2.91 (dt, $^3J$ = 4.4 Hz, $^3J$ = 13.0 Hz, 0.3H, —COCH<, syn), 2.80–2.85 (m, 0.7H, —COCH<, anti), 2.24 (s, 3H, $CH_3$), 1.66–2.40 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): 212.0 ($C{=}O_{Cyclohexanone}$), 161.0, 158.2, 149.0, 145.3, 144.8, 136.2, 132.9, 130.7, 124.5, 123.0, 119.6, 114.8, 114.5, 108.7, 108.6, 105.5, 105.4, 53.6, 53.5, 52.8, 52.6, 41.6, 41.5, 30.8, 30.5, 26.7, 25.9, 23.8, 23.5, 18.7 ppm; Anal. Calcd. for $C_{21}H_{20}BrCl_2NO_3$: C, 51.98; H, 4.15; N, 2.89. Found: C, 51.73; H, 4.53; N, 2.97.

***(Z)-4-Chloro-3-[1-chloro-3-(4-methoxyphenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4h).*** Anti/Syn: 75/25; Pale yellow solid, FTIR (KBr): 3343 (NH), 3039, 2936, 2865, 1729, 1694, 1620, 1543, 1507, 1442, 1301, 1246, 850, 774, 730 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.73–6.76 (m, 2H, $CH_{Ar}$), 6.61–6.65 (m, 2H, $CH_{Ar}$), 6.04–6.07 [3 × d: 6.06 (d, $^3J$ = 9.2 Hz, 0.25H, $CH_{Vinyl}$, syn), 6.06 (d, $^4J$ = 0.8 Hz, 0.75H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.04 (d, $^4J$ = 0.8 Hz, 0.25H, $CH_{\alpha\text{-Pyrone}}$, syn)], 5.99 (d, $^3J$ = 8.4 Hz, 0.75H, $CH_{Vinyl}$, anti), 4.43 (dd, $^3J$ = 3.7 Hz, $^3J$ = 9.3 Hz, 0.25H, CH—N, syn), 4.39 (dd, $^3J$ = 4.9 Hz, $^3J$ = 8.4 Hz, 0.75H, CH—N, anti), 3.71–3.72 (2 × s, 3H, —$OCH_3$), 2.90–2.95 (m, 0.25H, —COCH<, syn), 2.77–2.82 (m, 0.75H, —COCH<, anti), 2.22 (2 × s, 3H, $CH_3$), 1.65–2.40 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 212.0, 211.9 ($C{=}O_{Cyclohexanone}$), 160.9, 160.8, 158.2, 151.6, 151.5, 148.9, 148.6, 140.2, 139.8, 133.9, 132.0, 127.0, 126.7, 124.0, 122.8, 114.9, 114.5, 113.7, 113.6, 105.4, 105.3, 54.7, 54.6, 53.7, 52.7, 41.6, 41.4, 30.6, 29.6, 26.7, 26.0, 23.9, 23.5, 18.8, 18.7 ppm; Anal. Calcd. for $C_{22}H_{23}Cl_2NO_4$: C, 60.56; H, 5.31; N, 3.21. Found: C, 60.29; H, 5.70; N, 3.38.

***(Z)-3-[3-(4-Butylphenylamino)-1-chloro-3-(2-oxocyclohexyl) prop-1-enyl]-4-chloro-6-methyl-2H-pyran-2-one (4i).*** Anti/Syn: 80/20; Pale yellow solid, FTIR (KBr): 3381 (NH), 3094, 3019, 2930, 2861, 1733, 1684, 1623, 1550, 1517, 1299, 829, 743 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.97 (d, $^3J_{ortho}$ = 8.3 Hz, 2H, $CH_{Ar}$), 6.63 (d, $^3J_{ortho}$ = 8.3 Hz, 0.4H, $CH_{Ar}$, syn), 6.60 (d, $^3J_{ortho}$ = 8.3 Hz, 1.6H, $CH_{Ar}$, anti), 6.07 (d, $^3J$ = 9.4 Hz, 0.2H, $CH_{Vinyl}$, syn) 6.06 (d, $^4J$ = 0.7 Hz, 0.8H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.05 (d, $^4J$ = 0.7 Hz, 0.2H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.00 (d, $^3J$ = 8.3 Hz, 0.8H, $CH_{Vinyl}$, anti), 4.50 (dd, $^3J$ = 3.6 Hz, $^3J$ = 9.3 Hz, 0.2H, CH—N, syn), 4.44 (dd, $^3J$ = 4.8 Hz, $^3J$ = 8.3 Hz, 0.8H, CH—N, anti), 2.91–2.97 (m, 0.2H, —COCH<, syn), 2.79–2.85 (m, 0.8H, —COCH<, anti), 2.47 (t, $^3J$ = 7.6 Hz, 2H, $CH_{2\ Butyl}$), 2.23 (s, 3H, $CH_3$), 1.72–2.43 (m, 8H, $CH_{2\ Cyclohexanone}$), 1.48–1.55 (m, 2H, $CH_{2\ Butyl}$), 1.26–1.34 (m, 2H, $CH_{2\ Butyl}$), 0.89 (t, $^3J$ = 7.4 Hz, 3H, $CH_{3\ Butyl}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 212.0 ($C{=}O_{Cyclohexanone}$), 160.8, 158.2, 148.9, 143.9, 137.2, 131.5, 127.9, 122.6, 119.8, 113.4, 113.1, 105.4, 53.7, 53.0, 41.4, 33.6, 32.9, 30.6, 26.7, 26.0, 23.5, 21.2, 18.7, 12.9 ppm; Anal. Calcd. for $C_{25}H_{29}Cl_2NO_3$: C, 64.94; H, 6.32; N, 3.03. Found: C, 65.03; H, 6.29; N, 3.31.

***(Z)-4-Chloro-3-(1-chloro-3-(2-oxocycloheptyl)-3-(phenylamino)prop-1-enyl)-6-methyl-2H-pyran-2-one (4j).*** Anti/Syn: 70/30; Pale yellow solid, FTIR (KBr): 3381 (NH), 3094, 3050, 2928, 2857, 1732, 1695, 1623, 1606, 1550, 1503, 1440, 1301, 861, 744 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.13–7.17 (m, 2H, $CH_{Ar}$), 6.65–6.70 (m, 3H, $CH_{Ar}$), 6.06 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.82 (d, $^3J$ = 9.4 Hz, 0.3H, $CH_{Vinyl}$, syn), 5.80 (d, $^3J$ = 8.3 Hz, 0.7H, $CH_{Vinyl}$, anti), 4.60 (dd, $^3J$ = 4.1 Hz, $^3J$ = 9.4 Hz, 0.3H, CH—N, syn), 4.52 (dd, $^3J$ = 5.9 Hz, $^3J$ = 8.3 Hz, 0.7H, CH—N, anti), 2.98–3.08 (m, 1H, —COCH<, anti+syn), 2.50–2.55 (m, 2H, —$CH_2CO$—), 2.23 (s, 3H, $CH_3$), 1.20–2.08 (m, 8H, $CH_{2\ Cycloheptanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 215.8, 215.1 ($C{=}O_{Cycloheptanone}$), 160.9, 158.3, 148.9, 146.1, 145.4, 136.3, 133.6, 128.1, 124.3, 123.0, 119.7, 117.0, 116.8, 113.1, 112.7, 105.4, 55.3, 54.2, 54.1, 53.6, 43.3, 42.3, 28.9, 28.2, 27.9, 27.5, 27.1, 23.7, 23.1, 18.7 ppm; Anal. Calcd. for $C_{22}H_{23}Cl_2NO_3$: C, 62.86; H, 5.52; N, 3.33. Found: C, 62.82; H, 5.67; N, 3.51.

***(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-3-(2-oxocycloheptyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4k).*** Anti/Syn: 62/38; Pale yellow solid, FTIR (KBr): 3383 (NH), 3096, 3029, 2929, 2858, 1736, 1699, 1626, 1600, 1551, 1500, 1300, 1254, 861, 775, 732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.08–7.11 (m, 2H, $CH_{Ar}$), 6.56–6.60 (m, 2H, $CH_{Ar}$), 6.08 (s, 1H, $CH_{\alpha\text{-Pyrone}}$, anti+syn), 5.78 (d, $^3J$ = 9.9 Hz, 0.38H, $CH_{Vinyl}$, syn), 5.77 (d, $^3J$ = 8.2 Hz, 0.62H, $CH_{Vinyl}$, anti), 4.84 (s, br, 1H, NH), 4.53 (dd, $^3J$ = 4.0 Hz, $^3J$ = 9.5 Hz, 0.38H, CH—N, syn), 4.45 (dd, $^3J$ = 5.8 Hz, $^3J$ = 8.3 Hz, 0.62H, CH—N, anti), 3.03–3.07 (m, 0.62H, —COCH<, anti), 2.95–3.01 (m, 0.38H, —COCH<, syn), 2.49–2.51 (m, 2H, —$CH_2CO$—), 2.23 (s, 3H, $CH_3$), 1.24–2.17 (m, 8H, $CH_{2\ Cycloheptanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 215.9, 215.1 ($C{=}O_{Cycloheptanone}$), 161.1, 158.2, 149.0, 148.9, 144.7, 144.1, 135.8, 133.1, 127.9, 124.7, 123.4, 121.5, 121.4, 119.6, 114.2, 113.8, 105.4, 55.2, 54.4, 54.2, 53.3, 43.3, 42.4, 28.9, 28.6, 28.3, 28.2, 27.6, 27.1, 23.7, 22.9, 18.7 ppm. Anal. Calcd. for $C_{22}H_{22}Cl_3NO_3$: C, 58.10; H, 4.88; N, 3.08. Found: C, 57.92; H, 5.06; N, 3.36.

***4-Chloro-3-[(1Z)-1-chloro-3-(2-oxocyclohexylidene)prop-1-enyl]-6-methyl-2H-pyran-2-one (5).*** White solid; Mp. 154–156°C; FTIR (KBr): 3039, 2962, 2930, 2876, 1728, 1675, 1634, 1614, 1580, 1302, 857, 803, 775 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.41–7.43 (m, 1H, $CH_{Vinyl}$), 6.60 (d, $^3J$ = 11.3 Hz, 1H, $CH_{Vinyl}$), 6.17 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.67 (td, $^4J$ = 1.9 Hz, $^3J$ = 7.0 Hz, 2H, $CH_{2\ Cyclohexanone}$), 2.49 (t, $^3J$ = 6.6 Hz, 2H, —$CH_2CO$—), 2.28 (s, 3H, $CH_3$), 1.84–1.89 (m, 2H, $CH_2$), 1.76–1.80 (m, 2H, $CH_2$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 199.6 ($C{=}O_{Cyclohexanone}$), 161.3, 158.2, 149.2, 138.4, 129.0, 127.0, 126.7, 120.3, 105.7, 39.2, 26.6, 22.2, 22.0, 18.8 ppm. Anal. calcd. for $C_{15}H_{14}Cl_2O_3$: C, 57.53; H, 4.51. Found: C, 57.58; H, 4.69.

***4-Chloro-3-[(1Z)-1-chloro-3-(2-oxocyclopentylidene)prop-1-enyl]-6-methyl-2H-pyran-2-one (6).*** White solid, Mp. 182–184°C; FTIR (KBr): 3106, 3034, 2958, 1728, 1708, 1623, 1549, 1297, 1172, 861, 805 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$):δ 7.34 (dt, $^4J$ = 2.8 Hz, $^3J$ = 11.2 Hz, 1H, $CH_{Vinyl}$), 6.52 (d, $^3J$ = 11.2 Hz, 1H, $CH_{Vinyl}$), 6.18 (d, $^4J$ = 0.7 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.71 (td, $^4J$ = 2.8 Hz, $^3J$ = 7.3 Hz, 2H, $CH_{2\ Cyclopentanone}$), 2.39 (t, $^3J$ = 7.9 Hz, 2H, —$CH_2CO$—), 2.29 (d, $^4J$ = 0.4 Hz, 3H, $CH_3$), 1.95–2.03 (m, 2H, $CH_{2\ Cyclopentanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 206.0 ($C{=}O_{Cyclopentanone}$),

161.4, 158.1, 149.2, 140.1, 129.8, 128.5, 123.7, 120.1, 105.7, 37.5, 26.6, 18.8, 18.6 ppm. Anal. Calcd. for $C_{14}H_{12}Cl_2O_3$: C, 56.21; H, 4.04. Found: C, 55.83; H, 4.06.

***(Z)-4-Chloro-3-[1-chloro-5-oxo-3-(phenylamino)hex-1-enyl]-6-methyl-2H-pyran-2-one (7a).*** Pale yellow solid, Mp. 30–32°C; FTIR (KBr): 3384 (NH), 3095, 3052, 3024, 2959, 2924, 1734, 1669, 1626, 1602, 1550, 1503, 1302, 860, 752, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.15–7.19 (m, 2H, $CH_{Ar}$), 6.71–6.74 (m, 1H, $CH_{Ar}$), 6.66–6.68 (m, 2H, $CH_{Ar}$), 6.08 (d, $^4J$ = 0.8 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.95 (d, $^3J$ = 7.9 Hz, 1H, $CH_{Vinyl}$), 4.70–4.74 (dt, $^3J$ = 5.2 Hz, $^3J$ = 7.9 Hz, 1H, CH—N), 4.54 (s, br, 1H, NH), 2.98 (d, $^3J$ = 5.2 Hz, 2H, $CH_2$), 2.24 (d, $^4J$ = 0.5 Hz, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 2.23 (s, 3H, $CH_3CO$—) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 206.5 ($C{=}O_{Ketone}$), 161.1, 158.2, 149.1, 145.1, 136.3, 128.2, 123.0, 119.5, 117.8, 113.4, 105.4, 48.7, 45.3, 29.5, 18.7 ppm; Anal. Calcd. for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82. Found: C, 58.91; H, 4.98; N, 4.02.

***(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-5-oxohex-1-enyl]-6-methyl-2H-pyran-2-one (7b).*** Pale yellow solid, Mp. 34–36°C; FTIR (KBr): 3370 (NH), 3095, 3050, 2959, 2925, 2854, 1730, 1667, 1621, 1548, 1490, 1436, 1254, 863, 821, 773, 732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.10–7.13 (m, 2H, $CH_{Ar}$), 6.61–6.65 (m, 2H, $CH_{Ar}$), 6.09 (d, $^4J$ = 0.7 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.92 (d, $^3J$ = 8.0 Hz, 1H, $CH_{Vinyl}$), 4.63–4.68 (ddd, $^3J$ = 4.3 Hz, $^3J$ = 6.1 Hz, $^3J$ = 7.9 Hz, 1H, CH—N), 2.92–3.04 [2 × dd: 3.02 (dd, $^3J$ = 6.2 Hz, $^2J$ = 17.1 Hz, 1H, $CH_2$), 2.95 (dd, $^3J$ = 4.3 Hz, $^2J$ = 17.1 Hz, 1H, $CH_2$), $CH_{2\ Diastrotopic\ Protons}$], 2.24 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 2.22 (s, 3H, $CH_3CO$—) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 206.6 ($C{=}O_{Ketone}$), 161.3, 158.2, 149.1, 143.7, 135.7, 128.0, 123.4, 122.5, 119.4, 114.6, 105.4, 48.8, 45.1, 29.6, 18.7 ppm; Anal. Calcd. for $C_{18}H_{16}Cl_3NO_3$: C, 53.96; H, 4.02; N, 3.50. Found: C, 54.07; H, 4.18; N, 3.38.

***(Z)-4-Chloro-3-[1-chloro-5-oxo-5-phenyl-3-(phenylamino)-pent-1-enyl]-6-methyl-2H-pyran-2-one (7c).*** Pale yellow solid, Mp. 126–128°C; FTIR (KBr): 3381 (NH), 3092, 3056, 3028, 2924, 2855, 1729, 1685, 1625, 1600, 1548, 1293, 1265, 861, 751, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.98–8.00 (m, 2H, $CH_{Ar}$), 7.57–7.60 (m, 1H, $CH_{Ar}$), 7.46–7.51 (m, 2H, $CH_{Ar}$), 7.14–7.19 (m, 2H, $CH_{Ar}$), 6.69–6.74 (m, 3H, $CH_{Ar}$), 6.07 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 6.07 (d, $^3J$ = 7.8 Hz, 1H, $CH_{Vinyl}$), 4.89–4.93 (m, 1H, CH—N), 3.46–3.57 (m, 2H, $CH_2$), 2.23 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 197.7 ($C{=}O_{Ketone}$), 161.0, 158.2, 149.1, 145.6, 137.1, 135.5, 132.6, 128.2, 127.7, 127.6, 127.3, 122.8, 117.3, 113.1, 105.4, 48.8, 40.6, 18.7 ppm; Anal. Calcd. for $C_{23}H_{19}Cl_2NO_3$: C, 64.50; H, 4.47; N, 3.27. Found: C, 64.35; H, 4.65; N, 3.55.

***(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-5-oxo-5-phenylpent-1-enyl]-6-methyl-2H-pyran-2-one (7d).*** Pale yellow solid, Mp. 128–130°C; FTIR (KBr): 3371 (NH), 3172, 3060, 3031, 2924, 2855, 1731, 1695, 1621, 1547, 1493, 1456, 1213, 811, 742 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.96–7.99 (m, 2H, $CH_{Ar}$), 7.59–7.63 (m, 1H, $CH_{Ar}$), 7.47–7.53 (m, 2H, $CH_{Ar}$), 7.20–7.22 (m, 2H, $CH_{Ar}$), 6.95–6.97 (m, 2H, $CH_{Ar}$), 6.19 (d, $^3J$ = 8.4 Hz, 1H, $CH_{Vinyl}$), 6.08 (d, $^4J$ = 0.8 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 4.90–4.95 (m, 1H, CH—N), 3.55–3.77 [2 × dd: 3.74 (dd, $^3J$ = 6.8 Hz, $^2J$ = 17.1 Hz, 1H, $CH_2$), 3.58 (dd, $^3J$ = 4.0 Hz, $^2J$ = 17.3 Hz, 1H, $CH_2$), $CH_{2\ Diastrotopic\ Protons}$], 2.25 (d, $^4J$ = 0.6 Hz, 3H, $CH_{3\ \alpha\text{-Pyrone}}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 198.7 ($C{=}O_{Ketone}$), 162.2, 159.2, 150.1, 145.3, 137.6, 136.4, 133.7, 129.0, 128.8, 128.3, 127.4, 124.2, 122.9, 115.2, 106.5, 49.9, 41.5, 19.8 ppm; Anal. Calcd. for $C_{23}H_{18}Cl_3NO_3$: C, 59.70; H, 3.92; N, 3.03. Found: C, 59.92; H, 4.07; N, 3.36.

***(Z)-Dimethyl 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8a).*** yellow solid, Mp. 54–56°C; FTIR (KBr): 3096, 2948, 2926, 2852, 1734, 1694, 1629, 1586, 1551, 1290, 1208, 860, 771, 732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.39–7.45 (m, 3H, $CH_{Ar}$), 7.10–7.13 (m, 2H, $CH_{Ar}$), 6.10 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.71 (d, $^3J$ = 9.4 Hz, 1H, $CH_{Vinyl}$), 5.15 (d, $^3J$ = 9.4 Hz, 1H, $CH_{Dihydropyridine}$), 3.77 (s, 6H, —$OCH_3$), 2.29 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 1.98 (s, 6H, $CH_{3\ Dihydropyridine}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 167.2 ($C{=}O_{Ester}$), 160.5, 158.3, 148.5, 147.3, 139.1, 134.5, 129.3, 128.4, 127.6, 120.9, 118.6, 105.4, 101.4, 50.3, 33.5, 18.7, 17.3 ppm; Anal. Calcd. for $C_{25}H_{23}Cl_2NO_6$: C, 59.53; H, 4.60; N, 2.78. Found: C, 59.68; H, 4.63; N, 2.88.

***(Z)-Diethyl 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8b).*** yellow solid, Mp. 42–44°C; FTIR (KBr): 3092, 3059, 2980, 2936, 1734, 1691, 1631, 1583, 1552, 1203, 742 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.40–7.43 (m, 3H, $CH_{Ar}$), 7.10–7.12 (m, 2H, $CH_{Ar}$), 6.10 (d, $^4J$ = 0.7 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.71 (d, $^3J$ = 9.5 Hz, 1H, $CH_{Vinyl}$), 5.15 (d, $^3J$ = 9.5 Hz, 1H, $CH_{Dihydropyridine}$), 4.23 (m, 4H, $CH_{2\ Ethyl}$), 2.24 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 1.99 (s, 6H, $CH_3$), 1.35 (t, $^3J$ = 7.1 Hz, 6H, $CH_{3\ Ethyl}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.7 ($C{=}O_{Ester}$), 160.4, 158.3, 148.4, 147.1, 139.1, 134.5, 129.3, 128.3, 127.6, 120.9, 118.1, 105.4, 101.7, 59.2, 33.2, 18.7, 17.3, 13.4 ppm. Anal. Calcd. for $C_{27}H_{27}Cl_2NO_6$: C, 60.91; H, 5.11; N, 2.63. Found: C, 60.93; H, 5.18; N, 2.90.

***5-Benzyloxy-2-[(2-oxocyclohexyl)(phenylamino)methyl]-4H-pyran-4-one (11a).*** Anti/Syn: 40/60; White solid; FTIR (KBr): 3408 (NH), 3031, 2935, 2861, 1708, 1642, 1555, 1523, 1455, 1246, 1208, 992 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 0.4H, $CH_{Pyrone\ 6\text{-position}}$, anti), 7.49 (s, 0.6H, $CH_{Pyrone\ 6\text{-position}}$, syn), 7.28–7.37 (m, 5H, $CH_{Ar}$), 7.13 (m, 2H, $CH_{Ar}$), 6.71–6.75 (m, 1H, $CH_{Ar}$), 6.59 (m, 2H, $CH_{Ar}$), 6.50 (s, 0.6H, $CH_{Pyrone\ 3\text{-position}}$, syn), 6.49 (s, 0.4H, $CH_{Pyrone\ 3\text{-position}}$, anti), 4.99–5.00 [2 × s: 5.00 (s, 0.8H, —$CH_2O$—, anti), 4.99 (s, 1.2H, —$CH_2O$—, syn), 4.64 (d, $^3J$ = 5.4 Hz, 0.4H, CH—N, anti), 4.41 (d, $^3J$ = 4.9 Hz, 0.6H, CH—N, syn), 4.20 (s, br, 1H, NH), 2.98–3.04 (m, 0.6H, —COCH<, syn), 2.84–2.92 (m, 0.4H, —COCH<, anti), 2.25–2.41 (m, 2H, —$CH_2CO$—) 1.57–2.04 (m, 6H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 209.7, 208.4 ($C{=}O_{Cyclohexanone}$), 173.4 ($C{=}O_{Pyrone}$), 166.1, 165.7, 146.0, 144.9, 144.7, 140.3, 139.8, 134.6, 128.3, 128.2, 127.7, 127.6, 127.4, 127.3, 126.6, 126.6, 118.0, 117.8, 113.0, 112.9, 112.8, 112.4, 70.8, 70.6, 54.6, 53.8, 52.2, 52.1, 41.1, 41.0, 28.2, 28.1, 26.4, 25.9, 23.6, 23.4 ppm; Anal. calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.08; H, 6.46; N, 3.21.

***5-Benzyloxy-2-[(4-chlorophenylamino)(2-oxocyclohexyl)-methyl]-4H-pyran-4-one (11b).*** Anti/Syn: 55/45; White solid, FTIR (KBr): 3333 (NH), 3088, 3034, 2933, 2861, 1708, 1644, 1600, 1497, 1202, 816, 738 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 0.55H, $CH_{Pyrone\ 6\text{-position}}$, anti), 7.49 (s, 0.45H, $CH_{Pyrone\ 6\text{-position}}$, syn), 7.30–7.35 (m, 5H, $CH_{Ar}$), 7.05–7.08 (m, 2H, $CH_{Ar}$), 6.49–6.54 (m, 2H, $CH_{Ar}$), 6.47 (s, 0.45H, $CH_{Pyrone\ 3\text{-position}}$, syn), 6.45 (s, 0.55H, $CH_{Pyrone\ 3\text{-position}}$, anti),

5.00 (2 × s: 2H, —$CH_2O$—), 4.59 (d, $^3J$ = 5.1 Hz, 0.55H, CH—N, anti), 4.34 (d, $^3J$ = 4.8 Hz, 0.45H, CH—N, syn), 2.97–3.02 (m, 0.45H, —COCH<, syn), 2.84–2.89 (m, 0.55H, —COCH<, anti), 2.29–2.45 (m, 2H, —$CH_2CO$—$_{Cyclohexanone}$) 1.55–2.13 (m, 6H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 209.7, 208.3 (C=$O_{\ Cyclohexanone}$), 173.3 (C=$O_{Pyrone}$), 165.9, 165.6, 146.0, 143.7, 143.5, 139.9, 134.6, 134.5, 128.2, 128.1, 127.7, 127.6, 127.4, 127.3, 126.6, 122.5, 114.0, 113.4, 112.9, 112.7, 70.7, 54.8, 53.8, 52.3, 52.0, 41.2, 41.0, 28.0, 27.9, 26.5, 25.8, 23.7, 23.6 ppm; Anal. calcd. for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20. Found: C, 68.21; H, 5.38; N, 3.18.

***5-Benzyloxy-2-[(3,4-dichlorophenylamino)(2-oxocyclohexyl) methyl]-4H-pyran-4-one (11c).*** Anti/Syn: 75/25; White solid, FTIR (KBr): 3336 (NH), 3067, 3031, 2939, 2865, 1708, 1642, 1595, 1476, 1208, 812, 749, 696 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 0.75H, $CH_{Pyrone\ 6\text{-}position}$, anti), 7.49 (s, 0.25H, $CH_{Pyrone\ 6\text{-}position}$, syn), 7.29–7.37 (m, 5H, $CH_{Ar}$), 7.11–7.15 [2 × d: 7.14 (d, $^3J_{ortho}$ = 8.7 Hz, 0.25H, $CH_{Ar}$, syn), 7.12 (d, $^3J_{ortho}$ = 8.7 Hz, 0.75H, $CH_{Ar}$, anti)], 6.69 (d, $^4J_{meta}$ = 2.7 Hz, 0.75H, $CH_{Ar}$, anti), 6.63 (d, $^4J_{meta}$ = 2.7 Hz, 0.25H, $CH_{Ar}$, syn), 6.40–6.47 [m, 2H, (1H, $CH_{Ar}$) and (1H, $CH_{Pyrone\ 3\text{-}position}$)] 5.00 (s, 2H, —$CH_2O$—), 4.59 (d, $^3J$ = 5.1 Hz, 0.75H, CH—N, anti), 4.30 (d, $^3J$ = 4.6 Hz, 0.25H, CH—N, syn), 3.01–3.06 (m, 0.25H, —COCH<, syn), 2.83–2.89 (m, 0.75H, —COCH<, anti), 2.24–2.45 (m, 2H, —$CH_2CO$—$_{Cyclohexanone}$) 1.53–2.12 (m, 6H, $CH_{2\ Cyclohexanone}$) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 209.7, 208.1 (C=$O_{\ Cyclohexanone}$), 173.3 (C=$O_{Pyrone}$), 165.7, 146.1, 146.0, 144.9, 144.7, 139.9, 134.6, 134.5, 131.9, 131.8, 129.7, 129.6, 127.7, 127.6, 127.4, 127.3, 126.7, 123.5, 120.2, 113.9, 113.3, 112.7, 112.5, 112.3, 111.9, 70.7, 54.6, 53.5, 52.2, 51.9, 41.3, 40.9, 28.0, 27.7, 26.6, 25.7, 23.6, 23.6 ppm; Anal. calcd. for $C_{25}H_{23}Cl_2NO_4$: C, 63.57; H, 4.91; N, 2.97. Found: C, 63.67; H, 4.89; N, 3.06.

## REFERENCES AND NOTES

[1] (a) Chatterjee, A.; Biswas, K. M. J Org Chem 1973, 38, 4002; (b) Sayah, B.; Léon, N. P.; Milet, A.; Guindet, J. P.; Vallée, Y. J Org Chem 2001, 66, 2522; (c) Pundeer, R.; Ranjan, P.; Pannu, K.; Prakash, O. Synth Commun 2009, 39, 316.

[2] Jones, G.; Stanforth, S. P. Org React 2000, 56, 355.

[3] Marson, C. M. Tetrahedron 1992, 48, 3659.

[4] (a) Benson, W. R.; Pohland, A. E. J Org Chem 1965, 30, 1126; (b) Paquette, L. A.; Johnson, B. A.; Hinga, F. M. Organic Synth Cell 1973, 5, 215; (c) Karmakar, A. C.; Sharma, S.; Chattrejee, B. G.; Ray, J. K. Indian J Chem 1988, 27B, 364; (d) Ziegenbein, W.; Lang, W. Chem Ber 1960, 93, 2433; (e) Ziegenbein, W.; Franke, W. Angew Chem 1959, 71, 573; (f) Arnold, Z.; Zemilca, J. Collect Czech Chem Commun 1959, 24, 2378; (g) Gupta, S.; Kar, G. K.; Ray, J. K. Synth Commun 2000, 30, 2393; (h) Vashkevich, E. V.; Potkin, V. I.; Kozlov, N. G.; Skakovskii, E. D. Russ J Org Chem 2003, 39, 1587; (i) Gordon, A. J.; Ford, R. A. The Chemist's Companion; Wiley: New York, 1972 [Translated under the title Sputnik khimika, Moscow: Mir, 1976, p. 302]; (j) Chakraborty, A.; Ray, J. K. Synth Commun 1995, 25, 1869; (k) Prim, D.; Fuss, A.; Kirsch, G.; Silva, A. M. S. J Chem Soc Perkin Trans 2 1999, 1175; (l) Kirsch, G.; Prim, D.; Leising, F.; Mignani, G. J Heterocycl Chem 1994, 31, 1005; (m) Ziegenbein, W.; Franke, W. Ger. Pat.1.071.684 (1959); Chem Abstr 1961, 55, 16488f; (n) Brahma, S.; Ray, J. K. Tetrahedron 2008, 64, 2883; (o) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Cruz-Lopez, O.; Preti, D.; Tolomeo, M.; Grimaudo, S.; Di Cristina, A.; Zonta, N.; Balzarini, J.; Brancale, A.; Sarkar, T.; Hamel, E. Bioorg Med Chem 2008, 16, 5367.

[5] Arend, M.; Westermann, B.; Risch, N. Angew Chem Int Ed 1998, 37, 1044.

[6] (a) Tramontini, M.; Angiolini, L. Mannich-Bases, Chemistry and Uses; CRC: Boca Raton, FL, 1994 and reference cited therein; (b) Volkmann, R. A. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol.1, p 355 and references cited therein.

[7] (a) Kleinmann, E. F. In Comprehensive Organic Synthesis; Trost, B. M., Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol.2, Chapter 4.1; (b) Kobayashi, S.; Ishitani, H. Chem Rev 1999, 99, 1069; (c) Denmark, S.; Nicaise, O. J.-C. In Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol.2, p 93; (d) Juaristi, E., Ed. Enantioselective Synthesis of β-Amino Acids; Wiley-VCH: New York, 1997.

[8] (a) Azizi, N.; Torkiyan, L.; Saidi, M. R. Org Lett 2006, 8, 2079; (b) Wu, Y.-S.; Cai, J.; Hu, Z.-Y.; Lin, G.-X. Tetrahedron Lett 2004, 45, 8949; (c) Chen, W. Y.; Li, X.; Lu, J. Synth Commun 2008, 38, 546; (d) Ibrahem, I.; Casas, J.; Córdova, A. Angew Chem Int Ed 2004, 43, 6528. For reviews of catalytic Mannich reactions, see: (e) Kobayashi, S.; Ueno, M. In Comprehensive Asymmetric Catalysis, Supplement; Springer: Berlin, 2004; Vol.1, p 143; (f) Xu, L.-W.; Xia, C.-G.; Li, L. J Org Chem 2004, 69, 8482; (g) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. J Am Chem Soc 2004, 126, 3734; (h) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. J Am Chem Soc 2007, 129, 3790; (i) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. J Org Chem 2008, 73, 5859; (j) Ferlin, M. G.; Chiarelotto, G.; Castagliuolo, I. J Heterocycl Chem 2002, 39, 631; (k) Shi, H.; Shi, H.; Wang, Z. J Heterocycl Chem 2001, 38, 929.

[9] (a) Shi, M.; Cui, S. C.; Li, Q. J. Tetrahedron 2004, 60, 6679; (b) Bhanushali, M. J.; Nandurkar, N. S.; Jagtap, S. R.; Bhanage, B. M. Synth Commun 2009, 39, 845; (c) Hashemi, M. M.; Eftekhari-Sis, B.; Abdollahifar, A.; Khalili, B. Tetrahedron 2006, 62, 672; (d) Eftekhari-Sis, B.; Abdollahifar, A.; Hashemi, M. M.; Zirak, M. Eur J Org Chem 2006, 5152; (e) Smitha, S.; Reddy, C. S. Synthesis 2004, 834.

[10] Riley, J. P.; Chester, R. Introduction to Marine Chemistry; Academic Press: NY, 1971.

[11] Farnworth, F.; Jones, S. L.; McAlpine, I. Speciality Inorganic Chemicals Special publication No 40; Royal Society of Chemistry: London, 1980.

[12] (a) Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J.; Mohan, R. S. Tetrahedron Lett 2000, 41, 1527; (b) Crouch, R. D.; Romany, C. A.; Kreshock, A. C.; Menconi, K. A.; Zile, J. L. Tetrahedron Lett 2004, 45, 1279; (c) Ghosh, R.; Maiti, S.; Chakraborty, A. Tetrahedron Lett 2004, 45, 6775.

[13] (a) Shahrisa, A.; Saraei, M. J Heterocycl Chem 2009, 46, 268; (b) Shahrisa, A.; Ghasemi, Z.; Saraei, M. J Heterocycl Chem 2009, 46, 273.

[14] Rudas, M.; Fejes, I.; Nyerges, M.; Szollosy, A.; Toke, L.; Groundwater, P. W. J Chem Soc Perkin Trans 1 1999, 1167.

# The Facile Syntheses of 2,3-Dihydro-1*H*-1,5-benzodiazepines and Their Ribofuranosides



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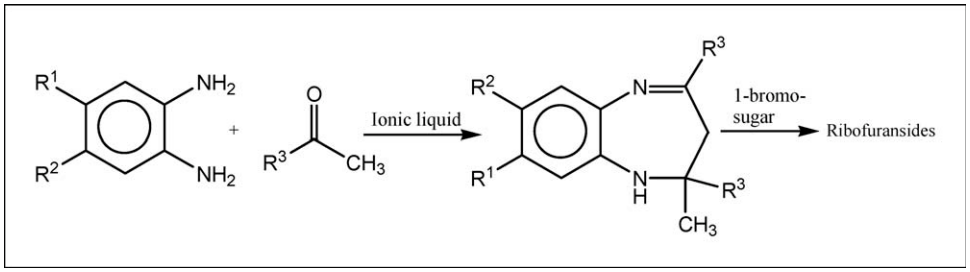


The facile syntheses of 2,3-dihydro-1*H*-benzodiazepines containing heterocyclic moieties and their ribofuranosides have been accomplished in ionic liquids at ambient temperature. The characterization of all these compounds has been done unambiguously by IR, $^1$H NMR, $^{13}$C NMR, GC-MS spectroscopy, and elemental analysis.

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## INTRODUCTION

The 1,5-Benzodiazepines have attracted tremendous attention due to their diversified medicinal properties [1–4], *e.g.* analgesic, hypnotic, sedative, antianxiety, anticonvulsant, antidepressant, and anti-inflammatory activities. These derivatives have also been used in viral infections and cardiovasulcar disorders [5]. Commercial applications of this heterocyclic system as dyes for acrylic fibres and in photography have also been reported [6].

These derivatives also act as key intermediates for the synthesis of fused ring derivatives [7], viz., triazolo-, oxadiazolo-, oxazino-, furano-, and pyrido- benzodiazepines.

A survey of the literature reveals that the synthesis of 1,5-benzodiazepines involves the condensation of *o*-phenylenediamine with β-haloketones [8], α,β-unsaturated carbonyl compounds [9] or ketones in the presence of $BF_3$-etherate [10], polyphosphoric acid or $SiO_2$ [11], $NaBH_4$ [12], MgO-$POCl_3$ [13], $InBr_3$ [14], $InCl_3$ [15], ionic liquids [16], Amberlyst [17] or zinc montmorillonite [18], etc.

The chemistry of nucleosides has been an active area of research in academia and in industry as it has demonstrated significant importance in cancer and viral therapy [19]. Also, protected nucleosides serve as building blocks for the synthesis of oligonucleotides, which has been used as probes for diagnostic purposes [20] and in antisense therapeutics [21]. The antisense oligonucleotides and siRNA have been extensively employed in selective inhibition of gene expression [22]. To our knowledge, only scanty information is available in regard to the synthesis of 1,5-benzodiazepine derivatives containing heterocyclic moieties, their spiro derivatives [23] and nucleosides. Furthermore, the reported methods are associated with several drawbacks, such as expensive reagents, drastic reaction conditions, extended reaction times, formation of the side products, unsatisfactory yields, complex experimental procedures, and involving the use of environmentally black listed solvents, *e.g.* *N*,*N*-dimethylformamide, *N*-methylpyrrolidine, *etc*.

In view of our continuous interest in the synthesis of nucleosides [24] and the only report on ionic liquid promoted lipase catalysed synthesis of nucleosides [25], we have developed a facile synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines containing heterocyclic moieties and their spiro derivatives at ambient temperature in environmentally benign ionic liquid (IL). These derivatives could be subsequently transformed to their ribofuranosides in the same pot under mild conditions.

## RESULTS AND DISCUSSION

In our strategy, we first attempted the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines containing heterocyclic moieties/spiro derivatives from the reaction between *o*-phenylenediamine and an heterocyclic ketone(s) in an IL, *viz*. 1,3-di-*n*-butylimidazolium bromide [BBIM]Br, 1,3-di-*n*-butylimidazolium tetrafluoroborate [BBIM]$BF_4$, 1,3-di-*n*-butylimidazolium hexafluorophosphate [BBIM]$PF_6$, 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]TFA, and 1-

methoxyethyl-3-methylimidazolium mesylates [MOEMIM]Ms at ambient temperature (28 ± 2°). The reaction afforded 2,3-dihydro-1*H*-1,5-benzodiazepine containing heterocyclic moieties or their spiro derivatives in excellent yields (Table 1).

The chracterization of the compounds **3a-k** have been carried out by IR, $^1$H NMR, $^{13}$C NMR, GC-MS spectroscopy and elemental analysis.

A plausible mechanism of the reaction appears to involve nucleophilic attack of *o*-phenylenediamine on the carbonyl carbon of the heterocyclic ketone to generate diaminoalcohol followed by loss of water to afford diimine intermediate **A**. The latter may undergo 1,3-hydrogen shift to yield isomeric imine-enamine intermediate **B**, which on cyclization affords 2,3-dihydro-1*H*-1,5-benzodiazepines/spiro compounds *via* dipolar intermediate (Scheme 1).

To devise our goal of designing a one pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepiene ribofuranosides **4a-k**, the solubility of the compounds **3a** and **3j** was checked in ionic liquids by dissolving till saturation in 1 mL of IL. These data are summarized in Table 2.

The data presented in Table 2 suggest that the compounds **3a** and **3j** show better solubility in [MOEMIM]Ms, [MOEMIM]TFA, which may therefore be used for ribofuranosylation. This may be attributed due to the ability of oxygenated cation to hydrogen bond with -NH of the 1,5-benzodiazepine.

In a one-pot synthesis of 1,5-benzodiazepine ribofuranosides, *o*-phenylenediame (entry 1 Table 1) was first reacted with heterocyclic ketone **2a** in [MOEMIM]TFA, the progress of the reaction being monitored by TLC. After completion of the reaction, the sugar, viz., β-D-ribofuranose-1-bromo-2,3,5-tribenzoate was added and the contents were further stirred. After workup compound **4a** was obtained in 92% yield. On carrying out this reaction in [MOEMIM]Ms, **4a** was obtained in 80% yield (Scheme 2).

These investigations suggest that [MOEMIM]TFA is a better protocol for the synthesis of compounds **4a**, which is in consonance with the earlier report [26]. Same method was employed for the synthesis of ribofuranosides **4a-k**.

The compounds **4a-k** have been characterized on the basis of IR, $^1$H NMR, $^{13}$C NMR, GC-MS spectroscopy, and elemental analysis.

We also checked the recyclability of the ionic liquid [MOEMIM]TFA for one pot synthesis of compound **4a** from *o*-phenylenediameine, and heterocyclic ketone **2a** as described earlier. The results of the recyclability are shown in Table 3, which suggest that the yield of the compound **4a** decreases by 5.6 and 10%, respectively in first and second recycling of [MOEMIM]TFA. However, in the third cycle, the decrease in yield was significant.

## SUMMARY

In summary, a facile one pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives containing heterocyclic moieties, their spiro derivatives and their ribofuranosides have been developed at ambient temperature in environmentally benign ionic liquids(s). [MOEMIM]TFA was found to be a better solvent for this purpose. The simplicity of the procedure, easy recovery and reuse of the reaction media *viz*. ionic liquid make this methodology a convenient, efficient, economic, and attractive.

## EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR spectrometer using KBr pellets. $^1$H NMR spectra were recorded on a JEOL AL-300 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard (chemical shift in δ ppm). $^{13}$C NMR spectra were recorded on a JEOL AL-75 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were measured on HP 5890 GC-MS (70eV.EI). The purity of the products was checked by TLC using silica gel 60F 254 aluminium sheets and visualization was accomplished by iodine/UV light. Ionic liquids were prepared by reported methods [27,28]. All reagents were used as obtained commercially.

**Synthesis of 2,3-dihydro-1H-1,5-benzodiazepines (3a-k).** *o*-Phenylenediamine (0.005 mol) and heterocyclic ketone (0.010 mol) were added to IL (0.015 mol). The contents were stirred magnetically at room temperature (28 ± 2°C). The progress of the reaction was monitored by TLC using silica gel 60F 254 aluminum sheet in pet.ether/EtOAc 7:3. Upon completion of the reaction, water (20 mL) was added to it. The organic compound was then extracted with EtOAc (2 × 15 mL). The combined organic layer was distilled under reduced pressure (10 mmHg) at 50°C to afford compounds **3a-k**. All these products were further purified by column chromatography on silica gel 60–120 mesh by eluting with pet.ether-EtOAc (7:3).

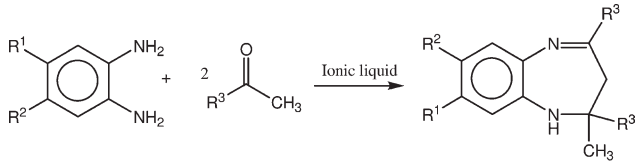
***2,4-Di(2′-Furyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3a).*** Solid, mp = 152–153°C; $R_f$ = 0.45 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 1.69 (s, 3H, —$CH_3$), 2.90 (d, $J$ = 13.2 Hz, 1H, methylene), 3.05 (d, $J$ = 13.2 Hz, 1H methylene), 3.40 (s, 1H, NH), 6.46 (d, $J$ = 2.2 Hz, 1H, Furyl), 6.64 (d, $J$ = 3.0 Hz, 1H, Furyl), 6.90–7.03 (m, 2H, 1H furyl and 1H phenyl), 7.10–7.15 (m, 1H, phenyl), 7.28 (d, $J$ = 2.8 Hz, 1H, phenyl), 7.40 (d, $J$ = 3.0 Hz, 1H, phenyl), 7.51 (d, $J$ = 1.4 Hz, 1H, furyl), 7.60 (d, $J$ = 3.0 Hz, 1H, Furyl), 7.78 (d, $J$ = 1.4 Hz, 1H, Furyl); $^{13}$C NMR δ : 28.80, 39.60, 71.40, 105.10, 110.62, 112.10, 113.72, 122.55, 123.15, 126.50, 128.45, 137.70, 141.30, 142.00, 146.10, 154.10, 158.50, 159.90; IR (KBr $cm^{-1}$) ν: 3320, 3040, 2970, 1640; GC-MS : $M^+$, 292.

***2,4-Di(2′-thiophenyl)-2-methyl-2,3-dihydro-1H,1,5-benzodiazepine (3b).*** Solid, mp = 104–105°C; $R_f$ = 0.48 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 1.80 (s, 3H, $CH_3$), 2.95 (d, $J$ = 13.8 Hz, 1H, methylene), 3.05 (d, $J$ = 13.8 Hz, 1H, methylene), 3.60 (s, 1H, NH), 6.60–6.70 (m, 2H, 1H thiophenyl

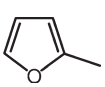
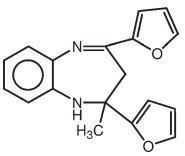
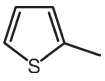
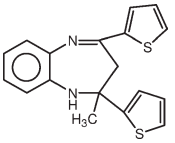
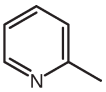
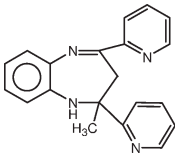
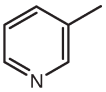
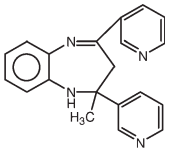
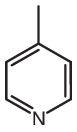
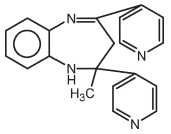
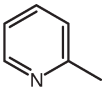
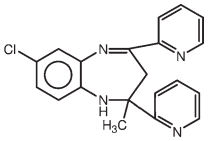
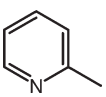
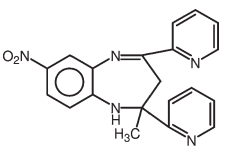
and 1H phenyl), 6.75 (dd, $J$ = 1.4 Hz, 1H, Phenyl), 6.80–6.85 (m, 2H, 1H thiophenyl and 1H phenyl), 6.92–6.98 (m, 2H, 1H thiophenyl and 1H phenyl), 7.05 (dd, $J$ = 1.3 Hz, 1H, thiophenyl), 7.29 (d, $J$ = 1.5 Hz, 1H, thiophenyl), 7.37 (d, $J$ = 3.0 Hz, 1H, Thiophenyl); $^{13}$C NMR δ : 31.10, 44.82, 73.10, 106.45, 111.20, 113.80, 114.60, 122.10, 124.20, 127.78,

**Table 1**

Synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines.

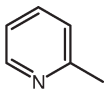
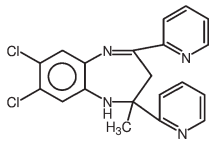
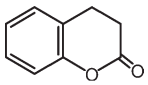
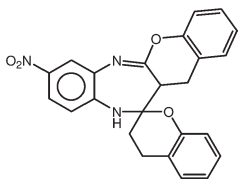
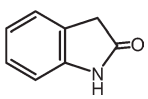
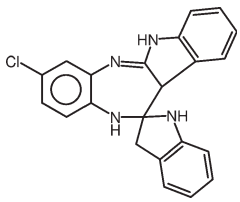
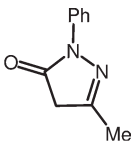
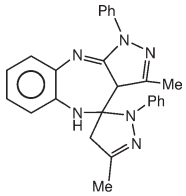



**1** **2** **3**

| Entry | Compd. | OPD $R^1$ | OPD $R^2$ | $R^3$ | Product | Yield of 1,5-bezodiazepines (%)/time (h) [BBIM]Br | [BBIM]$BF_4$ | [BBIM]$PF_6$ | [MOEMIM]TFA | [MOEMIM]Ms |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **3a** | H | H |  |  | 85/7.5 | 87/6.5 | 90/5.5 | 92/4.5 | 80/4.5 |
| 2 | **3b** | H | H |  |  | 80/7.0 | 85/6.0 | 87/5.5 | 90/5.0 | 90/5.5 |
| 3 | **3c** | H | H |  |  | 78/6.5 | 83/6.0 | 85/5.5 | 94/5.0 | 90/5.5 |
| 4 | **3d** | H | H |  |  | 80/7.0 | 82/6.5 | 86/6.0 | 92/5.0 | 88/5.5 |
| 5 | **3e** | H | H |  |  | 82/7.0 | 85/6.5 | 85/6.0 | 94/5.0 | 90/5.5 |
| 6 | **3f** | H | Cl |  |  | 78/7.0 | 83/6.5 | 86/6.0 | 90/5.0 | 88/5.5 |
| 7 | **3g** | H | $NO_2$ |  |  | 73/7.0 | 79/6.5 | 82/6.0 | 85/5.0 | 80/5.5 |

(*Continued*)

**Table 1**
(*Continued*)

| Entry | Compd. | OPD $R^1$ | OPD $R^2$ | $R^3$ | Product | Yield of 1,5-bezodiazepines (%)/time (h) [BBIM]Br | [BBIM]$BF_4$ | [BBIM]$PF_6$ | [MOEMIM]TFA | [MOEMIM]Ms |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 | **3h** | Cl | Cl |  |  | 63/7.5 | 69/7.0 | 72/6.5 | 79/5.5 | 75/6.5 |
| 9 | **3i** | H | $NO_2$ |  |  | 67/7.5 | 72/7.0 | 75/6.5 | 80/5.5 | 76/6.5 |
| 10 | **3j** | H | Cl |  |  | 75/7.0 | 78/6.5 | 80/6.5 | 82/5.5 | 76/6.0 |
| 11 | **3k** | H | H |  |  | 75/7.5 | 77/6.5 | 82/6.5 | 90/5.0 | 85/6.0 |

128.20, 128.50, 130.48, 137.50, 141.40, 147.95, 153.78, 162.80; IR (KBr, $cm^{-1}$) ν : 3325, 3040, 2970, 1625; GC-MS : $M^+$, 324.

***2,4-Di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3c).*** Solid, mp = 162°C; $R_f$ = 0.46 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 1.82 (s, 3H, $CH_3$), 2.91 (d, $J$ = 13.2 Hz, 1H, methylene), 3.05 (d, $J$ = 13.2 Hz, 1H, Mehtylene), 3.40 (s, 1H, NH), 6.80 (m, 1H, phenyl), 6.90 (m, 1H, phenyl), 6.95 (d, $J$ = 3.0 Hz, 1H, phenyl), 7.24 (dd, $J$ = 3.4 Hz, 1H, pyridyl), 7.46 (d, $J$ = 3.0 Hz, 1H, phenyl), 7.55 (d, $J$ = 3.4 Hz, 1H, pyridyl), 7.66 (dd, $J$ = 3.4 Hz, 1H, pyridyl), 7.83 (t, $J$ = 4.9 Hz, 1H, pyridyl), 7.86 (dd, $J$ = 7.0 Hz, 1H, pyridyl), 8.63 (d, $J$ = 7.2 Hz, 1H, pyridyl), 8.68(d, $J$ = 4.6 Hz, 1H, pyridyl), 8.80 (d, $J$ = 4.6 Hz, 1H, pyridyl); $^{13}$C NMR δ : 31.15, 37.05, 73.25, 119.65, 120.68, 121.30, 123.95, 124.08, 126.56, 128.55, 128.80, 135.90, 136.00, 138.90, 139.15, 147.80, 148.26, 156.30, 165.15, 167.20; IR (KBr, $cm^{-1}$) ν : 3315, 3015, 2970, 1635; GC-MS : $M^+$, 314.

***2,4-Di(3′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3d).*** Solid, mp = 168°C; $R_f$ = 0.42 (pet.ether - ethylacetate = 7:3); $^1$H NMR δ : 1.82 (s, 3H, $CH_3$), 2.98 (d, $J$ = 13.2 Hz, 1H, methylene), 3.08 (d, $J$ = 13.2 Hz, 1H, methylene), 3.50 (s, 1H, NH) 6.85–6.90 (m, 1H, phenyl), 6.95–6.98 (m, 1H, phenyl), 7.30 (t, $J$ = 3.6 Hz, 1H, pyridyl), 7.35 (d, $J$ = 1.8 Hz, 1H, phenyl), 7.40 (dd, $J$ = 3.0 Hz, 1H, phenyl), 7.50 (s, 1H, pyridyl), 7.55 (d, $J$ = 1.8 Hz, 1H, pyridyl), 7.80 (t, $J$ = 3.4 Hz, 1H, pyridyl), 7.96 (s, 1H, pyridyl), 8.20 (d, $J$ = 7.0 Hz, 1H, pyridyl), 8.71 (d, $J$ = 1.8 Hz, 1H, pyridyl), 8.80 (d, $J$ = 1.8 Hz, 1H pyridyl); $^{13}$C NMR δ : 29.70, 42.70, 72.50, 121.45, 122.05, 122.95, 127.00, 128.80, 133.30, 133.45, 133.92, 134.10, 137.28, 139.40, 142.15, 147.35, 148.40, 150.45, 161.42, 164.60; IR (KBr, $cm^{-1}$) ν : 3320, 3020, 2980, 1640; GC-MS : $M^+$, 314.

***2,4-Di(4′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3e).*** Solid, mp = 170°C; $R_f$ = 0.44 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 1.89 (s, 3H, $CH_3$), 2.90 (d, $J$ = 13.4 Hz, 1H, methylene), 3.17 (d, $J$ = 13.4 Hz, 1H, methylene), 3.81 (s, 1H, NH), 6.90 (dd, $J$ = 1.3 Hz, 1H, phenyl), 6.98 (dd, $J$ = 1.3 Hz, 1H, Phenyl), 7.13 (d, $J$ = 1.3 Hz, 1H phenyl), 7.25 (d, $J$ = 1.3 Hz, 1H, phenyl), 7.30 (d, $J$ = 1.75 Hz, 1H, pyridyl), 7.48 (d, $J$ = 2.10 Hz, 1H, pyridyl), 7.75 (d, $J$ = 2.4Hz, 1H, pyridyl), 7.98 (d, $J$ = 1.5 Hz, 1H, pyridyl), 8.10 (d, $J$ = 1.5 Hz, 1H, pyridyl), 8.28 (d, $J$ = 1.4 Hz, 1H, pyridyl), 8.70 (d, $J$ = 1.75 Hz, 1H, pyridyl), 8.80 (d, $J$ = 2.15 Hz, 1H, pyridyl); $^{13}$C NMR δ : 29.76, 42.80, 72.60, 121.40, 122.07, 122.90, 127.02, 128.75, 133.20, 133.40, 133.85, 134.10. 137.25, 139.40, 147.30, 148.10, 148.30, 150.40, 161.45, 164.60; IR (KBr, $cm^{-1}$) ν: 3310, 3010, 2965, 1630; GC-MS : $M^+$, 314.

***7-Chloro-2,4-di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3f).*** Solid, mp = 161°C; $R_f$ = 0.48 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 1.82 (s, 3H, $CH_3$), 2.83 (d, $J$ = 13.0 Hz, 1H, methylene), 3.24 (d, $J$ = 13.0 Hz, 1H, methylene),

**Scheme 1**

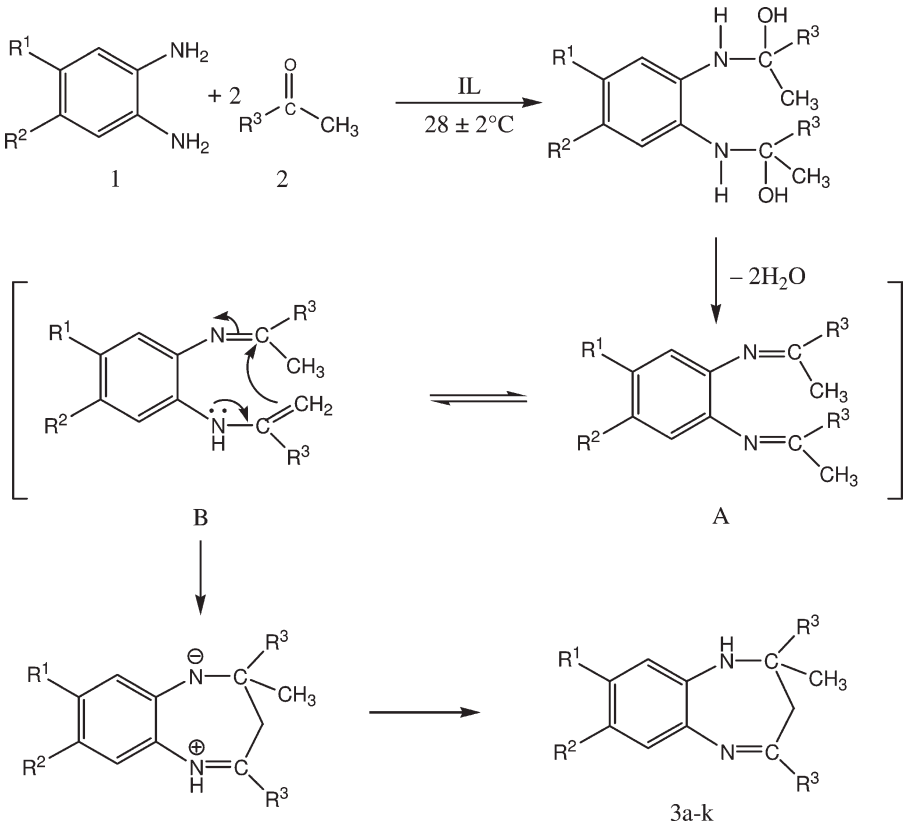



**Table 2**

Solubility analysis of compounds in ionic liquids (mg $mL^{-1}$), room temperature (22°C).

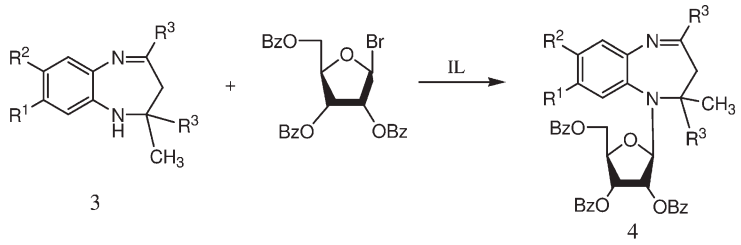
| | Solubility (mg $mL^{-1}$) | | | | |
|---|---|---|---|---|---|
| Compounds | [BBIM]Br | [BBIM]$BF_4$ | [BBIM]$PF_6$ | [MOEMIM]TFA | [MOEMIM]MS |
| **3a** | 40 | 120 | 290 | 390 | 370 |
| **3j** | 75 | 115 | 275 | 400 | 380 |

3.76 (s, 1H, NH), 7.02–7.06 (m, 2H, 1H pyridyl and 1H phenyl), 7.15–7.20 (m, 2H, 1H pyridyl and 1H phenyl), 7.28–7.30 (m, 2H, 1H pyridyl and 1H phenyl), 7.50 (t, $J$ = 2.8 Hz, 1H, pyridyl), 7.86 (t, $J$ = 1.2 Hz, 1H, pyridyl), 8.60 (dd, $J$ = 1.65 Hz, 1H, pyridyl), 8.68 (d, $J$ = 1.8 Hz, 1H, pyridyl), 8.70 (d, $J$ = 2.10 Hz, 1, pyridyl); $^{13}$C NMR δ : 31.28, 37.56, 73.50, 121.97, 122.46, 122.73, 124.38, 126.45, 127.14, 128.02, 130.45, 131.67, 136.46, 137.68, 140.21, 148.10, 148.31, 148.49, 156.31, 167.04; IR (KBr, $cm^{-1}$) ν : 3280, 3050, 2970, 1620; GC-MS : $M^+$, 349.

***7-Nitro-2,4-di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3g).*** Deep red solid, mp = 141°C; $R_f$ = 0.42 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 1.88 (s, 3H, $CH_3$), 2.92 (d, $J$ = 13.8 Hz, 1H, methylene), 3.26 (d, $J$ = 13.8 Hz, 1H, methylene), 3.28 (s, 1H, NH), 6.42 (s, 1H, phenyl), 6.56 (d, $J$ = 1.8 Hz, 1H, phenyl), 7.10 (d, $J$ = 1.8 Hz, 1H, phenyl), 7.25 (dd, $J$ = 1.3 Hz, 1H, pyridyl), 7.30–7.36 (m, 2H, pyridyl), 7.55 (d, $J$ = 1.9 Hz, 1H, pyridyl), 7.61 (dd, $J$ = 1.3 Hz, 1H, pyridyl), 8.16 (d, $J$ = 1.8 Hz, 1H, pyridyl), 8.65 (d, $J$ = 1.95 Hz, 1H, pyridyl), 8.70 (d, $J$ = 2.2 Hz, 1H, pyridyl); $^{13}$C NMR δ : 32.10, 36.50, 75.10, 114.40, 117.20, 122.52, 124.10, 124.20, 125.90, 127.20, 129.10, 130.88, 135.70, 136.10, 138.40, 149.08, 149.90, 152.60, 163.38, 164.60; IR (KBr, $cm^{-1}$) ν : 3325, 3140, 2940, 1620. Anal. Calcd for $C_{20}H_{17}N_5O_2$ : C, 66.82; H, 4.77; N, 19.49. Found : C, 66.85; H, 4.80; N, 19.47.

***7,8-Dichloro-2,4-di(2′-pyridyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3h).*** Deep brown solid, mp = 110°C; $R_f$ = 0.46 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ: 1.53 (s, 3H, –$CH_3$), 2.90 (d, $J$ = 13.2 Hz, 1H, methylene), 3.02 (d, $J$ = 13.2 Hz, 1H, methylene), 4.10 (s, 1H, NH), 7.00 (s, 1H, phenyl), 7.32 (d, $J$ = 1.70 Hz, 1H, pyridyl), 7.38 (d, $J$ = 2.9 Hz, 1H, pyridyl), 7.58 (d, $J$ = 2.8 Hz, 1H, pyridyl), 7.64 (d, $J$ = 2.9 Hz, 1H, pyridyl), 7.77 (dd, $J$ = 1.70 Hz, 1H, pyridyl), 7.80 (s, 1H, phenyl), 8.63 (d, $J$ = 1.90 Hz, 1H, pyridyl), 8.84 (d, $J$ = 2.10 Hz, 1H, pyridyl), 8.90 (d, $J$ = 1.70 Hz, 1H, pyridyl); $^{13}$C NMR δ : 31.52, 37.52, 77.10, 119.56, 123.40, 124.79, 129.51, 130.08, 130.21, 136.06, 136.57, 137.31, 138.53,

**Scheme 2**




| Ribofuranoside | 4a | 4b | 4c | 4d | 4e | 4f | 4g | 4h | 4i | 4j | 4k |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (h) taken (for one pot syntheses) | 7.5 | 7.0 | 7.5 | 7.5 | 7.0 | 7.5 | 7.5 | 7.5 | 8.5 | 8.5 | 9.0 |

**Table 3**

Recyclability studies of [MOEMIM]TFA for the synthesis of compound **4a**.

| No. of cycles | Yield (%)/time (h) |
|---|---|
| 0 | 90/3.0 |
| 1 | 85/3.0 |
| 2 | 81/3.0 |
| 3 | 78/3.5 |

138.97, 145.43, 148.33, 148.46, 156.10, 164.67, 168.53; IR (KBr, $cm^{-1}$) ν : 3310, 3050, 2940, 1620. Anal. Calcd for $C_{20}H_{16}N_4Cl_2$ : C, 62.64; H, 4.20; N, 14.61. Found : C, 62.66; H, 4.18; N, 14.64.

***7-Nitro-2-spiro(2′-chromane)-3″,4″-dihydrochromano[2,3-c]-2,3-dihydro-1H-1,5-benzodiazepine (3i).*** Dark brown solid, mp = 137°C; $R_f$ = 0.47 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ: 2.62 (d, *J* = 13.20 Hz, 1H, methylene), 2.68 (t, *J* = 12.4 Hz, 1H, methine), 2.70 (d, *J* = 13.20 Hz, 1H, methylene), 2.75 (t, *J* = 12.4 Hz, 2H, methylene), 2.90 (t, *J* = 13.4 Hz, 2H, methylene), 3.58 (s, 1H, NH), 6.60 (d, *J* = 2.4 Hz, 1H, cromanyl), 6.84 (dd, *J* = 2.1 Hz, 2H, chromanyl), 6.87 (dd, *J* = 1.8 Hz, 2H, cromanyl), 6.89 (d, 1.8 Hz, 1H, cromanyl), 7.07 (t, *J* = 2.1 Hz, 1H, cromanyl), 7.10 (t, *J* = 1.8 Hz, 1H, cromanyl), 7.20 (d, *J* = 2.1 Hz, 1H, phenyl), 7.24 (s, 1H, phenyl), 7.26 (d, *J* = 2.1 Hz, 1H, phenyl); $^{13}$C NMR δ : 15.70, 20.20, 20.43, 47.20, 81.40, 113.30, 114.10, 120.90, 122.10, 123.70, 124.10, 125.10, 126.35, 126.65, 127.10, 128.90, 129.10, 129.75, 137.90, 138.90, 147.70, 157.10, 158.90, 164.10; IR (KBr, $cm^{-1}$) ν : 3510, 3405, 2905, 1620. Anal. Calcd for $C_{24}H_{19}N_3O_4$ : C, 69.71; H, 4.63; N, 10.16. Found : C, 69.74; H, 4.65; N, 10.13.

***7-Chloro-2-spiro(2′-indoline)-indolino[2,3-c]-2,3-dihydro-1H-1,5-benzodiazepine (3j).*** Dark brown solid, mp = 158°C; $R_f$ = 0.48 (pet.ether - ethylacetate = 7:3); $^1$H NMR δ : 2.60 (s, 1H, methine), 2.68 (d, *J* = 13.20 Hz, 1H, methylene), 2.80 (d, *J* = 13.20; 1H, methylene), 3.50 (s, 1H, NH), 3.60 (s, 1H, NH), 3.80 (s, 1H, NH), 6.33 (d, *J* = 2.10 Hz, 1H, indolinyl), 6.38 (dd, *J* = 2.2 Hz, 2H, indolinyl), 6.87 (t, *J* = 2.3 Hz, 1H, indolinyl), 6.89 (t, *J* = 3.04 Hz, 1H, indolinyl), 6.96 (d, *J* = 2.0 Hz, 1H, indolinyl), 6.98 (dd, *J* = 1.8 Hz, 1H, indolinyl), 7.01 (d, *J* = 1.8 Hz, 1H, indolinyl), 7.33 (d, *J* = 2.0 Hz, 1H, phenyl), 7.71 (s, 1H, phenyl), 7.74 (d, *J* = 2.2 Hz, 1H, phenyl); $^{13}$C NMR δ : 52.10, 53.40, 54.20, 70.20, 72.10, 76.10, 108.20, 109.41, 109.61, 110.19, 112.28, 112.48, 117.30, 118.20, 122.30, 125.20, 127.44, 132.70, 137.36, 143.25, 143.38, 177.09. IR (KBr, $cm^{-1}$) ν : 3520, 3410, 2910, 1640. Anal. Calcd for $C_{22}H_{17}N_4Cl$ : C, 70.84; H, 4.59; N, 15.03. Found : C, 70.87; H, 4.55; N, 15.05.

***2-Spiro[5(3-methyl-1-phenylpyrazoline)]-3″-methyl-1″-phenyl pyrazolino[4,5-c]-2,3-dihydro-1H-1,5-benzodiazepine (3k).*** Brown solid, mp = 142°C; $R_f$ = 0.46 (pet.ether - ethyl acetate = 7:3); $^1$H NMR δ : 0.90 (s, 3H, $CH_3$), 1.06 (s, 3H, $CH_3$), 2.10 (s, 1H, methine), 2.60 (s, 2H, methylene), 3.70 (s, 1H, NH), 6.40–6.60 (m, 8H, phenyl), 6.90–7.02 (m, 3H, phenyl), 7.10–7.18 (m, 3H, phenyl); $^{13}$C NMR δ : 20.20, 21.50, 34.60, 42.40, 48.30, 54.30, 74.20, 110.90, 112.50, 113.60, 115.20, 116.10, 117.20, 122.20, 125.60, 127.60, 128.20, 129.10, 131.20, 132.80, 136.10 137.10, 141.20, 143.50, 146.70, 156.60; IR (KBr, $cm^{-1}$) ν : 3520, 3400, 2905, 1640. Anal. Calcd for $C_{26}H_{24}N_6$ : C, 74.25; H, 5.75; N, 19.99. Found : C, 74.28, H, 5.72, N, 19.97.

***Synthesis of 2,3,5-β-D-ribofuranose-1-bromo-2,3,5-tribenzoate.*** This has been synthesized by reported method [29].

***Synthesis of 2,3-dihydro-1,5-benzodiazepine ribofuranosides (4a-k).*** After completion of the reaction between OPD and heterocyclic ketone (monitored by TLC), 2,3,5-β-D-ribofuranose-1-bromo-2,3,5-tribenzoate equivalent to 1.1 mole of compound **3** was added to the reaction mixture. The contents were further stirred magnetically, till completion of the reaction (checked by TLC). The ribofuranoside was extracted with ethyl acetate (2 × 15 mL). The solvent was removed by distillation under reduced pressure and the product **4** so obtained was chromatographed over silica gel (60–120 mesh) column by eluting with pet.ether-EtOAc (7:3) to afford pure ribofuranosides.

***2,4-Di(2′-furyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4a).*** Solid, mp = 146–148°C; $R_f$ = 0.35 (pet.ether - ethyl acetate - 8:2 ); yield 86%; $^1$H NMR δ : 1.69 (s, 3H, –$CH_3$), 2.90 (d, *J* = 7.2 Hz, 1H, methylene), 3.05 (d, *J* = 7.2 Hz, 1H, methylene), 4.38 (d, *J* = 7.4 Hz, 2H, $C_5''$sugar), 4.89–4.93 (m, 3H, $C_2''$, $C_3''$, and $C_4''$ sugar), 6.60 (d, *J* = 8.4 Hz, 1H, $C_1''$ sugar), 6.85–7.25 (m, 10H, 4H phenyl and 6H furyl), 7.35–8.15 (m, 15H, OBz); $^{13}$C NMR δ : 28.40, 39.20, 45.60, 65.75, 68.90, 69.10, 70.0, 86.40, 105.10, 110.21, 112.40, 113.55, 119.25, 122.50, 123.10, 127.60, 128.45, 129.70, 130.25, 132.85, 133.40, 138.08, 164.65, 167.00; IR (KBr, $cm^{-1}$) ν : 3050, 1750, 1660, 1595. GC-MS : $M^+$, 736.

***2,4-Di(2′-thiophenyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4b).*** Solid, mp = 142–144°C; $R_f$ = 0.38 (pet.ether - ethyl acetate = 8:2); yield 90%; $^1$H NMR δ : 1.65 (s, 3H, $CH_3$), 2.85 (d, *J* = 7.2

Hz, 1H, methylene), 3.0 (d, $J$ = 7.2 1H, methylene), 4.37 (d, $J$ = 7.4 Hz, 2H, $C_5''$ sugar), 4.87–4.92, (m, 3H, $C_2''$, $C_3''$ & $C_4''$ sugar), 6.70 (d, $J$ = 8.4 Hz, 1H, $C_1''$), 6.75–7.28 (m, 10H, 4H phenyl and 6H thiopenyl), 7.38–8.02 (m, 15H, OBz); $^{13}$C NMR δ : 28.20, 39.10, 45.40, 65.75, 68.95, 69.10, 70.01, 86.40, 105.08, 110.20, 112.40, 113.50, 119.25, 122.40, 123.00, 127.65, 128.45, 129.70, 130.55, 132.80, 133.45, 138.00, 164.55, 167.00; IR (KBr, $cm^{-1}$) ν : 3040, 1760, 1665, 1590. Anal. Calcd for $C_{44}H_{36}N_2O_7S_2$ : C, 68.71; H, 4.72; N, 3.64. Found : 68.74; H, 4.75; N, 3.60.

***2,4-Di(2′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4c).*** Solid, mp = 134°C; $R_f$ = 0.36 (pet.ether - ethylacetate = 8:2); yield 88%; $^1$H NMR δ : 1.78 (s, 3H, –$CH_3$), 2.95 (d, $J$ = 7.4 Hz, 1H, methylene), 3.10 (d, $J$ = 7.4 Hz, 1H, methylene), 4.40 (d, $J$ = 7.4 Hz, 2H, $C_5''$ sugar), 4.90–4.95 (m, 3H, $C_2''$, $C_3''$ and $C_4''$ sugar), 6.80 (d, $J$ = 8.4 Hz, 1H, $C_1''$, sugar), 6.95–7.20 (m, 4H, phenyl), 7.35–8.59 (m, 23H, 15H OBz and 8H pyridyl); $^{13}$C NMR δ : 29.50, 40.20, 46.40, 65.70, 68.90, 69.15, 70.10, 86.45, 113.85, 119.80, 120.75, 123.50, 127.95, 128.40, 128.55, 129.75, 130.50, 132.78, 133.65, 136.10, 139.45, 149.10, 163.48, 164.65, 167.00; IR (KBr, $cm^{-1}$) ν : 3015, 1750, 1635, 1590. Anal. Calcd for $C_{48}H_{38}N_4O_7$ : C, 72.79; H, 5.05; N 7.38. Found : 72.81; H, 5.02; N, 7.42.

***2,4-Di(3′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4d).*** Solid, mp = 138°C; $R_f$ = 0.40 (pet.ether - ethyl acetate = 8:2); yield; 89%; $^1$H NMR δ : 1.75 (s, 3H, –$CH_3$); 2.94 (d, $J$ = 7.4 Hz, 1H, methylene), 3.08 (d, $J$ = 7.4 Hz, 1H, methylene), 4.39 (d, $J$ = 7.4 Hz, 2H, $C_5''$ sugar), 4.89–4.93 (m, 3H, $C_2''$, $C_3''$ & $C_4''$ sugar), 6.78 (d, $J$ = 8.4 Hz, 1H, $C_1''$ sugar), 6.98–7.20 (m, 4H, phenyl), 7.30–8.64 (m, 23H, 15H OBz & 8H pyridyl); $^{13}$C NMR δ : 29.42, 40.01, 46.25, 65.50, 68.91, 69.10, 70.01, 86.45, 113.85, 119.80, 120.75, 123.44, 127.85, 128.40, 128.55, 129.60, 130.55, 132.74, 133.65, 136.00, 139.45, 149.10, 163.25, 164.55, 167.00; IR (KBr, $cm^{-1}$) ν : 3020, 1745, 1640, 1595, GC-MS; $M^+$, 758.

***2,4-Di(4′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4e).*** Solid, mp = 144°C; $R_f$ = 0.39 (pet.ether - ethyl acetate = 8:2); yield 90%; $^1$H NMR δ : 1.72 (s, 3H, –$CH_3$), 2.92 (d, $J$ = 7.2 Hz, 1H, methylene), 3.05 (d, $J$ = 7.2 Hz, 1H, methylene), 4.37 (d, $J$ = 7.4 Hz, 2H, $C_5''$ sugar), 4.87–4.92 (m, 3H, C2″, C3″, and C4″ sugar), 6.82 (d, $J$ = 8.2 Hz, 1H, $C_1'$ sugar), 6.92–7.25 (m, 4H, phenyl), 7.35–8.60 (m, 23H, 15H OBz and 8H pyridyl); $^{13}$C NMR δ : 29.20, 40.10, 46.15, 65.45, 68.90, 69.10, 70.01, 86.45. 113.80. 119.80, 120.65, 123.32, 127.75, 128.42, 128.65, 129.55, 130.45, 132.60, 133.55, 136.25, 139.35, 149.05, 163.15, 164.20. 167.00; IR (KBr, $cm^{-1}$) ν : 3020, 1745, 1640, 1590. Anal. Calcd for $C_{46}H_{38}N_4O_7$ : C, 72.79; H, 5.05; N, 7.38. Found : C, 72.81; H, 5.02; N, 7.40.

***7-Chloro-2,4-di(2′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4f).*** Solid, mp = 149°C; $R_f$ = 0.38 (pet.ether - ethyl acetate = 8:2); yield 80%; $^1$H NMR δ : 1.78 (s, 3H, –$CH_3$), 2.95 (d, $J$ = 7.2 Hz, 1H, methylene), 3.08 (d, $J$ = 7.2 Hz, 1H, methylene), 4.42 (d, $J$ = 7.4 Hz, 2H, $C_5''$ sugar), 4.89–4.95 (m, 3H, $C_2''$, $C_3''$, and $C_4''$ sugar), 6.80 (d, $J$ = 8.2 Hz, 1H $C_1''$ sugar); 7.02–7.25 (m, 3H, phenyl), 7.40–8.70 (m, 23H, 15H OBz & 8H pyridyl), $^{13}$C NMR δ : 29.50, 40.25, 46.45, 65.70, 68.92, 69.10, 70.01, 86.45, 117.22, 119.75, 120.90, 124.25, 128.42, 128.85, 129.76, 130.55, 131.72, 132.85, 133.25, 136.45, 139.44, 149.32, 163.55, 164.65, 167.00; IR (KBr, $cm^{-1}$) ν : 3040, 1750, 1620, 1590. Anal. Calcd for $C_{46}H_{37}O_7Cl$ : C, 69.63; H, 4.70; N, 7.06. Found : C, 69.65; H, 4.67; N, 7. 09.

***7-Nitro-2,4-di(2′-pyridyl)-2-methyl-1-(2″,3″.5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4g).*** Solid, mp = 149°C; $R_f$ = 0.44 (pet.ether - ethyl acetate = 8:2); yield 78%; $^1$H NMR δ : 1.78 (s, 3H, –$CH_3$), 2.98 (d, $J$ = 7.4 Hz, 1H, methylene), 3.10 (d, $J$ = 7.4 Hz, 1H, methylene), 4.45 (d, $J$ = 8.2 Hz, 2H, $C_5''$ sugar), 4.88–4.96 (m, 3H, $C_2''$, $C_3''$ and $C_4''$ sugar), 6.82 (d, $J$ = 8.4 Hz, 1H, $C_1''$ sugar), 7.10–7.30 (m, 3H, phenyl), 7.38–8.65 (m, 23H, 15H OBz and 8H pyridyl); $^{13}$C NMR δ : 29.65, 40.32, 46.53, 65.75, 68.92, 69.25, 70.01, 86.45, 118.42, 120.00, 121.25, 124.64, 128.45, 128.88, 129.75, 130.50, 131.92, 132.85, 133.22, 136.45, 139.65, 149.32, 163.65, 164.60, 167.00; IR (KBr, $cm^{-1}$) ν : 3130, 1760, 1640, 1595. Anal. Calcd for $C_{46}H_{37}N_4O_9$ : C, 68.72; H, 4.64; N, 8.71. Found : C, 68.75; H, 4.67; N 8.68.

***7,8-Dichloro-2,4-di(2′-pyridyl)-2-methyl-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4h).*** Solid, mp. = 136°C; $R_f$ = 0.42 (pet.ether - ethyl acetate = 8:2); yield 75%; $^1$H NMR δ : 1.80 (s, 3H, $CH_3$), 2.98 (d, $J$ = 7.4 Hz, 1H, methylene), 3.12 (d, $J$ = 7.4 Hz, 1H, methylene), 4.48 (d, $J$ = 8.2 Hz, 2H, $C_5''$ sugar), 4.88–4.99 (m, 3H, $C_2''$, $C_3''$, and $C_4''$ sugar), 6.85 (d, $J$ = 8.2 Hz, 1H, $C_1''$ sugar), 7.35–8.75 (m, 25H, 15H OBz, 2H phenyl and 8H pyridyl); $^{13}$C NMR δ : 29.66, 40.48, 46.65, 65.75, 68.90, 69.25, 70.01, 86.45, 124.22, 124.45, 128.80, 129.75, 130.52 131.95, 132.66, 132.84, 133.25, 136.40, 139.65, 149.35, 163.60, 164.50, 167.00; IR (KBr. $cm^{-1}$) ν : 3090, 1763, 1765, 1625, 1590. Anal. Calcd for $C_{46}H_{36}N_4O_7Cl_2$ : C, 66.72; H, 4.38; N, 6.77. Found : C, 66.75; H, 4.40, N, 6.75.

***7-Nitro-2-spiro(2′-chromane)-3″,4″-dihydrochromano[2,3-c]-1-(2‴, 3‴,5‴-tri-o-benzoyl -β-D-rifuranosyl)-2,3-dihydro-1,5-benzodiazepine (4i).*** Solid, mp = 152–154°C; $R_f$ = 0.47 (pet.ether - ethyl acetate = 8:2); yield 75%; $^1$H NMR δ : 2.35 (t, $J$ = 12.4 Hz, 2H, methylene), 2.50 (t, $J$ = 12.4 Hz, 2H, methylene), 2.62 (d, $J$ = 12.2 Hz, 2H, methylene), 2.68 (t, $J$ = 13.20 Hz, 1H, methine), 4.35 (d, $J$ = 7.2 Hz, 2H, $C_5'''$ sugar), 4.78–4.90 (m, 3H, $C_2'''$,$C_3'''$, and $C_4'''$ sugar), 6.78 (d, $J$ = 8.2 Hz, 1H, $C_1'''$ sugar), 6.85–7.30 (m, 11H, 3H phenyl and 8H chromanyl), 7.38–8.20 (m, 15H, OBz); $^{13}$C NMR δ : 25.40, 27.95, 41.90, 45.55, 46.65, 65.72, 68.92, 69.22, 70.00, 86.42, 118.45, 120.42, 120.95, 124.65, 128.42, 128.85, 129.70, 130.55, 131.75, 132.66, 133.25, 136.42, 139.55, 149.32, 163.50, 164.66, 167.00; IR (KBr, $cm^{-1}$) ν : 2920, 1750, 1630, 1595. Anal. Calcd for $C_{50}H_{39}N_3O_{11}$ : C, 69.99; H, 4.58; N, 4.90. Found : C, 69.72; H, 4.60 N, 4.87.

***7-Chloro-2-spiro(2′-indoline)-indolino[2,3-c]-1-(2″,3″,5″-tri-o-benzoyl-β-D-ribofuranosyl)-N,N-di(2″,3″,5″-tri-o-benzoyl-β-ribofuranosyl)-2,3-dihydro-1,5-benzodiazepine (4j).*** Solid, mp = 158°C; $R_f$ = 0.43 (pet.ether - ethyl acetate = 8:2); yield 77%; $^1$H NMR δ : 2.50 (s, 2H, methylene), 2.70 (s, 1H, methine), 4.37 (d, $J$ = 7.4 Hz, 6H, 3 × $C_5''$ sugar) 4.80–4.93 (m, 9H, 3 × $C_2''$, $C_3''$, and $C_4''$ sugar), 6.80 (d, $J$ = 8.2 Hz, 3H, 3 × $C_1''$ sugar), 6.90–7.25 (m, 11H, 3H phenyl and 8H indolinyl), 7.35–8.40 (m, 45H, 3 × OBz); $^{13}$C NMR δ : 27.95, 45.60, 52.50, 65.70, 68.90, 69.21, 70.01, 86.45, 118.45, 120.22, 124.65, 128.42, 128.85, 129.70, 130.50, 131.75, 132.66, 133.20, 136.45, 139.55, 149.30, 163.45, 165.65, 167.00; IR (KBr, $cm^{-1}$) ν : 2915, 1760, 1620, 1592. Anal.

Calcd for $C_{100}H_{77}N_4O_{21}$ : C, 71.87; H, 4.64; N, 3.35. Found : C, 71.90; H, 4.62, 3.38.

***2-Spiro[5-(3-methyl-1′-phenylpyrazoline)]-3″-methyl-1″-phenylpyrazolino[4,5-c]-1-(2‴,3‴,5‴-tri-o-benzoyl-β-D-ribofuranosyl) -2,3-dihydro-1,5-benzodiazepine (4k).*** Solid, mp = 154–156°C; $R_f$ = 0.37 (pet.ether - ethyl acetate = 8:2); yield 85%, $^1$H NMR δ : 1.85 (s, 3H, —$CH_3$), 1.88 (s, 3H, —$CH_3$), 2.40 (s, 2H, methylene), 2.50 (s, 1H, methine), 4.36 (d, $J$ = 7.2 Hz, 2H, $C_5‴$ sugar), 4.80–4.92 (m, 3H, $C_2‴$, $C_3‴$, and $C_4‴$ sugar), 6.60–7.10 (m, 15H, 14H phenyl, and 1H $C_1‴$ sugar), 7.25–8.30 (m, 15H, OBz); $^{13}$C NMR δ : 27.90, 41.45, 45.62, 51.40, 51.65, 65.72, 68.92, 69.20, 70.01, 86.45, 113.50, 119.52, 123.25, 127.62, 128.45, 129.72, 130.55, 132.84, 133.45, 138.00, 162.62, 162.68, 164.65, 170.00; IR (KBr, $cm^{-1}$) ν : 2910, 1760, 1625. Anal. Calcd for $C_{55}H_{44}N_6O_7$ : C, 72.19; H, 5.13; N, 9.72. Found : C, 72.22; H, 5.15, N, 9.70.

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## REFERENCES AND NOTES

[1] Randall, L. O.; Kappel, B. In Benzodiazepines; Grattani, S., Mussini, E., Randall, L. O. Eds.; Raven Press: New York, 1973; p 27.

[2] Schutz, H. Benzodiazepines; Springer: Heildberg, 1982; Vol.2, p 240.

[3] Smalley, R. K. In Comprehensive Organic Chemistry; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, U.K., 1979; Vol.4, p 600.

[4] Landquist, J. K. In Comprehensive Heterocyclic Chemistry; Katritzky, A. K., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol.11, p 166, 170.

[5] (a) Atwal, K. S.; Bergey, J. L.; Hedberg, A.; Moreland, S. J Med Chem 1987, 30, 635; (b) Braccio, G.; Roma, G.; Vargin, L.; Mura, M.; Marongiu, M. E. J Med Chem 2001, 36, 935.

[6] (a) Harris, R. C.; Straley, J. M. U. S. Pat.153,775(1968); (b) Harris, R. C.; Straley, J. M. Chem Abstr 1970, 73, 100054w.

[7] (a) Essaber, M.; Baourd, A.; Hasnaoui, A.; Benharref, A.; Lavergne, J. P. Synth Commun 1998, 28, 4097; (b) Reddy, K. V. V.; Rao, P. S; Ashok, D. Synth Commun 2000, 30, 1825.

[8] Reid, W.; Torinus, E. Chem Ber 1959, 92, 2902.

[9] Stahlofen, P.; Reid, W. Chem Ber 1954, 90, 815.

[10] Herbert, J. A. L.; Suschitzky, H. J Chem Soc Perkin Trans I 1974, 1, 2657.

[11] Jung, D. I.; Choi, T. W.; Kim, Y. Y. I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. Synth Commun 1999, 29, 1941.

[12] Marales, R. H.; Bulbarela, A.; Contreas, R. Heterocycles 1986, 24, 135.

[13] Balakrishna, M. S.; Kaboudin, B. Tetrahedron Lett 2001, 42, 1127.

[14] Yadav, J. S.; Reddy, B. V. S.; Kumar, S. P.; Nagaiah, K. Synthesis 2005, 3, 480.

[15] Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Srinivasulu, G.; Kanwar, A. C. Arkivoc 2005(III), 221.

[16] Jarikote, D. V., Siddiqui, S. A.; Rajagopal, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Tetrahedron Lett 2003, 40, 1835.

[17] Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Anuradha, K. Green Chem 2002, 4, 592.

[18] Varala, R.; Ramu, E.; Adapa, S. R. Arkivoc 2006(III), 171 (and the references cited therein).

[19] (a) Mac Cross, M.; Robins, M. J. In Chemistry of Antitumor Agents; Wilman, D. E. V., Ed; Blackie and Son: Glasgow, UK, 1990; p 261; (b) Robins, R. K.Kini, G. D. In Chemistry of Antitumor Agents; Wilman, D. E. V., Ed.; Blackie and Son: Glasgow, UK, 1988, p 11; (c) Robins, R. K.; Revankar, G. In Antiviral Drug Development; De Clercq, E., Walker, R. T., Eds.; Plenum: New York, 1998; p 11; (d) Sanghvi, Y. S.; Cook, P. D. In Nucleosides and Nucleotides as Antitumor and Antiviral Agents; Chu, C. K., Baker, D. C., Eds.; Plenum: New York, 1993; p 311.

[20] Lerman, L. DNA Probes, Application in Genetic and Infectious Disease and Cancer; Cold Spring Harbor Laboratory: Cold Spring Harbor, USA, 1986.

[21] Crooke, S. T.; Lebleu, B. In Antisense Research and Applications; CRC Press: Boca Raton, FL, 1993; p 311.

[22] (a) Uhlmann, A.; Peyman, A. Chem Rev, 1990, 90, 543; (b) Singh, I.; Hecker, W.; Prasad, A. K.; Parmar, V. S.; Seitz, O. Chem Commun 2002, 5004; (c) Wagner, R. W. Nature 1994, 372, 333.

[23] (a) Khodairy, A.; El-sayed, A. M.; Sahah, H.; Abdel-Ghamy, H. Synth Commun 2007, 37, 3245 and references cited therein; (b) Jung, D.; Song, J.; Kim, Y.; Lee, D.; Lee, Y.; Park, Y.; Choi, S.; Hahn, Bull Kor Chem Soc 2007, 28, 1877 and references cited therein.

[24] Singh, G.; Kumar, N.; Yadav, A. K.; Mishra, A. K. Heteroat Chem 2002, 13, 620 and references cited therein.

[25] Liu, B. K.; Way, N.; Wang, N.; Chen, Z. C.; Wu, Q.; Lin, X. F. Bioorganic and Medicinal Chem Lett 2006, 16, 3769.

[26] Kumar, V.; Parmar, V. S.; Malhotra, S. V. Tetrahedron Lett 2007, 48, 9.

[27] Palimaker, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R.; Srinivasan, K. V. J Org Chem 2003, 40, 20.

[28] Bonhote, P.; Dias, A. P., Papageorgiou, N.; Kalyanasundaram, K.; Graetzel, M. Inorg Chem 1996, **35**, 1168.

[29] Prakash, L.; Gupta, A. Boll Chimico Farma 1994, 133, 163.

# Diastereoselective Synthesis of Nicotine Derivatives *via* 1,3-Dipolar Cycloaddition Reactions



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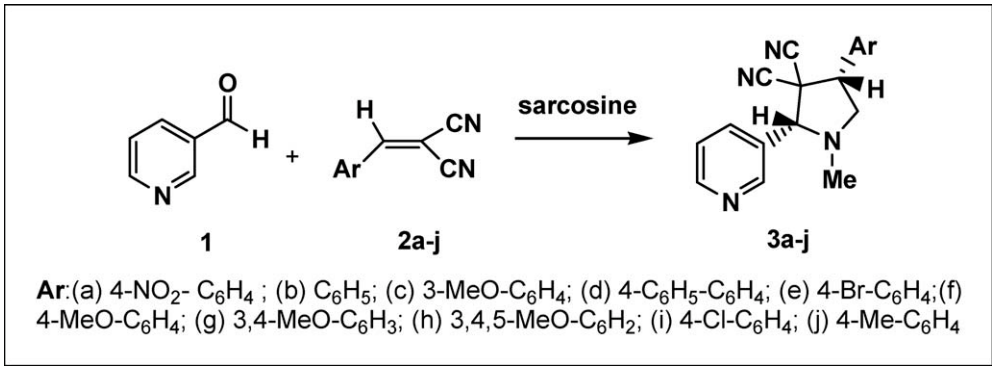


A simple diastereoselective route to nicotine derivatives is presented. The one-pot three component 1,3-dipolar cycloaddition reaction of the Knöevenagel adducts of a number of aromatic aldehydes and malononitrile with an azomethine ylide derived *in situ* from pyridine-3-carbaldehyde and sarcosine give access to nicotine derivatives in good yields.

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## INTRODUCTION

(S)-Nicotine is present together with a number of minor alkaloids in tobacco and a wide variety of other plants (Fig. 1). Dried leaves of the tobacco plants *Nicotiana rustica* and *N. tabacum* contain as much as 2–8% of (S)-nicotine [1]. A large scale application of nicotine was its use as an insecticide, as ~2800 tons of (S)-nicotine was used as a crop protectant per year [2]. Aqueous solutions of nicotine sulfate are still used throughout the world as insecticides. (S)-Nicotine has drawn a lot of interest in the last few decades due to its potential role in therapeutics for the central nervous system (CNS) [1]. In particular, (S)-nicotine may have beneficial effects in the treatment of Parkinson's disease (PD), Alzheimer's disease (AD), Tourette's syndrome, anxiety, schizophrenia, uterative colitis, and other disorders [3]. Detrimental effects including actions on both the cardiovascular and gastrointestinal systems, sleep disturbance, and at higher doses, neuromuscular effects and seizures limit the use of nicotine as a therapeutic reagent [4]. These side effects are due to subtype selectivity, or a lack thereof, among the various *n*AChRs [5]. Hence, there has been a need to synthesize nicotine derivatives that are more selective in their binding to ACh sites to minimize side effects while retaining beneficial activity.

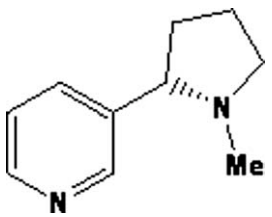
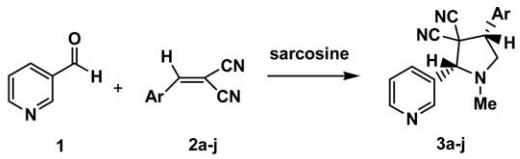



**Figure 1.** (S)-Nicotine.

## RESULTS AND DISCUSSION

Considerable attention has been given to the synthesis of nicotine derivatives that would exhibit the beneficial biological properties at lower toxicity [6]. Most of the approaches have been directed toward the synthesis of nicotine [3] and nicotine analog derivatives [7] with modification on the pyridine ring. 1,3-Dipolar cycloaddition reactions of azomethine ylides with various alkenes and alkynes represent an efficient and convergent method for the construction of pyrrolidine and pyrrolizine units [8]. To the best of our knowledge, a few reports are present in literature for the preparation of nicotine derivatives with modification at the pyrrolidine ring *via* cycloaddition of azomethine ylides to chalcones. 1,3-Dipolar cycloaddition of phenylvinyl sulfone with azomethine ylide generated based on the

**Scheme 1.** Synthesis of Nicotine derivatives **3**.




**Ar**:(a) 4-$NO_2$- $C_6H_4$ ; (b) $C_6H_5$; (c) 3-MeO-$C_6H_4$; (d) 4-$C_6H_5$-$C_6H_4$; (e) 4-Br-$C_6H_4$;(f) 4-MeO-$C_6H_4$; (g) 3,4-MeO-$C_6H_3$; (h) 3,4,5-MeO-$C_6H_2$; (i) 4-Cl-$C_6H_4$; (j) 4-Me-$C_6H_4$

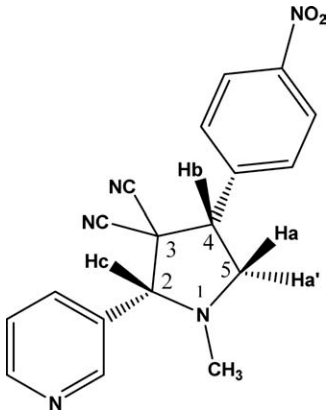
*in situ*, fluorine-mediated desilylation of cyanoaminosilane afforded 3-benzensulfonylnicotine [9]. Recently, Zhai and his coworkers utilized the azomethine ylide–alkene [3+2] cycloadditions toward the synthesis of conformationally restricted nicotine derivatives [10]. Herein, we describe a simple diastereoselective synthesis of nicotine derivatives *via* one-pot three component 1,3-dipolar cycloaddition reaction of the Knöevenagel adducts of a number of aromatic aldehydes and malononitrile with an azomethine ylide derived *in situ* from pyridine-3-carbaldehyde and sarcosine in refluxing toluene.

The Knöevenagel adducts **2a**–**j** were prepared from the condensation of malononitrile with a series of aromatic aldehydes *via* the previously reported procedure [8c]. These adducts were subsequently treated with pyridine-3-carbaldehyde **1** and sarcosine in refluxing toluene for 3 h (Scheme 1). After evaporation of solvent under reduced pressure, methanol was added, and the solid products were filtered and recrystallized from methanol resulting in nicotine derivatives **3a**–**j**.

Identification of the products was carried out by spectroscopic methods. The $^1$H NMR spectrum of **3a** (Scheme 2) exhibited a singlet at δ 2.42 for N—$CH_3$, a doublet of doublets appears as a triplet at δ 3.26 ($J$ = 10.3 Hz, Ha′), a doublet of doublets at δ 3.83 ($J$ = 10.3, 5.7 Hz, Ha), a singlet at δ 4.15 (Hc), a doublet of doublets at δ 4.25 ($J$ = 10.3, 5.7 Hz, Hb), a multiplet at δ 7.46 (pyridine-*m*-H), a doublet at δ 7.76 ($J$ = 8.6 Hz, Ar-*m*-2H), a broad doublet at δ 7.98 (pyridine-*p*-H), a doublet at δ 8.34 ($J$ = 8.6 Hz, Ar-*o*-2H), a broad doublet at δ 8.76 (pyridine-*o*-H), and a singlet at δ 8.82 (pyridine-*o*-H). The $^{13}$C NMR spectrum of **3a** showed 16 signals at δ 39.8, 50.4, 52.2, 58.6, 76.5, 111.7, 114.2, 124.4, 124.8, 128.8, 130.0, 136.3, 142.5, 148.9, 150.4, and 152.2. The MS (EI) spectrum revealed the molecular ion peak at *m*/*z* 333 corresponding to the molecular weight of **3a**.

The relative configuration of the stereocenters in **3a** was assigned using X-ray crystallographic study of its single crystal (Fig. 2), which implied a cis (syn diastereomer) arrangement between C-2 and C-4 [11]. On the basis of this result, we propose a transition-state model to account for the diastereoselectivity of the reaction (Scheme 3). Hence, the structure of the azomethine ylides generated *in situ* may be represented as *E* and *Z* diastereomers. These two can approach the chalcone *via* **I**, **II**, and **I**′, **II**′ structures, respectively. **I** and **I**′ are sterically favored relative to **II** and **II**′ since the latter two experience more steric hindrance from aryl and methyl groups which are eclipsed to each other (Scheme 3). The formation of the 2,4-syn diastereomer as the sole product in most cases reveals that the azomethine ylide with the structure of **I***E* configuration has been implicated in the reaction pathway. Since **3c** and **3h** are generated as a mixture of dl, and identified as syn and anti with the ratios of 3:2 and 2:1, respectively, the involvement of both **I***E* and **II***E* azomethine configurations in reaction should be taken into consideration. We believe that **2c** and **2h** albeit have different number of methoxy substituents, behave similarly since the electron withdrawing effect of the 5-methoxy group of **2h** on the Michael addition rate of zomethine ylide to ArCH=$C(CN)_2$ roughly offsets the electron donating effect of the 4-methoxy group. Therefore, the disfavored steric effect present in **II***E* in retarding the reaction rate of **2h** seems to be compensated by rate enhancement

**Scheme 2.** Strucure of derivative **3a**.



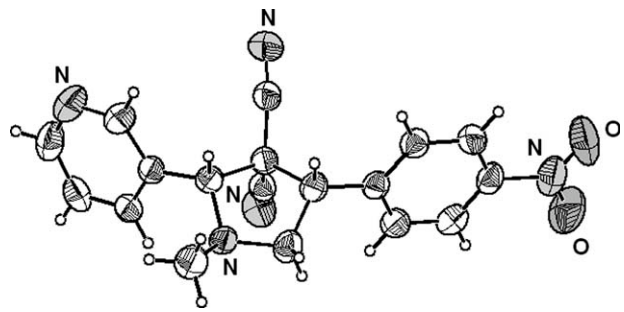
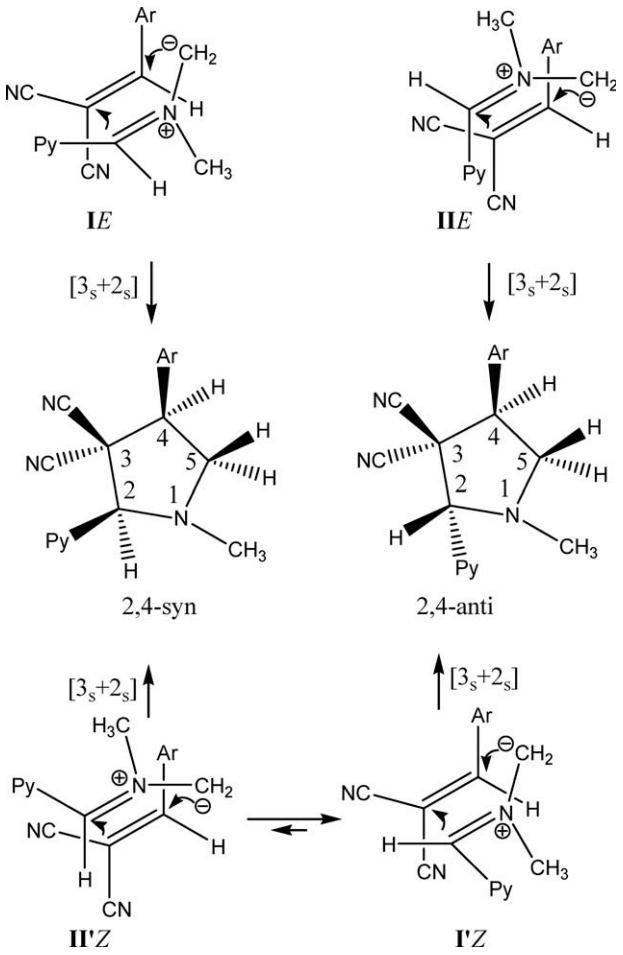




**Figure 2.** ORTEP diagram of **3a**.

**Scheme 3.** Transition state models evoked to account for reaction diastereoselectivities.

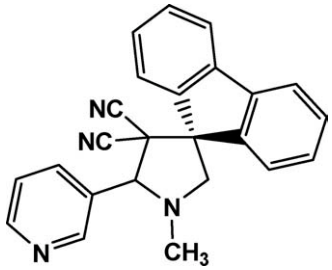



due to the favored electronic effect of the 3-methoxy group.

Under similar conditions, utilization of the Knöevenagel adduct of fluorenone with malononitrile afforded the corresponding 4-spironicotine derivative **3k** in 75% yield (Scheme 4). This reaction exhibits the diversity of the method in applying different chalcones.

In summary, a range of nicotine derivatives have been synthesized *via* the one-pot three component 1,3-dipolar cycloaddition reaction of the Knöevenagel adducts of a number of aromatic aldehydes and malononitrile with an azomethine ylide derived *in situ* from sarcosine and pyridine-3-carbaldehyde.

**Scheme 4.** Structure of derivative **3k**.



## EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer; in $cm^{-1}$. $^1H$ and $^{13}C$ NMR Spectra: Bruker DRX-500-AVANCE spectrometer at 500 ($^1H$) and 125.7 MHz ($^{13}C$); $CDCl_3$ solns.; δ in ppm, *J* in Hz. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, MA).

**General procedure for the synthesis of *N*-methyl-4-(X-substituted)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3a–k).** A mixture of sarcosine (2.0 mmol), pyridine-3-carbaldehyde (2.0 mmol), and chalcone (2.0 mmol) in dry toluene (20 mL) containing molecular sieves 4 Å (1000 mg) was refluxed with stirring for 3 h. The progress of the reaction was followed by TLC. After completion, the solvent was removed under reduced pressure. After addition of methanol (1 mL), the resulting solid was filtered and recrystallized from methanol to afford a crystalline product (Table 1).

***N*-methyl-4-(4-nitrophenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3a).** Yellow crystals; Yield: 70%; mp 188–189°C; IR (KBr): 2250 $cm^{-1}$; $^1$PH NMR: 2.42 (s, 3H), 3.26 (t, *J* = 10.3, 1H), 3.83 (dd, *J* = 10.3, 5.7, 1H), 4.15 (s, 1H), 4.25 (dd, *J* = 10.3, 5.7, 1H), 7.46 (m, 1H), 7.76 (d, *J* = 8.6, 2H), 7.98 (bd, 1H), 8.34 (d, *J* = 8.6, 2H), 8.76 (bd, 1H), 8.82 (s, 1H); $^{13}C$ NMR: 39.8, 50.4, 52.2, 58.6, 76.4, 111.7, 114.2, 124.4, 124.8, 128.8, 130.0, 136.3, 142.6, 148.9, 150.4, 152.2; MS: *m*/*z* = 333 [$M^+$]; Anal. Calcd. For $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.50; N, 21.02%. Found: C, 64.39; H, 4.38; N, 20.69%.

***N*-methyl-4-phenyl-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3b).** White crystals; Yield: 72%; mp 127–128°C; IR

**Table 1**

Results of synthesized nicotine derivaties.

| Entry | Ar | Product | Yield (%) |
|---|---|---|---|
| 1 | 4-Nitrophenyl | **3a** | 70 |
| 2 | Phenyl | **3b** | 72 |
| 3 | 3-Methoxyphenyl[a] | **3c** | 65 |
| 4 | Biphenyl | **3d** | 75 |
| 5 | 4-Bromophenyl | **3e** | 73 |
| 6 | 4-Methoxyphenyl | **3f** | 64 |
| 7 | 3,4-Methoxyphenyl | **3g** | 70 |
| 8 | 3,4,5-Methoxyphenyl[a] | **3h** | 68 |
| 9 | 4-Chlorophenyl | **3i** | 77 |
| 10 | 4-Methylphenyl | **3j** | 75 |

[a] Obtained as a mixture of dr, identified as 3:2 and 2:1 of anti:syn, respectively, by $^1H$ NMR.

(KBr): 2250 $cm^{-1}$; $^1$PH NMR: 2.39 (s, 3H), 3.20 (t, $J$ = 10.2, 1H), 3.85 (dd, $J$ = 10.2, 6.6, 1H), 4.14 (m, 2H), 7.44–7.57 (m, 6H), 8.00 (bd, 1H), 8.74 (bd, 1H), 8.83 (s, 1H); $^{13}$C NMR: 39.9, 50.9, 52.8, 58.4, 76.4, 112.0, 114.6, 124.3, 128.8, 129.4, 129.6, 129.7, 135.0, 136.4, 150.4, 151.9; MS: $m/z$ = 288 [$M^+$]; Anal. Calcd. For $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43%. Found: C, 74.56; H, 5.23; N, 19.72%.

***N-methyl-4-(3-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3c).*** White crystals; Yield: 75%; IR (KBr): 2248 $cm^{-1}$; $^1$PH NMR (syn/anti): 2.37 (s, 3H)/2.38 (s, 3H), 3.17 (t, $J$ = 10.2, 1H)/3.05 (t, $J$ = 10.2, 1H), 3.84 (dd, $J$ = 10.2, 7.0, 1H)/3.73 (dd, $J$ = 10.2, 7.0, 1H), 3.86 (s, 3H)/3.85, s, 3H), 4.12 (dd, $J$ = 10.2, 7.0, 1H)/4.10 (dd, $J$ = 10.2, 7.0, 1H), 4.14 (s, 1H)/4.04 (s, 1H), 6.93–6.96 (m, 2H)/7.00–7.03 (m, 2H), 7.13 (bd, 1H)/7.01 (bd, 1H), 7.36–7.39 (m, 2H)/7.41–7.45 (m, 2H), 7.99 (bd, 1H)/7.92 (bd, 1H), 8.73 (bd, 1H)/8.72 (bd, 1H), 8.82 (s, 1H)/8.79 (s, 1H); $^{13}$C NMR (syn and anti mixture): 39.9, 49.4, 50.8, 52.7, 53.9, 55.8, 58.3, 60.1, 67.3, 76.9, 112.1, 113.8, 114.6, 114.6, 114.8, 114.9, 115.0, 115.2, 121.0, 121.1, 124.3, 124.3, 129.4, 130.6, 130.7, 130.8, 136.0, 136.4, 136.4, 136.5, 150.3, 150.4, 151.8, 151.9, 160.4, 160.49; MS: $m/z$ = 318 [$M^+$]; Anal. Calcd. For $C_{19}H_{18}N_4O$: C, 71.66; H, 5.70; N, 17.60%. Found: C, 71.15; H, 6.10; N, 17.14%.

***N-methyl-4-biphenyl-2-(pyridine-3-yl) pyrrolidine-3,3-dicarbonitrile (3d).*** White crystals; Yield: 77%; mp 152–153°C; IR (KBr): 2246 $cm^{-1}$; $^1$PH NMR: 2.42 (s, 3H), 3.23 (t, $J$ = 10.2, 1H), 3.88 (dd, $J$ = 10.2, 6.6, 1H), 4.17 (s, 1H), 4.19 (dd, $J$ = 10.2, 6.6, 1H), 7.39–7.53 (m, 4H), 7.64 (bd, 4H), 7.71 (bd, 2H), 8.03 (bd, 2H), 8.76 (bd, 1H), 8.82 (s, 1H); $^{13}$C NMR: 39.9, 50.9, 52.6, 58.4, 76.3, 112.1, 114.6, 124.3, 127.6, 128.2, 128.3, 129.3, 129.3, 129.4, 129.5, 133.8, 136.4, 136.4, 140.6, 142.6, 150.4, 152.0; MS: $m/z$ = 364 [$M^+$]; Anal. Calcd. For $C_{24}H_{20}N_4$: C, 79.12; H, 5.49; N, 15.38%. Found: C, 78.69; H, 5.51; N, 15.27%.

***N-methyl-4-(4-bromophenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3e).*** White crystals; Yield: 73%; mp 154–155°C; IR (KBr): 2250 $cm^{-1}$; $^1$PH NMR: 2.37 (s, 3H), 3.19 (t, $J$ = 10.2, 1H), 3.77 (dd, $J$ = 10.2, 6.3, 1H), 4.09 (dd, $J$ = 10.2, 6.3, 1H), 4.12 (s, 1H), 7.42–7.46 (m, 3H), 7.60 (bd, 2H), 7.98 (bd, 1H), 8.74 (bd, 1H), 8.80 (s, 1H); $^{13}$C NMR: 39.8, 50.7, 52.2, 58.4, 76.3, 112.0, 114.4, 124.0, 124.3, 129.2, 130.5, 130.6, 132.9, 134.2, 136.3, 150.4, 151.9, 152.0; MS: $m/z$ = 367 [$M^+$]; Anal. Calcd. For $C_{18}H_{15}N_4Br$: C, 58.85; H, 4.11; N, 15.25%. Found: C, 58.36; H, 3.89; N, 15.05%.

***N-methyl-4-(4-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3f).*** White crystals; Yield: 64%; mp 138–139°C; IR (KBr): 2248 $cm^{-1}$; $^1$PH NMR: 2.37 (s, 3H), 3.17 (t, $J$ = 10.2, 1H), 3.78 (dd, $J$ = 10.2, 6.7, 1H), 3.84 (s, 3H), 4.10 (dd, $J$ = 10.2, 6.7, 1H), 4.12 (s, 1H), 6.98 (d, $J$ = 8.6, 2H), 7.42 (m, 1H), 7.47 (d, $J$ = 8.6, 2H), 7.99 (bd, 1H), 8.72 (bd, 1H), 8.82 (s, 1H); $^{13}$C NMR: 39.9, 51.2, 52.4, 55.8, 58.4, 76.2, 112.2, 114.7, 115.0, 124.3, 126.8, 129.6, 130.0, 136.3, 150.4, 151.9, 160.7; MS: $m/z$ = 318 [$M^+$]; Anal. Calcd. For $C_{19}H_{18}N_4O$: C, 71.66; H, 5.70; N, 17.60%. Found: C, 71.33; H, 5.42; N, 17.47%.

***N-methyl-4-(3,4-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3g).*** White crystals; Yield: 70%; mp 111–112°C; IR (KBr): 2252 $cm^{-1}$; $^1$PH NMR: 2.37 (s, 3H), 3.18 (t, $J$ = 10.2, 1H), 3.80 (dd, $J$ = 10.2, 7.0, 1H), 3.91 (s, 3H), 3.95 (s, 3H), 4.08 (dd, $J$ = 10.2, 7.0, 1H), 4.12 (s, 1H), 6.92 (d, $J$ = 8.2, 2H), 7.06 (s, 1H), 7.10 (d, $J$ = 8.2, 2H), 8.72 (bd, 1H), 8.81 (s, 1H); $^{13}$C NMR: 39.9, 51.2, 52.9, 56.3, 56.5, 58.3, 76.1, 111.7, 111.8, 112.3, 114.6, 121.4, 124.3, 127.0, 129.4, 136.3, 149.8, 150.3, 150.3, 151.8; MS: $m/z$ = 348 [$M^+$] Anal. Calcd. For $C_{20}H_{20}N_4O_2$: C, 68.93; H, 5.79; N, 16.08%. Found: C, 68.35; H, 5.29; N, 15.83%.

***N-methyl-4-(3,4,5-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3h).*** White crystals; Yield: 64%; IR (KBr): 2245 $cm^{-1}$; $^1$PH NMR (syn/anti): 2.38 (s, 3H)/2.39 (s, 3H), 3.18 (t, $J$ = 10.3, 1H)/3.03 (t, $J$ = 10.3, 1H), 3.80 (dd, $J$ = 10.3, 7.0, 1H)/3.70 (dd, $J$ = 10.3, 7.0, 1H), 3.91 (s, 9H)/3.89 (s, 9H), 4.07 (dd, $J$ = 10.3, 7.0, 1H)/4.04 (dd, $J$ = 10.3, 7.0, 1H), 4.13 (s, 1H)/4.05 (s, 1H), 6.75 (s, 2H)/6.62 (s, 2H), 7.46 (bd, 1H)/7.43 (bd, 1H), 7.99 (bd, 1H)/7.91 (bd, 1H), 8.73 (bd, 1H)/8.72 (bd, 1H), 8.82 (s, 1H)/8.79 (s, 1H); $^{13}$C NMR (syn and anti mixture): 39.9, 40.0, 49.3, 51.0, 53.3, 54.5, 56.7, 56.8, 58.3, 60.1, 61.3, 61.3, 76.1, 106.0, 106.3, 112.2, 114.1, 114.6, 114.8, 124.3, 124.3; MS: $m/z$ = 378 [$M^+$]; Anal. Calcd. For $C_{21}H_{22}N_4O_3$: C, 66.63; H, 5.86; N, 14.80%. Found: C, 66.76; H, 6.12; N, 14.73%.

***N-methyl-4-(4-chlorophenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3i).*** White crystals; Yield: 77%; mp 147–148°C; IR (KBr): 2250 $cm^{-1}$; $^1$PH NMR: 2.38 (s, 3H), 3.19 (t, $J$ = 10.2, 1H), 3.77 (dd, $J$ = 10.2, 6.3, 1H), 4.11 (m, 2H), 7.37–7.50 (m, 5H), 7.98 (bd, 1H), 8.74 (bd, 1H), 8.82 (s, 1H); $^{13}$C NMR: 39.8, 50.8, 52.2, 58.5, 76.3, 112.0, 114.4, 124.3, 129.2, 129.9, 129.9, 130.2, 130.3, 133.6, 135.8, 136.3, 150.4, 152.0; MS: $m/z$ = 322 [$M^+$]; Anal. Calcd. For $C_{18}H_{15}N_4Cl$: C, 66.96; H, 4.68; N, 17.36%. Found: C, 66.85; H, 4.94; N, 17.23%.

***N-methyl-4-(4-methylphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3j).*** White crystals; Yield: 75%; mp 146–147°C; IR (KBr): 2250 $cm^{-1}$; $^1$PH NMR: 2.38 (s, 3H), 2.40 (s, 3H), 3.18 (t, $J$ = 10.2, 1H), 3.83 (dd, $J$ = 10.2, 6.7, 1H), 4.11 (dd, $J$ = 10.2, 6.7, 1H), 4.13 (s, 1H), 7.28 (d, $J$ = 8.0, 1H), 7.43 (m, 1H), 7.45 (d, $J$ = 8.0, 1H), 8.00 (bd, 1H), 8.73 (bd, 1H), 8.83 (s, 1H); $^{13}$C NMR: 21.6, 39.9, 51.9, 52.6, 58.3, 76.2, 112.2, 114.7, 124.3, 128.7, 128.9, 129.6, 130.3, 131.9, 136.4, 139.6, 150.4, 151.9; MS: $m/z$ = 302 [$M^+$]; Anal. Calcd. For $C_{19}H_{18}N_4$: C, 75.46; H, 6.00; N, 18.53%. Found: C, 74.96; H, 6.38; N, 18.26%.

***Spiro[9,4]-1-N-methyl-2(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3k).*** White crystals; Yield: 75%; mp 222–223°C; IR (KBr): 2243 $cm^{-1}$; $^1$PH NMR: 2.46 (s, 3H), 3.28 (d, $J$ = 10.3, 1H), 3.78 (d, $J$ = 10.3, 1H), 4.44 (s, 1H), 7.45–7.56 (m, 5H), 7.71 (d, $J$ = 7.5, 1H), 7.76 (d, $J$ = 7.3, 1H), 7.80 (d, $J$ = 7.4, 1H), 8.01 (d, $J$ = 7.4, 1H), 8.01 (d, $J$ = 7.8, 1H), 8.77 (d, $J$ = 3.6, 1H), 8.96 (s, 1H); $^{13}$C NMR: 39.9, 53.8, 60.8, 65.9, 77.4, 113.1, 113.3, 120.7, 121.1, 124.4, 125.9, 126.6, 128.4, 128.6, 129.6, 130.2, 130.5, 136.8, 140.6, 141.2, 144.6, 145.4, 150.6, 152.0; MS: $m/z$ = 362 [$M^+$]; Anal. Calcd. For $C_{24}H_{18}N_4$: C, 79.56; H, 4.97; N, 15.47%. Found: C, 79.34; H, 4.63; N, 15.48%.

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## REFERENCES AND NOTES

[1] (a) Pailer, M. In Tobacco Alkaloids and Related Compounds; von Euler, U. S., Ed.; Pergamon: New York, 1965; p 15; (b) Gorrod, J. W.; Jacob, P. In Analytical Determination of Nicotine and Related Compounds and Their Metabolites; Elsevier: New York, 1999; pp 1–9.

[2] Shepard, H. H. In The Chemistry and Action of Insecticides; McGraw-Hill: New York, 1951.

[3] (a) Levin, E. D. J Neurobiol 2002, 53, 633; (b) Newhouse, P. A.; Kelton, M. Pharm Acta Helv 2000, 74, 91; (c) Holladay, M. K.; Dart, M. J.; Lynch, J. K. J Med Chem 1997, 40, 4169; (d) Breining, S. R. Curr Top Med Chem 2004, 4, 609; (e) Jensen, A. A.; Frølund, B.; Liljefors, T.; Krosgsgaard-Larsen, P. J Med Chem 2005, 48, 4705.

[4] (a) McDonald, I. A.; Vernier, J.-M.; Cosford, N.; Corey-Naeve, J. Curr Pharm Des 1996, 2, 357; (b) Cosford, N. D. P.; Bleiker, L.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F. M.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. J Med Chem 1996, 39, 3235.

[5] Ondachi, P. W.; Comins, D. L. Tetrahedron Lett 2008, 49, 569.

[6] Smith, E. D.; Février, F. C.; Comins, D. L. Org Lett 2006, 8, 179.

[7] (a) Gurpinder, S.; Ishar, M. P. S.; Girdhar, N. K.; Singh, L. J Heterocycl Chem 2005, 42, 1047; (b) Gurpinder, S.; Munusamy, E.; Venkatesan, S.; Ishar, M. P. S. Heterocycles 2006, 68, 1409.

[8] (a) Ramesh, E.; Kathiresan, M.; Raghunathan, R. Tetrahedron Lett 2007, 48, 1835; (b) Wang, C.; Liang, G.; Xue, Z.; Gao, F. J Am Chem Soc 2008, 130, 17250; (c) Ghandi, M.; Tabatabaei Rezaei, S. J.; Yari, A.; Taheri, A. Tetrahedron Lett 2008, 49, 5899; (d) Ghandi, M.; Yari, A.; Tabatabaei Rezaei, S. J.; Taheri, A. Tetrahedron Lett 2009, 50, 4724.

[9] Pearson, W. H. In Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Padwa, A., Ed.; Wiley: New York, 2002; pp 170–172.

[10] Zhai, H.; Liu, P.; Luo, S.; Fang, F.; Zhao, M. Org Lett 2002, 4, 4385.

[11] Crystallographic data for **3a** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 748115. Copies of these data can be obtained free of charge *via* www.ccdc.ca-m.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

# Efficient Synthesis of 1,3,4-Thiadiazoles Using Hydrogen Bond Donor (Thio)urea Derivatives as Organocatalysts

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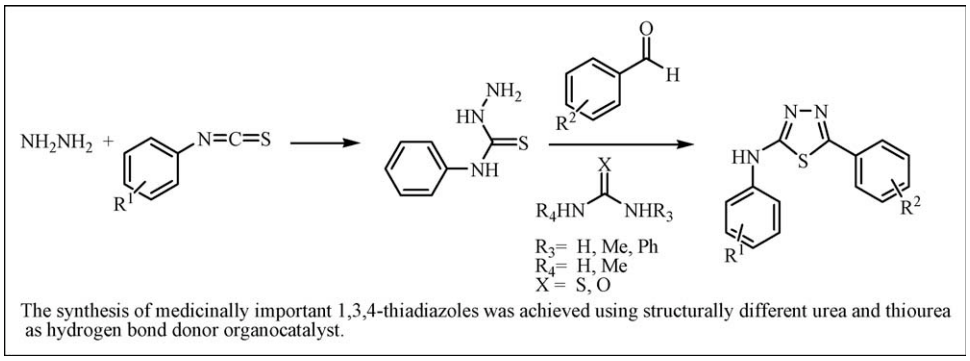


The synthesis of medicinally important 1,3,4-thiadiazoles was achieved using structurally different urea and thiourea as hydrogen bond donor organocatalyst.

A simple and efficient procedure for the synthesis of 1,3,4-thiadiazoles has been achieved using thiourea as organocatalyst. In this study, the steric and electronic effects using structurally different derivatives of urea and thiourea in different solvents were evaluated. The best yields and the rate of the reactions were obtained using 30 mol % of thiourea as catalyst in acetonitrile at room temperature. The molecular structures of the products were established by $^{1}H$ and $^{13}C$ NMR spectral data.

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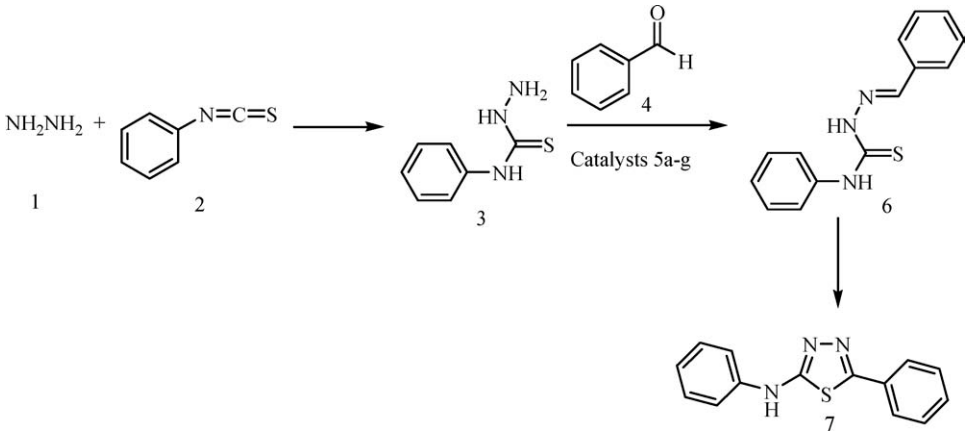
## INTRODUCTION

1,3,4-Thiadiazoles are a group of heterocyclic building blocks for which a wide variety of applications have been reported including dyes [1], lubricating agents [2], optically active liquid crystals [3], and photographic materials [4]. In the medicinal field, therapeutic properties such as antitumor [5], hypoglycemic [6], anticonvulsant [7], hypotensive [8], antiproliferative [9] and antituberculosis [10a,b], antileishmanial [11a,b], and anti-*Helicobacter pylori* [12a,b] activities have been assigned to their various derivatives. Moreover, these compounds have recently been the subject of some theoretical and computational studies because of their significance [13,14]. Also, the research on the synthesis and discovery of new 1,3,4-thiadiazole derivatives with specific medicinal properties is still an active area of research [15]. Literature survey of synthetic methods for these interesting compounds indicates that there are three main categories for the synthesis of 1,3,4-thiadiazoles: (1) cyclizations involving one-bond formation [16a–h], (2) cyclizations involving formation of two bonds [16a,d–g], and (3) cyclizations involving formation of three bonds [16a,h]. Very recently, we reported a new three-bond forming one-pot protocol for the synthesis of some 1,3,4-thiadiazoles with potential antituberculosis activity using Brönsted acidic ionic liquid [Bmim]$BF_4$ as dual solvent and catalyst [17].

With a view to designing more selective, robust, environmentally benign, and functional-group tolerant catalysts, chemists have begun to reconsider using the proton as the simplest Lewis acid. Therefore, taking their cue from natural enzymatic systems, chemists have attempted to explore the development of weak acid–base interactions/hydrogen bonding which is one of the most dominant forces in molecular interaction and recognition in biological systems [18], as a basis for catalyst design and as an impressive option to replace the proton and other commonly known Lewis and Brönsted acids. So, small organic molecules called organocatalysts [19,20], which can form hydrogen bonds, contain no metallic atoms and are favorable in terms of environmental viewpoints that can be used as efficient catalysts for various organic transformations [21]. Recently, thiourea derivatives have been the subject of extensive research in the field of designing hydrogen bond catalyst and several excellent reviews are available on this subject (for example see [22]). Various thiourea catalysts have been utilized to catalyze organic reactions through hydrogen bonding, either for asymmetric or for nonasymmetric catalysis. Herein, we only refer to some of

**Scheme 1.** Model reaction for the organocatalyzed synthesis of 1,3,4-thiadiazoles.




the most recently reported studies such as chlorohydrins synthesis [23], enantioselective Michael addition [24], asymmetric Bayliss-Hillman reaction [25], Diels-Alder reaction [26], acetallization of aldehydes and ketones [27], nitro-Michael addition [28], nucleophilic addition to acyl imines [29], and enantioselective tandem Michael-Knoevenagel reaction [30]. To the best of our knowledge, there is no report on the role and application of organocatalysts for the preparation of 1,3,4-thiadiazoles in the literature. On the basis of the aforementioned considerations, we decided to investigate the steric and electronic effect of urea and thiourea in different solvents to represent a novel efficient catalytic protocol for the synthesis of some 1,3,4-thiadiazoles derivatives possessing arylamino and aryl moieties on positions 3 and 5 of thiadiazole ring.

## RESULTS AND DISCUSSION

At the beginning to determine the appropriate catalyst, we examined the effect of hydrogen bond donor catalyst structure on the synthesis of 1,3,4-thiadiazoles. The model reaction is shown in Scheme 1. For this study, derivatives of urea and thiourea along with two guanidinium salts are used in different solvents and temperatures (Schemes 1 and 2, Tables 1 and 2). As can be deduced from Tables 1 and 2, the best results were obtained when 30 mol % of the thiourea as catalyst was used relative to reactants at room temperature (Table 1, entries 4–6).

The results shown in Tables 1 and 2 indicate an important point about the nature of catalysis and the proper type of solvent used in the process. In water as solvent, no reaction was observed for both urea and thiourea as catalyst (Table 1, entries 1 and 13). So, this solvent was not tested anymore in the case of other catalysts. This means that reactants do not form hydrogen bonds with catalysts in water because the catalysts form very stronger hydrogen bonds with water molecules, especially since the water molecules are present in such a great numbers as solvent [31]. In addition, when we chose ethanol as a hydroxylic solvent capable of forming hydrogen bonds weaker than water, the process did not proceed well either (Table 1, entries 2 and 14). In these two cases, we only obtained the semicarbazone intermediate 6 as the only product and not the desired heterocyclic compound. With a polar aprotic solvent such as acetonitrile, we managed to obtain the thiadiazole product with moderate to good yields and in relatively short reaction times (Table 1, entries 3, 4, and 7–12). This is undoubtedly due to the effective hydrogen bond formation between the substrates and the catalyst in acetonitrile. Solvents such as dimethylformamide (DMF) and dimehtylsulfoxide (DMSO) were also effective in the case of catalysts **5b**, **5c**, **5d**, **5e** but the yields were lower and the reaction times were much longer in these solvents (Table 1, entries 5 and 6, Table 2, entries 6–11), whereas in the case of catalysts **5f** and **5g**, no reaction was observed (Table 2, entries 12–15). Moreover, when the temperature was changed from 30°C to reflux condition, no remarkable change in the yield and the reaction time was observed (Table 1, entries 9–12). It is

**Scheme 2.** Urea, thiourea, and guanidinium salts as organocatalysts employed in this study.

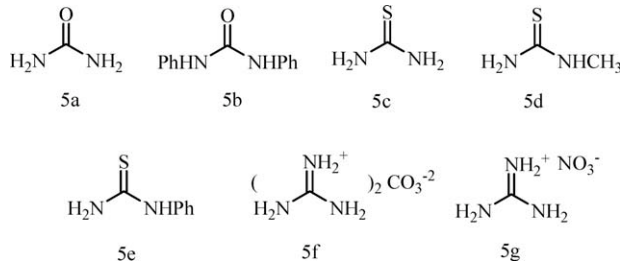


**Table 1**

Screening of the effect of temperature and the type solvent for the synthesis of 1,3,4-thiadiazoles using simple thiourea and urea.

| Entry | Catalyst type | Catalyst loading (%) | Solvent | Temperature (°C) | Reaction time | Comments[a] |
|---|---|---|---|---|---|---|
| 1 | **5a** | 30 | Water | 30 | 24 h | No reaction |
| 2 | **5a** | 30 | Ethanol | 30 | 24 h | Only intermediate **6**, Yield 60% |
| 3 | **5a** | 30 | $CH_3CN$ | 30 | 4.5 h | Product **7**, Yield 50% |
| 4 | **5c** | 30 | $CH_3CN$ | 30 | 75 min | Product **7**, Yield 81% |
| 5 | **5c** | 30 | DMF | 30 | 2.5 h | Product **7**, Yield 76% |
| 6 | **5c** | 30 | DMSO | 30 | 2.5 h | Product **7**, Yield 70% |
| 7 | **5c** | 20 | $CH_3CN$ | 30 | 3 h | Product **7**, Yield 40% |
| 8 | **5c** | 40 | $CH_3CN$ | 30 | 70 min | Product **7**, Yield 80% |
| 9 | **5c** | 30 | $CH_3CN$ | 40 | 70 min | Product **7**, Yield 80% |
| 10 | **5c** | 30 | $CH_3CN$ | 60 | 70 min | Product **7**, Yield 83% |
| 11 | **5c** | 30 | $CH_3CN$ | 70 | 70 min | Product **7**, Yield 80% |
| 12 | **5c** | 30 | $CH_3CN$ | reflux | 70 min | Product **7**, Yield 77% |
| 13 | **5c** | 30 | Water | 30 | 24 h | No reaction |
| 14 | **5c** | 30 | Ethanol | 30 | 24 h | Only intermediate **6**, Yield 40% |

[a] Isolated yield.

worth mentioning that the reaction was best performed at 30°C (Table 1, entry 4).

The amount of 30 mol % of the catalyst was found to be the optimum amount for the present process. When we applied a lower amount of thiourea (20 mol %, Table 1, entry 7), the reaction yield was decreased to nearly half of that found with 30 mol % of the catalyst. Moreover, using higher amounts of catalyst (40 mol %, Table 1, entry 8) did not make any remarkable difference in the yield and the reaction time.

To find out which catalyst could be the most beneficial one for our purpose and what would be the nature of the catalytic effect, we examined five derivatives of urea and thiourea along with two guanidinium salts in this process (Tables 1 and 2, Scheme 2). The chemical nature of catalyst effect here in this process could be both steric and electronic. Taking a precise look at the results in Table 1, upon going from thiourea to *N*-methylthiourea, reveals that even a small change in the structure (replacing H with $CH_3$) has led to a drastic reduction in the reaction rate and a remarkable decrease in the yield of formation of thiadiazole (Table 1, entry 4 and Table 2, entry 2). This can be better deduced in the case of *N*, *N*′-diphenylurea and *N*-phenylthiourea (Table 2, entries 1 and 2) with their unsubstituted analogs (Table 1, entries 3 and 4). Observing a longer reaction time for *N*-phenylthiourea in comparison with the case of thiourea indicates that steric demands are the major factors governing the formation of the hydrogen bond between catalysts and the substrates. With a more sterically hindered catalyst like *N*-phenylthiourea, the catalyst is not capable of forming effective hydrogen bridges with

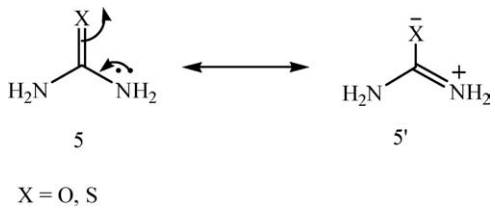
**Table 2**

Comparison of the urea and thiourea derivatives as organocalysts in the synthesis of 1,3,4-thiadiazoles.

| Entry | Catalyst type | Catalyst loading (%) | Solvent | Temperature (°C) | Reaction time (h) | Comments[a] |
|---|---|---|---|---|---|---|
| 1 | **5b** | 30 | $CH_3CN$ | 30 | 24 | Trace of intermediate **6** |
| 2 | **5d** | 30 | $CH_3CN$ | 30 | 4.5 | Product **7**, Yield 45% |
| 3 | **5e** | 30 | $CH_3CN$ | 30 | 24 | Product **7**, Yield 40% |
| 4 | **5f** | 30 | $CH_3CN$ | 30 | 24 | No reaction |
| 5 | **5g** | 30 | $CH_3CN$ | 30 | 24 | No reaction |
| 6 | **5b** | 30 | DMF | 30 | 24 | Trace of product **7** |
| 7 | **5b** | 30 | DMSO | 30 | 24 | Trace of product **7** |
| 8 | **5d** | 30 | DMF | 30 | 24 | Product **7**, Yield 30% |
| 9 | **5d** | 30 | DMSO | 30 | 24 | Product **7**, yield 25% |
| 10 | **5e** | 30 | DMF | 30 | 24 | Product **7**, Yield 36% |
| 11 | **5e** | 30 | DMSO | 30 | 24 | Product **7**, Yield 27% |
| 12 | **5f** | 30 | DMF | 30 | 24 | No reaction |
| 13 | **5f** | 30 | DMSO | 30 | 24 | No reaction |
| 14 | **5g** | 30 | DMF | 30 | 24 | No reaction |
| 15 | **5g** | 30 | DMSO | 30 | 24 | No reaction |

[a] Isolated yield.

**Scheme 3.** Resonance structures of urea and thiourea.




substrates. This will result in a decrease in the reactivity of the substrate, much longer reaction time, and much lower yield of the product (Table 2, entry 3). Moreover, the application of *N*,*N*′-diphenylurea, as a catalyst with two very bulky substituents on nitrogen atoms, led to the formation of the intermediate **6** (Scheme 1) in trace amounts and no sign of formation of thiadiazole ring (Table 2, entry 1).

The difference in catalytic activity of thiourea and urea can be clearly seen in Table 1 (entries 3 and 4) as one of the most interesting points of this study. Thiourea has catalyzed the reaction faster than urea in acetonitril as solvent at room temperature. The possible reason for this observation is the fact that in thiourea the sulfur heteroatom has more polarizability in comparison to oxygen. So, when drawing the resonance structures for urea and thiourea, the **5′** contribution in the resonance structure is higher for thiourea because the negative charge could be better stabilized on sulfur than on oxygen atom (Scheme 3). Accordingly, more positive charge on nitrogen and on the hydrogen atom in **5′** resonance structure has lead to stronger hydrogen bonding with the reactants and a more catalytic effect. Moreover, the p$K_a$ value for thiourea is less than the one for urea [32] which means thiourea is more acidic than urea. Therefore, thiourea should be able to catalyze the cyclization step better than urea.

To prove that the electronic effects do not play a distinct role in hydrogen bond catalyzed synthesis of 1,3,4-thiadiazoles, we repeated this process using various phenylisothiocyanate and benzaldehyde derivatives with different electron demands (Scheme 4, Table 3, compounds **7a–n**). Both the reaction times and isolated yields in Table 2 indicate no general pattern for derivatives with electron withdrawing or electron donating substituents. Reaction times are in the range of 30–75 min for all products and the yields vary between 81% and 95%. Taking these facts into consideration, we can only lay emphasis on the role of steric, and not, electronic effects on the preparation of 1,3,4-thiadiazoles using (thio)urea organocatalysts. Then, we performed some control experiments to confirm the role of thiourea as catalyst in this process. Primarily we performed the process by using equivalent amounts of phenylisothiocyanate, hydrazine hydrate, and benzaldehyde and the use of thiourea (30 mol % relative to reactants) in dry acetonitrile as solvent under $N_2$ inert atmosphere. As expected, we observed the formation of intermediate **6** (Scheme 1) as the only product and no sign of the desired thiadiazole product was observed. When we performed the test experiment in EtOH as solvent and in the absence of any catalyst, only trace amounts of intermediate **6** were obtained. These control experiments show that hydrogen bonds of thiourea are necessary to promote the reaction and solvents such as water and ethanol cannot play the role of a hydrogen bond donor to catalyze this process. According to these results, we proposed a reasonable reaction pathway for the preparation of 1,3,4-thiadiazoles using thiourea as catalyst (Scheme 5).

The main interesting point that can be observed through this proposed reaction pathway is that when one of the hydrogen on nitrogen atom of thiourea (nitrogen atom on the left side of thiourea) is replaced with a more sterically hindered substituent like methyl and phenyl, one of the hydrogen bond connections has actually been removed which prevents self formation of the template between the catalyst with the two reactants. In the case of thiourea as catalyst, this template of hydrogen bridges facilitates the approaching of 4-phenylthiosemicarbazide to benzaldehyde and the formation of 4-phenylthiosemicarbazone intermediate. The ease of hydrogen bond formation also facilitates the cyclization to 2,3-dihydrothiadiazoline intermediate in the second step.

**Scheme 4.** General reaction pattern used for the synthesis of substituted 1,3,4-thiadiazoles.

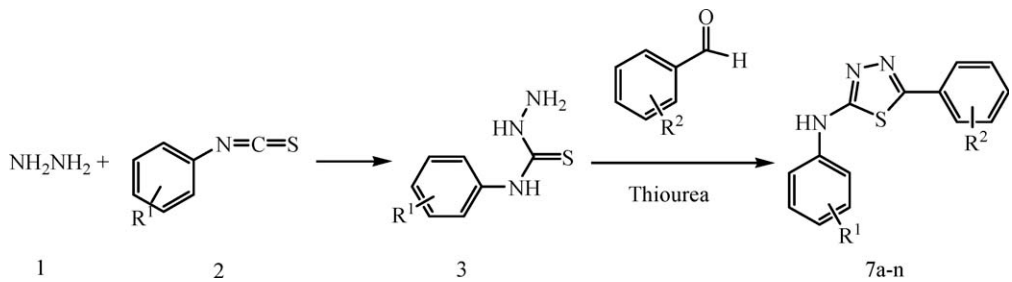


**Table 3**

Organocatalytic synthesis of 1,3,4-thiadiazoles using thiourea as hydrogen bond catalyst.

| Entry | $R^1$ | $R^2$ | Reaction time (min) | Yield[a] (%) | M. P. (°C) (Lit.) [ref.] |
|---|---|---|---|---|---|
| **7a** | H | H | 75 | 81 | 200–202 (199–200) [10] |
| **7b** | H | 4-Br | 60 | 95 | 320–323 (338–339) [10] |
| **7c** | H | 4-Cl | 45 | 92 | 217–219 (216–217) [10] |
| **7d** | H | 4-F | 45 | 87 | 252–254 (258–262) [10] |
| **7e** | H | 4-$NO_2$ | 30 | 93 | 267–269 (275–277) [10] |
| **7f** | 4-$NO_2$ | H | 30 | 90 | 207–211 (216–220) [10] |
| **7g** | 4-$NO_2$ | 4-Br | 40 | 95 | 281–284 (293–294) [10] |
| **7h** | 4-$NO_2$ | 4-Cl | 35 | 92 | 288–290 (300–302) [10] |
| **7i** | 4-$NO_2$ | 4-$NO_2$ | 40 | 90 | 343–347 (368) [10] |
| **7j** | 4-Me | H | 60 | 80 | 177–179 (176–180) [10] |
| **7k** | 4-Me | 4-Cl | 50 | 89 | 220–224 (213–214) [10] |
| **7l** | 4-Me | 4-F | 60 | 86 | 203–207 (210–214) [10] |
| **7m** | 4-Me | 4-$NO_2$ | 65 | 90 | 270–273 (280–284) [10] |
| **7n** | 3-Me | H | 60 | 95 | 180–182 (176) [33] |

[a] Isolated yield.

The hydrogen bonding in this step of the reaction is responsible for the activation of C=N double bond and the motivation for cyclization. Herein, the existence of more bulky groups like methyl and phenyl also will result in improper hydrogen bonding of the catalyst to 4-phenylthiosemicarbazone.

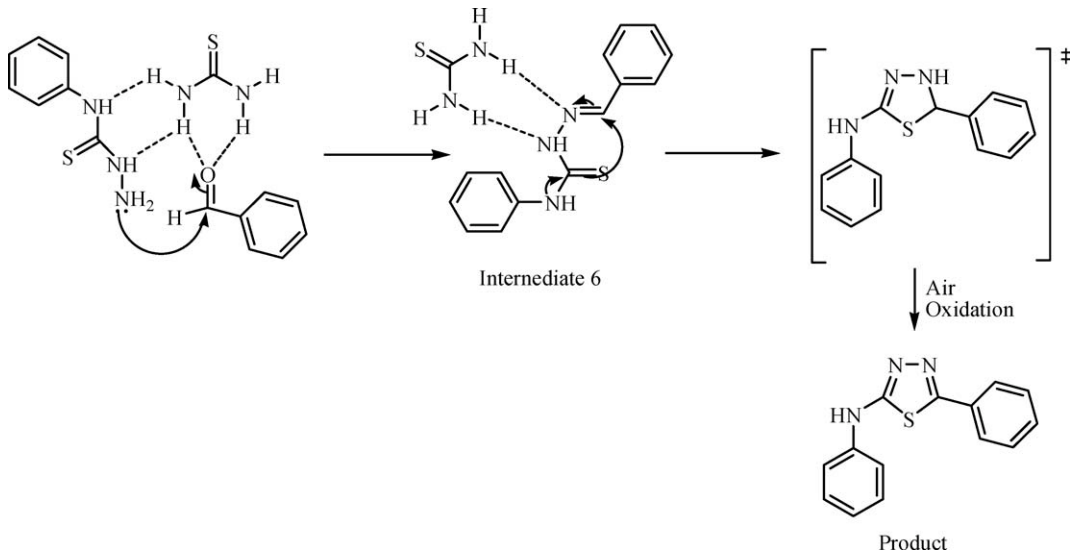
The case of guanidinium salts with no catalytic activity can simply be explained in another way. The guanidinium cations strongly form hydrogen bonds with their counterions carbonates or nitrates, and, consequently will not be able to form such bonds with the substrates in the reaction (Table 1, entries 18 and 19).

In comparison to our previous work [15], this study has several advantages. Apart from the similarity in yields, thiourea derivatives have been used which are cheaper than ionic liquids [bmim]. In addition, ionic liquids [bmim] $BF_4$ may release HF and decompose after some time, whereas thiourea derivatives do not have such a problem and can also be handled and kept more easily than ionic liquids. The only difference with this study is slightly longer reaction times.

## CONCLUSIONS

In summary, we have developed a study on hydrogen bond catalysis in the synthesis of 1,3,4-thiadiazoles as a group of medicinally important heterocyclic

**Scheme 5.** The proposed reaction pathway for the formation of 1,3,4-thiadiazole in which a template of hydrogen bond thiourea organocatalyst has the main role.



compounds. We examined several urea, thiourea, and gunidinium compounds to realize the major factors governing the catalytic activity of these compounds and realized that the true feature of the catalytic effect is steric, and not, electronic effect because the rates and yields of the reaction are strongly dependent on the steric bulk of the catalyst. Application of *N*-methyl- and *N*-phenylthiourea resulted in lower yields and slower reaction rates in comparison with thiourea. Finally, this process provides easy access to important thiadiazole heterocyclic building block in relatively short reaction times and various derivatives with different electron demands on substituents were prepared. We think that this process has a great potential to be applied for the catalytic purposes of synthetic protocols for other important heterocycles and we are working to develop this idea for the purpose of organic and heterocyclic synthesis.

## EXPERIMENTAL

Melting points were measured on a Büchi B-540 apparatus and are uncorrected. IR spectra were measured on Bomem FTIR ABB FTLA200-100 spectrometer. $^1$H and $^{13}$C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a High Resolution Agilent Technology EX mass spectrometer. Chemicals were obtained from Merck, Darmstadt, Germany and Sigma-Aldrich Saint Quentin Falavier, Cedex, France and used without further purification.

**Typical experimental procedure for organocatalytic preparation of 1,3,4-thiadiazoles using (thio)urea derivatives.** To a round bottomed flask was added phenylisothiocyanate derivative (0.24 mL, 2 mmoles), acetonitrile as solvent (2 mL), and hydrazine hydrate (0.1 mL, 2 mmoles) (Scheme 3). This mixture was stirred at 25–30°C for 10 min, Then thiourea (0.045 g, 0.6 mmoles, 30 mol %) and substituted benzaldehyde (2 mmoles) were added to the reaction vessel. The reaction mixture was then stirred for the specified time at 30°C (Table 2). After completion of reaction (as monitored by TLC, ethyl acetate:petroleum ether, 1:4), the resulting precipitates were vacuum filtered using a Büchi funnel. The results are shown in Table 2. The precipitates were further purified with either ethanol or ethanol/water and were further characterized by mp, IR, NMR, and MS spectroscopy. This procedure was repeated the same in the case of other urea or thiourea derivatives (Table 1).

**Analytical data for substituted 1,3,4-thiadiazoles.** ***N,5-diphenyl-1,3,4-thiadiazol-2-amine (7a).*** This compound was obtained as white crystalline solid, mp 200–202°C (Lit. mp 199–200°C [10]), ir: 3297, 3148 (NH) 1606 (C=N) 680 cm$^{-1}$ (C—S—C), $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.06 (t, 1H, *J* = 9.0 Hz), 7.31 (m, 4H), 7.46 (d, 2H, *J* = 9.0 Hz, ortho to thiadiazole ring), 7.81 (m, 2H, meta to thiadiazole ring), 8.31 (s, 1H, para to thiadiazole ring), 10.33 (1H, NH), 11.62 (1H, NH). (Presence of two tautomeric isomers [34].)

***5-(4-Bromopheny)-N-phenyl-1,3,4-thiadiazol-2-amine (7b).*** This compound was obtained as white crystalline solid, mp 320–323°C (Lit. mp 338–339°C [10]), ir: 3302, 3122 (NH) 1595 (C=N) 679 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.06 (t, 1H, *J* = 6.5 Hz), 7.29 (t, 2H, *J* = 6.5 Hz, ortho to thiadiazole ring on phenyl), 7.49 (m, 4H, 2H meta to thiadiazole ring and 2H on phenylamino group), 7.76 (m, 2H), 8.04 (s, 2H), 10.21 (1H, NH), 11.79 (1H, NH). (Presence of two tautomeric isomers [34].)

***5-(4-Chlorophenyl)-N-phenyl-1,3,4-thiadiazol-2-amine (7c).*** This compound was obtained as white crystalline solid, mp 217–219°C (Lit. mp 216–217°C [10]), ir 3306, 3132 (NH) 1586 (C=N) 690 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.21 (t, 1H, *J* = 6.9 Hz), 7.35 (m, 4H), 7.54 (t, 4H, *J* = 7.5 Hz, meta to thiadiazole ring on phenyl group), 10.39 (s, 1H, NH).

***5-(4-Fluorophenyl)-N-phenyl-1,3,4-thiadiazol-2-amine (7d).*** This compound was obtained as white crystalline solid, mp 252–254°C (Lit. mp 258–262°C [10]), ir: 3322, 3132 (NH) 1606 (C=N) 690 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.25 (t, 1H, *J* = 6.0 Hz), 7.31 (t, 2H, *J* = 6.0 Hz), 7.44 (t, 2H, *J* = 9.0 Hz, ortho to thiadiazole ring on phenyl group), 7.66 (d, 2H, *J* = 6.0 Hz, meta to thiadiazole ring on phenyl group), 8.11 (m, 2H), 10.23 (s, 1H, NH).

***5-(4-Nitrophenyl)-N-phenyl-1,3,4-thiadiazol-2-amine (7e).*** This compound was obtained as light yellow crystalline solid, mp 267–269°C (Lit. mp 275–277°C [10]), ir: 3347, 3137 (NH) 2978 (CH) 1596 (C=N) 695 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.19 (t, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.5 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 8.21 (d, 2H, *J* = 8.4 Hz, ortho to thiadiazole ring on phenyl group), 8.44 (d, 2H, *J* = 8.4 Hz, meta to thiadiazole ring on phenyl group).

***N-(4-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (7f).*** This compound was obtained as light yellow crystalline solid, mp 207–211°C (Lit. mp 216–220°C [10]), ir: 3311, 3154 (NH) 2980 (CH) 1601 (C=N) 690 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.56 (m, 3H), 7.83 (m, 2H), 8.15 (d, 2H, *J* = 9.0 Hz, meta to thiadiazole ring on phenyl group), 8.49 (d, 2H, *J* = 9.0 Hz), 10.66 (s, 1H, NH).

***5-(4-Bromophenyl)-N-(4-nitrophenylamino)-1,3,4-thiadiazol-2-amine (7g).*** This compound was obtained as light yellow crystalline solid, mp 281–284°C (Lit. mp 293–294°C [10]), ir: 3301 3147 (NH) 3003 (CH) 1598 (C=N) 695 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.66 (d, 2H, *J* = 8.1 Hz, ortho to thiadiazole ring on phenyl group), 7.89 (d, 2H, *J* = 8.1 Hz), 8.21 (m, 2H, meta to thiadiazole ring on phenyl group), 8.77 (br. s, 2H), 10.59 (br. s, 1H, NH).

***5-(4-Chlorophenyl)-N-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7h).*** This compound was obtained as light yellow crystalline solid, mp 288–290°C (Lit. mp 300–302°C [10]), ir: 3311, 3167 (NH) 3014 (CH) 1611 (C=N) 690 cm$^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.59 (d, 2H, *J* = 9.0 Hz, ortho to thiadiazole ring on phenyl group), 7.88 (d, 2H, *J* = 9.0 Hz, meta on thiadiazole ring), 8.11 (d, 2H, *J* = 9.0 Hz), 8.31 (d, 2H, *J* = 9.0 Hz), 10.52 (s, 1H, NH).

***N-(4-nitrophenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7i).*** This compound was obtained as reddish yellow crystalline solid, mp 343–347°C (Lit. mp 368°C [10]), ir: 3302, 3128 (NH) 2990 (CH) 1596 (C=N) 695 cm$^{-1}$ (C—S—C); $^1$H NMR

(300 MHz, DMSO-$d_6$): δ 8.12 (d, 2H, $J$ = 9.0 Hz), 8.26 (d, 2H, $J$ = 9.0 Hz), 8.33 (d, 2H, $J$ = 4.2 Hz, ortho to thiadiazole ring on phenyl group), 8.41 (d, 2H, $J$ = 4.2 Hz, meta to thiadiazole ring on phenyl group), 10.53 (br. s, 1H, NH).

***N-(4-methylphenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (7j).*** This compound was obtained as white crystalline solid, mp 177–179°C (Lit. mp 176–180°C [10]), ir: 3260, 3200 (NH) 1615 (C=N) 699 $cm^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.33 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 7.22 (m, 2H), 7.52 (m, 4H, meta to thiadiazole ring), 7.97 (m, 2H, ortho to thiadiazole ring), 8.29 (s, 1H, ortho to thiadiazole ring), 10.19 (1H, NH). (Presence of two tautomeric isomers [34].)

***5-(4-Chlorophenyl)-N-(4-methylphenyl)-1,3,4-thiadiazol-2-amine(7k).*** This compound was obtained as white crystalline solid, mp 220–224°C (Lit. mp 213–214°C [10]), ir: 3342, 3142 (NH) 2978 (CH) 1596 (C=N) 685 $cm^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.34 (s, 3H, $CH_3$), 7.27 (d, 2H, $J$ = 8.1), 7.51 (d, 2H, $J$ = 8.1), 7.63 (d, 2H, $J$ = 6.9, ortho to thiadiazole ring on phenyl group), 8.09 (d, 2H, $J$ = 6.9, meta to thiadiazole ring on phenyl group), 10.22 (s, 1H, NH).

***5-(4-Fluorophenyl)-N-(4-methylphenyl)-1,3,4-thiadiazol-2-amine (7l).*** This compound was obtained as white crystalline solid, mp 203–207°C (Lit. mp 210–214°C [10]), ir: 3322, 3132 (NH) 1606 (C=N) 690 $cm^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.34 (s, 3H, $CH_3$), 7.27 (d, 2H, $J$ = 8.1 Hz), 7.48 (d, 2H, $J$ = 8.1 Hz), 7.61 (d, 2H, $J$ = 6.0 Hz, ortho to thiadiazole ring on phenyl group) 8.09 (m, 2H, meta to thiadiazole ring on phenyl group), 10.30 (s, 1H, NH).

***N-(4-methylphenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7m).*** This compound was obtained as light yellow crystalline solid, mp 270–273°C (Lit. mp 280–284°C [10]), ir: 3306, 3126 (NH) 2988 (CH) 1591 (C=N) 690 $cm^{-1}$ (C—S—C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.31 (s, 3H, $CH_3$), 7.21 (d, 2H, $J$ = 8.4 Hz), 7.44 (d, 2H, $J$ = 8.4 Hz), 8.28 (d, 2H, $J$ = 9.0 Hz, ortho to thiadiazole ring on phenyl group), 8.34 (d, 2H, $J$ = 9.0 Hz, meta to thiadiazole ring on phenyl group).

***N-(3-methylphenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (7n).*** This compound was obtained as white crystalline solid, mp 180–182°C, ir: 3312, 3163 (NH) 1602 (C=N) 699 $cm^{-1}$ (C—S—C), $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.35 (s, 3H, $CH_3$), 7.12 (d, 1H, $J$ = 6.9 Hz), 7.33 (t, 1H, $J$ = 6.9 Hz), 7.52 (m, 4H), 8.08 (m, 2H, meta to thiadiazole ring on phenyl group), 8.25 (s, 1H, para to thiadiazole ring on phenyl group), 10.15 (1H, NH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 23.34, 123.76, 126.77, 127.24, 128.11, 128.35, 129.21, 130.66 (C-para to thiadiazole ring on phenyl group), 134.75 (quaternary carbon on phenyl ring), 137.81, 139.41, 144.11 (C-2 in thiadiazole ring), 178.33 (C-5 in thiadiazole ring); ms m/z = 267; Anal. Calcd. For $C_{15}H_{13}N_3S$ (267.08): C, 67.39; H, 4.90; N, 15.72; S, 11.99; Found: C, 67.69; H, 4.69; N, 15.32; S, 11.72.

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## REFERENCES AND NOTES

[1] Zareba, S. Pharmazie 1993, 48, 782.

[2] Gao, Y. L.; Zhang, Z. J.; Xue, Q. Mater Res Bull 1999, 34, 1867.

[3] Choi, U. S.; T Kim, W.; Jung, S. W.; Kim, C. J. Bull Korean Chem Soc 1998, 19, 299.

[4] Chen, S. L.; Ji, S. X.; Zhu, Z. H.; Yao, Z. G. Dyes Pig 1993, 23, 275.

[5] Miyamoto, K.; Koshiura, R.; Mori, M.; Yokoi, H.; Mori, C.; Hasegawa, T.; Takatori, K. Chem Pharm Bull 1985, 33, 5126.

[6] Mhasalkar, M. Y.; Shah, M. H.; Pilankar, P. D.; Nikam, S. T.; Anantarayanan, K. G.; Deliwala, C. V. J Med Chem 1971, 14, 1000.

[7] Chapleo, C. B.; Myres, P. L.; Smith, A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S. J Med Chem 1988, 31, 7.

[8] Grant, A. M.; Krees, S. V.; Mauger, A. B.; Rzezotarski, W. J.; Wolff, F. W. J Med Chem 1972, 15, 1082.

[9] Matysiak, J.; Opolski, A. Bioorg Med Chem 2006, 14, 4483.

[10] (a) Oruc, E. E.; Rollas, S.; Kandemirli, F.; Shvets, N.; Dimoglo, A. S. J Med Chem 2004, 47, 6760; (b) Mahdiuni, H.; Mobasheri, H.; Shafiee, A.; Foroumadi, A. Biochem Biophys Res Commun 2008, 376, 174.

[11] (a) Poorrajab, F.; Kabudanian Ardestani, S.; Emami, S.; Behrouzi-Fardmoghadam, M.; Shafiee, A.; Foroumadi, A. Eur J Med Chem 2009, 44, 1758; (b) Poorrajab, F.; Ardestani, S. K.; Foroumadi, A.; Emami, S.; Kariminia, A.; Behrouzi-Fardmoghadam, M.; Shafiee, A. Exp Parasitol 2009, 121, 2323.

[12] (a) Mirzaei, J.; Siavoshi, F.; Emami, S.; Safari, F.; Khoshayand, M. R.; Shafiee, A.; Foroumadi, A. Eur J Med Chem 2008, 43, 1575; (b) Mohammadhosseini, N.; Letafat, B.; Siavoshi, F.; Emami, S.; Safari, F.; Shafiee, A.; Foroumadi, A. Med Chem Res 1.578, 17, 2008; DOI 10.1007/s00044–008-9099-y.

[13] Feki, H.; Fourati, N.; Abid, Y.; Minot, C. J Mol Struct (THEOCHEM) 2008, 852, 87.

[14] Yakuphanoglua, F.; Atalay, Y.; Sekercic, M. J Mol Struct 2005, 779, 72.

[15] Radi, M.; Crespan, E.; Botta, G.; Falchi, F.; Maga, G.; Manetti, F.; Corradi, V.; Mancini, M.; Santucci, M. A.; Schenoned, S.; Botta, M. Bioorg Med Chem Lett 2008, 18, 1207.

[16] (a) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. In Comprehensive Heterocyclic Chemistry; Pergamon Press, 1996; Vol.II, p. 379 and the references cited therein; (b) Okawara, T.; Tateyama, Y.; Yamasaki, T.; Furukawa, M. J Heterocycl Chem 1988, 25, 1071; (c) Li, C. K.; Cao, L. H. J Chin Chem Soc 2008, 55, 1313; (d) Elmoghayar, M. R. H.; Abdalla, S. O.; Abdel-Samad Nasr, M. Y. J Heterocycl Chem 1984, 21, 781; (e) Flowers, W. T.; Robinson, J. F.; Taylor, D. R.; Tipping, A. E. J Chem Soc Perkin Trans 1 356, 1981; (f) Polshettiwar, V.; Varma, R. S. Tetrahedron Lett 2008, 49, 879; (g) Kilburn, J. P.; Lau, J.; Jones, R. C. F. Tetrahedron Lett 2003, 44, 7825; (h) Lebrini, M.; Bentiss, F.; Lagrenée, M. J Heterocycl Chem 2005, 42, 991.

[17] Rostamizadeh, Sh.; Aryan, R.; Ghaieni, H. R.; Amani, A. M. Heteroatom Chem 2008, 19, 320.

[18] Silverman, R. B. The Organic Chemistry of Enzyme-Catalyzed Reactions; Academic Press:San Diego, 2002.

[19] Schreiner, P. R. Chem Soc Rev 2003, 32, 289.

[20] Pihko, P. M. Angew Chem Int Ed 2004, 43, 2062.

[21] Notz, W.; Tanaka, F.; Barbas, C. F. Acc Chem Res 2004, 37, 580.

[22] (a) Connon, S. J. Chem Eur J 2006, 12, 5418; (b) Doyle, A. G.; Jacobsen, E. N. Chem Rev 2007, 107, 5713.

[23] Bentley, P. A.; Mei, Y.; Du, J. Tetrahedron Lett 2008, 49, 1425.

[24] Gu, C.-L.; Liu, L.; Sui, Y.; Zhao, J.-L.; Wanga, D.; Chen, Y.-J. Tetrahedron Asymmetry 2007, 18, 455.

[25] Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. Tetrahedron Lett 2004, 45, 5589.

[26] Wittkopp, A.; Schreiner, P. R. Chem Eur J 2003, 9, 407.
[27] Kotke, M.; Schreiner, P. R. Tetrahedron 2006, 62, 434.
[28] Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. Catal Today 2007, 121, 151.
[29] Bode, C. M.; Ting, A.; Schaus, S. E. Tetrahedron 2006, 62, 11499.
[30] Dodda, R.; Mandal, T.; Zhao, C.-G. Tetrahedron Lett 2008, 49, 1899.
[31] Stahl, N.; Jencks, W. P. J Am Chem Soc 1986, 108, 4196.
[32] Hodgman, C. D. In Handbook of Chemistry and Physics; Chemical Rubber Publishing Company:Cleveland, OH, 1951; p 1636–1637.
[33] De, S. C.; Roy-Choudhury, S. K. J Indian Chem Soc 1928, 5, 269.
[34] Stanovnik, B.; Tisler, M. J Org Chem 1960, 25, 2234.

# Solvent-Free Synthesis of Monastrol Derivatives Catalyzed by $NaHSO_4$

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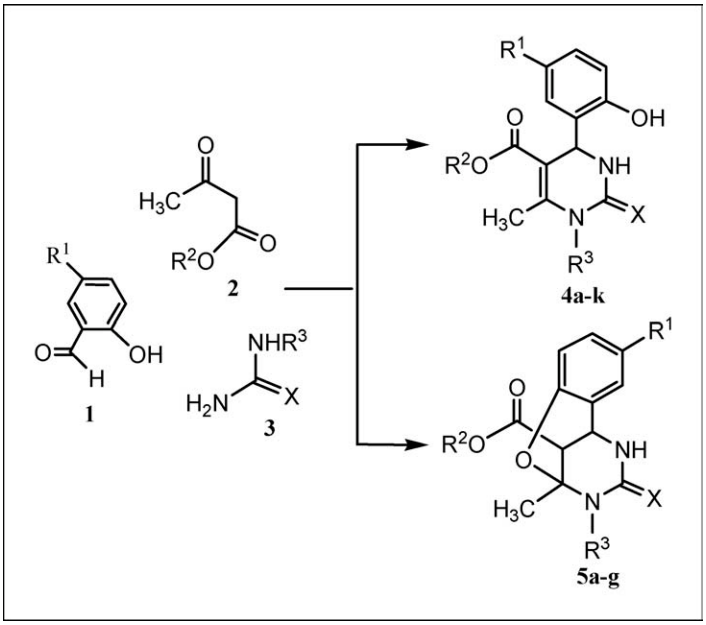


Monastrol derivatives were synthesized by environment-friendly three component condensation reaction of salicylaldehyde analogues, β-ketoester, and urea or thiourea under solvent-free conditions with $NaHSO_4$ as catalyst in high yields. The reactions formed two different monastrol products, 4-(2-hydroxyphenyl)pyrimidines **4** and 9- methyl- 11-oxo(or thioxo)-8-oxa-10,12-diazatricyclotrideca derivatives **5**.

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## INTRODUCTION

It is well known that 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their derivatives are an important class of heterocyclic compounds having important biological activities, pharmaceutical and therapeutic properties, such as antiviral [1], antitumour [2], antibacterial, anti-inflammatory, and antihypertensive [3]. Therefore, the preparation of this heterocyclic nucleus has gained great importance in organic synthesis. One of the simple and direct method for the synthesis of this class of compounds is known as Biginelli reaction involving one-pot condensation of aldehyde, β-ketoester, and urea under strong acidic conditions, which was first reported by Biginelli in 1893 [4]. In this class of compounds, Monastrol, ethyl 6-methyl-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, is a recently highlighted Biginelli compound [5,6], which showed promise in a new strategic approach to cancer research [7] and has been found to affect the function of mitotic kinesin Eg5, a motor protein responsible for spindle bipolarity [8]. Thus, kinesin spindle protein represents an attractive target for biochemical studies because human Eg5 inhibitors induce cell death *via* apoptosis [9]. Owing to the versatile biological activity of Monastrol derivatives, development of an alternative synthetic methodology is of paramount importance. This has led to the development of several new synthetic strategies involving combinations of Lewis acids and transition metal salts, e.g. $Sr(OTf)_2$ [10], *p*-TsOH [11,12], HPA [13], NiCl2.6H2O [14], $LaCl_3$ [15], $InBr_3$ [16] and Bakers' yeast [17]. Obviously, most of these catalysts

**Table 1**

NaHSO4 mediated synthesis of monastrol derivatives.

| Products[a] | $R^1$ | $R^2$ | $R^3$ | X | Time (h) | Yield[b] (%) | Mp (°C) |
|---|---|---|---|---|---|---|---|
| 4a | H | Et | H | O | 3 | 91 | 201–202 |
| 4b | H | Et | H | S | 3 | 86 | 162–164 |
| 4c | H | Et | Ph | O | 4 | 83 | 98–100 |
| 4d | Cl | Et | H | O | 3.5 | 88 | 228–230 |
| 4e | Br | Et | H | O | 3.5 | 86 | 231–233 |
| 4f | Cl | Et | Ph | O | 4.5 | 82 | 102–104 |
| 4g | Br | Et | Ph | O | 4.5 | 81 | 111–113 |
| 4h | Cl | Me | H | O | 3.5 | 84 | 257–259 |
| 4i | Br | Me | H | O | 3.5 | 82 | 215–217 |
| 4j | Cl | Me | Ph | O | 4.5 | 82 | 107–109 |
| 4k | Br | Me | Ph | O | 4.5 | 81 | 114–116 |
| 5a | H | Me | H | O | 3 | 92 | 197–200 |
| 5b | H | Me | Ph | O | 3.5 | 89 | 118–120 |
| 5c | H | Me | H | S | 3 | 90 | 148–150 |
| 5d | Cl | Me | H | S | 4 | 86 | 238–240 |
| 5e | Cl | Et | H | S | 3.5 | 84 | 216–218 |
| 5f | Br | Me | H | S | 4 | 85 | 157–159 |
| 5g | Br | Et | H | S | 3.5 | 83 | 127–129 |

[a] Products were characterized by $^1H$, $^{13}C$ NMR, IR, MS, and elemental analyses.
[b] Isolated yield.

and solvents are not acceptable in the context of green synthesis. Thus, as a part of our program towards green synthesis [18], and continuing our studies on the Multi-Component reactions (MCRs) [19], we report herein, a simple, facile, and efficient MCRs for the preparation of some new Monastrol analogues with NaHSO4 as a non-toxic, inexpensive, and easily available reagent.

Herein we wish to report the utilization of NaHSO4 as a catalyst in Biginelli's reaction of substitued salicylaldehydes, β-ketoester and urea or thiourea for the synthesis of some new Monastrol derivatives under solvent-free conditions.

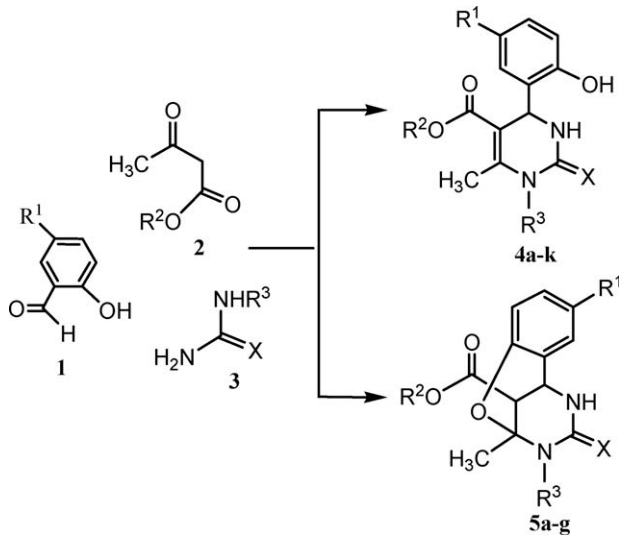
The three-component cyclocondensation reaction was performed under relatively simple reaction conditions by heating together the three components, salicylaldehyde, β-ketoester, and urea or thiourea, in the ratio of 1:1:1.5 and NaHSO4 (20 mol %), to 90°C with stirring. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice. From which the Monastrol derivatives were isolated by filtration and recrystallized from ethanol as indicated in Table 1.

Reactions of salicylaldehyde, methyl acetoacetate with urea (or thiourea, phenylurea) as well as reactions of 5-chloro or 5-bromo salicylaldehyde, methyl (or ethyl) acetoacetate with thiourea did not give the expected free hydroxyl compounds **4,** however, the product is the 9-methyl-11-oxo(or thioxo)-8-oxa-10,12-diazatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6-triene **5a-g** (Scheme 1).

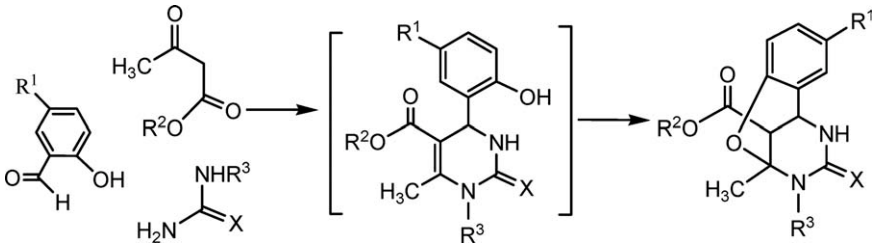
The results presented in the Table 1 indicate the scope and generality of the method, which is efficient, not only for urea or thiourea, but also for salicylaldehydes as well as 5-chloro and 5-bromo salicylaldehydes. In most cases, the reactions proceeded smoothly to produce the corresponding Monastrol derivatives in high yields.

In the course of our work, we have observed that the product from reactions involving salicylaldehyde, methyl acetoacetate with urea (or thiourea, phenylurea) is in fact the 9-methyl-11-oxo(or thioxo)-8-oxa-10, 12-diazatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6-triene **5a-c** rather than a free hydroxyl compounds, 4-(2-

**Scheme 1**



**Scheme 2**



hydroxyphenyl)pyrimidines **4**. However, this oxygen-bridged pyrimidine structures were not discussed in several recent reports [13–15,20,21], but were supported by others [12,16,17]. The product from reactions involving 5-chloro or 5-bromosalicylaldehyde, methyl (or ethyl) acetoacetate with thiourea is also an oxygen-bridged compounds **5d-g** rather than the corresponding 4-(2-hydroxyphenyl)pyrimidines.

The production of compounds **5a-g** can be explained by the isomerization reaction of the 4-(2-hydroxyphenyl) pyrimidines, **4** which were initially formed (Scheme 2).

In summary, we have described a convenient, environment-friendly method for the preparation of some new Monastrol derivatives by the Biginelli cyclocondensation reaction of salicylaldehyde analogues, β-ketoester with urea or thiourea using nontoxic, cheap $NaHSO_4$ catalyst. Additionally, when using salicylaldehyde as the aldehyde reagent, methyl acetoacetate as the active methylene compound, urea (or thiourea, phenylurea) as the condensation reagent, as well as using 5-chloro or 5-bromo salicylaldehyde as the aldehyde reagent, methyl (or ethyl) acetoacetate as the active methylene compound, thiourea as the condensation reagent, the Biginelli product will be an oxygen-bridged compound, 9-methyl-11-oxo(or thioxo)-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene **5** rather than 4-(2-hydroxyphenyl)pyrimidines **4**.

## EXPERIMENTAL

IR spectra were recorded on a Nicolet FTIR-500 spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 400 MHz and 75 MHz. Elemental analysis was performed on an Elementar Vario EL III analyzer. Melting points were determined on a XT-5A digital melting-points apparatus and are uncorrected.

**General procedure for the synthesis of Monastrol derivatives 4a-k and 5a-g.** A mixture of the appropriate salicylaldehyde (2 mmol), β-ketoester (2 mmol), urea or thiourea (3 mmol), and NaHSO4 (0.4 mmol) was heated with stirring at 90°C for the time period as indicated in Table 1. After completion of the reaction (TLC analysis), ice water was added to the mixture, and the crude products collected by filtration were recrystallized from EtOH, to give the products **4a-k** or **5a-g** (Table 1). All products were characterized by $^1$H, $^{13}$C NMR, IR, MS spectral, and by elemental analyses.

***Ethyl 6-methyl-2-oxo-4-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a).*** Yellow powder, yield 91%, mp 201–202°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3355, 3267, 1683, 1597. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.6 (s, 1H, NH), 9.10 (s, 1H, NH), 6.68–7.16 (m, 5H, arom, OH), 5.45 (s, 1H, H-4), 3.93 (q, $J$ = 6.8 Hz, 2H, $CH_2$), 2.26 (s, 3H, $CH_3$), 1.01 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.9, 18.6, 44.7, 59.8, 98.6, 116.1, 119.6, 121.3, 128.1, 129.5, 149.4, 151.5, 155.5, 169.3. MS(ESI) *m*/*z*: 277.0 (M+H). Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found : C, 60.89; H, 5.88; N, 10.17.

***Ethyl 6-methyl-2-thioxo-4-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b).*** Yellow powder, yield 86%, mp 162–164°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3359, 3279, 1689. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.72 (s, 1H, NH), 9.10 (s, 1H, NH), 6.83–7.31 (m, 5H, arom, OH), 5.51 (s, 1H, H-4), 4.14 (q, $J$ = 7.3 Hz, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$), 1.13 (t, $J$ = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.4, 18.9, 44.2, 58.6, 102.5, 118.7, 120.9, 127.2, 129.1, 130.1, 148.3, 150.5, 169.2, 177.5. MS(ESI) *m*/*z*: 293.1 (M+H). Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.51; H, 5.52; N, 9.58. Found : C, 57.46; H, 5.44; N, 9.65.

***Ethyl 1-phenyl-6-methyl-2-oxo-4-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c).*** Green powder, yield 83%, mp 98–100°C, IR (KBr), ($\nu_{max}$/cm$^{-1}$): 3347, 3268, 1681, 1589. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 7.50 (s, 1H, NH), 6.83–7.45 (m, 10H, arom, OH), 5.58 (s, 1H, H-4), 4.22 (q, $J$ = 6.9 Hz, 2H, $CH_2$), 2.29 (s, 3H, $CH_3$), 1.28 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.7, 18.9, 44.9, 59.2, 99.3, 113.1, 117.5, 119.3, 121.5, 127.6, 129.1, 129.8, 130.7, 149.6, 150.1, 152.2, 155.9, 169.7. MS(ESI) *m*/*z*: 353.1 (M+H). Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found : C, 68.22; H, 5.75; N, 7.87.

***Ethyl 6-methyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d).*** Yellow powder, yield 88%, mp 228–230°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3344, 3249, 1679, 1605. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.93 (s, 1H, NH), 9.17 (s, 1H, NH), 6.80 (t, $J$ = 6.8 Hz, 1H, ArH), 6.92 (s, 1H, ArH ), 7.19 (t, $J$ = 6.8 Hz, 1H, ArH), 7.28 (s, 1H, OH ), 5.41 (s, 1H, H-4), 3.92 (q, $J$ = 7.0 Hz, 2H, $CH_2$), 2.27 (s, 3H, $CH_3$), 1.04 (t, $J$ = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.4, 18.2, 51.2, 59.5, 97.7, 117.6, 122.5, 127.6, 128.4, 132.5, 149.4, 152.5, 154.2, 165.8. MS (ESI) *m*/*z*: 309.0 (M-H). Anal. Calcd. for $C_{14}H_{15}N_2O_4Cl$: C, 54.11; H, 4.87; N, 9.02. Found : C, 54.16; H, 4.92; N, 9.07.

***Ethyl 6-methyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e).*** Gray powder, yield 86%, mp 231–233°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3339, 3252, 1677, 1609. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.91 (s, 1H, NH), 9.19 (s, 1H, NH), 6.77 (t, $J$ = 6.9 Hz, 1H, ArH), 6.95 (s, 1H, ArH),

7.23 (t, $J$ = 6.9 Hz, 1H, ArH), 7.31 (s, 1H, OH ), 5.42 (s, 1H, H-4), 5.42 (s, 1H, H-4), 3.90 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 2.29 (s, 3H, $CH_3$), 1.07 (t, $J$ = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.5, 18.6, 51.1, 59.3, 97.5, 110.2, 118.2, 129.7, 132.0, 132.5, 149.7, 152.8, 154.5, 166.8. MS(ESI) *m*/*z*: 356.9 (M+H). Anal. Calcd. for $C_{14}H_{15}N_2O_4Br$: C, 47.34; H, 4.26; N,7.89. Found: C, 47.38; H, 4.22; N, 7.83.

***Ethyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f).*** Yellow powder, yield 82%, mp 102–104°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3355, 3269, 1688, 1611. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.06 (s, 1H, NH), 6.86–7.45 (m, 9H, arom, OH), 5.48 (s, 1H, H-4), 4.12 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 2.27 (s, 3H, $CH_3$), 1.25 (t, $J$ = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.9, 18.6, 50.3, 59.4, 99.8, 113.1, 117.3, 118.1, 122.1, 127.9, 129.1, 129.9, 132.4, 149.5, 150.3, 152.6, 154.9, 167.4. MS(ESI) *m*/*z*: 385.1 (M-H). Anal. Calcd. for $C_{20}H_{19}N_2O_4Cl$: C, 62.11; H, 4.95; N, 7.24. Found: C, 62.07; H, 4.88; N, 7.29.

***Ethyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g).*** Yellow powder, yield 81%, mp 111–113°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3349, 3257, 1678, 1599. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.09 (s, 1H, NH), 6.73–7.32 (m, 9H, arom, OH), 5.49 (s, 1H, H-4), 4.12 (q, $J$ = 6.9 Hz, 2H, $CH_2$), 2.29 (s, 3H, $CH_3$), 1.26 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 14.4, 18.2, 50.9, 58.9, 98.4, 110.5, 117.8, 118.4, 122.6, 129.4, 129.9, 132.8, 133.3, 149.6, 150.8, 152.7, 154.8, 168.1. MS(ESI) *m*/*z*: 432.9 (M+H). Anal. Calcd. for $C_{20}H_{19}N_2O_4Br$: C, 55.70; H, 4.44; N, 6.50. Found : C, 55.66; H, 4.41; N, 6.57.

***Methyl 6-methyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h).*** Yellow powder, yield 84%, mp 257–259°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3346, 3261, 1688, 1592. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.96 (s, 1H, NH), 9.22 (s, 1H, NH), 6.78 (t, $J$ = 7.0 Hz, 1H, ArH), 7.05 (s, 1H, ArH ), 7.24 (t, $J$ = 7.0 Hz, 1H, ArH), 7.29 (s, 1H, OH ), 5.41 (s, 1H, H-4), −7.24 (m, 4H, arom, OH), 5.37 (s, 1H, H-4), 3.41 (s, 3H, $CH_3$), 2.19 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 18.4, 48.9, 50.8, 98.3, 110.1, 118.1, 129.1, 130.7, 132.2, 147.9, 151.2, 154.3, 164.9. MS(ESI) *m*/*z*: 297.1. Anal. Calcd. for $C_{13}H_{13}N_2O_4Cl$: C, 52.62; H, 4.42; N, 9.44. Found : C, 52.67; H, 4.38; N, 9.48.

***Methyl 6-methyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i).*** Yellow powder, yield 82%, mp 215–217°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3339, 3254, 1676, 1599. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 10.03 (s, 1H, NH), 9.21 (s, 1H, NH), 6.77 (t, $J$ = 7.2 Hz, 1H, ArH), 7.02 (s, 1H, ArH ), 7.22 (t, $J$ = 7.2 Hz, 1H, ArH), 7.27 (s, 1H, OH ), 5.41 (s, 1H, H-4), 5.41 (s, 1H, H-4), 3.50 (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 18.3, 49.6, 51.2, 97.5, 110.3, 118.3, 130.0, 131.4, 132.8, 149.8, 152.6, 154.7, 166.2. MS(ESI) *m*/*z*: 342.9 (M+H). Anal. Calcd. for $C_{13}H_{13}N_2O_4Br$: C, 45.77; H, 3.84; N, 8.21. Found: C, 45.73; H, 3.89; N, 8.26.

***Methyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j).*** Brown powder, yield 82%, mp 107–109°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3341, 3269, 1682, 1603. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.11 (s, 1H, NH), 6.71–7.39 (m, 9H, arom, OH), 5.44 (s, 1H, H-4), 3.45 (s, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 18.1, 48.4, 51.3, 99.6, 112.1, 117.4, 118.5, 122.3, 128.1, 129.5, 130.1, 132.6, 148.4, 150.2, 152.8, 154.2, 166.9. MS(ESI) *m*/*z*: 373.1. Anal. Calcd. for $C_{19}H_{17}N_2O_4Cl$: C, 61.21; H, 4.60; N, 7.53. Found : C, 61.16; H, 4.53; N, 7.56.

***Methyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k).*** Yellow powder, yield 81%, mp 114–116°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3336, 3258, 1671, 1589. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.15 (s, 1H, NH), 6.69–7.37 (m, 9H, arom, OH), 5.49 (s, 1H, H-4), 3.52 (s, 3H, $CH_3$), 2.26 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 18.2, 49.1, 51.7, 98.6, 111.3, 115.7, 118.3, 120.4, 128.3, 129.1, 130.6, 131.5, 149.1, 151.9, 153.7, 154.2, 167.1. MS(ESI) *m*/*z*: 418.9 (M+H). Anal. Calcd. for $C_{19}H_{17}N_2O_4Br$: C, 54.69; H, 4.11; N, 6.72. Found : C, 54.62; H, 4.06; N, 6.78.

***13-Methoxycarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5a).*** Yellow powder, yield 92%, mp 117–120°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3308, 3075, 1683, 1643. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 7.19 (s, 1H, NH), 6.78–7.18 (m, 5H, arom, NH), 4.61 (dd, $J$ = 2.8, 2.8 Hz, 1H, H-1), 3.69 (s, 3H, $CH_3$), 3.49–3.52 (m, 1H, H-13), 1.78 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 24.7, 44.0, 48.9, 51.8, 82.1, 116.4, 121.7, 124.6, 128.5, 130.1, 151.3, 155.8, 169.1. MS(ESI) *m*/*z*: 262.9 (M+H). Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found : C, 59.58; H, 5.35; N, 10.62.

***13-Methoxycarbonyl-9-methyl-10-phenyl-11-oxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5b).*** Green powder, yield 89%, mp 118–120°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3316, 3089, 1675, 1653. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 8.51 (s, 1H, NH), 6.78–7.68 (m, 9H, arom), 4.38 (dd, $J$ = 2.9, 2.9 Hz, 1H, H-1), 3.70 (s, 3H, $CH_3$), 3.43–3.58 (m, 1H, H-13), 1.85 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 25.1, 47.2, 49.1, 51.8, 83.1, 112.3, 116.5, 117.8, 120.9, 123.5, 128.3, 129.7, 130.4, 150.6, 151.7, 156.4, 167.3. MS(ESI) *m*/*z*: 339.1 (M+H). Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found : C, 67.48; H, 5.31; N, 8.25.

***13-Methoxycarbonyl-9-methyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5c).*** Yellow powder, yield 90%, mp 148–150°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3307, 3073, 1670. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 9.17 (s, 1H, NH), 6.81–7.22 (m, 4H, ArH), 4.58 (dd, $J$ = 3.1, 2.4 Hz, 1H, H-1), 3.69 (s, 3H, $CH_3$), 3.34–3.37 (m, 1H, H-13), 1.77 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 24.2, 43.0, 48.8, 53.0, 82.2, 117.3, 121.7, 124.6, 129.6, 130.6, 151.3, 169.2, 177.2. MS(ESI) *m*/*z*: 279.0 (M+H). Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.09; H, 5.07; N, 10.07. Found : C, 56.13; H, 5.13; N, 10.02.

***13-Methoxycarbonyl-9-methyl-4-chlor-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5d).*** Gray powder, yield 86%, mp 238–240°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3298, 3079, 1689. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 10.01 (s, 1H, NH), 9.22 (s, 1H, NH), 6.80 (t, $J$ = 6.7 Hz, 1H, ArH), 6.90 (s, 1H, ArH ), 7.13 (t, $J$ = 6.7Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.55 (dd, $J$ = 3.2, 2.4 Hz, 1H, H-1), 3.56 (s, 3H, $CH_3$), 3.35–3.41 (m, 1H, H-13), 1.82 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-*d*6) $\delta_C$: 24.5, 43.5, 47.2, 52.5, 82.1, 117.8, 122.7, 125.0, 129.4, 131.3, 150.2, 168.1, 177.2. MS(ESI) *m*/*z*: 313.0 (M+H). Anal. Calcd. for $C_{13}H_{13}N_2O_3SCl$: C, 49.92; H, 4.19; N, 8.96. Found : C, 49.88; H, 5.15; N, 8.93.

***13-Ethoxycarbonyl-9-methyl-4-chlor-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5e).*** Yellow powder, yield 84%, mp 216–218°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3315, 3091, 1689. $^1$H NMR (DMSO-*d*6) $\delta_H$ : 10.06 (s, 1H, NH), 9.23 (s, 1H, NH), 6.82 (t, $J$ = 7.1 Hz, 1H, ArH), 6.94 (s, 1H, ArH ), 7.18 (t, $J$ = 7.1 Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.58 (dd, $J$ = 3.0, 2.6 Hz, 1H, H-1), 4.03 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.34–3.44 (m, 1H, H-13), 1.80 (s, 3H, $CH_3$), 1.24 (t, $J$

= 7.1 Hz, 3H, $CH_3$). $^{13}C$ NMR (DMSO-*d*6) $\delta_C$: 14.9, 24.4, 43.1, 47.3, 57.5, 82.2, 117.9, 123.3, 125.6, 130.4, 133.5, 152.2, 167.1, 177.1. MS(ESI) *m*/*z*: 328.5 (M+H). Anal. Calcd. for $C_{14}H_{15}N_2O_3SCl$: C, 51.45; H, 4.63; N, 8.57. Found : C, 51.48; H, 4.67; N, 8.53.

***13-Methoxycarbonyl-9-methyl-4-bromo-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5f).*** Gray powder, yield 85%, mp 157–159°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3295, 3077, 1681. $^1H$ NMR (DMSO-*d*6) $\delta_H$ : 10.04 (s, 1H, NH), 9.25 (s, 1H, NH), 6.77 (t, *J* = 6.8 Hz, 1H, ArH), 6.95 (s, 1H, ArH ), 7.27 (t, *J* = 6.8 Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.57 (dd, *J* = 3.0, 2.4 Hz, 1H, H-1), 3.61 (s, 3H, $CH_3$), 3.41 (m, 1H, H-13), 1.75 (s, 3H, $CH_3$). $^{13}C$ NMR (DMSO-*d*6) $\delta_C$: 24.3, 43.2, 47.6, 52.3, 82.3, 113.5, 120.4, 124.5, 130.8, 131.7, 149.9, 168.8, 177.5. MS(ESI) *m*/*z*: 358.9 (M+H). Anal. Calcd. for $C_{13}H_{13}N_2O_3SBr$: C, 43.71; H, 3.67; N, 7.84. Found : C, 43.78; H, 3.72; N, 7.81.

***13-Ethoxycarbonyl-9-methyl-4-bromo-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-triene (5g).*** Gray powder, yield 83%, mp 127–129°C, IR(KBr), ($\nu_{max}$/cm$^{-1}$): 3309, 3091, 1673. $^1H$ NMR (DMSO-*d*6) $\delta_H$ : 10.04 (s, 1H, NH), 9.21 (s, 1H, NH), 6.75 (t, *J* = 7.0 Hz, 1H, ArH), 7.04 (s, 1H, ArH ), 7.24 (t, *J* = 7.0 Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.54 (dd, *J* = 3.2, 2.2 Hz, 1H, H-1), 3.92 (q, *J* = 7.1 Hz, 2H, $CH_2$), 3.35∼3.42 (m, 1H, H-13), 1.78 (s, 3H, $CH_3$), 1.23 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}C$ NMR (DMSO-*d*6) $\delta_C$: 14.3, 24.5, 43.4, 47.2, 61.2, 82.1, 112.6, 119.2, 125.6, 131.8, 132.2, 150.7, 167.5, 177.2. MS(ESI) *m*/*z*: 372.9 (M+H). Anal. Calcd. for $C_{14}H_{15}N_2O_3SBr$: C, 45.29; H, 4.07; N, 7.55. Found : C, 45.23; H, 4.04; N, 7.52.

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## REFERENCES AND NOTES

[1] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[2] Kappe, C. O.; Kumar, D.; Varma, R.S. Synthesis 1999, 10, 1799.

[3] Grover, G. J.; Dzwonczyk, S.; Mc Multen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P.G.; Moreland, S. J Cardiovasc Pharmacol 1995, 26, 289.

[4] Kappe, C. O. Tetrahedron 1993, 49, 6937.

[5] Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. J.; Mitchison, T. J. Science 1999, 286, 971.

[6] Kapoor, T. M.; Mayer, T. U.; Coughlin, M. L.; Mitchison, T. J. J Cell Biol 2000, 150, 975.

[7] Wood, K.W.; Bergnes, G. Annu Rep Med Chem 2004, 39, 173.

[8] (a) Sharp, D. J.; Rogers, G. C.; Scholey, J. M. Nature 2000, 407, 41; (b) Endow, S. A.; Baker, D. S. Annu Rev Physiol 2003, 65, 161.

[9] (a) Walczak, C. E.; Vernos, I.; Mitchison, T. J.; Karsenti, E.; Heald, R. Curr Biol 1998, 8, 903; (b) Marcus, A. I.; Peters, U.; Thomas, S. L.; Garrett, S.; Zelnak, A.; Kapoor, T. M.; Giannakakou, P. J Biol Chem 2005, 280, 11569.

[10] Su, W.; Li, J.; Zheng, Z.; Shen, Y. Tetrahedron Lett 2005, 46, 6037.

[11] Azizian, J.; Mohammadi, A. A.; Kohshari, M.; Karimi, A. R.; Mohammadizadeh, M. R. J Heterocycl Chem 2007, 44, 455.

[12] Světlík, J.; Veizerová, L.; Kettmann, V. Tetrahedron Lett 2008, 49, 3520.

[13] Rafiee, E.; Jafari, H. Bioorg Med Chem Lett 2006, 16, 2463.

[14] Lu, J.; Bai, Y. Synthesis, 2002, 4, 466.

[15] Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. Tetrahedron Lett 2000, 41, 9075.

[16] Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. Tetrahedron 2002, 58, 4801.

[17] Kumar, A.; Maurya, R. A. Tetrahedron Lett 2007, 48, 4569.

[18] Cheng, Q. F.; Xu, X. Y.; Ma, W. X.; Zhang, H.; Liu, L. S.; Liu, F.; Yang, X. J. Chin J Org Chem 2008, 28, 1767.

[19] Cheng, Q. F.; Xu, X. Y.; Ruan, M. J.; Wen, Y. L.; He, X. J.; Yang, X. J. Chin J Org Chem 2009, 29, 1138.

[20] Tu, S.; Fang, F.; Zhu, S.; Li, T.; Zhang, X.; Zhuang, Q. Synlett 2004, 3, 537.

[21] Folkers, K.; Harwood, H. J.; Johnson, T. B. J Am Chem Soc 1932, 54, 3751.

# On the Reaction of 3-Cyanochromones with Phenyl- and Methylhydrazines: Structural Revision and a Simple Synthesis of Chromeno[4,3-*c*]pyrazol-4-Ones

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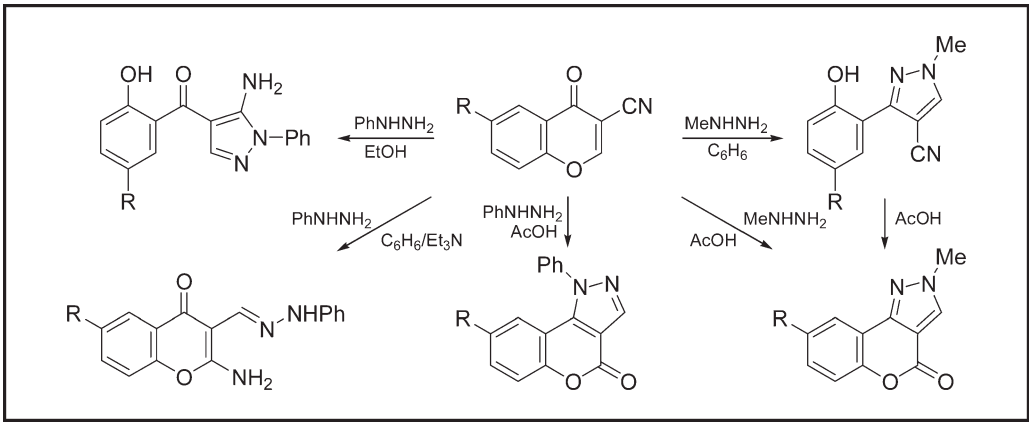


Reactions of 3-cyanochromones with phenylhydrazine gave the corresponding 5-amino-4-salicyloyl-1-phenylpyrazoles, 2-aminochromone-3-carbaldehyde *N*-phenylhydrazones, and 1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one, depending on the reaction conditions. With methylhydrazine, 3-(2-hydroxyaryl)-1-methylpyrazole-4-carbonitriles and 2-methylchromeno[4,3-*c*]pyrazol-4(2*H*)-ones were obtained in moderate to high yields.

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## INTRODUCTION

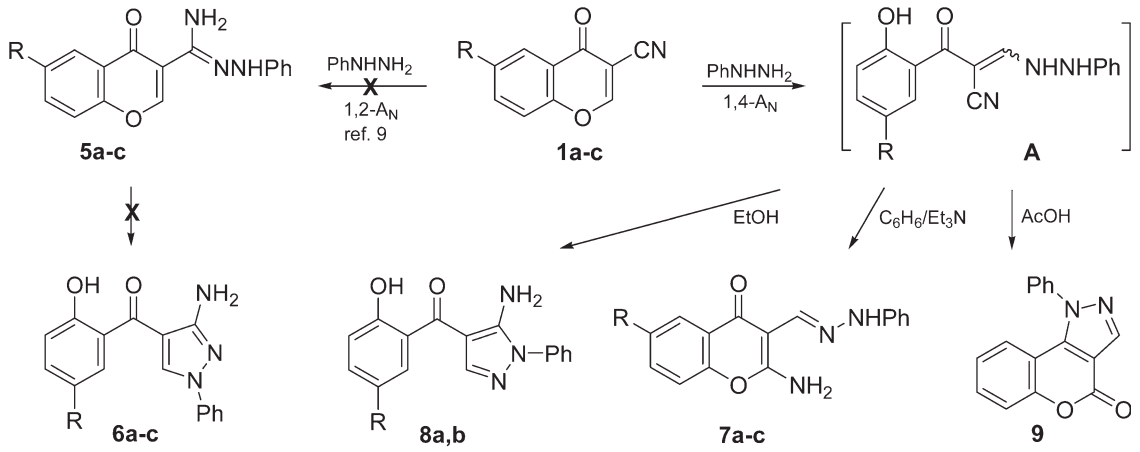
The chemistry of 3-cyanochromones has been developed since the mid-1970s after the simple and convenient Vilsmeier-Haack method was proposed for the synthesis of 3-formylchromones from 2-hydroxyacetophenones, DMF, and $POCl_3$ [1]. Treatment of 3-formylchromones with hydroxylamine via 3-formylchromone-3-oximes leads to 3-cyanochromones **1** [2,3]. In addition, **1** can be synthesized directly from 2-hydroxyacetophenones and hydroxylamine under the Vilsmeier-Haack conditions [4] and from O-methylated chromone-3-oximes [5].

The introduction of the electron-withdrawing CN group at the 3-position of the chromone system changes crucially the reactivity of the pyrone ring with respect to nucleophiles, and provides a broad synthetic potential of 3-cyanochromones **1** [6]. The diversity of properties of these compounds is due to the fact that, being highly reactive geminally activated push–pull alkenes (α,β-unsaturated ketones and nitriles simultaneously) with a good leaving group at the β-carbon atom, whose role is played by the phenolate anion (a fragment of the enol ether), they acquire the ability to undergo a nucleophilic 1,4-attack followed by additional transformations related to γ-pyrone ring opening and heterocyclizations at the C-4 atom and/or at the cyano group. However, although nucleophilic 1,4-addition occurs easily, which is clearly demonstrated by the transformation of 3-cyanochromones **1** into 2-amino-3-formylchromones under basic conditions [3,7], the reactions of **1** with dinucleophiles were further interpreted from both the viewpoint of 1,4-addition at the C-2 atom (this direction is equivalent to the 1,2-attack at the CHO group of 2-amino-3-formylchromone) and 1,2-addition to the cyano group, which inevitably led to contradictory results [6,8,9].

## RESULTS AND DISCUSSION

Recently [10], we reported on the ring transformations of the chromones **1** to 2-aminochromone-3-carboxamide, 3-amino-4*H*-chromeno[3,4-*d*]isoxazol-4-one, and 3-(diaminomethylene)chroman-2,4-dione under the action of hydroxylamine in alkaline medium, some of which were previously incorrectly formulated [6]. Now we were

**Scheme 1**




R = H (**a**), Me (**b**), Cl (**c**)

interested in the course of the reactions of 3-cyanochromones **1** with phenyl- and methylhydrazines. The reaction with phenylhydrazine has already been the subject of investigations and to the intermediate was assigned the structure **5** without NMR spectral data [9]. The authors believed that the reaction occurred via 1,2-addition of phenylhydrazine to the cyano group of **1a–c** to give amidohydrazones **5a–c**, which on prolonged refluxing in ethanol afforded 3-aminopyrazoles **6a–c** [6,9]. On the other hand, it was claimed that refluxing benzene induces the initial 1,4-addition of phenylhydrazine producing ultimately the phenylhydrazone derivatives **7** [8]. It should be noted that the pyrazole structure **6** was not established with certainly and in the light of our previous results [10] it seemed more logical to us that the more nucleophilic nitrogen atom of the phenylhydrazine would attack at the 2-position of the chromone rather than at the CN group.

We studied repeatedly the reactions of chromones **1** with phenylhydrazine under the conditions described in refs. 8 and 9 and confirmed the structure of compounds **7a–c**, which can easily be prepared in refluxing benzene in the presence of $Et_3N$ for 0.5 h (for **1c** this reaction occurs both in benzene and ethanol without $Et_3N$, whereas for **1b** the reaction in benzene without $Et_3N$ gives a complex mixture of isomeric open-chain intermediates and **7b**). However, we were unable to reproduce the claimed synthesis of **6a–c**; instead, 5-aminopyrazoles **8a**,**b** as mixtures with **7a**,**b** were obtained in refluxing ethanol (**8a**:**7a** = 82:18 and **8b**:**7b** = 76:26). When these mixtures were treated with 20% sulfuric acid in ethanol [9], 5-aminopyrazoles **8a**,**b** were isolated as pure compounds in 44–49% yields. Refluxing an ethanolic solution of **1c** with phenylhydrazine afforded only the hydrazone **7c** with no traces of **8c**.

On the basis of $^1H$ and $^{13}H$ NMR spectroscopy and using 2D HSQC, HMBC, and NOESY experiments we found that the reaction products of **1a**,**b** and phenylhydrazine were, in fact, 5-amino-1-phenyl-4-salicyloylpyrazoles **8a**,**b** (Scheme 1). The structural assignment for these compounds as the 5-aminopyrazoles was based on the presence of a NOESY cross-peak from the ortho protons of the phenyl (δ 7.55–7.60 ppm, H-2″, H-6″) onto the $NH_2$ group and the absence of cross-peak between pyrazole H-3 proton and *ipso*-C of N–Ph in the HMBC spectrum (for **8a**). In addition, all the signals in the $^1H$ and $^{13}C$ NMR spectra of compound **8a** were assigned on the basis of 2D $^1H$–$^{13}C$ HSQC and HMBC experiments. Besides the signals expected for the aromatic protons, the $^1H$ NMR spectra of **8a**,**b** in DMSO-$d_6$ showed three singlets due to the $NH_2$ group (δ 7.1 ppm), pyrazole H-3 proton (δ 7.7 ppm) and phenolic hydroxyl (δ 10.5–10.8 ppm). It is concluded that the series of the reported products such as **5**, was not in fact obtained. Moreover, based on the similarities between the $^1H$ NMR spectral data of **8** with those reported for **6** in $CDCl_3$ [9], it is clearly evident that the structure **6** should be revised to **8**.

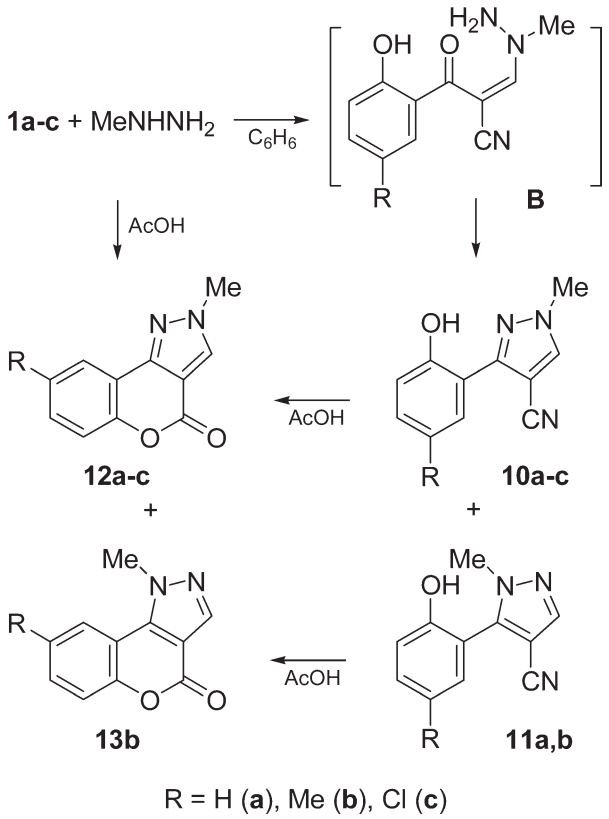
We also found that chromone **1a**, when treated with phenylhydrazine in refluxing AcOH, underwent transformation into 1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one **9** (55% yield). This observation is in line with other report on the condensation of 3-cyano-2-methylchromone with arylhydrazines, which leads to 1-aryl-3-methylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones [11], and not to the claimed earlier 4-methyl-2-phenylchromeno[4,3-*c*]pyrazol-3(2*H*)-one [12]. Previously, compound **9** was obtained by the reactions of phenylhydrazine with chromone-3-carboxylic acid [13], 4-chloro-3-coumarincarbaldehyde [14], and 4-azido-3-coumarincarbaldehydes [15].

Products **7–9** can result from the initial nucleophilic 1,4-addition of phenylhydrazine to the C-2 atom of **1** to give, as a mixture of isomers, the open chain intermediate **A**, further transformation of which is controlled by the nucleophilicity of the OH and NH groups and depends on the reaction conditions. Two different reaction paths for **A** may be envisaged. In refluxing ethanol, intramolecular addition of the NHPh function to the CN group with subsequent hydrogen shift leads to 5-aminopyrazole **8** as a major product. The alternative cyclization of **A** involving the phenolic hydroxyl and the cyano group to form hydrazone **7** occurs in refluxing benzene in the presence of $Et_3N$. When **1** was allowed to react with phenylhydrazine in refluxing acetic acid, the initially formed hydrazone **7** could not be isolated and underwent intramolecular cyclization at the keto group to give chromeno[4,3-*c*]pyrazol-4(1*H*)-one **9**. Thus, the initial Michael addition of phenylhydrazine to **1** leads to three different types of products and the 1,2-addition at the CN group was not observed at all (Scheme 1). This clearly indicates that the C-2 atom of 3-cyanochromone is more susceptible to nucleophilic attack than the CN group. Note that in its reaction with sodium azide, it behaves as a simple arylnitrile to form 3-(1*H*-tetrazol-5-yl)chromone [2a,16].

It is of interest that chromones 1 react in different manner with methylhydrazine to provide a completely different regiochemistry pattern. When an equimolar mixture of **1a–c** and methylhydrazine was refluxed in benzene for 0.5 h, 3-arylpyrazoles **10a–c** were obtained in 40–46% yields (Scheme 2). This reaction exhibits high regioselectivity and pyrazole **10c** was isolated as the single product. However, in the case of **10a**,**b**, some amount of 5-arylpyrazoles **11a**,**b** was observed (7 and 25%, respectively). The determination of the isomers ratio can easily be performed by $^1$H NMR spectroscopic analysis. The $^1$H NMR spectra of compounds **10a–c** in DMSO-$d_6$ consisted of a characteristic singlet due to the phenolic hydroxyl in the region of δ 9.8–10.4 ppm and two singlets due to the resonances of the pyrazole proton and the MeN group at δ 8.56–8.58 and 3.94 ppm. The IR spectra are also of diagnostic value in this 4-cyanopyrazole series ($\nu_{CN} = 2230$ cm$^{-1}$).

The formation of these pyrazoles may be rationalized by initial 1,4-addition of the more nucleophilic secondary nitrogen atom of methylhydrazine on the C-2 atom of **1** with concomitant opening of the pyrone ring to give intermediate **B**. Further, the intramolecular heterocyclization occurs between the $NH_2$ group and the carbonyl, which seems more reactive than the cyano group. Compounds **10a–c**, so obtained, were then allowed to react under more vigorous conditions (boiling acetic acid for 5 h). This afforded coumarins **12a–c** in high yields (70–92%), which were also obtained directly

**Scheme 2**




from **1a–c** and methylhydrazine under the same reaction conditions, however, better yields were achieved if the transformation was performed in a two-step approach. The regioisomeric compounds **13** were not detected, except for the reactions of **1b**, in which case the $^1$H NMR spectra of the products showed the presence of **13b** (25–28%) along with compound **12b** as the major product (Scheme 2).

Spectral data and melting point of **12a** were consistent with previous reported [17], this confirms the regiochemistry of the reaction with methylhydrazine. Interestingly, although the chemistry of the tricyclic chromeno[4,3-*c*]pyrazol-4-one system has been well documented [11–15], we have found that compound **12a** has been obtained only very recently from chromeno[4,3-*b*][1,5]benzodiazepin-7(8*H*)-one and methylhydrazine [17], while derivatives **12b**,**c** are hitherto unreported. In conjunction with the pharmaceutical importance known for the fused heterocycles incorporating a coumarin moiety [18], this simple synthesis of chromeno[4,3-*c*]pyrazol-4-ones from readily available 3-cyanochromones is noteworthy and will complement the published synthetic methods.

In conclusion, 3-cyanochromone represents a very reactive system and its reactions with phenyl- and

methylhydrazines give a variety of products. As the identity of some of these products was in doubt, we have reinvestigated the reaction with phenylhydrazine and found that by varying the conditions, 5-amino-4-salisyloyl-1-phenylpyrazoles, 2-aminochromone-3-carbaldehyde *N*-phenylhydrazones, and 1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one could be prepared in moderate to good yields. With methylhydrazine, 3-(2-hydroxyaryl)-1-methylpyrazole-4-carbonitriles and 2-methylchromeno [4,3-*c*]pyrazol-4(2*H*)-ones were obtained. A simple and convenient synthesis of chromeno[4,3-*c*]pyrazol-4-ones was developed and the generality of this method is being investigated further.

## EXPERIMENTAL

$^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-$d_6$ with TMS as the internal standard. IR spectra were recorded on Perkin–Elmer Spectrum BX-II instrument (KBr) and Bruker Alpha instrument (ATR, ZnSe). Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting 3-cyanochromones **1a–c** were prepared according to described procedures [16].

**General procedure for the preparation of 2-aminochromone-3-carbaldehyde *N*-phenylhydrazones (7a–c).** A solution of chromone **1** (1.2 mmol), phenylhydrazine (130 mg, 1.2 mmol) and two drops of $Et_3N$ in benzene (5 mL) was refluxed for 0.5 h and the reaction mixture cooled. The deposited phenylhydrazone **7** was filtetred and washed with benzene. For **1c** this reaction occurs both in benzene and ethanol without $Et_3N$.

***2-Aminochromone-3-carbaldehyde N-phenylhydrazone (7a).*** Yield 46%, mp 274–275°C (lit. [8a] mp 270°C); IR (KBr): 3317, 3256, 3109, 1646, 1600, 1532 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 6.71 (tt, 1H, H-4′, $J$ = 7.3, 1.0 Hz), 6.85–6.89 (m, 2H, H-2′, H-6′), 7.19–7.24 (m, 2H, H-3′, H-5′), 7.41 (ddd, 1H, H-6, $J$ = 7.8, 7.2, 1.0 Hz), 7.45 (dd, 1H, H-8, $J$ = 8.4, 1.0 Hz), 7.68 (ddd, 1H, H-7, $J$ = 8.4, 7.2, 1.7 Hz), 8.02 (dd, 1H, H-5, $J$ = 7.8, 1.7 Hz), 8.45 (s, 1H, HC=N), 8.98 (br s, 2H, $NH_2$), 10.10 (s, 1H, NH). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.83; H, 4.72; N, 15.06.

***2-Amino-6-methylchromone-3-carbaldehyde N-phenylhydrazone (7b).*** Yield 79%, mp 298–300°C (lit. [8a] mp 275°C); IR (ATR, ZnSe): 3243, 1640, 1604, 1594, 1549, 1520 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.40 (s, 3H, Me), 6.71 (tt, 1H, H-4′, $J$ = 7.4. 1.0 Hz), 6.85–6.89 (m, 2H, H-2′, H-6′), 7.19–7.23 (m, 2H, H-3′, H-5′), 7.34 (d, 1H, H-8, $J$ = 8.4 Hz), 7.48 (ddq, 1H, H-7, $J$ = 8.4, 2.3, 0.6 Hz), 7.82 (br d, 1H, H-5, $J$ = 2.0 Hz), 8.45 (s, 1H, HC=N), 8.93 (br s, 2H, $NH_2$), 10.07 (s, 1H, NH). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.53; H, 5.06; N, 14.41.

***2-Amino-6-chlorochromone-3-carbaldehyde N-phenylhydrazone (7c).*** Yield 71%, mp 308–310°C (lit. [8a] mp 290°C); IR (ATR, ZnSe): 3375, 3245, 1610, 1600, 1579, 1529 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 6.72 (tt, 1H, H-4′, $J$ = 7.4, 1.2 Hz), 6.86–6.89 (m, 2H, H-2′, H-6′), 7.19–7.24 (m, 2H, H-3′, H-5′), 7.51 (d, 1H, H-8, $J$ = 8.8 Hz), 7.71 (dd, 1H, H-7, $J$ = 8.8, 2.7 Hz), 7.94 (d, 1H, H-5, $J$ = 2.7 Hz), 8.42 (s, 1H, HC=N), 9.07 (br s, 2H, $NH_2$), 10.14 (s, 1H, NH). Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 60.91; H, 3.88; N, 13.01.

***5-Amino-4-salicyloyl-1-phenylpyrazole (8a).*** This compound was prepared from chromone **1a** and phenylhydrazine according to the procedure described previously for **6a** [9]. Yield 44%, mp 143–144°C (lit. [9] mp 144°C); $^1$H NMR (DMSO-$d_6$): δ 6.94 (ddd, 1H, H-5′, $J$ = 7.7, 7.3, 0.9 Hz), 6.97 (dd, 1H, H-3′, $J$ = 8.4, 0.9 Hz), 7.15 (s, 2H, $NH_2$), 7.40 (ddd, 1H, H-4′, $J$ = 8.4, 7.3, 1.6 Hz), 7.45 (m, 1H, H-4″), 7.55–7.61 (m, 5H, H-6′, H-2″, H-3″, H-5″, H-6″), 7.74 (s, 1H, H-3), 10.79 (s, 1H, OH); $^1$H NMR ($CDCl_3$): δ 6.08 (s, 2H, $NH_2$), 6.97 (td, 1H, H-5′, $J$ = 7.5, 1.0 Hz), 7.04 (dd, 1H, H-3′, $J$ = 8.4, 0.9 Hz), 7.43–7.49 (m, 2H, H-4′, H-4″), 7.55–7.58 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.90 (dd, 1H, H-6′, $J$ = 7.9, 1.6 Hz), 7.97 (s, 1H, H-3), 11.84 (s, 1H, OH); $^{13}$C NMR (DMSO-$d_6$): δ 104.35 (C4), 116.94 (C3′), 119.02 (C5′), 123.75 (C2″, C6″), 124.81 (C1′), 127.72 (C4″), 129.44 (C6′), 129.53 (C3″, C5″), 132.61 (C4′), 137.39 (C1″), 141.89 (C3), 150.65 (C5), 157.04 (C2′), 189.03 (C=O); MS (EI): *m*/*z* (%) 279 $[M]^+$ (45), 159 $[M+1-HOC_6H_4CO]^+$ (100), 158 $[M-HOC_6H_4CO]^+$ (29), 121 $[HOC_6H_4CO]^+$ (27), 93 $[HOC_6H_4]^+$ (15), 77 $[Ph]^+$ (34), 69 (30). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.51; H, 4.86; N, 15.01.

***5-Amino-4-(2-hydroxy-5-methylbenzoyl)-1-phenylpyrazole (8b).*** This compound was prepared from chromone **1b** and phenylhydrazine according to the procedure described previously for **6b** [9]. Yield 49%, mp 148–149°C (lit. [9] mp 151°C); IR (ATR, ZnSe): 1597, 1573, 1531 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.28 (s, 3H, Me), 6.86 (d, 1H, H-3′, $J$ = 8.2 Hz), 7.11 (s, 2H, $NH_2$), 7.20 (dd, 1H, H-4′, $J$ = 8.2, 2.0 Hz), 7.36 (d, 1H, H-6′, $J$ = 2.0 Hz), 7.43–7.47 (m, 1H, H-4″), 7.55–7.60 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.75 (s, 1H, H-3), 10.53 (s, 1H, OH). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.74; H, 5.36; N, 14.26.

***1-Phenylchromeno[4,3-c]pyrazol-4(1H)-one (9).*** A solution of chromone **1a** (250 mg, 1.46 mmol) and phenylhydrazine (160 mg, 1.48 mmol) in 5 mL of glacial acetic acid was heated at reflux for 4 h. The resulting reaction mixture was then diluted with water (15 mL) and the solid that formed was filtered, washed with water, dried, and recrystallized from acetonitrile to give **9** as colorless needles in 55% yield (210 mg), mp 192–193°C (lit. [13] mp 191°C, lit. [14] mp 183–185°C, lit. [15] mp 209–210°C). $^1$H NMR (DMSO-$d_6$): δ 7.07 (dd, 1H, H-9, $J$ = 8.0, 1.8 Hz), 7.11 (ddd, 1H, H-8, $J$ = 8.0, 6.8, 1.0 Hz), 7.47 (dd, 1H, H-6, $J$ = 8.4, 1.0 Hz), 7.54 (ddd, 1H, H-7, $J$ = 8.4, 6.8, 1.8 Hz), 7.59–7.62 (m, 2H, Ph), 7.68–7.71 (m, 3H, Ph), 8.35 (s, 1H, H-3).

**General procedure for the preparation of 3-(2-hydroxyaryl)-1-methylpyrazole-4-carbonitriles (10a–c).** A solution of chromone 1 (1.0 mmol) and methylhydrazine (55 mg, 1.2 mmol) in 4 mL of benzene was refluxed for 0.5 h. The resulting reaction mixture was then diluted with hexane (5 mL) and the solid that formed was filtered and washed with benzene/hexane mixture (1:1) to give **10** as yellow crystals.

***3-(2-Hydroxyphenyl)-1-methylpyrazole-4-carbonitrile (10a).*** Yield 40%, mp 155–156°C; IR (KBr): 3130, 2229, 1621, 1586, 1542, 1506, 1462 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): (**10a**, 93%) δ

3.94 (s, 3H, MeN), 6.91 (td, 1H, H-5′, $J$ = 7.5, 1.1 Hz), 6.97 (dd, 1H, H-3′, $J$ = 8.2, 1.1 Hz), 7.29 (ddd, 1H, H-4′, $J$ = 8.2, 7.3, 1.7 Hz), 7.50 (dd, 1H, H-6′, $J$ = 7.7, 1.7 Hz), 8.57 (s, 1H, H-5), 10.05 (s, 1H, OH); 5-(2-hydroxyphenyl)-1-methylpyrazole-4-carbonitrile (**11a**, 7%) δ 3.72 (s, 3H, Me), 6.98 (td, 1H, H-5′, $J$ = 7.5, 1.0 Hz), 7.06 (dd, 1H, H-3′, $J$ = 8.2, 1.0 Hz), 7.30 (dd, 1H, H-6′, $J$ = 7.7, 1.7 Hz), 7.41 (ddd, 1H, H-4′, $J$ = 8.2, 7.3, 1.7 Hz), 8.09 (s, 1H, H-3), 10.05 (br s, 1H, OH); MS (EI): $m/z$ (%) 199 $[M]^+$ (100), 171 (20), 156 (22), 42 (27). Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 65.96; H, 4.58; N, 20.74.

***3-(2-Hydroxy-5-methylphenyl)-1-methylpyrazole-4-carbonitrile (10b).*** Yield 42%, mp 150–151°C; IR (KBr): 3176, 3120, 2230, 1621, 1591, 1543, 1503, 1467 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): (**10b**, 75%) δ 2.24 (s, 3H, Me), 3.94 (s, 3H, MeN), 6.86 (d, 1H, H-3′, $J$ = 8.3 Hz), 7.08 (dd, 1H, H-4′, $J$ = 8.3, 2.0 Hz), 7.30 (d, 1H, H-6′, $J$ = 2.0 Hz), 8.56 (s, 1H, H-5), 9.79 (br s, 1H, OH); 5-(2-hydroxy-5-methylphenyl)-1-methylpyrazole-4-carbonitrile (**11b**, 25%) δ 2.26 (s, 3H, Me), 3.70 (s, 3H, MeN), 6.95 (d, 1H, H-3′, $J$ = 8.3 Hz), 7.10 (d, 1H, H-6′, $J$ = 2.0 Hz), 7.21 (dd, 1H, H-4′, $J$ = 8.3, 2.0 Hz), 8.08 (s, 1H, H-3), 10.07 (br s, 1H, OH). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.18; H, 5.15; N, 19.42.

***3-(5-Chloro-2-hydroxyphenyl)-1-methylpyrazole-4-carbonitrile (10c).*** Yield 46%, mp 213–214°C; IR (KBr): 3122, 2231, 1621, 1580, 1541, 1498, 1461 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.94 (s, 3H, MeN), 6.98 (d, 1H, H-3′, $J$ = 8.7 Hz), 7.33 (dd, 1H, H-4′, $J$ = 8.7, 2.7 Hz), 7.43 (d, 1H, H-6′, $J$ = 2.7 Hz), 8.58 (s, 1H, H-5), 10.37 (br s, 1H, OH). Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.45; N, 17.98. Found: C, 56.54; H, 3.64; N, 17.85.

**General procedure for the preparation of 2-methylchromeno[4,3-*c*]pyrazol-4(2*H*)-ones (12a–c).** A solution of pyrazole **10** (1.0 mmol) in 3 mL of glacial acetic acid was refluxed for 5 h. The resulting reaction mixture was then diluted with water (10 mL) and the solid that formed was filtered, washed with water, and dried to give **12** as colorless crystals.

***2-Methylchromeno[4,3-c]pyrazol-4(2H)-one (12a).*** Yield 92%, mp 209–210°C (lit. [17] mp 210°C); $^1H$ NMR (DMSO-$d_6$): δ 4.09 (d, 3H, Me, $J$ = 0.5 Hz), 7.38 (ddd, 1H, H-8, $J$ = 7.7, 7.3, 1.2 Hz), 7.44 (ddd, 1H, H-6, $J$ = 8.4, 1.2, 0.4 Hz), 7.55 (ddd, 1H, H-7, $J$ = 8.4, 7.3, 1.7 Hz), 7.99 (ddd, 1H, H-9, $J$ = 7.7, 1.7, 0.4 Hz), 8.79 (q, 1H, H-3, $J$ = 0.5 Hz). Anal. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.64; H, 4.08; N, 13.84.

***2,8-Dimethylchromeno[4,3-c]pyrazol-4(2H)-one (12b).*** Yield 70%, mp 158–160°C; IR (ATR, ZnSe): 1743, 1591, 1557, 1524 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): (**12b**, 72%) δ 2.43 (s, 3H, Me), 4.09 (s, 3H, NMe), 7.22 (d, 1H, H-6, $J$ = 8.5 Hz), 7.28 (dd, 1H, H-7, $J$ = 8.5, 2.0 Hz), 7.76 (br s, 1H, H-9), 8.67 (s, 1H, H-3); 1,8-dimethylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (**13b**, 28%) δ 2.49 (s, 3H, Me), 4.36 (s, 3H, NMe), 7.35 (d, 1H, H-6, $J$ = 8.5 Hz), 7.40 (dd, 1H, H-7, $J$ = 8.5, 2.0 Hz), 7.94 (br s, 1H, H-9), 8.07 (s, 1H, H-3). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.96; H, 4.81; N, 13.06.

***8-Chloro-2-methylchromeno[4,3-c]pyrazol-4(2H)-one (12c).*** Yield 92%, mp 228–230°C; IR (ATR, ZnSe): 1747, 1736, 1589, 1554, 1511 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.10 (s, 3H, Me), 7.38 (d, 1H, H-6, $J$ = 8.8 Hz), 7.47 (dd, 1H, H-7, $J$ = 8.8, 2.5 Hz), 7.91 (d, 1H, H-9, $J$ = 2.5 Hz), 8.74 (s, 1H, H-3). Anal. Calcd for $C_{11}H_7ClN_2O_2$: C, 56.31; H, 3.01; N, 11.04. Found: C, 55.96; H, 2.88; N, 11.42.

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## REFERENCES AND NOTES

[1] (a) Harnisch, H. Justus Liebigs Ann Chem 1972, 765, 8; (b) Nohara, A.; Umetani, T.; Sanno, Y. Tetrahedron Lett 1973, 1995; (c) Nohara, A.; Umetani, T.; Sanno, Y. Tetrahedron 1974, 30, 3553.

[2] (a) Nohara, A. Tetrahedron Lett 1974, 1187; (b) Klutchko, S.; Cohen, M. P.; Shavel, J.; von Strandtmann, M. J Heterocycl Chem 1974, 11, 183.

[3] (a) Petersen, U.; Heitzer, H. Justus Liebigs Ann Chem 1976, 1659; (b) Hagen, H.; Nilz, G.; Walter, H.; Landes, A.; Freund, W. D.E. Pat. 4,039,281, (1992); Chem Abstr 1992, 117, 111473.

[4] Reddy, G. J.; Latha, D.; Thirupathaiah, C.; Rao, K. S. Tetrahedron Lett 2004, 45, 847.

[5] Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Zehnder, L. R.; Park, F.; Kim, M.; Tran, T.-T. T. J Org Chem 1999, 64, 8736.

[6] Ghosh, C. K.; Karak, S. K. J Heterocycl Chem 2005, 42, 1035.

[7] Nohara, A.; Ishiguro, T.; Ukawa, K.; Sugihara, H.; Maki, Y.; Sanno, Y. J Med Chem 1985, 28, 559.

[8] (a) Ghosh, C. K.; Tewari, N.; Bandyopadhyay, C. Indian J Chem 1983, 22B, 1200; (b) Ghosh, C. K.; Ghosh, C.; Patra, A. Indian J Chem 1998, 37B, 387.

[9] Ghosh, C. K.; SinhaRoy, D. K.; Mukhopadhyay, K. K. J Chem Soc Perkin Trans 1 1979, 1964.

[10] Sosnovskikh, V. Ya.; Moshkin, V. S.; Kodess, M. I. Tetrahedron Lett 2008, 49, 6856.

[11] (a) Colotta, V.; Cecchi, L.; Melani, F.; Palazzino, G.; Filacchioni, G. Tetrahedron Lett 1987, 28, 5165.

[12] Ghosh, C. K.; Pal, C. Indian J Chem 1985, 24B, 1288.

[13] Chantegrel, B.; Nadi, A.-I.; Gelin, S. Tetrahedron Lett 1983, 24, 381.

[14] (a) Moorty, S. R.; Sundaramurthy, V.; Subba Rao, N. V. Indian J Chem 1973, 11, 854; (b) Strakova, I.; Petrova, M.; Belyakov, S.; Strakovs, A. Chem Heterocycl Comp 2003, 39, 1608.

[15] Steinführer, T.; Hantschmann, A.; Pietsch, M.; Weißenfels, M. Justus Liebigs Ann Chem 1992, 23.

[16] Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y. J Med Chem 1977, 20, 141.

[17] Trimeche, B.; Gharbi, R.; Houla, S. E.; Martin, M.-T.; Nuzillard, J. M.; Mighri, Z. J Chem Res 2004, 170.

[18] (a) Darbarwar, M.; Sundaramurthy, V. Synthesis 1982, 337; (b) Colotta, V.; Cecchi, L.; Filacchioni, G.; Melani, F.; Palazzino, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. J Med Chem 1988, 31, 1; (c) Ibrahim, M. A.ARKIVOC 2008, xvii, 192.

# Thieno[2,3-*d*]pyrimidines and -[1,3]oxazines as Glutamate Antagonists and Investigations on the Inhibitory Potency toward Human Leukocyte Elastase

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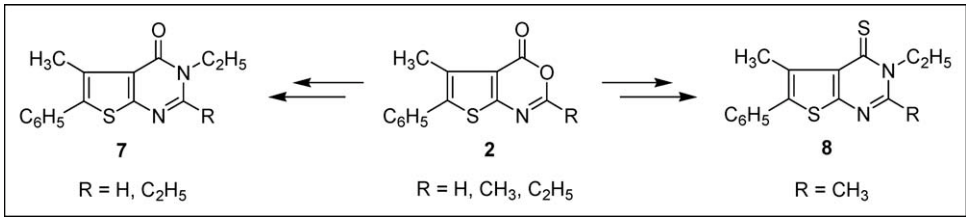


A series of fused thiophene derivatives, that is, representatives of thieno[2,3-*d*]pyrimidines, thieno[2,3-*d*][1,3]oxazines and thieno[2,3-*d*][1,3]thiazines, with the common 5-methyl-6-phenyl substitution pattern was synthesized. The target compounds, *e.g.*, **7** or **8**, were designed as cyclic analogs of ethyl 2-amino-4-methyl-5-phenylthiophene-3-carboxylate, an antagonist at the GluR6 kainate receptor. Thieno[2,3-*d*][1,3]oxazin-4-one **2** (R = $C_2H_5$) was identified as new a potent inhibitor ($IC_{50}$ = 17 μ*M*) of this receptor subtype. The inhibitory potency of **2** (R = $C_2H_5$) against human leukocyte elastase was also examined. The compound was characterized as a noncovalent inhibitor with an $IC_{50}$ value of 8.8 μ*M*.

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## INTRODUCTION

Even well-established anticonvulsants, such as carbamazepine, valproic acid, phenytoin, or benzodiazepines can cause undesired side effects. Moreover, certain forms of epilepsy, that is, focal seizures, cannot be treated sufficiently with such drugs. This provided the impetus behind the development of new drugs to improve the prospects for mono- and combined therapy. In the course of the continuing search for new anticonvulsants, substituted quinazolines and the bioisosteric thieno[2,3-*d*]pyrimidines have been reported to be active [1,2]. Kainate glutamate receptors may represent an interesting new target for the development of innovative anticonvulsants [3,4]. The kainate receptor subtype GluR6, expressed in the excitatory pyramid cells of the hippocampus, appears to be particularly significant. The GluR6 and GlyR5 subtypes might play opposing roles during the hippocampal excitation [3,5].

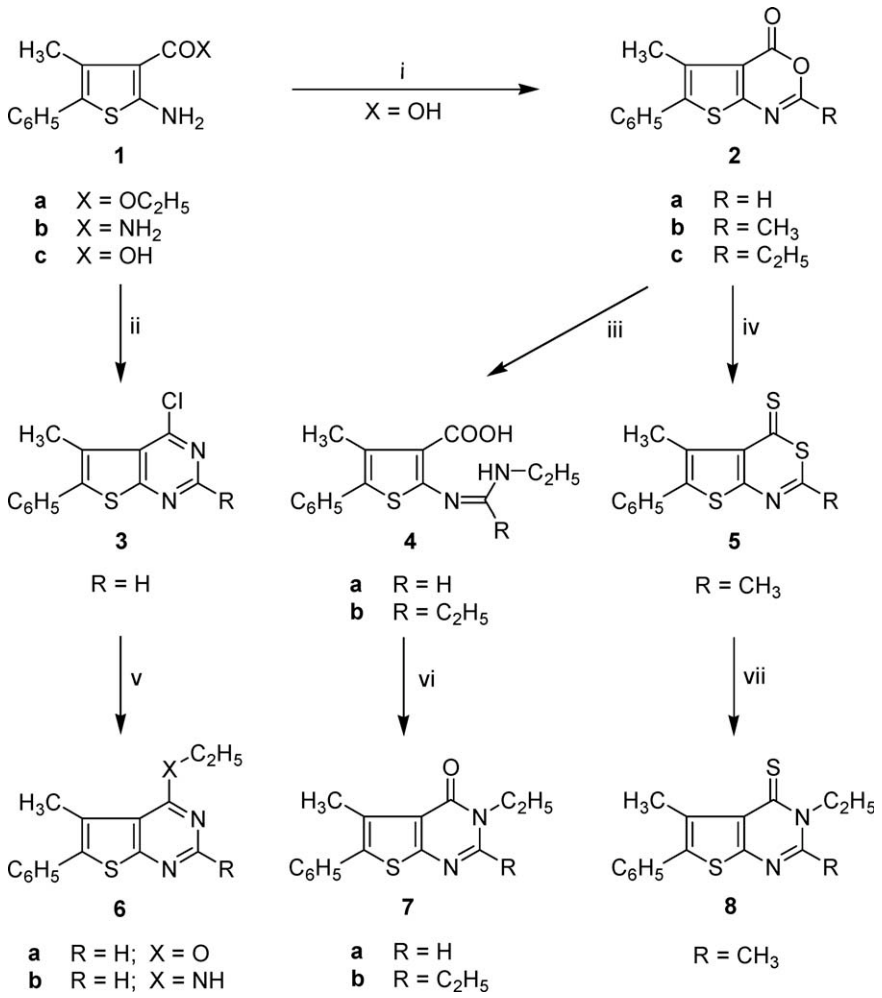
The know antagonists of the GluR6 kainate receptor comprise two groups, compounds which contain glutamate or its isosterically modified fragments on the one hand, and compounds with a structure not related to glutamate on the other hand. Diarylureas and quinoxalinediones are predominant examples of the latter group [6–10].

Substituted alkyl thiophene-3-carboxylates have been identified as a new class of selective GluR6 antagonists [11]. As a result of a screening of several thiophene esters, 2-amino-4-methyl-5-phenylthiophene derivatives proved to be particularly active. The ethyl ester **1a** ($IC_{50}$ = 0.75 μ*M*) exceeded other esters, e.g., methyl, propyl, with respect to selectivity for the GluR6 kainate receptor [11]. On the basis of these findings, we envisaged cyclic analogs of **1a** and focused on the synthesis of thienopyrimidines (Scheme 1). Selected compounds were also evaluated as inhibitors of human leukocyte elastase (HLE), a serine protease of the chymotrypsin family. Under normal conditions, the activity of HLE is regulated by endogenous inhibitors, but uncontrolled activity of HLE may result in several pathological states, including emphysema, chronic obstructive pulmonary disease, cystic fibrosis and rheumatoid arthritis. HLE inhibitors are therefore of relevance for the therapy of such afflictions [12–15].

## RESULTS AND DISCUSSION

The synthetic routes to bicyclic thiophenes with the common 5-methyl-6-phenyl substitution pattern are outlined in Scheme 1. Using known methods, the fused pyrimidine ring was formed in the reaction of the thiophene-3-carboxamide

**Scheme 1.** Conditions: i) $HC(OC_2H_5)_3$, 12 h, reflux, or $(RCO)_2O$, 1.5 h, reflux; ii) 1. $HC(OC_2H_5)_3$, 12 h, reflux, 2. $POCl_3$, 5 h, reflux; iii) $NH_2CH_2CH_3$ (70% aqueous solution); iv) $P_4S_{10}$ / toluene, 3 h, reflux; v) $NaOCH_2CH_3$ / $CH_2CH_3OH$, 12 h, or $NH_2CH_2CH_3$ (70% aqueous solution) / $CH_2Cl_2$; vi) $SOCl_2$, $CHCl_3$, 30 min, reflux; vii) $NH_2CH_2CH_3$ (70% aqueous solution).




**1b** [16] with ethyl orthoformate. Subsequent treatment with phosphorous oxychloride afforded the 4-chlorothienopyrimidine **3**. The conversion of **3** with sodium ethoxide gave **6a**, in which the carboxylic ester moiety of **1a** is replaced by a semicyclic ethyl imidate substructure. The corresponding replacement by an ethyl amidine substructure in **6b** was accomplished when **3** was treated with ethylamine. The reactions of the thiophene-3-carboxylic acid **1c** [17] with carboxylic anhydrides or carboxylic acid ortho esters provided an access to thieno[2,3-*d*][1,3]oxazin-4-ones **2**. Oxazinones **2** bear two electrophilic sites, C-2 and C-4. Ethylamine exclusively attacked **2** at the C-2 carbon, leading to the formation of amidino carboxylic acids **4**. Treatment of **4** with thionyl chloride furnished compounds **7a**, **b** with N-ethyl lactam structure. The thieno[2,3-*d*][1,3]thiazine-4-thione **5**, accessible by thionation of the corresponding oxazinone **2b** with diphosphorous pentasulfide [17], was reacted with ethylamine to give the thienopyrimidine **8** with N-ethyl thiolactam structure. It should be noted that **8** was directly produced and a corresponding ring-open thiophene derivative could not be isolated. Such a compound with amidine and dithiocarboxylate moieties, formed through an attack of ethylamine at C-2 of **5**, might remain in solution or undergo different transformations, thus accounting for the low yield of **8**. In the mass spectra of the thienopyrimidines **7** and **8**, the molecular peaks appear with highest intensities. Elimination of $C_2H_4$ was the main fragmentation reaction leading to the detection of fragment ions with the anticipated structure **9**. Similarly, the loss the ethyl chain was the predominant fragmentation of **6**.

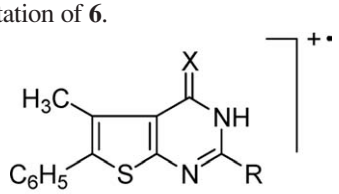


**Table 1**

Inhibition (% of Control) of fractional luminescence or $IC_{50}$ value.

| Compd. | GluR5 | GluR6 |
|---|---|---|
| **2c** | 11 | $IC_{50} = 17$ μ*M* |
| **6a** | 9 | 14 |
| **6b** | −7 | 3 |
| **7a** | −6 | 9 |
| **7b** | 7 | 5 |
| **8** | −11 | 0 |

The thienopyrimidines **6a**,**b**, **7a**,**b**, **8**, and the oxazinone **2c** were evaluated as antagonists of the kainate receptor subtypes GluR5 and GluR6 (Table 1). The experiments were performed with human embryonic kidney (HEK) cells stably expressing the GluR5 and GluR6 receptor. The antagonistic activity was determined by measuring the glutamate-mediated luminescence. The photoprotein aequorin was used as a bioluminescent reporter. The complete luminescence of the cells was determined with the detergent triton X-100 [11]. While the thienopyrimidines **6a**,**b**, **7a**,**b**, and **8**, at a concentration of 10 μ*M*, did barely influence the luminescence signal in the GluR5 and GluR6 assays, 2-ethylthieno[2,3-*d*][1,3]oxazin-4-one (**2c**) inhibited the glutamate response in the GluR6 aequorin assay with an $IC_{50}$ value of 17 μ*M*. Thus, this compound will serve as a lead for further chemical modification to develop new anticonvulsants.

Representatives of 3,1-benzoxazin-4-ones have been reported as alternate substrate inhibitors of HLE [18–20]. It has been shown that the introduction of small alkyl groups connected *via* an O, S, or N atom to the position 2 of the heterocyclic system resulted in potent inhibition [18]. Bioisosteric thieno[1,3]oxazin-4-ones react in an analogous manner as alternate substrate inhibitors with serine proteases and esterases [21–24]. The interaction involves the nucleophilic attack of the active site serine (SerOH), formation of an acyl-enzyme and hydrolytic cleavage to release the modified ring-opened inhibitor and the free enzyme (Fig. 1).

We have selected the thieno[2,3-*d*][1,3]oxazin-4-ones **2a**–**c** and determined their inhibitory activity against HLE. Compound **2c** was identified as an HLE inhibitor ($IC_{50} = 8.8$ μ*M*, Fig. 2), whereas **2a** was not sufficiently soluble in the assay medium, and **2b** failed to inhibit HLE ($IC_{50} > 40$ μ*M*). It can be suspected, that the ethyl group in **2c** interacts with the S1 pocket of HLE, thus reflecting the primary substrate specificity for small aliphatic amino acids at P1 position of a substrate.

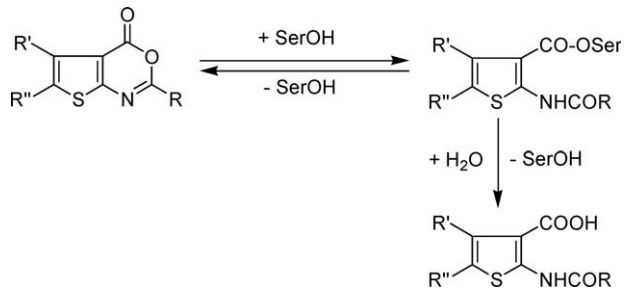



**Figure 1.** Enzyme-catalyzed conversion of thieno[2,3-*d*][1,3]oxazin-4-ones.

To elucidate the mechanism of elastase inhibition by **2c**, we examined a possible enzyme-catalyzed degradation of the inhibitor by means of HPLC. Compound **2c** was incubated at 25°C, pH 7.8, with HLE in a 200-fold higher concentration compared to that used in the inhibition assays. Despite the inhibition of HLE by **2c**, an accelerated hydrolysis in the presence of such a high amount of enzyme could be expected [24]. However, the decrease in concentration of **2c** was weak (<20% within 4 h) and similarly observed in the control experiment, where **2c** was incubated in the absence of HLE. It can therefore be concluded that **2c** does not act as an alternate substrate inhibitor of HLE, but most probably as a competitive noncovalent inhibitor. This behavior differs from that of thieno[1,3]oxazin-4-ones with alkoxy, alkylthio, or (di)alkylamino substituents at 2-position. Such compounds have been characterized [22] to interact with HLE in the way outlined in Figure 1.

## EXPERIMENTAL

Melting points were obtained on a Büchi melting point apparatus 535 and are uncorrected. Mass spectra (EI, 70 eV) were measured on a VG Analytics VG ZAB-HSQ spectrometer. ESI-HRMS spectra were recorded on a Bruker Daltonics

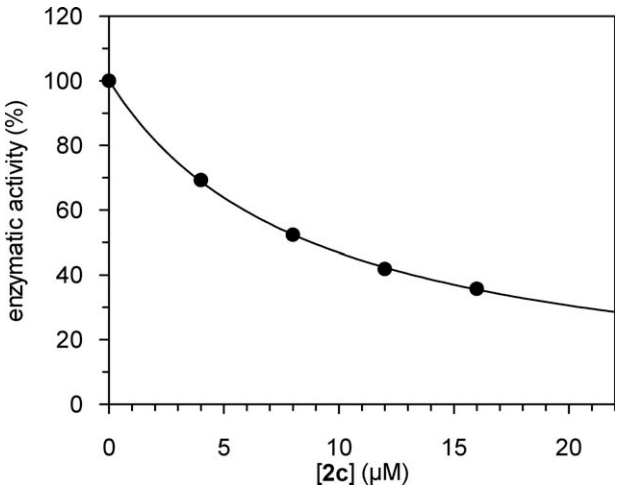



**Figure 2.** Inhibition of HLE by **2c** in the presence of 100 μ*M* of the chromogenic substrate MeO-Suc-Ala-Ala-Pro-Val-pNA. The data are mean values of duplicate measurements. The reactions were followed over 10 min, and the rates, *v*, were determined by linear regression. The rates in absence of inhibitor, $v_0$, were set to 100%. Nonlinear regression according to the equation $v = v_0/([I]/(IC_{50} + 1)$ gave a value $IC_{50} = 8.8 \pm 0.1$ μ*M*.

7T Apex II FT-ICR mass spectrometer. $^1$H NMR spectra were recorded on a Varian Gemini-300 spectrometer at 300.08 MHz. $^{13}$C NMR spectra were recorded on a Varian Gemini-300 spectrometer at 75.45 MHz. IR spectra were recorded on a Perkin–Elmer FT-IR PC 16 instrument. 5-Methyl-6-phenylthieno[2,3-*d*][1,3]oxazin-4-one (**2a**) [17], 2,5-dimethyl-6-phenylthieno[2,3-*d*][1,3]oxazin-4-one (**2b**) [17], and 4-chloro-5-methyl-6-phenylthieno[2,3-*d*]pyrimidine (**3**) [16] were prepared as reported.

**2-Ethyl-5-methyl-6-phenylthieno[2,3-*d*][1,3]oxazin-4-one (2c).** A mixture of compound **1c** [11] (2 g, 8.58 mmol) and propionic anhydride (10 mL, 78 mmol) was refluxed for 90 min. The precipitate, formed after cooling, was filtered off, dried, and recrystallized from ethanol. Yield 1.2 g (34%). Colorless crystals, mp 99–100°C; ms: *m/z* (%) 271 ($M^{+\cdot}$, 100), 242 (40); $^1$H NMR (deuteriochloroform): δ 1.33 (t, 3H, $CH_3$, $J$ = 7.5 Hz), 2.56 (s, 3H, $CH_3$), 2.72 (q, 2H, $CH_2$, $J$ = 7.5 Hz), 7.39–7.46 (m, 5H, phenyl-H); ir (potassium bromide): ν 1744 (C=O), 1596, 1158–1075 cm$^{-1}$. Anal. Calcd. for $C_{15}H_{13}NO_2S \times 0.5\ H_2O$: C, 64.26; H, 5.03; N, 5.00; S, 11.44. Found C, 64.03; H, 5.16; N, 5.37; S, 11.48.

**2-(Ethylaminomethylenamino)-4-methyl-5-phenylthiophene-3-carboxylic acid (4a).** Ethylamine (10 mL of a 70% aqueous solution, 0.126 mol) was added dropwise to compound **2a** [17] (1.4 g, 5.7 mmol). The mixture was kept at 0°C until the crystallization was finished. The precipitate was separated and dried to obtain a crude product which was not further purified. Yield 1.1 g (70%). Beige solid, mp 180–183°C; ms: *m/z* (%) 288 ($M^{+\cdot}$, 97), 215 (100); ESI-HRMS: *m/z* 577.19433 ($[2M+H]^+$)$^\cdot$ ($C_{30}H_{33}N_4O_4S_2^+$ requires 577.19377); 289.10042 ($[M+H]^+$)$^\cdot$ ($C_{15}H_{17}N_2O_2S^+$ requires 289.10052); 599.17642 ($[2M+Na]^+$)$^\cdot$ ($C_{30}H_{32}N_4NaO_4S_2^+$ requires 599.17572); 311.08269 ($[M+Na]^+$)$^\cdot$ ($C_{15}H_{16}N_2NaO_2S^+$ requires 311.08247); $^1$H NMR (DMSO-$d_6$): δ 1.16 (t, 3H, $CH_3$, $J$ = 7.2 Hz), 2.36 (s, 3H, $CH_3$), 3.29 (q, 2H, $CH_2$, $J$ = 7.0 Hz), 7.38–7.50 (m, 5H, phenyl-H), 8.14 (s, 1H, CH), 8.34 (s, br, 0.5H, NH, exchangeable with $D_2O$), 14.30 (s, br, 0.5H, OH, exchangeable with $D_2O$); ir (potassium bromide): ν 3221 (N—H), 3069–2873, 1694 (C=O), 1632, 1577 cm$^{-1}$.

**2-(1-Ethylaminopropane-1-ylidenamino)-4-methyl-5-phenylthiophene-3-carboxylic acid (4b).** Compound **4b** was prepared from **2c** (1.2 g, 4.4 mmol) following the aforementioned procedure. Yield 1.2 g (89%). Beige solid, mp 152–155°C (crude product); ms: *m/z* (%) 316 ($M^{+\cdot}$, 18), 242 (100); $^1$H NMR (DMSO-$d_6$): δ 1.20 (t, 6H, 2 $CH_3$, $J$ = 7.5 Hz), 2.41 (s, 3H, $CH_3$), 2.7 (q, 2H, $CH_2$, $J$ = 7.8 Hz), 3.27 (q, 2H, $CH_2$, $J$ = 7.5 Hz), 7.40–7.54 (m, 5H, phenyl-H), 8.42 (s, br, 1H, NH, exchangeable with $D_2O$); ir (potassium bromide): ν 3237 (N—H), 2978–2937, 1684 (C=O), 1592, 1490, 1238, 1073 cm$^{-1}$. Anal. Calcd. for $C_{17}H_{20}N_2O_2S$: C, 64.53; H, 6.37; N, 8.85; S, 10.13. Found C, 64.22; H, 6.34; N, 8.79; S, 10.07.

**2,5-Dimethyl-6-phenylthieno[2,3-*d*][1,3]thiazin-4-thione (5) [17].** Compound **2b** [17] (2.57 g, 10 mmol) was dissolved in 80 mL of dry toluene. After addition of diphosphorous pentasulfide (22.2 g, 100 mmol), the mixture was refluxed for 2 h. The formed inorganic precipitate was filtered off and washed several times with hot toluene. The combined toluene solutions were evaporated and the precipitated crude product was separated and recrystallized from ethanol. Yield 1.16 g (40%). Red crystals, mp 135°C ($C_2H_5OH$); ms: *m/z* (%) 291 ([$M^{+\cdot}$ + 2], 26), 289 ($M^{+\cdot}$, 100), 274 (10), 256 (12), 247 (15), 230 (11), 224 (12), 215 (41), 203 (13), 184 (9), 171 (31), 127 (10), 121 (17), 115 (27), 89 (9), 77 (14); $^1$H NMR (deuteriochloroform): δ 2.61 (s, 3H, $CH_3$), 2.78 (s, 3H, $CH_3$), 7.48–7.51 (m 5H, phenyl-H); $^{13}$C NMR (deuteriochloroform): δ 19.0 (5-$CH_3$), 25.5 (2-$CH_3$), 127.1 (C-4a), 128.7 (C-4′), 128.9 (C-2′, C-6′), 130.1 (C-3′, C-5′), 130.8 (C-6), 132.1 (C-1′), 132.8 (C-5), 136.8 (C-7a), 170.1 (C-2), 201.6 (C=S); ir (potassium bromide): ν 1545, 1262, 1052 cm$^{-1}$.

**4-Ethoxy-5-methyl-6-phenylthieno[2,3-*d*]pyrimidine (6a).** Compound **3** [16] (0.5 g, 1.9 mmol) was refluxed in 10 mL of a solution of sodium ethoxide in ethanol (1 mol/L) for 12 h. The solvent was evaporated, the precipitate was isolated, washed with water and recrystallized from ethanol. Yield 0.4 g (78%). Colorless crystals, mp 103°C ($C_2H_5OH$); ms: *m/z* (%) 270 ($M^{+\cdot}$, 100), 255 (36), 242 (78); $^1$H NMR (DMSO-$d_6$): δ 1.40 (t, 3H, $CH_3$, $J$ = 7.2 Hz), 2.50 (s, 3H, $CH_3$), 4.53 (q, 2H, $CH_2$, $J$ = 7.2 Hz), 7.44–7.52 (m, 5H, phenyl-H), 8.60 (s, 1H, CH); $^{13}$C NMR (deuteriochloroform): δ 14.9 ($CH_3$), 15.4 ($CH_3$), 63.3 ($OCH_2$), 120.2 ($C_q$), 126.3 ($C_q$), 129.3 (CH, Ph), 129.7 (2 × CH, Ph), 130.2 (2 × CH, Ph), 133.4 ($C_q$), 135.4 ($C_q$), 153.7 (CH), 164.7 ($C_q$), 167.1 ($C_q$); ESI-HRMS: *m/z* 271.09014 ($[M+H]^+$)$^\cdot$ ($C_{15}H_{15}N_2OS^+$ requires 271.08996); 563.15462 ($[2M+Na]^+$)$^\cdot$ ($C_{30}H_{28}N_4NaO_2S_2^+$ requires 563.15459); 293.07211 ($[M+Na]^+$)$^\cdot$ ($C_{15}H_{14}N_4NaOS^{+\cdot}$ requires 293.07190); ir (potassium bromide): ν 3446 (br, traces from water), 3064–2978, 1555–1450, 1332, 1063, 1044 cm$^{-1}$. Anal. Calcd. for $C_{15}H_{14}N_2OS \times H_2O$: C, 62.47; H, 5.59; N, 9.71; Found C, 62.69; H, 4.96; N, 9.67.

**4-Ethylamino-5-methyl-6-phenylthieno[2,3-*d*]pyrimidine (6b).** Compound **3** [16] (0.3 g, 1.15 mmol) was dissolved in dichloromethane (3 mL) and treated with ethylamine (100 mL of a 70% aqueous solution, 1.26 mol). If no crystallization occurred, water was added to the mixture. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 0.2 g (65%). Yellow crystals, mp 155–158°C ($C_2H_5OH$); ms: *m/z* (%) 269 ($M^{+\cdot}$, 100), 254 (27), 240 (30); $^1$H NMR (deuteriochloroform): δ 1.35 (t, 3H, $CH_3$, $J$ = 7.2 Hz), 2.63 (s, 3H, $CH_3$), 3.66–3.75 (m, 2H, $CH_2$, $J$ = 7.2 Hz), 5.57 (s, br, NH, exchangeable with $D_2O$), 7.41–7,50 (m, 5H, phenyl-H), 8.49 (s, 1H, CH); ir (potassium bromide): ν 3419 (NH), 2988–2863, 1574–1460, 1128–1012 cm$^{-1}$. Anal. Calcd. for $C_{15}H_{15}N_3S \times 0.5\ C_2H_5OH$: C, 65.72; H, 6.20; N, 14.37; S, 10.96. Found C, 65.30; H, 5.76; N, 14.75; S, 11.23.

**3-Ethyl-5-methyl-6-phenylthieno[2,3-*d*]pyrimidin-4-one (7a).** Compound **4a** (0.3 g, 1 mmol) was dissolved in anhydrous chloroform (10 mL). After addition of thionyl chloride (1.19 g, 10 mmol), the mixture was refluxed for 30 min. The solvent was evaporated at room temperature, the precipitate formed was filtered off, and dried. The crude product was purified by column chromatography on silica gel (63–200 μm, Merck) with ethanol. Yield 0.087 g (30%). Red solid, mp 90°C ($C_2H_5OH$); ms: *m/z* (%) 270 ($M^{+\cdot}$, 100), 242 (42); ESI-HRMS: *m/z* 541.17313 ($[2M+H]^+$)$^\cdot$ ($C_{30}H_{29}N_4O_2S_2^+$ requires 541.17264); 271.08999 ($[M+H]^+$)$^\cdot$ ($C_{15}H_{15}N_2OS^+$ requires 271.08996); 563.15500 ($[2M+Na]^+$)$^\cdot$ ($C_{30}H_{28}N_4NaO_2S_2^+$ requires 563.15459); 293.07208 ($[M+Na]^+$)$^\cdot$ ($C_{15}H_{14}N_4NaOS^+$ requires 293.07190); $^1$H NMR (deuteriochloroform): δ 1.43 (t, 3H, $CH_3$, $J$ = 7.2 Hz), 2.64 (s, 3H, $CH_3$), 4.07 (q, 2H, $CH_2$, $J$ = 7.3 Hz), 7.39–7.47 (m, 5H, phenyl-H), 7.97 (s, 1H, CH); $^{13}$C NMR (deuteriochloroform): δ 14.9 ($CH_3$), 15.4 ($CH_3$), 42.1 ($NCH_2$), 124.4 ($C_q$), 128.3 (CH, Ph), 128.9 (2 × CH, Ph),

129.9 (2 × CH, Ph), 130.3 ($C_q$), 133.6 ($C_q$), 135.5 ($C_q$), 146.0 (CH), 158.5 ($C_q$), 163.0 ($C_q$); ir (potassium bromide): ν 1666, 1658 (C=O), 1600, 1576, 1234–1083 $cm^{-1}$. Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.32; H, 5.40; N, 10.13.

**2,3-Diethyl-5-methyl-6-phenylthieno[2,3-*d*]pyrimidin-4-one (7b).** Thionyl chloride (2.38 g, 20 mmol) was added to a solution of **4b** (1.2 g, 3.8 mmol) in anhydrous chloroform (30 mL). The mixture was refluxed for 30 min. The solvent was evaporated at room temperature. The precipitate was filtered off and dried. The crude product was thoroughly washed with acetone and recrystallized from acetonitrile. Yield 0.5 g (40%). Beige solid, mp 175–179°C ($CH_3CN$); ms: *m/z* (%) 298 ($M^{+\cdot}$, 100), 270 (69), 215 (66); $^1$H NMR (DMSO-$d_6$): δ 1.24–1.32 (m, 6H, 2 $CH_3$, $J$ = 7.2 Hz, $J$ = 6.9 Hz), 2.53 (s, 3H, $CH_3$), 2.93 (q, 2H, $CH_2$, $J$ = 7.2 Hz), 4.10 (q, 2H, $CH_2$, $J$ = 6.9 Hz), 7.44–7.53 (m, 5H, phenyl-H); ir (potassium bromide): ν 3434 (br, traces of water), 1670 (C=O), 1596, 1543 $cm^{-1}$. Anal. Calcd. for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39, S 10.74. Found C, 68.16; H, 5.83; N, 8.92; S, 10.27.

**3-Ethyl-2,5-dimethyl-6-phenylthieno[2,3-*d*]pyrimidine-4-thione (8).** Ethylamine (3 mL of a 70% aqueous solution, 0.04 mol) was added dropwise to **5** (0.4 g, 1.38 mmol). The mixture was kept at 0°C until the crystallization was finished. The precipitate was separated and dried. Yield 0.1 g (24%). Light yellow crystals, mp 89–91°C ($CH_3CN$); ms: *m/z* (%) 302 ([$M^{+\cdot}$ + 2], 13), 300 ($M^{+\cdot}$, 100), 272 (51); $^1$H NMR (DMSO-$d_6$): δ 1.35 (t, 3H, $CH_3$, $J$ = 6.9 Hz), 2.74 (s, 3H, $CH_3$), 2.81 (s, 3H, $CH_3$), 4.79 (s, br, 2H, $CH_2$), 7.52–7.59 (m, 5H, phenyl-H), ir (potassium bromide): ν 3440 (br, traces of water), 2974–2926, 1557 (strong, C=S), 1493, 1444, 1191, 1093 $cm^{-1}$. Anal. Calcd. for $C_{16}H_{16}N_2S_2 \times 0.5\ H_2O$: C, 62.10; H, 5.54; N, 9.05; S, 20.72. Found C, 62.40; H, 5.23; N, 9.11; S, 20.88.

**Kainate receptor-aequorin assay.** Human embryonic kidney cells (HEK 293 cells) which stably express the GluR5 or GluR6 receptor, respectively, together with the luminescent protein aequorin were used as screening assay for kainate receptor antagonists. GluR5- (or GluR6-) and aequorin-expressing HEK 293 cells were cultivated in a MEM growth medium together with Earle's salts and Glutamax-I (Life Technologies), containing 10% FKS, 1% nonessential amino acids, 100 IU/mL penicillin, 100 μg/mL streptomycin, 600 μg/mL G 418 (Calbiochem) and 500 n*M* ouabaine. One day before the measurement, 60,000 cells per cavity were seeded into white, nontransparent 96-well microtiter plates (Costar). On the test day, cells were incubated with 5 μ*M* coelenterazine for 1 h at 37°C. Then the medium was poured off and replaced by 80 μL assay buffer, and 10 μL test compound was added. The assay buffer contained 150 m*M* NaCl, 2.5 m*M* KCl, 10 m*M* HEPES, 1 m*M* $MgCl_2$, 10 m*M* glucose, 0.3 mg/mL concanavaline A (ConA) and (for GluR6) 100 m*M* $CaCl_2$ (pH = 7.3). Afterwards the cells were incubated for 10 min at room temperature.

The luminescence measurement was performed in a luminometer (LUMIstar, BMG) equipped with two computer-controlled injectors, over a period of 26 s per cavity (13 intervals of 2 s). After the first second 10 μL of a 2.75 m*M* glutamate-solution in assay buffer was injected (to receive a glutamate concentration of 275 μ*M* per cavity, according to the $EC_{50}$ value of glutamate for GluR6) or 10 μL of 0.8 m*M* glutamate (due to 80 μ*M* = $EC_{50}$ for GluR5). A second injection of 100 μL triton X-100 in assay buffer (without $Ca^{2+}$) was carried out after 20 s into the same cavity.

The calculation of specific channel activity induced by an agonist was determined as fractional luminescence, which was calculated from respective sum of signals of agonist- and triton-induced luminescence. For determination of the $IC_{50}$ value, a Hill plot (4-parameter model) was used.

**HLE inhibition assay.** The spectrophotometric assay for HLE was done on a Varian Cary 50 Bio UV/VIS spectrometer with a cell holder equipped with a constant temperature water bath. HLE was available from a previous study [24]. Reactions were followed at 405 nm at 25°C for 10 min. Stock solutions of the inhibitors were prepared in DMSO. $IC_{50}$ values were calculated from the linear steady-state turnover of the substrate. Assay buffer was 50 m*M* sodium phosphate buffer, 500 m*M* NaCl, pH 7.8. An enzyme stock solution of 50 μg/mL was prepared in 100 m*M* sodium acetate buffer, pH 5.5 and diluted with assay buffer. A 50 m*M* stock solution of the chromogenic substrate MeOSuc-Ala-Ala-Pro-Val-pNA (Bachem, Bubendorf, Switzerland) was prepared in DMSO and diluted with assay buffer containing 10% DMSO. The final concentration of the substrate was 100 μ*M*, of DMSO was 1.5% and of HLE was 25 ng/mL. Into a cuvette containing 890 μL assay buffer, 10 μL of an inhibitor solution and 50 μL of a substrate solution were added and thoroughly mixed. The reaction was initiated by adding 50 μL of the HLE solution (500 ng/mL).

**HLE incubation experiment.** Compound **2c**, dissolved in acetonitrile, and a solution of HLE were added to assay buffer and incubated for 4 h at 25°C in a quartz cuvette. The final concentration of **2c** was 20 μ*M*, of acetonitrile was 2% and of HLE was 5 μg/mL. In the control experiment, **2c** was incubated in assay buffer without HLE. In 60-min intervals, 10 μL aliquots were injected into the HPLC system (Dionex P580, Phenomenex Gemini 5 μ, $C_{18}$, mobile phase A: $H_2O$/acetonitrile/$CF_3CO_2H$ (475:25:0.3), mobile phase B: $H_2O$/acetonitrile/tetrahydrofuran/$CF_3CO_2H$ (25:465:10:0.3), gradient 0–25 min: 70–10% A, 30–90% B, 27–30 min: 70% A, 30% B, UV detection, 310 nm). The retention time of **2c** was 17.33–17.35 min.

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## REFERENCES AND NOTES

[1] Allgeier, H.; Froestl, W.; Koller, M.; Mattes, H.; Nozulak, J.; Ofner, S.; Orain, D.; Rasetti, V.; Renaud, J.; Soldermann, N.; Floersheim, P. Patent (Novartis AG, Switzerland) Appl. WO 2006010591; Chem Abstr 2006, 144, 192265.

[2] Mkrtchyan, A. P.; Noravyan, A. S.; Petrosyan, V. M. Khim Geterotsikl Soedin 2002, 2, 261.

[3] Pinheiro, P. S.; Mulle, C. Nat Rev Neurosci 2008, 9, 423.

[4] Epsztein, J.; Represa, A.; Joquera, I.; Ben, Y.; Crepel, V. J Neurosci 2005, 25, 8229.

[5] Frerking, M.; Nicoll, R. A. Curr Opin Neurobiol 2000, 10, 342.

[6] Lerma, J.; Paternain, A. V.; Rodriguez-Moreno, A.; Lopez-Garcia, J. C. Physiol Rev 2001, 81, 971.

[7] Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P. J Med Chem 2000, 43, 2609.

[8] Christensen, J. K.; Varming, T.; Ahring, P. K.; Jørgensen, T. D.; Nielsen, E. Ø. J Pharmacol Exp Ther 2004, 309, 1003.

[9] Catarzi, D.; Colotta, V.; Varano, F.; Calabri, F. R.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. J Med Chem 2004, 47, 262.

[10] Dominguez, E.; Iyengar, S.; Shannon, H. E.; Bleakman, D.; Alt, A.; Arnold, B. M.; Bell, M. G.; Bleisch, T. J.; Buckmaster, J. L.; Castano, A. M.; Del Prado, M.; Escribano, A.; Filla, S. A.; Ho, K. H.; Hudziak, K. J.; Jones, C. K.; Martinez-Perez J. A.; Mateo, A.; Mathes, B. M.; Mattiuz, E. L.; Ogden, A. M.; Simmons, R. M.; Stack, D. R.; Stratford, R. E.; Winter, M. A.; Wu, Z.; Ornstein, P. L. J Med Chem 2005, 48, 4200.

[11] Briel, D.; Rybak, A.; Kronbach, C.; Unverferth, K. Eur J Med Chem 2010, 45, 69.

[12] Chua, F.; Laurent, G. J. Proc Am Thorac Soc 2006, 3, 424.

[13] Korkmaz, B.; Moreau, T.; Gauthier, F. Biochimie 2008, 90, 227.

[14] Taggart, C. C.; Greene, C. M.; Carroll, T. P.; O'Neill, S. J.; McElvaney, N. G. Am J Respir Crit Care Med 2005, 171, 1070.

[15] Pham, C. T. Nat Rev Immunol 2006, 6, 541.

[16] Briel, D.; Rybak, A.; Kronbach, C.; Unverferth, K. Pharmazie, 2008, 63, 823.

[17] Briel, D.; Rybak, A.; Mann, S.; Kronbach, C.; Unverferth, K. Curr Med Chem 2009, 6, 4704.

[18] Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp. L. J.; Thomas, E. M.; Rafferty, S. P. J Med Chem 1990, 33, 464.

[19] Stein, R. L.; Strimpler, A. M.; Viscarello, B. R.; Wildonger, R. A.; Mauger, R. C.; Trainor, D. A. Biochemistry 1987, 26, 4126.

[20] Gütschow M.; Neumann, U.; Sieler, J.; Eger, K. Pharm Acta Helv 1998, 73, 95.

[21] Jarvest, R. L.; Parratt, M. J.; Debouck, C. M.; Gorniak, J. G.; Jennings, L. J.; Serafinowska, H. T.; Strickler, J. E. Bioorg Med Chem Lett 1996, 6, 2463.

[22] Gütschow, M.; Neumann, U. J Med Chem 1998, 41, 1729.

[23] Gütschow, M.; Kuerschner, L.; Neumann, U.; Pietsch, M.; Löser, R.; Koglin, N.; Eger, K. J Med Chem 1999, 42, 5437.

[24] Pietsch, M.; Gütschow M. J Biol Chem 2002, 277, 24006.

# Novel Tetracyclic Imidazole Derivatives: Synthesis, Dynamic NMR Study, and Anti-Inflammatory Evaluation

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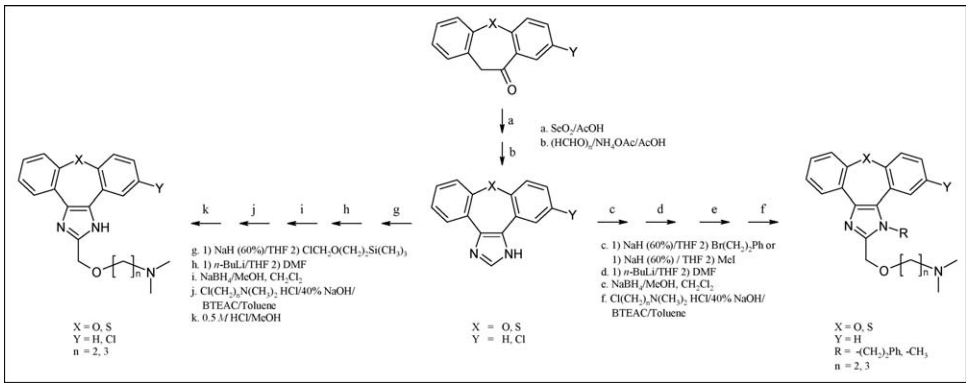


A series of tetracyclic imidazole derivatives **9a–9v** and **10a–10h** are prepared by multistep route starting from the known tricyclic diketones **2a–2d**. Intermediary dibenzooxepin[4,5-*d*]imidazoles (**3a**, **3c**) and dibenzothiepin[4,5-*d*]imidazoles (**3b**, **3d**) are *N*-protected to **4e, 4f** and to the isomeric compounds **5a**, **5b** and **6a**, **6b**. The isomeric compounds **5** and **6** are separated. Compounds **4**, **5,** and **6** are formylated at C(2) to afford **7a–7j**. In the last steps, aldehyde group is reduced, then alkylated to the two sets of isomeric ω-dimethylaminoalkyl derivatives **9a–9v**. *N*-deprotection of **9i–9v** led to the compounds **10a–10h**. Assignment of the *syn*/*anti* structure to **5a** and **6a** was supported by 1D selective ROESY NMR spectra, whereas conformational mobility for the selected representatives **8a** and **8b** is studied by dynamic NMR. Activation energies (energy barriers for interconversion) are determined to be ∼11.5 and 16.2 kcal/mol, respectively. A series of derivatives **9** and **10** were tested *in vitro* for their anti-inflammatory activity.

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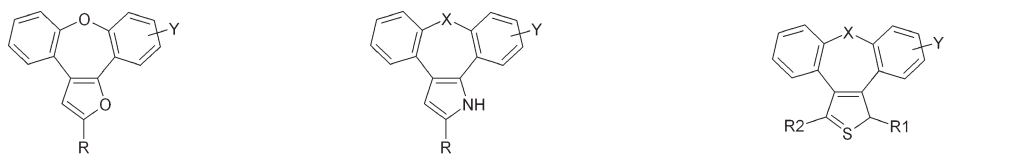
## INTRODUCTION

In our continuing efforts toward the development of disease modifying treatments for rheumatoid arthritis (RA), we are targeting inhibition of overproduction of tumor necrosis factor alpha cytokine (TNF-α) that is recognized as a key cytokine in RA progression. A small molecule inhibitor of TNF-α would be a novel potent anti-inflammatory drug having this distinguished mechanism of action. In the frame of our project aimed toward synthesis, structure determination of tetracyclic imidazoles, and screening of their activity on the selected biological targets, we entered the study of a large series of dibenzo-oxepin- and dibenzo-thiepin imidazole derivatives. In our previous articles we have reported on the synthesis, properties, and preliminary biological results of oxa-, aza-, and thia-dibenzoazulenes, characterized by the annulated furane **I** [2], pyrrole **II**, **III** [3], and thiophene **IV**, **V** [4] ring (Fig. 1). Preliminary results have revealed activity of these polycyclic systems in the *in vitro* anti-inflammatory test in lipopolysaccharide (LPS) induced TNF-α production in human peripheral blood mononuclear cells (hPBMCs) that encouraged us to extend our effort on other five membered heterocyclic systems [5,6].

Generally, structural complexity of this specific class of recently studied non-steroidal anti-inflammatory compounds increases from diaryl-substituted heterocycles general formulae **VI**, to polycondensed heterocyclic structures **VII**. Representatives of the former are vicinaly substituted polycyclic aryl/pyridine-4-yls, potent inhibitors of p38 MAP kinase (p38) [7,8], while 2-substituted-4,5-diarylimidazoles **VIII** are claimed as *in vivo* anti-inflammatory active structures (Fig. 2) [9–14].

Moreover, polycondensed heterocycles with non-aromatic dibenzoazulene core and annelated 5-membered heterocycles are repeatedly claimed as anti-inflammatory active compounds. Among them are 2-substituted-1*H*-phenanthro[9,10-*d*]imidazoles **IX** [15], 2-substituted dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazoles **X** [16–20], 2-substituted dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazoles, and their corresponding sulfoxides and sulfones **XI** (Fig. 3) [21].

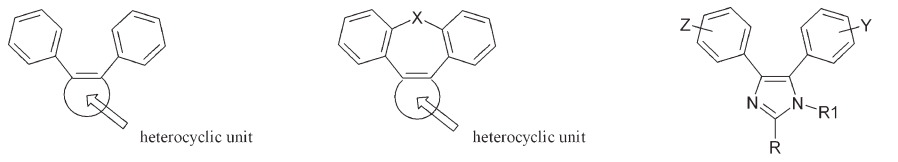



**I** Y = H, Cl, R = various substituents

**II** X = O, Y = H, Cl, R = various substituents
**III** X = S, Y = H, Cl, R = various substituents

**IV** X = O, Y = H, Cl, R1, R2 = various substituents
**V** X = S, Y = H, Cl, R1, R2 = various substituents

**Figure 1.** Previously described oxa-, aza-, and thia-dibenzoazulenes.

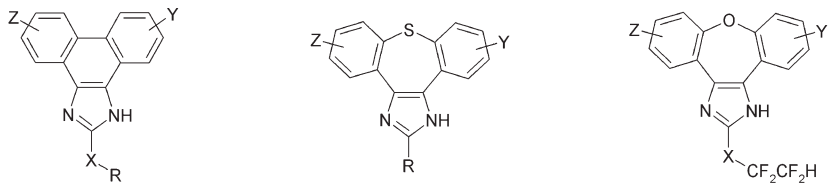



**VI**

**VII** X = O, S, $CH_2$

**VIII** Z, Y, R, R1 = various substituents

**Figure 2.** Non-steroidal heterocyclic anti-inflammatory compounds.




**IX** X = S, SO, $SO_2$,
Y, Z, R = various substituents

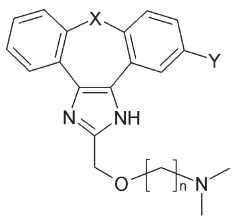
**X** Y, Z, R = various substituents

**XI** X = S, SO, $SO_2$,
Y, Z = various substituents

**Figure 3.** Polycondensed heterocycles with non-aromatic dibenzoazulene core.

Process for preparation of 2-formylimidazole acetals is also claimed [22], as well as 4,5-disubstituted imidazole derivatives and their use in CSBP/PK/p38 kinase mediated diseases [13]. First synthesis of tetracyclic, polycondensed imidazoles, presented by the formulae **X**, was reported by Lombardino [17], based on the general imidazole synthesis of Davidson *et al*. [23]. The same author claimed that a wide range of polycyclic compounds have anti-inflammatory and some other activities [16,18–20]. This method has been recently improved using microwave irradiation [24,25].

We have extended our effort to the imidazo-derivatives general formulae **XII**, wherein an extra basic unit was introduced at the imidazole ring to improve physicochemical properties of this series of compounds (Fig. 4).




**XII** X = O, S, Y = H, Cl
n = 2, 3

**Figure 4.** Novel tetracyclic imidazole derivatives.

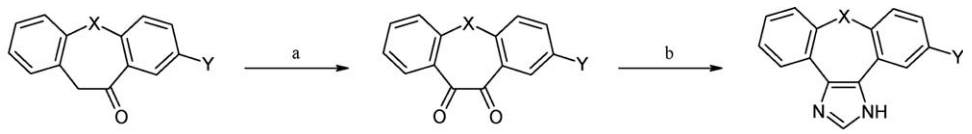
## RESULTS AND DISCUSSION

**Chemistry.** Tetracyclic imidazoles **3a–3d** were prepared starting from the known 11*H*-dibenzo[*b*,*f*]oxepin-10-ones **1a**, **1c** or 11*H*-dibenzo[*b*,*f*]thiepin-10-ones **1b**, **1d**, cyclic ketones characterized by activated methylene group in the α-position to carbonyl group [16–20]. This group was oxidized by selenium dioxide to give α-diketones **2a–2d.** Synthesis of imidazoles **3a–3d** was completed by condensation of dicarbonyl compounds **2a–2d** with paraformaldehyde and ammonium acetate in acetic acid, according to Davidson *et al*., Scheme 1 [23].

*N*-Alkylated compounds **4a–4f** were obtained from **3a**, **3b** using a modified method by Wolkenberg *et al*. [25], on treatment with sodium hydride in tetrahydrofuran at 0°C followed by alkylation at elevated temperatures, Scheme 2 [26].

We have used 2-trimethylsilyl-ethoxymethyl (SEM) as effective protecting group for imidazole N(1) atom

**Scheme 1**



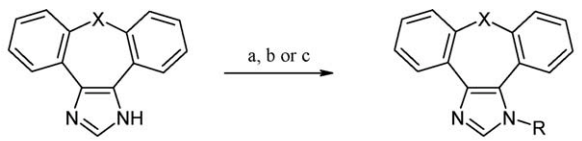
**1a** X = O, Y = H
**1b** X = S, Y = H
**1c** X = O, Y = Cl
**1d** X = S, Y = Cl

**2a** X = O, Y = H
**2b** X = S, Y = H
**2c** X = O, Y = Cl
**2d** X = S, Y = Cl

**3a** X = O, Y = H
**3b** X = S, Y = H
**3c** X = O, Y = Cl
**3d** X = S, Y = Cl

Reagents and conditions:
a. $SeO_2$/AcOH/reflux
b. $(HCHO)_n$/$NH_4OAc$/AcOH/reflux

**Scheme 2**



**3a** X = O
**3b** X = S

**4a** X = O, R = -$CH_3$
**4b** X = S, R = -$CH_3$
**4c** X = O, R = -$(CH_2)_2$Ph
**4d** X = S, R = -$(CH_2)_2$Ph
**4e** X = O, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**4f** X = S, R = -$CH_2O(CH_2)_2Si(CH_3)_3$

Reagents and conditions:
a. 1) NaH (60%)/THF/0 °C 2) $Br(CH_2)_2Ph$/reflux
b. 1) NaH (60%)/THF/0 °C 2) MeI/rt
c. 1) NaH (60%)/THF/0 °C 2) $ClCH_2O(CH_2)_2Si(CH_3)_3$/rt

which was introduced using (2-trimethylsilyl)-ethoxymethyl chloride (SEMCl) [27].

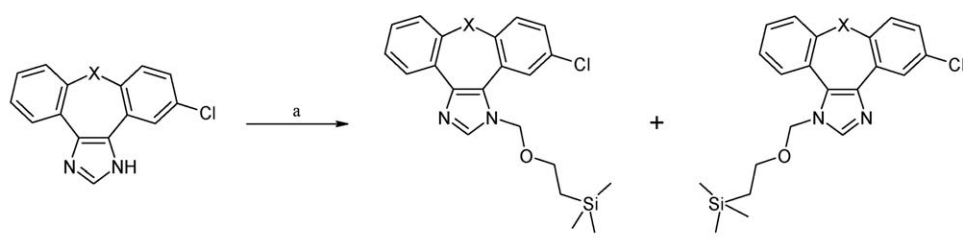
In the polycondensed imidazole derivatives **3a**, **3b** (Y = H) two tautomeric forms are equivalent and, therefore, single isomers **4a–4f** are obtained on alkylation. However, *N*(1)-alkylation of **3c**, **3d** affords structural isomers **5** and **6**, Scheme 3.

*N*-Trimethylsylil-ethoxymethylated compounds **5a**, **6a** and **5b**, **6b** were separated by purification on silica gel SPE cartridge using step gradient system for elution with ethyl acetate/*n*-hexane. In both cases, regioisomers **5a**, **6a** and **5b**, **6b** are obtained in ~1:1 ratio, revealing minor effect of electron-withdrawing chlorine in the *meta*-position of the aromatic ring. 1D NMR spectra of compounds in the isomeric series **5** and **6** did not give any clue on exact position of the side-chain on N(1) atom of imidazole. Straightforward determination required combined use of 2D NMR techniques and 1D selective ROESY spectrum, as exemplified for the compounds **5a** and **6a** (Fig. 5).

Correlation peaks from COSY, HMBC, HMQC, and 2D TPPI NOESY spectra afforded ambiguous information due to the overlap of key signals, so final solution for this problem came from the analysis of the selective 1D ROESY spectrum. Selective excitation was applied to methylenic protons of N—$CH_2$—O unit at 5.356 and 5.372 ppm. NOE interactions were expected between methylenic protons of N—$CH_2$—O group and *ortho*-protons in the vicinal aromatic ring, $H_B$ for **5a** and $H_A$ for **6a**, which are close enough to engage in dipolar interaction through space, (Fig. 6).

Protons $H_A$ and $H_B$ in both **5a** and **6a** have very close chemical shifts at the applied magnetic field, and are unequivocally assigned on the basis of their coupling patterns. Thus, $H_A$ is coupled with *ortho*- and *meta*-proton giving dd at 7.84 ppm, whereas $H_B$ is coupled only with *meta*-situated proton giving doublet at 7.86 ppm. On selective excitation of methylenic protons of N—$CH_2$—O unit in **6a** doublet of $H_B$ proton disappeared, while resonance lines for proton $H_A$ remained, revealing its vicinity to the methylenic group, and thus *syn* (*cis*) orientation of the side chain on N(1) of imidazole ring to the aromatic ring that has no chlorine in *meta*-position to the annulated heterocycle.

**Scheme 3**



**3c** X = O
**3d** X = S

**5a** X = O
**5b** X = S

**6a** X = O
**6b** X = S

Reagents and conditions:
a. 1) NaH (60%)/THF/0 °C 2) $ClCH_2O(CH_2)_2Si(CH_3)_3$/rt

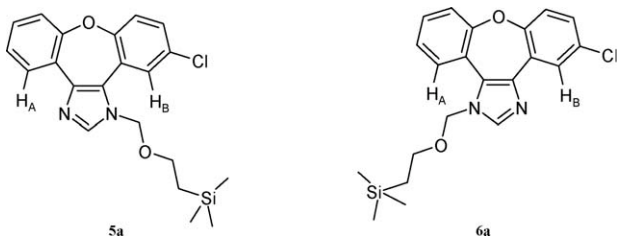



**Figure 5.** Regioisomeres determined by 2D NMR techniques and 1D selective ROESY spectrum.

Having this result in hands, ulterior synthetic steps have been performed on the separated isomers with known structure. From **4**, **5,** and **6** are obtained C(2) formylated derivatives **7** on generation of carbanion at C(2) of imidazole ring by *n*-butyllithium/tetrahydrofuran at −78°C, followed by treatment with DMF at r.t., Scheme 4 [9,28].

Reduction of **7a–7h** with sodium borohydride at r.t. afforded benzylic alcohols **8a–8h**. From **7i** and **7j** under the same conditions are obtained **8i** and **8j**. Both sets of hydroxymethyl imidazole derivatives are converted to dialkylaminoalkyl ethers **9a–9v** on treatment with ω-chloroalkyl-dimethylamines under phase transfer conditions in the presence of benzyltriethylammonium chloride (BTEAC), Scheme 5 [4,29].

Products **10a–10h** are obtained on cleavage of 2-(trimethylsilyl)ethoxymethyl group with 0.5*M* hydrochloric acid/methanol, Scheme 6 [9].

**Conformational properties of representative oxepin (8a) and thiepin (8b) tetracycles.** Conformational mobility and preferred conformation in solution of the 7-membered ring play an important role in biological activity of non-aromatic polycyclic compounds. Illustrative example represents octoclothepin **14** (Fig. 7), centrochiral, and planar-chiral compound with dibenzo-thiepine tricyclic core, wherein two conformers with inversed 7-membered ring are diastereotopic. An early study of (*S*)-**14** (Fig. 7), neuroleptic compound that binds on dopamine D-2 receptor [30], has revealed that stable conformation of (*S*)-**14**, which is responsible for the dopamine D-2 receptor antagonism, is significantly different from the one observed in the crystal [31].

On the other hand, conformational mobility of dibenzothiepines with sulfide **1b** and sulfoxide **15** unit in the bridge, was studied by dynamic NMR [32]. Huge difference in the activation energies for ring-inversion was observed; 9.3 kcal/mol for **1b** and 23 kcal/mol for **15**, revealing that at ambient temperature only the later may be separated into stable conformers (Fig. 8).

For many condensed non-aromatic heterocycles with one heteroatom in the 7-membered ring correlation between conformational properties and biological activities are studied. Detailed study of *N*-acylbenzazepines with interesting pharmacological properties [33], by dynamic NMR is an instructive case [34–36]. For dihydrobenz/*b*/azepines thermodynamic parameters for conformation equilibria are determined by dynamic NMR [37,38].

In view of the importance of conformational mobility of non-aromatic polycondensed heterocycles, we have determined difference in conformational mobility of the two representatives of oxepines and thiepines, compounds **8a** and **8b**, respectively. They are selected due

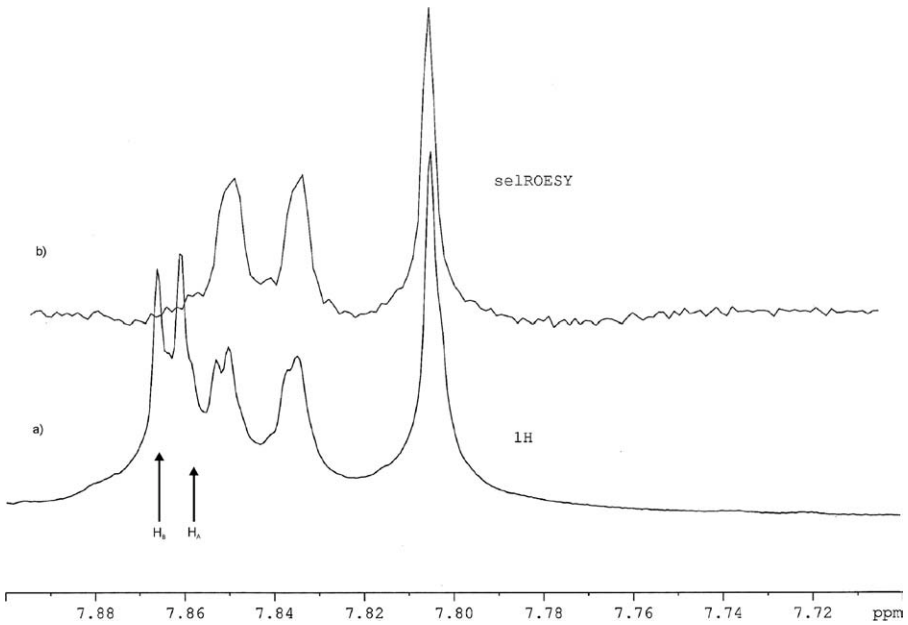
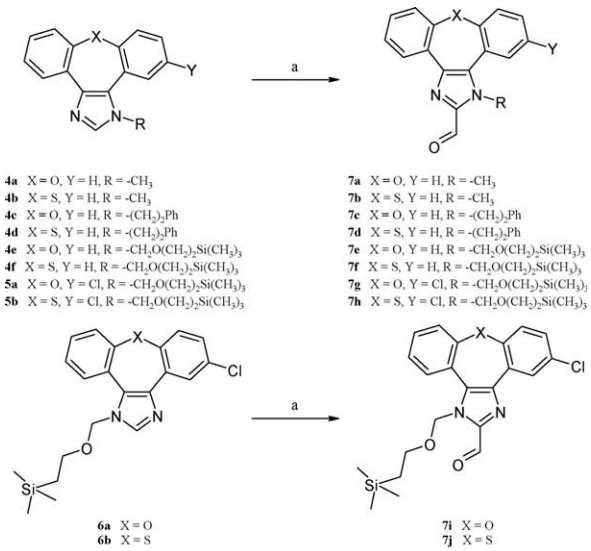



**Figure 6.** Comparison between aromatic region of $^1$H (a) and 1D selective ROESY (b) spectra of **6a**.

**Scheme 4**




**4a** X = O, Y = H, R = -$CH_3$
**4b** X = S, Y = H, R = -$CH_3$
**4c** X = O, Y = H, R = -$(CH_2)_2$Ph
**4d** X = S, Y = H, R = -$(CH_2)_2$Ph
**4e** X = O, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**4f** X = S, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**5a** X = O, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**5b** X = S, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$

**7a** X = O, Y = H, R = -$CH_3$
**7b** X = S, Y = H, R = -$CH_3$
**7c** X = O, Y = H, R = -$(CH_2)_2$Ph
**7d** X = S, Y = H, R = -$(CH_2)_2$Ph
**7e** X = O, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**7f** X = S, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**7g** X = O, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**7h** X = S, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$

**6a** X = O
**6b** X = S

**7i** X = O
**7j** X = S

Reagents and conditions:
a. 1) *n*-BuLi/THF/-78 °C 2) DMF/rt

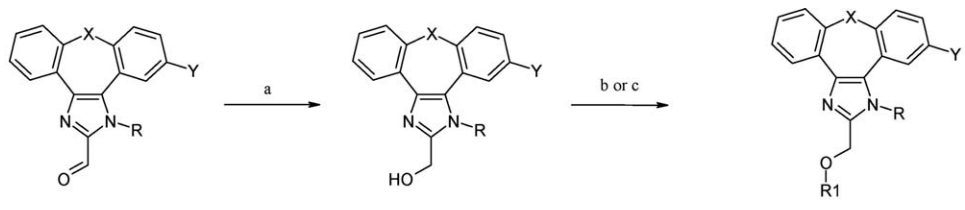
to their well resolved peaks for methylenic protons $H_A$, $H_B$, present in the 5-member chelate ring C(2)─$CH_AH_B$─O─H···N(3) formed by hydrogen bond to N(3) atom, formulae **8a**, **8b** (Fig. 9).

On the basis of the reported results, we expected notable difference of the energy for conformational inversion for these two compounds. To our satisfaction, dynamic NMR study has revealed two different temperature intervals for the collapse of the AB(X) system into $A_2$ system of the methylenic protons. Series of proton NMR spectra acquired in temperature range where the coalescence of proton signals occurs are shown in the Figures 10 and 11.

Activation energies (energy barriers for interconversion) for compounds **8a** and **8b** are determined and results are presented in Table 1.

**Biology.** Among many discovered biological targets in the past 30 years, TNF-α, interleukin 1 (IL-1), p38, and COX-2 enzyme belong to the group of the most studied and the most relevant mediators of

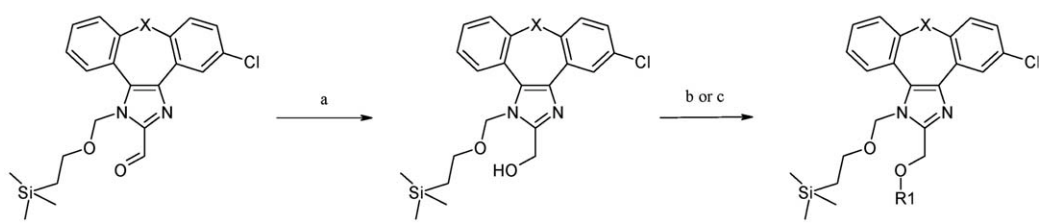
**Scheme 5**




**7a** X = O, Y = H, R = -$CH_3$
**7b** X = O, Y = H, R = -$(CH_2)_2$Ph
**7c** X = O, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**7d** X = S, R = -$CH_3$
**7e** X = S, Y = H, R = -$(CH_2)_2$Ph
**7f** X = S, Y = H R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**7g** X = O, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**7h** X = S, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$

**8a** X = O, Y = H, R = -$CH_3$
**8b** X = S, Y = H, R = -$CH_3$
**8c** X = O, Y = H, R = -$(CH_2)_2$Ph
**8d** X = S, Y = H, R = -$(CH_2)_2$Ph
**8e** X = O, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**8f** X = S, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**8g** X = O, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$
**8h** X = S, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$

**9a** X = O, Y = H, R = -$CH_3$, R1 = -$(CH_2)_2N(CH_3)_2$
**9b** X = O, Y = H, R = -$CH_3$, R1 = -$(CH_2)_3N(CH_3)_2$
**9c** X = S, Y = H, R = -$CH_3$, R1 = -$(CH_2)_2N(CH_3)_2$
**9d** X = S, Y = H, R = -$CH_3$, R1 = -$(CH_2)_3N(CH_3)_2$
**9e** X = O, Y = H, R = -$(CH_2)_2$Ph, R1 = -$(CH_2)_2N(CH_3)_2$
**9f** X = O, Y = H, R = -$(CH_2)_2$Ph, R1 = -$(CH_2)_3N(CH_3)_2$
**9g** X = S, Y = H, R = -$(CH_2)_2$Ph, R1 = -$(CH_2)_2N(CH_3)_2$
**9h** X = S, Y = H, R = -$(CH_2)_2$Ph, R1 = -$(CH_2)_3N(CH_3)_2$
**9i** X = O, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, R1 = -$(CH_2)_2N(CH_3)_2$
**9j** X = O, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, R1 = -$(CH_2)_3N(CH_3)_2$
**9k** X = S, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9l** X = S, Y = H, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, $R_1$ = -$(CH_2)_3N(CH_3)_2$
**9m** X = O, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9n** X = O, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, $R_1$ = -$(CH_2)_3N(CH_3)$
**9o** X = S, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9p** X = S, Y = Cl, R = -$CH_2O(CH_2)_2Si(CH_3)_3$, $R_1$ = -$(CH_2)_3N(CH_3)$



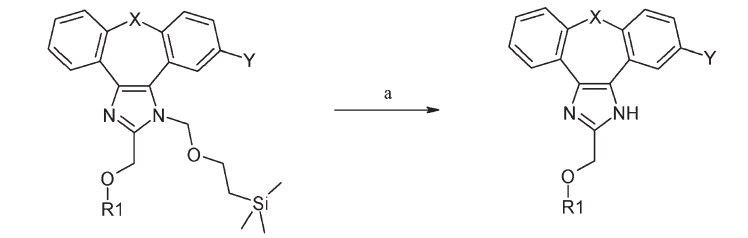

**7i** X = O
**7j** X = S

**8i** X = O
**8j** X = S

**9r** X = O, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9s** X = O, $R_1$ = -$(CH_2)_3N(CH_3)_2$
**9t** X = S, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9v** X = S, $R_1$ = -$(CH)_3N(CH_3)_2$

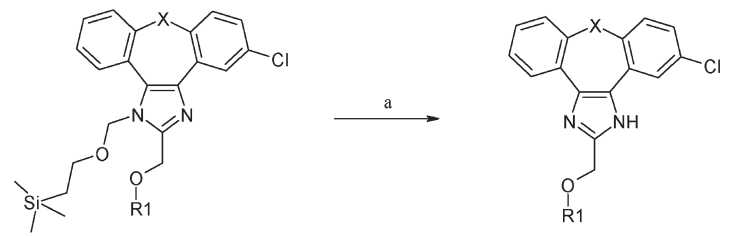
Reagents and conditions:
a. $NaBH_4$/MeOH, DCM/rt
b. $ClCH_2CH_2N(CH_3)_2$ HCl/40% NaOH/BTEAC/Toluene/109 °C
c. $ClCH_2CH_2CH_2N(CH_3)_2$ HCl/40% NaOH/BTEAC/Toluene/109 °C

**Scheme 6**



**9i** X = O, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
**9j** X = O, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
**9k** X = S, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
**9l** X = S, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
**9m** X = O, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
**9n** X = O, Y = Cl, R1 = -$(CH_2)_3N(CH_3)$
**9o** X = S, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
**9p** X = S, Y = Cl, R1 = -$(CH_2)_3N(CH_3)_2$

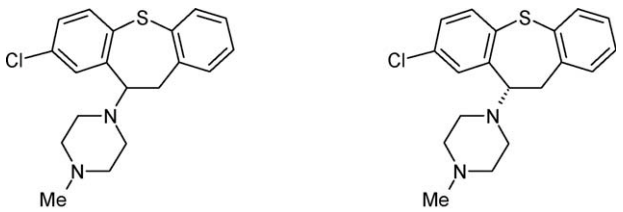
**10a** X = O, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
**10b** X = O, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
**10c** X = S, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
**10d** X = S, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
**10e** X = O, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
**10f** X = O, Y = Cl, R1 = -$(CH_2)_3N(CH_3)$
**10g** X = S, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
**10h** X = S, Y = Cl, R1 = -$(CH_2)_3N(CH_3)_2$



**9r** X = O, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9s** X = O, $R_1$ = -$(CH_2)_3N(CH_3)_2$
**9t** X = S, $R_1$ = -$(CH_2)_2N(CH_3)_2$
**9v** X = S, $R_1$ = -$(CH)_3N(CH_3)_2$

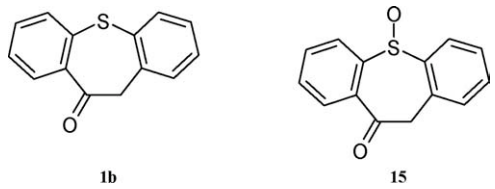
**10e** X = O, R1 = -$(CH_2)_2N(CH_3)_2$
**10f** X = O, R1 = -$(CH_2)_3N(CH_3)$
**10g** X = S, R1 = -$(CH_2)_2N(CH_3)_2$
**10h** X = S, R1 = -$(CH_2)_3N(CH_3)_2$

Reagents and conditions:
a. 0.5 *M* HCl in MeOH/MeOH/reflux



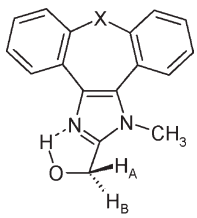
**14** (*S*)-**14**

**Figure 7.** Octoclothepin and its (*S*)-conformer.



**1b** **15**

**Figure 8.** Dibenzothiepines with sulfide and sulfoxide unit in the bridge.



**8a** X = O
**8b** X = S

**Figure 9.** Methylenic protons $H_A$ and $H_B$ in the 5-membered chelate ring.

inflammation [39]. Overproduction inhibition of these cytokines which are responsible for inflammation has been proposed as a disease modifying approach towards the treatment of inflammatory disorders. The over-expression of TNF-α cytokine has been implicated in a number of serious inflammatory disorders. Consequently, agents that inhibit the production of TNF-α can decrease levels of inflammatory response, and thereby reduce inflammation and prevent further tissue destruction.

From medicinal chemistry point of view, connecting previous knowledge about anti-inflammatory properties of some compounds with today's understanding of important key players in inflammation mechanism could provide rational approach to the lead molecules that may be further optimized for better activity and

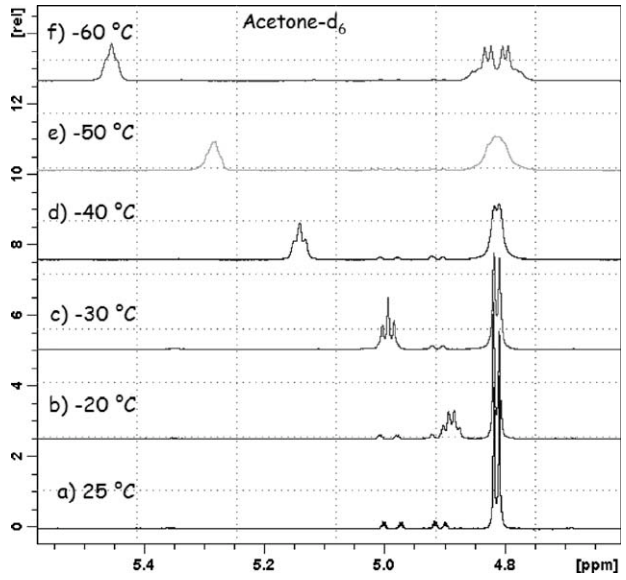



**Figure 10.** $^1$H NMR spectra of **8a** acquired in acetone-$d_6$ in the temperature intervals from 25°C to −60°C (coalescence range for the $H_A$ and $H_B$ protons signals).

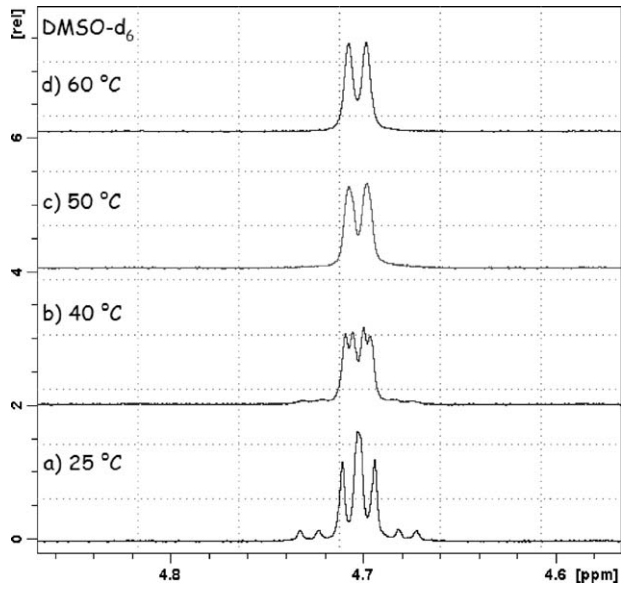



**Figure 11.** $^1$H NMR spectra of **8b** acquired in DMSO-$d_6$ in the temperature intervals from 25°C to 60°C (coalescence range for the $H_A$ and $H_B$ protons signals).

selectivity profile and desirable pharmacokinetic properties. Along this line we have continued our project of the synthesis of tetracyclic target structures and their testing on inhibition of LPS stimulated TNF-α production. *In vitro* biological tests are performed on some intermediates and all tetracyclic compounds **9** and **10** to test their ability to inhibit TNF-α production in LPS-activated hPBMC assay [5,6].

**Table 1**

Activation energies for compounds **8a** and **8b**.

| Compound | **8a** | **8b** |
|---|---|---|
| Solvent | Acetone-$d_6$ | DMSO-$d_6$ |
| Starting temperature (°C) | 25 | 25 |
| Ending temperature (°C) | −60 | 80 |
| Coalescence temperature $T_C$ (°C) | −40 | 50 |
| Separation between signals Δν (Hz) | 17.3 | 4.9 |
| Coupling constant $^2J_{A,B}$ (Hz) | 13.1 | 13.1 |
| Rate constant at the coalescence temperature $k_C$ (Hz) | 80.9 | 72.1 |
| Gibbs energy $\Delta G_C^{\ddagger}$ (kcal/mol) | 11.5 | 16.2 |

$^{\ddagger}$ Activated complex, transition state.

Compounds possessing alkoxymethylene linker (ether) at position C(2) on imidazole ring showed potency to inhibit TNF-α production *in vitro* in low micromolar range with IC50 values for the most potent compounds in the range of 1–3 μ*M*.

According to obtained results dibenzo-oxepin- and dibenzo-thiepin imidazole derivatives were recognized as a novel class of tetracyclic compounds with anti-inflammatory activity through specific inhibition of TNF-α secretion.

## EXPERIMENTAL

**Chemistry.** Commercial reagents were used as received without additional purification. All used chemicals and solvents were p.a. purity. Differential scanning calorimetry data were collected on a Mettler Toledo differential scanning calorimeter 822$^e$/500 using Mettler Toledo STAR$^e$ software. Samples about 5 mg were weighed into Al-pans (40 μL) with pierced cover. Dry nitrogen was used as purge gas (purge: 50 mL/min). The heating rate of 10°C/min over the range 25–300°C was used. The instrument was calibrated using certified indium and zinc. IR spectra were recorded as potassium bromide (KBr) pastilles or as a film on a sodium chloride plate, on a Nicolet Magna IR 760 FT IR-spectrophotometer, and on a Bruker Vertex 70 as ATR (ZnSe) powder or film cast from DCM solution. One- and two-dimensional NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz), Bruker Avance DRX 500 (500 MHz), and Bruker Avance III 600 (600 MHz) spectrometers. Deuterated dimethylsulfoxide (DMSO-$d_6$) and deuterated chloroform ($CDCl_3$) were used as solvents and tetramethylsilan (TMS) as an internal standard. Purity of the compounds was obtained on a Waters HPLC-UV/MS Autopurification System with a Micromass ZQ and a Waters 996 Photodiode Array Detector, and on Varian Chrompack CP-3800 Gas Chromatograph with a Varian Chrompack Saturn 2000 MS/MS detector. HRMS data were acquired using Q-TOF 2 Waters system. Thin layer chromatography (TLC) was run on Merck Silica gel 60 $F_{254}$ plates, spots detected with UV light at 254 and/or 365 nm. Proportions of solvents used for TLC are by volume.

Products were purified using Solid Phase Extraction (SPE) columns on an automated SPE purification system (FlashMaster II).

**General procedure for reaction of ketones 1 with selenium dioxide (preparation of compounds 2).** To the suspension of selenium dioxide (1.74 g, 15.70 mmol) in glacial acetic acid (10 mL) was added a solution of ketone **1** (14.3 mmol) in glacial acetic acid (30 mL). The suspension was heated for 2 h at 100°C and undissolved material filtered off. The filtrate was diluted with water (50 mL) and extracted with dichloromethane (2 × 50 mL). Organic extracts were washed with water (3 × 50 mL), and saturated sodium hydrogencarbonate (3 × 50 mL), dried over anhydrous sodium sulfate, concentrated, and then precipitated from *n*-hexane/dichloromethane to give compound **2**.

***Dibenzo[*b,f*]oxepin-10,11-dione (2a).*** Obtained from **1a** as a yellow solid: Yield 85%; mp 116.68°C; IR (KBr): 1670, 1600, 1469, 1447, 1281, 1220, 926, 771 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.35 (td, $J$ = 7.55, 1.07 Hz, 2H), 7.42–7.43 (m, 1H), 7.43–7.45 (m, 1H), 7.64–7.68 (m, 2H), 7.99 (d, $J$ = 1.83 Hz, 1H), 8.00 ppm (d, $J$ = 1.83 Hz, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$): δ 121.60, 125.50, 126.11, 131.71, 135.83, 156.65, 186.31 ppm; MS: $m/z$ 225.00 $[M+H]^+$.

***Dibenzo[*b,f*]thiepin-10,11-dione (2b).*** Obtained from **1b** as a yellow solid: Yield 80%; mp 122.69°C; IR (KBr): 1675, 1581, 1435, 1280, 1258, 1219, 916, 760 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.31–7.37 (m, 4H), 7.51 (dd, $J$ = 7.63, 1.53 Hz, 2H), 7.69 ppm (dd, $J$ = 7.17, 1.98 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 129.23, 131.26, 132.09, 132.98, 134.55, 139.35, 190.62 ppm; MS: $m/z$ 240.09 $[M+H]^+$.

***2-Chlorodibenzo[*b,f*]oxepin-10,11-dione (2c).*** Obtained from **1c** as a yellow solid: Yield 74%; mp 103.23°C; IR (KBr): 1691, 1673, 1599, 1467, 1449, 1402, 1290, 1266, 1224, 1118, 842, 765 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.35–7.44 (m, 3H), 7.60 (dd, $J$ = 8.70, 2.59 Hz, 1H), 7.65–7.70 (m, 1H), 7.95–8.01 ppm (m, 2H); $^{13}C$ NMR (126 MHz, $CDCl_3$): δ 156.42, 136.01, 135.74, 131.87, 131.10, 130.89, 125.87, 123.36, 121.52 ppm; MS: $m/z$ 259.1 $[M+H]^+$.

***2-Chlorodibenzo[*b,f*]thiepin-10,11-dione (2d).*** Obtained from **1d** as a yellow solid: Yield 79%; mp 167.94°C; IR (KBr): 1689, 1583, 1274, 1213, 1094, 829, 761 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.40–7.52 (m, 3H), 7.56–7.65 (m, 2H), 7.77 (d, $J$ = 2.14 Hz, 1H), 7.80 ppm (dd, $J$ = 7.02, 1.83 Hz, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$): δ 129.78, 131.25, 131.65, 132.44, 133.08, 133.21, 133.41, 133.73, 134.21, 135.92, 139.49, 140.76, 189.21, 189.83 ppm; MS: $m/z$ 275.0 $[M+H]^+$.

**General procedure for reaction of diketones 2 with paraformaldehyde (preparation of compounds 3).** A suspension of compound **2** (5.35 mmol), ammonium acetate (4.13 g, 53.5 mmol), and paraformaldehyde (0.19 g, 5.0 mmol) in glacial acetic acid (32 mL) was heated to reflux. After 2 h, reaction mixture was cooled, diluted with water (100 mL), and extracted with ethyl acetate (2 × 50 mL). Organic extracts were washed with water (3 × 100 mL), saturated sodium hydrogencarbonate (3 × 100 mL), and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and then purified on silica gel SPE cartridge using step gradient system for elution dichloromethane/(dichloromethane/methanol/ammonium hydroxide 90:9:1.5) to give compound **3**.

***1*H*-Dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (3a).*** Obtained from **2a** as a white solid: Yield 81%; mp 234.05°C; IR (KBr): 3286, 2941, 2871, 1730, 1165, 1096, 856 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 7.27 (d, $J$ = 4.88 Hz, 2H), 7.32 (br. s., 2H), 7.37 (br. s., 2H), 7.55 (d, $J$ = 7.02 Hz, 1H), 7.76 (d, $J$ = 6.71 Hz, 1H), 7.96 (s, 1H), 12.92 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 121.48, 122.63, 126.44, 127.08, 127.36, 132.06, 136.66, 155.30 ppm; HRMS: $m/z$ calcd. for $C_{15}H_{11}N_2O$: 235.0871 $[M+H]^+$, found 235.0865.

***1*H*-Dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (3b).*** Obtained from **2b** as a yellow solid: Yield 75%; mp 263.23°C; IR (KBr): 2815, 2641, 1511, 1478, 953, 758, 651 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 7.37 (t, $J$ = 7.17 Hz, 2H), 7.44 (t, $J$ = 7.32 Hz, 2H), 7.59 (br. s., 3H), 7.81 (br. s., 1H), 7.99 (s, 1H), 12.92 ppm (br. s., 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 136.85, 133.60, 132.60, 132.17, 131.63, 130.90, 128.75, 128.35, 127.65, 126.85 ppm; HRMS: $m/z$ calcd. for $C_{15}H_{11}N_2S$: 251.0638 $[M+H]+$, found 251.0630.

***11-Chloro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (3c).*** Obtained from **2c** as a beige amorphous solid: Yield 84%; IR (KBr): 3113, 14785, 953, 758, 651 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$): δ 7.29 (dt, $J$ = 7.76, 3.97 Hz, 1H), 7.33–7.45 (m, 4H), 7.66 (br. s., 2H), 8.00 (s, 1H), 13.00 ppm (br. s., 1H), $^{13}C$ NMR (151 MHz, DMSO-$d_6$): δ 153.81, 152.60, 137.92, 129.36, 125.58, 123.37 ppm; HRMS: $m/z$ calcd. for $C_{15}H_{10}ClN_2O$: 269.0482 $[M+H]^+$, found 269.0468.

***11-Chloro-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (3d).*** Obtained from **2d** as a yellow solid: Yield 68%; mp 241.28°C; IR (KBr): 2806, 2639, 1475, 768, 649 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 7.33–7.53 (m, 3H), 7.53–7.67 (m, 3H), 7.78 (br. s., 1H), 8.04 (s, 1H), 13.03 ppm (d, $J$ = 13.73 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 127.23, 127.48, 128.26, 129.55, 129.72, 130.00, 130.85, 131.02, 133.23, 133.31, 133.79, 133.97, 135.90, 137.76, 138.30 ppm; HRMS: $m/z$ calcd. for $C_{15}H_{10}ClN_2S$: 285.0253 $[M+H]^+$, found 285.0245.

**General procedures for *N*-alkylation of the compounds 3 (preparation of compounds 4).** **N-*Methylation.*** To a solution of **3** (0.5 g, 2.13 mmol) in dry tetrahydrofuran (23 mL) the 60% suspension of NaH in mineral oil (0.26 g, 6.4 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then MeI (0.13 mL, 2.13 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Then it was concentrated, diluted with water (100 mL), and extracted with dichloromethane (3 × 50 mL). The organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution dichloromethane/(dichloromethane/methanol/ammonium hydroxide 90:5:0.5) *N*-methylated compounds **4a** and **4b** were isolated.

***1-Methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (4a).*** Obtained from **3a** as a yellowish solid: Yield 73%; mp 138.05°C; IR (KBr): 1514, 1444, 1248, 1201, 810, 765, 733 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 3.91 (s, 3H), 7.26 (ddd, $J$ = 7.55, 6.49, 2.14 Hz, 1H), 7.29–7.38 (m, 3H), 7.39–7.44 (m, 1H), 7.45–7.48 (m, 1H), 7.66 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.71–7.74 (m, 1H), 7.94 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 33.62, 121.47, 122.63, 123.27, 125.78, 125.85, 126.65, 126.72, 126.83, 128.20, 129.20, 129.65, 137.54, 141.60, 155.79, 155.89 ppm; HRMS: $m/z$ calcd. for $C_{16}H_{13}N_2O$: 249.1028 $[M+H]^+$, found 249.1019.

***1-Methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (4b).*** Obtained from **3b** as a yellowish solid: Yield 94%; mp 137.12°C; IR (KBr): 3051, 2922, 1510, 1467, 773, 758, 741,

643 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 3.83 (s, 3H), 7.33–7.37 (m, 1H), 7.40–7.50 (m, 3H), 7.57 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.64 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.70 (dd, $J$ = 7.48, 1.37 Hz, 1H), 7.78 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.97 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 33.49, 128.23, 128.37, 128.78, 129.15, 129.26, 130.57, 132.50, 133.16, 133.84, 134.16, 138.41, 140.73, 141.29 ppm; HRMS: *m/z* calcd. for $C_{16}H_{13}N_2S$: 265.0799 $[M+H]^+$, found 265.0791.

**N-*Phenylethylation.*** To a solution of **3** (0.2 g, 0.85 mmol) in dry tetrahydrofuran (7 mL) the 60% suspension of sodium hydride in mineral oil (0.10 g, 2.56 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then 2-phenylethyl bromide (0.17 mL, 1.28 mmol) was added and reaction mixture was heated under stirring and reflux. After 2 h, another portion of the 60% suspension of sodium hydride in mineral oil (0.03 g, 0.85 mmol) and 2-phenylethyl bromide (0.12 mL, 0.85 mmol) were added and stirring under reflux was continued. After 1 day, another portion of the 60% suspension of sodium hydride in mineral oil (0.03 g, 0.85 mmol) and 2-phenylethyl bromide (0.12 mL, 0.85 mmol) were added and stirring under reflux was continued for 1 day. Then it was cooled to room temperature, concentrated, and diluted with water (50 mL) and extracted with dichloromethane (3 × 30 mL). The organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution *n*-hexane/ethyl acetate *N*-phenylethylated compounds **4c** and **4d** were isolated.

***1-(2-Phenylethyl)-1*H-*dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (4c).*** Obtained from **3a** as a yellowish amorphous solid: Yield 64%; IR (KBr): 1509, 1443, 1201, 1079, 809, 762, 741, 696 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 3.02 (t, $J$ = 7.48 Hz, 2H), 4.55 (t, $J$ = 7.48 Hz, 2H), 7.13–7.17 (m, 2H), 7.17–7.22 (m, 1H), 7.23–7.28 (m, 3H), 7.30–7.39 (m, 3H), 7.40–7.45 (m, 1H), 7.46–7.49 (m, 1H), 7.64–7.72 (m, 2H), 7.89 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 36.10, 47.44, 121.43, 122.69, 123.49, 125.75, 126.02, 126.07, 126.31, 126.82, 126.95, 128.13, 128.80, 128.99, 129.26, 129.72, 137.93, 138.02, 141.15, 155.81, 156.10 ppm; HRMS: *m/z* calcd. for $C_{23}H_{19}N_2O$: 339.1497 $[M+H]^+$, found 339.1496.

***1-(2-Phenylethyl)-1*H-*dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (4d).*** Obtained from **3b** as a white solid: Yield 79%; mp 156.93°C; IR (KBr): 3049, 3022, 2939, 1505, 756, 740, 658 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.79–2.95 (m, 2H), 4.36–4.45 (m, 1H), 4.58 (ddd, $J$ = 13.73, 7.78, 5.34 Hz, 1H), 7.05–7.09 (m, 2H), 7.14–7.24 (m, 3H), 7.32–7.37 (m, 1H), 7.39–7.45 (m, 2H), 7.48 (td, $J$ = 7.55, 1.37 Hz, 1H), 7.58 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.64 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.71 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.75 (dd, $J$ = 7.93, 1.53 Hz, 1H), 7.85 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 36.15, 47.36, 126.86, 127.97, 128.30, 128.73, 128.78, 128.99, 129.13, 129.31, 129.84, 132.50, 132.84, 133.59, 133.87, 134.39, 137.96, 138.32, 140.28, 141.84 ppm; HRMS: *m/z* calcd. for $C_{23}H_{19}N_2S$: 355.1269 $[M+H]^+$, found 355.1273.

**N-*Trimethylsylil-ethoxymethylation.*** To a solution of **3** (0.5 g, 2.13 mmol) in dry tetrahydrofuran (23 mL) the 60% suspension of sodium hydride in mineral oil (0.26 g, 6.40 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then 2-(trimethylsilyl)ethoxymethyl chloride (0.38 mL, 2.13 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Then it was concentrated, diluted with water (100 mL), and extracted with dichloromethane (3 × 50 mL). The organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution ethyl acetate/*n*-hexane *N*-trimethylsylil-ethoxymethylated compounds **4e** and **4f** were isolated.

***1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H-*dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (4e).*** Obtained from **3a** as a yellowish solid: Yield 60%; mp 98.50°C; IR (KBr): 1513, 1250, 1244, 1080, 838, 766 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.93–0.98 (m, 2H), 3.68–3.73 (m, 2H), 5.57 (s, 2H), 7.29–7.36 (m, 2H), 7.39–7.42 (m, 2H), 7.44–7.52 (m, 2H), 7.78 (ddd, $J$ = 7.48, 1.22, 1.07 Hz, 1H), 7.91 (dd, $J$ = 7.93, 1.53 Hz, 1H), 8.22 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.03, 17.58, 65.96, 74.46, 121.50, 122.66, 123.16, 125.83, 125.98, 126.76, 126.94, 127.14, 127.92, 129.52, 130.04, 137.99, 141.99, 156.01, 156.09 ppm; HRMS: *m/z* calcd. for $C_{21}H_{25}N_2O_2Si$: 365.1685 $[M+H]^+$, found 365.1660.

***1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H-*dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (4f).*** Obtained from **3b** as a yellowish solid: Yield 79%; mp 104.47°C; IR (KBr): 2955, 1504, 1248, 1083, 863, 835, 776, 763 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.85–0.97 (m, 2H), 3.55 (td, $J$ = 9.54, 6.56 Hz, 1H), 3.69 (td, $J$ = 9.46, 6.71 Hz, 1H), 5.46 (d, $J$ = 11.29 Hz, 1H), 5.66 (d, 1H), 7.41–7.46 (m, 1H), 7.47–7.55 (m, 3H), 7.64 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.75–7.79 (m, 1H), 7.85 (dd, $J$ = 7.93, 1.22 Hz, 2H), 8.27 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.61, 66.02, 74.52, 128.46, 128.70, 129.06, 129.20, 129.27, 129.61, 130.49, 132.51, 132.61, 133.45, 133.90, 134.50, 138.08, 141.16, 141.69 ppm; HRMS: *m/z* calcd. for $C_{21}H_{25}N_2OSSi$: 381.1451 $[M+H]^+$, found 381.1436.

**General procedure for *N*-trimethylsylil-ethoxymethylation of the compounds 3 (preparation of structural isomers 5 and 6).** To a solution of **3** (1.0 g, 3.72 mmol) in dry tetrahydrofuran (30 mL) the 60% suspension of sodium hydride in mineral oil (0.45 g, 11.20 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then 2-(trimethylsilyl)ethoxymethyl chloride (0.66 mL, 3.72 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Then it was concentrated, diluted with water (30 mL), and extracted with dichloromethane (3 × 25 mL). The organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution ethyl acetate/*n*-hexane structural isomers **5** and **6** were isolated.

***11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H-*dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (5a).*** Obtained from **3c** as a yellowish solid: Yield 31%; mp 84.67°C; IR (KBr): 3093, 2957, 1515, 1245, 1200, 1077, 833, 768 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.96 (t, $J$ = 7.9 Hz, 2H), 3.72 (t, $J$ = 8.0 Hz, 2H), 5.56 (s, 2H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H), 7.77 (d, $J$ = 7.0 Hz, 1H), 7.96 (d, $J$ = 1.8 Hz, 1H), 8.25 ppm (s, 1H) $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ−1.04, 17.58, 66.04, 74.55, 122.69, 122.80, 123.46, 126.04, 126.28, 127.27, 127.47, 129.07, 129.74, 129.94, 130.37, 136.67, 142.32, 154.50, 155.78 ppm ; HRMS: *m/z* calcd. for $C_{21}H_{24}N_2O_2SiCl$: 399.1296 $[M+H]^+$, found 399.1281.

***11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H-*dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (5b).*** Obtained from **3d** as

a yellowish solid: Yield 33%; mp 117.74°C; IR (KBr): 2976, 2940, 1738, 1621, 1456, 1381, 1169, 1074, 1014, 732 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$): δ 0.00 (m, 9H), 0.932 (m, 2H), 3.60 (td, $J$ = 9.7, 6.4 Hz, 1H), 3.71 (td, $J$ = 9.7, 6.5 Hz, 1H), 5.41 (d, $J$ = 11.3 Hz, 1H), 5.63 (d, $J$ = 11.3 Hz, 1H), 7.43 (ddd, $J$ = 7.6, 7.5, 1.5 Hz, 1H), 7.50 (td, $J$ = 7.5, 1.3 Hz, 1H), 7.53 (dd, $J$ = 8.3, 2.4 Hz, 1H), 7.62 (dd, $J$ = 7.8, 1.0 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.83 (dd, $J$ = 7.7, 1.2 Hz, 1H), 7.95 (d, $J$ = 2.3 Hz, 1H), 8.28 ppm (s, 1H); $^{13}C$ NMR (151 MHz, DMSO-$d_6$): δ −0.01, 18.67, 67.04, 75.52, 129.00, 129.61, 130.20, 130.28, 130.38, 130.43, 133.55, 134.00, 134.08, 135.18, 135.36, 136.37, 138.88, 142.55, 143.45 ppm ; HRMS: *m/z* calcd. for $C_{21}H_{24}N_2OSClSi$: 415.1067 $[M+H]^+$, found 415.1067.

***5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazole (6a).*** Obtained from **3c** as a yellowish solid: Yield 47%; mp 93.25°C; IR (KBr): 2950, 1514, 1246, 1094, 1074, 834, 811 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (m, 9H), 0.96 (t, $J$ = 7.9 Hz, 2H), 3.72 (t, $J$ = 8.0 Hz, 2H), 5.56 (s, 2H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H), 7.77 (d, $J$ = 7.0 Hz, 1H), 7.96 (d, $J$ = 1.8 Hz, 1H), 8.25 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −0.98, 17.57, 66.03, 74.42, 121.50, 124.37, 124.95, 125.53, 126.11, 126.45, 127.06, 127.56, 129.53, 129.86, 130.17, 138.80, 142.44, 154.55, 155.76 ppm ; HRMS: *m/z* calcd. for $C_{21}H_{24}N_2O_2SiCl$: 399.1296 $[M+H]^+$, found 399.1289.

***5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazole (6b).*** Obtained from **3d** as a yellowish solid: Yield 49%; mp 113.80°C; IR (KBr): 3098, 2950, 1583, 1505, 1407, 1330, 1263, 1249, 1091, 1083, 1071, 1019, 859, 838, 810, 767, 638 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.91 (m, 2H), 3.55 (td, $J$ = 9.6, 6.7 Hz, 1H), 3.69 (td, $J$ = 9.5, 6.8 Hz, 1H), 5.48 (d, $J$ = 11.3 Hz, 1H), 5.67 (d, $J$ = 11.3 Hz, 1H), 7.50 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.53 (m, 1H), 7.55 (m, 1H), 7.66 (d, $J$ = 8.4 Hz, 1H), 7.77 (m, 1H), 7.81 (d, $J$ = 2.4 Hz, 1H), 7.87 (m, 1H), 8.31 ppm (s, 1H); $^{13}C$ NMR (151 MHz, DMSO-$d_6$): δ 0.00, 18.67, 67.16, 75.69, 128.73, 129.81, 129.88, 130.62, 130.99, 132.24, 133.21, 133.45, 134.96, 135.04, 135.08, 135.22, 140.88, 141.49, 142.55 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_2OSClSi$: 415.1067 $[M+H]^+$, found 415.1053.

**General procedure for C(2) formylation of the compounds 4, 5, and 6 (preparation of compounds 7).** To a solution of **4** (0.44 g, 1.77 mmol) in dry tetrahydrofuran (8 mL) 1.6*M* solution of *n*-butyllithium in *n*-hexane (1.22 mL, 1.95 mmol) was added under stirring at −78°C. The reaction mixture was stirred for 15 min at −78°C, then dry DMF (0.17 mL, 2.13 mmol) was added and reaction mixture was stirred at room temperature for 1 h. Then it was diluted with water (50 mL) and extracted with dichloromethane (3 × 30 mL). The organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, evaporated, and then purified on silica gel SPE cartridge using step gradient system for elution *n*-hexane/dichloromethane to give compound **7**.

***1-Methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazole-2-carbaldehyde (7a).*** Obtained from **4a** as a yellow solid: Yield 74%; mp 161.69°C; IR (ATR): 2921, 2849, 1681, 1511, 1445, 1209, 800, 768, 745 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 4.17 (s, 3H), 7.31–7.41 (m, 2H), 7.44–7.46 (m, 2H), 7.55–7.57 (m, 2H), 7.74–7.80 (m, 1H), 7.83 (d, $J$ = 7.63 Hz, 1H), 9.88 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 34.48, 121.44, 121.73, 122.96, 126.13, 126.21, 126.75, 127.16, 128.33, 130.46, 131.64, 133.19, 139.34, 144.74, 156.88, 157.26, 182.69 ppm; HRMS: *m/z* calcd. for $C_{17}H_{13}N_2O_2$: 277.0977 $[M+H]^+$, found 277.0963.

***1-Methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazole-2-carbaldehyde (7b).*** Obtained from **4b** as a yellow solid: Yield 52%; mp 215.10°C; IR (ATR): 2918, 2835, 1682, 1443, 825, 760 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 4.08 (s, 3H), 7.41–7.52 (m, 2H), 7.52–7.57 (m, 2H), 7.65 (dd, $J$ = 7.78, 1.37 Hz, 1H), 7.71–7.80 (m, 2H), 7.87 (dd, $J$ = 7.78, 1.68 Hz, 1H), 9.92 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 34.46, 128.63, 129.39, 129.58, 129.72, 129.85, 130.80, 130.89, 132.78, 134.26, 134.30, 135.74, 136.40, 137.03, 142.85, 143.76, 182.99 ppm; HRMS: *m/z* calcd. for $C_{17}H_{13}N_2OS$: 293.0749 $[M+H]^+$, found 293.0740.

***1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazole-2-carbaldehyde (7c).*** Obtained from **4c** as a yellowish solid: Yield 70%; mp 157.69°C; IR (ATR): 3062, 3025, 2821, 1674, 1508, 1449, 1421, 1202, 770, 743 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 3.03 (t, $J$ = 7.32 Hz, 2H), 4.90 (t, $J$ = 7.48 Hz, 2H), 7.07–7.11 (m, 2H), 7.15–7.24 (m, 3H), 7.33 (ddd, $J$ = 7.55, 6.03, 2.59 Hz, 1H), 7.38–7.49 (m, 3H), 7.49–7.57 (m, 2H), 7.75–7.82 (m, 2H), 9.82 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 36.41, 47.23, 121.64, 123.02, 126.17, 126.31, 126.72, 127.06, 127.29, 127.72, 128.79, 128.88, 130.51, 131.65, 132.70, 137.41, 139.83, 144.54, 157.18, 157.57 ppm, 182.55; HRMS: *m/z* calcd. for $C_{24}H_{19}N_2O_2$: 367.1447 $[M+H]^+$, found 367.1454.

***1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazole-2-carbaldehyde (7d).*** Obtained from **4d** as a yellowish solid: Yield 52%; mp 193.04°C; IR (ATR): 1684, 1421, 827, 748, 696 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.80–2.95 (m, 2H), 4.74 (dt, $J$ = 14.04, 7.02 Hz, 1H), 5.04 (dt, $J$ = 14.11, 7.13 Hz, 1H), 6.95–6.99 (m, 2H), 7.12–7.17 (m, 3H), 7.42 (td, $J$ = 7.55, 1.68 Hz, 1H), 7.46–7.57 (m, 3H), 7.62 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.72–7.77 (m, 2H), 7.83 (dd, $J$ = 7.48, 1.68 Hz, 1H), 9.81 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 36.48, 46.88, 126.91, 128.68, 128.72, 128.89, 129.29, 129.51, 129.71, 130.69, 131.12, 132.71, 132.77, 134.26, 134.90, 136.03, 136.38, 136.97, 137.30, 143.46, 182.82 ppm; HRMS: *m/z* calcd. for $C_{24}H_{19}N_2OS$: 383.1218 $[M+H]^+$, found 383.1229.

***1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazole-2-carbaldehyde (7e).*** Obtained from **4e** as a white solid: Yield 78%; mp 83.24°C; IR (ATR): 952, 1686, 1507, 1450, 1430, 1240, 1211, 1082, 856, 832, 801, 762, 691 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.93–0.98 (m, 2H), 3.73–3.79 (m, 2H), 5.93 (s, 2H), 7.36–7.46 (m, 2H), 7.49–7.57 (m, 2H), 7.57–7.65 (m, 2H), 7.87–7.96 (m, 1H), 7.96–8.04 (m, 1H), 9.97 ppm (s, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.71, 66.45, 73.60, 121.51, 121.71, 123.04, 126.26, 126.35, 126.51, 127.35, 128.47, 130.72, 132.01, 133.32, 139.67, 144.69, 157.02, 157.56, 182.76 ppm; HRMS: *m/z* calcd. for $C_{22}H_{25}N_2O_3Si$: 393.1634 $[M+H]^+$, found 393.1631.

***1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazole-2-carbaldehyde (7f).*** Obtained from **4f** as a yellowish solid: Yield 74%; mp 82.94°C; IR (ATR): 2951, 1687, 1445, 1420, 1083, 831, 760 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.88 (t, $J$ = 8.24 Hz, 2H), 3.51 (td, $J$ = 9.08, 7.78 Hz, 1H), 3.66 (td, $J$ = 9.08, 8.09 Hz, 1H), 5.87–5.93 (m, 1H), 5.93–6.00 (m, 1H), 7.53–7.63 (m,

2H), 7.63–7.66 (m, 2H), 7.75 (dd, $J$ = 7.78, 1.37 Hz, 1H), 7.86–7.95 (m, 2H), 7.97 (dd, $J$ = 7.63, 1.53 Hz, 1H), 10.04 ppm (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ −1.14, 17.58, 66.23, 73.80, 128.82, 129.61, 129.64, 129.97, 131.09, 131.11, 132.78, 134.31, 134.58, 136.05, 136.52, 136.70, 143.11, 143.79, 182.87 ppm; HRMS: *m/z* calcd. for $C_{22}H_{25}N_2O_2SiS$: 409.1406 $[M+H]^+$, found 409.1398.

***11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazole-2-carbaldehyde (7g).*** Obtained from **5a** as a yellowish solid: Yield 78%; mp 94.58°C; IR (ATR): 2952, 1684, 1449, 1215, 1073, 824, 772 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.94–0.99 (m, 2H), 3.74–3.80 (m, 2H), 5.90 (s, 2H), 7.37–7.42 (m, 1H), 7.49–7.54 (m, 2H), 7.61–7.68 (m, 2H), 7.87 (ddd, $J$ = 7.48, 1.22, 1.07 Hz, 1H), 8.08 (d, $J$ = 2.44 Hz, 1H), 9.96 ppm (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ −1.03, 17.76, 66.45, 73.50, 121.70, 123.34, 124.78, 126.22, 126.50, 127.44, 127.77, 130.49, 130.97, 131.49, 131.90, 140.12, 144.81, 156.01, 156.74, 182.96 ppm; HRMS: *m/z* calcd. for $C_{22}H_{24}N_2O_3SiCl$: 427.1245 $[M+H]^+$, found 427.1228.

***11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazole-2-carbaldehyde (7h).*** Obtained from **5b** as an amorphous yellowish solid: Yield 78%; IR (ATR): 2951, 1690, 1248, 1081, 832, 762 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.89–0.93 (m, 2H), 3.55–3.64 (m, 1H), 3.64–3.72 (m, 1H), 5.75 (d, $J$ = 10.68 Hz, 1H), 5.99 (d, $J$ = 10.68 Hz, 1H), 7.52–7.61 (m, 2H), 7.66–7.73 (m, 2H), 7.85 (d, $J$ = 8.54 Hz, 1H), 7.94 (dd, $J$ = 7.78, 1.37 Hz, 1H), 8.04 (d, $J$ = 2.44 Hz, 1H), 10.02 ppm (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ −1.09, 17.71, 66.21, 73.79, 128.93, 129.26, 129.84, 130.20, 130.74, 132.83, 132.88, 134.10, 134.45, 134.63, 135.05, 135.77, 136.53, 143.53, 143.88, 183.02 ppm; HRMS: *m/z* calcd. for $C_{22}H_{24}N_2O_2SiSCl$: 443.1016 $[M+H]^+$, found 443.1005.

***5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazole-2-carbaldehyde (7i).*** Obtained from **6a** as a yellowish solid: Yield 83%; mp 113.81°C; IR (ATR): 2946, 1688, 1238, 1211, 1083, 825, 773 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.92–0.99 (m, 2H), 3.72–3.79 (m, 2H), 5.92 (s, 2H), 7.43–7.49 (m, 1H), 7.54–7.59 (m, 2H), 7.59–7.67 (m, 2H), 7.83 (dd, $J$ = 2.29, 0.76 Hz, 1H), 8.01–8.05 (m, 1H), 9.96 ppm (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ –1.08, 17.71, 66.51, 73.70, 121.23, 123.07, 123.70, 126.51, 126.63, 128.32, 128.55, 130.29, 130.33, 132.26, 133.73, 138.24, 144.82, 155.53, 157.19, 182.77 ppm; HRMS: *m/z* calcd. for $C_{22}H_{24}N_2O_3ClSi$: 427.1245 $[M+H]^+$, found 427.1229.

***5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazole-2-carbaldehyde (7j).*** Obtained from **6b** as an amorphous yellowish solid: Yield 62%; IR (ATR): 2950, 1688, 1434, 1247, 1084, 833, 767 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.85–0.91 (m, 2H), 3.52 (td, $J$ = 9.00, 7.63 Hz, 1H), 3.66 (td, $J$ = 9.16, 7.93 Hz, 1H), 5.88–5.93 (m, 1H), 5.93–5.99 (m, 1H), 7.61 (dd, $J$ = 8.24, 2.44 Hz, 1H), 7.64–7.69 (m, 2H), 7.76 (d, $J$ = 8.54 Hz, 1H), 7.87–7.97 (m, 3H), 10.05 ppm (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ −1.14, 17.58, 66.29, 73.91, 128.09, 129.65, 129.87, 130.07, 130.94, 131.34, 133.31, 134.36, 134.40, 134.44, 135.38, 136.93, 138.44, 141.74, 143.94, 182.88 ppm; HRMS: *m/z* calcd. for $C_{22}H_{24}N_2O_2SiSCl$: 443.1016 $[M+H]^+$, found 443.1002.

**General procedure for reduction of aldehydes 7 (preparation of compounds 8).** To a solution of **7** (0.34 g, 1.23 mmol) in mixture of methanol (15 mL) and dichloromethane (45 mL) sodium borohydride (0.074 g, 1.97 mmol) was added portionwise. The reaction mixture was stirred for 2 h at room temperature, pH adjusted to 5–6, concentrated, diluted with water (50 mL), and extracted with dichloromethane (3 × 30 mL). The organic extract was washed with saturated sodium hydrogencarbonate (50 mL), dried over anhydrous sodium sulfate and evaporated to give compound **8**.

***(1-Methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methanol (8a).*** Obtained from **7a** as a white solid: Yield 97%; mp 237.31°C; IR (ATR): 3184, 2923, 1515, 1196, 1024, 742 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 3.88 (s, 3H), 4.67 (d, $J$ = 5.80 Hz, 2H), 5.52 (t, $J$ = 5.65 Hz, 1H), 7.22–7.27 (m, 1H), 7.29–7.38 (m, 3H), 7.42 (td, $J$ = 7.63, 1.53 Hz, 1H), 7.45–7.49 (m, 1H), 7.62 (dd, $J$ = 7.78, 1.68 Hz, 1H), 7.72 ppm (dd, $J$ = 8.09, 1.68 Hz, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 32.81, 56.46, 121.46, 122.65, 123.41, 125.76, 125.88, 126.59, 126.72, 127.95, 128.09, 129.10, 129.61, 135.65, 150.62, 155.84, 156.01 ppm; HRMS: *m/z* calcd. for $C_{17}H_{14}N_2O_2Na$: 301.0953 $[M+Na]^+$, found 301.0957.

***(1-Methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methanol (8b).*** Obtained from **7b** as a white solid: Yield 77%; mp 182.69°C; IR (ATR): 3179, 2957, 2919, 1451, 1375, 1031, 1018, 759, 741, 719 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 3.81 (s, 3H), 4.66–4.74 (m, 2H), 5.55 (t, $J$ = 5.65 Hz, 1H), 7.31–7.38 (m, 1H), 7.38–7.51 (m, 3H), 7.54–7.60 (m, 2H), 7.70 (dd, $J$ = 7.78, 1.07 Hz, 1H), 7.78 ppm (dd, $J$ = 7.63, 1.53 Hz, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 32.73, 56.57, 128.10, 128.45, 128.70, 129.12, 129.17, 129.26, 131.67, 132.51, 132.71, 133.22, 133.90, 134.08, 138.25, 139.56, 149.69 ppm; HRMS: *m/z* calcd. for $C_{17}H_{14}N_2OSNa$: 317.0725 $[M+Na]^+$, found 317.0716.

***[1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methanol (8c).*** Obtained from **7c** as a white solid: Yield 98%; mp 169.09°C; IR (ATR): 3119, 3059, 3030, 1513, 1451, 1207, 1029, 763, 738, 696 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 2.94 (t, $J$ = 7.48 Hz, 2H), 4.49 (d, $J$ = 5.49 Hz, 2H), 4.60 (t, $J$ = 7.63 Hz, 2H), 5.57–5.60 (m, 1H), 7.08–7.11 (m, 2H), 7.17–7.27 (m, 4H), 7.32–7.39 (m, 3H), 7.41–7.50 (m, 2H), 7.68–7.76 ppm (m, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 36.26, 46.43, 56.56, 121.39, 122.72, 123.69, 125.75, 126.01, 126.07, 126.78, 126.98, 128.07, 128.81, 128.95, 129.23, 129.72, 136.50, 138.12, 150.84, 156.00, 156.35 ppm; HRMS: *m/z* calcd. for $C_{24}H_{20}N_2O_2Na$: 391.1422 $[M+Na]^+$, found 391.1423.

***[1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methanol (8d).*** Obtained from **7d** as a white solid: Yield 97%; mp 188.04°C; IR (ATR): 3162, 1454, 1418, 1036, 754, 715, 692 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 2.68–2.83 (m, 2H), 4.29 (d, $J$ = 13.12 Hz, 1H), 4.42–4.54 (m, 2H), 4.62–4.71 (m, 1H), 5.59 (br. s., 1H), 6.97–7.03 (m, 2H), 7.13–7.23 (m, 3H), 7.32–7.53 (m, 4H), 7.58 (dd, $J$ = 7.78, 1.37 Hz, 1H), 7.66–7.78 ppm (m, $J$ = 16.25, 16.25, 7.63, 1.37 Hz, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 36.24, 46.31, 56.46, 126.89, 127.80, 128.21, 128.75, 128.97, 129.12, 129.30, 129.37, 130.79, 132.50, 133.03, 133.91, 134.62, 138.08, 138.21, 140.51, 149.91 ppm; HRMS: *m/z* calcd. for $C_{24}H_{21}N_2OS$: 385.1375 $[M+H]^+$, found 385.1375.

***[1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methanol (8e).*** Obtained from **7e** as a white solid: Yield 99%; mp 147.68°C; IR (ATR): 3189, 2951, 2893, 1450, 1210, 1080, 835, 765, 743 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.92–0.98 (m, 2H), 3.67–3.73 (m, 2H), 4.76 (d, $J$ = 5.80 Hz, 2H), 5.63 (s, 2H), 5.69 (t, $J$ = 5.80 Hz, 1H), 7.28–7.37 (m, 2H), 7.38–7.44 (m, 2H), 7.45–7.54 (m, 2H), 7.75–7.81 (m, 1H), 7.84 ppm (dd, $J$ = 7.93, 1.53 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.06, 17.68, 56.48, 65.96, 73.15, 121.47, 122.65, 123.30, 125.80, 125.98, 126.82, 127.10, 127.78, 128.06, 129.45, 130.00, 136.08, 151.14, 156.21 ppm; HRMS: $m/z$ calcd. for $C_{22}H_{26}N_2O_3SiNa$: 417.1610 $[M+Na]^+$, found 417.1591.

***[1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methanol (8f).*** Obtained from **7f** as a white amorphous solid: Yield 98%; IR (ATR): 3195, 3051, 2952, 1487, 1249, 1082, 1033, 858, 835, 760, 740 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.84–0.91 (m, 2H), 3.40–3.47 (m, 1H), 3.59–3.66 (m, 1H), 4.78–4.86 (m, 2H), 5.58–5.65 (m, 1H), 5.65–5.72 (m, 1H), 5.75 (t, $J$ = 5.65 Hz, 1H), 7.43–7.48 (m, 1H), 7.50–7.60 (m, 3H), 7.67 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.74 (dd, $J$ = 7.48, 1.68 Hz, 1H), 7.80 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.88 ppm (dd, $J$ = 7.63, 1.53 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.12, 17.58, 56.58, 65.75, 73.13, 128.32, 128.75, 129.01, 129.20, 129.32, 129.60, 131.90, 132.54, 132.69, 133.58, 133.90, 134.58, 137.86, 139.89, 150.40 ppm; HRMS: $m/z$ calcd. for $C_{22}H_{27}N_2O_2SSi$: 411.1563 $[M+H]^+$, found 411.1548.

***[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methanol (8g).*** Obtained from **7g** as a white amorphous solid: Yield 100%; IR (ATR): 3179, 2951, 1491, 1446, 1248, 1211, 1076, 1031, 828, 773, 741 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.93–1.02 (m, 2H), 3.69–3.77 (m, 2H), 4.73 (d, $J$ = 5.80 Hz, 2H), 5.58 (s, 2H), 5.69 (t, $J$ = 5.65 Hz, 1H), 7.26–7.34 (m, 1H), 7.37–7.44 (m, 2H), 7.47–7.55 (m, 2H), 7.72–7.78 (m, 1H), 7.91 ppm (d, $J$ = 2.44 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.02, 17.80, 56.36, 65.93, 73.08, 121.47, 124.35, 125.08, 126.08, 126.42, 126.81, 126.94, 127.43, 129.51, 129.79, 130.19, 136.90, 151.50, 154.65, 155.95 ppm; HRMS: $m/z$ calcd. for $C_{22}H_{26}ClN_2O_3Si$: 429.1401 $[M+H]^+$, found 429.1398.

***[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methanol (8h).*** Obtained from **7h** as a white amorphous solid: Yield 99%; IR (ATR): 3191, 3070, 2952, 2923, 2889, 1581, 1480, 1366, 1249, 1078, 1030, 858, 835, 769, 736 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.90–0.97 (m, 2H), 3.53 (td, $J$ = 9.00, 7.93 Hz, 1H), 3.60–3.72 (m, 1H), 4.77 (d, $J$ = 5.80 Hz, 2H), 5.44 (d, $J$ = 10.99 Hz, 1H), 5.66 (d, $J$ = 10.99 Hz, 1H), 5.72 (t, $J$ = 5.65 Hz, 1H), 7.41–7.52 (m, 2H), 7.55 (dd, $J$ = 8.39, 2.29 Hz, 1H), 7.63 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.75 (d, $J$ = 8.24 Hz, 1H), 7.81–7.87 ppm (m, 2H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.79, 56.42, 65.72, 73.11, 127.97, 128.46, 129.28, 129.32, 129.42, 130.50, 132.58, 133.09, 134.19, 134.43, 135.37, 137.65, 140.63, 150.67 ppm; HRMS: $m/z$ calcd. for $C_{22}H_{26}ClN_2O_2SSi$: 445.1173 $[M+H]^+$, found 445.1157.

***[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methanol (8i).*** Obtained from **7i** as a white amorphous solid: Yield 93%; IR (ATR): 3203, 3066, 2953, 2895, 1496, 1446, 1249, 1216, 10991, 1081, 856, 835, 771, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.91–0.98 (m, 2H), 3.67–3.73 (m, 2H), 4.76 (d, $J$ = 5.80 Hz, 2H), 5.64 (s, 2H), 5.72 (t, $J$ = 5.80 Hz, 1H), 7.35–7.41 (m, 1H), 7.44–7.56 (m, 4H), 7.71 (dd, $J$ = 1.98, 0.76 Hz, 1H), 7.86 ppm (dd, $J$ = 7.78, 1.37 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.67, 56.45, 66.03, 73.24, 122.69, 122.94, 123.42, 125.93, 126.30, 127.23, 128.76, 129.00, 129.59, 129.91, 130.34, 134.79, 151.49, 154.69, 155.87 ppm; HRMS: $m/z$ calcd. for $C_{22}H_{26}ClN_2O_3Si$: 429.1401 $[M+H]^+$, found 429.1395.

***[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methanol (8j).*** Obtained from **7j** as a white amorphous solid: Yield 99%; IR (ATR): 3184, 3059, 2951, 1582, 1483, 1247, 1080, 1036, 834, 766, 749 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.82–0.93 (m, 2H), 3.43–3.54 (m, 1H), 3.54–3.66 (m, 1H), 4.82 (dd, $J$ = 5.65, 2.29 Hz, 2H), 5.59–5.66 (m, 1H), 5.66–5.74 (m, 1H), 5.77 (t, $J$ = 5.65 Hz, 1H), 7.52 (dd, $J$ = 8.24, 2.44 Hz, 1H), 7.54–7.62 (m, 2H), 7.69 (d, $J$ = 8.24 Hz, 1H), 7.75–7.82 (m, 2H), 7.83 ppm (d, $J$ = 2.44 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.13, 17.57, 56.53, 65.82, 73.23, 127.52, 128.68, 128.87, 129.61, 129.94, 132.26, 132.46, 132.58, 133.90, 133.95, 134.03, 134.17, 138.65, 139.60, 150.75 ppm; HRMS: $m/z$ calcd. for $C_{22}H_{26}ClN_2O_2SSi$: 445.1173 $[M+H]^+$, found 445.1164.

**General procedure for preparation of compounds 9.** To a 40% aq sodium hydroxide (1.66 mL) solution of **8** (60 mg, 0.216 mmol) in toluene (2.8 mL), appropriate ω-chloroalkyldimethylamine (0.862 mmol), and a catalytic amount of benzyltriethylammonium chloride were added. Reaction mixture was heated at reflux until TLC indicated the reaction was complete, and then cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (3 × 15 mL). The organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution *n*-hexane/(ethyl acetate/*n*-hexane/diethylamine 10:10:1.5) compound **9** was isolated.

***Dimethyl(2-{[(1-methyl-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)amine (9a).*** Obtained from **8a** as a yellowish amorphous solid: Yield 59%; IR (ATR): 3059, 2939, 2859, 2820, 2770, 1516, 1496, 1456, 1444, 1207, 1106, 1090, 1029, 762, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.15 (s, 6H), 2.45 (t, $J$ = 5.95 Hz, 2H), 3.61 (t, $J$ = 5.95 Hz, 2H), 3.87 (s, 3H), 4.69 (s, 2H), 7.22–7.28 (m, 1H), 7.30–7.39 (m, 3H), 7.41–7.50 (m, 2H), 7.63 (dd, $J$ = 7.78, 1.68 Hz, 1H), 7.70–7.75 ppm (m, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 32.77, 45.86, 58.61, 64.80, 68.31, 121.48, 122.67, 123.22, 125.81, 125.91, 126.67, 126.86, 127.89, 128.30, 129.26, 129.80, 135.88, 147.59, 155.92, 156.06 ppm; HRMS: $m/z$ calcd. for $C_{21}H_{24}N_3O_2$: 350.1869 $[M+H]^+$, found 350.1854.

***Dimethyl(3-{[(1-methyl-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)amine (9b).*** Obtained from **8a** as a yellowish amorphous solid: Yield 80%; IR (ATR): 3062, 2944, 2859, 2817, 2768, 1517, 1497, 1458, 1444, 1207, 1089, 798, 763, 743 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.68 (quin, $J$ = 6.79 Hz, 2H), 2.10 (s, 6H), 2.26 (t, $J$ = 7.17 Hz, 2H), 3.55 (t, $J$ = 6.41 Hz, 2H), 3.87 (s, 3H), 4.66 (s, 2H), 7.22–7.28 (m, 1H), 7.30–7.50 (m, 5H), 7.64 (dd, $J$ = 7.93, 1.53 Hz, 1H), 7.68–7.75 ppm (m, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 27.65, 32.75,

45.54, 56.30, 64.85, 68.58, 121.48, 122.66, 123.22, 125.80, 125.91, 126.67, 126.88, 127.88, 128.30, 129.26, 129.80, 135.87, 147.64, 155.93, 156.06 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}N_3O_2$: 364.2025 $[M+H]^+$, found 364.2014.

***Dimethyl(2-{[(1-methyl-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)amine (9c).*** Obtained from **8b** as a yellowish amorphous solid: Yield 62%; IR (ATR): 3051, 2940, 2859, 2819, 2770, 1487, 1452, 1103, 1031, 759, 741 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.16 (s, 6H), 2.46 (t, $J$ = 5.80 Hz, 2H), 3.58–3.69 (m, 2H), 3.79 (d, $J$ = 0.92 Hz, 3H), 4.68–4.75 (m, 2H), 7.32–7.52 (m, 4H), 7.55–7.61 (m, 2H), 7.69–7.74 (m, 1H), 7.74–7.81 ppm (m, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 32.69, 45.88, 58.65, 64.96, 68.40, 128.19, 128.57, 128.79, 129.15, 129.20, 129.39, 131.96, 132.52, 132.55, 133.34, 133.93, 134.22, 138.10, 139.79, 146.71 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3OS$: 366.1640 $[M+H]^+$, found 366.1628.

***Dimethyl(3-{[(1-methyl-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)amine (9d).*** Obtained from **8b** as a yellowish amorphous solid: Yield 80%; IR (ATR): 3051, 2943, 2857, 2816, 2766, 1487, 1453, 1092, 1030, 759, 741 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.70 (quin, $J$ = 6.82 Hz, 2H), 2.11 (s, 6 H), 2.27 (t, $J$ = 7.32 Hz, 2H), 3.53–3.62 (m, 2H), 3.79 (s, 3H), 4.65–4.72 (m, 2H), 7.32–7.52 (m, 4H), 7.59 (ddd, $J$ = 10.83, 7.63, 1.37 Hz, 2H), 7.71 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.78 ppm (dd, $J$ = 7.63, 1.53 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 27.68, 32.69, 45.57, 56.32, 65.01, 68.70, 128.18, 128.59, 128.80, 129.14, 129.19, 129.39, 131.96, 132.52, 132.55, 133.33, 133.92, 134.20, 138.09, 139.76, 146.76 ppm; HRMS: *m/z* calcd. for $C_{22}H_{25}N_3OSNa$: 402.1616 $[M+Na]^+$, found 402.1610.

***Dimethyl[2-({[1-(2-phenylethyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9e).*** Obtained from **8c** as a yellowish amorphous solid: Yield 72%; IR (ATR): 3062, 3025, 2939, 2860, 2819, 2769, 1513, 1495, 1450, 1207, 1095, 1037, 760, 743, 699 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.15 (s, 6H), 2.45 (t, $J$ = 5.80 Hz, 2H), 2.94 (t, $J$ = 7.63 Hz, 2H), 3.59 (t, $J$ = 5.80 Hz, 2H), 4.53 (s, 2H), 4.57 (t, $J$ = 7.48 Hz, 2H), 7.08–7.13 (m, 2H), 7.17–7.28 (m, 4H), 7.32–7.40 (m, 3H), 7.42–7.50 (m, 2H), 7.69–7.77 ppm (m, 2H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 36.20, 45.87, 46.44, 58.67, 64.82, 68.27, 121.40, 122.75, 123.49, 125.79, 126.09, 126.16, 126.86, 127.01, 127.34, 127.87, 128.84, 128.94, 129.38, 129.91, 136.73, 138.02, 147.68, 156.11, 156.41 ppm; HRMS: *m/z* calcd. for $C_{28}H_{30}N_3O_2$: 440.2338 $[M+H]^+$, found 440.2325.

***Dimethyl[3-({[1-(2-phenylethyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9f).*** Obtained from **8c** as a yellowish amorphous solid: Yield 52%; IR (ATR): 3059, 3025, 2942, 2859, 2816, 2766, 1513, 1495, 1450, 1207, 1092, 761, 743, 699 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.68 (quin, $J$ = 6.72 Hz, 2H), 2.07 (s, 6H), 2.25 (t, $J$ = 7.17 Hz, 2H), 2.94 (t, $J$ = 7.63 Hz, 2H), 3.53 (t, $J$ = 6.41 Hz, 2H), 4.50 (s, 2H), 4.57 (t, $J$ = 7.48 Hz, 2H), 7.08–7.12 (m, 2H), 7.18–7.28 (m, 4H), 7.32–7.40 (m, 3H), 7.42–7.50 (m, 2H), 7.69–7.76 ppm (m, 2H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 27.69, 36.23, 45.51, 46.43, 56.34, 64.90, 68.69, 121.40, 122.75, 123.48, 125.78, 126.08, 126.17, 126.86, 127.04, 127.36, 127.86, 128.85, 128.91, 129.38, 129.91, 136.70, 137.98, 147.70, 156.12, 156.41 ppm; HRMS: *m/z* calcd. for $C_{29}H_{32}N_3O_2$: 454.2495 $[M+H]^+$, found 454.2498.

***Dimethyl[2-({[1-(2-phenylethyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9g).*** Obtained from **8d** as a yellowish amorphous solid: Yield 44%; IR (ATR): 3055, 2939, 2859, 2818, 2768, 1485, 1454, 1422, 1109, 1057, 1032, 758, 741, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.15 (s, 6H), 2.45 (t, $J$ = 5.80 Hz, 2H), 2.68–2.83 (m, 2H), 3.53–3.64 (m, 2H), 4.34 (d, $J$ = 12.51 Hz, 1H), 4.37–4.46 (m, 1H), 4.54 (d, $J$ = 12.21 Hz, 1H), 4.66 (ddd, $J$ = 14.19, 8.24, 5.34 Hz, 1H), 6.98–7.03 (m, 2H), 7.14–7.23 (m, 3H), 7.33–7.53 (m, 4H), 7.59 (dd, $J$ = 7.78, 1.37 Hz, 1H), 7.67–7.78 ppm (m, 3H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 36.17, 45.88, 46.33, 58.68, 64.84, 68.30, 126.92, 127.93, 128.30, 128.77, 128.84, 128.96, 129.15, 129.39, 129.42, 131.10, 132.51, 132.86, 133.93, 134.03, 134.80, 138.00, 138.05, 140.73, 146.74 ppm; HRMS: *m/z* calcd. for $C_{28}H_{30}N_3OS$: 456.2110 $[M+H]^+$, found 456.2095.

***Dimethyl[3-({[1-(2-phenylethyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9h).*** Obtained from **8d** as a yellowish amorphous solid: Yield 65%; IR (ATR): 3055, 3025, 2941, 2857, 2815, 2765, 1485, 1455, 1432, 1089, 1078, 758, 741, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.68 (quin, $J$ = 6.79 Hz, 2H), 2.09 (s, 6H), 2.21–2.32 (m, 2H), 2.68–2.84 (m, 2H), 3.46–3.59 (m, 2H), 4.29 (d, $J$ = 12.51 Hz, 1H), 4.39 (ddd, $J$ = 14.88, 7.78, 7.55 Hz, 1H), 4.53 (d, $J$ = 12.21 Hz, 1H), 4.62–4.71 (m, 1H), 6.98–7.02 (m, 2H), 7.14–7.22 (m, 3H), 7.33–7.38 (m, 1H), 7.40–7.47 (m, 2H), 7.50 (td, $J$ = 7.55, 1.37 Hz, 1H), 7.59 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.67–7.77 ppm (m, 3H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 27.67, 36.21, 45.52, 46.33, 56.34, 64.92, 68.74, 126.94, 127.94, 128.30, 128.79, 128.85, 128.93, 129.14, 129.37, 129.42, 131.12, 132.51, 132.84, 133.93, 134.03, 134.79, 137.96, 138.02, 140.69, 146.78 ppm; HRMS: *m/z* calcd. for $C_{29}H_{32}N_3OS$: 470.2266 $[M+H]^+$, found 470.2253.

***Dimethyl[2-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9i).*** Obtained from **8e** as a yellowish amorphous solid: Yield 74%; IR (ATR): 2949, 2893, 2851, 2819, 2769, 1450, 1248, 1210, 1077, 856, 834, 763, 743 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ −0.01 (br. s., 9H), 0.94 (t, $J$ = 7.93 Hz, 2H), 2.20 (s, 6H), 2.49 (t, $J$ = 5.95 Hz, 2H), 3.63–3.73 (m, 4H), 4.77 (s, 2H), 5.59 (s, 2H), 7.27–7.38 (m, 2H), 7.38–7.45 (m, 2H), 7.45–7.55 (m, 2H), 7.73–7.80 (m, 1H), 7.81–7.88 ppm (m, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.04, 17.74, 45.90, 58.62, 64.74, 65.99, 68.42, 73.32, 121.48, 122.68, 122.71, 123.15, 125.85, 126.02, 126.90, 127.20, 127.62, 128.37, 129.59, 130.17, 136.32, 147.98, 156.27 ppm; HRMS: *m/z* calcd. for $C_{26}H_{36}N_3O_3Si$: 466.2526 $[M+H]^+$, found 466.2529.

***Dimethyl[3-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9j).*** Obtained from **8e** as a yellowish amorphous solid: Yield 83%; IR (ATR): 2949, 2855, 2815, 2765, 1450, 1210, 1075, 857, 833, 764, 743 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.91–0.99 (m, 2H), 1.72 (quin, $J$ = 6.82 Hz, 2H), 2.14 (s, 6H), 2.29 (t, $J$ = 7.17 Hz, 2H), 3.60 (t, $J$ = 6.41 Hz, 2H), 3.66–3.73 (m, 2H), 4.73 (s, 2H), 5.58 (s, 2H), 7.27–7.38 (m, 2H), 7.38–7.44 (m, 2H), 7.45–7.54 (m, 2H), 7.74–7.79 (m, 1H), 7.84 ppm (dd, $J$ = 7.93, 1.22 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.74, 27.66, 45.55, 56.31, 64.84, 66.02, 68.80, 73.30, 121.48, 122.68, 123.15, 125.83, 126.01, 126.90, 127.19, 127.62, 128.39, 129.58, 130.17, 136.29, 148.01, 156.27 ppm; HRMS: *m/z* calcd. for $C_{27}H_{38}N_3O_3Si$: 480.2682 $[M+H]^+$, found 480.2692.

***Dimethyl[2-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9k).*** Obtained from **8f** as a yellowish amorphous solid: Yield

61%; IR (ATR): 2949, 2897, 2863, 2818, 2768, 1485, 1461, 1365, 1248, 1077, 1037, 833, 759 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.84–0.91 (m, 2H), 2.25 (s, 6H), 2.55 (t, $J$ = 5.95 Hz, 2H), 3.38–3.48 (m, 1H), 3.58–3.66 (m, 1H), 3.69–3.78 (m, 2H), 4.78–4.87 (m, 2H), 5.55 (d, $J$ = 10.99 Hz, 1H), 5.67 (d, $J$ = 10.99 Hz, 1H), 7.42–7.48 (m, 1H), 7.49–7.59 (m, 3H), 7.67 (d, $J$ = 7.63 Hz, 1H), 7.73–7.82 (m, 2H), 7.87 ppm (dd, $J$ = 7.78, 1.37 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.12, 17.63, 45.91, 58.64, 64.88, 65.77, 68.55, 73.31, 128.39, 128.83, 129.09, 129.22, 129.34, 129.71, 132.14, 132.54, 132.56, 133.71, 133.93, 134.67, 137.72, 140.13, 147.25 ppm; HRMS: *m/z* calcd. for $C_{26}H_{36}N_3O_2SSi$: 482.2298 $[M+H]^+$, found 482.2314.

***Dimethyl[3-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9l).*** Obtained from **8f** as a yellowish amorphous solid: Yield 82%; IR (ATR): 2949, 2859, 2815, 2764, 1485, 1461, 1248, 1076, 833, 759, 694 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 1.78 (quin, $J$ = 6.79 Hz, 2H), 2.19 (s, 6H), 2.31–2.40 (m, 2H), 3.37–3.49 (m, 1H), 3.58–3.71 (m, 3H), 4.74–4.84 (m, 2H), 5.53 (d, $J$ = 11.29 Hz, 1H), 5.66 (d, $J$ = 11.29 Hz, 1H), 7.42–7.49 (m, 1H), 7.49–7.60 (m, 3H), 7.67 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.78 (ddd, $J$ = 18.16, 7.48, 1.53 Hz, 2H), 7.87 ppm (dd, $J$ = 7.78, 1.37 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.14, 17.64, 27.68, 45.57, 56.32, 64.96, 65.80, 68.92, 73.31, 128.40, 128.84, 129.09, 129.22, 129.33, 129.72, 132.15, 132.54, 132.56, 133.70, 133.93, 134.66, 137.70, 140.09, 147.30 ppm; HRMS: *m/z* calcd. for $C_{27}H_{38}N_3O_2SSi$: 482.2298 $[M+H]^+$, found 482.2314.

***[2-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9m).*** Obtained from **8g** as a yellowish amorphous solid: Yield 72%; IR (ATR): 2949, 2893, 2859, 2819, 2769, 1491, 1446, 1248, 1211, 1075, 830, 773, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.94–1.00 (m, 2H), 2.19 (s, 6H), 2.48 (t, $J$ = 5.80 Hz, 2H), 3.65 (t, $J$ = 5.80 Hz, 2H), 3.68–3.76 (m, 2H), 4.75 (s, 2H), 5.55 (s, 2H), 7.27–7.34 (m, 1H), 7.41 (d, $J$ = 3.66 Hz, 2H), 7.49–7.55 (m, 2H), 7.75 (dd, $J$ = 7.02, 0.61 Hz, 1H), 7.92 ppm (d, $J$ = 2.14 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.02, 17.87, 45.83, 58.55, 64.58, 65.93, 68.35, 73.24, 121.48, 124.38, 124.93, 126.11, 126.52, 127.01, 127.14, 127.27, 129.68, 129.91, 130.20, 137.12, 148.37, 154.71, 156.01 ppm; HRMS: *m/z* calcd. for $C_{26}H_{35}ClN_3O_3Si$: 500.2136 $[M+H]^+$, found 500.2136.

***[3-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9n).*** Obtained from **8g** as a yellowish amorphous solid: Yield 85%; IR (ATR): 2950, 2860, 2816, 2765, 1492, 1446, 1249, 1212, 1074, 857, 831, 772, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.94–1.00 (m, 2H), 1.70 (quin, $J$ = 6.79 Hz, 2H), 2.12 (s, 6H), 2.27 (t, $J$ = 7.17 Hz, 2H), 3.57 (t, $J$ = 6.41 Hz, 2H), 3.68–3.75 (m, 2H), 4.71 (s, 2H), 5.53 (s, 2H), 7.28–7.33 (m, 1H), 7.41 (d, $J$ = 3.66 Hz, 2H), 7.49–7.55 (m, 2H), 7.74–7.77 (m, 1H), 7.92 ppm (d, $J$ = 2.14 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.04, 17.86, 27.62, 45.52, 56.28, 64.69, 65.96, 68.81, 73.23, 121.49, 124.38, 124.92, 126.11, 126.50, 127.02, 127.15, 127.25, 129.68, 129.91, 130.20, 137.08, 148.43, 154.71, 156.01 ppm; HRMS: *m/z* calcd. for $C_{27}H_{37}ClN_3O_3Si$: 514.2293 $[M+H]^+$, found 514.2288.

***[2-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9o).*** Obtained from **8h** as a yellowish amorphous solid: Yield 62%; IR (ATR): 2949, 2893, 2863, 2863, 2768, 1580, 1479, 1460, 1364, 1248, 1101, 1076, 1030, 833, 769, 744 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.88–0.96 (m, 2H), 2.21 (s, 6H), 2.50 (t, $J$ = 5.80 Hz, 2H), 3.52 (td, $J$ = 9.16, 7.93 Hz, 1H), 3.62–3.74 (m, 3H), 4.78 (s, 2H), 5.41 (d, $J$ = 10.99 Hz, 1H), 5.63 (d, $J$ = 10.68 Hz, 1H), 7.41–7.53 (m, 2H), 7.56 (dd, $J$ = 8.39, 2.29 Hz, 1H), 7.63 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.76 (d, $J$ = 8.54 Hz, 1H), 7.83 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.87 ppm (d, $J$ = 2.14 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.82, 45.90, 58.62, 64.68, 65.71, 68.55, 73.28, 128.07, 128.53, 129.41, 129.46, 130.77, 132.59, 133.19, 133.23, 134.21, 134.30, 135.39, 137.49, 140.83, 147.58 ppm; HRMS: *m/z* calcd. for $C_{26}H_{35}ClN_3O_2SSi$: 516.1908 $[M+H]^+$, found 516.1909.

***[3-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9p).*** Obtained from **8h** as a yellowish amorphous solid: Yield 77%; IR (ATR): 2949, 2859, 2815, 2765, 1581, 1461, 1365, 1248, 1075, 1029, 857, 833, 769, 744 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.89–0.98 (m, 2H), 1.74 (quin, $J$ = 6.79 Hz, 2H), 2.15 (s, 6H), 2.26–2.37 (m, 2H), 3.47–3.56 (m, 1H), 3.58–3.72 (m, 3H), 4.71–4.80 (m, 2H), 5.41 (d, $J$ = 10.99 Hz, 1H), 5.62 (d, $J$ = 10.99 Hz, 1H), 7.41–7.53 (m, 2H), 7.56 (dd, $J$ = 8.24, 2.14 Hz, 1H), 7.63 (dd, $J$ = 7.63, 1.22 Hz, 1H), 7.76 (d, $J$ = 8.24 Hz, 1H), 7.83 (dd, $J$ = 7.63, 1.53 Hz, 1H), 7.87 ppm (d, $J$ = 2.44 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.09, 17.82, 27.66, 45.56, 56.30, 64.78, 65.74, 68.91, 73.29, 128.07, 128.53, 129.41, 129.46, 130.79, 132.60, 133.19, 133.22, 134.21, 134.30, 135.39, 137.48, 137.50, 140.80, 147.64 ppm; HRMS: *m/z* calcd. for $C_{27}H_{37}ClN_3O_2SSi$: 530.2064 $[M+H]^+$, found 530.2061.

***[2-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9r).*** Obtained from **8i** as a yellowish amorphous solid: Yield 74%; IR (ATR): 2949, 2893, 2859, 2814, 2765, 1495, 1445, 1213, 1098, 1075, 853, 828, 769, 745 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.91–0.98 (m, 2H), 2.20 (s, 6H), 2.50 (t, $J$ = 5.80 Hz, 2H), 3.63–3.74 (m, 4H), 4.77 (s, 2H), 5.61 (s, 2H), 7.34–7.41 (m, 1H), 7.44–7.57 (m, 4H), 7.70–7.73 (m, 1H), 7.87 ppm (dd, $J$ = 7.78, 1.37 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.07, 17.72, 45.89, 58.61, 64.67, 66.06, 68.45, 73.42, 122.72, 122.80, 123.43, 126.01, 126.32, 127.32, 129.07, 129.12, 129.43, 129.95, 130.49, 135.03, 148.33, 154.76, 155.94 ppm; HRMS: *m/z* calcd. for $C_{26}H_{35}ClN_3O_3Si$: 500.2136 $[M+H]^+$, found 500.2135.

***[3-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9s).*** Obtained from **8i** as a yellowish amorphous solid: Yield 81%; IR (ATR): 2949, 2855, 2816, 2765, 1495, 1478, 1445, 1247, 1213, 1074, 854, 828, 769 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.91–0.98 (m, 2H), 1.73 (quin, $J$ = 6.82 Hz, 2H), 2.14 (s, 6 H), 2.30 (t, $J$ = 7.17 Hz, 2H), 3.60 (t, $J$ = 6.41 Hz, 2H), 3.67–3.73 (m, 2H), 4.74 (s, 2H), 5.59 (s, 2H), 7.38 (ddd, $J$ = 7.78, 7.02, 1.37 Hz, 1H), 7.44–7.57 (m, 4H), 7.71 (t, $J$ = 0.92 Hz, 1H), 7.86 ppm (dd, $J$ = 7.78, 1.37 Hz, 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.08, 17.72, 27.65, 45.54, 56.30, 64.74, 66.09, 68.83, 73.40,

122.72, 122.79, 123.43, 126.01, 126.32, 127.32, 129.08, 129.13, 129.42, 129.95, 130.51, 135.00, 148.38, 154.75, 155.94 ppm; HRMS: *m/z* calcd. for $C_{27}H_{37}ClN_3O_3Si$: 514.2293 $[M+H]^+$, found 514.2296.

***[2-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9t).*** Obtained from **8j** as a yellowish amorphous solid: Yield 82%; IR (ATR): 2949, 2889, 2859, 2765, 1582, 1482, 1456, 1248, 1078, 1038, 834, 765, 748 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.84–0.92 (m, 2H), 2.26 (s, 6H), 2.56 (t, $J$ = 5.80 Hz, 2H), 3.40–3.48 (m, 1H), 3.58–3.66 (m, 1H), 3.69–3.78 (m, 2H), 4.78–4.88 (m, 2H), 5.57 (d, $J$ = 11.29 Hz, 1H), 5.68 (d, $J$ = 10.99 Hz, 1H), 7.50–7.62 (m, 3H), 7.69 (d, $J$ = 8.24 Hz, 1H), 7.76–7.85 ppm (m, 3H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.14, 17.60, 45.89, 58.62, 64.80, 65.84, 68.58, 73.42, 127.59, 128.78, 128.96, 129.63, 130.05, 132.33, 132.39, 132.81, 134.00, 134.02, 134.06, 134.19, 138.87, 139.44, 147.62 ppm; HRMS: *m/z* calcd. for $C_{26}H_{35}ClN_3O_2SSi$: 516.1908 $[M+H]^+$, found 516.1909.

***[3-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9v).*** Obtained from **8j** as a yellowish oil: Yield 87%; IR (ATR): 2949, 2859, 2815, 2765, 1582, 1460, 1248, 1077, 834, 766, 748 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 0.00 (s, 9H), 0.85–0.92 (m, 2H), 1.79 (quin, $J$ = 6.82 Hz, 2H), 2.20 (s, 6H), 2.37 (t, $J$ = 6.87 Hz, 2H), 3.57–3.73 (m, 4H), 4.74–4.85 (m, 2H), 5.55 (d, $J$ = 11.29 Hz, 1H), 5.67 (d, $J$ = 11.29 Hz, 1H), 7.50–7.62 (m, 3H), 7.69 (d, $J$ = 8.24 Hz, 1H), 7.76–7.85 ppm (m, 3H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ −1.14, 17.61, 27.63, 40.37, 45.54, 56.30, 64.85, 65.87, 68.93, 73.41, 127.59, 128.79, 128.97, 129.63, 130.07, 132.32, 132.38, 132.81, 134.00, 134.06, 134.19, 138.84, 139.43, 147.68 ppm; HRMS: *m/z* calcd. for $C_{27}H_{37}ClN_3O_2SSi$: 530.2064 $[M+H]^+$, found 530.2048.

**General procedure for preparation of compounds 10.** To a solution of **9** (61.6 mg, 0.132 mmol) in methanol (3.4 mL), 0.5*M* hydrochloric acid in methanol (1.15 mL) was slowly added. The reaction mixture was heated for 2 h at 60°C, then cooled to room temperature, and concentrated. Ethyl acetate (4 mL) and water were added (6 mL) and pH adjusted to 1.0 using a 3*M* hydrochloric acid. The layers were separated and the aqueous layer washed with diethyl ether (2 × 10 mL). The pH of the aqueous layer was adjusted to pH 9.5 with 5*M* sodium hydroxide and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off, and solvent was removed *in vacuo* to give the crude product **10**.

***{2-[(1H-Dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-ylmethyl)oxy]ethyl}dimethylamine (10a).*** Obtained from **9i** as a yellowish amorphous solid: Yield 89%; IR (ATR): 3055, 2947, 2858, 2826, 2772, 1501, 1454, 1341, 1216, 1098, 1035, 743 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.17 (s, 6H), 2.48 (t, $J$ = 5.95 Hz, 2H), 3.63 (t, $J$ = 5.80 Hz, 2H), 4.60 (s, 2H), 7.21–7.30 (m, 2H), 7.30–7.37 (m, 4H), 7.64 (d, $J$ = 7.32 Hz, 2H), 12.98 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 45.83, 58.59, 65.67, 68.49, 122.01, 125.78, 126.05, 129.30, 147.43, 154.61 ppm; HRMS: *m/z* calcd. for $C_{20}H_{22}N_3O_2$: 336.1712 $[M+H]^+$, found 336.1726.

***{3-[(1H-Dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-ylmethyl)oxy]propyl}dimethylamine (10b).*** Obtained from **9j** as a yellowish amorphous solid: Yield 76%; IR (ATR): 3055, 2946, 2860, 2824, 2776, 1501, 1453, 1216, 1096, 1031, 760, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.69 (quin, $J$ = 6.82 Hz, 2H), 2.11 (s, 6H), 2.27 (t, $J$ = 7.17 Hz, 2H), 3.55 (t, $J$ = 6.56 Hz, 2H), 4.56 (s, 2H), 7.21–7.29 (m, 2H), 7.30–7.39 (m, 4H), 7.65 (d, $J$ = 6.10 Hz, 2H), 12.91 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 27.66, 45.51, 56.34, 65.61, 68.70, 122.00, 125.75, 126.11, 129.31, 147.34, 154.62 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3O_2$: 350.1869 $[M+H]^+$, found 350.1854.

***{2-[(1H-Dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-ylmethyl)oxy]ethyl}dimethylamine (10c).*** Obtained from **9k** as a yellowish amorphous solid: Yield 90%; IR (ATR): 3044, 2944, 2855, 2824, 2772, 1489, 1459, 1340, 1115, 1032, 757 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.18 (s, 6H), 2.49 (t, $J$ = 6.10 Hz, 2H), 3.66 (t, $J$ = 5.80 Hz, 2H), 4.62 (s, 2H), 7.32–7.47 (m, 4H), 7.58 (d, $J$ = 7.63 Hz, 2H), 7.67 (d, $J$ = 2.75 Hz, 2H), 13.02 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 45.81, 58.60, 65.64, 68.60, 127.69, 129.09, 129.20, 131.71, 132.87, 146.82 ppm; HRMS: *m/z* calcd. for $C_{20}H_{22}N_3OS$: 352.1484 $[M+H]^+$, found 352.1477.

***{3-[(1H-Dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-ylmethyl)oxy]propyl}dimethylamine (10d).*** Obtained from **9l** as a yellowish amorphous solid: Yield 86%; IR (ATR): 3051, 2944, 2860, 2820, 2772, 1489, 1461, 1355, 1093, 1032, 757 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.70 (quin, $J$ = 6.82 Hz, 2H), 2.11 (s, 6H), 2.29 (t, $J$ = 7.32 Hz, 2H), 3.57 (t, $J$ = 6.41 Hz, 2H), 4.59 (s, 2H), 7.33–7.47 (m, 4H), 7.58 (d, $J$ = 7.63 Hz, 2H), 7.67 (br. s., 2H), 12.90 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 45.81, 58.60, 65.64, 68.60, 127.69, 129.09, 129.20, 131.71, 132.87, 146.82 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3OS$: 366.1640 $[M+H]^+$, found 366.1646.

***(2-{[(11-Chloro-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)dimethylamine (10e)..*** Obtained either from **9m** (yield 90%) or **9r** (yield 83%) as a yellowish amorphous solid: IR (ATR): 3059, 2946, 2858, 2825, 2772, 1601, 1497, 1444, 1220, 1101, 836, 768, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.18 (s, 6H), 2.48 (t, $J$ = 5.95 Hz, 2H), 3.63 (t, $J$ = 5.80 Hz, 2H), 4.60 (s, 2H), 7.25–7.32 (m, 1H), 7.34–7.41 (m, 4H), 7.61–7.68 (m, 2H), 13.00 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 45.82, 58.58, 65.64, 68.54, 122.09, 123.83, 125.28, 126.07, 126.14, 128.68, 129.71, 129.84, 147.94, 153.09, 154.29 ppm; HRMS: *m/z* calcd. for $C_{20}H_{21}N_3O_2Cl$: 370.1322 $[M+H]^+$, found 370.1335.

***(3-{[(11-Chloro-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)dimethylamine (10f).*** Obtained either from **9n** (yield 89.0%) or **9s** (yield 88.0%) as a yellowish amorphous solid: IR (ATR): 3055, 2946, 2861, 2823, 2776, 1496, 1446, 1220, 1092, 835, 814, 767, 741 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.69 (quin, $J$ = 6.82 Hz, 2H), 2.11 (s, 6H), 2.28 (t, $J$ = 7.32 Hz, 2H), 3.55 (t, $J$ = 6.56 Hz, 2H), 4.56 (s, 2H), 7.24–7.31 (m, 1H), 7.34–7.40 (m, 4H), 7.62–7.70 (m, 2H), 12.96 ppm (br. s., 1H); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ 27.63, 45.50, 56.32, 65.57, 68.76, 122.08, 123.82, 125.33, 126.04, 126.21, 128.69, 129.71, 129.83, 147.87, 153.09, 154.29 ppm; HRMS: *m/z* calcd. for $C_{21}H_{23}N_3O_2Cl$: 384.1479 $[M+H]^+$, found 384.1471.

***(2-{[(11-Chloro-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)dimethylamine (10g).*** Obtained either from **9o** (yield 90%) or **9t** (yield 91%) as a white amorphous solid: IR (ATR): 3202, 2937, 2865, 2824, 2773, 1580, 1485, 1456, 1353, 1093, 1030, 811, 766 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.18 (s, 6H), 2.50 (t, $J$ = 6.10 Hz, 2H), 3.66 (t,

$J$ = 5.80 Hz, 2H), 4.63 (s, 2H), 7.36–7.50 (m, 3H), 7.56–7.62 (m, 2H), 7.63–7.72 (m, 2H), 13.07 ppm (br. s., 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 45.79, 58.57, 65.60, 68.64, 126.99, 127.78, 128.61, 129.48, 130.29, 131.20, 133.03, 133.95, 134.41, 147.33 ppm; HRMS: *m/z* calcd. for $C_{20}H_{21}N_3OSCl$: 386.1094 $[M+H]^+$, found 386.1110.

***(3-{[(11-Chloro-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)dimethylamine (10h).*** Obtained either from **9p** (yield 95%) or **9v** (yield 91%) as a yellowish amorphous solid: IR (ATR): 2943, 2860, 2819, 2772, 1579, 1484, 1459, 1094, 1030, 810, 765 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 1.70 (quin, $J$ = 6.82 Hz, 2H), 2.11 (s, 6H), 2.29 (t, $J$ = 7.32 Hz, 2H), 3.58 (t, $J$ = 6.56 Hz, 2H), 4.59 (s, 2H), 7.34–7.49 (m, 3H), 7.54–7.62 (m, 2H), 7.62–7.75 (m, 2H), 13.01 ppm (br. s., 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 27.65, 45.52, 56.34, 65.51, 68.85, 127.05, 127.86, 128.62, 129.46, 129.50, 130.30, 131.22, 133.02, 133.94, 134.40, 147.21 ppm; HRMS: *m/z* calcd. for $C_{21}H_{23}N_3OSCl$: 400.1250 $[M+H]^+$, found 400.1254.

**Biology**

***Cell isolation.*** Peripheral blood mononuclear cells (PBMC) were obtained from buffy coat of healthy volunteer donors by a density gradient centrifugation. Buffy coat was mixed with one volume of sterile saline, sample layered over FicollPaqueTM Plus (Amersham Biosciences), and centrifuged at 400 × *g* for 30 min. PBMCs were collected, washed in RPMI 1640 medium, and centrifuged. Finally, cells were resuspended in RPMI 1640 containing 10% heat inactivated fetal bovine serum (Biowest) and counted.

***Cell culture.*** PBMCs were cultured at a concentration of 3.5 × 104 in 200 μL volumes in 96-well cell culture plates (Falcon, St. Albans, UK) at 37°C in humidified atmosphere containing 5% $CO_2$. The cells were either stimulated with LPS (serotype 0111:B4, Sigma) at 1 ng/mL final concentration or left unstimulated (cultured in medium alone). Compound stock solutions were prepared as 10 m*M* in DMSO. Final 10 μ*M* and 3 μ*M* (10–0.03 μ*M*) concentration made in cell culture medium were tested when they had been added together with LPS. The final DMSO volume ratio in all assays did not exceed 0.1%. Negative and LPS control samples were prepared in sextaplicates and tested compound samples in triplicates.

***Cytokine measurement.*** Cell free supernatants were taken after overnight period and quantified for TNF-α content by enzyme linked immunosorbent assay (ELISA). To ensure the detection specificity and sensitivity, assay was performed according to manufacturer instructions (R&D Systems) using suggested pair of antibodies specific for human TNF-α. Test sensitivity for measuring human TNF-α was under 5 pg/mL. To calculate results, standard curve was made out of measured OD values for recombinant TNF-α of known concentrations. TNF-α content in unknown samples was calculated out of OD values extrapolated from the standard curve. Inhibition values were calculated according to formula:

$$X = \frac{\text{Conc(compound)} - \text{Conc(medium control)}}{\text{Conc(LPS control)} - \text{Conc (medium control)}} \times 100(\%)$$

IC50 values are calculated using GraphPad Prism software.

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## REFERENCES AND NOTES

[1] Current address: Department of Translational Medicine, Children's Hospital "Srebrnjak," Srebrnjak 100, Zagreb HR-10000, Croatia.

[2] Pešić, D.; Ozimec Landek, I.; Merćep, M.; Mesić, M. J Heterocycl Chem 2006, 43, 749.

[3] Pešić, D.; Ozimec Landek, I.; Čikoš, A.; Metelko, B.; Gabelica, V.; Stanić, B.; Merćep, M.; Mesić, M. J Heterocycl Chem 2007, 44, 1129.

[4] Ozimec Landek, I.; Pešić, D.; Novak, P.; Stanić, B.; Nujić, K.; Merćep, M.; Mesić, M. Heterocycles 2009, 78, 2489.

[5] Corall, L. G.; Haslett, A. J.; Muller, G. W.; Chen, R.; Wong, L. M.; Ocampo, C. J.; Paterson, R. T.; Stirling, D. I.; Kaplan, G. J Immunol 1999, 163, 380.

[6] Muller, G. W.; Chen, R.; Huang, S. Y.; Corall, G. L.; Wong, L. M.; Paterson, R. T.; Chen, Y.; Kaplan, G.; Stirling, D. I. Bioorg Med Chem Lett 1999, 9, 1625.

[7] Hanson, G. J. Expert Opin Ther Pat 1997, 7, 729.

[8] Boehm, J. C.; Adams, J. L. Expert Opin Ther Pat 2000, 10, 25.

[9] Beers, S. A.; Malloy, E.; Wachter, M. P.; Wu, W. WO Pat.9,847,892 A1, 1998; Chem Abstr 1998, 129, 330728.

[10] Harris, N. V.; Smith, C. EP Pat.0,424,195 A1, 1991; Chem Abstr 1991, 115, 92279.

[11] Harris, N. V.; Smith, C.; Stuttle, K. A. J.; Walsh, R. J. A.; Wyman, B. M. EP Pat.0,506,437 A1, 1992; Chem Abstr 1993, 118, 80943.

[12] Bamborough, P. L.; Collis, A. J.; Halley, F.; Lewis, R. A.; Lythgoe, D. J.; McKenna, J. M.; Mclay, I. Mc.; Porter, B.; Ratcliffe, A. J.; Wallace, P. A. WO Pat.9856788 A1, 1998; Chem Abstr 1993, 130, 66503.

[13] Adams, J. L.; Gallagher, T. F.; Sisko, J.; Peng, Z.-Q.; Osifo, I. K.; Boehm, J. C. WO Pat.9,640,143 A1, 1996; Chem Abstr 1997, 126, 144274.

[14] Gallagher, T. F.; Fier-Thompson, S. M.; Garigipati, R. S.; Sorenson, M. E.; Smietana, J. M.; Lee, D.; Bender, P. E.; Lee, J. C.; Laydon, J. T.; Chabot-Fletcher, M. C.; Breton, J. J.; Adams, J. L. Bioorg Med Chem Lett 1995, 5, 1171.

[15] Cherkofsky, S. C.; Sharpe, T. R. US Pat.4,215,135, 1980; Chem Abstr 1981, 94, 47331.

[16] Lombardino, J. G. FR Pat.2,211,218, 1974; Chem Abstr 1975, 82, 98006.

[17] Lombardino, J. G. J Heterocycl Chem 1974, 11, 17.

[18] Lombardino, J. G. US Pat.3,711,489, 1973; Chem Abstr 1973, 78, 84410.

[19] Lombardino, J. G. US Pat.3,781,294, 1973; Chem Abstr 1974, 80, 70805.

[20] Lombardino, J. G. CA Pat.967573, 1975; Chem Abstr 1975, 83, 147479.

[21] Cherkofsky, S. C.; Sharpe, T. R. US4,198,421, 1980; Chem Abstr 1980, 93, 71783.

[22] Schouteeten, A.; Christidis, Y. FR Pat.2,717,474 A1, 1995; Chem Abstr 1995, 124, 146153.

[23] Davidson, D.; Weiss, M.; Jelling, J. J Org Chem 1937, 2, 319.

[24] Coleman, C. M.; MacElroy, J. M. D.; Gallagher, J. F.; O'Shea, D. F. J Comb Chem 2002, 4, 87.

[25] Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. Org Lett 2004, 6, 1453.

[26] Lopez-Rodrigez, M. L.; Benhamu, B.; Ayala, D.; Rominguera, J. L.; Murcia, M.; Ramos, J. A.; Viso, A. Tetrahedron 2000, 56, 3245.

[27] Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. J Org Chem 1986, 51, 1891.

[28] Katritzky, A. R.; Rewcastle, G. W.; Fan, W.-Q. J Org Chem 1983, 53, 5685.

[29] Menozzi, G.; Mosti, L.; Fossa, P.; Mattioli, F.; Ghia, M. J Heterocycl Chem 1997, 34, 963.

[30] Liljefors, T.; Bogeso, K. P. J Med Chem 1988, 31, 306.

[31] Bogeso, K. P.; Liljefors, T.; Arnt, J.; Hyttel, J.; Pedersen, H. J Med Chem 1991, 34, 2023.

[32] Durr, H. Zeitschr fur Naturforsch 1967, 22, 786.

[33] Werner, H.; Ricca, S.; Rossi, A.; DeStevens, G. J Med Chem 1967, 10, 575.

[34] Hassner, A.; Amit, B. Tetrahedron Lett 1977, 18, 3023.

[35] Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. J Org Chem 2005, 70, 1545.

[36] Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. J Org Chem 2005, 70, 1552.

[37] Abraham, J.; Kricka, L. J.; Ledwith, A. J. C. S. Perkin II 1974, 1648.

[38] Nogradi, M.; Ollis, W. D.; Sutherland, I. O. Chem Commun 1970, 158.

[39] Pearce, G. J.; Chikanza, I. C. BioDrugs 2001, 15, 139.

# Quinolone Analogues 10: Synthesis of Antimalarial Quinolones Having Pyridyl Moiety in N1-Side Chain

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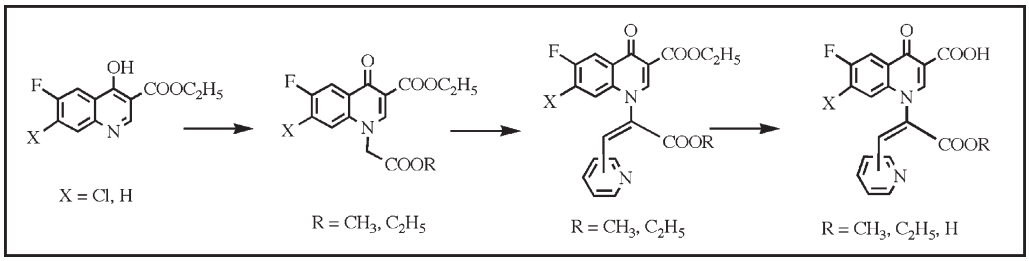


Novel 4-quinolone-3-carboxylates **6,7** and 4-quinolone-3-carboxylic acids **8–11** were synthesized from 4-hydroxyquinoline-3-carboxylates. Ethyl 1-[1-ethoxycarbonyl-2-(4-pyridyl)vinyl]-6-fluoro-4-oxoquinoline-3-carboxylate **7a** was found to show antimalarial activity from the screening data.

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## INTRODUCTION

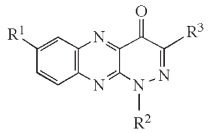
In previous articles [1–9], we reported the synthesis of the 1-alkyl-4-oxopyridazino[3,4-*b*]quinoxalines **1** (Chart 1) as candidates of antibacterial quinolone analogues, in which the 3-H [5], 3-methyl [3], 3-trifluoromethyl [4], and 3-bromo [6] derivatives showed good antibacterial, antifungal, and/or algicidal activities. To search for novel compounds with biological activities, we converted the target ring system from the 4-oxopyridazino[3,4-*b*]quinoxaline to the 4-quinolone nucleus, which was included in the excellent antibacterial agents such as new quinolones. A novel type of new quinolones is still developed nowadays as an antibacterial agents. On the other hand, Wentland et al. [10] reported the antiherpetic activity of the 7-(4-pyridyl)-4-quinolone-3-carboxamide **2** derived from its parent 3-carboxylic acid **3** (Chart 1).

Since quinolone antibacterials have been known to act on the DNA gyrase, some other biological activities such as antifungal and antiviral [10] activities are expected for quinolone analogues. In fact, some of our 1-methyl-4-oxopyridazino[3,4-*b*]quinoxalines **1** ($R^1$ = Cl, $R^2$ = $CH_3$, $R^3$ = H, $CH_3$, Br) exhibited antifungal activities in addition to antibacterial activities [9]. In this investigation, we undertook the structural transformation of ordinary new quinolones **4** into compounds **6–11** as shown in Scheme 1. Namely, the C7-basic moiety is shifted to the N1-side chain leading to compound **5**, and the linker part is inserted between the N1 and the basic moiety. Furthermore, a carboxyl group was introduced in the linker part to provide a proximal pair of the acid and base moieties. This article describes the synthesis of compounds **6–11**, some of which are found to exhibit antimalarial activity from the screening data.

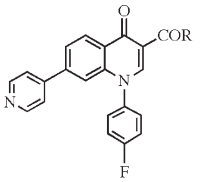
## RESULTS AND DISCUSSION

**Synthesis of compounds 6–11.** The reaction of ethyl 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate **12** [11,12] with methyl bromoacetate or ethyl 6-fluoro-4-hydroxyquinoline-3-carboxylate **13** [11,12] with ethyl

**Chart 1**

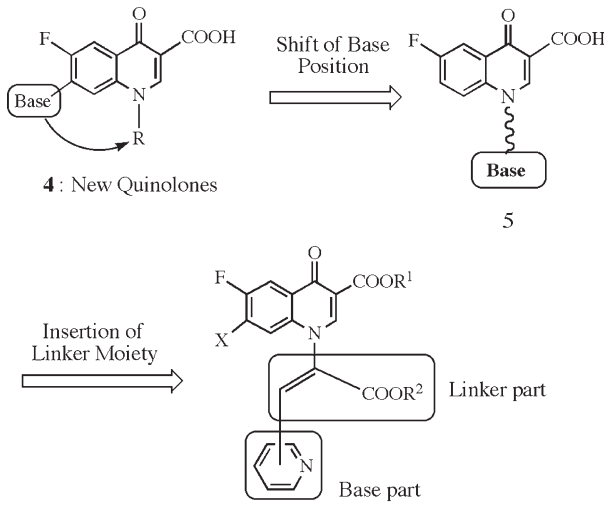


**1**: 1-Alkyl-4-oxopyridazino[3,4-*b*]quinoxalines
$R^1$ = H, Cl; $R^2$ = $CH_3$, $C_2H_5$;
$R^3$ = H, $CH_3$, $CF_3$, Br



**2**: R = $NH_2$; **3**: R = OH

**Scheme 1**




**6a,b**: X = Cl; $R^1 = C_2H_5$; $R^2 = CH_3$

**7a-c**: X = H; $R^1 = R^2 = C_2H_5$

**8a,b**: X = Cl; $R^1$ = H; $R^2 = CH_3$

**9a-c**: X = H; $R^1$ = H; $R^2 = C_2H_5$

**10a,b**: X = Cl; $R^1 = R^2$ = H

**11a-c**: X = H; $R^1 = R^2$ = H

**a**: 4-Pyridyl; **b**: 3-Pyridyl; **c**: 2-Pyridyl

**Table 1**

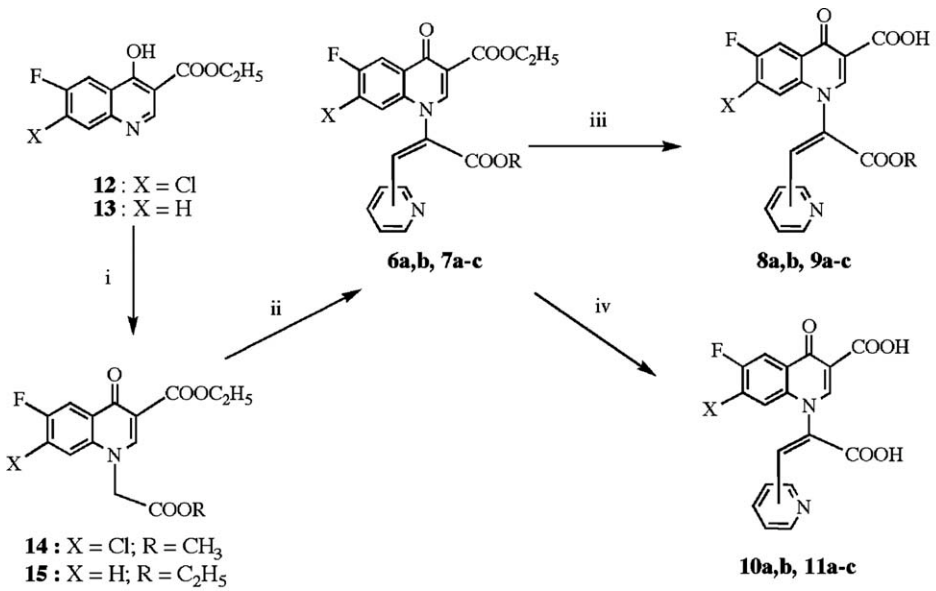
*In vitro* antimalarial activity for compounds **7**, **9**, and **11**.

| Compound | *Plasmodium falciparum*, $IC_{50}$ (μmol) | Mouse FM3A Cell,[a] $IC_{50}$ (μmol) | Chemotherapeutic coefficient |
|---|---|---|---|
| **7a** | 8.2 | >24 | >2.9 |
| **7b** | 26 | 100 | 3.8 |
| **9b** | 29 | >100 | >3.4 |
| **9c** | 21 | >100 | >4.8 |
| **11b** | 24 | >100 | >4.2 |
| **11c** | 21 | >100 | >4.8 |

[a] Mouse breast cancer cell, F28-7 strain.

bromoacetate gave the methyl (7-chloro-6-fluoro-4-quinolon-1-yl)acetate **14** or ethyl (6-fluoro-4-quinolon-1-yl)-acetate **15**, respectively (Scheme 2). The reaction of compound **14** with 4- and 3-pyridinecarbaldehydes or the reaction of compound **15** with 4-, 3-, and 2-pyridinecarbaldehydes afforded the methyl 2-(7-chloro-6-fluoroquinolon-1-yl)-3-(4- and 3-pyridyl)acrylates **6a,b** or ethyl 2-(6-fluoroquinolon-1-yl)-3-(4-, 3-, and 2-pyridyl)acrylates **7a–c**, respectively. Reflux of compounds **6a,b** in sulfuric acid/acetic acid/water was clarified to hydrolyze the ethyl ester of quinolone nucleus from the analytical and spectral data, providing the quinolone-3-carboxylic acids **8a,b**, respectively. Similar reaction of

**Scheme 2**

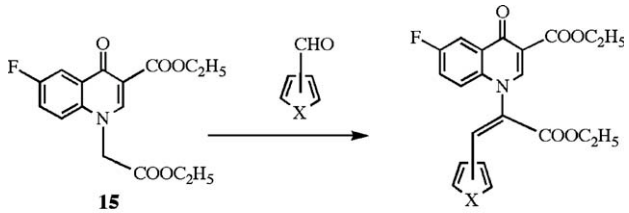



**Reagents**: i) $BrCH_2COOR$, $K_2CO_3$ in *N,N*-Dimethylformamide; ii) Pyridinecarbaldehyde, DBU in *N,N*-Dimethylformamide; iii) $H_2SO_4$, $H_2O$ in $CH_3COOH$, then NaOH; iv) NaOH, $H_2O$ in EtOH, then HCl

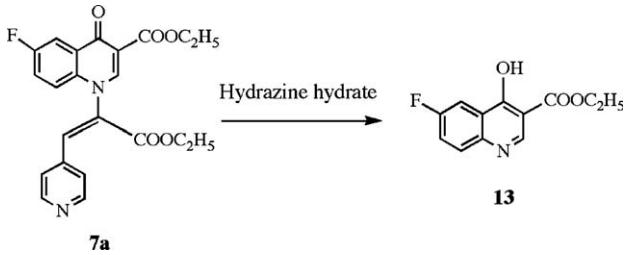
**6a,b**: X = Cl; R = $CH_3$ ; **7a-c**: X = H; R = $C_2H_5$ ; **8a,b**: X = Cl; R = $CH_3$ ; **9a-c**: X = H; R = $C_2H_5$ ;

**10a,b**: X = Cl ; **11a-c**: X = H ; **a**: 4-Pyridyl ; **b**: 3-Pyridyl; **c**: 2-Pyridyl

**Scheme 3**




**Scheme 4**




compounds **7a–c** gave the quinolone-3-carboxylic acids **9a–c**, respectively. On the other hand, the hydrolysis of **6a,b** and **7a–c** with sodium hydroxide afforded the dicarboxylic acids **10a,b** and **11a–c**, respectively.

**Antimalarial activity.** The *in vitro* screening to antimalarial activity was carried out for compounds **6–11** according to a method in literatures [13], and the data are shown in Table 1. The $IC_{50}$ of the diester **7a** was 8.2 μmol to *Plasmodium falciparum*, whose value was referred as effective. The $IC_{50}$ of the diester **7a** to mouse FM3A cell F28-7 strain was 24 μmol, and the chemical therapeutic coefficient was the value of 2.9. The diester **7b** with the 3-pyridyl moiety had a weaker activity than the diester **7a** with the 4-pyridyl moiety. Moreover, compounds with carboxyl group in the quinolone nucleus and/or N1-side chain or compounds with the C7-chlorine atom in the quinolone nucleus represented no antimalarial activity, suggesting the unfavorable effect of such carboxyl group and chlorine atom on the activity.

The 4-pyridyl moiety in the N1-substituent of the diester **7a** was found not to be replaced with the nonbasic moiety. That is, compounds **16–18** (Scheme 3) with furyl or thienyl moiety in the N1-substituent were clarified to exhibit no antimalarial activity.

**Trial for modification of compound 7a.** An attempt was unsuccessful to convert the ester group into carbohydrazide group to install an additional basic moiety in the N1-side chain of compound **7a**. As shown in Scheme 4, the reaction of compound **7a** with hydrazine hydrate resulted in the bond cleavage between the N1 and acrylate moiety.

**Analytical and spectral data.** The structural assignment of novel compounds **6–11** was based on the analytical and spectral data. Especially, the NOE spectral data among the vinyl, pyridyl, and quinolone 8-H protons of compounds **7a–c** shown in Table 2 ascertained the presence of the pyridylacrylate moiety in the N1 of the quinolone nucleus. Moreover, the NOE between the vinyl and quinolone 8-H proton signals suggested the *E*-isomer for compounds **6–11** and **16–18**, whereas the NOE between the pyridine 3-H and quinolone 2-H proton signals supported the presence of the *Z*-isomer for compounds **7a** and **9a** (Table 2). There was no difference in the proton chemical shifts between the *E*- and *Z*-isomers in compounds **7a** and **9a**.

In the $^1$H-NMR spectra of compounds **6b**, **8a**, **11a**, and **17**, two kinds of quinolone 2-H proton signals were observed [14] (Table 3), which would not be due to the presence of the *E*- and *Z*-isomers, because compounds **7a** and **9a** existing as the *E*- and *Z*-isomers in solution exhibited a single quinolone 2-H proton signal.

**Table 2**

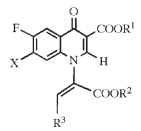
NOE data for compounds **7**, **9**, **11**, and **16–18**.

| Radiation | NOE | 7a | 7b | 7c | 9a | 9b | 9c | 11b | 16 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vinyl H | Quinolone 8-H | 1.2[a] | 1.4 | 1.0 | 1.6 | – | – | – | 1.0 | 1.5 | 1.1 |
| | Quinolone 2-H | – | 2.7 | 0.6 | – | – | – | – | – | – | – |
| | Pyridyl 4-H | – | 2.8 | – | – | 2.7 | – | 3.8 | – | – | – |
| | Pyridyl 3-H | 8.8 | – | 6.1 | 10.9 | – | 12.0 | – | – | – | – |
| | Pyridyl 2-H | – | 8.1 | – | – | 13.7 | – | 7.7 | – | – | – |
| | Furyl 3-H | – | – | – | – | – | – | – | 3.9 | – | – |
| | Thienyl 4-H | – | – | – | – | – | – | – | – | – | 2.5 |
| | Thienyl 3-H | – | – | – | – | – | – | – | – | 6.5 | – |
| | Thienyl 2-H | – | – | – | – | – | – | – | – | – | 7.4 |
| Pyridyl 3-H | Vinyl H | 8.4 | – | – | – | – | – | – | – | – | – |
| | Pyridyl 2-H | 17.9 | – | – | – | – | – | – | – | – | – |
| Quinolone 2-H | Pyridyl 3-H | 2.3 | – | – | 2.0 | – | – | – | – | – | – |

[a] NOE (%) Observed.

**Table 3**

Compounds showing two kinds of quinolone 2-H proton signals [14].

| | Compound | $R^1$ | $R^2$ | $R^3$ | X | Chemical Shift (δ) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Quinolone 2-H | | Ratio |
|  | **6b** | $C_2H_5$ | $CH_3$ | 3-Pyridyl | Cl | 8.66 | 8.60 | 40 : 60 |
| | **8a** | H | $CH_3$ | 4-Pyridyl | Cl | 9.05 | 8.90 | 72 : 28 |
| | **11a** | H | H | 4-Pyridyl | H | 9.11 | 9.03 | 23 : 77 |
| | **17** | $C_2H_5$ | $C_2H_5$ | 2-Thienyl | H | 8.59 | 8.55 | 45 : 55 |

Moreover, two kinds of quinolone 2-H, 8-H, vinyl, pyridine 5-H, and ethyl ester $CH_2$ proton signals were observed in the $^1$H-NMR spectra of compound **6b**, suggesting the presence of two kinds of isomers [14]. Further investigation to clarify the aforementioned phenomena is in progress, and the results will be reported elsewhere.

The $^{13}$C-NMR spectral data are shown in Table 4, which includes the respective carbon chemical shifts of the typical our quinolones **6a**, **7a**, **14**, and **16** assigned by the dHSQC and gHMBC spectral data.

## EXPERIMENTAL

All melting points were determined on a Yazawa micro-melting point BY-2 apparatus and are uncorrected. The IR spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrometer. The $^1$H-NMR and dHSOC/gHMBC spectra were measured with a Varian XL-400 and Varian INOVA 600 spectrometers at 400 and 600 MHz, respectively. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

Compounds **12** and **13** were synthesized by a method reported in literatures [11,12], refluxing in diphenyl ether at 250°.

**Methyl (7-chloro-3-ethoxycarbonyl-6-fluoro-1,4-dihydro-4-oxoquinolin-1-yl)acetate 14.** A mixture of compound **12** (5.0 g, 18.6 mmol), ethyl bromoacetate (5.09 g, 33.5 mmol), potassium carbonate (5.0 g, 36.2 mmol) in dry *N*,*N*-dimethylformamide (200 mL) was heated at 100–120° with stirring for 2 h and filtrated while the mixture was hot. Evaporation of the solvent *in vacuo* gave colorless crystals, which were recrystallized from *N*,*N*-dimethylformamide/ethanol/water to afford colorless needles **14** (5.13 g, 81%); mp: 251–252°; IR: ν 1725 $cm^{-1}$; ms: m/z 341 ($M^+$), 343 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 8.73 (s, 1H, 2-H), 8.06 (d, $J = 6.0$ Hz, 1H, 8-H), 8.02 (d, $J = 9.5$ Hz, 1H, 5-H), 5.39 (s, 2H, $CH_2$), 4.22 (q, $J = 7.0$ Hz, 2H, $CH_2$), 3.72 (s, 3H, $CH_3$), 1.27 (t, $J = 7.0$ Hz, 3H, $CH_3$). Anal. Calcd. for $C_{15}H_{13}ClFNO_5$: C, 52.72; H, 3.83; N, 4.10. Found: C, 52.45; H, 3.94; N, 4.36.

**Ethyl (3-ethoxycarbonyl-6-fluoro-1,4-dihydro-4-oxoquinolin-1-yl)acetate 15.** A mixture of compound **13** (5.0 g, 21.3 mmol), ethyl bromoacetate (5.33 g, 31.9 mmol), potassium carbonate (4.40 g, 31.9 mmol) in dry *N*,*N*-dimethylformamide (200 mL) was heated at 100–120° with stirring for 2 h and filtrated while the mixture was hot. Then, ethanol (100 mL) was added to the filtrate with stirring, and the solution was allowed to stand at room temperature to precipitate colorless needles **15**, which were collected by suction and then washed with *n*-hexane (5.97 g, 87%); mp: 274–275°; IR: ν 1740, 1720 $cm^{-1}$; ms: m/z 321 ($M^+$); NMR (deuteriotrifluoroacetic acid): 9.14 (s, 1H, 2-H), 8.11 (dd, $J = 7.5$, 2.8 Hz, 1H, 5-H), 7.82 (dd, $J = 10.0$, 4.0 Hz, 1H, 8-H), 7.75 (ddd, $J = 10.0$, 7.5, 2.8 Hz, 1H, 7-H), 5.50 (s, 2H, $CH_2$), 4.42 (q, $J = 7.0$ Hz, 2H, $CH_2$), 4.16 (q, $J = 7.0$ Hz, 2H, $CH_2$), 1.24 (t, $J = 7.0$ Hz, 3H, $CH_3$), 1.08 (t, $J = 7.0$ Hz, 3H, $CH_3$). Anal. Calcd. for $C_{16}H_{16}ClFNO_5$: C, 59.81; H, 5.02; N, 4.36. Found: C, 59.64; H, 5.09; N, 4.59.

**Table 4**

$^{13}$C-NMR spectral data for compounds **6a**, **7a**, **14**, and **16**.

| | Compounds | | | |
|---|---|---|---|---|
| Carbon | **14** | **6a** | **7a** | **16** |
| 2-C | 151.1 | 149.0 | 148.5 | 149.4 |
| 3-C | 110.5 | 112.4 | 111.9 | 111.3 |
| 4-C=O | 171.7 | 171.8 | 172.4 | 172.5 |
| 4a-C | 128.2 | 127.9 | 129.2 | 129.2 |
| 5-C | 112.6 | 113.1 | 111.4 | 111.1 |
| 6-C | 154.6 | 155.0 | 159.8 | 159.5 |
| 7-C | 125.8 | 126.5 | 122.0 | 121.6 |
| 8-C | 120.3 | 119.9 | 120.2 | 120.2 |
| 8a-C | 136.9 | 136.1 | 135.7 | 136.5 |
| 1N-Methylene | 53.5 | – | – | – |
| 3-Ester C=O | 164.2 | 163.8 | 164.0 | 164.3 |
| Other Ester C=O | 168.4 | 162.9 | 162.5 | 163.0 |
| Vinyl 1-C | – | 130.3 | 130.9 | 123.0 |
| Vinyl 2-C | – | 140.0 | 139.1 | 128.0 |
| Pyridyl 2,6-C | – | 150.9 | 150.9 | – |
| Pyridyl 3,5-C | – | 123.5 | 123.4 | – |
| Pyridyl 4-C | – | 138.0 | 138.0 | – |
| Furyl 2-C | – | – | – | 147.2 |
| Furyl 3-C | – | – | – | 121.8 |
| Furyl 4-C | – | – | – | 113.5 |
| Furyl 5-C | – | – | – | 149.0 |
| $CH_3$ | 14.3 | 14.4 | 14.1 | 14.2 |
| | 53.6 | 52.8 | 14.3 | 14.4 |
| $CH_2$ | 60.5 | 60.2 | 60.4 | 60.2 |
| | – | – | 62.6 | 62.0 |

**Ethyl 7-chloro-6-fluoro-1,4-dihydro-1-[(*Z*)-1-methoxycarbonyl-2-(4- and 3-pyridyl)vinyl]-4-oxoquinoline-3-carboxylates 6a,b.** ***General procedure.*** A solution of compound **14** (5.0 g, 14.6 mmol), 4- or 3-pyridinecarbaldehyde (2.50 g, 23.4 mmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (1.19 g, 7.80 mmol) in dry dioxane (100 mL) was refluxed with stirring for 10 h. Acetic acid (5 mL) was added to the solution, and the solvent was evaporated *in vacuo* to give colorless crystals. Recrystallization from dioxane/water afforded colorless needles **6a** or **6b**.

Compound **6a** was obtained in 55% yield (3.48 g); mp 226–227°; IR: ν 1730 $cm^{-1}$; ms: m/z 430 ($M^+$), 432 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 8.65 (s, 1H, 2-H), 8.54 (d, $J = 6.5$ Hz, 2H, pyridine 2-H and 6-H), 8.24 (s, 1H, vinylic H), 8.07 (d, $J = 9.0$ Hz, 1H, 5-H), 7.81 (d, $J = 6.0$ Hz, 1H, 8-H), 7.12 (d, $J = 6.5$ Hz, 2H, pyridine 3-H and 5-H), 4.18 (q, $J = 7.0$ Hz, 2H, $CH_2$), 3.81 (s, 3H, $CH_3$), 1.22 (t, $J = 7.0$ Hz, 3H, $CH_3$). Anal. Calcd. for $C_{21}H_{16}ClFN_2O_5 \cdot 1/3H_2O$ [15]: C, 57.74; H, 3.85; N, 6.41. Found: C, 57.79; H, 3.81; N, 6.36.

Compound **6b** was obtained in 61% yield (3.82 g); mp 214–215°; IR: ν 1735, 1720 $cm^{-1}$; ms: m/z 430 ($M^+$), 432 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): (isomer A) [14] 8.66 (s, 1H, 2-H), 8.29 (s, 1H, vinylic H), 8.08 (d, $J = 9.0$ Hz, 1H, 5-H), 7.81 (d, $J = 6.0$, Hz, 1H, 8-H), 7.41 (ddd, $J = 4.0$, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.34 (dd, $J = 8.0$, 4.0 Hz, 1H, pyridine 5-H), 8.57–8.52 (m, 2H, pyridine 2-H and 6-H), 4.21 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.17 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 3.81 (s, 3H, $CH_3$), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, $CH_3$); (isomer B) [14] 8.60 (s, 1H, 2-H), 8.22 (s, 1H, vinylic H), 8.08 (d, $J = 9.0$ Hz, 1H, 5-H), 7.73 (d, $J = 6.0$ Hz, 1H, 8-H), 7.41 (ddd, $J = 4.0$, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.33 (dd, $J = 8.0$, 4.0 Hz, 1H, pyridine 5-H), 8.57–8.52 (m, 2H, pyridine 2-H and 6-H), 4.20 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.16 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 3.81 (s, 3H, $CH_3$), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, $CH_3$). The 5-H, pyridine 4-H, ester methyl proton signals of the above isomers A and B were observed in the same magnetic field. Anal. Calcd. for $C_{21}H_{16}ClFN_2O_5 \cdot 1/2H_2O$ [15]: C, 57.35; H, 3.90; N, 6.37. Found: C, 57.39; H, 3.75; N, 6.42.

**Methyl 1-[(*Z*)-1-ethoxycarbonyl-2-(4-, 3-, and 2-pyridyl)-vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylates 7a–c.** ***General procedure.*** A solution of compound **15** (5.0 g, 15.6 mmol), 4-, 3-, or 2-pyridinecarbaldehyde (2.50 g, 23.4 mmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (1.19 g, 7.80 mmol) in dry dioxane (100 mL) was refluxed with stirring for 10 h. Acetic acid (5 mL) was added to the solution, and the solvent was evaporated *in vacuo* to give colorless crystals. Recrystallization from dioxane/water afforded colorless needles **7a**, **7b**, or **7c**.

Compound **7a** [16] was obtained in 59% yield (3.75 g); mp 226–227°; IR: ν 1725 $cm^{-1}$; ms: m/z 410 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.63 (s, 1H, 2-H), 8.54 (d, $J = 6.0$ Hz, 2H, pyridine 2-H and 6-H), 8.25 (s, 1H, vinylic H), 7.92 (dd, 9.3, 3.0 Hz, 1H, 5-H), 7.58 (ddd, 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.50 (dd, $J = 9.0$, 4.5 Hz, 1H, 8-H), 7.11 (d, $J = 6.0$ Hz, 2H, pyridine 3-H and 5-H), 4.28 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.24 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.18 (q, $J = 7.0$ Hz, 2H, $CH_2$), 1.22 (dd, $J = 7.0$, 7.0 Hz, 3H, $CH_3$), 1.21 (t, $J = 7.0$ Hz, 3H, $CH_3$). Anal. Calcd. for $C_{22}H_{19}FN_2O_5$: C, 64.39; H, 4.67; N, 6.83. Found: C, 64.39; H, 4.67; N, 6.86.

Compound **7b** was obtained in 49% yield (3.10 g); mp 140–141°; IR: ν 1725, 1690 $cm^{-1}$; ms: m/z 410 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.65 (s, 1H, 2-H), 8.55 (d, $J = 2.0$ Hz, 1H, pyridine 2-H), 8.53 (dd, $J = 4.5$, 2.0 Hz, 1H, pyridine 6-H), 8.29 (s, 1H, vinylic H), 7.92 (dd, 9.0, 3.0 Hz, 1H, 5-H), 7.57 (ddd, $J = 9.0$, 8.0, 3.0 Hz, 1H, 7-H), 7.50 (dd, $J = 9.0$, 4.5 Hz, 1H, 8-H), 7.39 (ddd, $J = 8.0$, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.33 (dd, $J = 8.0$, 4.5 Hz, 1H, pyridine 5-H), 4.28 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.24 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.22 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.17 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, $CH_3$), 1.22 (dd, $J = 7.0$, 7.0 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{22}H_{19}FN_2O_5$: C, 64.39; H, 4.67; N, 6.83. Found: C, 64.16; H, 4.67; N, 6.90.

Compound **7c** was obtained in 58% yield (3.73 g); mp 166–167°; IR: ν 1700 $cm^{-1}$; ms: m/z 410 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.56 (s, 1H, 2-H), 8.27 (ddd, $J = 5.0$, 1.5, 0.5 Hz, 1H, pyridine 6-H), 8.24 (s, 1H, vinylic H), 7.99 (dd, $J = 9.0$, 3.0 Hz, 1H, 5-H), 7.83 (ddd, 7.5, 7.5, 1.5 Hz, 1H, pyridine 4-H), 7.69 (ddd, $J = 7.5$, 1.0, 0.5 Hz, 1H, pyridine 3-H), 7.50 (ddd, $J = 9.0$, 8.0, 3.0 Hz, 1H, 7-H), 7.41 (dd, $J = 9.0$, 4.5 Hz, 1H, 8-H), 7.29 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H, pyridine 5-H), 4.30 (dq, $J = 10.5$, 7.0 Hz, 1H, methylene CH), 4.25 (dq, $J = 10.5$, 7.0 Hz, 1H, methylene CH), 4.17 (q, $J = 7.0$ Hz, 2H, $CH_2$), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, $CH_3$), 1.22 (t, $J = 7.0$ Hz, 3H, $CH_3$). Anal. Calcd. for $C_{22}H_{19}FN_2O_5$: C, 64.39; H, 4.67; N, 6.83. Found: C, 64.00; H, 4.69; N, 6.85.

**7-Chloro-6-fluoro-1,4-dihydro-1-[(*Z*)-1-methoxycarbonyl-2-(4- and 3-pyridyl)vinyl]-4-oxoquinoline-3-carboxylic acids 8a,b.** ***General procedure.*** A solution of compound **6a** or **6b** (1.0 g, 2.33 mmol) in concentrated sulfuric acid (0.4 mL), water (1.0 mL), and acetic acid (40 mL) was refluxed with stirring for 2 h. The solvent was evaporated *in vacuo* to give an oily product, which was dissolved in ethanol (10 mL) and then neutralized with sodium hydrogen carbonate to afford crystals. The crystals were collected by suction, and then recrystallization from *N*,*N*-dimethylformamide/ethanol/water provided yellow needles **8a** or **8b**.

Compound **8a** was obtained in 87% yield (810 mg); mp 244–245°; IR: ν 1740 $cm^{-1}$; ms: m/z 402 ($M^+$), 404 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 14.23 (brs, 1H, COOH), 9.05, 8.90 [14] (s, 1H, 2-H), 8.52 (d, $J = 6.0$ Hz, 2H, pyridine 2-H and 6-H), 8.28 (s, 1H, vinylic H), 8.25 (d, $J = 9.0$ Hz, 1H, 5-H), 8.07 (d, $J = 6.0$ Hz, 1H, 8-H), 7.09 (d, $J = 6.0$ Hz, 2H, pyridine 3-H and 5-H), 3.80 (s, 3H, $CH_3$). Anal. Calcd. for $C_{19}H_{12}ClFN_2O_5 \cdot 1/5H_2O$ [15]: C, 56.16; H, 3.08; N, 6.89. Found: C, 56.08; H, 3.07; N, 6.93.

Compound **8b** was obtained in 51% yield (470 mg); mp 216–217°; IR: ν 1725 $cm^{-1}$; ms: m/z 402 ($M^+$), 404 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 14.22 (brs, 1H, COOH), 9.06 (s, 1H, 2-H), 8.60 (s, 1H, pyridine 2-H), 8.55 (dd, $J = 3.6$, 1.0 Hz, 1H, pyridine 6-H), 8.34 (s, 1H, vinylic H), 8.26 (dd, 9.1, 1.0 Hz, 1H, 5-H), 8.08 (dd, $J = 4.0$, 1.0 Hz, 1H, 8-H), 7.34 (dd, $J = 5.0$, 1.0 Hz, 1H, pyridine 4-H), 7.30 (dd, $J = 5.0$, 3.6 Hz, 1H, pyridine 5-H), 3.82 (s, 3H, $CH_3$). Anal. Calcd. for $C_{19}H_{12}ClFN_2O_5 \cdot 1/3H_2O$ [15]: C, 55.83; H, 3.12; N, 6.85. Found: C, 55.83; H, 3.11; N, 6.96.

**1-[(*Z*)-1-Ethoxycarbonyl-2-(4-, 3-, and 2-pyridyl)vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids 9a–c.** ***General procedure.*** A solution of compound **7a**, **7b**, or **7c** (1.0 g, 2.44 mmol) in concentrated sulfuric acid (0.4 mL),

water (1.0 mL), and acetic acid (40 mL) was refluxed with stirring for 2 h. The solvent was evaporated *in vacuo* to give an oily product, which was dissolved in ethanol (10 mL) and then neutralized with sodium hydrogen carbonate to afford crystals. The crystals were collected by suction, and then recrystallization from *N*,*N*-dimethylformamide/ethanol/water provided yellow needles **9a**, **9b**, or **9c**.

Compound **9a** [16] was obtained in 67% yield (620 mg); mp 228–229°; IR: ν 1740, 1720 $cm^{-1}$; ms: m/z 382 ($M^+$); NMR (deuteriodimethyl sulfoxide): 14.45 (brs, 1H, COOH), 9.06 (s, 1H, 2-H), 8.51 (d, $J$ = 6.5 Hz, 2H, pyridine 2-H and 6-H), 8.30 (s, 1H, vinylic H), 8.09 (ddd, 9.0, 8.5, 2.0 Hz, 1H, 7-H), 7.77 (dd, 10.0, 2.0 Hz, 1H, 5-H), 7.74 (dd, $J$ = 9.0, 3.5 Hz, 1H, 8-H), 7.07 (d, $J$ = 6.5 Hz, 2H, pyridine 3-H and 5-H), 4.28 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 4.24 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 1.21 (dd, $J$ = 7.0, 7.0 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{19}H_{15}FN_2O_5$: C, 62.83; H, 3.95; N, 7.33. Found: C, 62.66; H, 3.98; N, 7.42.

Compound **9b** was obtained in 64% yield (600 mg); mp 168–169°; IR: ν 1725, 1620 $cm^{-1}$; ms: m/z 382 ($M^+$); NMR (deuteriodimethyl sulfoxide): 14.48 (brs, 1H, COOH), 9.07 (s, 1H, 2-H), 8.56 (dd, $J$ = 1.5, 1.5 Hz, 1H, pyridine 2-H), 8.52 (dd, $J$ = 4.0, 2.5 Hz, 1H, pyridine 5-H), 8.35 (s, 1H, vinylic H), 8.09 (ddd, 8.5, 8.5, 1.5 Hz, 1H, 7-H), 7.74 ($J$ = 8.5, 6.0, 1.5 Hz, 2H, 5-H and 8-H), 7.28 [ (dd, $J$ = 4.0, 1.5 Hz, 1H), (dd, $J$ = 2.5, 1.5 Hz, 1H), pyridine 4-H and 6-H], 4.28 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 4.23 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 1.22 (dd, $J$ = 7.0, 7.0 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{19}H_{15}FN_2O_5$: C, 62.83; H, 3.95; N, 7.33. Found: C, 62.57; H, 3.95; N, 7.36.

Compound **9c** was obtained in 70% yield (652 mg); mp 200–201°; IR: ν 1720, 1620 $cm^{-1}$; ms: m/z 382 ($M^+$); NMR (deuteriodimethyl sulfoxide): 14.75 (s, 1H, COOH), 8.99 (s, 1H, 2-H), 8.30 (s, 1H, vinylic H), 8.16 (dd, $J$ = 4.5, 2.5 Hz, 1H, pyridine 6-H), 8.06 (dd, $J$ = 8.5, 2.0 Hz, 1H, 5-H), 7.84 (ddd, $J$ = 8.0, 7.0, 2.5 Hz, 1H, pyridine 4-H), 7.80 (dd, $J$ = 8.0, 1.5 Hz, 1H, pyridine 3-H), 7.70 (ddd, $J$ = 7.0, 7.0, 2.0 Hz, 1H, 7-H), 7.66 (dd, $J$ = 7.0, 2.0 Hz, 1H, 8-H), 7.27 (ddd, $J$ = 7.0, 4.5, 1.5 Hz, 1H, pyridine 5-H), 4.30 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 4.25 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 1.23 (dd, $J$ = 7.0, 7.0 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{20}H_{15}FN_2O_5$: C, 61.86; H, 4.07; N, 7.21. Found: C, 62.06; H, 3.98; N, 7.28.

**1-[(*Z*)-1-Carboxy-2-(4- and 3-pyridyl)vinyl]-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids 10a,b.** ***General procedure.*** A solution of potassium hydroxide (290 mg, 5.13 mmol) in water (2 mL) was added to a solution of compound **6a** or **6b** (1.0 g, 2.33 mmol) in ethanol (40 mL), and the solution was refluxed for 2 h to precipitate crystals. After cooling of the reaction mixture and then neutralization with hydrochloric acid (1 mol solution), the solvent was evaporated *in vacuo* to afford crystals, which were collected by suction. Recrystallization from *N*,*N*-dimethylformamide/ethanol/water gave yellow needles.

Compound **10a** was obtained in 89% yield (800 mg); mp 285–286°; IR: ν 1730 $cm^{-1}$; ms: m/z 388 ($M^+$), 390 ($M^+$ + 2); NMR (deuteriodimethyl sulfoxide): 14.28 (brs, 1H, COOH), 9.01 (s, 1H, 2-H), 8.51 (d, $J$ = 6.5 Hz, 2H, pyridine 2-H and 6-H), 8.25 (d, $J$ = 9.0 Hz, 1H, 5-H), 8.22 (s, 1H, vinylic H), 8.01 (d, $J$ = 6.0 Hz, 1H, 8-H), 7.93 (s, formyl H of *N*,*N*-dimethylformamide), 7.10 (d, $J$ = 6.0 Hz, 2H, pyridine 3-H and 5-H), 2.81 (s, $CH_3$ of *N*,*N*-dimethylformamide), 2.71 (s, $CH_3$ of *N*,*N*-dimethylformamide). One of two COOH proton signals was not observed presumably due to flattening. Anal. Calcd. for $C_{17}H_{10}ClFN_2O_5 \cdot 1/3H_2O \cdot 2/3HCON(CH_3)_2$ [15]: C, 56.16; H, 3.08; N, 6.89. Found: C, 56.08; H, 3.07; N, 6.93.

Compound **10b** was obtained in 95% yield (860 mg); mp 284–285°; IR: ν 1720 $cm^{-1}$; ms: m/z 388 ($M^+$), 390 ($M^+$ + 2); NMR (deuteriodimethyl sulfoxide): 14.29 (brs, 1H, COOH), 9.02 (s, 1H, 2-H), 8.56 (d, $J$ = 2.0 Hz, 1H, pyridine 2-H), 8.52 (dd, $J$ = 4.5, 2.0 Hz, 1H, pyridine 6-H), 8.27 (s, 1H, vinylic H), 8.25 (d, $J$ = 9.0 Hz, 1H, 5-H), 7.99 (d, $J$ = 6.0 Hz, 1H, 8-H), 7.33 (ddd, $J$ = 8.0, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.28 (dd, $J$ = 8.0, 4.5 Hz, 1H, pyridine 5-H). One of two COOH proton signals was not observed presumably due to flattening. Anal. Calcd. for $C_{17}H_{10}ClFN_2O_5$: C, 55.61; H, 2.59; N, 7.21. Found: C, 55.33; H, 2.70; N, 7.23.

**1-[(*Z*)-1-Carboxy-2-(4-, 3-, and 2-pyridyl)vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids 11a–c.** ***General procedure.*** A solution of potassium hydroxide (300 mg, 5.37 mmol) in water (2 mL) was added to a solution of compound **7a**, **7b**, or **7c** (1.0 g, 2.44 mmol) in ethanol (40 mL), and the solution was refluxed for 2 h to precipitate crystals. After cooling of the reaction mixture and then neutralization with hydrochloric acid (1 mol solution), the solvent was evaporated *in vacuo* to afford crystals, which were collected by suction. Recrystallization from ethanol/water gave analytically pure sample.

Compound **11a** was obtained in 58% yield (500 mg) as yellow needles; mp 270–271°; IR: ν 1720 $cm^{-1}$; ms: m/z 354 ($M^+$); NMR (deuteriodimethyl sulfoxide): 14.80 (brs [17], COOH), 14.51 (brs, 1H, COOH), 9.11, 9.03 [14] (s, 1H, 2-H), 8.50 (d, $J$ = 6.0 Hz, 2H, pyridine 2-H and 6-H), 8.26 (s, 1H, vinylic H), 8.08 (dd, 8.5, 2.5 Hz, 1H, 5-H), 7.76 (ddd, 8.5, 8.5, 2.5 Hz, 1H, 7-H), 7.73 (dd, $J$ = 8.5, 4.5 Hz, 1H, 8-H), 7.06 (d, $J$ = 6.0 Hz, 2H, pyridine 3-H and 5-H). Anal. Calcd. for $C_{17}H_{11}FN_2O_5 \cdot H_2O$ [15]: C, 58.07; H, 3.52; N, 7.52. Found: C, 58.34; H, 3.48; N, 7.40.

Compound **11b** was obtained in 73% yield (630 mg) as colorless needles; mp 246–247°; IR: ν 1710 $cm^{-1}$; ms: m/z 354 ($M^+$); NMR (deuteriodimethyl sulfoxide): 14.53 (brs, 1H, COOH), 9.04 (s, 1H, 2-H), 8.54 (d, $J$ = 2.0 Hz, 1H, pyridine 2-H), 8.51 (dd, $J$ = 4.0, 2.5 Hz, 1H, pyridine 6-H), 8.31 (s, 1H, vinylic H), 8.09 (ddd, $J$ = 8.5, 8.5, 2.5 Hz, 1H, 7-H), 7.75 (dd, $J$ = 7.0, 2.5 Hz, 1H, 5-H), 7.74 ($J$ = 8.5, 5.0 Hz, 1H, 8-H), 7.29 (ddd, $J$ = 8.0, 2.5, 2.0 Hz, 1H, pyridine 4-H), 7.28 (dd, $J$ = 8.0, 4.0 Hz, 1H, pyridine 5-H). One of two COOH proton signals was not observed presumably due to flattening. Anal. Calcd. for $C_{17}H_{11}FN_2O_5 \cdot 2/5H_2O$ [15]: C, 59.57; H, 3.26; N, 7.81. Found: C, 59.47; H, 3.52; N, 7.67.

Compound **11c** was obtained in 56% yield (480 mg) as colorless needles; mp 242–243°; IR: ν 1715 $cm^{-1}$; ms: m/z 354 ($M^+$); NMR (deuteriodimethyl sulfoxide): 14.80 (s, 1H, COOH), 14.05 (brs, 1H, COOH), 8.95 (s, 1H, 2-H), 8.27 (s, 1H, vinylic H), 8.17 (ddd, $J$ = 4.5, 2.0, 0.5 Hz, 1H, pyridine 6-H), 8.06 (dd, $J$ = 8.5, 3.0 Hz, 1H, 5-H), 7.84 (ddd, $J$ = 8.5, 8.0, 2.0 Hz, 1H, pyridine 4-H), 7.76 (dd, $J$ = 8.5, 0.5 Hz, 1H, pyridine 3-H), 7.70 (ddd, $J$ = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.66 (dd, $J$ = 9.0, 4.5 Hz, 1H, 8-H), 7.28 (dd, $J$ = 8.0, 4.5 Hz, 1H, pyridine 5-H). Anal. Calcd. for $C_{17}H_{11}FN_2O_5$: C, 61.02; H, 3.13; N, 7.91. Found: C, 60.72; H, 3.30; N, 7.76.

**Ethyl 1-[(*Z*)-1-ethoxycarbonyl-2-(2-furyl, 2-thienyl, and 3-thienyl)vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylates 16–18.** ***General procedure.*** A solution of compound **15** (2.0 g, 6.23 mmol), [furfural (898 mg, 9.35 mmol), thiophene-2-carbaldehyde (1.74 g, 15.6 mmol), or thiophene-3-carbaldehyde (1.74 g, 15.6 mmol)], 1,8-diazabicyclo[5.4.0]-7-undecene (0.3 mL) in dry *N*,*N*-dimethylformamide (30 mL) was refluxed for 2 h with stirring. Evaporation of the solvent *in vacuo* gave an oily substance, which was crystallized from ethanol/water to afford yellow needles **16**, **17**, or **18**.

Compound **16** was obtained in 59% yield (1.46 g); mp 154–155°; IR: ν 1715, 1700 $cm^{-1}$; ms: m/z 399 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.61 (s, 1H, 2-H), 8.08 (s, 1H, vinylic H), 7.92 (dd, 8.5, 3.0 Hz, 1H, 5-H), 7.75 (d, $J$ = 2.0 Hz, 1H, furan 5-H), 7.55 (ddd, $J$ = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.42 (dd, $J$ = 9.0, 4.5 Hz, 1H, 8-H), 7.00 (d, $J$ = 3.5 Hz, 1H, furan 3-H), 6.60 (dd, $J$ = 3.5, 2.0 Hz, 1H, furan 4-H), 4.26 (dq, $J$ = 10.0, 6.5 Hz, 1H, methylene CH), 4.21 (dq, $J$ = 10.0, 6.5 Hz, 1H, methylene CH), 4.20 (q, $J$ = 6.5 Hz, 2H, $CH_2$), 1.24 (dd, $J$ = 6.5, 6.5 Hz, 3H, $CH_3$), 1.21 (t, $J$ = 6.5 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{21}H_{18}FNO_6$: C, 63.16; H, 4.54; N, 3.51. Found: C, 63.16; H, 4.56; N, 3.68.

Compound **17** was obtained in 60% yield (1.55 g); mp 182–183°; IR: ν 1720 $cm^{-1}$; ms: m/z 415 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.59, 8.55 [14] (s, 1H, 2-H), 8.55 (s, 1H, vinylic H), 7.94 (dd, 9.0, 3.0 Hz, 1H, 5-H), 7.82 (d, $J$ = 3.5, 1.0 Hz, 1H, thiophene 3-H), 7.78 (dd, $J$ = 5.0, 1.0 Hz, 1H, thiophene 5-H), 7.55 (ddd, $J$ = 9.5, 8.0, 3.0 Hz, 1H, 7-H), 7.43 (dd, $J$ = 9.5, 4.5 Hz, 1H, 8-H), 7.16 (dd, $J$ = 5.0, 3.5 Hz, 1H, thiophene 4-H), 4.26 (dq, $J$ = 10.5, 7.0 Hz, 1H, methylene CH), 4.20 (q, $J$ = 7.0 Hz, 2H, $CH_2$), 4.19 (dq, $J$ = 10.5, 7.0 Hz, 1H, methylene CH), 1.24 (dd, $J$ = 7.0, 7.0 Hz, 3H, $CH_3$), 1.22 (t, $J$ = 7.0 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{21}H_{18}FNO_5S$: C, 60.71; H, 4.37; N, 3.37. Found: C, 60.79; H, 4.31; N, 3.74.

Compound **18** was obtained in 51% yield (1.31 g); mp 180–181°; IR: ν 1710, 1682 $cm^{-1}$; ms: m/z 415 ($M^+$); NMR (deuteriodimethyl sulfoxide): 8.59 (s, 1H, 2-H), 8.29 (dd, $J$ = 0.5, 0.5 Hz, 1H, vinylic H), 8.04 (ddd, $J$ = 3.0, 1.5, 0.5 Hz, 1H, thiophene 2-H), 7.94 (dd, $J$ = 9.0, 3.0 Hz, 1H, 5-H), 7.56 (ddd, $J$ = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.52 (dd, $J$ = 5.0, 3.0 Hz, 1H, thiophene 5-H), 7.44 (dd, $J$ = 9.0, 4.0 Hz, 1H, 8-H), 6.45 (ddd, $J$ = 5.0, 1.5, 0.5 Hz, 1H, thiophene 4-H), 4.25 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 4.19 (q, $J$ = 7.0 Hz, 2H, $CH_2$), 4.18 (dq, $J$ = 11.0, 7.0 Hz, 1H, methylene CH), 1.24 (dd, $J$ = 7.0, 7.0 Hz, 3H, $CH_3$), 1.21 (t, $J$ = 7.0 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{21}H_{18}FNO_5S$: C, 60.71; H, 4.37; N, 3.37. Found: C, 60.68; H, 4.40; N, 3.54.

**Conversion of compound 7a into compound 13.** A solution of compound **7a** (2.0 g, 4.88 mmol), hydrazine hydrate (700 mg, 14.0 mmol) in dioxane (36 mL)/*N*,*N*-dimethylformamide (24 mL) was refluxed for 2 h with stirring to precipitate colorless needles. After cooling the reaction mixture, crystals were collected by suction and washed with ethanol to give an analytically pure sample **13** (460 mg, 40%).

## REFERENCES AND NOTES

[1] Kurasawa, Y.; Tsuruoka, A.; Rikiishi, N.; Fujiwara, N.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2000, 37, 791.

[2] Kurasawa, Y.; Sakurai, K.; Kajiwara, S.; Harada, K.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2000, 37, 1257.

[3] Kurasawa, Y.; Ohshima, S.; Kishimoto, Y.; Ogura, M.; Okamoto, Y.; Kim, H. S. Heterocycles 2001, 54, 359.

[4] Kurasawa, Y.; Matsuzaki, I.; Satoh, W.; Okamoto, Y.; Kim, H. S. Heterocycles 2002, 56, 291.

[5] Kurasawa, Y.; Takizawa, J.; Maesaki, Y.; Kawase, A.; Okamoto, Y.; Kim, H. S. Heterocycles 2002, 58, 359.

[6] Kurasawa, Y.; Satoh, W.; Matsuzaki, I.; Maesaki, Y.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2003, 40, 837.

[7] Kurasawa, Y.; Kaji, E.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2005, 42, 249.

[8] Kurasawa, Y.; Kawase, A.; Takizawa, J.; Maesaki, Y.; Kaji, E.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2005, 42, 551.

[9] Kurasawa, Y.; Nakamura, M.; Ashida, H.; Masuda, M.; Kaji, E.; Okamoto, Y.; Kim, H. S. J Heterocycl Chem 2007, 44, 1231.

[10] Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Brundage, R. P.; Castaldi, M. J.; Bailey, T. R.; Carabateas, P. M.; Bacon, E. R.; Young, D. C.; Woods, M. G.; Rosi, D.; Drozd, M. L.; Kullnig, R. K.; Dutko, F. J. J Med Chem 1993, 36, 1580.

[11] Matsumoto, J.; Minami, S. J Med Chem 1968, 11, 160.

[12] Sheu, J.-Y.; Chen, Y.-L.; Fang, K.-C.; Wang, T.-C.; Pen, C.-F.; Tzeng, C.-C. J Heterocycl Chem 1998, 35, 955.

[13] (a) Jensen, J. B.; Trager, W. J Parasitol 1997, 63, 883; (b) Desjardins, R. E.; Canfield, C. J.; Haynes, D. M.; Chulay, J. D. Antimicrob Agents Chemother 1979, 16, 710; (c) Trager, W.; Jensen, J. B. Science 1976, 193, 673; (d) Kim, H. S.; Shibata, Y.; Tshichiya, K.; Masuyama, A.; Nokima, M. J Med Chem 1999, 42, 2604.

[14] Conformational analysis might be necessary for the clarification of such NMR spectral data.

[15] Compounds **6a,b**, **8a,b**, **10a**, and **11a,b** were found to absorb moisture while the procedures of the elemental analyses.

[16] The NOE spectral data (Table 2) showed that compounds **7a** and **9a** were a mixture of the *E*- and *Z*-isomers.

[17] The integral curve of the COOH proton signal was less than 1H size presumably due to flattening by moisture in the sample tube.

# Application of 1,3-Azomethine Ylides Derived from α-Dicarbonyl Compounds and L-Proline to the Synthesis of Pyrrolizidines

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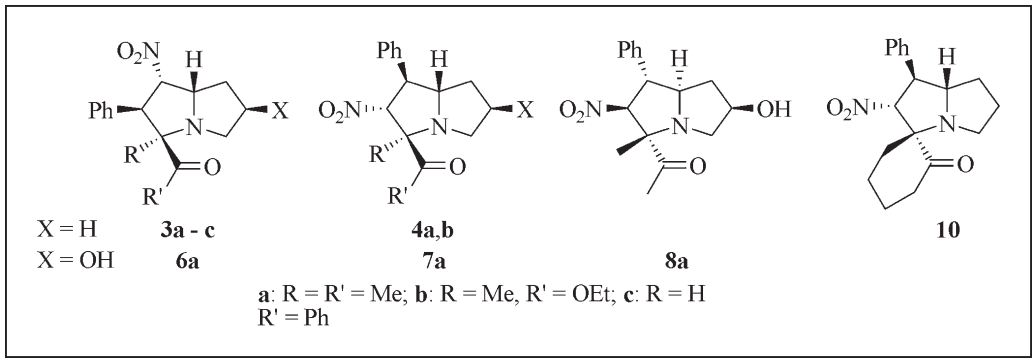


The reaction of 2,3-butanedione, ethyl pyruvate, and phenylglyoxal with β-nitrostyrene and L-proline in isopropanol at room temperature gives substituted pyrrolizidines, as a result of one-pot three component reaction. On the contrary, a spiropyrrolizidine is formed from 1,2-cyclohexanedione only when the reaction is carried out in refluxing isopropanol, whereas at room temperature, incorporation of the amine component into the products is not observed and bicyclo[3.2.1]octanones are formed, as a result of a tandem Michael-Henry reaction. In this latter case, L-proline acts as an organocatalyst, although with modest enantioselectivity. The stereochemistry of the products is given and the mechanism of formation of products is postulated, on the basis of stereochemical arguments.

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## INTRODUCTION

The 1-azabicyclo[3.3.0]octane ring is part of naturally occurring and biologically active pyrrolizidine alkaloids, which are studied for their interesting diverse physiological properties [1]. Construction, also asymmetric, of the pyrrolizidine ring are usually made through multistep reactions [2] and also [3+2]cycloadditions between 1,3-azomethine ylides and activated olefins are widely used [3]. A possible source of 1,3-azomethine ylides is derived from activated carbonyl compounds and L-proline, which can loose carbon dioxide when heated. The resulting 1,3-dipoles can react with aldehydes, to give bicyclic 1,3-oxazolidines [4], or with α,β-unsaturated esters [3(a,e,f)], or nitroolefins [3(b)] to give pyrrolizidine derivatives.

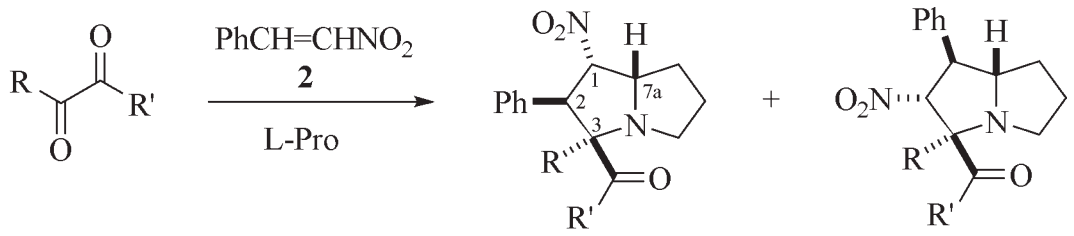
In this work, we report the application of 1,3-azomethine ylides derived from α-dicarbonyl compounds and L-proline to the synthesis of pyrrolizidines by means of 1,3-dipolar cycloaddition reactions to β-nitrostyrene. The use of (2*S*,4*R*)-4-hydroxyproline gave enantiopure polysubstituted pyrrolizidines.

## RESULTS AND DISCUSSION

The α-dicarbonyl compounds examined in this study have been 2,3-butanedione **1a**, ethyl pyruvate **1b**, phenylglyoxal **1c** (Scheme 1), and 1,2-cyclohexanedione **9** (Scheme 3), which were reacted with β-nitrostyrene **2** in isopropanol at room temperature, in the presence of an equimolar amount of L-proline. The reaction of 2,3-butanedione **1a** with β-nitrostyrene **2** in isopropanol at room temperature for 3 days gave two regioisomeric cycloadducts in 3:2 ratio, which were assigned the structures **3a** and **4a**, respectively, on the basis of difference NOE measurements (Table 1). The analogous cycloaddition of ethyl pyruvate **1b** to **2** gave two adducts **3b** and **4b** in 9:1 ratio (Scheme 1), with structural assignments based on analogy and difference NOE measurements (Table 1), while the addition of phenylglyoxal **1c** to **2** furnished a single regioisomer **3c**.

To determine the mechanism of formation of the pyrrolizidines, a reaction was carried out between 2,3-butanedione **1a**, β-nitrostyrene **2** and (2*S*,4*R*)-4-hydroxyproline **5** in isopropanol, so to take advantage of the

**Scheme 1**




| | | | | |
|---|---|---|---|---|
| R = R' = Me | **1a** | 87% (3:2) | **3a** | **4a** |
| R = Me, R' = OEt | **1b** | 90% (9:1) | **3b** | **4b** |
| R = H, R' = Ph | **1c** | 80% | **3c** | |

presence of a stereocenter of known configuration. The reaction was much slower, owing to solubility problems, and gentle warming was necessary to drive the reaction to completion. The reaction products isolated were the pyrrolizidines **6a** and **7a**, analogous to **3a** and **4a**, together with a third isomer **8a**, whose formation can be surely ascribed to the higher temperature used. The relative ratio of compounds **6a–8a** was 1:4:1 (Scheme 2).

X-ray analysis of compound **6a** (Fig. 1) showed the geometry of the substituents and the *cis* fusion of the rings. To validate the use of NOE measurements to determine the geometry of the other pyrrolizidines, difference NOE experiments (Table 1) were carried out also on **6a**, whose results were in complete accordance with the X-ray determination. The ring junction in all pyrrolizidines was determined by an analysis of their IR spectra. The Bohlmann bands [5] between 2800 and 2600 $cm^{-1}$, which are correlated with the presence of a C—H bond antiperiplanar to the nitrogen lone pair, were present only for compound **8a** (2724 and 2671 $cm^{-1}$), which was therefore assigned the *trans* fusion, whereas pyrrolizidines **3a–c**, **4a**,**b** and **6a**, **7a** which lack these bands, were assigned the *cis* fusion.

1,2-Cyclohexanedione **9** has been chosen as another candidate for synthesizing pyrrolizidine target compounds. Indeed, the reaction of the substrate **9** with β-nitrostyrene **2**, carried out in refluxing isopropanol for 2 h gave as the main reaction product (90%) the nitrospiro pyrrolizidine **10** (Scheme 3, right side). Its stereochemistry was assigned as depicted in Scheme 3. The relative configuration of the spiro carbon atom C-3′ was confirmed by the resonance value found for the axial proton

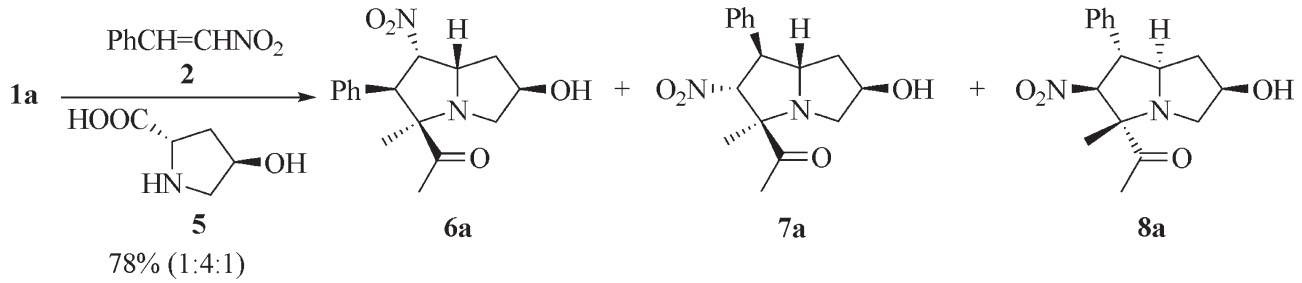
**Table 1**

Difference NOE experiments carried out on the pyrrolizidines.

| | Irradiated protons | | | | | |
|---|---|---|---|---|---|---|
| Compound | H-1 (H-1′ for **10**) | H-2 (H-2′ for **10**) | H-3 | H-6 | H-7a (H-7′a for **10**) | Me |
| **3a** | *o*-Ph (8), H-7a (9) | Me (4), H-5 at 2.91 (6), H-7 at 1.33 (2) | | | H-1 (9), H-7 at 2.04 (5) | H-2 (4) |
| **3b** | *o*-Ph (10), H-7a (10) | Me (9), H-5 at 2.90 (4) | | | H-1 (10), H-7 at 2.07 (6) | H-2 (9) |
| **3c** | *o*-Ph (7), H-7a (11) | H-3 (7), H-5 at 2.81 (4) | H-2 (9), H-5 at 2.81 (6) | | H-1 (10), *o*-Ph (7), H-7 at 2.06 (8) | |
| **4a** | Me (6), H-5 at 3.19 (5), H-7 at 1.75 (4) | *o*-Ph (5), H-7a (3) | | | *o*-Ph (6), H-2 (3), MeCO (2) | H-1 (6), H-5 at 3.19 (5) |
| **4b** | H-5 at 3.13 (3), H-7 at 1.72 (4), Me (3) | *o*-Ph (8), H-7a (4) | | | Me (4), *o*-Ph (11), H-2 (4), H-5 at 3.13 (3) | H-7a (4), H-5 at 3.13 (3) |
| **6a** | *o*-Ph (11), H-7a (8) | Me (7), H-5 at 3.12 (5), H-6 (4) | | H-2 (4), H-5 at 3.12 (3), H-7 at 1.63 (4) | H-1 (8), H-7 at 2.15 (3) | H-2 (4) |
| **7a** | H-5 at 3.37 (6), H-7 at 2.18 (6) | *o*-Ph (5), H-7a (5), H-7 at 2.03 (4) | | H-5 at 3.37 (5), H-7 at 2.18 (8) | *o*-Ph (4), MeCO (2), H-7 at 2.03 (3) | H-5 at 3.37 (2), MeCO (2) |
| **8a** | H-5 at 3.21 (3), H-7 at 1.74 (6), Me (1) | *o*-Ph (8) | | H-5 at 3.34 (5), H-7 at 2.32 (4) | *o*-Ph (5) | H-5 at 3.21 (6) |
| **10** | H-7 at 3.20 (2) | *o*-Ph (7), H-5 at 1.64 (2) | | | *o*-Ph (5) | |

η Values (%) in parenthesis for enhanced protons.

**Scheme 2**




at C-2 which is strongly deshielded with respect to its geminal equatorial one (3.20 *vs*. 2.39 ppm) by the anisotropic effect of the nitro group that is spatially close to it.

Interestingly, when the same reaction was carried out at room temperature, even under solvent-free conditions, two adducts were obtained in 9:1 ratio (Scheme 3, left side). These compounds were assigned the structures **11** and **12**, on the basis of $^1$H NMR spectra and X-ray analysis carried out on compound **12**. The two isomers were separated by flash chromatography and they proved weakly optically active ($[\alpha]_D^{25} = +0.05$ (*c* 2.65, MeOH) for **11** and $[\alpha]_D^{25} = -2.6$ (*c* 0.15, MeOH) for **12**, 14% e.e., determined by HPLC on chiral column), thus demonstrating the organocatalytic capability of L-proline, albeit modest, in this particular case.

X-ray analysis of compound **12** (Fig. 2) showed that the geometry of phenyl and the nitro group was *cis,* both groups being *exo* oriented. The stereochemistry of its diastereomer **11** was determined by $^1$H NMR analysis. In fact, in **12,** the coupling constant between H-6 and H-7 was larger than in **11** ($J_{6,7} = J_{endo,exo} = 5.8$ Hz for **11**, $J_{6,7} = J_{endo,endo} = 9.5$ Hz for **12**), thus demonstrating the *trans* relationship between the phenyl group and the nitro group in **11** [6]. The orientation of the phenyl group was assigned as *exo* also in **11**. In fact, the coupling constant between H-5 and the benzylic proton H-6 was zero, thus indicating a dihedral angle of 90° between them, which is only consistent with the *endo* orientation of the benzylic proton itself.

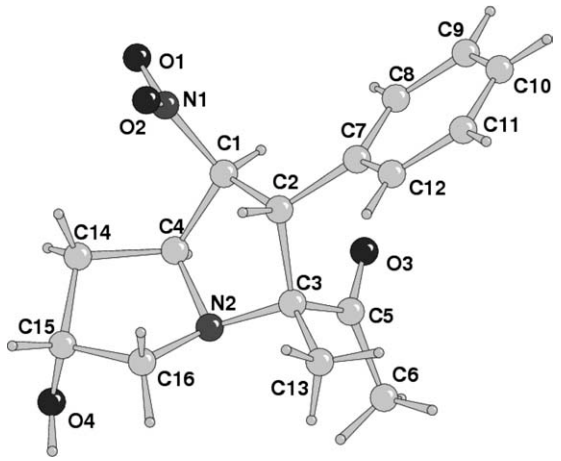



**Figure 1.** Molecular structure of compound **6a.**

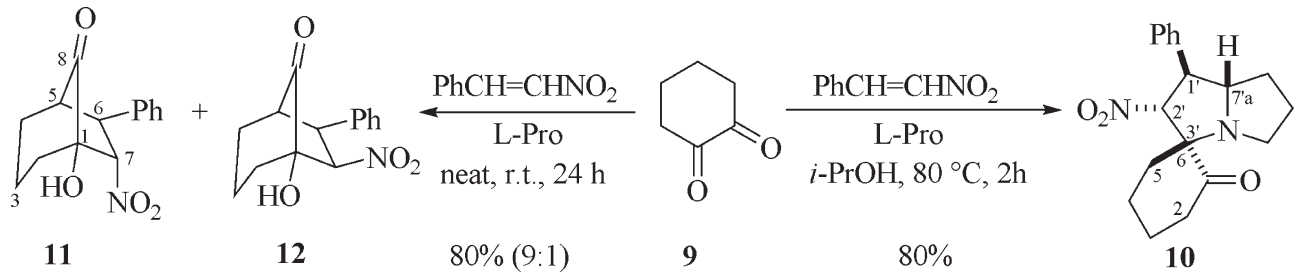
## MECHANISM OF THE REACTIONS

The mechanism of pyrrolizidine formation can be inferred from the stereochemistry of the products and in particular from compounds **6a** and **7a**, whose absolute configurations are known, given the *R* absolute configuration of the carbinol carbon atom. Since the majority of the pyrrolizidines in this work are *cis* fused [7], the first formed carbon—carbon bond (C1-C7a) occupies the same position as the carboxy group in the original pyrrolidine ring. Therefore, it seems reasonable to postulate that formation of the intermediate **13** (Scheme 4, illustrated for 2,3-butanedione **1a** as the substrate) is immediately followed by elimination of carbon dioxide with the creation of the 1,3-dipole **14**, existing in two resonance structures **a** and **b**. Both regioisomeric adducts **6a** and **7a** derived from the less encumbered *exo-anti* transition states, while adduct **8a** arose from the *exo-syn* transition state. The same reaction mechanism may be invoked for the formation of the other pyrrolizidines **3a–c**, **4a**,**b** derived from linear 1,2,-dicarbonyl compounds and **10** derived from 1,2-cyclohexanedione.

In the reaction of 1,2-cyclohexanedione **9** with β-nitrostyrene **2** performed at room temperature, L-proline initially reacts with the substrate **9** to give the corresponding cross-conjugated enaminone **15** (Scheme 5) which reacts with the nitroolefin in a Michael-type addition, through a two step mechanism, with subsequent ring closure in **16**, by collapse of the carbanion onto the carbonyl carbon atom. The consequent zwitterion **17** is hydrolysed *in situ* to afford eventually the two diastereomers **11** and **12**.

The easier loss of carbon dioxide observed for the adduct between L-proline and 2,3-butanedione with respect to the analogous intermediate from 1,2-cyclohexanedione could be ascribed to the s-*trans* geometry

**Scheme 3**




between the carbonyl group and the iminium group in the former which would facilitate the expulsion of carbon dioxide in the former compound.

## EXPERIMENTAL

IR spectra were recorded on a Jasco FT/IR 200 spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were run on a Jeol EX-400 spectrometer (400 MHz for proton, 100.1 MHz for carbon), and on a Jeol EX-270 spectrometer (270 MHz for proton, 68 MHz for carbon) using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in parts per million (δ). Coupling constants are given in Hz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. Mass spectra were recorded on a ion trap instrument Finnigan GCQ (70 eV). HPLC analysis were run on a Hewlett Packard Series 1100 instrument the chiral column being a Lux 5 μm Cellulose-2 (Phenomenex) with a Cellulose tris(3-chloro-4-methylphenylcarbammate) chiral stationary phase, eluent: *n*-hexane/isopropanol 75:25, detector UV 220 nm; TLC's were performed on Polygram® Sil G/UV$_{254}$ silica gel pre-coated plastic sheets. Flash chromatography was run on silica gel for flash-chromatography (BDH). Elemental analyses were determined on a Carlo Erba 1106 instrument, at the Department of Chemical Sciences and Technologies of the University of Udine, Italy. Light petroleum refers to the fraction with b.p. 40–70°C and ether to diethyl ether. 2,3-Butanedione, L-proline, (2*S*,4*R*)-4-hydroxyproline, and β-nitrostyrene were purchased from Sigma-Aldrich and 1,2-cyclohexanedione was purchased from Lancaster.

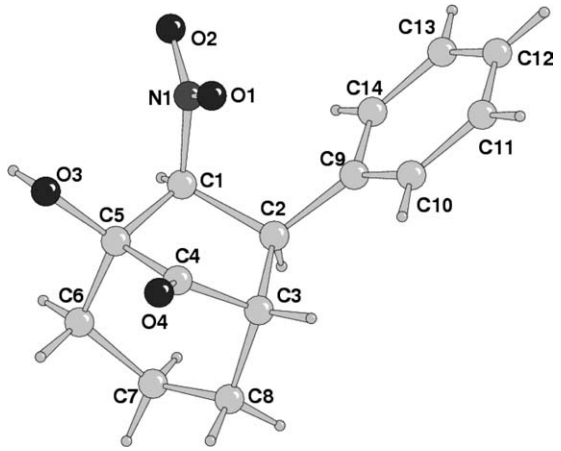


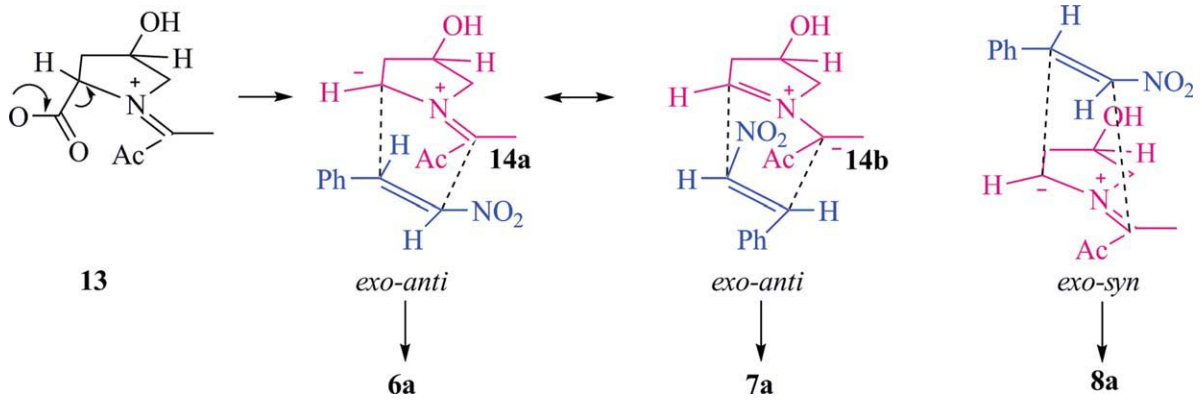

**Figure 2.** Molecular structure of compound **12**.

**General procedure for the reactions between α-dicarbonyl compounds 1a–c and 9, β-nitrostyrene 2 and L-proline or (2*S*,4*R*)-4-hydroxyproline 5.** To the α-dicarbonyl compound (1.0 mmol) in isopropanol (10 mL), β-nitrostyrene (1.0 mmol) and the appropriate proline derivative (1.0 mmol) were added. The mixture was set aside at room temperature until completion of the reaction, which needed different times depending on the substrate (96 h for diacetyl and 24 h for 1,2-cyclohexanedione). The solvent was eliminated and the crude reaction mixture was chromatographed on silica gel (eluent: *n*-heptane–ethyl acetate, gradient).

**(1S*,2S*,3R*,7aS*)-3-Acetyl-3-methyl-1-nitro-2-phenylazabicyclo[3.3.0]octane (3a).** Oil, 52% yield, after purification. $R_f$ 0.15 (eluent: light petroleum–ethyl acetate 4:1). IR (neat) 3050, 3032, 1603, 1498, 761, 733, 702 (Ph), 1708 (C=O), 1545, 1375, 1352 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 5H, Ph), 5.95 (dd, $J_1$ = 10.6 Hz, $J_2$ = 9.1 Hz, 1H, H-1), 4.30 (dt, $J_1$ = 9.1 Hz, $J_2$ = $J_3$ = 7.8 Hz, 1H, H-7a), 3.85 (d, $J$ = 10.6 Hz, 1H, H-2), 3.04 (m, 1H, H-5), 2.93 (ddd, $J_1$ = 11.2 Hz, $J_2$ = 8.1 Hz, $J_3$ = 5.3 Hz, 1H, H-5), 2.05 (m, 1H, H-7), 1.94 (m, 1H, H-6), 1.91 (s, 3H, $CH_3CO$), 1.83 (m, 1H, H-6), 1.38 (s, 3H, $CH_3$), 1.33 (m, 1H, H-7); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 207.7 (s), 133.8 (s), 129.0 (2d), 128.6 (2d), 127.7 (d), 93.1 (d, C-1), 74.5 (s, C-3), 64.0 (d, C-7a), 55.2 (d, C-2), 48.9 (t, C-5), 27.7 (t, C-7), 27.1 (q, $CH_3CO$), 25.6 (t, C-6), 19.2 (q, $CH_3$); *m/z* 289 (2, M+1), 245 (45, M+1—$CH_3CO$), 199 (100, 245—$NO_2$), 184 (56, 199—$CH_3$). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; Found: C, 66.82; H, 7.12; N, 9.88.

**(1S*,2R*,3R*,7aS*)-3-Acetyl-3-methyl-2-nitro-1-phenylazabicyclo[3.3.0]octane (4a).** Oil, 35% yield, after purification. $R_f$ 0.65 (eluent: light petroleum–ethyl acetate 4:1). IR (neat) 3063, 3030, 1603, 1496, 742, 700 (Ph), 1714 (C=O), 1548, 1361 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 3H, Ph), 7.25 (bd, 2H, Ph), 6.09 (d, $J$ = 8.4 Hz, 1H, H-2), 3.84 (dd, $J_1$ = 8.4 Hz, $J_2$ = 9.6 Hz, 1H, H-1), 3.22 (m, 1H, H-7a), 3.19 (dd, $J_1$ = 8.8 Hz, $J_2$ = 6.9 Hz, 1H, H-5), 3.01 (m, 1H, H-5), 2.46 (s, 3H, $CH_3CO$), 2.10 (m, 1H, H-6), 2.05 (m, 2H, H-6, H-7), 1.76 (m, 1H, H-7), 1.46 (s, 3H, $CH_3$); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 207.6 (s), 137.8 (s), 128.9 (2d), 127.8 (2d), 127.5 (d), 98.4 (d, C-2), 76.4 (s, C-3), 70.8 (d, C-7a), 56.7 (d, C-1), 46.4 (t, C-5), 28.2 (t, C-7), 24.4 (t, C-6), 24.1 (q, $CH_3CO$), 16.1 (q, $CH_3$); *m/z* 289 (5, M+1), 245 (40, M+1—$CH_3CO$), 199 (100, 245—$NO_2$), 184 (60, 199—$CH_3$). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; Found: C, 66.91; H, 6.80; N, 9.56.

**Scheme 4**

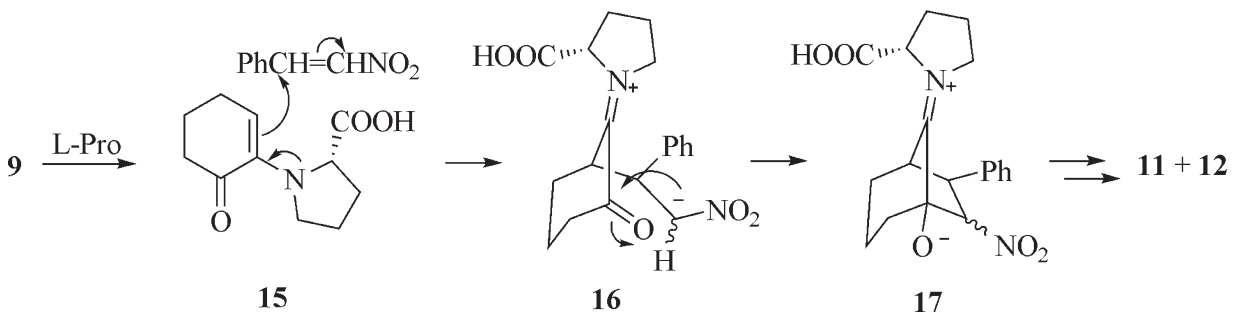



**(1S*,2S*,3R*,7aS*)-3-Methyl-1-nitro-2-phenylazabicyclo[3.3.0] octane-3-carboxylic acid ethyl ester (3b).** Mp 101–102°C, 85% yield, after purification. $R_f$ 0.30 (eluent: *n*-heptane–ethyl acetate 4:1). IR ($CHCl_3$) 3080, 3060, 1598, 1498, 770, 701, 669 (Ph), 1686 (C=O), 1549, 1376 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H, Ph), 7.19 (m, 2H, *o*-Ph), 5.90 (dd, $J_1$ = 10.6 Hz, $J_2$ = 9.1 Hz, 1H, H-1), 4.64 (bq, $J$ = 9.1 Hz, 1H, H-7a), 3.99 (dq, 2H, $CH_2O$), 3.90 (d, $J$ = 10.6 Hz, 1H, H-2), 3.04 (m, 1H, H-5 *cis* to H-7a), 2.90 (m, 1H, H-5 *trans* to H-7a), 2.07 (m, 1H, H-7 *cis* to H-7a), 1.93 (m, 1H, H-6), 1.85 (m, 1H, H-6), 1.48 (s, 3H, $CH_3$), 1.35 (m, 1H, H-7), 1.08 (t, 3H, $CH_3CH_2O$); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 172.6 (s), 133.7 (s), 128.6 (2d), 128.1 (2d), 128.0 (d), 93.3 (d, C-1), 72.4 (s, C-3), 65.0 (d, C-7a), 61.0 (t, $CH_2O$), 55.8 (d, C-2), 49.5 (t, C-5), 27.9 (t, C-7), 25.5 (t, C-6), 18.5 (q, $CH_3$), 13.8 (q, $CH_3CH_2O$); *m/z* 319 (12, M+1), 272 (38, M—$NO_2$), 245 (50, M—COOEt), 199 (30, M—COOEt—$NO_2$), 198 (100, M—COOEt—$HNO_2$), 183 (15), 170 (20). Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80; Found: C, 63.85; H, 6.83; N, 8.73.

**(1S*,2R*,3R*,7aS*)-3-Methyl-2-nitro-1-phenylazabicyclo[3.3.0] octane-3-carboxylic acid ethyl ester (4b).** Oil, 5% yield, after purification. $R_f$ 0.50 (eluent: *n*-heptane–ethyl acetate 4:1). IR (neat) 3064, 3031, 1603, 1498, 752, 701 (Ph), 1723 (C=O), 1550, 1367 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H, Ph), 5.92 (d, $J$ = 9.6 Hz, 1H, H-2), 4.30 (dq, 2H, $CH_2O$), 3.72 (q, 1H, H-7a), 3.69 (dd, $J_1$ = 8.4 Hz, $J_2$ = 9.6 Hz, 1H, H-1), 3.13 (dd, $J_1$ = 9.0 Hz, $J_2$ = 6.8 Hz, 1H, H-5 *trans* to H-7a), 2.93 (m, 1H, H-5 *cis* to H-7a), 2.00 (3H, m, 2 H-6, H-7), 1.76 (m, 1H, H-7), 1.45 (s, 3H, $CH_3$), 1.34 (t, 3H, $CH_3CH_2O$); $^1$H NMR (400 MHz, $CD_3OH$): δ 7.30 (m, 5H, Ph), 5.90 (d, $J$ = 9.9 Hz, 1H, H-2), 4.29 (dq, 2H, $CH_2O$), 3.71 (t, $J_1$ = 9.9 Hz, $J_2$ = 10.1 Hz, 1H, H-1), 3.63 (m, 1H, H-7a), 3.17 (m, 1H, H-5 *trans* to H-7a), 2.88 (m, 1H, H-5 *cis* to H-7a), 2.04 (m, 1H, H-6), 1.91 (m, 2H, H-6, H-7), 1.73 (m, 1H, H-7), 1.42 (s, 3H, $CH_3$), 1.32 (t, 3H, $CH_3CH_2O$); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 172.5 (s), 137.8 (s), 128.9 (2d), 127.7 (2d), 127.6 (d), 99.2 (d, C-2), 70.6 (s, C-3), 70.2 (d, C-7a), 62.2 (t, $CH_2O$), 54.8 (d, C-1), 46.6 (t, C-5), 29.0 (t, C-7), 25.2 (t, C-6), 16.0 (q, $CH_3$), 14.0 (q, $CH_3CH_2O$); *m/z* 319 (10, M+1), 272 (40, M—$NO_2$), 245 (90, M—COOEt), 199 (100, M—COOEt—$NO_2$), 198 (80, M—COOEt—$HNO_2$), 184 (80, 199—$CH_3$). Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80; Found: C, 64.86; H, 6.74; N, 8.68.

**(1S*,2S*,3R*,7aS*)-3-Benzoyl-1-nitro-2-phenylazabicyclo[3.3.0] octane (3c).** Oil, 80% yield, after purification. $R_f$ 0.15 (eluent: light petroleum–ethyl acetate 4:1). IR (neat) 3088, 3065, 1598, 1581, 1496, 754, 698 (Ph), 1686 (C=O), 1545, 1375 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.65 (bd, 2H, *o*-PhCO), 7.45 (bt, 1H, *p*-PhCO), 7.32 (bt, 2H, *m*-PhCO), 7.09 (m, 5H, Ph), 5.48 (dd, $J_1$ = 7.8 Hz, $J_2$ = 5.3 Hz, 1H, H-1), 5.32 (d, $J$ = 7.3 Hz, 1H, H-3), 4.49 (m, 2H, H-2, H-7a), 3.42 (m, 1H, H-5), 2.81 (m, 1H, H-5), 2.06 (m, 3H, 2 H-6, H-7), 1.49 (m, 1H, H-7); $^1$H NMR (400 MHz, $CD_3OH$): δ 8.05 (bd, 2H, *o*-PhCO), 7.70 (bd, 2H, *o*-Ph), 7.55 (bt, 1H, *p*-PhCO), 7.32 (bt, 2H, *m*-PhCO), 7.10 (m, 3H, Ph), 5.50 (t, $J$ = 7.8 Hz, 9.5 Hz, 1H, H-1), 5.18 (d, $J$ = 7.7 Hz, 1H, H-3), 4.51 (dd, $J_1$ = 9.5 Hz, $J_2$ = 7.7 Hz, 1H, H-2), 4.31 (dt, $J_1$ = 9.5 Hz, $J_2$ = 7.7 Hz, 1H, H-7a), 3.35 (m, 1H, H-5), 2.89 (m, 1H, H-5), 2.30 (m, 3H, 2 H-6, H-7), 2.15 (m, 1H, H-7); $^{13}$C NMR (100.1

**Scheme 5**



MHz, $CDCl_3$): δ 198.2 (s), 136.8 (s), 135.1 (s), 133.0 (d, *p*-PhCO), 128.8 (2d, Ph), 128.5 (2d, *m*-PhCO), 128.1 (d, Ph), 127.9 (2d, Ph), 127.9 (2d, *o*-PhCO), 92.6 (d, C-1), 73.5 (s, C-3), 67.0 (d, C-7a), 55.6 (t, C-5), 53.3 (d, C-2), 28.2 (t, C-7), 27.4 (t, C-6); *m*/*z* 317 (2, M+1), 286 (20), 231 (95, M—PhCO), 184 (100, M—PhCO—$HNO_2$), 156 (45). Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.02; H, 5.72; N, 8.40.

**(1S,2S,3R,6R,7aS)-3-Acetyl-6-hydroxy-3-methyl-1-nitro-2-phenylazabicyclo[3.3.0]octane (6a).** Colorless solid, mp 118–119°C, 48% yield, after purification. $R_f$ 0.10 (eluent: *n*-heptane: ethyl acetate 1:3). IR ($CDCl_3$) 3399 (OH), 3051, 3032, 1590, 1501, 734, 702 (Ph), 1706 (C=O), 1546, 1376 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 5H, Ph), 5.95 (dd, $J_1$ = 10.2 Hz, $J_2$ = 9.1 Hz, 1H, H-1), 4.51 (bq, $J$ = 8.2 Hz, 1H, H-7a), 4.49 (b signal, 1H, H-6), 3.87 (d, $J$ = 10.2 Hz, 1H, H-2), 3.13, 3.06 (part AB of an ABX system, $J_{AB}$ = 9.5 Hz, $J_{AX}$ = 3.3 Hz, $J_{BX}$ = 1.2 Hz, 2H, 2 H-5), 2.12 (dd, $J_1$ = 8.2 Hz, $J_2$ = 14.3 Hz, 1H, H-7), 2.06 (bs, 1H, OH), 1.91 (s, 3H, $CH_3CO$), 1.65 (ddd, $J_1$ = 14.3 Hz, $J_2$ = 7.9 Hz, $J_3$ = 5.3 Hz, 1H, H-7), 1.56 (s, 3H, $CH_3$); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 207.6 (s), 133.5 (s), 129.0 (2d), 128.7 (2d), 127.9 (d), 93.4 (d, C-1), 74.5 (s, C-3), 72.0 (d, C-6), 62.8 (d, C-7a), 56.2 (t, C-5), 55.9 (d, C-2), 36.9 (t, C-7), 27.3 (q, $CH_3CO$), 19.4 (q, $CH_3$); *m*/*z* 304 (<1, $M^{+\bullet}$), 261 (56, M—$CH_3CO$), 215 (28, M—$CH_3CO$—$NO_2$), 214 (100, M—$CH_3CO$—$HNO_2$), 196 (25, 214—$H_2O$), 170 (10); Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 63.14; H, 6.62; N, 9.20; Found: C, 63.27; H, 6.80; N, 9.09; $[\alpha]_D^{25}$ = –120.5 (*c* 0.36, $CHCl_3$).

**(1S,2R,3R,6R,7aS)-3-Acetyl-6-hydroxy-3-methyl-2-nitro-1-phenylazabicyclo[3.3.0]octane (7a).** Semisolid material, 15% yield, after purification, $R_f$ 0.23 (eluent: *n*-heptane: ethyl acetate 1:3). IR ($CDCl_3$) 3406 (OH), 3050, 3032, 1603, 1496, 731, 701 (Ph), 1713 (C=O), 1549, 1359 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (m, 3H, Ph), 7.15 (bd, 2H, Ph), 6.10 (d, $J$ = 8.1 Hz, 1H, H-2), 4.57 (b signal, 1H, H-6), 3.83 (dd, $J_1$ = 8.1 Hz, $J_2$ = 10.6 Hz, 1H, H-1), 3.39, 3.37 (m + dd, $J_1$ = 4.0 Hz, $J_2$ = 9.9 Hz, 2H, H-7a, H-5), 3.05 (bd, $J$ = 9.9 Hz, 1H, H-5), 2.42 (s, 3H, $CH_3CO$), 2.18 (ddd, $J_1$ = 3.3 Hz, $J_2$ = 5.9 Hz, $J_3$ = 14.6 Hz, 1H, H-7), 2.06 (s + ddt, $J_1$ = 14.6 Hz, $J_2$ = 7.5 Hz, $J_3$ = 1.2 Hz, 2H, OH + H-7), 1.39 (s, 3H, $CH_3$); $^1$H NMR (400 MHz, $CD_3OH$): δ 7.30 (m, 5H, Ph), 6.00 (d, $J$ = 8.8 Hz, 1H, H-2), 4.55 (b signal, 1H, H-6), 3.82 (dd, $J_1$ = 8.8 Hz, $J_2$ = 9.9 Hz, 1H, H-1), 3.46 (ddd, 1H, H-7a), 3.36 (dd, $J_1$ = 4.6 Hz, $J_2$ = 10.1 Hz, 1H, H-5), 2.99 (d, $J$ = 10.1 Hz, 1H, H-5), 2.43 (s, 3H, $CH_3CO$), 2.14 (ddd, 1H, H-7), 1.91 (ddt, 1H, H-7), 1.34 (s, 3H, $CH_3$); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 207.0 (s), 137.2 (s), 129.1 (2d), 127.8 (2d), 127.7 (d), 98.5 (d, C-2), 76.1 (s, C-3), 72.3 (d, C-6), 69.1 (d, C-7a), 57.1 (d, C-1), 55.1 (t, C-5), 39.7 (t, C-7), 24.2 (q, $CH_3CO$), 16.2 (q, $CH_3$); *m*/*z* 304 (<1, $M^{+\bullet}$), 261 (58, M—$CH_3CO$), 215 (100, M—$CH_3CO$—$NO_2$), 214 (18, M—$CH_3CO$—$HNO_2$), 200 (28), 170 (15). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 63.14; H, 6.62; N, 9.20; Found: C, 63.32; H, 6.85; N, 9.02; $[\alpha]_D^{25}$ = +71.8 (*c* 0.87, $CHCl_3$).

**(1R,2S,3S,6R,7aR)-3-Acetyl-6-hydroxy-3-methyl-2-nitro-1-phenylazabicyclo[3.3.0]octane (8a).** Colorless solid, mp 166–167°C, 15% yield, after purification, $R_f$ 0.27 (eluent: *n*-heptane: ethyl acetate 1:3). IR (nujol) 3181 (OH), 2724, 2671 (CH), 1713 (C=O), 1602, 1493, 701 (Ph), 1549, 1359 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 3H, Ph), 7.25 (bd, 2H, Ph), 6.10 (d, $J$ = 8.4 Hz, 1H, H-2), 4.59 (b signal, 1H, H-6), 4.18 (dd, $J_1$ = 8.4 Hz, $J_2$ = 10.5 Hz, 1H, H-1), 3.35 (dd, $J_1$ = 9.0 Hz, $J_2$ = 6.4 Hz, 1H, H-5), 3.22 (dd, $J_1$ = 9.0 Hz, $J_2$ = 7.3 Hz, 1H, H-5), 3.20 (ddd, $J_1$ = 2.9 Hz, $J_2$ = 7.7 Hz, $J_3$ = 10.5 Hz, 1H, H-7a), 2.34 (s + m, 4H, $CH_3CO$, H-7), 1.84 (bd, 1H, OH), 1.78 (ddd, $J_1$ = 2.9 Hz, $J_2$ = 5.1 Hz, $J_3$ = 13.7 Hz, 1H, H-7), 1.38 (s, 3H, $CH_3$); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 207.0 (s), 137.4 (s), 129.0 (2d), 127.8 (2d), 127.7 (d), 98.0 (d, C-2), 77.2 (s, C-3), 72.3 (d, C-6), 69.8 (d, C-7a), 57.1 (d, C-1), 54.4 (t, C-5), 38.0 (t, C-7), 24.1 (q, $CH_3CO$), 16.2 (q, $CH_3$); *m*/*z* 304 (<1, $M^{+\bullet}$), 261 (56, M—$CH_3CO$), 215 (30, M—$CH_3CO$—$NO_2$), 214 (100, M—$CH_3CO$—$HNO_2$), 196 (32, 214—$H_2O$), 170 (12). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 63.14; H, 6.62; N, 9.20; Found: C, 63.22; H, 6.74; N, 9.13; $[\alpha]_D^{25}$ = –83.3 (*c* 0.09, $CHCl_3$).

**(1′S*,2′R*,3′S*,7′aS*)-2′-Nitro-1′-phenylspiro[cyclohexanone-6,3′-pyrrolizidine (10).** Colorless oil, 70% yield, after purification. IR (neat) 3063, 3029, 1603, 1497, 757, 701 (Ph), 1713 (CO), 1545, 1361 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H, Ph), 6.16 (d, $J$ = 7.7 Hz, 1H, H-2′), 3.81 (dd, $J_1$ = 10.6 Hz, $J_2$ = 7.7 Hz, 1H, H-1′), 3.28–3.15 (m, 3H, H-2, H-5′, H-7′a) [The three overlapping signals are as follows: 3.20 (dt, $J_1$ = $J_2$ = 14.0 Hz, $J_3$ = 6.0 Hz, 1H, H-2), 3.20 (m, 2H, H-5′), 3.18 (m, 1H, H-7′a)], 3.12 (dt, 1H, H-5′), 2.39 (bd, $J$ = 14.0 Hz, 1H, H-2), 2.20–2.05 (m, 3H, H-5, H-6′, H-7′), 2.00–1.77 (m, 4H, H-3, H-4, H-6′, H-7′), 1.77–1.58 (m + dt, 2H, H-3, H-5); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 207.8 (s), 138.2 (s), 128.9 (2d), 128.1 (2d), 127.4 (d), 98.3 (d, C-2′), 76.9 (s, C-3′), 70.7 (d, C-7′a), 56.8 (d, C-1′), 45.0 (t, C-5′), 37.9 (t, C-2), 30.9 (t, C-5), 27.0 (t, C-7′), 26.9 (t, C-3), 23.4 (t, C-6′), 22.2 (t, C-4); *m*/*z* 315 (10, M+1), 268 (78, M+1—$NO_2$), 240 (45, 268—CO), 171 (100), 143 (30), 129 (92), 70 (65). Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91; Found: C, 68.91; H, 7.25; N, 8.75.

**(1S*,5S*,6R*,7R)-1-Hydroxy-7-nitro-6-phenylbicyclo[3.2.1]octan-8-one (11).** Semisolid material, 73% yield, after purification, $R_f$ 0.40 (eluent: light petroleum–ethyl acetate 4:1). IR ($CCl_4$) 3454 (OH), 3050, 3030, 1498, 788, 754, 700 (Ph), 1764 (C=O), 1549, 1370 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 3H, Ph), 7.15 (bd, 2H, Ph), 4.81 (d, $J$ = 5.8 Hz, 1H, H-7), 4.18 (d, $J$ = 5.8 Hz, 1H, H-6), 3.36 (bs, 1H, OH), 2.78 (dd, $J_1$ = 4.4 Hz, $J_2$ = 1.8 Hz, 1H, H-5), 2.35 (m, 2H, $CH_2$), 2.11 (m, 1H, ring CH), 2.00 (s, 2H, $CH_2$), 1.75 (m, 1H, ring CH); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 212.5 (s), 142.3 (s), 129.4 (2d), 127.8 (d), 126.7 (2d), 93.6 (d, C-7), 81.6 (s, C-1), 51.6 (d, C-5), 43.9 (d, C-6), 39.8 (t, C-2), 36.0 (t, C-4), 17.9 (t, C-3); *m*/*z* 261 (11, $M^{+\bullet}$), 229 (20, M—NO—$H_2$), 197 (10, M—$NO_2$—$H_2O$), 169 (100, 197–28), 141 (48, 169–28). Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; Found: C, 64.40; H, 5.87; N, 5.40.

**(1S*,5S*,6R*,7S)]-1-Hydroxy-7-nitro-6-phenylbicyclo[3.2.1]octan-8-one (12).** Mp 146–147°C, from cyclohexane, 7% yield, after purification. $R_f$ 0.30 (eluent: light petroleum–ethyl acetate 4:1). IR (nujol) 3425 (OH), 3050, 3030, 1496, 743, 721, 695 (Ph), 1752 (C=O), 1553 ($NO_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H, Ph), 7.16 (bd, 2H, Ph), 5.29 (d, $J$ = 9.5 Hz, 1H, H-7), 3.92 (d, $J$ = 9.5 Hz, 1H, H-6), 3.22 (bs, 1H, OH), 3.05 (b signal, $W_H$ = 9.2 Hz, 1H, H-5), 2.41 (m, 1H), 2.20–2.05 (m, 3H, ring CH), 2.02–1.83 (m, 2H); $^{13}$C NMR (100.1 MHz, $CDCl_3$): δ 213.9 (s), 136.3 (s), 128.7 (2d), 128.5 (2d), 127.8 (d), 91.0 (d, C-7), 80.0 (s, C-1), 47.1 (d, C-5), 44.3 (d, C-6), 41.2 (t, C-2), 35.9 (t, C-4), 17.6 (t, C-3). Anal. Calcd.

for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; Found: C, 64.42; H, 5.93; N, 5.50.

**Crystal structure determinations.** Diffraction data for the structures reported were collected at room temperature on a Nonius DIP-1030H system (Mo-K$\alpha$ radiation, $\lambda = 0.71073$ Å). Both the structures were solved by direct methods and refined by the full-matrix least-squares method based on $F^2$ with all observed reflections [8]. The calculations were performed using the WinGX System, Ver 1.80.05 [9].

**Crystal data for 6a.** $C_{16}{\cdot}H_{20}{\cdot}N_2{\cdot}O_4$, fw = 304.34 g/mol; Tetragonal, $P\ 4_1$, $a = 13.640(3)$, $c = 8.299(2)$ Å, $V = 1544.0(6)$ Å$^3$, $Z = 4$, $D_{calcd} = 1.309$ g/cm$^3$, $\mu$(Mo-K$\alpha$) = 0.095 mm$^{-1}$, $F(000) = 648$, $\theta = 24.71°$. Final $R_1 = 0.0426$, $wR_2 = 0.0996$, GOF = 0.850 for 132 parameters and 1370 unique reflections, of which 815 with $I > 2\sigma(I)$, residuals in $\Delta F$ map 0.186, –0.181 e. Å$^{-3}$.

**Crystal data for 12.** $C_{14}{\cdot}H_{15}{\cdot}NO_4$, fw = 261.27 g/mol; Monoclinic, $P\ 2_1$, $a = 8.323(2)$, $b = 6.309(2)$, $c = 12.535(3)$ Å, $\beta = 104.31(3)°$, $V = 637.8(3)$ Å$^3$, $Z = 2$, $D_{calcd} = 1.361$ g/cm$^3$, $\mu$(Mo-K$\alpha$) = 0.100 mm$^{-1}$, $F(000) = 276$, $\theta = 24.69°$. Final $R_1 = 0.0341$, $wR_2 = 0.0890$, GOF = 0.889 for 173 parameters and 1107 unique reflections, of which 717 with $I > 2\sigma(I)$, residuals in $\Delta F$ map 0.101, –0.156 e. Å$^{-3}$.

## CONCLUSION

Although [3+2]cycloadditions between 1,3-azomethine ylides and activated olefins are known, the easy access to these polyfunctionalized pyrrolizidines is interesting, in particular, as far as the formation of the nitro spiro pyrrolizidine is concerned. In fact, a similar spiro pyrrolizidine of terpenoid nature, the (+)-nitropolyzonamine [10], extracted from a millipede, has been studied as a potential allomone to deter predators [11].

**Acknowledgment.** The authors thank MIUR (PRIN 2007) and the University of Trieste–Finanziamento Ricerca d'Ateneo for financial support.

### REFERENCES AND NOTES

[1] (a) Australia New Zealand Food Authority (ANZFA). Pyrrolizidine Alkaloids in Food. A Toxicological Review and Risk Assessment. Technical Report Series NO. 2, 2001. Available at: http://www.anzfa.gov.au; (b) Liddell, J. R. Nat Prod Rep 2001, 18, 441; (c) Hartmann, T.; Witte, L. In Chemistry, Biology and Chemoecology of the Pyrrolizidine Alkaloids, in Alkaloids: Chemical and Biologycal Perspectives; Pelletier, S. W., Ed.; Pergamon Press: Oxford, 1995; Vol. 9, pp 155–233; (d) Rizk, A.-F. M. In Naturally Occurring Pyrrolizidine Alkaloids; CRC Press: Boca Raton, FL, 1991; pp 1–90; (e) Mattocks, A. R. In Chemistry and Toxicology of Pyrrolizidine Alkaloids; Academic Press: New York, 1986.

[2] (a) Sletten, E. M.; Liotta, L. J. J Org Chem 2006, 71, 1335; (b) Dondoni, A.; Marra, A.; Richichi, B. Synlett 2003, 2345; (c) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. J Org Chem 2001, 66, 1351; (d) Denmark, S. E.; Herbert, B. J Am Chem Soc 1998, 120, 7357; (e) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. J Am Chem Soc 1998, 120, 7359; (f) Murray, A.; Proctor, G. R.; Murray, P. J. Tetrahedron 1996, 52, 3757; (g) Pilli, R. A.; Russowsky, D. J Org Chem 1996, 61, 3187; (h) Murray, A.; Proctor, G. R.; Murray, P. J. Tetrahedron Lett 1995, 36, 291; (k) Provot, O.; Célérier, J. P.; Petit, H.; Lhommet, G. J Org Chem 1992, 57, 2163; (i) Dai, W.-M.; Nagao, Y.; Fujita, E. Heterocycles 1990, 30, 1231.

[3] (a) Jadidi, K.; Moghaddam, M. M.; Aghapoor, K.; Gharemanzadeh, R. J Chem Res 2007, 71; (b) Poornachandra, M.; Raghunathan, R. Synth Commun 2007, 37, 2507; (c) Padwa, A. In Comprehensive Organic Synthesis; Trost, I., Fleming, B. M., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1069–1109; (d) Tsuge, O.; Kanemasa, S. In Advances in Heterocyclic Chemistry; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, pp 232–349; (e) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. Tetrahedron 1988, 44, 519; (f) Orsini, F.; Pelizzoni, F.; Forte, M.; Sisti, M.; Merati, F.; Gariboldi, P. J Heterocyclic Chem 1988, 25, 1665; (g) Wedejs, E. In Advances in Cycloaddition; Curan, D. P., Ed.; Jai Press: Greenwich, 1988; pp 33–51; (h) Lowing, J. W. In 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, pp 653–732; (k) Huisgen, R. J Org Chem 1976, 41, 403; (i) Huisgen, R. Angew Chem Int Ed 1963, 2, 565.

[4] Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. Angew Chem Int Ed 2005, 44, 3055.

[5] (a) Bohlmann, F. Chem Ber 1958, 91, 2157; (b) Bohlmann, F.; Arndt, C. Chem Ber 1958, 91, 2167.

[6] Jackman, L. M.; Sternhell, S. In Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd ed.; Pergamon Press: Oxford, 1969; p 286.

[7] Skvortsov, I. M. Chem Heterocyclic Comp 2006, 42, 1247.

[8] Sheldrick, G. M. SHELX97 Programs for Crystal Structure Analysis (Release 97-2); University of Göttingen: Germany, 1998.

[9] Farrugia, L. J. J Appl Crystallogr 1999, 32, 837.

[10] (a) Saporito, R. A.; Donnelly, M. A.; Hoffman, R. L.; Garraffo, H. M.; Daly, J. W. J Chem Ecology 2003, 29, 2781; (b) Takagi, Y.; Mori, K. J Braz Chem Soc 2000, 11, 578; (c) Mori, K.; Takagi, Y. Tetrahedron Lett 2000, 41, 6623; (d) Meinwald, J.; Smolanoff, J.; McPhail, A. T.; Miller, R. W. Tetrahedron Lett 1975, 2367.

[11] (a) Badio, B.; Shi, D.; Shin, Y.; Hutchinson, K. D.; Padgett, W. L.; Daly, J. W. Biochem Pharm 1996, 52, 933; (b) Hutchinson, K. D.; Silverton, J. V.; Daly, J. W. Tetrahedron 1994, 50, 6129.

# A Facile Synthesis of Tetrasubstituted 2,3-Dihydrofuran Derivatives Using Poly(ethylene glycol) as Soluble Support

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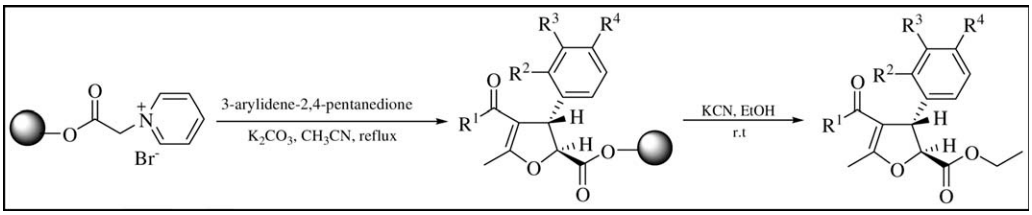


A facile synthesis of tetrasubstitude 2,3-dihydrofurans has been conducted using poly(ethylene glycol) (PEG) as a soluble polymer support. The PEG-supported pyridinium ylides react with 3-arylidene-2,4-pentanedione in the presence of triethylamine (TEA) via conjugate addition to form PEG-supported dihydrofuran derivatives, being cleaved by 1% KCN/EtOH to afford *trans*-tetrasubstitude-2,3-dihydrofurans, varying from good to excellent yields.

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## INTRODUCTION

Dihydrofurans are the most important heterocycles not only because of their biological activities [1] but also to potential usefulness as synthetic intermediates, for example, they are precursors of furans by oxidation. Searching for new and efficient methods for their synthesis is always an area of synthetic interest. With a number of methods available, though, the synthesis of dihydrofurans using polymer as support has never been reported. Our laboratory has accumulated abundant experience in soluble polymer supported synthesis [2] and has successfully synthesized indolizines using poly(ethylene glycol) (PEG)-supported pyridinium ylides [3]. Based on our previous work, herein we report the facile synthesis of tetrasubstituted dihydrofuran deriatives via the reaction of 3-arylidene-2,4-pentanedione analogues **3** [4] with PEG-supported pyridinium ylides 2 (Scheme 1).

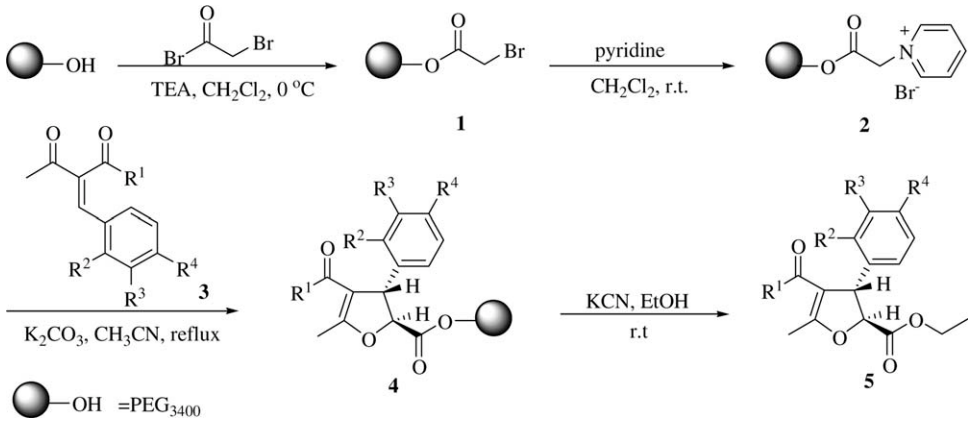
## RESULTS AND DISCUSSION

As shown in Scheme 1, $PEG_{3400}$ was first treated by two equivalent bromoacetyl bromide with equimultiple triethylamine (TEA) as base in dry dichloromethane at 0°C overnight to form **1**. The IR spectroscopy of **1** exhibits characteristic C=O absorption band at 1750 $cm^{-1}$ with the disappearance of the O—H absorption at 3448 $cm^{-1}$. After purification and vacuum drying, **1** was reacted with pyridine overnight in dry dichloromethane to afford PEG-supported pyridinium ylides **2**. The $^1H$ NMR spectroscopy of **2** shows a strong signal of the pyridine protons at δ 9.46, 8.62, and 8.20. The ylides reacted with 1.5 equivalent of 3-arylidene-2,4-pentanedione **3** at refluxing temperature via conjugate addition in dry acetonitrile using $K_2CO_3$ as a base, and **4** was obtained as brown powder in excellent yields. Finally, the 2,3-dihydrofuran **5** was cleaved from **4** by treating **4** with 1% KCN in dry ethanol solution at r.t. over night in 80–93% yields.

The earlier papers reported that using ylides react at 0°C or even −78°C gives birth to cyclopropane and dihydrofuran products, but if choosing higher temperature only dihydrofuran was obtained [5]. Probably because of the raise of temperature, the less stable carbon anionic intermediate **A** would transform to oxygen anionic intermediate **B**, thus resulting in the contrast of their chemselectivity; the higher the temperature is chosen the better chemselectivity is gained. Their common mechanism is shown in Scheme 2.

During the study of the mechanism, we envision that we could use PEG-supported pyridinium ylide to synthesize 2,3-dihydrofuran derivatives in acetonitrile at refluxing temperature. Indeed, we do obtain 2,3-dihydrofuran as the only product in our route. The stereochemistry of 5a is assigned from a combination of its COSY spectra in which a *trans*-geometry between the 4 and 5-

**Scheme 1**




positions is observed ($J = 4.2$ Hz) [6]. A plausible reaction mechanism is shown in Scheme 3. As the reaction conducts at refluxing temperature, the carbon anionic intermediate I is so instable that it would be transformed to oxygen anionic intermediate II, so no cyclopropane derives from a three-membered ring could be detected. There are two possible scenarios when the enolate oxygen attacks $C_2$ from the backside of leaving group ($Py^+$) such as III and IV. To be largely affected by the steric hindrance (Ar and PEG-OCO), especially by the group of PEG-OCO, IV is so instable as to be insignificant, thus *trans*-2,3-dihydrofuran is the only product detected in our route (Scheme 3).

Initial attempts worked perfectly with ethyl-2-(4-chlorobenzylidene)-3-oxobuancate **3a** and PEG-supported pyridinium ylieds **2** in acetonitrile at refluxing temperature with $K_2CO_3$ as base and *trans*-5-methyl-3-(3-nitrophenyl)-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester **5e** was formed in 82% yield (based on the loading capacity of PEG). To probe into the generality of this finding, we extend the investigation to a number of substrates, of which 17 products have never been reported. The results are summarized in Table 1.

This method has a number of advantages including high yields, simple purification, and absence of competing side reactions such as C-cyclization, which are all based on the features of PEG supported synthesis [7]: (a) in each step, the excess low molecular regents are used to promote the balance movement to the product direction so as to obtain high yields; (b) the PEG supported group provides huge steric hindrance to restrict enolate oxygen to attack carbon at a certain direction, thus leading to high stereoselectivity; and (c) PEG-bound products can be conveniently recrystalled in cold ethyl ether, and the by-products are removed by simple filtration, which simplifies the purification a lot.

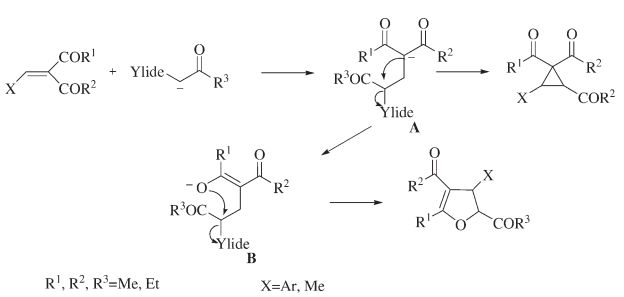
In conclusion, we have successfully synthesized 22 *trans*-tetrasubstituted 2,3-dihydrofuran derivatives via the reaction of 3-arylidene-2,4-pentanedione with PEG-supported pyridinium ylides in high yields, simple purification and 17 products have never been reported.

## EXPERIMENTAL

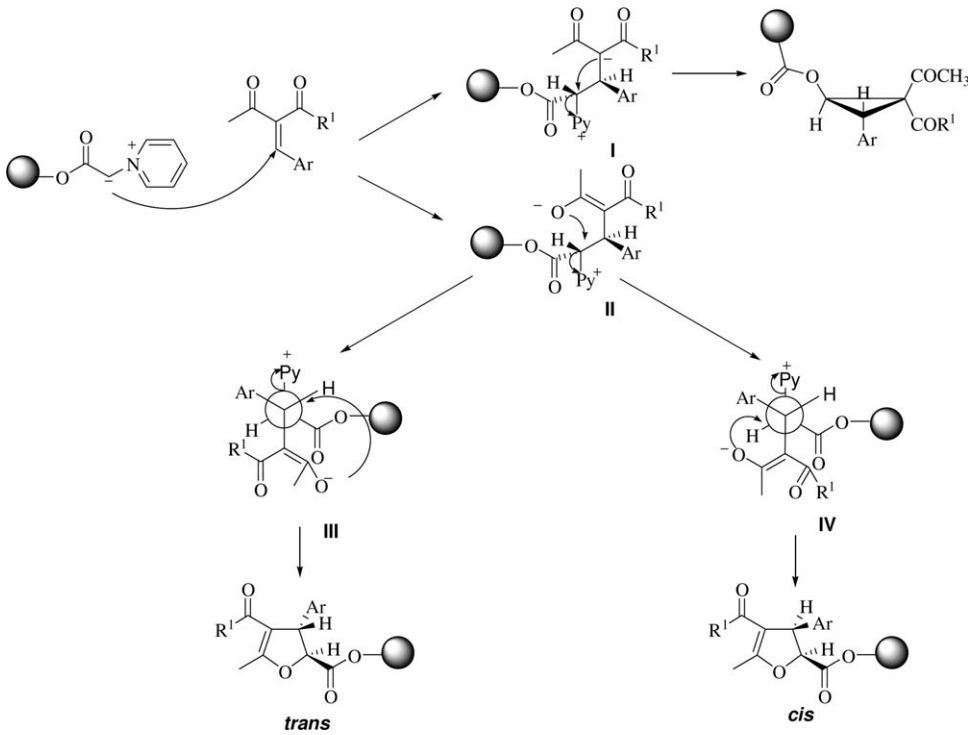
All organic solvents were dried by standard methods. $PEG_{3400}$ (Aldrich, 3015–3685) and PEG-supported compounds were melted in vacuum at 80°C for about 30 min before use, to remove any trace of moisture. Melting points were measured by a X-6 digital melting point apparatus and uncorrected. IR spectra were recorded in an IR-Spectrum One spectrometer (Perin Elmer), using NaCl pellets. Mass spectra were recorded on Finnigan LCQ DUO MS system. $^1H$ NMR (600 MHz) and $^{13}C$ NMR (150 MHz) spectra were recorded in a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS (0.03%) as internal standard.

**Preparation of PEG-supported pyridinium ylides 2.** A solution of bromoacetyl bromide (1.02 mL, 11.76 mmol) in dry $CH_2Cl_2$ (2 mL) was added dropwise to a solution of $PEG_{3400}$ (10.0 g, 5.88 mmol OH) and $Et_3N$ (1.65 mL, 11.76 mmol) in dry $CH_2Cl_2$ (30 mL) at 0°C and stirred at r.t. overnight. The mixture was washed with $H_2O$ to remove $Et_3N{\cdot}HBr$, dried over $Na_2SO_4$ and concentrated. After precipitation with cold $Et_2O$, washing with cold $Et_2O$ and drying under vacuum, a light yellow solid **1** was obtained. Pyridine (0.94 mL, 11.76 mmol) was added to a solution of **1** in dry $CH_2Cl_2$ (30 mL) and stirred at r.t overnight. After precipitation from cold $Et_2O$, the suspension was filtered and washed with cold $Et_2O$ to obtain solid **2** (11.0 g, 98%). TLC (EA:PE =

**Scheme 2**



**Scheme 3**




1:4) showed that the solid was free from any low molecular reactants and by-products. IR (NaCl): 3057, 2882, 1751, 1147, 1114, 730 $cm^{-1}$. $^1H$ NMR (600 MHz): δ = 9.46 (d, 2H, *J* = 4.2 Hz, α-pyridine), 8.62 (t, 1H, *J* = 6.4 Hz, γ-pyridine), 8.20 (t, 2H, *J* = 6.0 Hz, β-pyridine), 6.18 (s, 2H, —$CH_2COO$—), 3.64–3.51 (m, 4nH, —$O(CH_2CH_2O)n$—).

**Typical procedures for preparation of 2,3-dihydrofurans 5.** A mixture of PEG-supported pyridinium ylides **2** (2.3 mmol), 3-benzylidene-2,4-pentanedione (3.44 mmol), and $K_2CO_3$ (3.44 mmol) in $CH_3CN$ (20 mL) was refluxed for 12 h to form **4**. After the solvent was evaporated under vacuum, the residue was added to $CH_2Cl_2$ (5 mL) and recrystalled in cold $Et_2O$. Filtering the precipitation and being washed by the cold $Et_2O$ until no low molecular reactants and by-product, which were detected by the TLC (EA:PE = 1:4). Product **4** was treated with 1% solution of KCN in EtOH (30 mL) and stirred at r.t overnight, evaporated EtOH and precipitated with cold $Et_2O$ to obtain the crude products, which were purified by column chromatography on silica gel (EA:PE = 1:4) to afford the pure **5**.

***Trans-4-acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Aa) oil.*** IR (NaCl): 2956, 1759, 1702, 1651, 1462 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.313 (d, 2H, *J* = 8.4 Hz, ArH), 7.200 (d, 2H, *J* = 8.4 Hz, ArH), 4.782 (d, 1H, *J* = 4.2 Hz, OCH), 4.495 (d, 1H, *J* = 4.6 Hz, CH), 4.206 (m, 2H, $OCH_2$), 2.435 (s, 3H, $CH_3$), 1.994 (s, 3H, $CH_3$), 1.456 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.505, 168.870, 164.219, 140.222, 132.476, 130.104 (2C), 129.896 (2C), 105.957, 85.848, 62.202, 59.862, 29.670, 14.132, 13.893, 13.528. MS: *m*/*z* = 339.13 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-bromophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ab) oil.*** IR (NaCl): 2884, 1746, 1620, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.290 (d, 2H, *J* = 8.4 Hz, ArH), 7.173 (d, 2H, *J* = 8.4 Hz, ArH), 4.770 (d, 1H, *J* = 5.4 Hz, OCH), 4.394 (d, 1H, *J* = 3.6 Hz, CH), 4.280 (m, 2H, $OCH_2$), 4.023 (m, 2H, $OCH_2$), 2.397 (s, 3H, $CH_3$), 1.326 (t, 3H, $CH_3$), 1.095 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.413, 168.882, 164.307, 140.194, 132.430 (2C), 131.876 (2C), 121.782, 106.293, 85.814, 62.255, 59.971, 29.588, 14.076, 13.985, 13.859. MS: *m*/*z* = 383.02 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-cyanophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ac) oil.*** IR (NaCl): 2883, 1753, 1627, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.569 (d, 2H, *J* = 7.8 Hz, ArH), 7.287 (d, 2H, *J* = 7.8 Hz, ArH), 5.338 (d, 1H, *J* = 5.4 Hz, OCH), 4.646 (d, 1H, *J* = 3.6 Hz, CH), 4.007 (m, 2H, $OCH_2$), 3.796 (m, 2H, $OCH_2$), 2.397 (s, 3H, $CH_3$), 1.326 (t, 3H, $CH_3$), 1.023 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 168.843, 168.232, 164.117, 146.262, 133.945 (2C), 130.554 (2C), 117.852, 110.967, 105.729, 85.608, 61.940, 59.774, 29.637, 14.081, 13.953, 13.452. MS: *m*/*z* = 330.16 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-nitrophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ad) oil.*** IR (NaCl): 2885, 1750, 1629, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 8.156 (d, 2H, *J* = 8.4 Hz, ArH), 7.358 (d, 2H, *J* = 7.8 Hz, ArH), 5.244 (d, 1H, *J* = 4.2 Hz, OCH), 4.683 (d, 1H, *J* = 4.8 Hz, CH), 4.116 (m, 2H, $OCH_2$), 3.827 (s, 3H, $CH_3$), 2.481 (s, 3H, $CH_3$), 1.251 (t, 3H, $CH_3$),1.024 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.145, 168.427, 163.536, 146.893, 145.615, 128.774 (2C), 121.309 (2C), 105.697, 85.517, 61.823, 59.633, 29.621, 14.248, 13.978, 13.863. MS: *m*/*z* = 350.15 ($M^+ + 1$).

***Trans-4-acetyl-3-(3-nitrophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ae) oil.*** IR (NaCl): 2957, 1761, 1700, 1651, 1532 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ

**Table 1**

Synthesis of 2,3-dihydrofurans using PEG-supported pyridin ylide.

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%)[a] |
|---|---|---|---|---|---|
| 5Aa | OEt | H | H | Cl | 82 |
| 5Ab | OEt | H | H | Br | 85 |
| 5Ac | OEt | H | H | CN | 87 |
| 5Ad | OEt | H | H | $NO_2$ | 80 |
| 5Ae | OEt | H | $NO_2$ | H | 90 |
| 5Af | OEt | $NO_2$ | H | H | 81 |
| 5Ag | OEt | H | H | $OCH_3$ | 89 |
| 5Ah | OEt | $OCH_3$ | $OCH_3$ | H | 85 |
| 5Ai | OEt | H | H | $N(CH_3)_2$ | 90 |
| 5Aj | OEt | Cl | H | Cl | 83 |
| 5Ak | OEt | H | H | OH | 80 |
| 5Ba [5b] | $CH_3$ | H | H | Cl | 84 |
| 5Bb [5b] | $CH_3$ | H | H | Br | 86 |
| 5Bc | $CH_3$ | H | H | CN | 88 |
| 5Bd [5b] | $CH_3$ | H | H | $NO_2$ | 87 |
| 5Be | $CH_3$ | H | $NO_2$ | H | 93 |
| 5Bf | $CH_3$ | $NO_2$ | H | H | 85 |
| 5Bg | $CH_3$ | H | H | $OCH_3$ | 92 |
| 5Bh | $CH_3$ | $OCH_3$ | $OCH_3$ | H | 87 |
| 5Bi | $CH_3$ | H | H | $N(CH_3)_2$ | 89 |
| 5Bj [5b] | $CH_3$ | Cl | H | Cl | 84 |
| 5Bk | $CH_3$ | H | H | OH | 80 |

[a] Based on the loading capacity of PEG.

= 8.058 (m, 1H, ArH), 7.535–7.437 (m, 2H, ArH), 4.786 (d, 1H, $J$ = 5.4 Hz, OCH), 4.488 (d, 1H, $J$ = 4.2 Hz, CH), 4.208 (m, 2H, $OCH_2$), 3.954 (m, 2H, $OCH_2$), 2.355 (s, 3H, $CH_3$), 1.308 (s, 3H, $CH_3$), 1.022 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 168.945, 168.848, 163.609, 149.223, 136.138, 133.547, 128.841, 128.143, 124.198, 105.840, 86.077, 61.985, 59.682, 29.543, 14.108, 13.962, 13.439. MS: $m/z$ = 350.10 ($M^+ + 1$).

***Trans-4-acetyl-3-(2-nitrophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Af) oil.*** IR (NaCl): 2925, 1759, 1651, 1462 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.786 (d, 1H, $J$ = 7.8 Hz, ArH), 7.518 (m, 1H, ArH), 7.328 (t, 2H, ArH), 5.062 (d, 1H, $J$ = 4.2 Hz, OCH), 4.809 (d, 1H, $J$ = 4.8 Hz, CH), 4.249 (m, 2H, $OCH_2$), 3.893 (m, 2H, $OCH_2$), 2.350 (s, 3H, $CH_3$), 1.285 (s, 3H, $CH_3$), 0.911 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 169.635, 169.948, 164.202, 149.163, 136.793, 132.803, 129.837, 128.153, 124.289, 105.715, 85.407, 62.068, 59.712, 29.630, 14.076, 13.996, 13.954. MS: $m/z$ = 350.16 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-methoxyphenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ag) oil.*** IR (NaCl): 2880, 1751, 1636, 1467 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.018 (d, 2H, $J$ = 8.4 Hz, ArH), 6.878 (d, 2H, $J$ = 8.4 Hz, ArH), 4.799 (d, 1H, $J$ = 4.8 Hz, OCH), 4.406 (d, 1H, $J$ = 4.8 Hz, CH), 4.269 (m, 2H, $OCH_2$), 4.018 (m, 2H, $OCH_2$), 2.384 (s, 3H, $CH_3$), 1.323 (t, 3H, $CH_3$), 1.096 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 170.022, 169.923, 164.879, 159.743, 133.320, 128.845 (2C), 114.289 (2C), 105.729, 85.407, 62.068, 59.663, 56.014, 29.630, 14.076, 13.996, 13.954. MS: $m/z$ = 335.16 ($M^+ + 1$).

***Trans-3-(2,3-dimethoxyphenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ah) oil.*** IR (NaCl): 2884, 1746, 1620, 1467 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.032 (t, 1H, ArH), 6.851 (d, 1H, $J$ = 7.2 Hz, ArH), 6.680 (d, 1H, $J$ = 7.8 Hz, ArH), 4.919 (d, 1H, $J$ = 4.2 Hz, OCH), 4.618 (d, 1H, $J$ = 3.6 Hz, CH), 4.369 (m, 2H, $OCH_2$), 4.172 (m, 2H, $OCH_2$), 3.883 (s, 6H, $OCH_3$), 2.419 (s, 3H, $CH_3$), 1.448 (t, 3H, $CH_3$), 1.263 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 170.104, 169.945, 164.862, 150.739, 150.022, 127.242, 122.853, 121.197, 112.827, 105.723, 85.418, 62.053, 59.657, 56.542, 56.012, 29.629, 14.202, 13.988, 13.945. MS: $m/z$ = 365.20 ($M^+ + 1$).

***Trans-4-acetyl-3-(2,4-dichlorophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Aj) oil.*** IR (NaCl): 2885, 1750, 1629, 1467 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.394 (d, 1H, $J$ = 8.4 Hz, ArH), 7.264 (d, 1H, $J$ = 8.4 Hz m, ArH), 7.258–7.240 (m, 1H), 5.114 (d, 1H, $J$ = 4.2 Hz, OCH), 4.703 (d, 1H, $J$ = 4.8 Hz, CH), 4.244 (m, 2H, $OCH_2$), 4.013 (m, 2H, $OCH_2$), 2.463 (s, 3H, $CH_3$), 2.068 (s, 3H, $CH_3$), 1.216 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 169.324, 168.998, 163.545, 137.132, 136.454, 134.317, 130.623, 130.304, 126.492, 105.731, 85.772, 62.104, 59.672, 29.534, 14.088, 13.831, 13.456. MS: $m/z$ = 373.09 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-hydroxyphenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ak) oil.*** IR (NaCl): 2883, 1750, 1637, 1467 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 9.099 (s, 1H, OH), 7.469 (d, 2H, $J$ = 8.4 Hz, ArH), 6.922 (d, 1H, $J$ = 8.4 Hz, ArH), 4.843 (d, 1H, $J$ = 4.2 Hz, OCH), 4.307 (d, 1H, $J$ = 4.8 Hz, CH), 4.309 (m, 2H, $OCH_2$), 4.127 (m, 2H, $OCH_2$), 2.382 (s, 3H, $CH_3$), 1.954 (s, 3H, $CH_3$), 1.278 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 169.582, 168.763, 163.425, 156.753, 133.406, 130.287 (2C), 116.848 (2C), 105.724, 85.788, 62.146, 59.672, 29.630, 14.071, 13.835, 13.452. MS: $m/z$ = 321.19 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Ba) oil.*** IR (NaCl): 2957, 1760, 1704, 1651, 1459 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.401 (d, 2H, $J$ = 9.0 Hz, ArH), 7.374 (d, 2H, $J$ = 9.0 Hz, ArH), 4.729 (d, 1H, $J$ = 4.8 Hz, OCH), 4.474 (d, 1H, $J$ = 4.2 Hz, CH), 4.310 (m, 2H, $OCH_2$), 2.428 (s, 3H, $CH_3$), 1.994 (s, 3H, $CH_3$), 1.294 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 169.511, 168.864, 164.230, 140.217, 132.465, 130.109 (2C), 129.882 (2C), 105.943, 85.826, 62.213, 29.672, 14.162, 13.877, 13.519 MS: $m/z$ = 309.11 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-bromophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bb) oil.*** IR (NaCl): 2884, 1742, 1621, 1460 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.290 (d, 2H, $J$ = 8.4 Hz, ArH), 7.173 (d, 2H, $J$ = 8.4 Hz, ArH), 4.770 (d, 1H, $J$ = 5.4 Hz, OCH), 4.394 (d, 1H, $J$ = 3.6 Hz, CH), 4.280 (m, 2H, $OCH_2$), 4.023 (m, 2H, $OCH_2$), 2.397 (s, 3H, $CH_3$), 1.326 (t, 3H, $CH_3$), 1.095 (t, 3H, $CH_3$),$^{13}$C NMR (150 MHz, $CDCl_3$): δ = 169.405, 168.874, 164.311, 140.186, 132.418 (2C), 131.856 (2C), 121.796, 106.185, 85.801, 62.203, 29.463, 14.067, 13.993, 13.835. MS: $m/z$ = 353.07 ($M^+ + 1$).

***Trans-4-acetyl-3-(4-cyanophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bc) oil.*** IR (NaCl): 2884, 1752, 1623, 1459 $cm^{-1}$, $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.687 (d, 2H, $J$ = 3.6 Hz, ArH), 7.555 (d, 2H, $J$ = 4.8 Hz, ArH), 5.016 (d, 1H, $J$ = 4.8 Hz, OCH), 4.453 (d, 1H, $J$ = 4.8 Hz, CH), 4.076 (m, 2H, $OCH_2$), 2.423 (s, 3H, $CH_3$), 2.398 (s, 3H, $CH_3$), 1.265 (t, 3H, $CH_3$), $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 168.852, 168.229, 164.110, 146.258, 133.931 (2C), 130.567 (2C), 117.844, 110.960, 105.718, 85.614, 61.943, 29.626, 14.125, 13.948, 13.433. MS: $m/z$ = 302.14 ($M^+ + 1$).

***Tans-4-acetyl-3-(4-nitrohenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bd) oil.*** IR (NaCl): 2883, 1748, 1630, 1478 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 8.211 (d, 2H, *J* = 4.2 Hz, ArH), 7.424 (d, 2H, *J* = 8.4 Hz, ArH), 4.761 (d, 1H, *J* = 4.8 Hz, OCH), 4.609 (d, 1H, *J* = 4.2 Hz, CH), 4.308 (m, 2H, $OCH_2$), 2.468 (s, 3H, $CH_3$), 2.103 (s, 3H, $CH_3$), 1.251 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.138, 168.414, 163.552, 146.872, 145.609, 128.772 (2C), 121.319 (2C), 105.693, 85.523, 61.835, 29.624, 14.236, 13.994, 13.842. MS: *m/z* = 320.14 ($M^+$ + 1).

***Trans-4-acetyl-3-(3-nitrophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Be) oil.*** IR (NaCl): 2935, 1757, 1690, 1628, 1521 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.899 (d, 1H, *J* = 7.8 Hz, ArH), 7.609 (m, 1H, ArH), 7.352 (d, 1H, *J* = 7.2 Hz, ArH), 5.223 (d, 1H, *J* = 5.4 Hz, OCH), 4.853 (d, 1H, *J* = 4.2 Hz, CH), 4.402 (m, 2H, $OCH_2$), 2.4485 (s, 3H, $CH_3$), 2.020 (s, 3H, $CH_3$), 1.022 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 168.932, 168.824, 163.679, 149.235, 136.131, 133.459, 128.856, 128.258, 124.183, 105.833, 86.102, 61.973, 29.536, 14.112, 13.953, 13.538. MS: *m/z* = 320.13 ($M^+$ + 1).

***Trans-4-acetyl-3-(2-nitrophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bf) oil.*** IR (NaCl): 2913, 1762, 1651, 1469 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.899 (d, 1H, *J* = 7.8 Hz, ArH), 7.606 (t, 1H, ArH), 7.448 (t, 1H, ArH), 7.352 (d, 1H, *J* = 7.8 Hz, ArH), 5.234 (d, 1H, *J* = 3.6 Hz, OCH), 4.792 (d, 1H, *J* = 5.4 Hz, CH), 4.309 (m, 2H, $OCH_2$), 2.456 (s, 3H, $CH_3$), 2.015 (s, 3H, $CH_3$), 1.025 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.648, 169.932, 164.132, 149.153, 136.643, 133.311, 128.894, 128.073, 124.289, 105.715, 85.407, 62.068, 29.630, 14.076, 13.996, 13.954. MS: *m/z* = 320.09 ($M^+$ + 1).

***Trans-4-acetyl-3-(4-methoxyphenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bg) oil.*** IR (NaCl): 2882, 1753, 1639, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.024 (d, 2H, *J* = 8.4 Hz, ArH), 6.873 (d, 2H, *J* = 8.4 Hz, ArH), 4.798 (d, 1H, *J* = 5.4 Hz, OCH), 4.339 (d, 1H, *J* = 5.4 Hz, CH), 4.010 (m, 2H, $OCH_2$), 3.849 (s, 3H, $OCH_3$), 2.411 (s, 3H, $CH_3$), 1.319 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 170.102, 169.943, 164.867, 159.739, 133.321, 128.842 (2C), 114.287 (2C), 105.714, 85.401, 62.053, 59.657, 56.012, 29.618, 14.102, 13.982, 13.946. MS: *m/z* = 305.15 ($M^+$ + 1).

***Trans-3-(2,3-dimethoxyphenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bh) oil.*** IR (NaCl): 2885, 1750, 1631, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.805 (s, 1H, ArH), 7.042-6.977 (m, 2H, ArH), 4.609 (d, 1H, *J* = 5.4 Hz, OCH), 4.353 (d, 1H, *J* = 5.2 Hz, CH), 4.189 (m, 2H, $OCH_2$), 3.896 (s, 6H, $OCH_3$), 2.886 (s, 3H, $CH_3$), 2.440 (s, 3H, $CH_3$), 1.263 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 170.105, 169.943, 164.860, 150.734, 150.018, 127.238, 122.847, 121.186, 112.833, 105.719, 85.408, 62.048, 56.540, 56.018, 29.623, 14.210, 13.978, 13.953. MS: *m/z* = 335.17 ($M^+$ + 1).

***Trans-4-acetyl-3-(4-(dimethylamino)phenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ai) oil.*** IR (NaCl): 2883, 1753, 1627, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.310 (d, 2H, *J* = 8.4 Hz, ArH), 6.627 (d, 2H, *J* = 8.4 Hz, ArH), 4.793 (d, 1H, *J* = 4.8 Hz, OCH), 4.475 (d, 1H, *J* = 4.2 Hz, CH), 4.275 (m, 2H, $OCH_2$), 4.063 (m, 2H, $OCH_2$), 3.033 (s, 6H, $N(CH_3)_2$), 2.407 (s, 3H, $CH_3$), 1.305 (s, 3H, $CH_3$), 1.170 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.875, 168.843, 164.324, 146.738, 130.218, 129.236 (2C), 115.833 (2C), 106.119, 85.402, 62.029, 41.309 (2C), 29.425, 14.201, 13.977, 13.946. MS: *m/z* = 348.12 ($M^+$ + 1).

***Trans-4-acetyl-3-(4-(dimethylamino)phenyl-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bi) oil.*** IR (NaCl): 2884, 1752, 1628, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.307(d, 2H, *J* = 10.8 Hz, ArH), 6.662 (d, 2H, *J* = 8.4 Hz, ArH), 4.778 (d, 1H, *J* = 4.8 Hz, OCH), 4.425 (d, 1H, *J* = 4.2 Hz, CH), 4.364 (m, 2H, $OCH_2$), 3.046 (s, 6H, $N(CH_3)_2$), 2.413 (s, 3H, $CH_3$), 2.387 (s, 3H, $CH_3$), 1.317 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.870, 168.838, 164.322, 146.730, 130.222, 129.234 (2C), 115.829 (2C), 106.121, 85.389, 41.306 (2C), 29.414, 14.322, 13.984, 13.953. MS: *m/z* = 318.21 ($M^+$ + 1).

***Trans-4-acetyl-3-(2,4-dichlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bj)*** IR (NaCl): 2883, 1748, 1629, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.390 (d, 1H, *J* = 1.8 Hz, ArH), 7.254 (m, 1H, ArH), 7.095 (d, 1H, *J* = 8.4 Hz), 5.014 (d, 1H, *J* = 4.2 Hz, OCH), 4.699 (d, 1H, *J* = 4.8 Hz, CH), 4.292 (m, 2H, $OCH_2$), 2.444 (s, 3H, $CH_3$), 1.986 (s, 3H, $CH_3$), 1.299 (t, 3H, $CH_3$),$^{13}C$ NMR (150MHz, $CDCl_3$): δ = 169.321, 168.977, 163.541, 137.127, 136.439, 134.306, 130.640, 130.287, 126.488, 105.716, 85.759, 62.113, 29.530, 14.064, 13.845, 13.458. MS: *m/z* = 343.01 ($M^+$ + 1).

***Trans-4-acetyl-3-(4-hydroxyphenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bk) oil.*** IR (NaCl): 2883, 1755, 1628, 1467 $cm^{-1}$, $^1H$ NMR (600 MHz, $CDCl_3$): δ = 8.807 (s, 1H, OH), 7.321 (d, 2H, *J* = 8.4 Hz, ArH), 7.193 (d, 1H, *J* = 8.4 Hz, ArH), 4.767 (d, 1H, *J* = 4.8 Hz, OCH), 4.435 (d, 1H, *J* = 5.4 Hz, CH), 4.315 (m, 2H, $OCH_2$), 2.431 (s, 3H, $CH_3$), 2.052 (s, 3H, $CH_3$), 1.278 (t, 3H, $CH_3$), $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 169.580, 168.758, 163.422, 156.749, 133.401, 130.285 (2C), 116.832 (2C), 105.715, 85.764, 62.108, 59.712, 29.639, 14.063, 13.828, 13.457. MS: *m/z* = 291.09 ($M^+$ + 1).

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## REFERENCES AND NOTES

[1] (a) Hudlicky, T.; Lovelace, T. C. Synth Commun 1990, 20, 1721; (b) Dulere, J. P.; Baret, N.; Rodriguez, J. J Chem Soc Chem Commun 1994, 303.

[2] (a) Zhang, H.-Q.; Yang, G.-C.; Chen, J-.N.; Chen, Z.-X. Synthesis 2004, 18, 3055; (b) Behrendt, J.-M.; Bala, K.; Golding, P. Tetrahedron Lett 2005, 46, 643; (c) Yue, G.-Z.; Chen, Z.-X.; Yang, G.-C. J Heterocycl Chem 2006, 43, 781; (c) Yue, G.-Z.; Chen, Z.-X. Bioorg Med Chem Lett 2005, 15, 453; (d) Huang, Y.-L.; Lu, C.-F.; Chen, Z.-X.; Yang, G.-C. J Heterocycl Chem 2007, 44, 1421; (e) Xiang, F.-Y.; Zhang, S.-B.; Lu, C.-F.; Chen, Z.-X.; Yang, G.-C. Synth Commun 2008, 38, 953; (f) Xie, H.-W.; Lu, C.-F.; Chen, Z.-X.; Yang, G.-C. Synthesis 2009, 2, 205.

[3] Chen, Z.-X.; Yue, G.-Z. Synlett 2004, 1231.

[4] (a) Antonioletti, R.; Bovicelli, P.; Malancoha, S. Tetrahedron 2002, 58, 589; (b) Bartoli, G.; Bosco, M.; Carlone, A.; Daplozzo,

R.; Galzerano, P.; Melchiorre, P.; Sambri, L. Tetrahedron 2008, 49, 2555.

[5] (a) Payne, G.-B. J Org Chem 1967, 11, 3351; (b) Chuang, C.-P.; Tsai, A. I. Synthesis 2006, 4, 675; (c) Cao, W.-G.; Chen, G.-D.; Chen, J.; Chen, R.-Q. Synth Commun 2005, 35, 527.

[6] Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K. I.; Shioiri, T. Tetrahedron 1998, 39, 9739.

[7] (a) Far, A. R.; Tidwell, T. T. J Org Chem 1998, 63, 8636; (b) Pan, P.-C.; Sun, C.-M. Tetrahedron Lett 1998, 39, 9055; (c) Benaglia, M.; Cinquini, M.; Cozzi, F. Tetrahedron Lett 1999, 40, 2019; (d) Lopea-Pelegrin, J. A.; Wentworth, P.; Sieber, F.; Metz, W. A.; Janda, K. D. J Org Chem 2000, 65, 8527; (e) Behrendt, J. M.; Bala, K.; Golding, P.; Hailes, H. C. Tetrahedron Lett 2005, 46, 643.

# Synthesis and Pharmacological Screening of Derivatives of Isoxazolo[4,3-*d*]pyrimidine and Isoxazolo[4,5-*d*]pyrimidine

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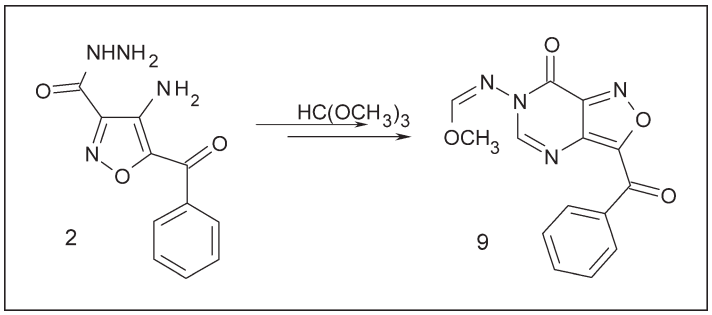


A number of derivatives of isoxazolo[4,3-*d*]pyrimidine and isoxazolo[4,5-*d*]pyrimidine were prepared with potential anticancer activity. Condensation of 4-amino-5-benzoyl-isoxazolo-3-carboxylic acid hydrazide with ethyl orthoformate and then with different amines gave a series of 3-benzoyl-7-oxo-7*H*-isoxazolo[4,3-*d*]pyrimidin-6-yl-aryliden-formamidine. A series of 5-aminomethyl-7-phenyl-isoxazolo[4,5-*d*]pyrimidine-3-carboxamide was obtained from 4-amino-5-benzoylisoxazole-3-carboxamide with acetonitrile, and chloroacetonitrile with gaseous hydrogen chloride. Some of these compounds were tested for their cytotoxic activity.

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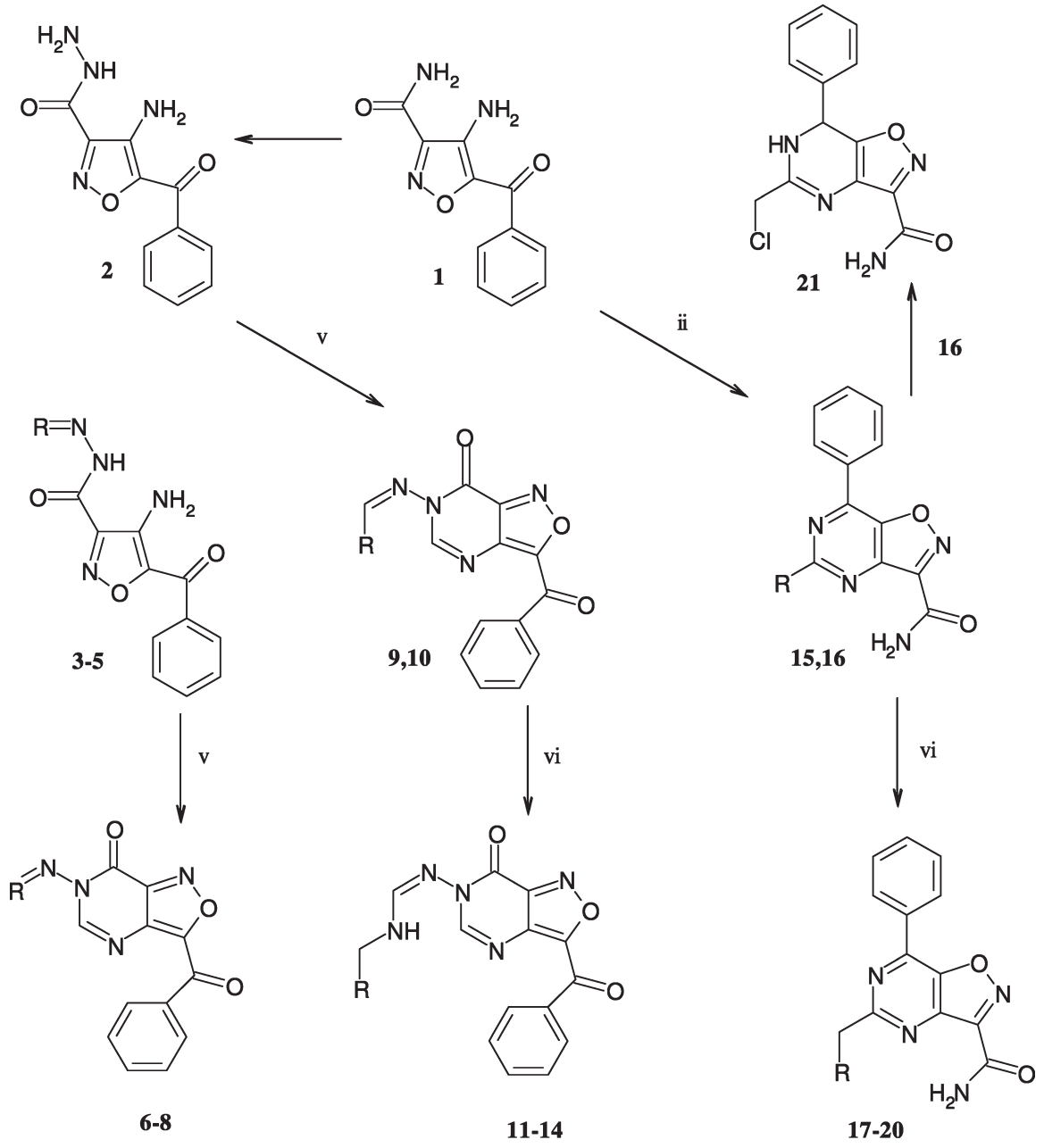
## INTRODUCTION

The bases of the 9*H*-purines adenosine (adenine) and the adenosine metabolite inosine (hypoxantine) are endogenous ligands of different receptors. Adenosine is an endogenous ligand of adenosine receptors (AR). They are subdivided into four subtypes ($A_1$, $A_{2A}$, $A_{2B}$, and $A_3$) [1]. Adenosine receptors have been actively studied as potential therapeutic targets in several disorders, such as Parkinson's disease, schizophrenia, analgesia, and ischemia, and as cytostatics. Inosine is a highly selective ligand for the $A_3$ receptor subtype [2,3] and so is a ligand of the benzodiazepine receptor [4,5]. The nitrogen atoms at positions 3 and 7 of both purines and their derivatives take part in the formation of a hydrogen bond with these receptors [5,6]. For example, substitution of the nitrogen atom at position 7 in inosine gave 7-methylinosine, which was ineffective in binding to the benzodiazepine receptor [5]. Therefore, we have been working on synthetic derivatives of two isomers of isoxazolopyrimidine, 4,3-*d* and 4,5-*d*, which may be considered as 7,9-dideaza-7-oxa-8-aza purines, and which may have high biological and similar receptor activity. Only the isomers from four isomers of isoxazolopyrimidine have nitrogen and oxygen heteroatoms at positions analogous to the 9*H*-purines. The literature concerning derivatives of both isomers contains a few same papers in which the authors obtained isoxazolo[4,5-*d*]pyrimidine but did not assay their biological activity [7–9]. Some derivatives of isoxazolo[4,5-*d*]pyrimidine were shown to be CRF (corticotrophin releasing factor) antagonist and may be useful as cCMP phosphodiesterase inhibitors [10,11]. Another derivatives of isoxazolo[4,5-*d*]pyrimidine that are structurally similar to hypoxantine can have anxiolytic activity comparable to that of diazepam [12]. In contrast, compared with diazepam the derivatives of isoxazolo[4,3-*d*]pyrimidine are devoid of anticonvulsant and anxiolytic properties [13].

## RESULTS AND DISCUSSION

**Synthesis.** In continuation of our program we report the synthesis of new derivatives of the title compounds. The synthetic pathways used to obtain the target compounds are depicted in Scheme 1. The starting material **1** was obtained by the Thorpe reaction according to Gewald et al. [14], by which it could be converted into hydrazide **2** [15]. Hydrazide **2** with aldehydes gave the new hydrazido-hydrazones **3**-**5**, which were condensed with ethyl orthoformate in the presence of the acetic anhydride, yielding the new derivatives of isoxazolo[4,3-

**Scheme 1**




Reagents: (i) $H_2N$-$NH_2$; (ii) nitrils; (v) $HC(OC_2H_5)_3$ or $HC(OCH_3)_3$; (vi) amines,

*d*]pyrimidines **6**-**8**. The acid hydrazide **2** was refluxed in a mixture with only equimolar amounts of triethyl ortho-formate, giving [4-amino-3-(1,3,4-oxadiazol-2-yl)isoxazol-5-yl]-(phenyl)methanone [15]. If hydrazide **2** was refluxed with an excess of triethyl orthoformate and acetic anhydride, then the derivatives of isoxazolo[4,3-*d*]pyrimidine **6**-**8** and **9**,**10** were formed, which with differ-rent amines formed new derivatives of 3-benzoyl-7-oxo-7*H*-isoxazole[4,3-*d*]pyrimidin-6-yl-aryliden-formamidine **11**–**14**. Compound **1** was heated in acetonitrile or chloroacetonitrile with gaseous hydrogen chloride to form the new derivatives of isoxazolo[4,5-*d*]pyrimidine **15**–**16**. Mechanism of the reaction was described earlier by Shishoo *et al* [16,17]. Compound **16** reacts with amines to form the new 5-(aminemethyl)-7-phenyl-isoxazolo[4,5-*d*]pyrimidine-3-carboxamide **17**–**20**. It is well

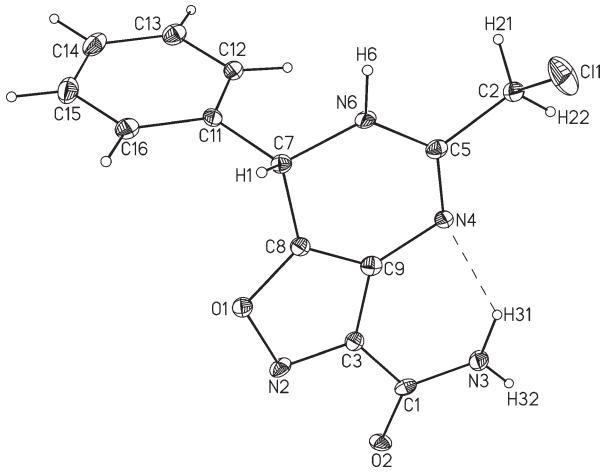



**Figure 1.** A view of the molecular structure of compound **21** with the atomic numbering scheme. Ellipsoids are at the 35% probability level.

known that isoxazole rings are readily cleaved by hydrogenation [18–21]. Thus the reduction of compound **16** followed by treatment with sodium borohydride in methanol at room temperature gave compound **21** with only one reduced double bond at position 6-7 from four. X-ray crystallography of compound **9** (Fig. 1) confirmed that the resulting structure was indeed compound **21** and **15**,**16**, and **17**-**20**.

However, amid **1** readily reacts with nitriles and forms compounds **15**,**16**. Of the compounds selected by the staff members of the NCI the derivatives isoxazole **3c**, isoxazole[4,3-*d*]pyrimidine **9**, and isoxazole[4,5-*d*]pyrimidine **19** were interesting.

**Crystallographic part.** X-ray diffraction studies: The X-ray diffraction data were collected at 100 K for a crystal of size 0.2 × 0.25 × 0.25 mm. All measurements were made on a KM4 CCD computer-controlled κ-axis diffractometer with graphite-monochromated $MoK_{\alpha}$(0.71073 Å) radiation. The intensities were corrected for Lorentz and polarization effects, but no corrections were made for absorption. The structure was solved by direct methods with SHELXS-97 and refined by full-matrix least-squares methods on $F^2$ using the SHELXL-97 [22] program. Nonhydrogen atoms were refined with anisotropic thermal parameters. All the H atoms were located using a differrence Fourier map and refined.

Figure 1 was drawn using the XP program [23]. Crystal data for 5-chloromethyl-7-phenyl-6,7-dihydro-isoxazlo[4,5-d]pyrimidine-3-carboxamide **21**: $C_{13}H_{11}N_4O_2Cl$, T = 100(2) K, $M$ = 290.71, orthorhombic, space group $Pna2_1$, with $a$ = 14.713(2) Å, $b$ = 16.745(2) Å, $c$ = 5.236(1) Å, $V$ = 1290.0(3) $Å^3$, $Z$ = 4, $D_c$ = 1.4969 g $cm^{-3}$, μ = 0.303 $mm^{-1}$. There were 2930 unique reflections, of which 2553 were considered as observed, with final $R$ = 0.0439 and wR = 0.079.

The molecular structure and atom numbering scheme are shown in Figure 1. Compound **21** crystallizes in a noncentrosymmetric $Pna2_1$ space group with one molecule per asymmetric unit. The determination of the structure of compound **21** confirms the S configuration of the chiral atom C7. The interatomic distances for C5-N4 [1.310(3) Å] and C3-N2 [1.320(3) Å] are typical of carbon-nitrogen double bonds [24] (1.279–1.329 Å) and the C9-N4 [1.401(3) Å] and C7-N6 [1.476(3) Å], bond lengths correspond to typical carbon-nitrogen single bonds (1.366–1.454 Å).

The isoxazole and pyrimidine rings are essentially planar, with maximum deviations from the calculated mean plane of 0.006(2) Å (C9) and 0.036(2) Å (C8), respectively. The dihedral angle between the best planes through the isoxazole ring and the pyrimidine ring is 3.0(2)°, indicating that the whole molecule is almost planar. The carboamide moiety deviates slightly from the isoxazole ring plane, the N3-C1-C3-N2 and O2-C1-C3-C9 torsion angles being −172.4(2)°, and –172.5(3)° respectively. The chloromethyl and phenyl moieties are nearly perpendicular, to the pyrimidine ring.

The dihedral angles between the pyrimidine ring plane and the Cl1-C2-C5 and C11-C16 planes are 66.6(1)° and 77.8(1)°, respectively.

In the present structure the nearly planar conformation of the title compound is stabilized by a network of intermolecular and intramolecular hydrogen bonds.

The hydrogen bond involving the amide H31 atom is bifurcated, H31 forming one intramolecular hydrogen bond with the N4 atom of the pyrimidine ring and the Cl1 atom of the chloromethyl moiety. The distances between the N(2)-H31...N(4) and N2-H31...Cl1(−x + 1, −y + 1, z − 1/2) atoms are 2.946(3) and 3.552(2) Å, respectively. Furthermore, the amide H6 forms an N6-H6...O2(x − 1/2, −y + 1/2, z + 1) hydrogen bond with the O2 atom of the carboamide group. The distances N6...O2 and H6...O2 are 2.908(3) and 2.22(3) Å, and the angle is 139(2)°. Additionally, the amide H32 atom on N2 interacts with the ring centroid Cg of the phenyl ring, forming a nonconventional hydrogen bond of the N2-H32...π (Cg) [H32... π, 2.71 Å N2... π 3.443(3) Å, N2-H32... π 149°; symmetry code: x + 1/2, −y + 1/2, z−1]. The molecules are also linked by the C7-H1...N4, C2-H21...O2, C12-H12...O2, and C15-H15...O1[3.523(3), 3.149(3), 3.550(3), and 3.437(3) Å] weak hydrogen bonds to form a chain running parallel to the axis. The distances H...O(N) [2.51(3)–2.85(3) Å] and angles [126(2)–163(2)°] suggest some kind of weak C—H...X hydrogen bond.

CCDC726160 contains the supplementary crystallographic data for this article. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html (or from the Cambridge Crystallographic Data

**Table 1**

Characterization data of compounds **3–20** and growth percent of some selected *in vitro* tumor cell lines (10 μmol).[a]

| Compound | R | Ovarian Cancer OVCAR-8 | Leukemia RPMI-8226 | Renal Cancer UO-31 | Melanoma SK-MEL-2 |
|---|---|---|---|---|---|
| **3** | $CHCH_3$ | | | | |
| **4** | $CHC_6H_5$ | | | | |
| **5** | $CHC_6H_4$-Cl-4 | 45.80 | | **−10.37** | 57.66 |
| **6** | $CHCH_3$ | 41.53 | | 62.54 | 42.59 |
| **7** | $CHC_6H_5$ | | | | |
| **8** | $C_6H_4$-Cl-4 | | | | |
| **9** | $OCH_3$ | 83.79 | 25.74 | **−12.84** | 60.83 |
| **10** | $OC_2H_5$ | | | | |
| **11** | 4-Pyridine | 45.76 | | 63.61 | 39.94 |
| **12** | $C_6H_5$ | | | | |
| **13** | $C_6H_4Cl$-4 | | | | |
| **14** | $C_6H_4$-F-4 | | | | |
| **15** | $CH_3$ | | | | |
| **16** | $CH_2Cl$ | | | | |
| **17** | 4-Morpholine | | | | |
| **18** | 4-Methylpiperazine | | | | |
| **19** | NH-4-morpholine | 42.20 | 55.00 | **−17.94** | |
| **20** | $N(C_4H_9)_2$ | | | | |

[a] Data obtained from the NCI's *in vitro* human tumor cell screen.

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**Cytotoxic screening.** The cytotoxic studies were performed at the National Cancer Institute, (NCI, Bethesda, MD). The screening is a two-stage process beginning with the evaluation of the compound against 60 different human tumor cell lines representing leukemia, melanoma, and cancers of the lung, colon, brain, breast, ovary, prostate, and kidney at a single dose of 10 μmol.

Evaluation of the cytotoxic activity was performed for compounds **5**, **6**, **9**, **11**, and **19**. Only compounds **5**, **9**, and **19** showed interesting activity in the panel 62 tumor cell lines, but chiefly on the renal cancer line UO-31. Data on the active compounds are presented in Table 1.

## EXPERIMENTAL

Melting points were determined with a Boethius apparatus and are uncorrected. The progress of the reaction and the purity of the compounds were monitored by TLC on analytical silica gel plates (Merck $F_{254}$, Darmstadt, Germany). IR spectra were recorded on a Specord M80 spectrometer (Zeiss/Analytic Jena, Germany) for KBr dises. $^1$H NMR spectra were recorded with a Bruker Avance ARX-300 instrument (Bruker Analytic, Karlsruhe, Germany; Bruker AG, Fallanden, Switzerland). Chemical shifts are reported in ppm downfield from the internal tetramethylsilane reference and the coupling constants are in Hz. Mass spectra were recorded on a Finningan Mat 95 GC-MS (Finningan, Bremen, Germany) with an ionization energy of 70 eV. Elemental analyses were performed on a Perkin Elmer 2400 analyzer (Waltham, MA) and the results are within ± 0.4% of the theoretical values obtained for the new compounds. The chemicals and reagents for synthesis were obtained from Alfa Aesar (Karlsruhe, Germany), Chempur (Piekary Sl., Poland), and Lancaster (Frankfurt am Main).

**General procedure for the synthesis of compounds 3-5.** To a stirred solution of acid hydrazide **2** (2.46 g, 0.01 mol) in 20 mL of anhydrous 1,4-dioxane heated at 80°C, the appropriate aldehyde (0.012 mol) was added. The reaction mixture was heated under reflux for 5 h and the solvent was rotoevaporated. The resulting solid was recrystallized from the appropriate solvent.

***4-Amino-5-benzoyl-N-(ethylideneamino)isoxazole-3-carboxamide (3).*** Yield: 1.78 g (65.5%), mp 191°C (1,4-dioxane); IR (potassium bromide): 3500, 3395 ($NH_2$), 3260 (NH), 1685, 1660 (CO), 1640 (C=N) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 1.94–2.00 (d, 3H, $CH_3$, $J$ = 6.0 Hz ), 6.41 (s, 2H, $NH_2$), 7.68 (m, 3H, arom.), 7.80–7.90 (q, 1H, CH, $J$ = 6.0 Hz), 8.00–8.10 (d, 2H, arom.), 12.06 (s, 1H, HN-CO). Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.21; H, 4.38; N, 20.37.

***4-Amino-5-benzoyl-N-(phenylmethylenebenzylideneamino)isoxazole-3-carboxamide (4).*** Yield: 2.52 g (75.5%), mp 215C (ethanol); IR (potassium bromide): 3420, 3305 ($NH_2$), 3260 (NH), 1685, 1660 (CO), 1640 (C=N) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 6.44 (s, 2H, $NH_2$), 7.50–8.66 (m, 10H, arom.), 8.57 (s, 1H, CH), 12.42 (s, 1H, HN-CO). Anal. Calcd. for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.22; N, 16.76. Found: C, 64.80; H, 4.23; N, 16.47.

***4-Amino-5-benzoyl-isoxazole-3-carboxylic acid (4-chlorobenzylidene)-hydrazide (5).*** Yield: 2.54 g (69.3%), mp 249°C (THF-ethanol 1:2); IR (potassium bromide): 3480, 3385 ($NH_2$), 3210 (NH), 1705, 1660 (CO), 1650 (C=N) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 6.49 (s, 2H, $NH_2$), 7.58–8.05 (m, 9H, arom.), 8.55 (s, 1H, CH), 12.48 (s, 1H, HN-CO). Anal. Calcd. for $C_{18}H_{13}ClN_4O_3$: C, 58.63; H, 3.55; N, 15.19. Found: C, 58.81; H, 3.48; N, 14.98.

**General procedure for the synthesis of compounds 6-8.** To an equimolar mixture of 12.5 mL of acetic anhydride and 22 mL of triethyl orthoformate was added 0.008 mol of

the compounds **3**–**5**, or **3c** and refluxed for 5 h. After concentration *in vacuo* the residual oil was poured into 50 mL of 10% ethanolic ammonia. After 1 h of stirring at room temperature the mixture was refrigerated. The resulting solid was filtrated, washed with water, vacuum dried, and recrystallized from the appropriate solvent.

***3-Benzoyl-6-ethylideneamino-6H-isoxazolo[4,3-d]pyrimidin-7-one (6).*** Yield: 2.23 g (79.1%), mp 180°C (1,4-dioxane); IR (potassium bromide): 1740, 1660 (CO), 1650 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.18–2.20 (d, 3H, $CH_3$, $J$ = 6.0 Hz), 7.59–7.64 (m, 3H, arom.), 7.74–7.80 (q, 1H, CH $J$ = 6.0 Hz), 8.02–8.05 (m, 2H, arom.), 8.57 (s, 1H, pos. 5) Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.38; H, 3.64; N, 20.04.

***3-Benzoyl-6-(benzylidene-amino)-6H-isoxazolo[4,3-d]pyrimidin-7-one (7).*** Yield: 2.49 g (72.5%), mp 205°C (ethanol); ir (potassium bromide): 1720, 1700 (CO), 1650 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 7.55–8.07 (m, 10H, arom.), 8.48 (s, 1H, CH), 9.15 (s, 1H, CH, pos. 5). Anal. Calcd. for $C_{19}H_{12}N_4O_3$: C, 66.28; H, 3.51; N, 16.27. Found: C, 66.29; H, 3.58; N, 16.11.

***3-Benzoyl-6-[(4-chloro-benzylidene)-amino]-6H-isoxazolo[4,3-d]pyrimidin-7-one (8).*** Yield: 2.24 g (59.4%), mp 235°C (THF); IR (potassium bromide): 1715, 1695 (C=O), 1650 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 7.61–8.11 (m, 9H, arom.), 8.47 (s, 1H, CH), 9.20 (s, 1H, CH pos. 5). Anal. Calcd. for $C_{19}H_{11}$ Cl $N_4O_3$: C, 60.25; H, 2.93; N, 14.79. Found: C, 60.46; H, 3.06; N, 15.03.

***Methyl N-(3-Benzoyl-7-oxo-7H-isoxazolo[4,3-d]pyrimidin-6-yl)-formimidate (9).*** A solution of 24.6 g (0.1 mol) of the acid hydrazide **2** in an equimolar mixture of 75 mL acetic anhydride and 87 mL of trimethyl orthoformate was refluxed for 4 hours. Then the reaction mixture was concentrated *in vacuo*, filtered, and recrystallized to give compound **9**. Yield: 2.26 g (76.0%), mp 226°C (methanol); IR (potassium bromide):1760, 1680 (C=O), 1660,1650 (C=N), 1160 (C—O—C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.09 (s, 3H, $CH_3$), 7.59–8.06 (m, 5H, arom.), 8.19 (s, 1H, pos. 5), 11.41 (s, 1H, pos. 6). Anal. Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.38; H, 3.38; N, 18.78. Found: C, 56.12; H, 3.22; N, 18.69.

***Ethyl N-(3-Benzoyl-7-oxo-7H-isoxazolo[4,3-d]pyrimidin-6-yl)formimidate (10).*** A solution of 2.46 g (0.01 mol) of the acid hydrazide **2** in a mixture of 12.5 mL acetic anhydride and 22 mL of trimethyl orthoformate was refluxed for 4 h. Then the reaction mixture was concentrated *in vacuo*, filtered, and recrystallized to give compound **10**. Yield: 2.12 g (68.0%), mp 222°C (1,4-dioxane); IR (potassium bromide): 1710, 1690 (C=O), 1650 (C=N), 1155 (C—O—C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.34–1.39 (t, 3H, $CH_3$), 4.33–4.40 (q, 2H, $CH_2$), 7.59–8.05 (m, 5H, arom.), 8.23 (s, 1H, pos. 5), 8.56 (s, 1H, pos. 6). Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.86; H, 3.83; N, 17.87.

**General procedure for the synthesis of compounds 11-14.** To a stirred solution of compound **9** (0.596g, 0.002 mol) in 15 mL of anhydrous 1,4-dioxane was added the appropriate amine (0.004 mol) and heated at 80°C for 4 h. The hot reaction mixture was treated with charcoal and filtered. Concentration of the filtrate to a small volume and addition of 5 mL ethanol resulted in the separation of a colorless solid which was collected by filtration, dried, washed with methanol, and recrystallized from ethanol.

***N-(3-Benzoyl-7-oxo-7H-isoxazolo[4,3-d]pyrimidin-6-yl)-N′-pyridin-4-ylmethyl-formamidine (11).*** Yield: 2.08 g (55.6%), mp 195°C (ethanol); IR (potassium bromide): 3300 (NH), 1725, 1680 (C=O), 1645 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.38 (s, 1H, NH), 4.61 (s, 2H, $CH_2$), 6.56 (s, 1H, CH), 7.27–7.42 (m, 3H, arom.), 7.56–7.68 (m, 3H, arom. + CH at pos. 5), 8.05–8.12 (m, 2H, arom.), 8.50–8.57 (dd, 2H, arom.). Anal. Calcd. for $C_{19}H_{14}N_6O_3$: C, 60.96; H, 3.77; N, 22.45. Found: C, 60.74; H, 3.65; N, 22.18.

***N-(3-Benzoyl-7-oxo-7H-isoxazolo[4,3-d]pyrimidin-6-yl)-N′-benzyl-formamidine (12).*** Yield: 2.20 g (59%), mp 164°C (ethanol); IR (potassium bromide): 3300 (NH), 1715, 1680 (C=O), 1645 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.68 (s, 1H, NH), 5.19 (s, 2H, $CH_2$), 6.72 (s, 1H, CH), 7.23–7.40 (m, 6H, arom.), 7.59–7.78 (m, 3H, arom. and H at pos. 5), 8.03–8.10 (m, 2H, arom.). Anal. Calcd. for $C_{20}H_{15}N_5O_3$: C, 64.34; H, 4.05; N, 18.76. Found: C, 64.56; H, 4.11; N, 18.89.

***N-(3-Benzoyl-7-oxo-7H-isoxazolo[4,3-d]pyrimidin-6-yl)-N′-[(4-chloro-benzyl)-formami-dine (13).*** Yield: 2.03 g (49.8%), mp 169°C (ethanol); IR (potassium bromide): 3310 (NH), 1710, 1690 (C=O), 1640 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.33 (s, 1H, NH), 4.56 (s, 2H, $CH_2$), 6.55 (s, 1H, CH), 7.18–7.46 (m, 5H, arom.), 7.56–7.68 (m, 3H, arom. and CH at pos. 5), 8.03–8.19 (m, 2H, arom.). Anal. Calcd. for $C_{20}H_{14}ClN_5O_3$: C, 58.90; H, 3.46; N, 17.17. Found: C, 59.08; H, 3.51; N, 17.30.

***N-(3-Benzoyl-7-oxo-7H-isoxazolo[4,3-d]pyrimidin-6-yl)-N′-(4-fluoro-benzyl)-formami-dine (14).*** Yield: 1.76 g (45.0%), mp 2202°C (ethanol); IR (potassium bromide): 3280 (NH), 1720, 1690 (C=O), 1645 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.32 (s, 1H, NH), 4.55 (s, 2H, $CH_2$), 6.54 (s, 1H, CH), 7.15–7.41 (m, 5H, arom.), 7.56–7.71 (m, 3H, arom. and CH at pos. 5), 8.06–8.08 (m, 2H, arom.). *Anal*. Calcd. for $C_{20}H_{14}FN_5O_3$: C, 61.38; H, 3.61; N, 17.89. Found: C, 61.49; H, 3.70; N, 18.08.

***5-Methyl-7-phenyl-isoxazolo[4,5-d]pyrimidine-3-carboxamide (15).*** To a solution of amide **1** (2.31 g, 0.01 mol) in anhydrous 1,4-dioxane (40 mL) was added anhydrous acetonitrile (7 mL) and dry gaseous hydrogen chloride was bubbled into the solution for 6 h at room temperature. The reaction mixture was stirred at room temperature for 6 days. Then the reaction mixture was concentrated, cooled, and the resulting solid was filtered, washed with water, dried, and recrystallized from ethanol. Yield: 2.17 g (85.3%), mp 227°C (ethanol); IR (potassium bromide): 3250 ($CONH_2$), 1690 (C=O), 1600 (C=N), 760 (phenyl) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.00 (s, 3H, $CH_3$), 7.70–7.73 (m, 3H, arom.), 8.48–8.49 (m, 2H, arom.), 8.50–8.52 (ss, 2H, $NH_2$). Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.62; H, 4.01; N, 21.84.

***5-Chloromethyl-7-phenyl-isoxazolo[4,5-d]pyrimidine-3-carboxamide (16).*** Compound **16** was prepared in the same manner as described above for compound **15** except that 23.1 g (0.1 mol) of amide **1** was added to a mixture of 330 mL anhydrous 1,4-dioxane and 90 mL anhydrous chloroacetonitrile. Yield: 2.33 g (81.0%), mp 226°C (benzene); Compound **16** was obtained by another method described in our previous paper [25].

***General procedure for the synthesis of compounds 17-20.*** A stirred mixture of compound **16** (0.576 g, 0.002 mol), 0.05 g KI, and the corresponding amine in 30 mL of anhydrous toluene was heated to ca. 80°C for 6 h. After cooling,

water (30 mL) was added and the reaction mixture was extracted with dichloromethane. The combined organic phases were washed with water, dried ($Na_2SO_4$), and concentrated to give a residue, which was recrystallized.

***5-Morpholin-4-ylmethyl-7-phenyl-isoxazolo[4,5-d]pyrimidine-3-carboxamide (17).*** Yield: 2.71 g (80.1%), mp 208°C (methanol); IR (potassium bromide): 3280 ($NH_2$), 1715 (C=O), 1620 (C=N), 1120 (C—O—C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.57–2.60 (m, 4H, $CH_2$—$CH_2$), 3.94 (s, 2H, $CH_2$), 7.58–7.68 (m, 3H, arom.), 8.41–8.45 (m, 4H, 2H, arom. and 2H, $NH_2$). Anal. Calcd. for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64. Found: C, 59.79; H, 5.15; N, 20.88.

***5-(4-Methyl-piperazin-1-ylmethyl)-7-phenyl-isoxazolo[4,5-d]pyrimidine-3-carboxamide (18).*** Yield: 2.16 g (61.5%), mp 188°C (methanol); Compound **18** was obtained by another method described in our previously paper [13], the physical and analytical data are identical.

***5-(Morpholin-4-ylaminomethyl)-7-phenyl-isoxazolo[4,5-d]pyrimidine-3-carboxamide (19).*** Yield: 2.48 g (70.4%), mp 228°C (methanol); Yield: 2.48 g (70.4%), mp 228°C (methanol); IR (potassium bromide): 3300, 3280 (NH, $NH_2$), 1705 (C=O), 1630 (C=N), 1115 (C—O—C) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.21–2.23 (m, 4H, $CH_2$—$CH_2$), 3.57–3.61 (m, 4H, $CH_2$—$CH_2$), 3.94 (s, 2H, $CH_2$), 4.31 (s, 1H, NH), 7.65–7.67 (m, 3H, arom.), 8.36 (s, 1H, NH), 8.42–8.44 (m, 2H, arom.), 8.48 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{18}N_6O_3$: C, 57.62; H, 5.12; N, 23.72. Found: C, 57.38; H, 5.18; N, 24.01.

***5-Dibutylaminomethyl-7-phenyl-isoxazolo[4,5-d]pyrimidine-3-carboxamide (20).*** Yield: 2.84g (74.6%), mp 130°C (1,4-dioxane); IR (potassium bromide): 3300, 3200 ($NH_2$), 1680 (C=O), 1630 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 0.82 (t, 6H, 2x$CH_3$), 1.20–1.32 (m, 4H, $CH_2CH_2$), 1.41–1.50 (m, 4H, $CH_2CH_2$), 2.49–2.57 (m, 4H, $N(CH_2)_2$), 4.03 (s, 2H, $CH_2$), 7.66–7.68 (m, 3H, arom.), 8.36 (s, 1H, NH), 8.44–8.47 (m, 2H, arom.), 8.49 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{27}N_5O_2$: C, 66.12; H, 7.13; N, 18.39. Found: C, 66.36; H, 7.06; N, 18.64.

***5-Chloromethyl-7-phenyl-6,7-dihydro-isoxazolo[4,5-d]pyrimidine-3-carboxamide (21).*** Sodium borohydride (2 g) was added portionwise to a stirred solution of compound **16** (1.44 g, 0.005 mol) in 90 mL of methanol at room temperature under nitrogen. The reaction mixture was stirred for 12 h, concentrated to ca. 30 mL *in vacuo*, and refrigerated. The solid was filtered, washed with water, vacuum dried, and recrystallized. Yield: 1.48 g (51.0%), mp 177°C (methanol); Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27. Found: C, 53.43; H, 3.82; N, 19.43.

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## REFERENCES AND NOTES

[1] Fredholm, B. B.; Abbacchio, M. P.; Burnstock, G.; Daly, J. W.; Harden, T. K.; Jacobson, K. A.; Leff, P.; Williams, M. Pharmacol Rev 1994, 46, 143.

[2] Merighi, S.; Mirandola, P.; Varani, K.; Gessi, S.; Leung, F.; Baraldi, P. G.; Tabrizi, M. A.; Borea, P. A. Pharmacol Ther 2003, 100, 31.

[3] Miller, Ch.E. Curr Topies Med Chem 2003, 3, 445.

[4] Asano, T.; Spector, S. Proc Natl Acad Sci USA 1979, 76, 977.

[5] Skolnick, P.; Syapin, P. J.; Paugh, B. A.; Moncada, Y.; Marangos, P. J.; Paul, S.M. Proc Natl Acad Sci USA 1979, 76, 1515.

[6] Cosyn, L.; Gao, Z. G.; Van Rompaey, P.; Lu, Ch.; Jacobson, K. A.; Van Calenbergh, S. Bioorg Med Chem 2006, 14, 1403.

[7] Desimoni, G.; Grünanger, P.; Finzi, P.V. Tetrahedron 1967, 23, 675.

[8] Laurent, S.; Barbieux-Flammang, M.; Van Haverbeke, Y.; Flammang, R.; Wentrup, C. Bull Soc Chim Belg 1994, 103, 181.

[9] Aliabiev, S. B.; Ivanov, J. S.; Ilyin, A. P.; Kravchenko, D. V.; Ivachtchenko, A. V. Synth Lett Org Chem 2007, 203.

[10] Niewochner, U.; Haning, H.; Lampe, T.; Es-Sayed, M.; Schmidt, G.; Bischoff, E.; Dembowsky, K.; Perzborn, E.; Schlemmeret, K. H. Ger Offen DE 19,962,925, 24 (2001).

[11] Frietze, W. E. US 1998–97,386 (1998).

[12] Wagner, E.; Becan, L.; Nowakowska, E. Bioorg Med Chem 2004, 12, 265.

[13] Poręba, K.; Wagner, E.; Jakowicz, I.; Balicka, D. II. Acta Pol Pharm Drug Res 1994, 51, 355–358.

[14] Gewald, K.; Bellmann, P.; Jänsh, H. J. Liebigs Ann Chem 1980, 10, 1623.

[15] Wagner, E.; Al-Kadasi, K.; Zimecki, M.; Sawka-Dobrowolska, W. Eur J Med Chem 2008, 43, 2498.

[16] Dave, K. G.; Shishoo, C. J.; Devani, M. B.; Kalyanaraman, R.; Ananthan, S.; Ulas, G. V.; Bhadti, V. S. J Heterocyclic Chem 1980, 17, 1497.

[17] Shishoo, C. J.; Devani, M. B.; Ananthan, S.; Ulas, G. V.; Bhadti, V.S. Tetrahedron Lett 1984, 25, 1291.

[18] Perold, G. W.; von Reiche, F. V. K. J Am Chem Soc 1957, 79, 465.

[19] LeBel, N. A.; Whand, J. J. J Am Chem Soc 1959, 81, 6334.

[20] Saxema, R.; Singh, V.; Batra, S. Tetrahedron 2004, 60, 10311.

[21] Taylor, E. C.; Garcia, E. E. J Org Chem 1964, 29, 2116.

[22] Sheldrick, G. M. SHELXS-97 and SHELXL-97: Programs for the Solution and Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

[23] Sheldrick, G. M. SHELXTL-NTV5.1, Brucker-AXS, 1999.

[24] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G. J Chem Soc Perkin Trans 2 1987, 1.

[25] Wagner, E.; Poręba, K.; Jakowicz, I.; Balicka, D.; Rutkowska, M.; Kędzierska-Goździk, L.; Szeląg, A. Il Farmaco 1995, 50, 183.

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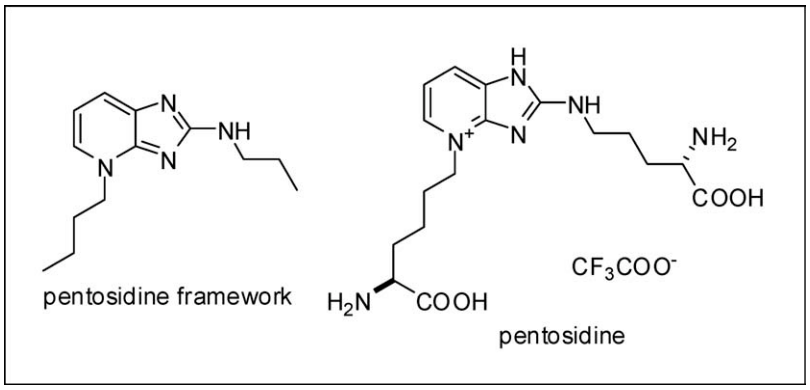
*This work was performed under Professor Sayre's direction. Professor Lawrence M. Sayre passed away May 8, 2009, following an incapacitating stroke. His impact on the lives of his colleagues, students, and friends was profound and he is deeply missed [3]. We dedicate this article to him as a great mentor and brilliant scientist.*




Pentosidine framework 4-butyl-2-propyl-4*H*-aminoimidazo[4,5-*b*]pyridine (**2**) was synthesized through a five steps reaction sequence. The regiochemistry of **2** was confirmed by an unambiguous synthesis, and the UV absorption and fluorescent properties of **2** were examined.

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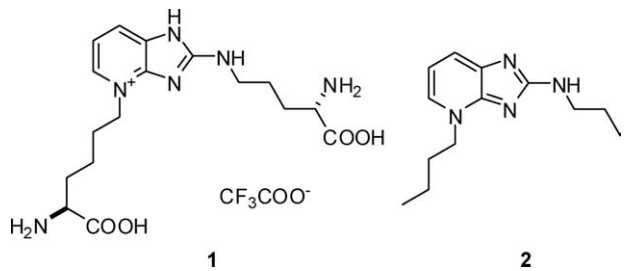
## INTRODUCTION

Pentosidine (**1**) is one of the major fluorescent advanced glycation end products that have been isolated and structurally characterized. It was isolated in trifluoroacetic acid salt form from dura mater by Sell and Monnier in 1989 [4]. It was postulated that pentosidine forms from a lysine residue and an arginine residue crosslinked by a pentose [4–6]. The fluorescent properties of pentosidine (ex/em 335/385 nm) make it an oxidative biomarker in many clinical conditions such as diabetes, kidney disease, and other vascular illnesses [7].



**1** **2**

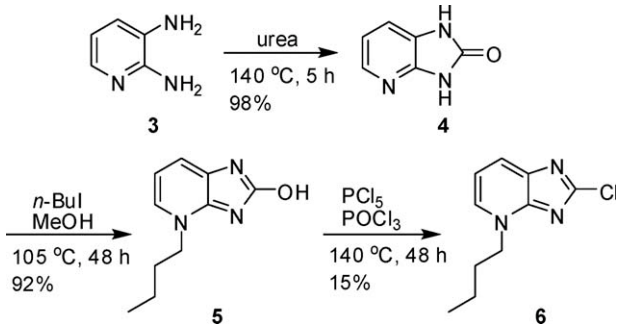
There has been only one total synthesis of pentosidine so far [8]. Shioiri and coworkers obtained 5.1 mg TFA salt of pentosidine (**1**) from their synthesis that involves an asymmetric alkylation of a chiral Schiff base to provide a lysine-like fragment, the intramolecular guanylation with mercury chloride, and the quaternization accompanied by the removal of trityl group as key steps [8].

In the investigation of the fluorescence properties of the pentosidine, one of our tasks was to evaluate the fluorescence property of the core of pentosidine, 4-alkyl-2-amino-4*H*-imidazo[4,5-*b*]pyridine, without the interference of amino acid chains. 2-Aminoimidazo[4,5-*b*]pyridine derivatives are important in medicinal chemistry because of their biological and pharmacological properties such as antihistamines, antibacterial agents, and integrin $\alpha_v\beta_3$ antagonists [9]. Therefore, a concise synthesis of the pentosidine framework 4-butyl-2-propyl-4*H*-aminoimidazo[4,5-*b*]pyridine (**2**) is of important for both biochemistry research of pentosidine and medicinal chemistry research. Herein, we report a straightforward synthesis of the pentosidine framework **2**.

## RESULTS AND DISCUSSION

Our synthesis of **2** commenced from 2,3-diaminopyridine **3** (Scheme 1). The reaction of **3** with urea furnished 1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (**4**) [10]. Alkylation of **4** gave 4-butyl-2-hydroxyimidazo[4,5-*b*]pyridine (**5**) in 92% yield. The transformation from **5** to **6** failed with most usual chlorodehydroxylation reagents such as thionyl chloride and phosphorus oxychloride,

**Scheme 1**

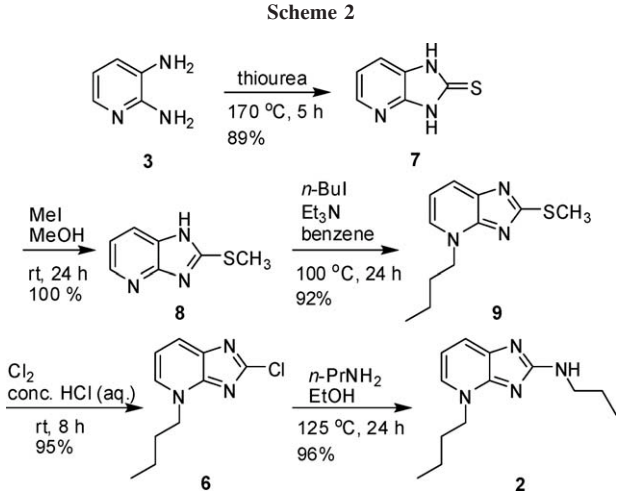



but compounds **6** could be obtained albeit in low yield (15%) after heating for 24 h in phosphorus oxychloride in the presence of phosphorus pentachloride [10].

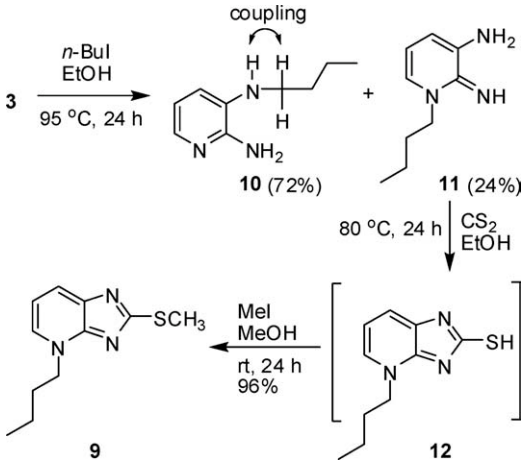
Our improved synthesis (Scheme 2) started with the reaction of 2,3-diaminopyridine **3** with thiourea, which afforded 1*H*-imidazo[4,5-b]pyridine-2(3H)-thione (**7**) [11]. Compound **7** is different from **4** in that alkylation of **7** would give an *S*-alkylated product instead of a pyridine *N*-alkylated product. Therefore, the sulfur in **7** was masked by prior methylation to give 2-(methylthio)imidazo[4,5-*b*]pyridine (**8**), which was alkylated by *n*-BuI regioselectively at the pyridine nitrogen to furnish **9** in good yields (78%) [12]. Compound **6** was obtained in good yield (96%) by bubbling $Cl_2$ through a concentrated hydrochloric acid solution of **9** followed by neutralization [13]. The reaction of **6** with *n*-$PrNH_2$ gave us the final target in good yields (97%) [14].

Although target compound **2** could be obtained according to the synthesis shown in Scheme 2 with satisfactory overall yields (75%), evidence for the regiochemistry of alkylation in **2**, **5**, **6**, and **9** was not fully discussed in the above description. We assigned both **5** and **9** as pyridine *N*-alkylated products based on the

**Scheme 2**




**Scheme 3**




expected greater nucleophilicity of the pyridine nitrogen relative to the imidazole nitrogens at positions **1** or **3** due to resonance [12]. To provide conclusive evidence for our structural assignment for **5** and **9**, as well as for compounds **6** and **2** that were obtained in subsequent steps, an unambiguous synthesis was used (Scheme 3). The synthesis started with alkylation of **3**, which was known to give only two alkylated products **10** and **11** [15]. The distinction of **11** from **10** could be made on the basis of both proton chemical shift and characteristic couplings. The chemical shift for the methylene group neighboring nitrogen in **10** is δ 3.08, whereas δ 4.22 in the case of **11** [15]. Furthermore, in **10**, the $HNCH_2$ vicinal coupling could be observed clearly in DMSO-$d_6$, whereas no such coupling was seen for **11**. The reaction of **11** with carbon disulfide and further methylation of sulfur could only provide 4-alkylated imidazo[4,5-*b*]pyridine structure **9** [16]. Compound **9** obtained through

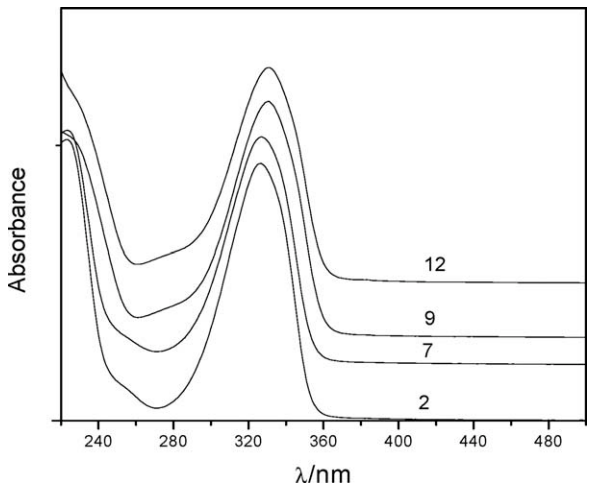



**Figure 1.** UV spectrum of **2** at pH = 2, 7, 9, and 12.

**Table 1**

Fluorescence property of pentosidine framework **2**.

| pH | Excitation $\lambda_{max}$ (nm) | Emission $\lambda_{max}$ (nm) | Relative fluorescence intensity[a] |
|---|---|---|---|
| 2 | 332 | 382 | 55 |
| 7 | 335 | 386 | 43 |
| 9 | 338 | 389 | 68 |
| 12 | | | None |

[a] When excitation $\lambda_{max}$ is 335 nm.

this route was found to be identical with the product obtained from the synthesis shown in Scheme 2. This conclusion was based not only by direct comparison of their NMR spectra run separately but also by the NMR spectrum of a 1:1 mixture.

The absorption spectra for the pentosidine framework **2** are shown in Figure 1, and its fluorescence properties (ex/em 335/385 nm) are listed in Table 1. The shifts of the $\lambda_{max}$ in different pH buffers were consistent with those of pentosidine **1** [4]. However, the variation of fluorescence intensity with pH values for **2** differed somewhat from that of **1**. Although we observed a decrease in fluorescence intensity upon increasing pH above 2, we did not observe the regain in fluorescence intensity observed for pentosidine at pH 12. As **2** lacks the free α-amino acid groups of pentosidine itself, we suggest that this is the basis of the different behavior.

In summary, pentosidine framework **2** was synthesized from readily commercially available 2,3-diaminopyridine in five steps, and the regiochemistry of the target was established by an unambiguous synthesis. This method is of material accessibility and operational simplicity and also serves as a general method to construct the 4-alkylated-2-amino-4*H*-imidazo[4,5-*b*]pyridines.

## EXPERIMENTAL

$^1$H-NMR (300 or 200 MHz) and $^{13}$C-NMR (75.1 or 50 MHz) were recorded on Varian Gemini 300 or Gemini 200 instruments. In the $^{13}$C-NMR line listings, attached proton test designations are given as (+) or (−) following the chemical shift. High-resolution mass spectra (HRMS) were obtained at 20 eV on a Kratos MS-25A instrument. UV–visible spectra were obtained with a Perkin-Elmer model Lambda 3B spectrophotometer, and fluorescence was determined using an Aminco-Bowman spectrofluorometer. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets, and UV light was used for detection. Flash column chromatography was done using E. Merck silica gel 60 (230–400 mesh). Solvent removal was accomplished by a rotary evaporator operating at vacuum (40–50 Torr).

**1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (4).** A mixture of 2,3-diaminopyridine (**3**, 763.9 mg, 7.0 mmol) and urea (1.40 g, 23.3 mmol) was heated at 140°C for 5 h. The cooled reaction mixture was extracted with boiling ethanol (5 × 6 mL), leaving crystals that were collected by filtration. A second crop of crystals was obtained from the cooled filtrate after standing overnight. The combined yield of pure **4** was 929.7 mg (98%). **4**: $^1$H-NMR (DMSO-$d_6$) δ 6.93 (dd, $J$ = 7.1, 5.9 Hz, 1H), 7.21 (d, $J$ = 7.1 Hz, 1H), 7.85 (d, $J$ = 5.8 Hz, 1H), 10.82 (s, 1H, NH), 11.29 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$) δ 114.4 (−), 116.6 (−), 123.6 (+), 139.6 (−), 144.8 (+), 154.4 (+). HRMS calcd for $C_6H_5N_3O$ ($M^+$) 135.0433, found 135.0428.

**4-Butyl-2-hydroxy-4*H*-imidazo[4,5-*b*]pyridine (5).** A mixture of **3** (810.7 mg, 6.0 mmol) and *n*-butyl iodide (5.52 g, 30.0 mmol) in MeOH (8 mL) was sealed in a Teflon-screwed high-pressure vessel and stirred at 105°C for 48 h and concentrated. The resulting residue was diluted with a mixed solvent of $CH_2Cl_2$/MeOH (9:1), basified with 28% aqueous $NH_4OH$ solution, and subjected to chromatography ($CH_2Cl_2$/MeOH/28% aqueous $NH_4OH$ = 90:10:1) to afford **5** (1.055 g, 92%): $^1$H-NMR ($CD_3OD$) δ 0.98 (t, $J$ = 7.1 Hz, 3H), 1.41 (m, 2H), 1.92 (m, 2H), 4.42 (t, $J$ = 7.5 Hz, 2H), 7.06 (dd, $J$ = 7.5, 6.8 Hz, 1H), 7.45 (d, $J$ = 7.5 Hz, 1H), 7.84 (d, $J$ = 6.7 Hz, 1H); $^{13}$C-NMR ($CD_3OD$) δ 14.1 (−), 20.8 (+), 32.3 (+), 54.7 (+), 115.2 (−), 116.3 (−), 131.8 (−), 132.6 (+), 152.1 (+) (one quaternary peak is missing); HRMS calcd for $C_{10}H_{13}N_3O$ ($M^+$) 191.1059, found 191.1056.

**4-Butyl-2-chloro-4*H*-imidazo[4,5-*b*]pyridine (6).** A suspension of **5** (956.2 mg, 5.0 mmol) and $PCl_5$ (1.20 g, 5.40 mmol) in $POCl_3$ (120 mL) was sealed in a Teflon-screwed high-pressure vessel and stirred at 140°C for 48 h. Then, $POCl_3$ was removed under reduced pressure, and the residue was dissolved in water (10 mL) and basified to pH = 8 with 2*N* aqueous solution of NaOH. The aqueous solution was extracted with $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 5:1) to afford **6** (157.3 mg, 15%). $^1$H-NMR ($CDCl_3$) δ 0.93 (t, $J$ = 7.3 Hz, 3H), 1.36 (m, 2H), 1.98 (m, 2H), 4.57 (t, $J$ = 7.5 Hz, 2H), 7.09 (dd, $J$ = 7.5, 6.5 Hz, 1H), 7.68 (d, $J$ = 6.5 Hz, 1H), 8.05 (d, $J$ = 7.6, 1H); $^{13}$C-NMR ($CDCl_3$) δ 13.6 (−), 19.8 (+), 31.7 (+), 54.2 (+), 113.5 (−), 127.7 (−), 130.1 (−), 144.1 (+), 152.5 (+), 160.7 (+); HRMS calcd for $C_{10}H_{12}N_3Cl$ ($M^+$) 209.0720, found 209.0724.

**1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (7).** A mixture of 2,3-diaminopyridine (**3**, 2.18 g, 20 mmol) and thiourea (7.6 g, 100 mmol) was heated at 170°C for 5 h. The reaction mixture was extracted with boiling ethanol (5 × 20 mL), leaving crystals that were collected by filtration. A second crop of crystals was obtained from the cooled filtrate after standing overnight. The combined yield of pure **7** was 2.7 g (89%). **7**: $^1$H-NMR (DMSO-$d_6$) δ 7.13 (dd, $J$ = 7.9, 5.0 Hz, 1H), 7.46 (d, $J$ = 7.9 Hz, 1H), 8.09 (d, $J$ = 5.0 Hz, 1H), 12.70 (s, 1H, NH), 13.12 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$) δ 116.2 (−), 118.1 (−), 125.4 (+), 142.3 (−), 146.4 (+), 169.8 (+). HRMS calcd for $C_6H_5N_3S$ ($M^+$) 151.0204, found 151.0204.

**2-(Methylthio)-1*H*-imidazo[4,5-*b*]pyridine (8).** A solution of **7** (2.26 g, 15.0 mmol) and methyl iodide (8.52 g, 60 mmol) in MeOH (30 mL) was stirred at room temperature for 24 h. Evaporation of the solvent and $CH_3I$ under reduced pressure gave pure **8** (3.32 g, 100%): $^1$H-NMR ($CD_3OD$) δ 2.75 (s, 3H), 7.20 (dd, $J$ = 7.9, 4.9 Hz, 1H), 7.82 (d, $J$ = 7.9 Hz, 1H), 8.21 (d, $J$ = 4.9 Hz, 1H); $^{13}$C-NMR ($CD_3OD$) δ 15.0 (−), 119.1 (−), 127.4 (−), 134.1 (+), 134.5 (−), 150.3 (+), 166.4

(+); HRMS calcd for $C_7H_7N_3S$ ($M^+$) 165.0361, found 165.0363.

**4-Butyl-2-(methylthio)-4*H*-imidazo[4,5-*b*]pyridine (9).** A suspension of **8** (1.65 g, 10.0 mmol) in a solution of *n*-butyl iodide (2.76 g, 15.0 mmol) and triethylamine (1.52 g, 15.0 mmol) in benzene (150 mL) was sealed in a Teflon-screwed high-pressure vessel and stirred at 100°C for 24 h and concentrated. The residue was diluted with mixed solvent of $CH_2Cl_2$/MeOH (9:1), basified with 28% aqueous $NH_4OH$ solution, and subjected to chromatography (EtOAc/acetone/MeOH/28%$NH_4OH$, 140:60:10:1) to afford **9** (2.03 g, 92%): $^1$H-NMR ($CDCl_3$) δ 0.97 (t, $J$ = 7.3 Hz, 3H), 1.38 (m, 2H), 2.01 (m, 2H), 2.78 (s, 3H), 4.60 (t, $J$ = 7.3 Hz, 2H), 7.07 (dd, $J$ = 7.7, 6.7 Hz, 1H), 7.45 (d, $J$ = 6.6 Hz, 1H), 7.84 (d, $J$ = 7.7 Hz, 1H); $^{13}$C-NMR ($CDCl_3$) δ 13.6 (−), 14.6 (−), 19.8 (+), 31.6 (+), 53.9 (+), 113.5 (−), 124.0 (−), 129.2 (−), 143.2 (+), 151.8 (+), 172.1 (+); HRMS calcd for $C_{11}H_{15}N_3S$ ($M^+$) 221.0987, found 221.0982.

**Preparation of 6 from 9.** Chlorine was introduced into a solution of **9** (664.0 mg, 3.0 mmol) in hydrochloric acid (12*N*, 300 mL) with stirring at room temperature for 8 h. After standing overnight, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with ice water (400 mL), basified with 2*N* aqueous solution of NaOH, and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated resulting in a crude, which was subjected to chromatography ($CH_2Cl_2$/$CH_3OH$, 5:1) to afford **6** (597.5 mg, 95%). $^1$H-NMR, $^{13}$C-NMR, and HRMS data were identical with those of **6** prepared from **5**.

**4-Butyl-2-(propylamino)-4*H*-imidazo[4,5-*b*]pyridine (2).** A mixture of **6** (524.2 mg, 2.50 mmol) and propylamine (1.18 g, 20.0 mmol) in EtOH (30 mL) was sealed in a Teflon-screwed high-pressure vessel and stirred at 125°C for 24 h and was evaporated to result in a residue, which was subjected to chromatography ($CH_2Cl_2$/MeOH, 5:1) to afford **2** (557.2 mg, 96%). $^1$H-NMR ($CD_3OD$) δ 0.98 (t, $J$ = 7.5 Hz, 3H), 1.01 (t, $J$ = 7.3 Hz, 3H), 1.38 (m, 2H), 1.72 (m, 2H), 1.96 (m, 2H), 3.46 (t, $J$ = 6.9, 2H), 4.56 (t, $J$ = 7.3, 2H), 7.16 (dd, $J$ = 7.6, 6.6 Hz, 1H), 7.75 (d, $J$ = 7.6 Hz, 1H), 8.00 (d, $J$ = 6.6, 1H); $^{13}$C-NMR ($CDCl_3$) δ 11.5 (−), 13.6 (−), 19.6 (+), 22.8 (+), 31.4 (+), 44.9 (+), 53.3 (+), 114.2 (−), 118.1 (−), 129.9 (−), 152.6 (+), 156.7 (+), 161.8 (+); HRMS calcd for $C_{13}H_{20}N_4$ ($M^+$) 232.1688, found 232.1685.

**2-Amino-3-(butylamino)pyridine (10) and 1-butyl-3-amino-2-pyridone imine (11).** A mixture of **4** (1.09 g, 10.0 mmol) and *n*-butyl iodide (7.36 g, 40.0 mmol) in EtOH (60 mL) was sealed in a Teflon-screwed high-pressure vessel and stirred at 95°C for 24 h and concentrated. The resulting residue was dissolved in a mixed solvent of MeOH and water (1:1) (160 mL), adjusted to pH 10 with 2*N* aqueous solution of NaOH, and evaporated ending in a crude, which was subjected to chromatographic (EtOAc/MeOH, 4:1) separation to afford **10** (1.19 g, 72%) and **11** (396.6 mg, 24%). **10**: $^1$H-NMR ($CDCl_3$) δ 0.97 (t, $J$ = 7.2 Hz, 3H), 1.45 (m, 2H), 1.64 (m, 2H), 3.08 (t, $J$ = 6.7 Hz, 2H), 6.70 (dd, $J$ = 7.6, 4.8 Hz, 1H), 6.80 (d, $J$ = 7.6 Hz, 1H), 7.57 (d, $J$ = 4.8 Hz, 1H); $^{13}$C-NMR ($CDCl_3$) δ 14.0 (−), 20.4 (+), 31.5 (+), 43.6 (+), 115.8 (−), 116.7 (−), 132.5 (+), 135.8 (−), 148.7 (+); HRMS calcd for $C_9H_{15}N_3$ ($M^+$) 165.1266, found 165.1264. **11**: $^1$H-NMR ($CD_3OD$) δ 0.98 (t, $J$ = 7.3 Hz, 3H), 1.42 (m, 2H), 1.79 (m, 2H), 4.22 (t, $J$ = 7.6 Hz, 2H), 6.77 (dd, $J$ = 7.7, 6.5 Hz, 1H), 7.13 (d, $J$ = 7.7 Hz, 1H), 7.37 (d, $J$ = 6.5 Hz, 1H); $^{13}$C-NMR ($CD_3OD$) δ 14.1 (−), 20.5 (+), 30.8 (+), 55.4 (+), 115.3 (−), 120.9 (−), 128.8 (−), 135.8 (+), 146.4 (+); HRMS calcd for $C_9H_{15}N_3$ ($M^+$) 165.1266, found 165.1265.

**Preparation of 9 from 11.** A solution of **11** (165.2 mg, 1.0 mmol) and $CS_2$ (5 mL) in EtOH (8 mL) in a sealed Teflon-screwed high-pressure vessel was stirred at 80°C for 24 h and concentrated. The residue was mixed with MeI (1.41 g, 10.0 mmol) in MeOH (6 mL), stirred at room temperature for 24 h, and concentrated resulting in a crude mixture, which was subjected to chromatography (EtOAc/MeOH, 4:1) to afford **9** (179.3 mg, 81%). $^1$H-NMR, $^{13}$C-NMR, and HRMS data were identical with those of **9** prepared from **8**.

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## REFERENCES AND NOTES

[1] Current address: Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121.

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[3] Salomon, R. G.; Zagorski, M. G. Chem Res Toxicol 2009, 22, 1369.

[4] Sell, D. R.; Monnier, V. M. J Biol Chem 1989, 264, 21587.

[5] Culbertson, S. M.; Vassilenko, E. I.; Morrison, L. D.; Ingold, K. U. J Biol Chem 2003, 278, 38384.

[6] Biemel, K. M.; Reihl, O.; Conrad, J.; Lederer, M. O. J Biol Chem 2001, 276, 23405.

[7] For some reviews, see: (a) Sugimoto, K.; Yasujima, M.; Yagihashi, S. Curr Pharm Des 2008, 14, 953; (b) Tsukahara, H. Curr Med Chem 2007, 14, 339.

[8] (a) Yokakawa, F.; Sugiyama, H.; Shioiri, T.; Katagiri, N.; Oda, O.; Ogawa, H. Tetrahedron Lett 1999, 40, 2569; (b) Yokakawa, F.; Sugiyama, H.; Shioiri, T.; Katagiri, N.; Oda, O.; Ogawa, H. Tetrahedron 2001, 57, 4759.

[9] For some examples: (a) Jarvest, R. L.; Armstrong, S. A.; Berge, J. M.; Brown, P.; Elder, J. S.; Brown, M. J.; Copley, R. C. B.; Forrest, A. K.; Hamprecht, D. W.; O'Hanlon, P. J.; Mitchell, D. J.; Rittenhouse, S.; Witty, D. R. Bioorg Med Chem Lett 2004, 14, 3937; (b) Pomarnacka, E.; Kornicka, A. Il Farmaco 2001, 56, 571; (c) Ishikawa, M.; Kubota, D.; Yamamoto, M.; Kuroda, C.; Iguchi, M.; Koyanagi, A.; Murakami, S.; Ajito, K. Bioorg Med Chem 2006, 14, 2109.

[10] Dornow, A.; Hahmann, O. Arch Pharm 1957, 290, 21.

[11] Petrow, V.; Saper, J. J Chem Soc 1948, 1389.

[12] Singh, M. P.; Bathini, Y.; Lown, J. W. Heterocycles 1993, 36, 971.

[13] Jung, F.; Delvare, C.; Boucherot, D.; Hamon, A. J Med Chem 1991, 34, 1110.

[14] Perkins, J. J.; Zartman, A. E.; Meissner, R. S. Tetrahedron Lett 1999, 40, 1103.

[15] Oyama, K.; Stewart, R. J Chem Soc Perkin Trans 1 1973, 673.

[16] Nicolai, E.; Goyard, J.; Benchetrit, T.; Teulon, J.; Caussade, F.; Virone, A.; Delchambre, C.; Cloarec, A. J Med Chem 1993, 36, 1175.

# An Efficient One-Pot Three-Component Synthesis of 4-Phenyl hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one Derivatives



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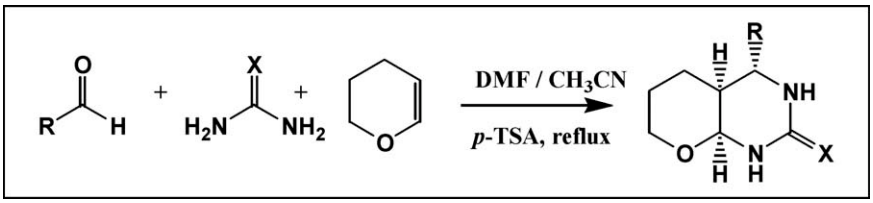


An efficient method for the synthesis of a series of 4-phenylhexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one derivatives via the one-pot three-component reaction of aromatic aldehydes, urea or thiourea and 3,4-dihydro-2*H*-pyran in DMF/$CH_3CN$ using *p*-TSA catalyst is described. Although three chiral centers are created, only one diastereomer is formed in a highly selective way. This method has several advantages such as higher yield, lower cost, and shorter reaction times.

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## INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry [1]. In times, where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses [2]. The synthesis of dihydropyrimidinones using variants of the well-established Biginelli reaction is one of the most recognized and often used MCRs for the generation of novel pyrimidine scaffolds [3]. Most notably are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors [4]. There is a widespread interest in the synthesis of pyranopyrimidinones and related fused ring pyrimidinones with diverse range of biological properties [5], such as antitumor, antibacterial, antihypertensive, vasodilator, bronchiodilator, hepatoprotective, cardiotonic, and antiallergic activities. Some of them also exhibit antimalarial, antifungal, analgesics, and herbicidal properties [6]. Recently, modified Biginelli reaction has been used in accessing fused pyrimidinones or spiro-fused pyrimidinones [3e,3f]. Recently, Wu and coworkers [7] reported a TMSCl catalyzed three-component diastereoselective reaction of 3,4-dihydro-(2*H*)-pyran with urea/thiourea and aromatic aldehydes to give respective 4-phenyl hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-ones (thiones). In continuation of our previous work on the synthesis of heterocyclic compounds [8], we wish to report an efficient one-pot three-component method for the preparation of substituted 4-phenyl hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-one derivatives using *p*-TSA as catalyst in DMF/$CH_3CN$ under reflux conditions. This method not only preserved the simplicity of Biginelli type one-pot condensation but also remarkably improved the yields of the pyrimidin-2-one derivatives in shorter reaction times (5–6 h) as against the longer reaction times required for the other catalysts (e.g., TMSCl).

## RESULTS AND DISCUSSION

Initially, we subjected the condensation of 4-fluoro benzaldehyde with urea and 3,4-dihydro-2*H*-pyran in the presence of various acid catalysts in different solvent systems at room temperature as well as under reflux conditions (Table 1). The best yield (95%) of product 4-(4-flurophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8 a*H*)-one **4g** was obtained when *p*-TSA was used as catalyst in DMF/$CH_3CN$ (1:1) under reflux conditions (entry 4, Table 1). The formation of product **4g** was confirmed by IR, $^1H$, $^{13}C$, and mass spectral analysis. Although theoretically three chiral centers are created, only one diastereomer was formed in a highly selective way. To access the stereochemistry of the product, we chose 4-methylbenzaldehyde as substrate and reacted with urea and 3,4-dihydro-2*H*-pyran in DMF/$CH_3CN$ (1:1) using *p*-TSA under identical reaction conditions. NMR spectral data determined the product as 4-(4-methylphenyl)hexa hydro-*1H*-pyrano [2,3-*d*]pyrimidin-2(8a*H*)-one **4a**. The spectral data obtained was closely identical to the literature reported [7], X-ray analyzed, diasteroselective product **4a**.

**Table 1**

Catalyst effect on the reaction of 4-fluorobenzaldehyde, urea, and 3,4-dihydro-2*H*-pyran.

| Entry | Catalyst | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Montmorillonite K10 | DMF/$CH_3CN$ | Reflux | 10 | 45 |
| 2 | PPA-$SiO_2$ | DMF/$CH_3CN$ | Reflux | 10 | No reaction |
| 3 | PPA-$SiO_2$ | Solvent free | 120 | 10 | No reaction |
| 4 | *p*-TSA | DMF/$CH_3CN$ | Reflux | 5.2 | 95 |
| 5 | TMSCl/NaI | $CH_3CN$ | Reflux | 10 | 62 |
| 6 | Silica sulfuric acid | DMF/$CH_3CN$ | Reflux | 10 | 35 |
| 7 | $HCLO_4$-$SIO_2$ | DMF/$CH_3CN$ | Reflux | 10 | 35 |
| 8 | *p*-TSA | DMF/$CH_3CN$ | r.t. | 24 | 15–20 |
| 9 | Montmorillonite K10 | DMF/$CH_3CN$ | r.t. | 24 | No reaction |

Because of its great facility and easy availability of catalyst, we further proceeded to examine the scope of this catalytic transformation. The reaction of 3,4-dihydro-2*H*-pyran with a range of other aromatic, and heterocyclic aldehydes and urea/thiourea under similar conditions using *p*-TSA, furnishing the respective pyrimidin-2-one derivatives **4a–4l** (Scheme 1) in excellent yields. The optimized results are listed in Table 2. All the products were fully characterized by IR, NMR, and Mass spectroscopic analysis. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. A variety of substituted aromatic heterocyclic aldehydes carrying either electron donating or withdrawing substituents afforded high yields of products in high purity. Thiourea has also been used with similar success to provide corresponding pyrimidin-2-thione derivatives, which are also of much interest with regard to the biological activity [9].

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of substituted 4-phenylhexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-ones (thiones) derivatives with excellent yields and short reaction times, which involves the use of inexpensive catalyst *p*-TSA under DMF/$CH_3CN$ reflux conditions. Furthermore, the present procedure is readily amenable to parallel synthesis and generation of combinatorial DHPMs libraries.

## EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. $^1$H and $^{13}$C NMR spectra were recorded on Varian FT-200/50 MHz (Gemini) and Bruker UX NMR FT-300/75 MHz (Avance) instruments, in deuterated dimethylsulfoxide [D6]-DMSO. Chemical shifts are reported in parts per million relative to TMS as internal standard. LC-mass spectra were recorded on a LC-MSD-Trap-SL mass spectrometer. Elemental analyses were performed by Elementar analyzer Vario EL. Melting points has been recorded on an Electrothermal melting point apparatus. The IR spectra were obtained with Perkin Elmer 240-C instrument using potassium bromide pellets/neat. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on glass).

**General procedure.** Aromatic aldehyde (5 mmol), 3,4-dihydro-2*H*-pyran (5 mmol) and urea or thiourea (6 mmol) in anhydrous DMF/$CH_3CN$ (1.5 mL/3 mL) were mixed in a flask and *p*-TSA (0.3 mmol) was added at room temperature. The resulting reaction mixture was stirred at reflux for 5–6 h and then poured into crushed ice with stirring. The precipitation was isolated by filtered through a Buechner funnel and washed with water followed by pet–ether, and then dried to give the desired product. All products obtained were fully characterized by spectroscopic methods such as IR, $^1$H NMR, $^{13}$C NMR, and mass spectroscopy and have been identified by the comparison of the spectral data with those reported.

**4-Phenylhexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4a.** mp 252–254°C; IR (KBr, $\nu_{max}$): 3290, 1685, 1512, 1479, 1181, 1125 cm$^{-1}$. $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.25–1.28 (m, 1H, $CH_2$), 1.46–1.89(m, 4H, $CH_2$ and H-10), 2.30 (s, 3H, $CH_3$), 3.47 (t, $J$ = 10.11 Hz, 1H, H-7), 3.97 (d, $J$ = 9.76 Hz, 1H, H-7), 4.48(q, $J$ = 1.92 Hz, 1H, H-9), 4.60 (d, $J$ = 11.15 Hz, 1H, H-4), 6.68(s, 1H, NH), 7.08–7.16 (m, 5H, ArH and NH) Mass LCMS $^+$MS 247. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.65; H, 7.86; N, 11.13.

**4-(3,4,5-Trimethoxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-one 4b.** mp 238–240°C; IR (KBr, $\nu_{max}$): 3371, 3215, 1683, 1597, 1460, 1127, 1033 cm$^{-1}$. $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.21–1.93 (m, 5H, $CH_2$ and H-10), 3.47–3.55 (m, 1H, H-7), 3.69 (s, 3H, $OCH_3$), 3.82 (s, 6H, $OCH_3$), 3.95–4.00 (m, 1H, H-7), 4.47–4.50 (m, 1H, H-9), 4.98 (d, $J$ = 10.64 Hz, 1H, H-4), 6.53 (s, 1H, NH), 6.69 (s, 2H, ArH), 7.30 (brs, 1H, NH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 20.3 ($CH_2$), 23.0 ($CH_2$), 37.5 (CH), 52.9 (CH), 55.9, 60.0 ($OCH_3$), 65.8 ($CH_2$), 80.2 (CH), 104.7 (ArCH), 125.5, 128.1, 136.9, 152.8 (ArC), 154.8 (C=O); Mass LCMS $^+$MS 323. Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.71; H, 6.91; N, 8.71.

**4-(4,5-Dimethoxy-2-nitrophenyl)hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-one 4c.** mp 231–233°C; IR (KBr, $\nu_{max}$): 3223, 2931, 1687, 1523, 1274, 1175, 1098 cm$^{-1}$; $^1$H NMR

**Scheme 1**

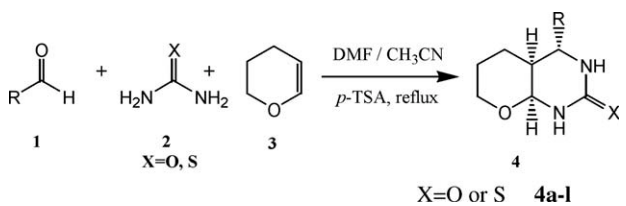

**Table 2**

Multicomponent reaction of 3,4-dihydro-2*H*-pyran, urea or thiourea, and aromatic aldehydes for the synthesis of **4a–4l**.

| Entry | R | X | Product | Time (h) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 | 4-$CH_3C_6H_4$ | O | **4a** | 5.5 | 98 | 7 |
| 2 | 3,4,5-$(OCH_3)_3C_6H_2$ | O | **4b** | 6.0 | 96 | – |
| 3 | 4,5-$(OCH_3)_2$-2-$NO_2$-$C_6H_2$ | O | **4c** | 5.5 | 89 | – |
| 4 | 4-$OCH_3C_6H_4$ | O | **4d** | 6.0 | 91 | 7 |
| 5 | 4-$OCH_3C_6H_4$ | S | **4e** | 6.0 | 88 | 7 |
| 6 | 4-$BrC_6H_4$ | O | **4f** | 5.0 | 97 | – |
| 7 | 4-$FC_6H_4$ | O | **4g** | 5.2 | 95 | – |
| 8 |  | S | **4h** | 6.0 | 88 | – |
| 9 | 2,4-$Cl_2$-$C_6H_3$ | S | **4i** | 5.0 | 84 | – |
| 10 | 3-$OHC_6H_4$ | O | **4j** | 5.5 | 90 | – |
| 11 | 2,4-$Cl_2$-$C_6H_3$ | O | **4k** | 5.0 | 97 | – |
| 12 | 4-$FC_6H_4$ | S | **4l** | 5.5 | 86 | 7 |

(200 MHz, DMSO-$d_6$): δ 1.22 (d, $J$ = 10.92 Hz, 2H, $CH_2$), 1.42–1.65 (m, 2H, $CH_2$), 2.17 (d, $J$ = 10.92 Hz, 1H, H-10), 3.40–3.52 (m, 2H, H-7), 3.87 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 4.47 (s, 1H, H-9), 5.16 (d, $J$ = 10.19 Hz, 1H, H-4), 6.73 (s, 1H, NH), 7.11 (s, 1H, ArH), 7.36 (brs, 1H, NH), 7.52 (s, 1H, ArH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 21.0 ($CH_2$), 23.1 ($CH_2$), 36.9 (CH), 47.4 (CH), 56.3 ($OCH_3$), 65.2 ($CH_2$), 79.9 (CH), 107.4, 110.6 (ArCH), 129.5, 142.5, 148.0, 152.8 (ArC), 154.9 (C=O); Mass LCMS $^+$MS 338. Anal. Calcd. for $C_{15}H_{19}N_3O_6$: C, 53.41; H, 5.68; N, 12.46. Found: C, 53.49; H, 5.59; N, 12.42.

**4-(4-Methoxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4d.** mp 220–222°C; IR (KBr, $\nu_{max}$): 3265, 1682, 1611, 1512, 1274, 1253, 1172, 1030 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.26–1.94 (m, 5H, $CH_2$ and H-10), 3.45 (t, $J$ = 11.65 Hz, 1H, H-7), 3.79 (s, 3H, $OCH_3$), 4.03 (d, $J$ = 8.73 Hz, 1H, H-7), 4.51 (s, 1H, H-9), 4.65 (d, $J$ = 10.92 Hz, 1H, H-4), 6.79 (s, 1H, NH), 6.86 (d, $J$ = 8.01 Hz, 2H, ArH),7.24 (d, $J$ = 8.73 Hz, 2H, ArH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 21.0, 23.3, 38.0, 53.2, 56.3, 65.9, 80.9, 115.1, 129.5, 129.9, 135.0, 155.2, 158.9; Mass LCMS $^+$MS 263. Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.02; H, 6.98; N, 10.68.

**4-(4-Methoxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-thione 4e.** mp 243–245°C; IR (KBr, $\nu_{max}$): 3267, 2935, 2857, 1683, 1611, 1512, 1463, 1254, 1031 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.31–1.95 (m, 5H, $CH_2$ and H-10), 3.58 (t, $J$ = 11.33 Hz, 1H, H-7), 3.79 (s, 3H, $OCH_3$), 3.99 (d, $J$ = 10.98 Hz, 1H, H-7), 4.50 (m, 1H, H-9), 4.57 (d, $J$ = 10.57 Hz, 1H, H-4), 6.88 (d, $J$ = 9.06 Hz, 2H, ArH), 7.22 (d, $J$ = 8.30 Hz, 2H, ArH) 7.36(brs 1H, NH) 8.47(brs, 1H, NH); Mass LCMS $^+$MS 279. Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.40; H, 6.52; N, 10.06. Found: C, 60.38; H, 6.51; N, 10.08.

**4-(4-Bromophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4f.** mp 253–256°C; IR (KBr, $\nu_{max}$): 3303, 3208, 1700, 1489, 1297, 1179, 1028 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.19–1.84 (m, 5H, $CH_2$ and H-10), 3.47 (t, $J$ = 11.14 Hz, 1H, H-7), 3.90 (d, $J$ = 11.14 Hz, 1H, H-7), 4.43 (m, 1H, H-9), 4.53 (d, $J$ = 10.76 Hz, 1H, H-4), 6.52 (s, 1H, NH), 7.20 (s, 1H, NH), 7.30 (d, $J$ = 7.93 Hz, 2H, ArH), 7.52 (d, $J$ = 7.93 Hz, 2H, ArH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 20.2 ($CH_2$), 22.7 ($CH_2$), 37.5 (CH), 52.0 (CH), 65.6 ($CH_2$), 80.1 (CH), 120.5, 129.6 (ArCH), 131.1, 140.8 (Arc), 154.5 (C=O); mass LCMS $^+$MS 311. Anal. Calcd. for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.20; H, 4.98; N, 8.96.

**4-(4-Fluorophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4g.** mp 218–220°C; IR (KBr, $\nu_{max}$): 3301, 3245, 1692, 1508, 1220, 1183, 1027 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.28–1.93 (m, 5H, $CH_2$ and H-10), 3.53 (t, $J$ = 11.58 Hz, 1H, H-7), 3.97–4.00 (m, 1H, H-7), 4.49 (m, 1H, H-9), 4.63 (d, $J$ = 10.76 Hz, 1H, H-4), 6.92 (s, 1H, NH), 7.00–7.09 (m, 2H, ArH), 7.29–7.36 (m, 2H, ArH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 20.2 ($CH_2$), 22.8 ($CH_2$), 37.7 (CH), 51.9 (CH), 65.8 ($CH_2$), 80.2 (CH), 114.9, 115.2, 129.4 (ArCH), 129.5, 137.5 (ArC), 154.7 (C=O); Mass LCMS $^+$MS 251. Anal. Calcd. for $C_{13}H_{15}FN_2O_2$: C, 62.39; H, 6.04; N, 11.19. Found: C, 62.32; H, 5.98; N, 11.25.

**4-Furan-2-yl-hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-thione 4h.** mp >300°C; IR (KBr, $\nu_{max}$): 3196, 2929, 2858, 1619, 1525, 1177, 1029 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.25–1.83 (m, 5H, $CH_2$ and H-10), 3.58–3.62 (m, 1H, H-7), 3.96 (d, $J$ = 10.97 Hz, 1H, H-7), 4.54 (m, 1H, H-9), 4.68 (d, $J$ = 9.50 Hz, 1H, H-4), 6.34 (s, 1H, NH), 7.14 (d, $J$ = 7.31 Hz, 1H, ArH), 7.40–7.42 (m, 1H, ArH), 7.63 (d, $J$ = 7.31 Hz, 1H, ArH), 8.48 (s, 1H, NH); Mass LCMS $^+$MS 239. Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 53.44; H, 5.92; N, 11.76. Found: C, 53.32; H, 5.82; N, 11.75.

**4-(2,4-Dichlorophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-thione 4i.** mp 232–234°C; IR (KBr, $\nu_{max}$): 3208, 2924, 1614, 1452, 1258, 1011 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.38–2.06 (m, 5H, $CH_2$ and H-10), 3.50 (m, 1H, H-7), 3.82 (d, $J$ = 10.93 Hz, 1H, H-7), 4.50 (m, 1H, H-9), 4.93 (d, $J$ = 8.59 Hz, 1H, H-4), 7.37–7.46 (m, 3H, ArH), 8.39 (s, 1H, NH), 8.80 (brs, 1H, NH); Mass LCMS $^+$MS 317. Anal. Calcd. for $C_{13}H_{14}Cl_2N_2OS$: C, 49.22; H, 4.45; N, 8.83. Found: C, 49.24; H, 4.46; N, 8.81.

**4-(3-Hydroxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4j.** mp 244–248°C; IR (KBr, $\nu_{max}$): 3305, 3228, 1685, 1604, 1508, 1279, 1033 cm$^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.18–1.76 (m, 5H, $CH_2$ and H-10), 3.40–3.42 (m, 1H, H-7), 3.90 (d, $J$ = 11.89 Hz, 1H, H-7), 4.40–4.45 (m, 2H, H-9 and H-4), 6.49 (s, 1H, NH), 6.66–6.75 (m, 3H, ArH), 7.16 (t, $J$ = 8.30 Hz, 1H, ArH) 7.22 (s, 1H, NH); $^{13}$C

NMR (75 MHz, DMSO-$d_6$): δ 20.3 ($CH_2$), 22.8 ($CH_2$), 37.7 (CH), 52.6 (CH), 65.6 ($CH_2$), 80.1 (CH), 113.9, 114.5, 118.1, 129.2 (ArCH), 142.9, 154.6 (ArC), 157.3 (C=O); Mass LCMS $^+$MS 249. Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.95; H, 6.52; N, 11.23.

**4-(2,4-Dichlorophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4k.** mp 258–260°C; IR (KBr, $\nu_{max}$): 3306, 2924, 1698, 1452, 1268, 1028 $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.13–1.92 (m, 5H, $CH_2$ and H-10), 3.45–3.49 (m, 1H, H-7), 3.80 (d, $J$ = 9.89 Hz, 1H, H-7), 4.40–4.52 (m, 1H, H-9), 4.92 (d, $J$ = 8.92 Hz, 1H,H-4), 6.62 (s, 1H, NH), 7.34–7.65 (m, 4H, ArH and NH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 21.0 ($CH_2$), 22.6 ($CH_2$), 37.0 (CH), 53.0 (CH), 65.2 ($CH_2$), 79.9 (CH), 127.9, 131.0 (ArCH), 136.8, 147.2, 150.3 (ArC), 154.3 (C=O); Mass LCMS $^+$MS 301. Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_2$: C, 51.84; H, 4.69; N, 9.30. Found: C, 51.86; H, 4.72; N, 9.42.

**4-(4-Fluoro-phenyl)-hexahydro-*1H*-pyrano[2,3-*d*]pyrimidine-2(8a*H*)-thione 4l.** mp 256–258°C; IR (KBr, $\nu_{max}$): 3185, 2972, 2875, 1608, 1555, 1512, 1490, 1012 $cm^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$): δ 1.24–1.88 (m, 5H, $CH_2$ and H-10), 3.52 (t, $J$ = 10.98 Hz, 1H, H-7), 3.92 (d, $J$ = 11.10 Hz, 1H, H-7), 4.42 (m, 1H, H-9), 4.48 (d, $J$ = 10.11 Hz, 1H, H-4), 7.20–7.42 (m, 4H, ArH), 8.40 (s, 1H, NH); Mass LCMS $^+$MS 267. Anal. Calcd. for $C_{13}H_{15}FN_2OS$: C, 58.62; H, 5.68; N, 10.52. Found: C, 58.54; H, 5.67; N, 10.54.

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## REFERENCES AND NOTES

[1] (a) Biginelli, Passerini three-component and Ugi four-component condensations are the most popular among many other reactions for their wide scope and synthetic utility. For reviews, see: (b) Bienayme, H. C.; Oddon, G.; Schmitt, P. Chem Eur J 2000, 6, 3321; (c) Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[2] Dax, S. L.; McNally, J. J.; Youngman, M. A. Curr Med Chem 1999, 6, 255.

[3] (a) Kappe, C. O. Tetrahedron 1993, 49, 6937; (b) Kappe, C. O. Molecules 1998, 3, 1; (c) Kappe, C. O. Acc Chem Res 2000, 33, 879; (d) Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. J Med Chem 2000, 43, 2703; (e) Zhu, Y.; Huang, S.; Pan, Y. Eur J Org Chem 2005, 2354; (f) Zhang, H.; Zhou, Z.; Yao, Z.; Xu, F.; Shen, Q. Tetrahedron Lett 2009, 50, 1622.

[4] Bose, D. S.; Sudharshan, M.; Chadhan, S. W. ARKIVOC 2005, 228.

[5] (a) Fosseheim, R.; Svarteng, K.; Mostad, A.; Romming, C.; Shefter, E.; Triggle, D. J. J Med Chem 1982, 25, 126; (b) Love, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. J Med Chem 1974, 17, 956; (c) Hull, R.; Swain, G. Brit. Pat. 868,030 (1961); (d) Hurst, E. W.; Hull, R. J. J Med Chem 1961, 3, 215; (e) Khania, E. L.; Sillinietse, G. O.; Ozol, Y. Y.; Dabur, G. Y.; Kimenis, A. A. Khim Pharm Zh 1978, 78, 1321.

[6] (a) Furuya, S.; Ohtaki, T. Eur. Pat. 608,565 (1994); (b) Coates, W. J. Eur. Pat. 351,058 (1990); (c) Fenn, D., Ed. The Pyrimidines; Wiley: New York, NY, 1994; (d) Heber, D.; Heers, C.; Ravens, U. Pharmazie 1993, 48, 537; (e) Davoll, J.; Clarke, J.; Elslager, E. F. J Med Chem 1972, 15, 837.

[7] Zhu, Y.; Huang, S.; Wan, J.; Yan, L.; Pan, Y.; Wu, A. Org Lett 2006, 8, 2599.

[8] (a) Srinivas, K.; Srinivasu, V. N. V.; Lingaiah, N. Catal Commun 2007, 8, 1857; (b) Srinivas, K.; Srinivasu, V. N. V.; Dhanraj O. B.; Lingaiah N. J Mol Catal A 2007, 266, 109; (c) Srinivas, K.; Rajashaker, B.; Lingaiah N. J Mol Catal A 2007, 269, 53; (d) Srinivas, K.; Rajashaker, B.; Lingaiah N. ARKIVOC 2006, xvi, 136; (e) Srinivas, K.; Srinivasu, V. N. V.; Rajashaker, B.; Lingaiah, N. J Heterocycl Chem 2008, 45, 1.

[9] Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Science 1999, 286, 971.

# Facile Synthesis of 2,6-Diaryl-4-Secondary Aminonicotinonitriles and Highly Substituted Unsymmetrical 2,2′-Bipyridines



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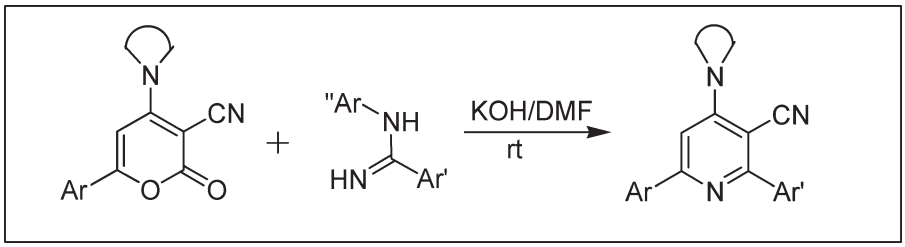


The ring transformation of *2H*-pyran-2-one by *N*-aryl amidine in the presence of KOH in DMF at room temperature resulted in a facile synthesis of the 2,6-diaryl-4-secondary aminonicotinonitrile and highly substituted unsymmetrical 2,2′-bipyridines in moderate yield.

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## INTRODUCTION

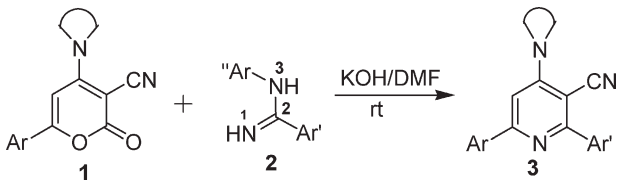
2*H*-pyran-2-ones are extensively used for the synthesis of a wide variety of heterocyclic compounds via ring transformation [1]. Ram and coworkers applied this strategy for the synthesis of various organic compounds like pyrimidine, fused heterocycles, congested benzene [1j], and pyridine [2]. The pyridine ring is one of the fundamental heterocycle present in many biologically active natural products. The compounds containing pyridine ring possess a broad range of biological activities [3]. Kawamura et al. have synthesized 4-substituted 2,6-diphenyl pyridines and reported there bleaching herbicidal activity [3b]. It was also found that 2-(*p*-aminobenzamido) pyridines exhibit a powerful inhibiting effect on gastric ulcers in rats [3g]. The pyridines 2,2′-bi- and 2,2′,2″-ter-pyridine were used as metal chelating legends with various substituents [4a]. Similarly, pyridine derivatives are of growing relevance in material science and supramolecular chemistry [4b]. Therefore, there is a continuous interest to develop the new synthetic methods for pyridines and their derivatives. Classical routes to pyridine preparation are Hantzsch [5], Chichibabin [6], Petrenko-Kritschenko and Zoneff [7], Krohnke [8], and Guareschi-Thorpe [9] condensation reactions. The condensation of 1,5-diketone with ammonia followed by nitric acid oxidation is a common approach for the synthesis of pyridines [10]. The reaction of dienamine and ketone in the presence of Vilsmeier type 1-substituted-1,2,3-benzotriazole reagent results in the formation of nicotinonitriles [11]. The construction of unsymmetrically substituted pyridines was achieved by the reaction of 1,3-dicarbonyl compounds and 3-aminoenones or nitriles [12]. Saikai et al. reported indium trichloride catalyzed synthesis of tetrasubstituted pyridines [13]. Penieres et al. have synthesized pyridine by using microwave irradiated Hantzsch reaction [14]. A transition metal mediated 6-endo-dig cyclization of *N*-propargylamine derivative was carried out by Abbiati et al. to generate a pyridine ring [15]. Combinatorial approach also has been used for the synthesis of pyridine derivatives [16]. 2,4,6-trisubstituted pyridine derivatives were prepared from aroylketene dithioacetal by Potts et al. [17]. Recently, Ram and coworkers [18] have described the use of 2*H*-pyran-2-one for the synthesis of substituted pyridines, prompted us to carry out the synthesis of novel pyridines.

## RESULT AND DISCUSSION

We investigated that compound **3** in moderate yield can be constructed from 2H-pyran-2-one **1** and the *N*-aryl amidine **2** via a ring transformation reaction using KOH in DMF at room temperature (Scheme 1).

Pyridine **3** isolated in this study could arise by nucleophilic attack of amidine N-1 at C-6 position of 2*H*-pyran-2-one. The intermediate **4** formed is unstable and it undergoes cyclization with a retro [2 + 2] process to yield **3a–i** with the loss of carbon dioxide. In the event of ring transformation of 2*H*-pyran-2-one **1** (Scheme 2) with *N*-aryl amidine **2**, the N-1 takes part in the reaction as a nucleophile rather than N-3. It might be due to the lone pair electrons on N-3 are delocalized over the

**Scheme 1.** Preparation of 2,6-diaryl-4-secondary aminonicotinonitriles **3** from 2*H*-pyran-2-one **1** and *N*-aryl amidine **2**.




benzene nucleus by orbital overlap with the π-orbital of the aromatic ring; therefore, they are less available for nucleophilic attack.

To generalize our strategy, we examined this method for the reaction of 2*H*-pyran-2-one **1** with *N*-heteroaryl amidine **6** in the presence of KOH/DMF catalytic system (Scheme 3). The reaction of 2*H*-pyran-2-one with *N*-heteroaryl amidine furnished the corresponding 2,6-disubstituted nicotinonitrile **3** in the poor yields (Table 1). The structure of the newly synthesized compounds was confirmed by spectroscopic data. It was observed that there is no improvement of yield even after 48 h also. The plausible mechanistic pathway is shown in Scheme 4.

In 2H-pyran-2-one **1**, three electrophilic centers are present C-3, C-4, and C-6, in which C-6 is more electrophilic in nature due to presence of an electron withdrawing group (—CN) at C-3 position of the ring system. The synthesis of 2,6-diaryl nicotonitrile involves the nucleophilic attack by more basic N-1 of amidine **6** at C-6 of *2H*-pyran-2-one. The attack of amidine N-1 leads to form unstable intermediate **7** followed by ring closure and a retro [2 + 2] process with the elimination of carbon dioxide to form 2,6-diaryl nicotonitrile **3**. It is noteworthy that the pyridine ring nitrogen of amidine does not involve in ring transformation reaction. The structures of compounds **3a–i** (Table 2) were determined based on the spectroscopic data and elemental analysis. Thus, in both cases (Schemes 1 and 3), the 2,6-diaryl nicotonitriles were formed exclusively without any side product.

Finally, we used our strategy to synthesize highly substituted unsymmetrical 2,2-bipyridines (Scheme 5) in presence of powdered KOH and DMF at room temperature. The results show that the yield of obtained bipyridine was moderate (Table 2). We believe that the reaction proceeds with the same mechanistic pathway as depicted in Scheme 2.

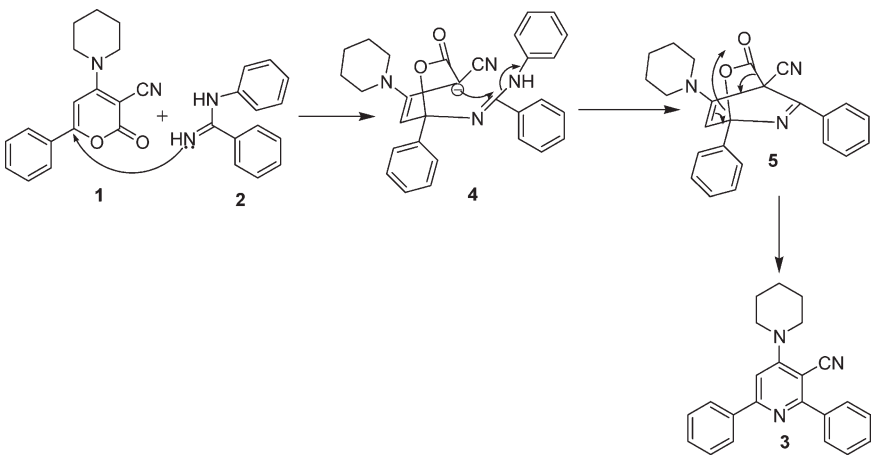
## CONCLUSIONS

In summary, this study demonstrates that the ring system proposed for nicotonitrile is correct with the substitution pattern. An additional finding is that the ring transformation of 2*H*-pyran-2-one by *N*-pyridyl amidine provides useful information for construction of the nicotonitrile ring system with 2,6-diaryl substituent. Furthermore, we synthesized highly substituted unsymmetrical bipyridine using this method. Further studies on the applications of this method for the synthesis of nicotonitrile with the 2,6-heteryl substituent are underway.

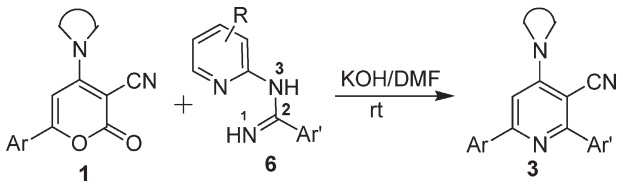
## EXPERIMENTAL

**General procedures.** Melting points were determined in open capillaries and are uncorrected. Progress of the reaction was monitored by TLC (visualization was effected by exposure to UV light). Commercial reagents were used without purification. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. Mass spectra were recorded under ESI mode, on Thermo Finnigan (model-LCQ Advantage MAX) mass spectrometer. $^1$H NMR and $^{13}$C NMR were recorded in $CDCl_3$ on a Bruker Spectrometers, operating at 300 MHz and 75 MHz for $^1$H NMR and $^{13}$C NMR, respectively, and shifts are given in ppm downfield from TMS as an internal standard.

**Scheme 2.** The plausible mechanism [18] for the formation of substituted compounds **3**.



**Scheme 3.** Reaction between 2*H*-pyran-2-one **1** and *N*-heteroaryl amidine **6** for synthesis of 2,6-disubstituted nicotinonitrile.




Elemental analysis was carried out on Thermo Quest microanalysis instrument, Whitehouse, NJ.

**General experimental procedure for the synthesis of 3a–l.** The mixture of 2H-pyran-2-one-3-carbonitrile (1.0 mmol), *N*-phenyl/heteroaryl benzamidine (1.0 mmol) and powdered KOH (2.0 mmol) in 5 mL DMF was stirred for 5–6 h at room temperature. The reaction was monitored by TLC. After completion of the reaction, excess DMF was removed under reduced pressure. Then the residue was poured into crushed ice with vigorous stirring. The aqueous solution was neutralized with 10% HCl, the precipitate obtained was filtered, and the obtained residue was purified by column chromatography on silica gel 60–120 by eluting 5% ethyl acetate:hexane.

***2,6-Diphenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3a).*** White solid, IR (KBr): 2209 (C≡N), 1568 (C=N) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.73 (d, *J* = 5.7 Hz, 2H, $CH_2$), 1.83 (d, *J* = 3.3 Hz, 4H, $2CH_2$), 3.54 (t, *J* = 9.9 Hz, 4H, $2CH_2N$), 6.91 (s, 1H, CH), 7.5 (m, 5H, ArH), 7.84 (d, *J* = 4.7 Hz, 2H, ArH), 8.05 (t, *J* = 9.5 Hz, 3H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 24.2, 26.1, 52.1, 96.4, 106.7, 118.7, 124.4, 125.3, 127.6, 128.5, 128.9, 129.6, 130.1, 138.9, 159.8, 162.9, 164.2. MS (ESI, 70 eV) *m/z* (%) = 340 (100) $[M^+]$, 341(27) $[(M+H)^+]$. Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.42; H, 6.20; N, 12.38.

***6-(4-Bromophenyl)-2-phenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3b).*** White solid, IR (KBr): 2212 (C≡N), 1568 (C=N) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.72 (d, 2H, $CH_2$), 1.8 (d, *J* = 5 Hz, 4H, $2CH_2$), 3.54 (t, *J* = 10.6 Hz, 4H, $2CH_2N$), 7.12 (s, 1H, CH), 7.51 (m, 3H, ArH), 7.59 (s,

**Scheme 4.** The plausible mechanism [18] for the formation of substituted 2,6-disubstituted nicotinonitrile.

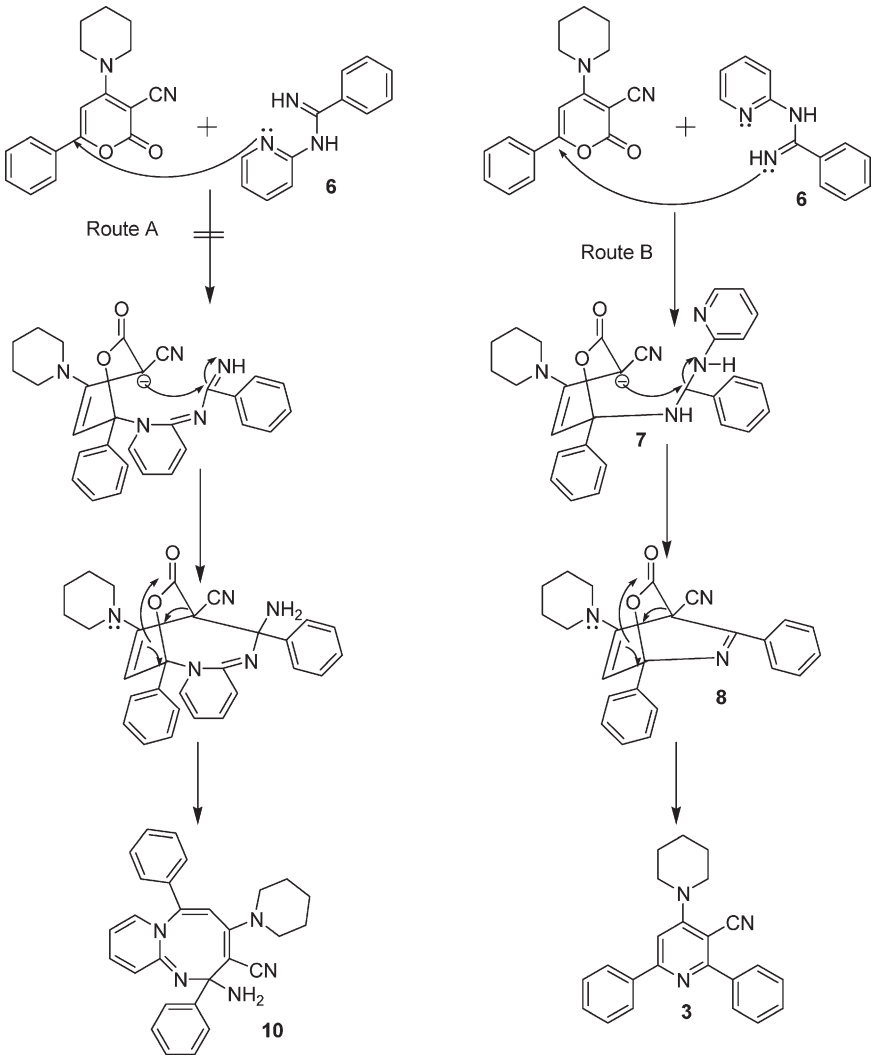


**Table 1**

Preparation of 2,6-diaryl-4-secondary aminonicotinonitriles **3**[a] from 2*H*-pyran-2-one **1** and *N*-aryl amidine **2**[b].

| Entry | Ar |  | Ar′ | Ar″ | Yields[c] (%) | m.p. |
|---|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | Piperidine | $C_6H_5$ | 4-F-$C_6H_4$ | 48% | 160°C |
| **3a** | $C_6H_5$ | Piperidine | $C_6H_5$ | $C_6H_5$ | 48% | 161°C |
| **3b** | 4-Br-$C_6H_4$ | Piperidine | $C_6H_5$ | $C_6H_5$ | 48% | 173°C |
| **3b** | 4-Br-$C_6H_4$ | Piperidine | $C_6H_5$ | 4-F-$C_6H_4$ | 42% | 173°C |
| **3c** | 4-Br-$C_6H_4$ | Morpholine | $C_6H_5$ | 4-F-$C_6H_4$ | 46% | 172°C |
| **3c** | 4-Br-$C_6H_4$ | Morpholine | $C_6H_5$ | $C_6H_5$ | 44% | 172°C |
| **3d** | 4-Cl-$C_6H_4$ | Morpholine | $C_6H_5$ | 4-F-$C_6H_4$ | 39% | 198°C |

[a] All products were characterized by using I.R., $^1$H, $^{13}$C NMR, mass spectroscopy, and elemental analysis.
[b] 2H-pyran-2-one **1** (1.0 mmol), *N*-aryl amidine **2** (1.0 mmol), KOH (2.0 mmol), and DMF (5 mL), room temperature.
[c] Isolated yield.

1H, ArH), 7.62 (s, 1H, ArH), 7.93 (m, 4H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 24.2, 26.1, 52.0, 96.8, 106.4, 118.6, 124.7, 128.6, 129.2, 129.6, 130.1, 132.1, 137.7, 138.7, 158.5, 162.9, 163.9. MS (ESI, 70 eV) *m/z* (%) = 418 (100) [$M^+$], 420 (92) [$(M+2H)^+$]. Anal. Calcd. for $C_{23}H_{20}BrN_3$: C, 66.04; H, 4.82; N, 10.04. Found: C, 66.01; H, 4.77; N, 10.08.

***6-(4-Bromophenyl)-4-(morpholin-4-yl)-2-phenylpyridine-3-carbonitrile (3c).*** White solid, IR (KBr): 2210 (C≡N), 1582 (C=N) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.55 (q, *J* = 13.5 Hz, 4H, $2CH_2N$), 3.94 (q, *J* = 14 Hz, 4H, $2CH_2O$), 6.73 (s, 1H, CH), 7.51 (q, *J* = 9.9 Hz, 3H, ArH), 7.59 (s, 1H, ArH), 7.63 (s, 1H, ArH), 7.92 (m, 3H, ArH), 7.97 (s, 1H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 50.9, 66.8, 97.3, 106.3, 118.2, 125.1, 128.6, 129.2, 129.5, 130.3, 132.2, 137.3, 138.3, 159.1, 162.6, 164.2. MS (ESI, 70 eV) *m/z* (%) = 420 (28%) [$M^+$], 422 (12%) [$(M+2H)^+$], 393 (8). Anal. Calcd. for $C_{22}H_{18}BrN_3O$: C, 62.87; H, 4.32; N, 10.00. Found: C, 62.82; H, 4.37; N, 10.11.

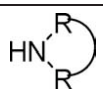
***6-(4-Chlorophenyl)-4-(morpholin-4-yl)-2-phenylpyridine-3-carbonitrile (3d).*** White solid, IR (KBr): 2216 (C≡N), 1583 (C=N) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.54 (q, *J* = 14.1 Hz, 4H, $2CH_2N$), 3.94 (q, *J* = 13.9 Hz, 4H, $2CH_2O$), 7.14 (s, 1H, CH), 7.51 (m, 5H, ArH), 7.89 (m, 2H, ArH), 8.00 (s, 1H, ArH), 8.04 (s, 1H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 50.9, 66.8, 97.2, 106.3, 118.2, 128.6, 128.9, 129.3, 129.5, 130.3, 136.7, 136.9, 138.3, 159.0, 162.7, 164.2. MS (ESI, 70 eV) *m/z* (%): 376 (100) [$M^+$], 378 (33) [$(M+2H)^+$]. Anal. Calcd. for $C_{22}H_{18}ClN_3O$: C, 70.30; H, 4.83; N, 11.18. Found: C, 70.34; H, 4.94; N, 11.23.

***2,6-Bis(4-bromophenyl)-4-(piperidin-1-yl)pyridine-3-carbonitrile (3e).*** White solid, IR (KBr): 2214 (C≡N), 1580 (C=N) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.79 (m, 6H, $3CH_2$), 3.53 (t, *J* = 15 Hz, 4H, $2CH_2N$), 7.12 (s, 1H, CH), 7.62 (m, 4H, ArH), 7.77 (d, *J* = 4.7 Hz, 1H, ArH), 7.81 (d, *J* = 3 Hz, 1H, ArH), 7.89 (d, *J* = 3 Hz, 1H, ArH), 7.93 (s, 1H, ArH). MS (ESI, 70 eV) *m/z* (%) = 497.8 (25) [$M^+$], 499 (12) [$(M+2H)^+$]. Anal. Calcd. for $C_{23}H_{19}Br_2N_3$: C, 55.56; H, 3.85; N, 8.45. Found: C, 55.59; H, 3.81; N, 8.48.

***6-(4-Chlorophenyl)-2-phenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3f).*** White solid, IR (KBr): 2214 (C≡N), 1568 (C=N) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.73 (d, *J* = 532 Hz, 2H, $CH_2$), 1.82 (d, *J* = 5.0 Hz, 4H, $2CH_2$), 3.55

**Table 2**

Reaction conditions with yields and m.p. for products[a] **3**.

| Entry | Ar |  | Ar′ | R | Yields[b] (%) | m.p. |
|---|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | Piperidine | $C_6H_5$ | H | 13% | 160°C |
| **3b** | 4-Br-$C_6H_4$ | Piperidine | $C_6H_5$ | H | 26% | 173°C |
| **3c** | 4-Br-$C_6H_4$ | Morpholine | $C_6H_5$ | H | 24% | 172°C |
| **3d** | 4-Cl-$C_6H_4$ | Morpholine | $C_6H_5$ | H | 24% | 198°C |
| **3e** | 4-Br-$C_6H_4$ | Piperidine | 4-Br-$C_6H_4$ | H | 22% | 168°C |
| **3f** | 4-Cl-$C_6H_4$ | Piperidine | $C_6H_5$ | H | 16% | 172°C |
| **3g** | 4-Cl-$C_6H_4$ | Pyrolidine | $C_6H_5$ | H | 19% | 156°C |
| **3g** | 4-Cl-$C_6H_4$ | Pyrolidine | $C_6H_5$ | 4-Br | 22% | 156°C |
| **3h** | 4-$CH_3O$-$C_6H_4$ | Piperidine | $C_6H_5$ | H | 38% | 166°C |
| **3i** | 4-Cl-$C_6H_4$ | Pyrolidine | 4-Br-$C_6H_4$ | H | 44% | 122°C |

[a] All products were characterized by using I.R., $^1$H, $^{13}$C NMR, mass spectroscopy, and elemental analysis.
[b] Isolated yield.

**Table 3**

Reaction conditions with yields and m.p. for products[a] **3**.

| Entry | Ar | HNRR | Ar″ | Yields[b] (%) | m.p. |
|---|---|---|---|---|---|
| **3j** | 4-Br-$C_6H_4$ | Pyrolidine | 4-Br-$C_6H_4$ | 43% | 206–208°C |
| **3k** | 4-Cl-$C_6H_4$ | Morpholine | 4-Br-$C_6H_4$ | 48% | 164–166°C |
| **3l** | $C_6H_5$ | Morpholine | 3,4-Cl-$C_6H_3$ | 52% | 152–154°C |

[a] All products were characterized by using I.R., $^1$H, $^{13}$C NMR, mass spectroscopy, and elemental analysis.
[b] Isolated yield.

(t, $J$ = 10.6 Hz, 4H, $2CH_2N$), 7.13 (s, 1H, CH), 7.44 (m, 5H, ArH), 7.93 (q, $J$ = 9.68 Hz, 2H, ArH), 8.00 (s, 1H, ArH), 8.03 (s, 1H, ArH). MS (ESI, 70 eV) $m/z$ (%) = 374 (100) [$M^+$], 376 (35) [$(M+H)^+$]. Anal. Calcd. for $C_{23}H_{20}ClN_3$: C, 73.89; H, 5.39; N, 11.24. Found: C, 73.97; H, 5.35; N, 11.36.

***6-(4-Chlorophenyl)-2-phenyl-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (3g).*** White solid, IR (KBr): 2199 (C≡N), 1590 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ 2.09 (m, 4H, $2CH_2$), 3.81 (t, $J$ = 13.2 Hz, 4H, $2CH_2N$), 6.85 (s, 1H, CH), 7.48 (m, 5H, ArH), 7.86 (q, $J$ = 9.6 Hz, 2H, ArH), 7.98 (d, $J$ = 8.66 Hz, 2H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 25.9, 50.5, 96.1, 106.5, 118.6, 128.4, 128.6, 129.0, 129.6, 129.8, 135.9, 137.5, 139.3, 158.6, 162.8, 163.1. MS (ESI, 70 eV) $m/z$ (%) = 360 (100) [$M^+$], 362 (32) [$(M+2H)^+$]. Anal. Calcd. for $C_{22}H_{18}ClN_3$: C, 73.43; H, 5.04; N, 11.68. Found: C, 73.42; H, 5.04; N, 11.03.

***6-(4-Methoxyphenyl)-2-phenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3h).*** White solid, IR (KBr): 2209 (C≡N), 1607 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.72 (d, $J$ = 5.1 Hz, 2H, $CH_2$), 1.83 (d, $J$ = 4.6 Hz, 4H, $2CH_2$), 3.52 (t, $J$ = 10.5 Hz, 4H, $2CH_2N$), 3.88 (s, 3H, $CH_3O$), 6.98 (s, 1H, CH), 7.01 (s, 1H, ArH), 7.12 (s, 1H, ArH), 7.50 (m, 3H, ArH), 7.94 (q, $J$ = 9.6 Hz, 2H, ArH), 8.04 (s, 1H, ArH), 8.06 (s, 1H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 24.3, 25.1, 52.1, 55.6, 95.9, 105.7, 114.3, 124.7, 124.9, 129.1, 131.2, 131.8, 131.8, 132.2, 137.5, 159.4, 161.5, 163.0. MS (ESI, 70 eV) $m/z$ (%) = 370 (100) [$M^+$], 371 (32) [$(M+2H)^+$]. Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.06; H, 6.29; N, 11.34.

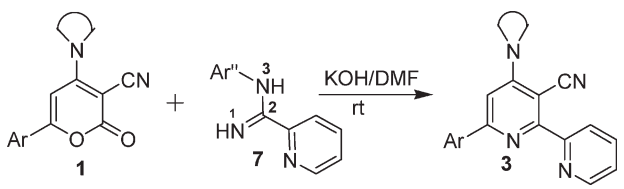
***2-(4-Bromophenyl)-6-(4-chlorophenyl)-4-(pyrrolidin-1-yl) pyridine-3-carbonitrile (3i).*** White solid, IR (KBr): 2115 (C≡N), 1590 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 2.08 (brs, 4H), 3.79 (brs, 4H), 6.84 (s, 1H), 7.43 (s, 2H), 7.63 (s, 2H), 7.73 (s, 2H), 7.96 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 25.2, 50.1, 88.5, 103.6, 119.5, 123.2, 128.6, 128.9, 131.1, 131.3, 134.3, 134.6, 136.7, 138.1, 155.1, 155.4, 162.7. MS (ESI, 70 eV) $m/z$ (%) = 438 [$M^+$, 43%], 440 [$(M+2H)^+$, 55%]. Anal. Calcd. for $C_{22}H_{17}BrClN_3$: C 60.22; H 3.91; N 9.58. Found: C, 60.42; H, 3.83; N, 9.42.

***6-(4-Bromophenyl)-2-(pyridine-2-yl)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (3j).*** Yellowish red solid, IR (KBr): 2190 (C≡N), 1566 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 2.07 (bs, 4H, $CH_2$), 3.82 (bs, 4H, $2NCH_2$), 6.91 (s, 1H, CH), 7.39 (s, 1H, ArH), 7.59 (s, 2H, ArH), 7.91 (bs, 3H, ArH), 8.02 (bs, 1H, ArH), 8.77 (bs, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ = 25.7, 50.4, 94.4, 103.9, 116.4, 123.9, 124.3, 128.8, 131.8, 136.7, 137.6, 146.7, 148.7, 158.3. MS (ESI, 70 eV) $m/z$ (%) = 405 (100) [$M^+$]. Anal. Calcd. for $C_{21}H_{17}BrN_4$: C, 62.23; H, 4.23; N, 13.82. Found: C, 62.43; H, 4.364; N, 13.87.

***6-(4-Chlorophenyl)-4-morpholino-2-(pyridine-2-yl)pyridine-3-carbonitrile (3k).*** Yellowish red solid, IR (KBr): 2225 (C≡N), 1566 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.55–3.58 (t, 4H, $2NCH_2$), 3.94–3.97 (t, 4H, $2OCH_2$), 7.21 (s, 1H, CH), 7.41–7.49 (m, 3H, ArH), 7.85–7.91 (m, 1H, ArH), 8.02–8.05 (q, 2H, ArH), 8.17–8.19 (d, $J$ = 7.8 Hz, 1H, ArH), 8.78–8.79 (dd, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ = 50.8, 66.6, 97.4, 107.3, 117.5, 123.7, 124.8, 128.8, 129.2, 136.7, 148.8, 155.4, 158.3, 162.8. MS (ESI, 70 eV) $m/z$ (%) = 377 [$M^+$, 100%], 379 [$(M+2H)^+$, 35%]. Anal. Calcd. for $C_{21}H_{17}ClN_4O$: C, 66.93; H, 4.55; N, 14.87. Found: C, 66.83; H, 4.64; N, 14.94.

***4-Morpholino-6-phenyl-2-(pyridin-2-yl)pyridine-3-carbonitrile (3l).*** Yellowish red solid, IR (KBr): 2215 (C≡N), 1574, 1538 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.55–3.58 (t, 4H, $2NCH_2$), 3.94–3.97 (t, 4H, $2OCH_2$), 7.25 (s, 1H, CH), 7.40–7.51 (m, 4H, ArH), 7.85–7.91 (m, 1H, ArH), 8.07–8.09 (t, 2H, ArH), 8.20–8.23 (d, $J$ = 7.8 Hz, 1H, ArH), 8.77–8.79 (d, $J$ = 4.2 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ = 50.7, 66.6, 97.3, 107.5, 117.6, 123.7, 124.7, 127.4, 128.8, 130.2, 136.8, 138.1, 148.6, 155.5, 159.5, 161.3, 162.7, 165.3. MS (ESI, 70 eV) $m/z$ (%) = 343 [$(M+H)^+$, 78%]. Anal. Calcd. for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.88; H, 5.42; N, 16.44.

**Scheme 5.** Synthesis of highly substituted unsymmetrical bipyridine.

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## REFERENCES AND NOTES

[1] (a) Farhanullah; Samrin, F.; Ram, V. J. Tetrahedron Lett 2007, 48, 8213; (b) Farhanullah; Samrin, F.; Ram, V. J. Tetrahedron Lett 2007, 48, 3187; (c) Sharon, A.; Pratap, R.; Ram, V. J.

Tetrahedron 2005, 61, 3781; (d) Ram, V. J.; Srivastava, P.; Goel, A. Tetrahedron 2003, 59, 7141; (e) Ram, V. J.; Srivastava, P.; Goel, A. Synthesis 2000, 6, 813; (f) Ram, V. J.; Agarwal, N.; Saxena, A. S.; Farhanullah; Sharon, A.; Maulik, P. R. J Chem Soc Perkin Trans 1, 2002, 1426; (g) Ram, V. J.; Srivastava, P.; Agarwal, N.; Sharon, A.; Maulik, P. R. J Chem Soc Perkin Trans 1, 2001, 1953; (h) Goel, A.; Verma, D.; Dixit, M.; Raghunandan, R.; Maulik, P. R. J Org Chem 2006, 71, 804; (i) Sharon, A.; Maulik, P. R.; Vithana, C.; Oshashi, Y.; Ram, V. J. Eur J Org Chem 2004, 886; (j) Goel, A.; Singh, F. V. Tetrahedron Lett 2005, 46, 5585.

[2] (a) Pratap, R.; Kushwaha, S. P.; Goel, A.; Ram, V. J. Tetrahedron Lett 2007, 48, 549; (b) Nath, M.; Srivastava, P.; Goel, A.; Ram, V. J. Eur J Org Chem 1998,2083; (c) Ram, V. J.; Agarwal, N. Tetrahedron Lett 2001, 42, 7127; (d) Pratap, R.; Roy, A. D.; Kushwaha, S. P.; Goel, A.; Roy, R.; Ram, V. J. Tetrahedron Lett 2007, 48, 5845; (e) Pratap, R.; Farhanullah; Raghunandan, R.; Maulik, P. R.; Ram, V. J. Tetrahedron Lett 2007, 48, 4939; (f) Goel, A.; Singh, F. V.; Verma, D. Synlett 2005, 13, 2027; (g) Farhanullah; Agarwal, N.; Goel, A.; Ram, V. J. J Org Chem 2003, 68, 2983.

[3] (a) Agrawal, K. C.; Sartorelli, A. C. J Med Chem 1978, 21, 218; (b) Kawamura, S.; Hamada, T.; Sato, R.; Sanemitsu, Y. J Agric Food Chem 1991, 39, 2279; (c) Li, A. H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X.-D.; Jacobsen, K. A. J Med Chem 1999, 42, 706; (d) Vacher, B.; Bonnaud, B.; Funes, F.; Jabaudt, N.; Koek, W.; Assie, M. D.; Cosi, C.; Kleven, M. J Med Chem 1999, 42, 1648; (e) Song, Z. S.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J.; Dolling, U. H.; Reider, P. J. J Org Chem 1999, 64, 9658; (f) Butler, D. E.; Bass, P.; Nordin, I. C.; Hauck, F. P., Jr.; L'Italien, Y. J. J Med Chem 1971, 14, 575; (g) Moffett, R. B.; Robert, A.; Skaletzky, L. L. J Med Chem 1971, 10, 963.

[4] (a) Wilkins, C. J.; Douglas, J. E. Inorg Chim Acta 1969, 3, 635; (b) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. L.; Zabel, M.; Konig, B. J Org Chem 2003, 68, 2882.

[5] Hantzsch, A. Justus Liebiegs Ann Chem 1882, 215, 1.

[6] Sprung, M. M. Chem Rev 1940, 71, 2629.

[7] Petrenko-Kritschenko, P.; Zoneff, N. Chem Ber 1906, 39, 1358.

[8] (a) Krohnke, F.; Zecher, W. Angew Chem Int Ed Engl 1962, 1, 626; (b) Krohnke, F. Synthesis 1976, 1.

[9] (a) Baron, H.; Remfry, F. G. P.; Thorpe, J. F. J Chem Soc 1904, 85, 1726; (b) Vogel, A. I. J Chem Soc 1934, 1758.

[10] Jones, G. In: Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pregamon: New York, NY, 1984; Vol. 2, Part 2, p 395.

[11] Alvarez-Insua, A. S.; Lora-Tamayo, M.; Soto, J. L. J Heterocycl Chem 1970, 7, 1305.

[12] Joule, J. A.; Smith, G.; Mills, K. Heterocyclic Chemistry, 3rd ed.; Chapman and Hill: London, 1995; pp 72–119.

[13] Saikai, P.; Prajapati, D.; Sandhu, J. S. Tetrahedron Lett 2003, 44, 8725.

[14] Penieres, G.; Garcia, O.; Franco, K.; Hernardez, O.; Alvarez, C. Heterocycl Commun 1996, 2, 359.

[15] Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Guuseppe, S.; Marinelli, F.; Rossi, E. J Org Chem 2003, 68, 6959.

[16] Gordeev, M. F.; Patel, D. V.; Gordon, E. M. J Org Chem 1996, 61, 924.

[17] Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridies, G. J Am Chem Soc 1981, 103, 3585.

[18] Pratap, R.; Kumar, B.; Ram, V. J. Tetrahedron 2007, 63, 10309.

# Synthesis of α,β-Unsaturated Caprolactams Starting from Heterocyclic Imines



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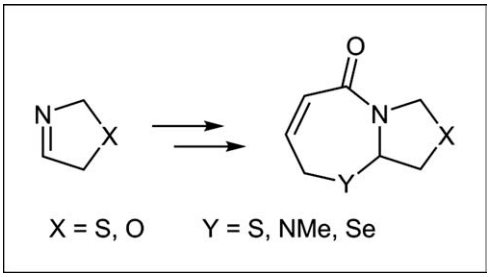


New classes of α,β-unsaturated caprolactams containing variable heteroatoms in δ-position were synthesized from heterocyclic imines as a starting material. The synthetic route is based on an acid chloride addition followed by a ring-closing metathesis using a ruthenium catalyst.

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## INTRODUCTION

α,β-Unsaturated lactams are categorized as interesting structures because of their high bioactivity depending on their functionalities as lactams and Michael acceptors. Derivatives of α,β-unsaturated caprolactams, for example, show central nervous system activity by causing convulsions and loss of muscle control [1]. Furthermore, anticancer activity was reported [2]. Saturated caprolactam derivatives, for example, were effective as anti-inflammatory agent [3] or growth-inhibiting activity on plants [4].

In the recent past, we were able to report the first synthesis of α,β-unsaturated δ-oxacaprolactams. This new substance class was synthesized by using heterocyclic imines as precursors [5]. The reaction of imines with unsaturated acid chlorides followed by treatment with allyl alcohol led to acryl amides, which were used as a starting material in ring-closing metathesis (RCM).

This synthetic route shows potential for further investigations (Fig. 1). Our aim to expand the application range of this technology was realized by inserting different heteroatoms in the lactam structure. In addition to sulfur and nitrogen, the insertion of selenium was shown in one example. Thus, the design of two new substance classes was achieved in case of nitrogen and selenium containing seven-membered lactam structures shown in Figure 1. A few derivatives of α,β-unsaturated δ-thiacaprolactams were yet known, but synthesized in a photochemical reaction [6].

## RESULTS AND DISCUSSION

We focused our attention on different heterocyclic imines serving as a starting material in the intended synthetic route. The monocyclic five-membered 2,5-dihydrothiazole **1a** [7] and 2,5-dihydrooxazole **1b** [8] were synthesized by a modified Asinger protocol [9] starting from the α-halogen aldehyde 2-chloro-2-methylpropanal.

In the first step of the synthesis, the heterocyclic imines 2,5-dihydrothiazole **1a** and 2,5-dihydrooxazole **1b** were used as precursors in the addition of unsaturated acid chloride. This type of reaction is based on Leuchs', Wulkow's, and Gerland's work [10], which described the addition of different acid chlorides to 3*H*-indole derivatives followed by addition of the nucleophiles, water, methanol, and ammonia. The insertion of thiols was published by Schwarze *et al*. [11]. Thus, the chosen acryloyl chloride and 2-methylacryloyl chloride were added to the heterocyclic imines **1** (Scheme 1). Without isolation of the α-chloro amides, allyl mercaptan or *N*-allylmethylamine was added in the presence of triethylamine to obtain the acryl amides **2** in yields up to 63% (Table 1).

The introduction of selenium into acryl amides is a demanding task because of the synthesis of allyl selenol. Because of exotic reagents used in known synthesis [12] of allyl selenol, we considered other procedures. The reaction of alkyl halogenides and sodium hydrogen selenide, formed in aqueous or ethanolic solution, leads to aliphatic selenols [13]. To prepare aromatic selenols,

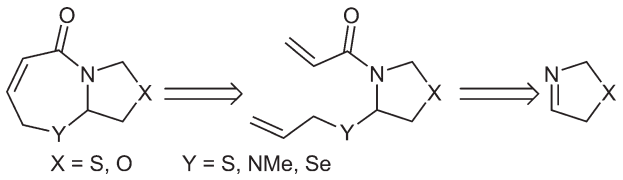
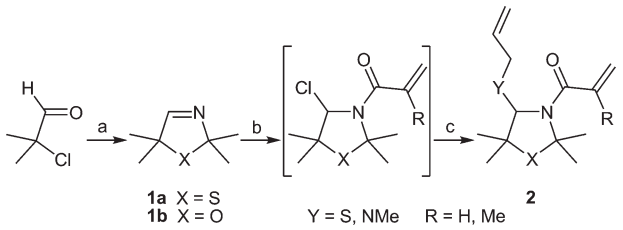



**Figure 1.** Retrosynthetical consideration of the target structure.

**Scheme 1.** Synthesis of acryl amides **2** starting from imines **1**. Reagents and conditions: (a) $(CH_3)_2CO$, $NH_3$, NaSH or $H_2O$, $CH_2Cl_2$, 0–5°C, (ii) r.t., 18 h; (b) (i) $H_2C{=}CRCOCl$, $CH_2Cl_2$, 0–5°C, (ii) r.t., 3 h; (c) (i) $H_2C{=}CHCH_2YH$, $Et_3N$, $CH_2Cl_2$, 0–5°C, (ii) **2d–f**: reflux, 5 h, 7–63%.




elementary selenium reacts with aryl magnesium halogenides (Grignard reagent) by inserting between magnesium and aryl moiety [14]. The first called option was not considered because water, respectively, ethanol in excess would act as nucleophile rather than the selenol. So, a selenium-Grignard reagent was formed and directly added to an α-chloro amide synthesized simultaneously of imine **1a** (Scheme 2). The acryl amide **2g** was obtained in small yield of only 6%.

Finally, the desired α,β-unsaturated caprolactams **3** were prepared from acryl amides **2** *via* RCM (Scheme 3). In the literature, only a few examples of RCM starting from acryl amides are described [5,15].

The optimized reaction conditions tested in the synthesis of α,β-unsaturated δ-oxacaprolactams [5] were transferred to the present reactions. The used ruthenium

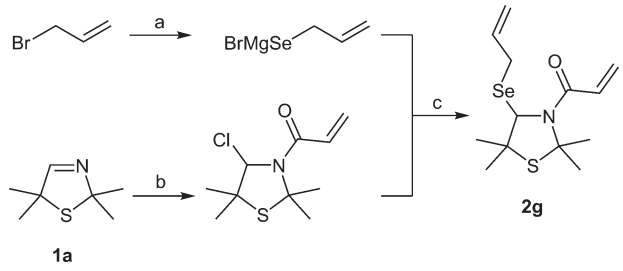
**Table 1**

Acryl amides **2**.

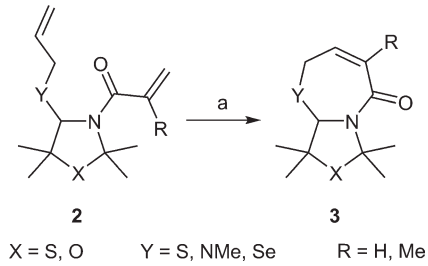
| Imine | Acryl amide | X | Y | R | Yield (%) |
|---|---|---|---|---|---|
| **1a** | **2a** | S | S | H | 44 |
| **1b** | **2b** | O | S | H | 15 |
| **1b** | **2c** | O | S | Me | 18 |
| **1a** | **2d** | S | NMe | H | 63 |
| **1b** | **2e** | O | NMe | H | 14 |
| **1b** | **2f** | O | NMe | Me | 7[a] |

[a] The product was not obtained pure.

**Scheme 2.** Preparation of selenium containing acryl amide **2g**. Reagents and conditions: (a) (i) Mg, $Et_2O$, (ii) Se, reflux, 1 h; (b) (i) $H_2C{=}CHCOCl$, $Et_2O$, 0–5°C, (ii) r.t., 3 h; (c) r.t., 18 h, 6%.




**Scheme 3.** Ring-closing metathesis to form lactams **3**. Reagents and conditions: (a) 5 mol% catalyst **I**, toluene, r.t. up to 70°C, 2–6 h, 36–90%.




catalyst **I** is comparable to a Grubbs catalyst of the second generation (Fig. 2). The RCM was performed in toluene, starting at room temperature and slowly increasing the temperature up to 70°C. The lactams **3** were obtained in good yields up to 90% (Table 2). Accordingly, the catalyst shows a high tolerance to several functional groups.

## CONCLUSION

In conclusion, we synthesized new α,β-unsaturated caprolactams **3** containing sulfur, nitrogen, or selenium in δ-position. Starting from heterocyclic imines **1**, an addition of unsaturated acid chlorides followed by

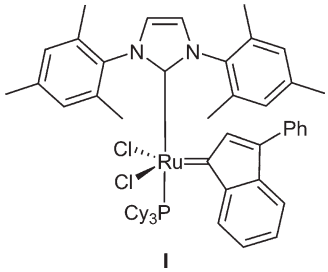



**Figure 2.** Used ruthenium catalyst **I**.

**Table 2**

α,β-Unsaturated caprolactams **3**.

| Acryl amide | Lactam | X | Y | R | Yield (%) |
|---|---|---|---|---|---|
| **2a** | **3a** | S | S | H | 74 |
| **2b** | **3b** | O | S | H | 45 |
| **2c** | **3c** | O | S | Me | 88 |
| **2d** | **3d** | S | NMe | H | 90 |
| **2e** | **3e** | O | NMe | H | 74 |
| **2f** | **3f** | O | NMe | Me | 50 |
| **2g** | **3g** | S | Se | H | 36 |

substituting the chloride with unsaturated nucleophiles and subsequent RCM led to lactams **3** offering opportunities for further functionalizations.

## EXPERIMENTAL

Synthetic procedures were performed on a vacuum line using standard Schlenk techniques under argon. All reagents and solvents were commercial grade and purified before use when necessary. The ruthenium catalyst **I**, catMETium®IMesPCy [CAS 254972-49-1], is available at Strem Chemicals. Preparative column chromatography was carried out using Grace $SiO_2$ (0.040–0.063 mm, type KG 60). TLC was performed on Merck $SiO_2$ F254 plates on aluminum sheets. $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker AMX R 500 and AM 300 spectrometers. NMR chemical shifts are reported in ppm using TMS as an internal standard. Assignments of the signals in the $^{13}C$ NMR spectrum were supported by measurements applying COSY and *J* modulated techniques. CI-MS and HRMS spectra were recorded on a Finnigan MAT 212 spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a GoldenGate diamond-ATR unit.

**General procedure for the preparation of acryl amides 2 (GP A)..** Under argon atmosphere, the respective imine **1** (1 equiv) dissolved in anhydrous dichloromethane (10 mL) was cooled down to 0–5°C before acid chloride (1.1 equiv) in anhydrous dichloromethane (15 mL) was added dropwise. After stirring for 3 h at room temperature, a mixture of allyl mercaptan or *N*-allylmethylamine (2 equiv) and anhydrous triethylamine (1.75 equiv) in anhydrous dichloromethane (10 mL) was added dropwise at 0–5 C. If *N*-allylmethylamine was used, the reaction mixture was refluxed for 5 h. After stirring overnight at room temperature, the solution was poured into ice-water (20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (20 mL), water (2 × 20 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the product was purified as described later.

**(*RS*)-1-(4-Allylsulfanyl-2,2,5,5-tetramethylthiazolidin-3-yl)-propenone (2a)..** Following **GP A**, 2,5-dihydrothiazole **1a** (0.20 g, 1.4 mmol), acryloyl chloride (0.14 g, 1.5 mmol), allyl mercaptan (70%) (0.30 g, 2.8 mmol), and triethylamine (0.25 g, 2.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.17 g (0.6 mmol, 44%); colorless solid; mp 33°C; $R_f$ = 0.53 (*n*-hexane–EtOAc, 7:3); IR: 3078, 2982, 2960, 2933, 1650, 1631, 1607, 1464, 1404, 1376, 1346, 957, 918 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.51 [s, 3 H, $SC(CH_3)_2CH$], 1.60 [s, 3 H, $SC(CH_3)_2CH$], 1.88 [s, 3 H, $SC(CH_3)_2N$], 1.96 [s, 3 H, $SC(CH_3)_2N$], 3.24 (dd, $^2J$ = 13.4 Hz, $^3J$ = 7.5 Hz, 1 H, $SCH_2CHCH_2$), 3.32 (dd, $^2J$ = 13.4 Hz, $^3J$ = 6.8 Hz, 1 H, $SCH_2CHCH_2$), 5.08 (br s, 1 H, NCH), 5.16–5.19 (m, 2 H, $SCH_2CHCH_2$), 5.69 (d, $^3J$ = 10.4 Hz, 1 H, $COCHCH_2$), 5.80–5.89 (m, 1 H, $SCH_2CHCH_2$), 6.32 (d, $^3J$ = 16.6 Hz, 1 H, $COCHCH_2$), 6.55 (dd, $^3J$ = 10.4 Hz, $^3J$ = 16.6 Hz, 1 H, $COCHCH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 25.2 [$SC(CH_3)_2CH$], 31.7 [$SC(CH_3)_2N$], 35.9 ($SCH_2CHCH_2$), 53.7 [$SC(CH_3)_2CH$], 72.3 [$SC(CH_3)_2N$], 78.0 (NCH), 117.9 ($SCH_2CHCH_2$), 127.9 ($COCHCH_2$), 130.6 ($COCHCH_2$), 133.8 ($SCH_2CHCH_2$), 165.0 (CO); MS (CI, isobutane): *m*/*z* (%): 272.1 (28) $[M + H]^+$, 198.1 (100) $[MH - CH_3SH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{13}H_{22}NOS_2]^+$: 272.1143; found: 272.1143.

**(*RS*)-1-(4-Allylsulfanyl-2,2,5,5-tetramethyloxazolidin-3-yl)-propenone (2b)..** Following **GP A**, 2,5-dihydrooxazole **1b** (0.64 g, 5.0 mmol), acryloyl chloride (0.50 g, 5.5 mmol), allyl mercaptan (70%) (1.06 g, 10.0 mmol), and triethylamine (0.89 g, 8.75 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.19 g (0.7 mmol, 15%); yellow oil; $R_f$ = 0.58 (*n*-hexane–EtOAc, 7:3); IR: 2980, 2937, 1655, 1614, 1411, 1356 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, $OC(CH_3)_2CH$], 1.50 [s, 3 H, $OC(CH_3)_2CH$], 1.60 [s, 3 H, $OC(CH_3)_2N$], 1.70 [s, 3 H, $OC(CH_3)_2N$], 3.15–3.27 (m, 2 H, $SCH_2CHCH_2$), 4.70 (br s, 1 H, NCH), 5.09–5.22 (m, 2 H, $SCH_2CHCH_2$), 5.72 (dd, $^2J$ = 1.8 Hz, $^3J$ = 10.3 Hz, 1 H, $COCHCH_2$), 5.82–5.91 (m, 1 H, $SCH_2CHCH_2$), 6.39 (dd, $^2J$ = 1.8 Hz, $^3J$ = 16.6 Hz, 1 H, $COCHCH_2$), 6.56 (dd, $^3J$ = 10.3 Hz, $^3J$ = 16.6 Hz, 1 H, $COCHCH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 25.2 [$OC(CH_3)_2CH$], 27.6 [$OC(CH_3)_2N$], 27.8 [$OC(CH_3)_2N$], 28.7 [$OC(CH_3)_2CH$], 35.6 ($SCH_2CHCH_2$), 69.7 (NCH), 82.0 [$OC(CH_3)_2CH$], 95.3 [$OC(CH_3)_2N$], 118.0 ($SCH_2CHCH_2$), 128.0 ($COCHCH_2$), 129.5 ($COCHCH_2$), 133.1 ($SCH_2CHCH_2$), 163.3 (CO); MS (CI, isobutane): *m*/*z* (%): 256.1 (100) $[M + H]^+$, 182.2 (55) $[M - SCH_2CHCH_2]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{13}H_{22}NO_2S]^+$: 256.1371; found: 256.1369.

**(*RS*)-1-(4-Allylsulfanyl-2,2,5,5-tetramethyloxazolidin-3-yl)-2-methylpropenone (2c)..** Following **GP A**, 2,5-dihydrooxazole **1b** (0.32 g, 2.5 mmol), 2-methylacryloyl chloride (0.29 g, 2.75 mmol), allyl mercaptan (70%) (0.53 g, 5.0 mmol), and triethylamine (0.45 g, 4.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.12 g (0.4 mmol, 18%); light yellow solid; mp 54–56 C; $R_f$ = 0.60 (*n*-hexane–EtOAc, 7:3); IR: 2979, 2936, 1652, 1630, 1410, 1391, 1368 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.39 [s, 3 H, $OC(CH_3)_2CH$], 1.45 [s, 3 H, $OC(CH_3)_2CH$], 1.60 [s, 3 H, $OC(CH_3)_2N$], 1.65 [s, 3 H, $OC(CH_3)_2N$], 2.04–2.05 [m, 3 H, $COC(CH_3)CH_2$], 3.15 (dd, $^2J$ = 13.5 Hz, $^3J$ = 7.5 Hz, 1 H, $SCH_2CHCH_2$), 3.20 (dd, $^2J$ = 13.5 Hz, $^3J$ = 7.1 Hz, 1 H, $SCH_2CHCH_2$), 4.96 (br s, 1 H, NCH), 5.05–5.11 (m, 2 H, $SCH_2CHCH_2$), 5.14–5.15 [m, 1 H, $COC(CH_3)CH_2$], 5.24–5.25 [m, 1 H, $COC(CH_3)CH_2$], 5.72–5.80 (m, 1 H, $SCH_2CHCH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 20.3 [$COC(CH_3)CH_2$], 25.5 [$OC(CH_3)_2CH$], 27.6 [$OC(CH_3)_2N$], 28.0 [$OC(CH_3)_2N$], 28.6 [$OC(CH_3)_2CH$], 36.3

($SCH_2CHCH_2$), 72.0 (NCH), 81.5 [$OC(CH_3)_2CH$], 94.8 [$OC(CH_3)_2N$], 115.4 ($COC(CH_3)CH_2$), 117.4 ($SCH_2CHCH_2$), 133.7 ($SCH_2CHCH_2$), 142.2 ($COC(CH_3)CH_2$), 170.5 (CO); MS (CI, isobutane): *m/z* (%): 270.1 (100) $[M + H]^+$, 196.1 (72) $[M - SCH_2CHCH_2]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{14}H_{24}NO_2S]^+$: 270.1528; found: 270.1529.

**(*RS*)-1-[4-(Allylmethylamino)-2,2,5,5-tetramethylthiazolidin-3-yl]-propenone (2d)..** Following **GP A**, 2,5-dihydrothiazole **1a** (0.20 g, 1.4 mmol), acryloyl chloride (0.14 g, 1.5 mmol), *N*-allylmethylamine (0.20 g, 2.8 mmol), and triethylamine (0.25 g, 2.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.24 g (0.9 mmol, 63%); colorless oil; $R_f = 0.67$ (*n*-hexane–EtOAc, 7:3); IR: 3077, 2982, 2932, 1652, 1612, 1468, 1406, 1338, 972, 918 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, $SC(CH_3)_2CH$], 1.54 [s, 3 H, $SC(CH_3)_2CH$], 1.93 [s, 3 H, $SC(CH_3)_2N$], 1.94 [s, 3 H, $SC(CH_3)_2N$], 2.57 (s, 3 H, $NCH_3$), 3.42 (dd, $^2J$ = 14.8 Hz, $^3J$ = 6.0 Hz, 1 H, $NCH_2CHCH_2$), 3.73 (d, $^2J$ = 14.8 Hz, 1 H, $NCH_2CHCH_2$), 4.68 (br s, 1 H, NCH), 5.06 (dd, $^2J$ = 1.5 Hz, $^3J$ = 10.0 Hz, 1 H, $NCH_2CHCH_2$), 5.13 (dd, $^2J$ = 1.5 Hz, $^3J$ = 17.1 Hz, 1 H, $NCH_2CHCH_2$), 5.62 (dd, $^2J$ = 1.6 Hz, $^3J$ = 10.4 Hz, 1 H, $COCHCH_2$), 5.64–5.71 (m, 1 H, $NCH_2CHCH_2$), 6.32 (dd, $^2J$ = 1.6 Hz, $^3J$ = 16.3 Hz, 1 H, $COCHCH_2$), 6.50 (dd, $^3J$ = 10.4 Hz, $^3J$ = 16.3 Hz, 1 H, $COCHCH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 24.6 [$SC(CH_3)_2CH$], 33.8 [$SC(CH_3)_2CH$], 28.9 [$SC(CH_3)_2N$], 32.1 [$SC(CH_3)_2N$], 37.2 ($NCH_3$), 53.1 [$SC(CH_3)_2CH$], 55.5 ($NCH_2CHCH_2$), 71.7 [$SC(CH_3)_2N$], 91.0 (NCH), 116.3 ($NCH_2CHCH_2$), 126.9 ($COCHCH_2$), 131.3 ($COCHCH_2$), 136.3 ($NCH_2CHCH_2$), 166.2 (CO); MS (CI, isobutane): *m/z* (%): 269.2 (100) $[M + H]^+$, 198.1 (50) $[MH - C_4H_9N]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{14}H_{25}N_2OS]^+$: 269.1688; found: 269.1688.

**(*RS*)-1-[4-(Allylmethylamino)-2,2,5,5-tetramethyloxazolidin-3-yl]-propenone (2e)..** Following **GP A**, 2,5-dihydrooxazole **1b** (0.32 g, 2.5 mmol), acryloyl chloride (0.25 g, 2.75 mmol), *N*-allylmethylamine (0.36 g, 5.0 mmol), and triethylamine (0.45 g, 4.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 0.09 g (0.4 mmol, 14%); light yellow oil; $R_f = 0.83$ (*n*-hexane–EtOAc, 1:1); IR: 2980, 2941, 1651, 1613, 1414, 1353 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.33 [s, 3 H, $OC(CH_3)_2CH$], 1.34 [s, 3 H, $OC(CH_3)_2CH$], 1.67 [s, 3 H, $OC(CH_3)_2N$], 1.72 [s, 3 H, $OC(CH_3)_2N$], 2.44 (s, 3 H, $NCH_3$), 3.31 (dd, $^2J$ = 14.6 Hz, $^3J$ = 6.0 Hz, 1 H, $NCH_2CHCH_2$), 3.43 (dd, $^2J$ = 14.6 Hz, $^3J$ = 5.8 Hz, 1 H, $NCH_2CHCH_2$), 4.50 (s, 1 H, NCH), 5.08 (dd, $^2J$ = 1.0 Hz, $^3J$ = 10.2 Hz, 1 H, $NCH_2CHCH_2$), 5.15 (dd, $^2J$ = 1.0 Hz, $^3J$ = 17.1 Hz, 1 H, $NCH_2CHCH_2$), 5.65 (dd, $^2J$ = 1.7 Hz, $^3J$ = 10.2 Hz, 1 H, $COCHCH_2$), 5.67–5.73 (m, 1 H, $NCH_2CHCH_2$), 6.38 (dd, $^2J$ = 1.7 Hz, $^3J$ = 16.7 Hz, 1 H, $COCHCH_2$), 6.53 (dd, $^3J$ = 10.2 Hz, $^3J$ = 16.7 Hz, 1 H, $COCHCH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 24.3 [$OC(CH_3)_2CH$], 27.2 [$OC(CH_3)_2N$], 28.1 [$OC(CH_3)_2N$], 30.0 [$OC(CH_3)_2CH$], 36.8 ($NCH_3$), 56.0 ($NCH_2CHCH_2$), 82.5 [$OC(CH_3)_2CH$], 83.9 (NCH), 94.5 [$OC(CH_3)_2N$], 116.6 ($NCH_2CHCH_2$), 127.3 ($COCHCH_2$), 130.2 ($COCHCH_2$), 136.2 ($NCH_2CHCH_2$), 164.6 (CO); MS (CI, isobutane): *m/z* (%): 253.2 (20) $[M + H]^+$, 182.1 (52) $[M - N(CH_3)CH_2CHCH_2]^+$, 142.1 (100) $[C_7H_{14}N_2O]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{14}H_{25}N_2O_2]^+$: 253.1916; found: 253.1916.

**(*RS*)-1-[4-(Allylmethylamino)-2,2,5,5-tetramethyloxazolidin-3-yl]-2-methylpropenone (2f)..** Following **GP A**, 2,5-dihydrooxazole **1b** (0.32 g, 2.5 mmol), 2-methylacryloyl chloride (0.29 g, 2.75 mmol), *N*-allylmethylamine (0.36 g, 5.0 mmol), and triethylamine (0.45 g, 4.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 0.05 g (0.2 mmol, 7%); yellow oil; $R_f$ = 0.83 (*n*-hexane–EtOAc, 1:1). The product was not obtained pure, but its structure was verified by MS, HRMS and further reaction to analytically pure (*RS*)-1,4,7,7,9,9-hexamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]diazepin-5-one **3f**; MS (CI, isobutane): *m/z* (%): 267.4 (12) $[M + H]^+$, 196.3 (60) $[M - N(CH_3)CH_2CHCH_2]^+$, 142.1 (100) $[C_7H_{14}N_2O]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{15}H_{27}N_2O_2]^+$: 267.2073; found: 267.2068.

**(*RS*)-1-(4-Allylselanyl-2,2,5,5-tetramethylthiazolidin-3-yl)-propenone (2g)..** Under argon atmosphere, 2,5-dihydrothiazole **1a** (0.30 g, 2.1 mmol) was dissolved in anhydrous diethyl ether (5 mL) and cooled to 0–5°C before acryloyl chloride (0.19 g, 2.1 mmol) dissolved in anhydrous diethyl ether (1 mL) was added dropwise. The solution was stirred for 3 h at room temperature. Simultaneously, in another flask magnesium turnings (0.08 g, 3.1 mmol) were covered with anhydrous diethyl ether (5 mL) under argon atmosphere. Under continuous boiling, allyl bromide (0.38 g, 3.1 mmol) was added dropwise. After finishing addition, selenium (0.25 g, 3.1 mmol) was added and the reaction mixture was refluxed for 1 h. At room temperature, the first prepared solution of α-chloro amide was added to selenium-Grignard reagent dropwise. After stirring overnight, water (10 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 43 mg (0.14 mmol, 6%); light yellow oil; $R_f = 0.53$ (*n*-hexane–EtOAc, 7:3); the product was not obtained pure, but its structure was verified by further reaction to analytically pure (*RS*)-7,7,9,9-tetramethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]selenazepin-5-one **3g**; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.53 [s, 3 H, $SC(CH_3)_2CH$], 1.65 [s, 3 H, $SC(CH_3)_2CH$], 1.87 [s, 3 H, $SC(CH_3)_2N$], 1.99 [s, 3 H, $SC(CH_3)_2N$], 3.32–3.43 (m, 2 H, $SeCH_2CHCH_2$), 5.09–5.12 (m, 2 H, $SeCH_2CHCH_2$), 5.30 (s, 1 H, NCH), 5.70 (dd, $^2J$ = 1.6 Hz, $^3J$ = 10.4 Hz, 1 H, $COCHCH_2$), 5.96 (dddd, $^3J$ = 7.8 Hz, $^3J$ = 7.8 Hz, $^3J$ = 9.6 Hz, $^3J$ = 17.3 Hz, 1 H, $SeCH_2CHCH_2$), 6.33 (dd, $^2J$ = 1.6 Hz, $^3J$ = 16.6 Hz, 1 H, $COCHCH_2$), 6.57 (dd, $^3J$ = 10.4 Hz, $^3J$ = 16.6 Hz, 1 H, $COCHCH_2$); MS (CI, isobutane): *m/z* (%): 320.1 (18) $[M + H]^+$, 198.1 (100) $[MH - C_3H_6Se]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{13}H_{22}NOSSe]^+$: 320.0587; found: 320.0587.

**General procedure for the preparation of lactams 3 (GP B)..** Acryl amide **2** (1 equiv) and the ruthenium catalyst **I** (0.05 equiv) were dissolved in toluene (8 mL) and heated to 30°C. Following the solution was slowly heated to at most 70°C over a period of 2-6 h (heating rate: about 10°C /h) until the reaction was complete as continuously controlled by TLC. The solvent was removed under reduced pressure and the product was purified as described later.

**(*RS*)-7,7,9,9-Tetramethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]thiazepin-5-one (3a)..** Following **GP B**, the acryl amide **2a** (41 mg, 0.15 mmol) and ruthenium catalyst **I** (7.2 mg, 8

μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 27 mg (0.11 mmol, 74%); colorless solid; mp 120°C; $R_f = 0.47$ (*n*-hexane–EtOAc, 1:1); IR: 2964, 2932, 1643, 1609, 1467, 1437, 1375, 1338, 808 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.46 [s, 3 H, $SC(CH_3)_2CH$], 1.67 [s, 3 H, $SC(CH_3)_2CH$], 1.95 [s, 3 H, $SC(CH_3)_2N$], 2.09 [s, 3 H, $SC(CH_3)_2N$], 3.14 (ddd, $^2J$ = 13.3 Hz, $^3J$ = 7.4 Hz, $^4J$ = 1.8 Hz, 1 H, $CH_2$), 3.40 (ddd, $^2J$ = 13.3 Hz, $^3J$ = 6.4 Hz, $^4J$ = 0.9 Hz, 1 H, $CH_2$), 5.10 (s, 1 H, NCH), 6.04–6.12 (m, 2 H, COCHCH); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 25.0 [$SC(CH_3)_2CH$], 30.2 [$SC(CH_3)_2CH$], 25.6 ($CH_2$), 32.6 [$SC(CH_3)_2N$], 32.9 [$SC(CH_3)_2N$], 51.7 [$SC(CH_3)_2CH$], 73.4 [$SC(CH_3)_2N$], 78.1 (NCH), 126.9 (CO*C*HCH), 129.7 (COCH*C*H), 166.3 (CO); MS (CI, isobutane): *m*/*z* (%): 244.1 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{11}H_{18}NOS_2]^+$: 244.0830; found: 244.0832.

**(*RS*)-7,7,9,9-Tetramethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]thiazepin-5-one (3b)..** Following **GP B**, the acryl amide **2b** (40 mg, 0.16 mmol) and ruthenium catalyst **I** (7.4 mg, 8 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 16 mg (0.07 mmol, 45%); colorless solid; mp 79–80°C; $R_f = 0.23$ (*n*-hexane–EtOAc, 7:3); IR: 2984, 2935, 1656, 1605, 1393, 1370, 1195 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.42 [s, 3 H, $OC(CH_3)_2CH$], 1.45 [s, 3 H, $OC(CH_3)_2CH$], 1.73 [s, 3 H, $OC(CH_3)_2N$], 1.79 [s, 3 H, $OC(CH_3)_2N$], 3.16 (dd, $^2J$ = 13.9 Hz, $^3J$ = 7.6 Hz, 1 H, $CH_2$), 3.35 (ddd, $^2J$ = 13.9 Hz, $^3J$ = 6.8 Hz, $^4J$ = 1.0 Hz, 1 H, $CH_2$), 4.88 (s, 1 H, NCH), 6.08 (dd, $^3J$ = 10.9 Hz, $^4J$ = 1.0 Hz, 1 H, COC*H*CH), 6.20 (ddd, $^3J$ = 6.8 Hz, $^3J$ = 7.6 Hz, $^3J$ = 10.9 Hz, 1 H, COCHC*H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 25.2 [$OC(CH_3)_2CH$], 26.2 ($CH_2$), 28.0 [$OC(CH_3)_2N$], 28.4 [$OC(CH_3)_2N$], 29.4 [$OC(CH_3)_2CH$], 69.7 (NCH), 80.6 [$OC(CH_3)_2CH$], 95.9 [$OC(CH_3)_2N$], 129.2 (CO*C*HCH), 129.6 (COCH*C*H), 164.5 (CO); MS (ESI): *m*/*z* (%): 250.0 (100) $[M + Na]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{11}H_{18}NO_2S]^+$: 228.1058; found: 228.1058.

**(*RS*)-4,7,7,9,9-Pentamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]thiazepin-5-one (3c)..** Following **GP B**, the acryl amide **2c** (40 mg, 0.15 mmol) and ruthenium catalyst **I** (7.0 mg, 7 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 31 mg (0.13 mmol, 88%); light yellow solid; mp 75–78°C; $R_f = 0.51$ (*n*-hexane–EtOAc, 7:3); IR: 2991, 2929, 1650, 1627, 1402, 1374, 1203 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.40 [s, 3 H, $OC(CH_3)_2CH$], 1.43 [s, 3 H, $OC(CH_3)_2CH$], 1.73 [s, 3 H, $OC(CH_3)_2N$], 1.80 [s, 3 H, $OC(CH_3)_2N$], 1.96 [dd, $^4J$ = 1.6 Hz, $^5J$ = 1.0 Hz, 3 H, $COC(CH_3)CH$], 2.97 (dd, $^2J$ = 13.2 Hz, $^3J$ = 8.4 Hz, 1 H, $CH_2$), 3.28 (ddd, $^2J$ = 13.2 Hz, $^3J$ = 7.7 Hz, $^5J$ = 1.0 Hz, 1 H, $CH_2$), 4.81 (s, 1 H, NCH), 5.83 [ddq, $^3J$ = 7.7 Hz, $^3J$ = 8.4 Hz, $^4J$ = 1.6 Hz, 1 H, $COC(CH_3)CH$]; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 18.1 [$COC(CH_3)CH$], 24.8 [$OC(CH_3)_2CH$], 25.3 ($CH_2$), 28.2 [$OC(CH_3)_2N$], 28.4 [$OC(CH_3)_2N$], 29.3 [$OC(CH_3)_2CH$], 69.5 (NCH), 80.5 [$OC(CH_3)_2CH$], 95.7 [$OC(CH_3)_2N$], 122.3 [$COC(CH_3)CH$], 137.9 [$COC(CH_3)CH$], 167.2 (CO); MS (CI, isobutane): *m*/*z*(%): 242.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{12}H_{20}NO_2S]^+$: 242.1215; found: 242.1213.

**(*RS*)-1,7,7,9,9-Pentamethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]diazepin-5-one (3d)..** Following **GP B**, the acryl amide **2d** (36 mg, 0.15 mmol) and ruthenium catalyst **I** (7.0 mg, 7 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 32 mg (0.13 mmol, 90%); colorless solid; mp 67°C; $R_f = 0.40$ (*n*-hexane–EtOAc, 1:1); IR: 2986, 2953, 2859, 1655, 1604, 1469, 1440, 1416, 1398, 1365, 1344, 815 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.31 [s, 3 H, $SC(CH_3)_2CH$], 1.57 [s, 3 H, $SC(CH_3)_2CH$], 1.89 [s, 3 H, $SC(CH_3)_2N$], 1.94 [s, 3 H, $SC(CH_3)_2N$], 2.54 (s, 3 H, $NCH_3$), 3.19–3.23 (m, 1 H, $CH_2$), 3.85 (ddd, $^2J$ = 20.7 Hz, $^3J$ = 2.8 Hz, $^4J$ = 2.6 Hz, 1 H, $CH_2$), 4.72 (s, 1 H, NCH), 5.91 (ddd, $^3J$ = 12.9 Hz, $^4J$ = 2.6 Hz, $^4J$ = 1.7 Hz, 1 H, COC*H*CH), 6.02 (ddd, $^3J$ = 2.8 Hz, $^3J$ = 2.9 Hz, $^3J$ = 12.9 Hz, 1 H, COCHC*H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 25.3 [$SC(CH_3)_2CH$], 34.7 [$SC(CH_3)_2CH$], 38.0 [$SC(CH_3)_2N$], 31.6 [$SC(CH_3)_2N$], 36.5 ($NCH_3$), 50.0 [$SC(CH_3)_2CH$], 59.2 ($CH_2$), 70.8 [$SC(CH_3)_2N$], 88.8 (NCH), 128.0 (CO*C*HCH), 140.4 (COCH*C*H), 165.6 (CO); MS (CI, isobutane): *m*/*z* (%): 241.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{12}H_{21}N_2OS]^+$: 241.1375; found: 241.1376.

**(*RS*)-1,7,7,9,9-Pentamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]diazepin-5-one (3e)..** Following **GP B**, the acryl amide **2e** (37 mg, 0.15 mmol) and ruthenium catalyst **I** (6.9 mg, 7 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 24 mg (0.11 mmol, 74%); colorless solid; mp 83–86°C, $R_f = 0.09$ (*n*-hexane–EtOAc, 7:3); IR: 2956, 2936, 2871, 1651, 1604, 1428, 1405, 1369, 1198 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.31 [s, 3 H, $OC(CH_3)_2CH$], 1.38 [s, 3 H, $OC(CH_3)_2CH$], 1.67 [s, 3 H, $OC(CH_3)_2N$], 1.69 [s, 3 H, $OC(CH_3)_2N$], 2.37 (s, 3 H, $NCH_3$), 3.25 (ddd, $^2J$ = 20.4 Hz, $^3J$ = 3.3 Hz, $^4J$ = 1.6 Hz, 1 H, $CH_2$), 3.83 (ddd, $^2J$ = 20.4 Hz, $^3J$ = 2.6 Hz, $^4J$ = 2.6 Hz, 1 H, $CH_2$), 4.53 (s, 1 H, NCH), 5.92 (ddd, $^3J$ = 13.1 Hz, $^4J$ = 1.6 Hz, $^4J$ = 2.6 Hz, 1 H, COC*H*CH), 6.05 (ddd, $^3J$ = 2.6 Hz, $^3J$ = 3.3 Hz, $^3J$ = 13.1 Hz, 1 H, COCHC*H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 24.2 [$OC(CH_3)_2CH$], 26.6 [$OC(CH_3)_2N$], 27.7 [$OC(CH_3)_2N$], 30.9 [$OC(CH_3)_2CH$], 36.5 ($NCH_3$), 58.8 ($CH_2$), 80.6 [$OC(CH_3)_2CH$], 82.2 (NCH), 93.9 [$OC(CH_3)_2N$], 127.5 (CO*C*HCH), 140.3 (COCH*C*H), 164.4 (CO); MS (CI, isobutane): *m*/*z* (%): 225.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{12}H_{21}N_2O_2]^+$: 225.1603; found: 225.1602.

**(*RS*)-1,4,7,7,9,9-Hexamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]diazepin-5-one (3f)..** Following **GP B**, the acryl amide **2f** (47 mg, 0.18 mmol) and ruthenium catalyst **I** (8.4 mg, 9 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 21 mg (0.09 mmol, 50%); colorless solid; mp 39–43°C; $R_f = 0.26$ (*n*-hexane–EtOAc, 7:3); IR: 2987, 2936, 1649, 1592, 1423, 1367, 1198 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.34 [s, 3 H, $OC(CH_3)_2CH$], 1.37 [s, 3 H, $OC(CH_3)_2CH$], 1.68 [s, 3 H, $OC(CH_3)_2N$], 1.71 [s, 3 H, $OC(CH_3)_2N$], 1.97–1.98 [m, 3 H, $COC(CH_3)CH$], 2.31 (s, 3 H, $NCH_3$), 3.29 (dd, $^2J$ = 18.9 Hz, $^3J$ = 2.2 Hz, 1 H, $CH_2$), 3.63 (d, $^2J$ = 18.9 Hz, 1 H, $CH_2$), 4.24 (s, 1 H, NCH), 6.00–6.02 [m, 1 H, $COC(CH_3)CH$]; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 21.7 [$COC(CH_3)CH$], 24.3 [$OC(CH_3)_2CH$], 27.0 [$OC(CH_3)_2N$], 28.0 [$OC(CH_3)_2N$], 30.5 [$OC(CH_3)_2N$], 37.7 ($NCH_3$), 56.7 ($CH_2$), 81.0 [$OC(CH_3)_2CH$], 82.1 (NCH), 94.5 [$OC(CH_3)_2N$], 133.6 [$COC(CH_3)CH$], 133.7 [$COC(CH_3)CH$], 166.2 (CO); MS (CI, isobutane): *m*/*z* (%): 239.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{13}H_{23}N_2O_2]^+$: 239.1760; found: 239.1760.

**(*RS*)-7,7,9,9-Tetramethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]selenazepin-5-one (3g)..** Following **GP B**, the acryl amide **2g** (15 mg, 0.05 mmol) and ruthenium catalyst **I** (2.4 mg, 3 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 5 mg (0.02 mmol, 36%); colorless solid; $R_f$ = 0.50 (*n*-hexane–EtOAc, 1:1); IR: 2964, 2925, 2855, 1655, 1612, 1465, 1377, 795 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.50 [s, 3 H, $SC(CH_3)_2CH$], 1.69 [s, 3 H, $SC(CH_3)_2CH$], 2.01 [s, 3 H, $SC(CH_3)_2N$], 2.10 [s, 3 H, $SC(CH_3)_2N$], 3.12 (ddd, $^2J$ = 11.8 Hz, $^3J$ = 7.6 Hz, $^4J$ = 1.9 Hz, 1 H, $CH_2$), 3.47 (dd, $^2J$ = 11.8 Hz, $^3J$ = 7.1 Hz, 1 H, $CH_2$), 5.31 (s, 1 H, NCH), 5.99–6.07 (m, 2 H, COCHCH); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 26.4 $[SC(CH_3)_2CH]$, 39.9 $[SC(CH_3)_2CH]$, 29.7 ($CH_2$), 32.2 $[SC(CH_3)_2N]$, 33.2 $[SC(CH_3)_2N]$, 52.5 $[SC(CH_3)_2CH]$, 73.7 $[SC(CH_3)_2N]$, 75.0 (NCH), 127.1 (COCHCH), 128.0 (COCHCH), 166.1 (CO); MS (CI, isobutane): *m*/*z* (%): 292.0 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{11}H_{18}NOSSe]^+$: 292.0274; found: 292.0276.

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## REFERENCES AND NOTES

[1] Hutchison, G. I.; Prager, R. H.; Ward, A. D. Aust J Chem 1980, 33, 2477.

[2] Catsoulacos, P.; Camoutsis, C.; Papageorgiou, A.; Margariti, E.; Psaraki, K.; Demopoulos, N. J Pharm Sci 1993, 82, 204.

[3] Ponec, M.; Haverkort, M.; Soei, Y. L.; Kempenaar, J.; Brussee, J.; Bodde, H. J Pharm Sci 1989, 78, 738.

[4] Hasegawa, K.; Knegt, E.; Bruinsma, J. Phytochemistry 1983, 22, 2611.

[5] Watzke, M.; Schulz, K.; Johannes, K.; Ullrich, P.; Martens, J. Eur J Org Chem 2008, 3859.

[6] Sakamato, M.; Watanabe, S.; Fujita, T.; Yanase, T. J Org Chem 1990, 55, 2986.

[7] Köpper, S.; Lindner, K.; Martens, J. Tetrahedron 1992, 48, 10277.

[8] Weber, M.; Jakob, J.; Martens, J. Liebigs Ann Chem 1992, 1.

[9] (a) Martens, J.; Offermanns, H.; Scherberich, P. Angew Chem 1981, 93, 680; (b) Martens, J.; Offermanns, H.; Scherberich, P. Angew Chem Int Ed Engl 1981, 20, 668.

[10] Leuchs, H.; Wulkow, G.; Gerland, H. Chem Ber 1932, 62, 1586.

[11] Schwarze, W.; Drauz, K.; Martens, J. Chem-Ztg 1987, 111, 149.

[12] Riague, E. H.; Guillemin, J.-C. Organometallics 2002, 21, 68.

[13] Klayman, D. L.; Griffin, T. S. J Am Chem Soc 1973, 95, 197.

[14] Taboury, F. Ann Chim Phys 1908, 15, 5.

[15] (a) Rodriguez, S.; Castillo, E.; Carda, M.; Marco, J. A. Tetrahedron 2002, 58, 1185; (b) Chen, Y.; Zhang, H.; Nan, F. J Comb Chem 2004, 6, 684; (c) Deiters, A.; Pettersson, M.; Martin, S. F. J Org Chem 2006, 71, 6547; (d) Liu, G.; Tai, W.-Y.; Li, Y.-L.; Nan, F.-J. Tetrahedron Lett 2006, 47, 3295; (e) Fiorelli, C.; Savoia, D. J Org Chem 2007, 72, 6022; (f) Schulz, K.; Watzke, M.; Johannes, K.; Ullrich, P.; Martens, J. Synthesis 2009, 665.

# $NbCl_5$ as an Efficient Catalyst for Rapid Synthesis of Quinoxaline Derivatives



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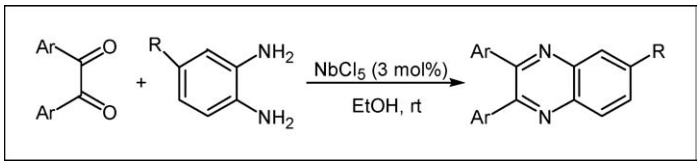


A series of quinoxaline derivatives have been synthesized in excellent yields by the condensation of 1,2-diketones and 1,2-phenylenediamines in the presence of a catalytic amount of $NbCl_5$ at room temperature in short times.

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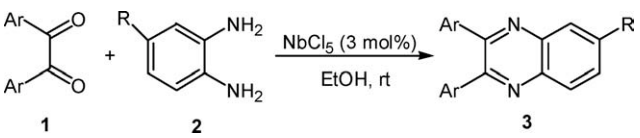
## INTRODUCTION

The quinoxaline derivatives are important heterocyclic compounds, which exhibit a diverse range of biological properties, such as antitumor [1], cytotoxic [2], antiviral, antibacterial, anti-inflammatory, and kinase inhibitor properties [3]. They have also been used as dyes, efficient electron luminescent material, organic semiconductors, DNA cleaving agents [4], photoinitiators in UV-cured coatings [5], and donor materials [6]. In addition, the quinoxaline ring is a part of a number of antibiotics, such as echinomycin, levomycin, and actinomycin that are known to inhibit the growth of gram-positive bacteria and are active against various transplantable tumors [7].

Therefore, the synthesis of this type of compounds has attracted considerable attention. Synthetic routes that are common to the preparation of these heterocycles typically involve the reaction of 1,2-diamine and 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid. Various catalysts, such as bismuth(III) triflate [8], metal hydrogen sulfates [9], gallium(III) triflate [10], molecular iodine [11], cerium (IV) ammonium nitrate [12], stannous chloride [7], zirconium tetrakis(dodecyl sulfate) [13], amidosulfonic acid [14], montmorillonite K-10 [15], binary metal oxides supported on Si-MCM-41 mesoporous molecular sieves [4], polyaniline-sulfate salt [16], Wells-Dawson heteropoly acid [17], and ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [18] have been used to promote this transformation. Alternative approaches, such as oxidative cyclization of α-hydroxyketones with *o*-phenylenediamines [19], reaction of *o*-phenylenediamine with α-bromoketonethe [20,21], reaction of α-keto oximes and 1,2-diamines [3], oxidative coupling of epoxides and ene-1,2-diamines [22], the coupling of α-diazoketones with aryl 1,2-diamines [23], reductive cyclization of 1,2-dicarbonyl compounds with 2-nitroanilines [7], heteroannulation of nitroketene *N*,*S*-aryliminoacetals with $POCl_3$ [24], intramolecular cyclizations of dialdimines [25], the reaction of aryl-1,2-diamines and diethyl bromomalonate [26], the reaction of *o*-phenylenediamines and ketones [27], reaction of *o*-phenylenediamines and vicinal-diols [28], and palladium-catalyzed reductive *N*-heteroannulation of enamines [29] have been also developed to prepare functionalized quinoxalines. However, the long reaction time [15], costly catalysts, such as bismuth(III) triflate [8] and gallium(III) triflate [10], requirement of special effect for catalyst preparation [4,16] and a special instrumentation, such as microwave [30], harsh reaction conditions, such as heating at 70°C [21] can not be avoided. Because of the importance of quinoxaline derivatives in organic synthesis, the development of a convenient, efficient and practically useful process for synthesis quinoxaline derivatives is in demand.

In recent years, niobium pentachloride has been considered as mild Lewis acid catalyst for a variety of organic transformations [31], such as one-pot Mannich-type reaction [32], alkoxide rearrangements [33], the intramolecular Friedel–Crafts acylation reaction [34], conversion of aldehydes and ketones to allylic halides [35], cyanosilylation of aldehydes [36], synthesis of α-aminonitriles [37], 1,1-diacetates [38], bis(indol)alkanes [39], and 1,5-benzodiazepine derivatives [40]. However, to the best of our knowledge, there is no report on the synthesis of quinoxaline derivatives using niobium pentachloride as a reagent. As part of our continuing interest in the development of new synthetic methodologies [41–46], we report herein an efficient and convenient

**Scheme 1**




procedure for the synthesis of quinoxaline derivatives by the condensation of 1,2-diketones and 1,2-phenylenediamines in the presence of a catalytic amount of niobium pentachloride at room temperature (Scheme 1).

## RESULTS AND DISCUSSION

At the onset of the research, we investigated the model reaction between 1,2-phenylenediamines and benzil in EtOH in the presence of a catalytic amount of $NbCl_5$ (3 mol%) at room temperature. To our delight, the product **3a** was formed and the complete conversion with 95% isolated yield was observed after 2 min. Further studies showed that EtOH was the best solvent among the solvents (MeOH, MeCN, THF, DMF, DMSO, $CH_2Cl_2$, and $CHCl_3$). Next, the amount of the catalyst was examined and we found that 3 mol% $NbCl_5$ was sufficient to drive the reaction completely in 95% yield. The less amount gave low yield even after a prolonged reaction time, and the more amount could not cause the obvious increase for the yield of product and could not shorten the reaction time. It is noteworthy to mention that the reaction gave only a 60% yield in the absence of $NbCl_5$ after 4 h.

To evaluate the generality of this method, we next investigated the scope and limitation of this reaction under optimized conditions (EtOH, 3 mol% of $NbCl_5$, RT) and the results are illustrated in Table 1. As shown in Table 1, a variety of structurally diverse 1,2-phenylenediamines and a wide of 1,2-diketones underwent the condensation reaction smoothly to afford the corresponding quinoxaline derivatives in excellent yields. The electronic property of the substituents on the aromatic ring of 1,2-phenylenediamines had an obvious effect on reaction time under the above optimal reaction conditions. It was observed that electron-withdrawing groups (Table 1, entries **i–o**) associated with 1,2-phenylenediamines decreased the reactivity of the substrate and long reaction times were required. It is worth noting that the reaction of 4-nitrobenzene-1,2-diamine with benzil failed to give the desired product. On the other hand, the effect of electronic factors associated with aromatic 1,2-diketons is opposite. For example, 4,4′-dibromolbenzil could react with 4-nitrobenzene-1,2-diamine to afford the corresponding product (**3o**) in 92% yield. Besides this, when 2,2′-furil and acenaphthylenequinone were subjected for condensation reaction, the corresponding products were obtained with excellent yields. All of the quinoxaline derivatives have been characterized by $^1H$ NMR, $^{13}C$ NMR, and IR spectra, and the known compounds were confirmed by comparison of their spectral data and melting points with those reported in the literature.

In conclusion, we have developed a simple, rapid, and efficient methodology for the synthesis of quinoxaline derivatives by the condensation 1,2-diketones and 1,2-phenylenediamines at room temperature using $NbCl_5$ as a novel catalyst. Simplicity of operation, high yields, short reaction time, and good substrate generality are the key advantages of this method.

## EXPERIMENTAL

Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were obtained using a Bruker-

**Table 1**

Synthesis of quinoxaline derivatives catalyzed by $NbCl_5$.

| Entry | 1,2-Diketones | R | Time (min) | Yield (%)[a] | Mp (°C) | Lit. Mp (°C) |
|---|---|---|---|---|---|---|
| **a** | Benzil | H | 2 | 95 | 120–121 | 124–125 [14] |
| **b** | 4,4′-Dimethylbenzil | H | 3 | 93 | 141–142 | 142–143 [7] |
| **c** | 4,4′-Dibromolbenzil | H | 1.5 | 94 | 190–192 | 190–191 [7] |
| **d** | Acenaphthylenequinone | H | 2 | 93 | 243–244 | 242–245 [8] |
| **e** | 2,2′-Furil | H | 2 | 94 | 130–131 | 129–130 [12] |
| **f** | Benzil | 4-Me | 2 | 95 | 113–114 | 112–113 [7] |
| **g** | 4,4′-Dibromolbenzil | 4-Me | 2 | 94 | 183–184 | 184–185 [18] |
| **h** | Acenaphthylenequinone | 4-Me | 2 | 93 | 234–236 | |
| **i** | Benzil | 4-Cl | 4 | 92 | 116–117 | 118–119 [7] |
| **j** | 4,4′-Dibromolbenzil | 4-Cl | 3 | 93 | 167–168 | 166–167 [7] |
| **k** | Acenaphthylenequinone | 4-Cl | 4 | 95 | 227–228 | |
| **l** | Benzil | 4-PhC=O | 20 | 93 | 152–153 | 140–142 [10] |
| **m** | 4,4′-Dibromolbenzil | 4-PhC=O | 5 | 94 | 203–204 | |
| **n** | Acenaphthylenequinone | 4-PhC=O | 4 | 95 | 255–256 | |
| **o** | 4,4′-Dibromolbenzil | 4-$NO_2$ | 20 | 92 | 187–189 | 188–190 [18] |

[a] Isolated yields after column chromatography.

TENSOR 27 spectrometer instrument. NMR spectra were taken with a Bruker DRX-500 spectrometer using TMS as internal standard. Elemental analyses were carried out on a Vario EL III CHNOS elemental analyzer.

**General procedure for the synthesis of quinoxaline derivatives (3).** A mixture of 1,2-phenylenediamine (1 mmol), 1,2-diketone (1.0 mmol), and $NbCl_5$ (0.03 mmol) in EtOH (3 mL) was stirred at room temperature. The progress of reaction was monitored by TLC. After completion, water was added and the product was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure to afford the crude product. The crude product was subjected to column chromatography over silica gel using hexane/ethyl acetate as eluent to obtain pure product.

***9-Methylacenaphtho[1,2-b]quinoxaline (3h).*** This compound was obtained as yellow needles; IR: 3053, 1635, 1616, 1483, 1434, 1419, 1299, 1212, 1099, 983, 829, 781 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.59 (dd, $J$ = 8.5, 2.0 Hz, 1H), 7.83 (td, $J$ = 8.5, 2.0 Hz, 2H), 7.99 (s, 1H), 8.08–8.10 (m, 3H), 8.41 (t, $J$ =7.0 Hz, 2H); *Anal*. Calcd. for $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found: C, 84.89; H, 4.70; N, 10.62.

***9-Chloroacenaphtho[1,2-b]quinoxaline (3k).*** This compound was obtained as yellow platelets; IR: 1635, 1616, 1419, 1298, 1101, 983, 781 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, $J$ = 8.0, 2.5 Hz, 1H), 7.86 (td, $J$ = 8.0, 2.5 Hz, 2H), 8.13–8.16 (m, 3H), 8.21 (d, $J$ = 2.5 Hz, 1H), 8.42–8.45 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 122.1, 122.3, 128.6, 128.7, 129.7, 129.9, 130.0, 130.1, 130.6, 131.4, 131.5, 134.8, 136.7, 139.7, 141.6, 154.2, 154.8; *Anal*. *Calcd*. for $C_{18}H_9ClN_2$: C, 74.88; H, 3.14; N, 9.70. Found: C, 75.02; H, 3.32; N, 9.55.

***(2,3-Diphenyl-quinoxalin-6-yl)phenylmethanone (3l).*** This compound was obtained as brown solid; IR: 1660, 1639, 1616, 1598, 1446, 1402, 1346, 1265, 1197, 1056, 1022, 891, 715 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.33–7.42 (m, 6H), 7.51–7.57 (m, 6H), 7.64 (t, $J$ = 7.5 Hz, 1H), 7.91 (d, $J$ = 7.5 Hz, 2H), 8.27 (dd, $J$ = 8.5, 2.0 Hz, 1H), 8.29 (d, $J$ = 9.0 Hz, 1H), 8.54 (d, $J$ = 2.0 Hz, 1H); *Anal*. Calcd. for $C_{27}H_{18}N_2O$: C, 83.92; H, 4.69; N, 7.25. Found: C, 84.10; H, 4.50; N, 7.08.

***[2,3-Bis(4-bromo-phenyl)-quinoxalin-6-yl]phenyl-methanone (3m).*** This compound was obtained as pale yellow solid; IR: 1683, 1652, 1616, 1598, 1334, 1074, 1010, 977, 719 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.41 (d, $J$ = 8.0 Hz, 2H), 7.44 (d, $J$ = 8.0 Hz, 2H), 7.51–7.55 (m, 6H), 7.66 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.90 (d, $J$ = 7.5 Hz, 2H), 8.27 (t, $J$ = 8.5 Hz, 2H), 8.51 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 124.1, 124.3, 128.5, 129.7, 130.1, 130.3, 131.3, 131.4, 131.8, 132.3, 132.5, 132.9, 137.0, 137.2, 137.3, 138.7, 140.2, 142.9, 153.0, 153.6, 195.6; *Anal*. *Calcd*. for $C_{27}H_{16}Br_2N_2O$: C, 59.59; H, 2.96; N, 5.15. Found: C, 59.75; H, 3.16; N, 4.98.

***Acenaphtho[1,2-b]quinoxalin-9-yl-phenyl-methanone (3n).*** This compound was obtained as pale brown needles; IR: 1683, 1647, 1616, 1596, 1436, 1317, 1301, 1263, 1101, 983, 713 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.56 (t, $J$ = 7.5 Hz, 2H), 7.66 (t, $J$ = 7.5 Hz, 1H), 7.87–7.95 (m, 4H), 8.18 (t, $J$ = 7.5 Hz, 2H), 8.27 (dd, $J$ = 7.5, 1.5 Hz, 1H), 8.34 (d, $J$ = 8.5 Hz, 1H), 8.45 (d, $J$ = 7.0 Hz, 1H), 8.51 (d, $J$ = 7.0 Hz, 1H), 8.60 (d, $J$ = 1.5 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 122.2, 122.5, 128.5, 128.8, 129.3, 129.8, 130.0, 130.1, 130.2, 131.3, 131.4, 132.7, 132.8, 136.9, 137.4, 137.6, 140.3, 143.7, 155.0, 155.6, 195.8; *Anal*. *Calcd*. for $C_{25}H_{14}N_2O$ C, 83.78; H, 3.94; N, 7.82. Found: C, 83.95; H, 4.13; N, 7.68.

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## REFERENCES AND NOTES

[1] Corona, P.; Carta, A.; Loriga, M.; Vitale, G.; Paglietti, G. Eur J Med Chem 2009, 44, 1579.

[2] Tanimori, S.; Nishimura, T.; Kirihata, M. Bioorg Med Chem Lett 2009, 19, 4119.

[3] Shaabani, A.; Maleki, A. Chem Pharm Bull 2008, 56, 79.

[4] Ajaikumar, S.; Pandurangan, A. Appl Catal A: Gen 2009, 357, 184.

[5] Balta, D. K.; Keskin, S.; Karasu, F.; Arsu, N. Prog Org Coat 2007, 60, 207.

[6] Lee, J. Y.; Shin, W. S.; Haw, J. R.; Moon, D. K. J Mater Chem 2009, 19, 4938.

[7] Shi, D. Q.; Dou, G. L.; Ni, S. N.; Shi, J. W.; Li, X. Y. J Heterocycl Chem 2008, 45, 1797.

[8] Yadav, J. S.; Reddy, B. V. S.; Premalatha, K.; Shankar, K. S. Synthesis 2008, 3787.

[9] Niknam, K.; Zolfigol, M. A.; Tavakoli, Z.; Heydari, Z. J Chin Chem Soc 2008, 55, 1373.

[10] Cai, J. J.; Zou, J. P.; Pan, X. Q.; Zhang, W. Tetrahedron Lett 2008, 49, 7386.

[11] Bhosale, R. S.; Sarda, S. R.; Ardhapure, S. S.; Jadhav, W. N.; Bhusare, S. R.; Pawar, R. P. Tetrahedron Lett 2005, 46, 7183.

[12] More, S. V.; Sastry, M. N. V.; Yao, C. F. Green Chem 2006, 8, 91.

[13] Hasaninejad, A.; Zare, A.; Zolfigol, M. A.; Shekouhy, M. Synth Commun 2009, 39, 569.

[14] Li, Z. J.; Li, W. S.; Sun, Y. J.; Huang, H.; Ouyang, P. K. J Heterocycl Chem 2008, 45, 285.

[15] Huang, T. K.; Wang, R.; Shi, L.; Lu, X. X. Catal Commun 2008, 9, 1143.

[16] Srinivas, C.; Kumar, C.; Rao, V. J.; Palaniappan, S. J Mol Catal A: Chem 2007, 265, 227.

[17] Heravi, M. M.; Bakhtiari, K.; Bamoharram, F. F.; Tehrani, M. H. Monatsh Chem 2007, 138, 465.

[18] Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. Synth Commun 2008, 38, 3601.

[19] Cho, C. S.; Ren, W. X. J Organomet Chem 2009, 694, 3215.

[20] Wan, J. P.; Gan, S. F.; Wu, J. M.; Pan, Y. J. Green Chem 2009, 11, 1633.

[21] Madhav, B.; Murthy, S. N.; Reddy, V. P.; Rao, K. R.; Nageswar, Y. V. D. Tetrahedron Lett 2009, 50, 6025.

[22] Antoniotti, S.; Dunach, E. Tetrahedron Lett 2002, 43, 3971.

[23] Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Narsaiah, A. V. Chem Lett 2008, 37, 348.

[24] Venkatesh, C.; Singh, B.; Mahata, P. K.; Ila, H.; Junjappa, H. Org Lett 2005, 7, 2169.

[25] Jesse, B.; Reich, E.; Justice, A. K.; Beckstead, B. T.; Reibenspies, J. H.; Miller, S. A. J Org Chem 2004, 69, 1357.

[26] Haldar, P.; Dutta, B.; Guin, J.; Ray, J. K. Tetrahedron Lett 2007, 48, 5855.

[27] Cho, C. S.; Ren, W. X.; Shim, S. C. Tetrahedron Lett 2007, 48, 4665.

[28] Cho, C. S.; Oh, S. G. Tetrahedron Lett 2006, 47, 5633.
[29] Wallace, J. M.; Soderberg, B. C. G.; Tamariz, J.; Akhmedov, N. G.; Hurley, M. T. Tetrahedron 2008, 64, 9675.
[30] Zhou, J. F.; Gong, G. X.; Zhi, S. J.; Duan, X. L. Synth Commun 2009, 39, 3743.
[31] Andrade, C. K. Z. Curr Org Synth 2004, 1, 333.
[32] Wang, R.; Li, B. G.; Huang, T. K.; Shi, L.; Lu, X. X. Tetrahedron Lett 2007, 48, 2071.
[33] Ravikumar, P. C.; Yao, L. H.; Fleming, F. F. J Org Chem 2009, 74, 7294.
[34] Polo, E. C.; Silva-Filho, L. C.; da Silva, G. V. J.; Constantino, M. G. Quim Nova 2008, 31, 763.
[35] Fleming, F. F.; Ravikumar, P. C.; Yao, L. H. Synlett 2009, 1077.
[36] Kim, S. S.; Rajagopal, G. Synthesis 2007, 215.
[37] Majhi, A.; Kim, S. S.; Kim, H. S. Appl Organomet Chem 2008, 22, 466.
[38] Gao, S. T.; Zhao, Y.; Li, C.; Ma, J. J.; Wang, C. Synth Commun 2009, 39, 2221.
[39] Heravi, M. M.; Nahavandi, F.; Sadjadi, S.; Oskooie, H. A.; Tajbakhsh, M. Synth Commun 2009, 39, 3285.
[40] Gao, S. T.; Liu, W. H.; Ma, J. J.; Wang, C.; Liang, Q. Synth Commun 2009, 39, 3278.
[41] Zhang, Z. H.; Li, J. J.; Gao, Y. Z.; Liu, Y. H. J Heterocycl Chem 2007, 44, 1509.
[42] Lü, H.-Y.; Li, J.-J.; Zhang, Z.-H. Appl Organomet Chem 2009, 23, 165.
[43] Zhang, Z.-H.; Tao, X.-Y. Aust J Chem 2008, 61, 77.
[44] Liu, Y.-H.; Liu, Q.-S.; Zhang, Z.-H. J Mol Catal A: Chem 2008, 296, 42.
[45] Liu, Y.-H.; Zhang, Z.-H.; Li, T.-S. Synthesis 2008, 3314.
[46] Liu, Y.-H.; Liu, Q.-S.; Zhang, Z.-H. Tetrahedron Lett 2009, 50, 916.

# Preparation and Properties *In Vitro* and *In Vivo* of Antitubercular Pyrroles



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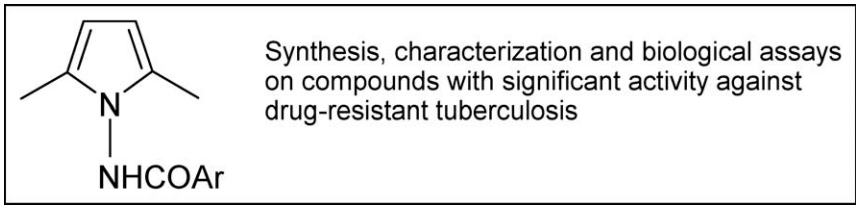


1-Acylamino-2,5-dimethylpyrroles were prepared in the exploration of heterocyclic structures useful for their antitubercular activity. The pyrroles were conveniently formed from the reaction of aromatic acid hydrazides with hexane-2,5-dione in water or ethanol, without resorting to acid catalysis. In each case, the procedure provided a single pyrrole in pure form, and the product was identified without difficulty on the basis of highly characteristic spectrometric features. Some members of this class have significant activities against drug-resistant tuberculosis *in vitro* and offer substantial protection in a rigorous mouse model of the disease.

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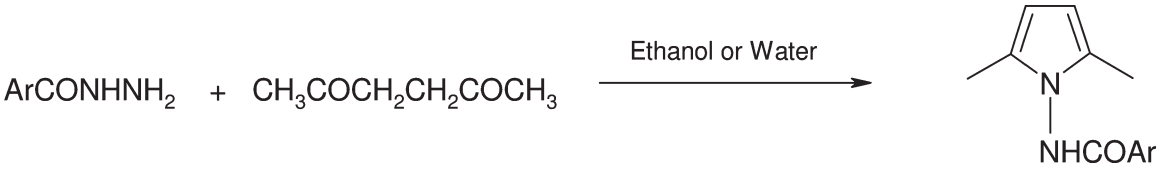
## INTRODUCTION

Worldwide, tuberculosis ranks first among the causes of death from a communicable disease [1]. This killer's designation as an international public health threat by the World Health Organization more than a decade ago [2] was followed by the mobilization of considerable resources from governments, pharmaceutical companies, philanthropic foundations, and public–private partnerships [3]. Even so, advances thus far against the disease have been hard-won, and fully one-third of the earth's population remains infected with the causative bacillus, *Mycobacterium tuberculosis* [4]. In industrialized countries, the unexpected reemergence of tuberculosis has come with substantial costs to the public health infrastructure. Among the populations of developing nations, the disease has persisted, and millions of deaths result each year from such infection [5]. Although tuberculosis can strike persons of any age, the sinister natural history of the disease makes it particularly devastating to those of middle years, during the most productive period of their lives. For those who do not themselves succumb, there is social and economic hardship as individuals, families, and communities struggle to deal with the collateral burdens of widespread infection. Progress in the development of strong new treatment regimens for tuberculosis has now been made both more difficult and more necessary by the emergence of strains of *M. tuberculosis* that are drug resistant or exceptionally virulent [6–9]. In the case of the most widely prescribed tuberculosis medication, isoniazid (isonicotinic acid hydrazide, INH), resistant strains have appeared that require drug concentrations 1000 times greater than those for susceptible bacteria. This renders the drug ineffective as a therapeutic mainstay for patients infected with those strains.

Against the urgency and seeming intransigence of this situation, there is increasing evidence that heterocyclic compounds will serve as significant leads for the discovery of robust new antitubercular medications and as valuable probes for gaining a better understanding of the life cycle of the pathogen [10–13]. Much, however, remains to be learned about the scope of heterocyclic structures that will possess this valuable antimicrobial activity [14,15]. As early as 1953, it had been reported that some pyrroles had antimycobacterial activity *in vitro* [16–20], but this perceptive observation was not given concerted follow-up at the time. More recently, significant work has resumed on antitubercular drug design using pyrroles as templates for synthesis [21–23], including elegant molecular modeling studies in conjunction with laboratory experiments [24,25]. Although much ground is still to be covered, it seems clear that the chemistry of pyrroles will provide both important lead compounds in the search for new antitubercular

**Scheme 1**




medications and tools for probing the complex interactions among pathogen, mammalian host, and drugs in tuberculosis treatment modalities.

Within this context, we wished to explore, using up-to-date methods, both the preparative chemistry and the antitubercular behavior of a class of acylaminopyrroles derived from acid hydrazides and diketones. We now report on the convenient preparation and useful antimycobacterial properties of a series of these compounds (**III**). We have found that the compounds are readily formed from aromatic carboxylic acid hydrazides (**I**) and 2,5-hexanedione (**II**) in excellent purity as stable highly crystalline solids (see Scheme 1). The reactions take place to give a single product without complication, and the resulting 1-acylamino-2,5-dimethylpyrroles may be characterized in clear-cut ways by standard spectrometric techniques. In a representative example, compound **II** was treated with INH (**I**, Ar = 4-$C_5H_4N$, 1.00 equivalent) in refluxing water for 2 h. After cooling and standing over night, the needles that formed were filtered off to give **III** (Ar = 4-$C_5H_4N$) in analytically pure form, with the distinguishing spectrometric features of the acylaminopyrrole. Notably, the features included: (1) the N—H band appropriate for the amide link near 3225 wavenumbers in the infrared spectrum; (2) the amide I and amide II peaks at 1673 and 1537 wavenumbers; (3) the N—H signal at δ 11.5 ppm in the hydrogen NMR spectrum, integrating for one hydrogen, quenched by the addition of $D_2O$; (4) the peak at δ 5.7, a singlet integrating for two hydrogens for the pyrrole ring protons; and (5) a signal at δ 11.3 ppm in the carbon nmr spectrum for the methyl groups at the 2- and 5-positions. The overall yield of the product was 67%. Our results on the preparation of these pyrroles **III** are summarized in Table 1.

In general, the preparation of a pyrrole by the reaction of a 2,5-dione with an amine, the Paal-Knorr synthesis [26], is sensitive to both the nucleophilicity of the amine and the specific reaction conditions employed. These issues have raised considerable interest within the synthesis community [27], and some trends have become apparent. Among aliphatic amines, for example, the steric environment of the carbon bearing the nitrogen appears to be crucial, with yields falling drastically as the carbon becomes more highly substituted [28]. Among substituted anilines, low reactivity is observed for those amines in which the aromatic ring is substituted with electron-withdrawing groups; thus 2,5-dichloroaniline fails to react with hexane-2,5-dione, whereas *o*-phenylenediamine is highly nucleophilic and reacts rapidly with two equivalents of the hexane-2,5-dione to produce a 1,2-dipyrrolyl benzene [28]. With respect to reaction conditions, some researchers have pointed out the accelerating role of acid catalysis [29], while others have noted that the amount of acid used, if any, should be adequate to allow for activation of the carbonyl functions of the dione but not enough to fully protonate the amine function and thereby render it nonnucleophilic [30]. In the present work, we found that in each case the terminal nitrogen of the hydrazide moiety was sufficiently nucleophilic to permit reaction in water or ethanol, without resorting to acid catalysis. This was true even for examples in which a strongly electron-withdrawing group was present, such as **IIIf**. The ability to carry out the reaction under neutral conditions considerably simplified the work-up and isolation of the products.

**Table 1**

Pyrroles **III**.

| Entry | Compound | Ar | % yield | mp (°C) | $\nu^{max}$ N—H ($cm^{-1}$) | $^1$H NMR, δ | $^{13}$C NMR, δ |
|---|---|---|---|---|---|---|---|
| 1 | **IIIa** | 4-$C_5H_4N$ | 67 | 151–153 | 3224 | 11.5 | 165 |
| 2 | **IIIb** | $C_6H_5$ | 89 | 175–177 | 3261 | 11.3 | 166 |
| 3 | **IIIc** | 4-$ClC_6H_4$ | 69 | 185 | 3274 | 11.3 | 165 |
| 4 | **IIId** | 4-$CH_3C_6H_4$ | 91 | 187–189 | 3281 | 11.2 | 166 |
| 5 | **IIIe** | 4-$BrC_6H_4$ | 77 | 207–210 | 3246 | 11.3 | 165 |
| 6 | **IIIf** | 4-$NO_2C_6H_4$ | 75 | 218–221 | 3278 | 11.3 | 165 |
| 7 | **IIIg** | 2-OH-4-$NH_2C_6H_3$ | 30 | 173–174 | 3270 | 10.9 | 162 |

**Table 2**

*In vitro* activities: Minimum inhibitory concentrations in fully susceptible Mtb Erdman.

| Entry | Compound | MIC (μg/mL)[a] |
|---|---|---|
| 1 | **IIIa** | 3.2[b] |
| 2 | **IIIb** | 16 |
| 3 | **IIIc** | 32 |
| 4 | **IIId** | >8 |
| 5 | **IIIe** | 32 |
| 6 | **IIIf** | 32 |
| 7 | **IIIg** | 2.6[c] |

[a] INH standard control MIC 0.06 μg/mL.
[b] Geometric mean of three determinations.
[c] Geometric mean of five determinations.

With respect to biological assessment, the pyrroles displayed a range of activities against both laboratory strains and drug-resistant clinical isolates of *M. tuberculosis*. Activities *in vitro* were initially determined for the pyrroles as minimum inhibitory concentration (MIC) values against *M. tuberculosis* strain Erdman (Mtb Erdman). The MIC represents the minimum concentration of the compound necessary to inhibit growth. Mtb Erdman is a fully drug-susceptible laboratory strain, often used in primary antimycobacterial assays. The determinations were referred to the known antitubercular INH as a standard control. Individual MIC values are reported in Table 2. The geometric mean of the MICs for the pyrroles tested was 12 μg/mL. For comparison purposes, tuberculosis drugs currently used in the clinic have MIC values typically ranging from 0.015 μg/mL (rifabutin) to 50 μg/mL (pyrazinamide) [31]. Of particular interest were compounds **IIIa** and **IIIg** with the lowest MICs of 3.2 and 2.6 μg/mL, respectively. These highly effective pyrroles were selected for further evaluation in a panel of three clinical strains isolated from patients showing significant drug resistance to INH, and the results are shown in Table 3. Compound **IIIa** was slightly more effective than INH itself, and compound **IIIg** clearly maintained its strong potency in the drug-resistant bacteria, demonstrating essentially the same activity *in vitro* for both INH-susceptible and INH-resistant strains.

**Table 3**

*In vitro* activities: Minimum inhibitory concentrations in drug-resistant clinical isolates.

| | | Clinical isolates | | |
|---|---|---|---|---|
| Entry | Compound | 303 | 1889 | 35829 |
| 1 | **IIIa** | 4 | 4 | 8 |
| | INH control | 8 | 4 | >8 |
| 2 | **IIIg** | 2 | 1 | 2 |
| | INH control | 64 | 8 | >64 |

**Table 4**

*In vivo* activities of pyrroles.

| Group | Log CFU/Lung |
|---|---|
| Untreated controls | 6.53 ± 0.16[a] |
| INH controls | 5.34 ± 0.22[a] |
| **IIIa** | 5.01 ± 0.73[a] |
| **IIIg** | 5.53 ± 0.16[b] |

[a] Six mice/group.
[b] Four mice/group.

For testing of compounds **IIIa** and **IIIg** *in vivo*, we used a short-course therapy model in mice, which has previously been described in detail [32]. This method provides an exacting test of the activities *in vivo* of investigational drugs and has the benefit of cutting in half the time required to produce data in animal studies, compared to the more traditional murine models. Our results are given in Table 4, in which the data are presented as the logarithms of bacterial colony-forming units (log CFU) per mouse lung, with and without administration of the candidate drugs. No overt toxicity or ill effects were observed when the drugs were administered at the therapeutic doses (see Experimental). For reference purposes, highly active drugs known to be tuberculocidal, such as INH, generally display a drop of one or more log CFU *versus* untreated controls when examined in the model. On the other hand, less-active drugs that have been characterized as tuberculostatic, as opposed to tuberculocidal, such as *p*-aminosalicylic acid (PAS), typically lead to a lowering of one-half log CFU *versus* untreated controls (see Experimental). In comparing the data for **IIIa** and **IIIg** with the untreated controls, there has been a reduction of 1.00 log CFU or more in each case, suggesting that both compounds **IIIa** and **IIIg** are bactericidal in tuberculosis-infected mice. Overall, the results *in vitro* and *in vivo* warrant further development of the antitubercular properties of pyrroles derived from aromatic acid hydrazides.

In conclusion, we have found that 1-acylamino-2,5-dimethylpyrroles, of interest in the investigation of heterocyclic structures for their antitubercular activity, can be conveniently prepared from the reaction of acid hydrazides with hexane-2,5-dione in water or ethanol without an acid catalyst. In each case, the process leads to a single pyrrole in pure form, product isolation is straightforward, and the resulting compound is readily identified on the basis of highly characteristic spectrometric features. Some members of this class have useful activities against drug-resistant tuberculosis *in vitro* and offer excellent protection in an animal model of the disease.

## EXPERIMENTAL

**General methods.** Elemental analyses were carried out by Galbraith Laboratories, Knoxville, TN. Melting points (mp; °C) were taken in open capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) and are corrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Fourier transform spectrometer as KBr pellets or Nujol mulls or on a Perkin-Elmer Spectrum One Fourier transform spectrophotometer fitted with a universal attenuated total reflectance sampling accessory, reported in wavenumbers (ν, $cm^{-1}$). Most reactants, reagents, and solvents were obtained from Aldrich Chemical Company (Milwaukee, WI) and Lancaster Synthesis (Windham, NH) and were used as received. Methyl 4-aminosalicylate was purchased from Nantong Chang Chemicals, Peking, China. Nuclear magnetic resonance (NMR) spectra were taken on a Bruker 300 Fourier transform instrument as dilute solutions in dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) or chloroform-d, recorded at 300 MHz ($^1$H NMR) or 75 MHz ($^{13}$C NMR) and are reported in parts per million delta (δ) downfield from internal tetramethylsilane as reference, with coupling constants given in cycles per second (cps). In some proton spectra, only signals in the region 0–10 ppm are reported. Appropriate solvent blanks were recorded to account for water and DMSO. Gas chromatography (GC) and low-resolution mass spectrometry (LR-MS) analyses were recorded with an HP 5890 Series II Plus gas chromatograph, using a crosslinked 5% diphenyl- 95% dimethylsiloxane column from Hewlett Packard, and an HP 5972 electrical ionization mass detector. High-resolution mass spectroscopy (HR-MS) data were obtained using the JEOL HX-110 double focusing mass spectrometer of the Michigan State University Mass Spectrometry Facility, courtesy of Professor D. Gage and Ms. B. Chamberlin. This magnetic sector instrument is equipped with a fast atom bombardment (FAB) ionization source. It is capable of performing high-resolution (peak matching) and tandem mass spectrometry. Safety notes: gloves were worn during the chemical syntheses, and the reactions were carried out in the hood. In general, any scale up of preparations of compounds with relatively high proportions of nitrogen and oxygen was done with due caution. No specific safety problems were encountered with the methods given below. No attempt was made to optimize yields. To monitor the progress of the pyrrole-forming reactions, a thin-layer chromatography (TLC) system was devised. In general, we used plastic sheets coated with silica gel (Merck-Darmstadt), eluted with absolute ethanol, with starting materials the subjects of parallel reference runs. Details are given in individual procedures, where applicable, but typical $R_f$ values were 0.5 for the acid hydrazide and 0.8 for the acylaminopyrroles. The dione was not observed in these runs.

**Biological assessments.** *M. tuberculosis* ATCC 35801 (strain Erdman) was obtained from the American Type Culture Collection (ATCC, Manassas, VA). Drug-resistant clinical isolates of *M. tuberculosis* (isolates 303, 1889, and 35829) were kindly provided by Dr. Sheldon Morris, United States Food and Drug Administration. The mutational origins of the drug resistance of these organisms have been characterized and data are available from the authors upon request. PAS was a gift of Jacobus Pharmaceutical Company. INH was purchased from Sigma Chemical Company (St. Louis, MO). For testing, a given investigational compound was dissolved in dimethyl sulfoxide and subsequently diluted in distilled water. INH and PAS were dissolved in distilled water. Stock solutions were filter-sterilized by passage through a membrane filter 0.22-μm pore size and stored at -20°C until use. The drugs were prepared each morning, before experimentation. With respect to testing against these isolates, the MICs of all antimicrobial agents were determined in modified 7H10 broth (7H10 agar formulation with agar and malachite green omitted; pH 6.6) supplemented with 10% Middlebrook oleic acid-albumin-dextrose-catalase (OADC) enrichment (Difco Laboratories, Detroit, MI) and 0.05% Tween 80 [33]. The activities of the antimicrobial agents were determined by a broth dilution method [34]. The organism was grown in the modified 7H10 broth with 10% OADC enrichment and 0.05% Tween 80 on a rotary shaker at 37°C for 5 days. The culture suspension was diluted in modified 7H10 broth to yield 100 Klett units/mL (Photoelectric Colorimeter, Manostat Corporation, New York, NY), or approximately $5 \times 10^7$ CFU/mL. The size of the inoculum was determined by titration and counting from triplicate 7H10 agar plates (BBL Microbiology Systems, Cockeysville, MD) supplemented with 10% OADC enrichment. The plates were incubated at 37°C in ambient air for 4 weeks before counting of the colonies. MIC values are reproducible to within 1–2 dilutions. Results *in vitro* (strain $H_{37}R_v$) were also determined according to the fully-documented protocols of the Tuberculosis Antimicrobial Acquisition and Coordinating Facility, of the National Institutes of Health [35].

In brief, for the short-course therapy studies *in vivo*, 4-week-old female $C_{57}$BL/6 mice (Charles River, Wilmington, MA) were infected intranasally with approximately one million viable *M. tuberculosis* organisms. As a negative control, groups of infected but untreated mice were sacrificed at the initiation of therapy. The known antitubercular drug INH was used as a positive control. Treatment began 1 day post-infection and was administered for 2 days. The agents were introduced by gavage: the INH control and a given pyrrole were dosed daily at 25 and 100 mg/kg of body weight, respectively. No overt toxicity or ill effects were noted at these doses. Mice were sacrificed by carbon dioxide inhalation 3 days post-infection. Their right lungs were removed aseptically and were ground in a tissue homogenizer (IdeaWorks! Laboratory Devices, Syracuse, NY). The number of viable organisms was determined by titration on 7H10 agar plates. The plates were incubated at 37°C in ambient air for 4 weeks before counting of the bacterial colonies. Data are presented as the logarithms of colony-forming units. The complete procedure for the short-course therapy model has been reported [32] in detail. As standards of reference, such tuberculocidal drugs as INH generally display a drop of one or more log CFU versus untreated controls in the model. By way of contrast, PAS is tuberculostatic, as distinct from tuberculocidal, typically leading to a falling-off of one-half log CFU versus untreated controls. A typical data set for PAS is as follows: dose 500 mg PAS/kg/day, six mice per group, untreated controls 5.78 ± 0.38 log CFU, PAS 5.32 ± 0.22 log CFU, positive control (INH) 4.44 ± 0.62 log CFU. The use of experimental animals complied with institutional policies and federal guidelines.

**1-(4-Pyridoyl)amino-2,5-dimethylpyrrole (IIIa).** Isonicotinic acid hydrazide (0.82 g, 6 mmol) was dissolved in deionized distilled water (25 mL). 2,5-Hexanedione (0.68 g, 6 mmol) was added and the mixture was heated at a gentle boil with reflux for 2 h. The mixture was then allowed to cool

overnight, after which time crystals of **IIIa** formed in solution and were collected by vacuum filtration. The mother liquor was allowed to evaporate on a watch glass and the resulting crystals were collected separately. The total yield was 67%, mp 151–153°C; IR 3224, 3041, 2923, 1673, 1595, 1537, 1490, 1410, 1322, 1289; $^1$H NMR (DMSO-$d_6$) δ 11.5 (s, 1 H, disappeared after $D_2O$ shake), 8.8 (d, $J$ = 6 cps, 2 H), 7.9 (d, $J$ = 6 cps, 2 H), 5.7 (s, 2 H), 2.0 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) δ 165, 151, 139, 127, 122, 104, 11.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09. Found: C, 66.84; H, 6.18.

**1-Benzoylamino-2,5-dimethylpyrrole (IIIb).** Benzoic acid hydrazide (0.82 g, 6 mmol) was heated to boiling in 35 mL deionized, distilled water with reflux. 2,5-Hexanedione (0.82 g, 7.2 mmol) was dissolved in 10 mL deionized, distilled water and added drop wise to the reflux flask without ever halting boiling. Reflux continued for 23 h. After cooling, crystals of **IIIb** appeared in solution and were collected by vacuum filtration (89%). A second crop of crystals was harvested by evaporation of the mother liquor (combined yield 97%). After recrystallization in a mixed system of ethanol/water, crystals were clean, very fine, and just slightly off-white in color, mp 175–177°C; IR 3261, 3061, 2919, 1684, 1602, 1580, 1536, 1488, 1440, 1282; $^1$H NMR (DMSO-$d_6$) δ 11.3 (s, 1 H, quenched by $D_2O$), 8.0 (d, second peak split, $J$ = 6, 2 cps, 2 H), 7.7 (tt, $J$ = 6, 2 cps, 1 H), 7.5 (t, $J$ = 6 cps, 2 H), 5.7 (s, 2 H), 2.1 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) δ 166, 133, 132, 129, 128, 127, 103, 11; major fragments in LR-MS *m/z* 105, 94; HR-MS (fast atom bombardment, $MH^+$) calculated for $C_{13}H_{15}N_2O$ 215.1184, found 215.1174.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59. Found: C, 72.69; H, 6.61.

**1-(4-Chlorobenzoyl)amino-2,5-dimethylpyrrole (IIIc).** 4-Chlorobenzoic hydrazide (1.02 g, 6 mmol) was dissolved in absolute ethanol (100 mL) and heated to a gentle boil with reflux. 2,5-Hexanedione (0.82 g, 7.2 mmol) was dissolved in absolute ethanol (10 mL) and added dropwise to the hydrazide solution. Reflux was continued for 50 h, during which time no solid precipitated from solution. TLC was used to monitor reaction progress and showed gradual progression from 4-chlorobenzoic hydrazide ($R_f$ 0.5) to **IIIc** ($R_f$ 0.8). The mixture was cooled to room temperature and kept over night. Excess ethanol was boiled off and cold water added, causing the precipitation of white solid **IIIc**. After vacuum filtration and drying, this solid dissolved easily and cleanly in DMSO, yield 69%, consistently isolated as the hemihydrate and analyzed as such, mp 185°C with decomposition; IR 3449, 3274, 2998, 2961, 1656, 1623, 1594, 1521, 1483, 1448, 1299, 1272; $^1$H NMR (DMSO-$d_6$) δ 11.3 (s, 1 H, quenched with $D_2O$), 8.0 (dd, $J$ = 6, 2 cps, 2 H), 7.6 (dd, $J$ = 6, 2 cps, 2 H), 5.7 (s, 2 H), 2.0 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) δ 165, 137, 131, 130, 129, 128, 127, 104, 11; major fragments in LR-MS *m/z* 139, 94; HR-MS (fast atom bombardment $MH^+$) calculated for $C_{12}H_{14}N_2OCl$: 249.0795, found 249.0801.

Anal. Calcd. for $C_{12}H_{13}N_2OCl$ x $0.5H_2O$: C, 60.58; H, 5.48. Found: C, 60.29; H, 5.19.

**1-(4-Toluoyl)amino-2,5-dimethylpyrrole (IIId).** 4-Toluic acid hydrazide (0.90 g, 6 mmol) was reacted with 2,5-hexanedione (0.82 g, 7.2 mmol), in a manner similar to that for **IIIc**. Reflux continued for 70 h, during which TLC was used to track reaction progress and no solid appeared in solution. After 70 h, TLC (silica gel, absolute ethanol) showed no remaining traces of the 4-toluic hydrazide. The reaction mixture was allowed to cool and placed on ice. To the reaction mixture on ice was added 50 mL of cold water, provoking the gradual precipitation of **IIId**. An additional 100 mL of cold water was necessary to keep the solution thin enough to pour into the filter. Vacuum filtration of the precipitate yielded tiny, fluffy, off-white crystals, 1.25 g (91%); mp 187–189°C; IR 3281, 2980, 2935, 1665, 1610, 1531, 1491, 1324, 1301, 1276; $^1$H NMR (DMSO-$d_6$) δ 11.2 (s, 1 H, quenched with $D_2O$), 7.9 (d, $J$ = 6 cps, 2 H), 7.4 (d, $J$ = 6 cps, 2 H), 5.7 (s, 2 H), 2.4 (s, 3 H), 2.0 (s, 6 H); $^{13}$C NMR (DMSO- $d_6$) δ 166, 143, 130, 129, 128, 127, 103, 22, 11; major fragments in LR-MS *m/z* 119, 94; HR-MS (fast atom bombardment $MH^+$) calculated for $C_{14}H_{17}N_2O$ 229.1341, found 229.1337.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06. Found: C, 73.76; H, 7.13.

**1-(4-Bromobenzoyl)amino-2,5-dimethylpyrrole (IIIe).** 4-Bromobenzoic hydrazide (1.29 g, 6 mmol) was reacted with 2,5-hexanedione (0.82 g, 7.2 mmol) in the manner described for the synthesis of **IIIc**. After 1 h of reflux, a fine suspended solid clouded the mixture, which the addition of 100 mL ethanol did not clear. The solid was not filterable from the reaction mixture. TLC analysis (silica gel, absolute ethanol) revealed a mixture of three species: 4-bromobenzoic hydrazide ($R_f$ 0.5), **IIIe** ($R_f$ 0.8), and a third compound ($R_f$ 0.7) postulated to be a reactive intermediate, as suggested in the work of Amarnath et al. [36] for a different family of pyrroles. After 27 h of reflux, the solid had disappeared, and TLC monitoring began to show a preponderance of **IIIe**, with small amounts of the other two compounds still present. Reflux was stopped after 47 h, no solid having reappeared in the intervening day. Crystals were precipitated from solution by the addition of cold water to the reaction mixture on ice, with a total yield of 1.34 g (77%); mp 207–210°C; IR 3246, 1660, 1588, 1534, 1521, 1465, 1377, 1322, 1300, 1268; $^1$H NMR (DMSO-$d_6$) δ 11.3 (s, 1 H, quenched with $D_2O$), 7.9 (dd, $J$ = 6, 2 cps, 2 H), 7.8 (dd, $J$ = 6, 2 cps, 2 H), 5.7 (s, 2 H), 2.0 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) 165, 132, 131, 130, 127, 126, 104, 11; major fragment in LR-MS *m/z* 94; HR-MS (fast atom bombardment $MH^+$) calculated for $C_{13}H_{14}N_2OBr$ 293.0290, found 293.0281.

Anal. Calculated for $C_{13}H_{13}N_2OBr$: C, 53.26; H, 4.47. Found: C, 53.36; H, 4.57.

**1-(4-Nitrobenzoyl)amino-2,5-dimethylpyrrole (IIIf).** 4-Nitrobenzoic hydrazide (1.09 g, 6 mmol) was reacted with 2,5-hexanedione (0.82 g, 7.2 mmol) following the procedure for the synthesis of **(IIIc)**. Solid clouded the reflux solution after 1 h; addition of 100 mL ethanol did not improve homogeneity. After 66 h, cloudiness persisted but TLC analysis revealed the material present to be entirely **IIIf**, with no traces of starting material or an intermediate. Reflux was stopped, and the solution was filtered while hot. After cooling, cold water was used to provoke the precipitation of **IIIf** from the mother liquor, with a yield of 1.16 g (75%); mp 218–221°C (recrystallization from ethanol and water); IR 3278, 1674, 1604, 1523, 1468, 1343, 1270; $^1$H NMR (DMSO-$d_6$) δ 11.3 (s, 1 H, quenched with $D_2O$), 8.4 (dd, $J$ = 6, 2 cps, 2 H), 8.2 (dd, $J$ = 6, 2 cps, 2 H), 5.7 (s, 2 H), 2.1 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) δ 165, 150, 138, 129, 127, 124, 104, 11; major fragment in LR-MS m/z 94; HR-MS (fast atom bombardment $MH^+$) calculated for $C_{13}H_{14}N_3O_3$ 258.0879, found 258.0876.

Anal. Calculated for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05. Found: C, 60.30; H, 5.17.

**1-(4-Aminosalicyloyl)amino-2,5-dimethylpyrrole (IIIg).** 4-Aminosalicylic acid hydrazide (ASAH) was obtained (58%) in pure form from the hydrazinolysis of methyl 4-aminosalicylate by a method that we have previously described in detail [37]. ASAH thus obtained (1.67 g, 10.0 mmoles) was weighed into a 100 mL round-bottom flask fitted for reflux with a temperature-controlled heating mantle, reflux condenser, and magnetic stirrer. Deionized distilled water (25 mL) was added, and the mixture was brought to the boil. Just below the boiling point, the mixture was heterogeneous, but a clear solution was obtained at the boiling point. 2,5-Hexanedione (1.14 g, 10.0 mmoles) was added and the mixture was refluxed for 2 h. Heating was stopped, and stirring was continued for an hour as the mixture slowly cooled. The resulting white solid was filtered off to provide the title compound **IIIg** (0.722 g, 30%), mp 173–174°C; IR 3371, 3270, 1612, 1494, 1385, 1334, 1312, 1270, 1200, 1161, 1012, 967, 833, 786, 757, 692; $^1$H NMR (DMSO-$d_6$) δ 12.1 (s, 1H), 10.9 (s, 1H), 7.6 (d, $J = 7$ cps, 1H), 6.2 (d, $J = 7$ cps, 1H), 6.1–6.0 (overlapping s, 3H), 5.7 (s, 2H), 2.0 (s, 6H); $^{13}$C NMR (DMSO-$d_6$) δ 169, 162, 155, 129, 127, 106, 103, 101, 99, 11; HR-MS (fast atom bombardment $MH^+$) calculated for $C_{13}H_{16}N_3O_2$ 246.1243, found 246.1244.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16. Found: C, 63.48; H, 6.28.

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## REFERENCES AND NOTES

[1] Di Perri, G.; Bonora, S. J Antimicrob Chemother 2004, 54, 593.

[2] World Health Organization. TB: A global emergency; Geneva, Switzerland, 1994; Report No. 14977.

[3] Hampton, T. JAMA 2004, 291, 2529.

[4] Global Alliance for Tuberculosis Drug Development. Scientific blueprint for TB drug development, 2001. Available at: www.tballiance.org/downloads/publications/TBA_Scientific_Blueprint.pdf. Accessed July 6, 2009.

[5] Cahn, P.; Perez, H.; Ben, G.; Ochoa, C. J Int Assoc Physicians AIDS Care 2003, 2, 106.

[6] Laughon, B. Curr Topics Med Chem 2007, 7, 463.

[7] Barry, C. E. Issues Infect Dis 2003, 2, 137.

[8] Davies, P.; Yew, W. Expert Opin Ther Targets 2003, 12, 1297.

[9] Miesel, L.; Rozwarski, D.; Sacchettini, J.; Jacobs, W. In Genetics and Tuberculosis, Novartis Foundation Symposia; Chadwick, D. J., Ed.; Wiley: Chichester, England, 1998; pp 209–227.

[10] Billington, D.; Coleman, M.; Ibiabuo, J.; Lambert, P.; Rathbone, D.; Tims, K. Drug Des Discov 1998, 15, 269.

[11] Pathak, A.; Pathak, V.; Seitz, L.; Suling, W.; Reynolds, R. J Med Chem 2004, 47, 273.

[12] Janin, Y. Bioorg Med Chem 2007, 15, 2479.

[13] de Souza, M.; Pais, K.; Kaiser, C.; Peralta, M.; Ferreira, M. L.; Lourenço, M. C. S. Bioorg Med Chem 2009, 17, 1474.

[14] Hearn, M. J.; Webster, E. R.; Cynamon, M. H. J Heterocycl Chem 2005, 42, 1225.

[15] Hearn, M. J.; Chanyaputhipong, P. J Heterocycl Chem 1995, 32, 1647.

[16] Youmans, G.; Doub, L.; Youmans, A. The Bacteriostatic Activity of 3500 Organic Compounds for *Mycobacterium tuberculosis var. hominis*; Chemical-Biological Coordination Center, National Research Council: Washington, DC, 1953; compound 2603.

[17] Cymerman-Craig, J.; Willis, D. J Chem Soc 1955, 4315.

[18] Gazave, J.; Buu-Hoi, N.; Xuong, N.; Mallet, J.; Pillot, J.; Savel, J.; Dufraisse, G. Therapie 1957, 12, 486.

[19] Yale, H.; Losee, K.; Martins, J.; Holsing, M.; Perry, F.; Bernstein, J. J Am Chem Soc 1953, 75, 1933.

[20] Zsolnai, T. Zentralblatt fuer Bakteriologie, Parasitenkunde, Infektionskrankheit und Hygiene, Abteilung 1: Medizinisch-Hygienische Bakteriologie, Virusforschung und Parasitologie, Orginale 1959, 175, 269.

[21] Hearn, M. J.; Terrot, M. S. Abstracts of Papers, American Chemical Society 221st National Meeting, San Diego, California, 2001, CHED-156.

[22] Bijev, A. Arzneimittelforschung 2009, 59, 34.

[23] Arora, S.; Sinha, N.; Sinha, R.; Uppadhayaya, R.; Modak, V.; Tilekar, A. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2004; Abstract Number F-1115.

[24] Biava, M.; Porretta, G. C.; Poce, G.; Logu, A. D.; Saddi, M.; Meleddu, R.; Manetti, F.; Rossi, E. D.; Botta, M. J Med Chem 2008, 51, 3644.

[25] Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Molicotti, P.; Manetti, F.; Botta, M. J Med Chem 2006, 49, 4946.

[26] Paal-Knorr Synthesis. In The Organic Chemistry Portal, 2009. Available at: www.organic-chemistry.org/namedreactions/paal-knorr-pyrrole-synthesis.shtm. Accessed July 31, 2009.

[27] Bellina, F.; Rossi, R. Tetrahedron 2006, 62, 7213.

[28] Buu-Hoi, N.; Xuong, N. J Org Chem 1955, 20, 850.

[29] Banik, B.; Samajdar, S.; Banik, I. J Org Chem 2004, 69, 213.

[30] Just, P. E.; Chane-Ching, K. I.; Lacaze, P. C. Tetrahedron 2002, 58, 3467.

[31] Global Alliance for Tuberculosis Drug Development.Tuberculosis 2008, 88, 85.

[32] Shoen, C.; DeStefano, M.; Sklaney, M.; Monica, B.; Slee, A.; Cynamon, M. J Antimicrob Chemother 2004, 53, 641.

[33] Vestal, A. L. Procedures for the Isolation and Identification of Mycobacteria; Laboratory Division, National Communicable Disease Center, Public Health Service: Atlanta, Georgia, 1969; publication number 1995, pp 113–115.

[34] Wong, C. S.; Palmer, G. S.; Cynamon, M. H. J Antimicrob Chemother 1988, 22, 863.

[35] Secrist, J.; Anathan, S.; Kwong, C.; Maddry, J.; Reynolds, R.; Poffenberger, A.; Michael, M.; Miller, L.; Krahenbuhl, J.; Adams, L.; Biswas, A.; Franzblau, S.; Rouse, D.; Winfield, D.; Brooks, J.; Orme, I. Antimicrob Agents Chemother 2001, 45, 1943.

[36] Amarnath, V.; Amarnath, K.; Valentine, W.; Eng, M.; Graham, D. Chem Res Toxicol 1995, 8, 234.

[37] Hearn, M. J.; Chen, M. F.; Cynamon, M. H.; Wang'ondu, R.; Webster, E. R. J Sulfur Chem 2006, 27, 149.

# Synthesis and Bio-Activity of Alkyl/Aryl [2-(1,2,4,5-Tetrahydro-3-Sulfanylene/Selenylene Naphtha[1,8][1,5,3]diazaphosphocin-3-yl)methyl Amino Acid Esters]



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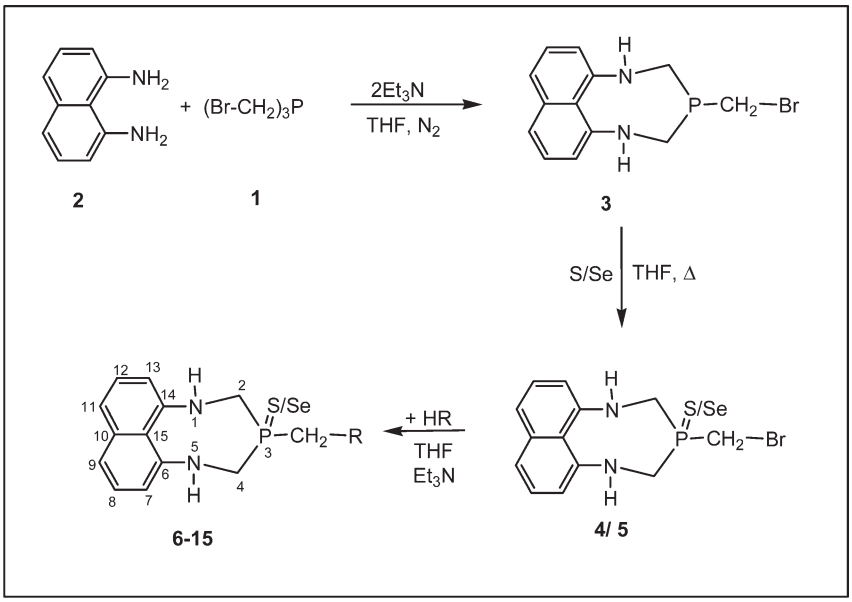


Synthesis of alkyl/aryl [2-(1,2,4,5-tetrahydro-3-sulfanylene/selenylene naphtha[1,8-*f*,*g*][1,5,3]diazaphosphocin-3-yl) methyl amino acid esters] (**6–15**) was accomplished in three steps. 1, 8-diamino naphthalene (**2**) was reacted with tris (bromomethyl) phosphine (**1**) in the presence of triethylamine in dry tetrahydrofuran (THF) under $N_2$ atmosphere to form a $P_{III}$ intermediate (**3**). It was converted to the corresponding sulfide (**4**) and selenide (**5**) by reacting with sulfur and selenium, respectively. The intermediates **4** and **5** were further reacted with amino acid esters to obtain the title compounds (**6–15**). The structures of the title compounds were established by elemental analysis and spectral data (IR, $^1$H, $^{13}$C, $^{31}$P NMR, and FAB mass). The antimicrobial activity of these compounds was evaluated and they exhibited significant activity.

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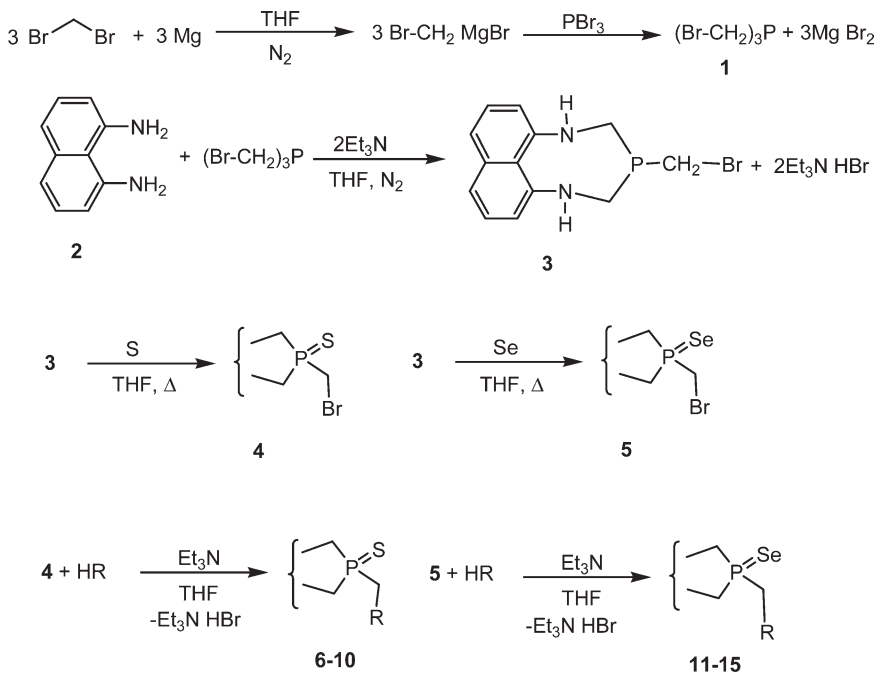
## INTRODUCTION

Organophosphate moiety is an important pharmacophore in agricultural and pharmaceutical chemistry [1]. Phosphocin/phosphepin and their related derivatives containing this group represent an important class of pesticides, antibiotics, herbicides, and antiviral agents [2]. Some of them are well known for their insecticidal activities [3] and are known to degrade hydrolytically and enzymatically to nontoxic residues. Discovery of their fungicidal properties also promotes interest in this research area. New chiral phosphorus ligands play vital role in asymmetric synthesis [4–8]. Synthesis of eight-membered phosphorus heterocyclic compounds, phosphocins have currently gained considerable interest in the polymer and oil industry because of their potential use as antioxidants and stabilizers, considerable research work is going on in the chemistry of the phosphocins [9,10]. Keeping in view the importance of eight-membered organophosphorus heterocyclic compounds, we herein report the synthesis, spectral characterization, and antimicrobial activity of the title compounds.

## RESULTS AND DISCUSSION

Preparation of a few eight-membered phosphorus heterocyclic compounds such as alkyl/aryl [2-(1,2,4,5-tetrahydro-3-sulfanylene/selenylene naphtha[1,8-*f*,*g*][1,5,3]diazaphosphocin-3-yl) methyl amino acid esters] (**6–15**) was accomplished in three steps. The synthetic

**Scheme 1**

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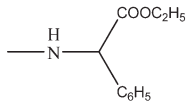
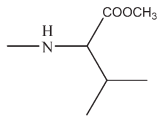
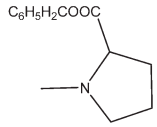
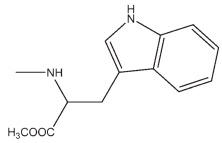
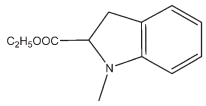
| 6 & 11 |  |
| 7 & 12 |  |
| 8 & 13 |  |
| 9 & 14 |  |
| 10 & 15 |  |

route (Scheme 1) involves the cyclization of equimolar quantities of 1,8-diamino naphthalene (**2**) with tris (bromomethyl) phosphine (**1**) in the presence of triethylamine in dry tetrahydrofuran (THF) under $N_2$ atmosphere to form the corresponding $P_{III}$ intermediate, 3-(bromomethyl)-1,2,4,5,-tetrahydro-1*H*-naphtho[1,8-

**Table 1**

Physical, IR, and $^{31}$P NMR spectral data of the compounds **6–15**.

| Compd. | Molecular formula | MP (°C) | Yield % | Elemental analysis % Found (Calcd.) | | | IR cm$^{-1}$ | | | $^{31}$P NMR |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | NH | P=S/Se | P—$C_{alip}$ | |
| **6** | $C_{23}H_{26}N_3O_2PS$ | 182–184 | 72 | 62.75 (62.84) | 5.90 (5.96) | 9.53 (9.56) | 3425 | 759 | 738 | 41.10 |
| **7** | $C_{19}H_{26}N_3O_2PS$ | 187–189 | 69 | 58.20 (58.28) | 6.65 (6.69) | 10.69 (10.74) | 3402 | 776 | 735 | 41.07 |
| **8** | $C_{25}H_{28}N_3O_2PS$ | 193–195 | 73 | 64.44 (64.49) | 6.04 (6.06) | 8.97 (9.03) | 3409 | 764 | 737 | 41.13 |
| **9** | $C_{25}H_{27}N_4O_2PS$ | 186–188 | 71 | 62.71 (62.75) | 5.67 (5.69) | 11.68 (11.71) | 3429 | 769 | 743 | 41.17 |
| **10** | $C_{24}H_{26}N_3O_2PS$ | 177–179 | 72 | 63.75 (63.83) | 5.75 (5.80) | 9.28 (9.31) | 3417 | 772 | 717 | 42.18 |
| **11** | $C_{23}H_{26}N_3O_2PSe$ | 192–194 | 64 | 56.60 (56.66) | 5.34 (5.37) | 8.58 (8.62) | 3410 | 625 | 719 | 83.19 |
| **12** | $C_{19}H_{26}N_3O_2PSe$ | 189–191 | 61 | 51.84 (51.92) | 5.92 (5.96) | 9.51 (9.56) | 3412 | 637 | 729 | 83.17 |
| **13** | $C_{25}H_{28}N_3O_2PSe$ | 187–189 | 69 | 58.40 (58.46) | 5.44 (5.49) | 8.13 (8.18) | 3404 | 629 | 752 | 82.45 |
| **14** | $C_{25}H_{27}N_4O_2PSe$ | 182–185 | 65 | 57.11 (57.15) | 5.15 (5.18) | 10.62 (10.66) | 3395 | 634 | 758 | 86.17 |
| **15** | $C_{24}H_{26}N_3O_2PSe$ | 179–181 | 66 | 57.63 (57.70) | 5.27 (5.25) | 8.35 (8.41) | 3405 | 627 | 753 | 86.14 |

*f*,*g*][1,5,3]diazaphosphocine (**3**). It was converted to the corresponding sulfide (**4**) and selenide (**5**) by reacting with sulfur and selenium, respectively. The compounds **4** and **5** were further reacted with amino acid esters in the presence of triethylamine in dry THF to obtain the title compounds (**6–15**) (Scheme 1) and mass fragments of compound **7** are given (Scheme 2).

The physical, elemental analyses, IR, and $^{31}$P NMR data of the compounds **6–15** are given in the Table 1. Compounds **6–15** exhibited characteristic P=S/Se stretching frequencies in the region 759–776 (P=S) and 625-637 (P=Se) cm$^{-1}$ [11]. Characteristic absorption bands for P—C $_{(aliphatic)}$ and N—H stretching vibrations were observed in the regions 717–758 and 3395–3429 cm$^{-1}$, respectively [12]. In the $^1$H NMR spectra, aromatic protons of the naphthyl ring of the **6–15** gave complex multiplets [13] in the region 6.53–7.17 ppm. The N—H proton resonated as a broad singlet at δ 4.02–4.18. The other aliphatic protons of **6–15** were observed in the expected region (Table 2). $^{13}$C NMR chemical shifts for aromatic carbons were observed in the expected region (Table 3). C-2 and C-4 which are directly linked to phosphorus experienced coupling with it and appeared as doublet in the region δ 54.21–55.26 ($J$ = 126–132 Hz). The carbons of amino acid esters resonated in the expected region [13].

The $^{31}$P NMR chemical shifts of 3-sulfides (**6–10**) appeared in the region 41.07–42.18 and the corresponding 3-selenides (**11–15**) were observed in the region

**Table 2**

$^1$H NMR spectral data[a] of the compounds **6–15**.

| Compd. | Ar—H | NH | P—$CH_2$—R |
|---|---|---|---|
| **6** | 6.54–7.17 (m, 11H) | 4.07 (br s) | 2.60–3.10 (m, 6H, $CH_2$-P(S)), 4.74 (d, 1H, *CH* Ar) ($J$ = 8.1 Hz), 4.12 (q, 2H, O—*$CH_2$*—$CH_3$), 1.30(t, 3H, O—$CH_2$—*$CH_3$*)($J$ = 6.2 Hz) |
| **7** | 6.54–7.10 (m, 6H) | 4.04 (br s) | 2.68–3.12 (m, 6H, $CH_2$—P(S)), 3.44 (t, 1H NH—*CH*), ($J$ = 6.1 Hz), 2.70 (m, 1H, —*CH*— $(CH_3)_2$), 1.01(d, 6H, CH—*$CH_3$*) ($J$ = 8.1Hz), 3.67(s, 3H, COO—*$CH_3$*) |
| **8** | 6.56–7.12 (m, 11H) | 4.09 (br s) | 2.61–3.15 (m, 6H, $CH_2$-P(S)), 2.60 (t, 2H, N—*$CH_2$*—$CH_2$ ) ($J$ = 6.2 Hz ), 2.60 (t, 2H N-$CH_2$—*$CH_2$* ) ($J$ = 6.1 Hz), 3.28 (t, 1H, N—*CH*—CO— 2.60 (t, 2H N—CH—*$CH_2$* ) ($J$ = 6.3 Hz). 3.67(s, 2H, Ar-*$CH_2$*) |
| **9** | 6.55–7.14 (m, 11H) | 4.02 (br s) | 2.65-3.40 (m, 6H, $CH_2$-P(S)), 3.45 ( d, 2H *$CH_2$*-CH) ($J$ = 8.0 Hz ) 3.26 (d, 1H $CH_2$—*CH*) ($J$ = 8.2 Hz), 4.12 (s, 3H COO*$CH_3$*). |
| **10** | 6.54–7.13 (m, 10H) | 4.12 (br s) | 3.10–3.40 (m, 6H, $CH_2$—P(S)), 3.26 (t, 1H *CH*—CO) ($J$ = 6.2 Hz), 3.84 (d, 2H, CH—*$CH_2$*) ($J$ = 8.1 Hz), 4.12(q, 2H, *$CH_2$*—$CH_3$), 1.30(t, 3H, $CH_2$—*$CH_3$*) ($J$ = 6.1 Hz). |
| **11** | 6.54–7.14 (m, 11H) | 4.11 (br s) | 2.61–3.12 (m, 6H, $CH_2$-P(S)), 4.76 (d, 1H *CH*Ar) ($J$ = 8.2 Hz), 4.14 (q, 2H, O-*$CH_2$*—$CH_3$), 1.31(t, 3H, O—$CH_2$—*$CH_3$*) ($J$ = 6.3 Hz) |
| **12** | 6.53–7.10 (m, 6H)) | 4.05 (br s) | 2.60–3.10 (m, 6H, $CH_2$—P(S)), 3.46 (t, 1H, NH—*CH*) ($J$ = 6.1 Hz), 2.72 (m, 1H, O—*CH*— $(CH_3)_2$). 1.03 (d, 6H, CH—*$CH_3$*) ($J$ = 8.3 Hz), 3.68(s, 3H, COO—*$CH_3$*) |
| **13** | 6.56–7.10 (m, 11H) | 4.18 (br s) | 2.64–3.14 (m, 6H, $CH_2$—P(S)), 2.62 (t, 2H, N—*$CH_2$*—$CH_2$ ) ($J$ = 6.2Hz ), 2.61 (t, 2H N—$CH_2$—*$CH_2$* ) ($J$ = 6.1 Hz), 3.25 (t, 1H, N—*CH*—CO— 2.62 (t, 2H N—CH—*$CH_2$* ) ($J$ = 6.2 Hz), 3.69 (s, 2H, Ar—*$CH_2$*) |
| **14** | 6.52–7.14 (m, 11H) | 4.02 (br s) | 2.64–3.42 (m, 6H, $CH_2$—P(S)), 3.46( d, 2H, *$CH_2$*—CH) ($J$ = 8.1 Hz ), 3.24 (d, 1H $CH_2$—*CH*) ($J$ = 8.2 Hz), 4.13 (s, 3H COO*$CH_3$*) |
| **15** | 6.55–7.13 (m, 10H) | 4.07 (br s) | 3.12–3.42 (m, 6H, $CH_2$—P(S)), 3.25 (t, 1H, *CH*—CO) ($J$ = 6.1 Hz), 3.83 (d, 2H, CH—*$CH_2$*) ($J$ = 8.2 Hz), 4.14(q, 2H, *$CH_2$*—$CH_3$), 1.32 (t, 3H, $CH_2$—*$CH_3$*) ($J$ = 6.2 Hz) |

[a] Recorded in DMSO $d_6$, and $J$ (Hz) given in parentheses.

**Table 3**

$^{13}$C NMR spectral data[a] of compounds **6, 7, 13**, and **14.**

| | **6** | **7** | **13** | **14** |
|---|---|---|---|---|
| $C_7$ and $C_{13}$ | 110.3 | 111.3 | 111.2 | 111.3 |
| $C_8$ and $C_{12}$ | 128.9 | 124.9 | 131.5 | 130.8 |
| $C_9$ and $C_{11}$ | 115.9 | 115.8 | 130.6 | 130.3 |
| C-10 | 132.8 | 132.8 | 129.9 | 129.8 |
| C-15 | 111.9 | 112.1 | 106.2 | 106.2 |
| C-6 and C-14 | 144.2 | 144.2 | 142.9 | 142.9 |
| $C_2$ and $C_4$ | 46.4 ($J$ = 128 Hz) | 47.1 ($J$ = 126 Hz) | 46.8 ($J$ = 132 Hz) | 46.7 ($J$ = 130 Hz) |
| (S)P—*C*H$_2$—NH | 54.9 ($J$ = 120 Hz) | 54.6 ($J$ = 122 Hz) | 54.3 ($J$ = 121 Hz) | 54.3 ($J$ = 124 Hz) |
| O—*C*H$_2$CH$_3$/O—*C*H$_3$/O—*C*H$_2$-Ph | 62.9 | 56.9 | 65.8 | 54.1 |
| O—CH$_2$*C*H$_3$ | 14.6 | – | – | – |
| $C_1^1$ | 135.8 | – | 139.5 | 140.3 |
| $C_2^1$ and $C_6^1$ | 128.8 | – | 127.7 | 122.8 |
| $C_3^1$ and $C_5^1$ | 129.8 | – | 129.1 | 149.7 |
| $C_4^1$ | 127.5 | – | 127.5 | 120.7 |
| NH—*C*H—CO | 70.2 | 70.9 | – | 62.2 |
| *C*H(CH$_3$)$_2$ | 30.7 | – | – | – |
| CH(*C*H$_3$)$_2$ | 17.8 | – | – | – |
| *C*OOCH$_3$ | 171.6 | – | – | – |
| COO*C*H$_3$ | 51.9 | – | – | – |
| N—*C*H$_2$—CH$_2$ | – | – | 56.5 | – |
| N—CH$_2$—*C*H$_2$ | – | – | 22.8 | – |
| N—CH—*C*H$_2$ | – | – | 29.1 | – |
| N—*C*H—CH$_2$ | – | – | 65.8 | – |
| NH—CH—*C*O | – | – | 171.6 | 172.8 |
| NH—*C*H—CO | – | – | – | 63.1 |
| O—*C*H$_2$—Ar | – | – | 68.5 | – |
| —NH—*C*H—C | – | – | – | 122.9 |
| —NH—CH—*C* | – | – | – | 112.1 |

[a] Recorded in DMSO $d_6$, and $J$ (Hz) given in parentheses

82.45–86.17 ppm as expected [14]. Mass spectral data of compounds **7** and **11** are given (Table 4).

## ANTIMICROIBIAL ACTIVITY

The compounds **6–15** were screened by disc diffusion method [15,16] for their antimicrobial activity against the fungi, *Aspergillus niger* and *Helminthosporium oryzae* and bacteria, *Escherichia coli* and *Staphylococcus aureus* by comparing with standard fungicide Griseofulvin and standard bactericide Penicillin at three different concentrations (100, 75, 50 ppm). The results are presented in Table 5.

## EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Microanalysis was performed at the Indian Institute of Science, Bangalore and Central Drug Research Institute, Lucknow. IR Spectra were recorded in Environmental Engineering Lab, S.V.University, Tirupati as KBr discs on a Nicolet 380 FTIR spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for $^1$H, 100 MHz for $^{13}$C and 161.9 MHz for $^{31}$P. The compounds were dissolved in DMSO-$d_6$. The $^1$H and $^{13}$C NMR chemical shifts were referenced to tetramethylsilane and $^{31}$P chemical shifts to 85% $H_3PO_4$. Mass spectra were recorded on a Jeol SX 102 DA/600 mass spectrometer using Argon/Xenon (6 keV, 10 mA) as the FAB gas.

**Preparation of tris (bromomethyl) phosphine (1).** Because of the sensitivity of the reagents and products to moisture and oxygen, all manipulations were performed in an anhydrous inert nitrogen atmosphere. In a dry 100 mL three-necked round bottomed flask fitted with dropping funnel, a reflux condenser attached to a calcium chloride tube, an inlet for dry nitrogen and a thermometer reaching close to the bottom in the flask were placed magnesium turnings (0.12 g, 0.005 mole) and dry THF (5.0 mL). The reaction mixture was kept under stirring and dibromo methane (0.78 g, 0.005 moles) in 10 mL of dry THF was added drop wise at 10–15°C. When the reaction started the temperature increased to 40–50°C. The mixture was cooled to room temperature and stirring was

**Table 4**

Mass spectral data of compounds **7** and **11**.

| Compd. | m/z (% relative abundance) |
|---|---|
| **7** | 391[$M^{+\bullet}$, 20], 277 (53), 261 (100), 219 (35), 184 (09), 155 (25), 126 (45), 73 (36) |
| **11** | 487[$M^{+\bullet}$, 19], 327 (26), 311 (56), 269 (100), 184 (13), 155 (29), 126 (81), 79 (19) |

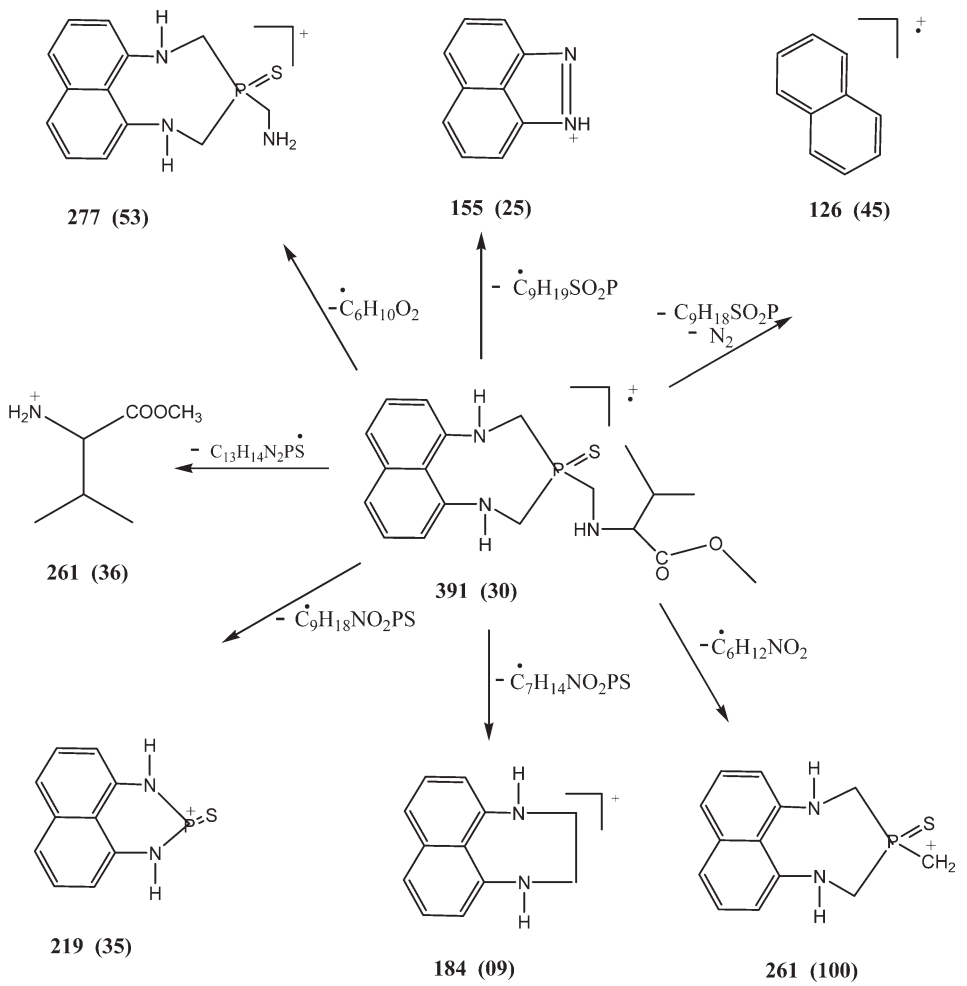
**Table 5**

Antimicrobial activity of the compounds **6–15.**

| | Zone of inhibition (%) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Escherichia coli* | | | *Staphylococcus aureus* | | | *Aspergillus niger* | | | *Helminthosporium oryzae* | | |
| Compound | 100 | 75 | 50 | 100 | 75 | 50 | 100 | 75 | 50 | 100 | 75 | 50 |
| **6** | 23 | 11 | 6 | 24 | 11 | 7 | 15 | 10 | 7 | 14 | 9 | 5 |
| **7** | 23 | 10 | 4 | 23 | 11 | 6 | 19 | 9 | 6 | 15 | 7 | 3 |
| **8** | 23 | 12 | 5 | 21 | 10 | 6 | 19 | 10 | 5 | 14 | 6 | 6 |
| **9** | 22 | 10 | 5 | 22 | 9 | 5 | 20 | 12 | 4 | 14 | 9 | 5 |
| **10** | 22 | 11 | 6 | 21 | 12 | 6 | 18 | 11 | 6 | 13 | 7 | 4 |
| **11** | 21 | 13 | 7 | 21 | 10 | 5 | 21 | 11 | 6 | 19 | 10 | 7 |
| **12** | 23 | 10 | 5 | 20 | 10 | 6 | 20 | 10 | 5 | 20 | 11 | 6 |
| **13** | 20 | 12 | 6 | 22 | 12 | 7 | 19 | 9 | 4 | 18 | 10 | 5 |
| **14** | 21 | 10 | 5 | 23 | 13 | 6 | 20 | 11 | 7 | 13 | 8 | 4 |
| **15** | 23 | 11 | 6 | 22 | 10 | 5 | 18 | 12 | 6 | 19 | 12 | 8 |
| Penicillin | 20 | 12 | 8 | 20 | 12 | 8 | | | | | | |
| Griseofulvin | | | | | | | 20 | 10 | 5 | 20 | 10 | 5 |

continued until the magnesium metal was dissolved to form bromo methyl magnesium bromide. It is further reacted with $PBr_3$ to form tris (bromo methyl) phosphine and magnesium bromide salt. The magnesium bromide salt was separated by filtration under nitrogen atmosphere and the solvent was distilled off to get tris (bromo methyl) phosphine (**1**).

**Scheme 2**



**3-(Bromomethyl)-2,3,4,5-tetrahydro-1*H*-naphtho [1, 8-*f*, *g*][1,5,3]diazaphosphocine (3).** To a cooled (10°C) and stirred solution of 1,8-diaminonaphthalene (**2**, 0.69 g, 0.005 mole) and triethyl amine (1.01g, 0.01 mole) in 10 mL of dry THF under nitrogen gas, a solution of tris (bromo methyl) phosphine(**1**, 1.35 g, 0.005 mole) in 10 mL of dry THF was added over a period of 20 min. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for 1 h to form the intermediate (**3**).The progress of the reaction was judged by the TLC analysis. After completion of the reaction, it was filtered under nitrogen atmosphere and removed triethylamine hydrobromide.

**3-(Bromomethyl)-1,2,4,5-tetrahydro-3-sulfanylene/selenylene-1*H*-naphtho[1,8- *f*,*g*][1,5,3]diazaphosphocine (4/5).** The intermediate (3) in dry THF was cooled to 5°C, sulfur powder/ selenium metal was added to it and heated slowly up to gentle reflux with stirring and continued for 2 h for the completion of the reaction as indicated by TLC analysis. The solvent was removed in a rota-evaporator and the residue was extracted with ethyl acetate. The extract after drying over anhydrous $MgSO_4$ was removed in a rota- evaporator. The obtained crude products (4 and 5) were purified by column chromatography (hexane-ethylacetate 2:1) to yield 1.20 and 1.30 g (59, 70%) of 4 and 5, m.p. 180–182°C, 156–158°C, respectively.

**General procedure for the preparation of 6–15.** To the intermediate (**4**) in dry THF, phenyl glycine ethyl ester in dry THF (10 mL) was added in the presence of tri ethylamine at 10–15°C over a period of 30 min. After the addition, temperature of the reaction mixture was slowly raised to 30–35°C and continued stirring. The progress of the reaction was monitored by the TLC analysis. After completion of the reaction, Et3N.HBr was separated by filtration and the solvent was removed from the filtrate in a rota-evaporator. The resulting crude product was recrystallized from 2-propanol to obtain pure compound of **6**. The same procedure was adopted for the preparation of other compounds **7–15**.

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## REFERENCES AND NOTES

[1] Demir, A. S.; Tanyeli, C.; Sesenoglu, O.; Demic, S.; Evin, O. Tetrahedron Lett 1996, 37, 404.

[2] Vasu Goverdhana Reddy, P.; Hari Babu, Y.; Suresh Reddy, C.; Srinivasulu, D. Heteroatom Chem 2002, 13, 340.

[3] Schrader, G. Die insektiziden Angew Chem 1957, 69, 86.

[4] Chi, Y.; Zhang, X. Tetrahedron Lett 2002, 43, 4849.

[5] Reetz, M. T.; Mehler, G. Angew Chem. Int Ed 2000, 39, 3889.

[6] Ojima, I., Ed. Catalytic Asymmetric Synthesis; VCH: New York, 2000.

[7] Nayori, R. Asymmetric Catalysis in Organic Synthesis; Wiley: New York, 1994.

[8] Li, G. Y.; Fagan, P. J.; Watson, P.-L. Angew Chem. Int Ed 2001, 40, 1106.

[9] (a) Spivack, J. D. Brit Pat 1984, 2087399; (b) Chem Abstr 1982, 97, 198374.

[10] Odorisio, P. A.; Paster, S. D.; Spivack, J. D. Phosphorus Sulfur,1984, 20, 273.

[11] Thomas, L. C.; Chittenden, R. A. Chem Ind (London) 1961, 1913.

[12] Thomas, L. C. Interpretation of the Infrared Spectra of Organophosphorus Compounds; Heydon; London, 1974.

[13] Silverstein, R. M.; Webster, F. X. Spectrometric Identification of Organic Compounds, 6th ed.; Wiley: New York, 1998.

[14] Quin, L. D.; Verkade, J. G. Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis; VCH: New York, 1994.

[15] Umamaheswari Devi, P.; Srinivasa Reddy, P.; Usha Rani, N. R.; Reddanna, P. Eur J Plant Path 2000, 106, 857.

[16] Colle, J. G.; Duguid, J. P.; Firaser, A. G.; Mannion, B. P. Mackie and Mecartney Practical Medicinal Microbiology, 13th ed.; Churchill: Edinburgh, 1989; Vol. 2.

# Bis-8-hydroxyquinoline and Bis-8-hydroxyquinaldine *N*-Substituted Amines: A Single Methyl Group Structural Difference between the Two Heterocycles, Which Modulates the Antiproliferative Effects

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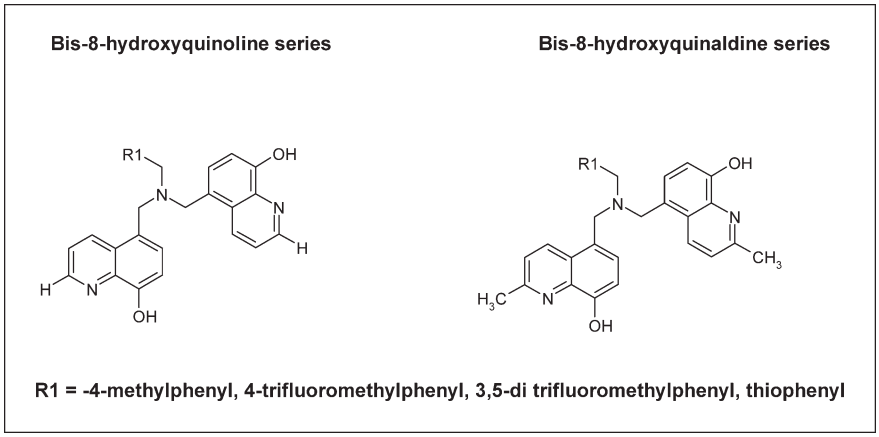


The synthesis of a series of bis-8-hydroxyquinoline- and bis-8-hydroxyquinaldine-substituted *N*-benzyl or thiophenyl amines and their corresponding bis-8-hydroxyquinoline is reported. *In vitro* growth inhibitory effects of both series have been evaluated. It has been observed that analogs from the bis-8-hydroxyquinoline series exert nanomolar range activity, whereas the antiproliferative activity of the corresponding analogs from the bis-8-hydroxyquinaldine series was found to be drastically lower. Molecular docking and chemical–physical properties account for these observed growth inhibitory differences between the two series of analogs, which differ only by the presence of a methyl group at the 2 position of the heterocyclic ring.

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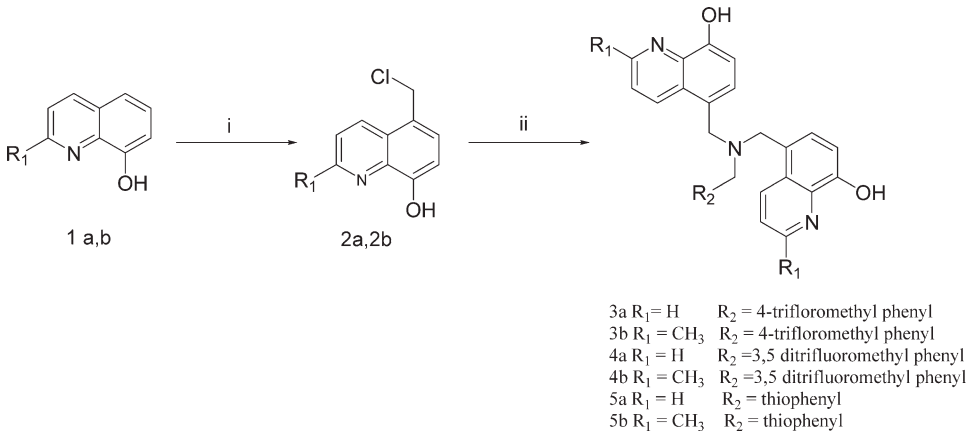
## INTRODUCTION

Hydroxyquinoline is a privileged structural moiety observed in many biologically active natural products; it is used as the source for many drugs diversely prescribed among a wide range of pathologies, including neurodegenerative [1], parasitic amoebic dysentery [2], and herpes viral diseases [3]. More specifically, 8-hydroxyquinoline (8-HQ) moiety has been mostly used for its capacity to strongly chelate metal ions, particularly $Cu^{++}$ and $Zn^{++}$ [4].

We have reported preliminary results on the antitumor activity of two analogs JLK1486 and JLK1472, which belong to the family of bis-8-hydroxyquinoline-substituted benzylamines [5]. From this work, we discover that a single methyl subtituent at the position 2 of the quinoline ring lead to what is called quinaldine series drastically that diminish the antiproliferative effect of the resulting compounds. For this purpose, we synthesized a new series of bis-8-hydroxyquinaldine *N*-substituted analogs, and we studied their anticancer activities in comparison with that of the corresponding bis-8-

**Scheme 1.** Reagents and conditions: (i) HCHO, 37% HCl in $H_2O$, HCl (gas), r.t., overnight, 80%; (ii) corresponding primary amine $K_2CO_3$, $CH_3CN$, r.t., overnight.




hydroxyquinoline *N*-substituted series. Molecular docking techniques and physicochemical studies were carried out to account for the observed differences in antitumor activity between the two families of 8-HQ and 8-hydroxyquinaldine (8-HQD) analogs.

## CHEMISTRY

Starting from 8-HQ (**1a**) or 8-HQD (**1b**), commercially available compounds, the corresponding 5-chloromethyl derivatives (**2a** and **2b**) were obtained in good yields by direct reaction with 37% formaldehyde in strong acidic conditions [6,7]. The solid compounds were directly collected by simple filtration and used without purification. The next step consisted in an addition on **2a** and **2b** of an excess of selected *N*-substituted primary amines that preferentially led to the formation of the desired bis-8-hydroxyquinoline or bis-8-hydroxyquinaldine benzyl or thiophenyl amines (Scheme 1). Under these experimental conditions, the desired bis-8-hydroxyquinoline and quinaldine derivatives (**3a**, **3b**, **4a**, **4b**, **5a**, **5b**) were obtained with moderate yields (40–50%), whereas mono-8-hydroxyquinoline or mono-8-hydroxyquinaldine by-products were only present as traces. The desired compounds were purified by column chromatography and fully identified by conventional spectral and centesimal analysis.

## RESULTS AND DISCUSSION

Compounds from the bis-8-hydroxyquinoline and bis-8-hydroxyquinaldine series were evaluated for their antiproliferative effect on a panel of 15 cancer cell lines [8–11].

The data in Table 1 clearly show that bis-8-hydroxyquinoline derivatives display higher *in vitro* antitumor activity than bis-8-hydroxyquinaldine derivatives. Indeed, in contrast to these bis-8-hydroxyquinoline derivatives for some of which antiproliferative effect could be observed in two digit n*M* range, the corresponding bis-8-hydroxyquinaldine analogs (**3b**, **4b**, **5b**) displayed antitumor effects higher than 5 μ*M*, and thus, revealing themselves 100–1000-fold weaker antiproliferative compounds when compared with 8-HQ derivatives. In addition, it must also be highlighted that the large variations observed in terms of antitumor activity for various bis-8-hydroxyquinoline derivative series on a given cancer cell line, say for example the BxPC3 pancreas cancer and the VM-47 melanoma cell lines.

These data prompted us to envisage preliminary structure–activity relationship analysis. Compounds (**2a**) and (**2b**), which are mono-8-hydroxyquinoline analogs and which include a chloromethyl moiety at the position 4 of the 8-HQ or 8-HQD nucleus, are found totally inactive in comparison with the *N*-substituted benzyl or thiophenylamine derivatives, a feature that reveals that the presence of a *N*-substituted amine moiety is essential for anticancer activity and also confirm that bis-8-hydroxyquinoline analogs are more potent antiproliferative compounds than the corresponding mono-8-hydroxyquinoline analog [5]. These observations led us, therefore, to try to understand why bis-8-hydroxyquinoline and bis-8-hydroxyquinaldine derivatives display such marked differences in terms of antiproliferative effect. Such observation that bis-8-hydroxyquinoline analogs are more potent bioactive molecules than their corresponding mono-8-hyroxy analog has been reported in the case of neurodegenerative diseases [12]. We have, thus, considered the possible electronic effects induced by the electron pair of the amine group in the 8-HQ or quinaldine system in terms of chemical reactivity, and the possible physical–chemical properties differences between the two scaffolds mainly in terms of nucleophilicity,

**Table 1**

Determination of the $IC_{50}$ (n*M*) *in vitro* growth inhibitory in 5 carcinoma, 5 glioma, and 5 melanoma.

| | Carcinoma | | | | | Glioma | | | | | Melanoma | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N° | A549 | BxPC3 | LoVo | MCF7 | PC3 | HS683 | T98G | U373 | U138 | GL19 | VM-21 | VM-48 | VM-47 | SKMEL-28 | B16F10 |
| **3a** | 8 | 4299 | 10 | 34 | 66 | 10 | 99 | 44 | 49 | 1241 | 81 | 1584 | 97 | >10 μ*M* | 92 |
| **4a** | 9 | 79 | 10 | 38 | 71 | 181 | 72 | 96 | 46 | 2143 | 47 | 98 | 146 | >10 μ*M* | 76 |
| **5a** | 27 | 89 | 40 | 35 | 44 | 35 | 88 | 85 | 44 | 3451 | 79 | 1757 | 1726 | 4826 | 86 |
| **3b** | >10 μ*M* | nd | 5565 | nd | 9605 | >10 μ*M* | nd | 7209 | nd | >10 μ*M* | nd | nd | nd | nd | nd |
| **4b** | 9713 | nd | 7954 | nd | 8787 | >10 μ*M* | nd | 8695 | nd | >10 μ*M* | nd | nd | nd | nd | nd |
| **5b** | >10 μ*M* | nd | >10 μ*M* | nd | >10 μ*M* | >10 μ*M* | nd | >10 μ*M* | nd | >10 μ*M* | nd | nd | nd | nd | nd |

Compound *in vitro* antiproliferative effect has been performed in 5 carcinoma, 5 glioma, and 5 melanoma cell lines. The cancer cells have been cultured in the presence of the drugs for 3 days. The $IC_{50}$ values were determined by means of the MTT colorimetric assay as detailed previously [6,8]. The values reported in this table are means obtained on six distinct values. The standard errors are not reported for the sake of clarity, because they are <5% as compared with the mean values.

$IC_{50}$ are expressed in n*M* unless in μ*M* when specified in the table.

Cell lines: A549, human alveolar epithelial; BxPC3, pancreatic cancer; LoVo, colon cancer; MCF7, breast cancer; PC3, humanprozstate cancer; HS683, human glioma; T98G, human glioblastoma; U373, human glioblastoma-astrocytoma epithelial; U318, human glioma; GL19, glioblastoma multiform; VM-21 and VM-47 are mutant melanoma; SKMEL-28 and B16F10 are human melanoma.

nd: not determined.

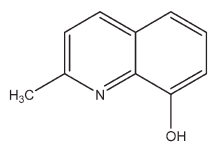
basicity, and hydrophobicity. There is a conceptual relationship between nucleophilicity and basicity. Both properties are involved in the formation of a new bond by donation of an electron pair to an electrophilic species. Basicity in the Brønsted sense involves formation of a bond to hydrogen, while generally nucleophilicity refers to the effect of a Lewis base on the rate of nucleophilic substitution reaction. The relative nucleophilicities may differ from reaction to reaction, and several parameters have significant influence on nucleophilicities. From literature reports [13], it can be seen that the presence of a methyl group in 8-HQD makes the nitrogen donor more basic in comparison with 8-HQ (Fig. 1).

Considering the possible biological mode of action of the compounds under study in which the proton of the hydroxyl group in the ground state could be involved in their antitumor mechanism(s) of action, the observed differences in pKa values (Fig. 1) could account for the observed differences in antiproliferative effects. Differences in the pKA values between the two systems could induce variations in the electronic driving force from the exocyclic nitrogen lone pair electron to the hydroxy group through the aromatic ring. Electronic effects induced by the presence of the methyl substituent at the 2 position of the quinoline ring influence the acidity of the OH proton and consequently, the conjugation between the nitrogen atom lone pair electron from the benzylamine moiety and the phenol group through the aromatic system.

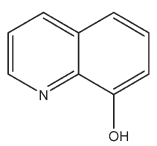
Next, we considered the differences in terms of hydrophobicity between the two scaffolds as a possible parameter which could influence cell permeation and consequently, the observed anticancer activities. The calculated clog*P* values determined for analogs **3a** (quinoline series) and **3b** (quinaldine series) were, respectively, 6.16 and 7.64 (calculated from ACD Labs/Log*P* dB 3.5 and ChemSketch 3.5). As expected, 8-HQD derivatives were slightly more hydrophobic than their corresponding analogs from the bis-8-hydroxyquinoline series, but these rather small differences in hydrophobicity cannot account alone for the observed drastic differences in antiproliferative effect.

As steric effects of substituted quinolines on lithium coordination geometry have been reported [14], we next examined the possible influence of steric hindrance induced by the methyl group at position 2 of the quinoline heterocycle. For this purpose, compounds **3a** and **3b** were selected as representative compounds for minimal energy conformational search. Minimal energy conformations for both analogs were generated and superimposed after a Monte Carlo Conformational Search (Macromodel version 6.5 was used for molecular mechanics calculations) [15].

After calculations, both lowest energy conformations for **3a** (132.8 kcal/mol) and **3b** (134.5 kcal/mol) were



8-hydroxy quinaldine scaffold



8 –Hydroxy-quinoline scaffold

**Figure 1.** pKa values: 8-hydroxyquinoline [$pK_{A1}$ = 5.13 ($NH_4$+/$NH_2$), $pK_{A2}$ = 9.89 ($OH/O^-$)] and 8-hydroxyquinaldine [$pK_{A1}$ = 5.67 ($NH_4$+/$NH_2$), $pK_{A2}$ = 9.97 ($OH/O^-$)].

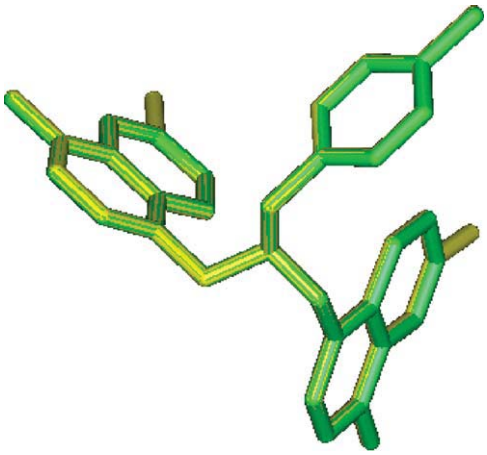


**Figure 2.** Superimposition of compounds **3a** (green) and **3b** (yellow)—best conformations obtained through a Monte Carlo conformational search. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

identical. They exhibit an energetic difference inferior to 2 kcal/mol between the two analogs, which could not account for the drastic drop in biological activity of the methylated compounds. Further, superimposition of the successively obtained conformations within a 3 kcal/mol span (from the lowest representative conformation) between these analogs revealed no differences between both analogs, which displayed similar poses with a similar energy difference in favor of the quinoline scaffold (Fig. 2).

From these results, steric effects induced by the presence of a methyl group at the position 2 appear to be too weak to entirely abolish the anticancer activity of all the 8-HQD analogs irrespective of the cancer cell lines (carcinoma, glioma, or melanoma) used in the assay.

## CONCLUSIONS

In conclusion, a series of bis-8-hydroxyquinolines *N*-benzyl or thiophenyl amines and their corresponding bis-8-hydroxyquinaldine derivatives have been prepared. We found that compounds that belong to the bis-8-hydroxyquinoline series have an *in vitro* potent antiproliferative effect on a large panel of cancer cell lines at lower nanomolar $IC_{50}$ values, while their corresponding 8-HQD counterparts display only weak (in the μ*M* range), if any, antiproliferative effect. Molecular docking studies and physico-chemical properties suggest that the presence of a methyl group in position 2 vicinal to the endocyclic nitrogen atom induces electronic factors (pKa values) that greatly influence the driving electronic force all along the aromatic system, including the exocyclic nitrogen. In contrast, Monte Carlo studies reveal only a small energy difference with less than 2 kcal/mol having been observed between the two series differing in the 2-methyl group only. The steric effect of a methyl group at the 2 position of the heterocycle and the difference in clog*P* values appeared to be too weak to account for the observed drastic antiproliferative differences between both series of analogs. Investigations on the mechanism of action and on the possible biological targets of those are underway.

## EXPERIMENTAL

Compounds **2a** and **3a** have been already reported [5]. Starting quinaldin-8-ol intermediate **2b** has been synthesized as follows:

**5-(Chloromethyl)-2-methylquinolin-8-ol hydrochloride (2b).** A mixture of 7.3 g (0.045 mol) of quinaldin-8-ol (Aldrich), 8 mL of concentrated hydrochloric acid, and 8 mL (0.05 mol) of 37% formaldehyde was treated with hydrogen chloride gas for 90 min. The yellow solid was collected on a filter and dried to give 8.5 g of compound (70% yield) mp 280°C $^1$NMR (250 MHz, DMSO): 9.14 (d, 1H, $J$ = 8.75 Hz), 8.05 (d, 1H, $J$ = 8.75 Hz), 7.83 (d, 1H, $J$ = 8 Hz), 7.56 (d, 1H, $J$ = 8 Hz), 5.233 (s, 2H), 2.5 (s, 3H). Anal. Calcd. for $C_{11}H_{11}NOCl_2$: C, 54.09; H, 4.51; N, 5.73. Found: C, 54.19; H, 4.45; N, 5.81.

**General procedure for the reaction of 5-chloromethyl 8-hydroxyquinaldine (2a) and (2b) with primary amines for the synthesis of analogs 4a, 5a, 3b, 4b, and 5b.** All of these reactions were carried out under a nitrogen atmosphere. To a solution of 5-chloromethyl quinolin-8-ol dihydrochloride (**2a)** or 5-chloromethylquinaldin-8-ol dihydrochloride (**2b)** (1.3 mmol) at 50°C in ethyl acetate (10 mL) was added appropriate primary amines (3.91 mmol). Stirring is maintained overnight. Then, the solution is cooled down to 0°C and filtrated; the filter cake is washed with cold ethyl acetate (5 mL). The filtrate is concentrated *in vaccuo*, diluted in diethyl ether (5 mL), and centrifuged. The ethereal phase is removed, and the obtained solid is washed two more time by centrifugation with diethyl ether at 0°C to give the desired products.

***5,5′-(4-(Trifluoromethyl)benzylazanediyl)bis(methylene)bis(2-methylquinolin-8-ol) (3b).*** This compound was obtained as colorless solid. (42%), mp = 205°C $^1$NMR (250 MHz, $CDCl_3$): 7.64 (d, 2H, $J$ = 7.75 Hz), 7.41–7.39 (m, 2H), 7.22–7.06 (m, 4H), 6.95–6.8 (m, 4H), 3.61 (s, 4H), 3.44 (s, 2H), 2.61 (s, 6H). MS, *m/z* ($C_{30}H_{26}F_3N_3O_2$): calcd. 518, $[M + H]^+$; found 518. Anal. Calcd. for $C_{30}H_{26}F_3N_3O_2$: C, 69.50; H, 5.02; N, 8.11. Found: C, 69.37; H, 5.04; N, 8.14.

***5,5″-(3,5-Bis(trifluorométhyl)benzylazanediyl)bis(methylene)diquinoline-8ol (4a).*** This compound was obtained as a yellow solid. (50%), mp = 193°C $^1$NMR (250 MHz, $CDCl_3$): 9.8 (m, 2H), 6.7–8.05 (m, 13H aromatic) 3.6–3.8 (m 6H, $CH_2$). MS, *m/z* ($C_{29}H_{21}F_6N_3O_2$): calcd. MW 558; found 558. Anal. Calcd. for $C_{29}H_{21}F_6N_3O_2$: C, 62.48; H, 3.80; N, 7.54. Found: C, 62.10; H, 3.89; N, 7.33.

***5,5′-(3,5-Bis(trifluorométhyl)benzylazanediyl)bis(methylene)diquinaldine-8-ol (4b).*** This compound was obtained as brown solid. (38%), mp = 207°C H$^1$NMR (250 MHz, $CDCl_3$): 8.76–8.74 (m, 2H), 7.96–7.92 (m, 2H), 7.64 (s, 1H), 7.43–7.38 (m, 4H), 724, (m, 5H) 7.19–7.13 (m, 4H), 7.08–7.05 (m, 2H), 3.89 (br s, 4H), 3.61 (s, 2H). 2,8 (3H). MS, *m/z* ($C_{31}H_{25}F_6N_3O_2$): calcd. 586, $[M + H]^+$; found 587. Anal. Calcd. for

$C_{31}H_{25}F_6N_3O_2$: C, 63.59; H, 4.30; N, 7.18. Found: C, 64.12; H, 4.26; N, 7.11.

***5,5′-(Thiophen-2-ylmethylazanediyl)bis(methylene)diquinolin-8-ol (5a).*** This compound was obtained as a brown solid. (48%), mp = 167 (decomp) $^1$NMR (250 MHz, MeOD): 8.79 (m, 2H), 8.13 (m, 2H), 7.43 (m, 3H), 7.23 (m, 2H), 7.01 (m, 4H), 3.86 (br s, 4H), 3.76 (s, 2H). MS, *m*/*z* ($C_{25}H_{21}N_3O_2S$): calcd. 428.1, $[M + H]^+$; found 428.1. Anal. Calcd. for $C_{25}H_{21}N_3O_2S$: C, 72.24; H, 9.83; N, 4.95. Found: C, 71.98; H, 9.86; N, 4.93.

***5,5′-(Thiophen-2-ylmethylazanediyl)bis(methylene)diquinaldine-8-ol (5b).*** This compound was obtained as a gray solid. (36%), mp = 205°C (decomp) $^1$NMR (250 MHz, MeOD): 9.83 (m, 2H), 6.8–8.05 (m, 8H), 6.74–7.06 (m, 3H thiophenyl ring), 3.5–3.6 (m 6H), 2.55 (s, 6H). MS, *m*/*z* ($C_{27}H_{25}N_3O_2S$): calcd. 455, $[M+H]^+$; found 55. Anal. Calcd. for $C_{27}H_{25}N_3O_2S$: C, 71.21; H, 5.50; N, 9.23. Found: C, 71.35; H, 5.38; N, 9.19.

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## REFERENCES AND NOTES

[1] Adlard, P. A.; Cherny, R. A.; Finkelstein, D. I.; Gautier, E.; Robb, E.; Cortes, M.; Volitakis, I.; Liu, X.; Smith, J. P.; Perez, K.; Laughton, K.; Li, Q. X.; Charman, S. A.; Nicolazzo, J. A.; Wilkins, S.; Deleva, K.; Lynch, T.; Kok, G.; Ritchie, C. W.; Tanzi, R. E.; Cappai, R.; Masters, C. L.; Barnham, K. J.; Bush, A. I. Neuron 2008, 59, 43.

[2] Thompson, P. E.; Reinertson, J. W. Am J Trop Med Hyg 1951, 31, 707.

[3] Oien, N. L.; Brideau, R. J.; Hopkins, T. A.; Wieber, J. L.; Knechtel, M. L.; Shelly, J. A.; Anstadt, R. A.; Wells, P. A.; Poorman, R. A.; Huang, A.; Vaillancourt, V. A.; Clayton, T. L.; Tucker, J. A.; Wathen, M. W. Antimicrob Agents Chemother 2002, 46, 724.

[4] Ji, H. F.; Zhang, H. Y. Bioorg Med Chem Lett 2005, 15, 21.

[5] Moret, V.; Laras, Y.; Cresteil, T.; Aubert, G.; Ping, D. Q.; Di, C.; Barthelemy-Requin, M.; Beclin, C.; Peyrot, V.; Allegro, D.; Rolland, A.; De Angelis, F.; Gatti, E.; Pierre, P.; Pasquini, L.; Petrucci, E.; Testa, U.; Kraus, J. L. Eur J Med Chem 2009, 44, 558.

[6] Burckhalter, J. H.; Leib, R. J Org Chem 1961, 26, 4078.

[7] Zhao, K.-Q.; Hu, P.; Zhou, Y.-Q.; Xu, H.-B. Molecules 2001, 6, M208.

[8] Van Quaquebeke, E.; Mahieu, T.; Dumont, P.; Dewelle, J.; Ribaucour, F.; Simon, G.; Sauvage, S.; Gaussin, J. F.; Tuti, J.; El Yazidi, M.; Van Vynckt, F.; Mijatovic, T.; Lefranc, F.; Darro, F.; Kiss, R. J Med Chem 2007, 50, 4122.

[9] Ingrassia, L.; Nshimyumukiza, P.; Dewelle, J.; Lefranc, F.; Wlodarczak, L.; Thomas, S.; Dielie, G.; Chiron, C.; Zedde, C.; Tisnes, P.; van Soest, R.; Braekman, J. C.; Darro, F.; Kiss, R. J Med Chem 2006, 49, 1800.

[10] Lefranc, F.; Sauvage, S.; Van Goietsenoven, G.; Mégalizzi, V.; Lamoral-Theys, D.; Debeir, O.; Spiegl-Kreinecker, S.; Berger, W.; Mathieu, V.; Decaestecker, C.; Kiss, R. Mol Cancer Ther 2009, 8, 1739.

[11] Mathieu, V.; Pirker, C.; Martin de Lassalle, E.; Vernier, M.; Mijatovic, T.; DeNeve, N.; Gaussin, J. F.; Dehoux, M.; Lefranc, F.; Berger, W.; Kiss, R. J Cell Mol Med, to appear.

[12] Deraeve, C.;.Boldron, C.;.Maraval, A.; Mazarguil, H.; Gornitzka, H.; Vendier, L.; Pitie, M.; Meunier, B. Chem A Eur J 2008, 14, 682.

[13] Garribba, E.; Micera, G.; Sanna, D.; Lodyga-Chruscinska, E. Inorg Chim Acta 2003, 348, 97.

[14] Rajeswaran, M.; Begley, W.; Olson, L. P.; Huo, S. Polyhedron 2007, 26, 3653.

[15] Saunders, M.; Houk, K. N.; Wu, Y. D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. J Am Chem Soc 1990, 112, 1419.

# An Efficient Microwave-Assisted Synthesis of 6,8-Dihydroimidazo[1,2-*a*] [1,3,5] Triazine Derivatives

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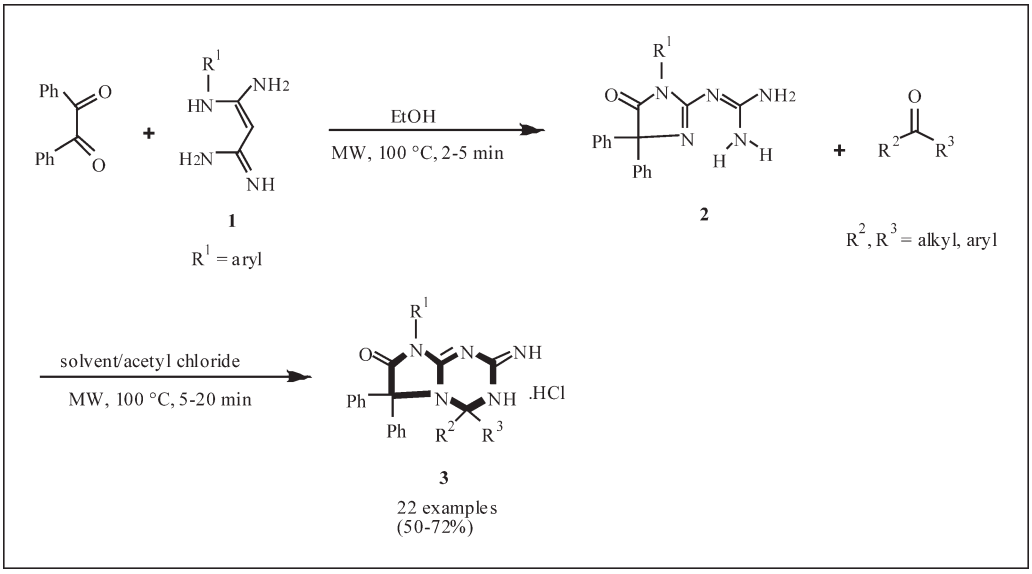


A simple, efficient, and general method has been developed for the synthesis of various 4-substituted 2-amino-6,6-diphenyl-8-aryl-6,8-dihydroimidazo[1,2-*a*] [1,3,5] triazine-7(4-*H*)ones **3a**–**3v**. This involved condensation of 1-(5-oxo-4,4-diphenyl-1-aryl-4,5-dihydro-1*H*-imidazol-2-yl)guanidines 2a and 2b, themselves obtained from the reaction of aryl biguanides 1a/b with benzil, with the requisite carbonyl compounds. Both steps were performed using microwave heating in sealed vessels.

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## INTRODUCTION

Microwave-assisted organic synthesis (MAOS) has emerged over the past decade as a valuable technology for synthetic organic and medicinal chemistry. Replacing the conventional oil bath as a heat source by a microwave reactor results in a marked reduction in reaction time and an increase in reaction yield for many important transformations [1,2]. In particular, the need for rapid construction and modification of biologically active heterocyclic compounds, a major concern in drug development, has stimulated intense development of microwave synthesis technology. This is reflected in the exponential increase in the number of scientific papers, books, and reviews related to the use of this technology [3,4].

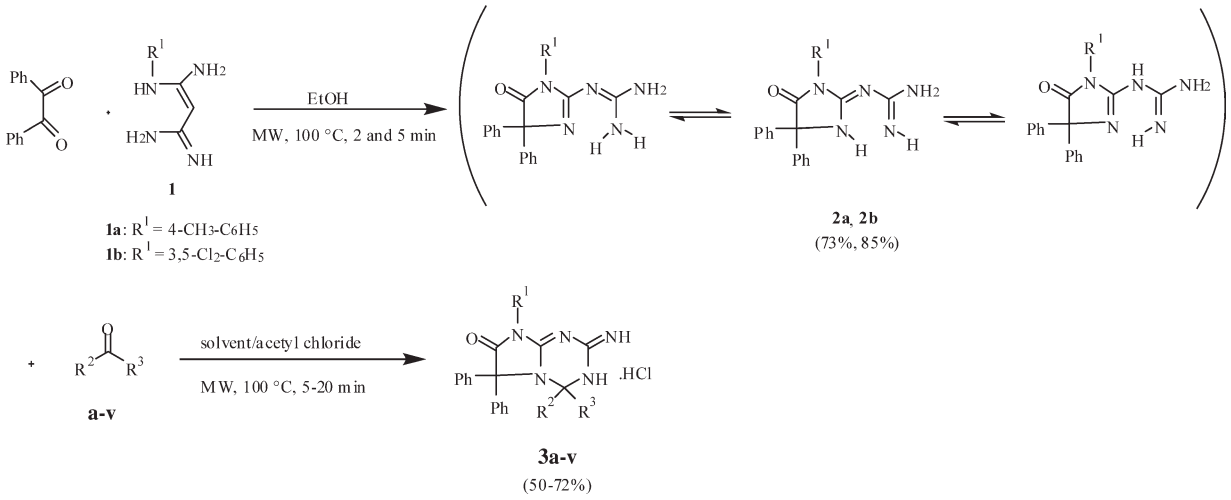
In this work, we report a simple and convenient method for the synthesis of 6,8-dihydroimidazo[1,2-a] [1,3,5] triazines under microwave irradiation conditions. The 6,8-dihydroimidazo[1,2-a] [1,3,5] triazine system is a core structure element in a number of molecules with potential application as antitumor, antibacterial, and antiparasitic agents, and as herbicide antagonists [5–21].

## RESULTS AND DISCUSSION

Imidazoltriazines with structure **3** have been obtained by a two-step procedure (Scheme 1) involving the heating of 1-substitued biguanides with benzil to give 1-(5-oxo-4,4-diphenyl-1-aryl-4,5-dihydro-1H-imidazol-2-yl)guanidine intermediates **2** as a mixture of tautomers, and subsequent ring closure of these mixtures to the target compounds on further heating [5,22–25].

Transposing this process to microwave conditions, it was found that the reaction of benzil (1 equiv) with the 1-substituted biguanides **1a** and **1b** (1 equiv) in ethanol in a sealed tube (pressure-rated reaction vial) at 100°C in a self-tuning single-mode microwave cavity (5CEM Discovery apparatus) was complete after only 2–5 min. On cooling, the precipitated material was isolated by simple filtration, washing with cold ethanol, and

**Scheme 1**




recrystallization to give the known 1-(5-oxo-4,4-diphenyl-1-aryl-4,5-dihydro-1H-imidazol-2-yl)guanidines **2a** and **2b** (73% and 85%, respectively) [22]. These intermediates were, in turn, reacted with a series of aldehydes and ketones using microwave irradiation to construct a 22 member library containing the novel 6,8-dihydroimidazo[1,2-a] [1,3,5] triazines **3a**–**3v** (Table 1). In the experiment, compounds **2a** or **2b** in acetone containing a catalytic amount of acetyl chloride (see Experimental) were place in a sealed vessel and reacted in the microwave cavity at 100°C. The reaction time was varied from 5 to 20 min in increments of 5 min. However, in general, the reactions were complete after heating for 10 min, as judged by TLC. When a temperature above 100°C was used a complex reaction mixture was obtained from which the product was obtained in lower yield. The mass, IR, and NMR spectra unambiguously confirmed the structures **3a–3w**.

**Table 1**

Microwave-assisted synthesis of 6,8-dihydroimidazo [1,2-a] [1,3,5] triazines **3a–3v**.

| Compound | Carbonyl Compound | $R^1$ | $R^2$ | $R^3$ | Time (min) | Yield (%) |
|---|---|---|---|---|---|---|
| **3a**[a] | Acetone | 4-$CH_3$-$C_6H_5$ | $CH_3$ | $CH_3$ | 10 | 65 |
| **3b**[a] | 2-Butanone | 4-$CH_3$-$C_6H_5$ | $CH_3$ | $CH_3CH_2$ | 15 | 68 |
| **3c**[a] | Cyclopentanone | 4-$CH_3$-$C_6H_5$ | $R^2 = R^3 = C_5H_8$ | | 20 | 50 |
| **3d**[b] | Anizaldehyde | 4-$CH_3$-$C_6H_5$ | H | 4-$OCH_3$-$C_6H_5$ | 10 | 72 |
| **3e**[b] | 2-Chlorobenzaldehyde | 4-$CH_3$-$C_6H_5$ | H | 2-Cl-$C_6H_5$ | 15 | 67 |
| **3f**[b] | 2,4-Dichlorobenzaldehyde | 4-$CH_3$-$C_6H_5$ | H | 2,4-$Cl_2$-$C_6H_5$ | 5 | 72 |
| **3g**[b] | *o*-Tolyl aldehyde | 4-$CH_3$-$C_6H_5$ | H | 2-$CH_3$-$C_6H_5$ | 15 | 65 |
| **3h**[b] | *m*-Tolyl aldehyde | 4-$CH_3$-$C_6H_5$ | H | 3-$CH_3$-$C_6H_5$ | 10 | 68 |
| **3i**[b] | 4-Biphenylaldehyde | 4-$CH_3$-$C_6H_5$ | H | $C_6H_5$-$C_6H_4$ | 20 | 69 |
| **3j**[b] | 3-Nitrobenzaldehyde | 4-$CH_3$-$C_6H_5$ | H | 3-$NO_2$-$C_6H_5$ | 15 | 71 |
| **3k**[b] | 3-(2-Nitrophenyl) propenal | 4-$CH_3$-$C_6H_5$ | H | 2-$NO_2$-$C_6H_5$CHCH | 5 | 68 |
| **3l**[b] | 4-Chlorobenzaldehyde | 4-$CH_3$-$C_6H_5$ | H | 2-Cl-$C_6H_5$ | 20 | 54 |
| **3m**[a] | Acetone | 3,5-$Cl_2$-$C_6H_5$ | $CH_3$ | $CH_3$ | 15 | 66 |
| **3n**[a] | 2-Pentanone | 3,5-$Cl_2$-$C_6H_5$ | $CH_3$ | $CH_3CH_2CH_2$ | 20 | 71 |
| **3o**[a] | 2-Butanone | 3,5-$Cl_2$-$C_6H_5$ | $CH_3$ | $CH_3CH_2$ | 15 | 67 |
| **3p**[a] | Cyclopentanone | 3,5-$Cl_2$-$C_6H_5$ | $R^2 = R^3 = C_5H_8$ | | 20 | 52 |
| **3q**[b] | *o*-Tolyl aldehyde | 3,5-$Cl_2$-C6H5 | H | 2-$CH_3$-$C_6H_5$ | 10 | 63 |
| **3r**[b] | *m*-Totyl aldehyde | 3,5-$Cl_2$-$C_6H_5$ | H | 3-$CH_3$-$C_6H_5$ | 10 | 58 |
| **3s**[b] | 2-Chlorobenzaldehyde | 3,5-$Cl_2$-$C_6H_5$ | H | 2-Cl-$C_6H_5$ | 10 | 61 |
| **3t**[b] | 2,4-Dichlorobenzaldehyde | 3,5-$Cl_2$-$C_6H_5$ | H | 2,4-$Cl_2$-$C_6H_5$ | 10 | 64 |
| **3u**[b] | 3-Nitrobenzaldehyde | 3,5-$Cl_2$-$C_6H_5$ | H | 3-$NO_2$-$C_6H_5$ | 10 | 63 |
| **3v**[b] | 3-(Nitrophenyl) propenal | 3,5-$Cl_2$-$C_6H_5$ | H | 2-$NO_2$-$C_6H_5$CHCH | 10 | 65 |

[a] Method A in the Experimental section.
[b] Method B in the Experimental section.

## CONCLUSIONS

An efficient, rapid, and clean method for the preparation of a 22-membered library of 6,8-dihydroimidazo[1,2-a] [1,3,5] triazines has been developed using microwave-assisted synthesis.

## EXPERIMENTAL

**Materials.** All commercially available reagents were used without further purification. Commercial solvents were distilled from an appropriate drying agent before use according to standard procedures.

**Analysis.** TLC analysis was performed on aluminum-precoated silica gel 60 plates. $^1$H NMR spectra were recorded on a Varian Unity Inova 400 MHz spectrometer using DMSO-$d_6$ as a solvent. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. IR spectra were taken on a Perkin-Elmer FT-IR 2000 spectrometer. Low-resolution mass spectra were obtained in the atmospheric pressure chemical ionization (positive or negative APCI) mode. All melting points (uncorrected) were recorded on a SMP2 apparatus.

**Equipment.** Microwave syntheses were carried out on a CEM Corp. Discover laboratory microwave with Explorer unit. Reaction times refer to hold times at the temperatures indicated and not to total irradiation time.

**General procedure for synthesis of 1-(5-Oxo-4,4-diphenyl-1-aryl-4,5-dihydro-1H-imidazol-2-yl)guanidines 2a and 2b.** Arylbiguanide hydrochloride (**1a** and correspondingly **1b**, 5 mmol) was added to the solution of sodium (0.11 g, 5 mmol) in absolute ethanol (25 mL). Precipitated sodium chloride is filtered off and benzil (1.05 g, 5 mmol) dissolved in absolute ethanol (6 mL) was added to the filtrate in a 30 mL microwave vial equipped with a pressure and temperature sensor, as well as a magnetic stirrer. The sealed tube was placed in a homogeneous microwave synthesis system. After irradiation at 100°C, measured by an internal fiber-optic temperature sensor immersed in the reaction mixture, for 2 (**2a**) and 5 (**2b**) min, respectively, the reaction mixture was cooled, and the precipitate was collected, washed with cold ethanol, and recrystallized from ethanol to give highly pure title.

***2-[1-(4-Methylphenyl)-5-oxo-4,4-diphenyl-2-imidazolline-2-yl]-guanidines (2a).*** $^1$H NMR (400 MHz, DMSO) δ 2.34 (s, 3H), 7.53–7.90 (m, 14H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3115, 3166, 3061, 1593, 1537; UV–vis (MeOH) $\lambda_{max}$/nm 204 (0.406).

***2-[1-(3,5-Dichlorophenyl)-5-oxo-4,4-diphenyl-2-imidazolline-2-yl]-guanidines (2b).*** $^1$H NMR (400 MHz, DMSO) δ 7.21–7.98 (m, 13H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3430, 3176, 3084, 1709, 1640, 1611, 1597, 1536, 798, 747, 697; UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.688).

**Method A: General procedure for synthesis of 6,8-dihydroimidazo[1,2-a] [1,3,5] triazines (3a–3c and 3m–3p) (carbonyl compounds with low boiling point).** To a suspension of 1 equiv arylbiguanide (**2a** or **2b**) (0.1 mmol, 38.3 mg or 43.8 mg) in 3 mL of ketone or aldehyde in a microwave vial, 5 equiv acetyl chloride (0.5 mmol, 57.5 mg) was added. The vial was sealed and irradiated in a microwave reactor at 100°C for 10–20 min. The precipitates were collected by filtration and recrystallized from ethanol to give corresponding compound **3**.

**Method B: General procedure for synthesis of 6,8-dihydroimidazo[1,2-a] [1,3,5] triazines (3d–3l and 3q–3v) (carbonyl compounds with high boiling point).** To a suspension of 1 equiv arylbiguanide (**2a** or **2b**) (0.1 mmol, 38.3 mg or 43.8 mg) and 5 equiv of the ketone or aldehyde (0.5 mmol) in ethanol (3mL) in a microwave vial, 5 equiv acetyl chloride (0.5 mmol, 57.5 mg) was added. The vial was sealed and irradiated in a microwave reactor at 100°C for 10–20 min. The precipitates were collected by filtration and recrystallized from ethanol to give corresponding compound **3**.

***2-Imino-4,4-dimethyl-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3a).*** mp: 255–257°C; $^1$H NMR (400 MHz, DMSO) δ 1.10 (s, 6H), 2.36 (s, 3H), 7.33–7.64 (m, 14H), 7.98 (s, 1H), 8.85 (s, 1H), 9.74 (s, 1H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3467, 3273, 3091, 2797, 1772, 1658, 1630, 1576, 1534, 1495, 1452, 1192, 967, 698; MS (positive APCI, *m*/*z*): 424 [35, (M + 1)], 423 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.510).

***2-Imino-4-methyl-4-ethyl-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3b).*** mp: 255–257°C; $^1$H NMR (400 MHz, DMSO) δ 0.66 (t, $J$ = 7.2 Hz, 3H), 0.78–0.84 (m, 1H), 1.04–1.11 (m, 1H), 1.37 (s, 3H), 2.35 (s, 3H), 7.32–7.66 (m, 14H), 8.21 (s, 1H), 8.89 (s, 1H), 10.29 (s, 1H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3374, 3073, 2970, 2726, 1766, 1678, 1611, 1569, 1513, 1491, 724; MS (positive APCI, *m*/*z*): 438 [23, (M + 1)], 437 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 259 (0.179), 249 (0.159), 204 (0.603).

***2-Imino-8-(4-methylpheyl)-6,6-diphenyl-4-spirocyclopentanon-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3c).*** mp: 270–272°C (dec.); $^1$H NMR (400 MHz, DMSO) δ 1.02–1.86 (m, 8H), 2.10 (s, 3H), 7.34–7.58 (m, 14H), 8.03 (s, 1H), 8.94 (s, 1H), 10.06 (s, 1H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3359, 3036, 2962, 2739, 1767, 1681, 1610, 1567, 1490, 1450, 1193, 727, 703; MS (positive APCI, *m*/*z*): 450 [25, (M + 1)], 449 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 205 (0.610).

***2-Imino-4-(4-methoxyphenyl)-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3d).*** mp: 274–276°C; $^1$H NMR (400 MHz, DMSO) δ 0.66 (t, $J$ = 7.2 Hz, 3H), 1.08 (m, 2H), 1.37 (s, 3H), 7.54–7.86 (m, 13H), 8.23 (s, 1H), 8.95 (s, 1H), 10.01 (s, 1H), IR (KBr) $\upsilon_{max}/cm^{-1}$: 3353, 3053, 2795, 1777, 1674, 1611, 1588, 1487, 728, 712; MS (positive APCI, *m*/*z*): 502 [37, (M + 1)], 501 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.554).

***2-Imino-4-(2-chlorophenyl)-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3e).*** mp: 277–279°C; $^1$H NMR (400 MHz, DMSO) δ 238 (s, 3H), 6.52 (s, 1H), 7.05–7.64 (m, 18H), 8.33 (s, 1H), 9.03 (s, 1H), 10.18 (s, 1H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3366, 3000, 2670, 1770, 1677, 1616, 1573, 1488, 1195, 760, 728; MS (positive APCI, *m*/*z*): 507 [40, (M + 2)], 506 [47, (M + 1)], 505 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 205 (0.569).

***2-Imino-4-(2,4-dichlorophenyl)-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3f).*** mp: 278–280°C; $^1$H NMR (400 MHz, DMSO) δ 2.38 (s, 3H), 6.55 (s, 1H), 7.11–7.63 (m, 17H), 8.23 (s, 1H), 9.04 (s, 1H), 10.21 (s, 1H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 3356, 3036, 2623, 1766, 1679, 1616, 1579, 1492, 1191, 762, 733, 693; MS (positive APCI, *m*/*z*): 541 [70, (M + 2)], 539 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.531).

***2-Imino-4-(2-methylpheyl)-8-(4-methylpheyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3g).*** mp: 278–280°C; $^1$H NMR (400 MHz, DMSO) δ 2.15 (s, 3H), 2.39 (s, 3H), 6.38 (s, 1H), 6.85–7.60 (m, 18H), 8.23 (s, 1H), 8.95 (s, 1H), 10.15 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3360, 3021, 2702, 1769, 1677, 1616, 1573, 1486, 1192, 725; MS (positive APCI, *m*/*z*): 486 [27, (M + 1)], 485 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.720).

***2-Imino-4-(3-methylpheyl)-8-(4-methylpheyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3h).*** mp: 220–222°C; $^1$H NMR (400 MHz, DMSO) δ 2.28 (s, 3H), 2.39 (s,3H), 6.33 (s,1H), 6.66–7.61 (m, 18H), 8.16 (s, 1H), 8.98 (s, 1H), 10.07 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3423, 3108, 2951, 1767, 1650, 1610, 1581, 1498, 1180, 696, 486; MS (positive APCI, *m*/*z*): 486 [25, (M + 1)], 485 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.529).

***2-Imino-4-(biphenyl-4-yl)-8-(4-methylpheyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3i).*** mp: 257–259°C; $^1$H NMR (400 MHz, DMSO) δ 2.39 (s, 3H), 6.48 (s, 1H), 7.04–7.62 (m, 23H), 8.54 (s, 1H), 9.03 (s, 1H), 10.17 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3352, 3060, 2747, 1768, 1665, 1615, 1579, 1495, 1193, 764, 732, 697; MS (positive APCI, *m*/*z*): 548 [47, (M + 1)], 547 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 260 (0.179), 243 (0.155), 205 (0.433).

***2-Imino-4-(3-nitrophenyl)-8-(4-methylpheyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3j).*** mp: 276–279°C; $^1$H NMR (400 MHz, DMSO) δ 2.39 (s, 3H), 6.69–7.99 (m, 18H), 8.46 (s, 1H), 9.10 (s, 1H), 10.27 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3187, 3096, 2960, 1771, 1675, 1650, 1606, 1493, 1193, 690; MS (positive APCI, *m*/*z*): 518 [17, (M + 2)], 516 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.606).

***2-Imino-4-(2-nitrostyryl)-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3k).*** mp: 279–281°C (dec.); $^1$H NMR (400 MHz, DMSO) δ 2.36 (s, 3H), 5.95 (d, $J$ = 8.4 Hz, 1H), 6.11 (dd, $J_1$ = 15.6 Hz, $J_2$ = 8.4 Hz, 1H) 6.49 (d, $J$ = 14.2 Hz, 1H), 7.07–7.86 (m, 16H), 7.85 (d, $J$ = 7.8 Hz, 1H), 8.26 (s, 1H), 9.00 (s, 1H), 9.71 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3424, 3115, 2363, 1773, 1675, 1660, 1612, 1518, 1198, 768, 695; MS (positive APCI, *m*/*z*): 543 [37, (M + 1)], 542 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 205 (0.466).

***2-Imino-4-(4-chlorophenyl)-8-(4-methylpheyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3l).*** mp: 283–285°C; $^1$H NMR (400 MHz, DMSO) δ 2.38 (s, 3H), 6.47 (s, 1H), 7.08–7.61 (m, 18H), 8.43 (s, 1H), 9.02 (s, 1H), 10.13 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3368, 3086, 2682, 1779, 1672, 1613, 1578, 1494, 1192, 728, 697; MS (positive APCI, *m*/*z*): 506 [55, (M + 1)], 505 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.456).

***2-Imino-4,4-dimethyl-8-(3,5-dichlorophenyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3m).*** mp: 271–273°C; $^1$H NMR (400 MHz, DMSO) δ 1.10 (s, 6H), 7.55–7.86 (m, 13H), 8.04 (s, 1H), 8.92 (s, 1H), 9.80 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3361, 3022, 2755, 1780, 1678, 1614, 1588, 1491, 1454, 1427, 1174, 1029, 728; MS (positive APCI, *m*/*z*): 479 [95, (M + 2)], 478 [35, (M + 1)], 477 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 208 (0.469).

***2-Imino-4-methyl-4-propyl-8-(3,5-dichlorophenyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3n).*** mp: 248–252°C; $^1$H NMR (400 MHz, DMSO) δ 0.50–0.53 (t, $J$ = 7.2 Hz, 3H), 0.66–0.75 (m, 2H), 1.03–1.19 (m, 1H), 1.19–1.23 (M, 1H), 1.43 (s, 3H), 7.34–7.87 (m, 17H), 8.03 (s, 1H), 8.88 (s, 1H), 9.76 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3360, 3026, 2778, 1777, 1675, 1613, 1589, 1492, 1197, 759, 727; MS (positive APCI, *m*/*z*): 507 [50, (M + 2)], 506 [27, (M + 1)], 505 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.887).

***2-Imino-4-methyl-4-ethyl-8-(3,5-dichlorophenyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3o).*** mp: 265–267°C; $^1$H NMR (400 MHz, DMSO) δ 0.66 (t, $J$ = 7.2 Hz, 3H), 1.08 (m, 2H), 1.37 (s, 3H), 7.54–7.86 (m, 13H), 8.23 (s, 1H), 8.95 (s, 1H), 10.01 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3353, 3053, 2795, 1777, 1674, 1611, 1588, 1487, 728, 712; MS (positive APCI, *m*/*z*): 492 [60, (M + 1)], 491 (85, M), 437 [80, (M-54)]; UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.554).

***2-Imino-8-(3,5-dichlorophenyl)-6,6-diphenyl-4-spirocyclopentanon-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3p).*** mp: 267–269°C (dec.); $^1$H NMR (400 MHz, DMSO) δ 1.01–2.06 (m, 8H), 7.54–7.89 (m, 13H), 8.07 (s, 1H), 9.00 (s, 1H), 10.08 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3360, 3021, 2800, 1778, 1676, 1611, 1588, 1486, 1186, 727, 710; MS (positive APCI, *m*/*z*): 505 [75, (M + 2)], 504 [35, (M + 1)], 503 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.452).

***2-Imino-4-(2-methylpheyl)-8-(3,5-dichlorophenyl)-6,6-diphenyl-2, 3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3q).*** mp: 273–275°C; $^1$H NMR (400 MHz, DMSO) δ 2.19 (s, 3H), 6.38 (s, 1H), 8.00–6.38 (m, 17H), 8.47 (s, 1H), 9.04 (s, 1H), 10.24 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3368, 3046, 2695, 1773, 1675, 1617, 1590, 1482, 759, 729, 706; MS (positive APCI, *m*/*z*): 541 [70, (M + 1)], 539 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm, 207 (0.425).

***2-Imino-4-(3-methylpheyl)-8-(3,5-dichlorophenyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3r).*** mp: 269–271°C; $^1$H NMR (400 MHz, DMSO) δ 2.49 (s, 3H), 6.30 (s, 1H), 6.67–7.96 (m, 17H), 8.39 (s, 1H), 9.00 (s, 1H), 9.98 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3358, 3059, 2696, 1776, 1677, 1659, 1619, 1575, 1490, 1187, 751, 697; MS (positive APCI, *m*/*z*): 541 [83, (M + 2)], 539 (100, M), 538 [55, (M-1)]; UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.383).

***2-Imino-4-(2-chlorophenyl)-8-(3,5-dichlorophenyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3s).*** mp: 280–282°C; $^1$H NMR (400 MHz, DMSO) δ 6.51 (s, 1H), 7.05–7.61 (m, 17H), 8.24 (s, 1H), 9.10 (s, 1H), 10.15 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3355, 3021, 2688, 1774, 1673, 1613, 1481, 1197, 758, 706; MS (positive APCI, *m*/*z*): 561 [100, (M + 2)], 560 [40, (M + 1)], 559 (55, M); UV–vis (MeOH) $\lambda_{max}$/nm 208 (0.419).

***2-Imino-4-(2,4-dichlorophenyl)-8-(3,5-dichlorophenyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one. HCl (3t).*** mp: 270–272°C; $^1$H NMR (400 MHz, DMSO) δ 6.54 (s, 1H), 7.07–7.95 (m, 16H), 8.51 (s, 1H), 9.15 (s, 1H), 10.40 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3355, 3062, 2680, 1781, 1673, 1617, 1587, 1494, 1449, 1186, 752, 698; MS (positive APCI, *m*/*z*): 597 [30, (M + 1)], 595 (M, 100), 593 [60, (M-2)]; UV–vis (MeOH) $\lambda_{max}$/nm 208 (0.325).

***2-Imino-4-(3-nitrophenyl)-8-(3,5-dichlorophenyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3u).*** mp: 274–276°C; $^1$H NMR (400 MHz, DMSO) δ 6,70 (s, 1H), 7.00–7.98 (m, 17H), 8.51 (s, 1H), 9.11 (s, 1H), 10.31 (s, 1H); IR (KBr) $\upsilon_{max}$/cm$^{-1}$: 3349, 3065, 2667, 1787, 1680, 1620, 1527, 1493, 1187, 753, 693, 680; MS (positive APCI, *m*/*z*): 572 [55, (M + 2)], 570 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 206 (0.497).

***2-Imino-4-(2-nitrostyryl)-8-(3,5-dichlorophenyl)-6,6-diphenyl-2,3-dihydro-4H-imidazo[2,3-d]-1,3,5-triazin-7(6H)one.HCl (3v).*** mp: 280–282°C (dec.); $^1$H NMR (400 MHz, DMSO) δ 5.98–6.07 (m, 2H), 6.51 (d, $J$ = 14.2 Hz, 1H), 7.06–7.92 (m, 16H), 8.39 (s, 1H), 9.07 (s, 1H), 9.83 (s, 1H); IR (KBr) $\upsilon_{max}/cm^{-1}$: 334, 3028, 2787, 1773, 1679, 1664, 1612, 1523, 1487, 1185, 734, 699; MS (positive APCI, *m/z*): 598 [97, (M + 2)], 597 [70, (M + 1)], 596 (100, M); UV–vis (MeOH) $\lambda_{max}$/nm 207 (0.614).

## REFERENCES AND NOTES

[1] (a) Kappe, C. O. Angew Chem Int Ed Engl 2004, 43, 6250; (b) Kappe, C. O.; Stadler, A. Microwaves in Organic and Medicinal Chemistry; Wiley-VCH: Weinheim, 2005; (c) Loupy, A., Ed. Microwaves in Organic Synthesis, 2nd ed.; Wiley-VCH: Weinheim, 2006.

[2] (a) Larhed, M.; Hallberg, A. Drug Discov Today 2001, 6, 406; (b) Wathey, B.; Tierney, J.; Lidström, P.; Westman, J. Drug Discov Today 2002, 7, 373; (c) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. Mini Rev Med Chem 2003, 3, 449; (d) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. Drug Discov Today Technol 2005, 2, 155; (e) Kappe, C. O.; Dallinger, D. Nat Rev Drug Discov 2006, 5, 51.

[3] (a) Loupy, A., Ed. Microwaves in Organic Synthesis; Wiley-VCH: Weinheim, 2002; (b) Hayes, B. L. Microwave Synthesis: Chemistry at the Speed of Light; CEM Publishing: Matthews, 2002; (c) Lidström, P.; Tierney, J. P., Eds.; Microwave-Assisted Organic Synthesis; Blackwell Scientific: Oxford, 2005.

[4] (a) Katritzky, A. R.; Singh, S. K. ARKIVOC 2003, xiii, 68; (b) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. Green Chem 2004, 6, 128; (c) Hayes, B. L. Aldrichimica Acta 2004, 37, 66; (d) Mavandadi, F.; Lidström, P. Curr Top Med Chem 2004, 4, 773; (e) De la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. Chem Soc Rev 2005, 34, 164.

[5] Dolzhenko, A. V.; Chui, W. K.; Dolzhenko, A. V.; Chan, L. W. J Fluorine Chem 2005, 126, 759.

[6] Novellino, E.; Abignente, E.; Cosimelli, B.; Greco, G.; Iadanza, M.; Laneri, S.; Lavecchia, A.; Rimoli, M. G.; Da Settimo, F.; Primofiore, G.; Tuscano, D.; Trincavelli, L.; Martini, C. J Med Chem 2002, 45, 5030.

[7] Cui, P.; Macdonald, T. L.; Chen, M.; Nadler, J. L. Bioorg Med Chem Lett 2006, 16, 3401.

[8] Schiewald, E.; Graubaum, H. W.; Martin, H. D.; Steinke, W.; Kramer, W.; Lange, N.; Mory, W.; Wolter, G. DD Pat. 2,27,035 (1985); Chem Abstr 104, 143975.

[9] Gulyas, G.; Emri, T.; Simon, A.; Gyorgydeak, Z. Folia Microbiol 2002, 47, 29.

[10] Toyoda, T.; Brobey, R. K. B.; Sano, G.; Horii, T.; Tomioka, N.; Itai, A. Biochem Biophys Res Commun 1997, 235, 515.

[11] Itai, A.; Toyota, T. Jpn. Pat. 10,310,526 (1998); Chem Abstr 130, 62956.

[12] Brzozowski, Z. Acta Pol Pharm 1998, **55**, 49.

[13] Ward, C. E.; Berthold, R. V.; Koerwer, J. F.; Tomlin, J. B.; Manning, D. T. J Agric Food Chem 1986, 34, 1005.

[14] Schiewald, E.; Graubaum, H. W.; Martin, H. D.; Steinke, W.; Kramer, W.; Lange, N.; Mory, W.; Wolter, G. DD Pat. 2,27,035 (1985); Chem Abstr 104, 143975.

[15] Schiewald, E.; Graubaum, H. W.; Martin, H. D.; Lange, N.; Wolter, G.; Kochmann, W.; Kramer, W.; Steinke, W. DD Pat. 2,14,054 (1984); Chem Abstr 102, 127347.

[16] Ward, C. E.; Berthold, R. V. CA Pat. 1,159,065 (1983); Chem Abstr 100, 209880.

[17] Koerwer, J. F. CA Pat. 11,46,376 (1983); Chem Abstr 99, 175809.

[18] Bennion, C.; Robinson, D. EP Pat. 93,515 (1983); Chem Abstr 100, 85727.

[19] Daum, W.; Frohberger, P. E. DE Pat. 25,27,677 (1977); Chem Abstr 86, 155704.

[20] Bose, E. A.; White, E. R. U.S. Pat. 37,25,406 (1973); Chem Abstr 79, 62595.

[21] Schroeder, L.; Ost, W.; Thomas, K. DE Pat. 21,44,505 (1973); Chem Abstr 78, 159686.

[22] (a) Schramm, H. W. Sci Pharm 1991, 59, 275; (b) Schramm, H. W. Sci Pharm 1991, 59, 203; (c) Schramm, H. W.; Treiber, J.; Schubert-Zsilavecz, M. Sci Pharm 1991, 59, 191; (d) Schramm, H. W. Sci Pharm 1991, 59, 123; (e) Schramm, H. W. Sci Pharm 1991, 59, 115; (f) Schramm, H. W.; Reidlinger, H.; Wendelin, W. Sci Pharm 1990, 58, 379; (g) Schramm, H. W. Sci Pharm 1989, 57, 385.

[23] Schramm, H. W.; Klingspiegl, B. Diplom Thesis, Graz University, 1989.

[24] Schramm, H. W.; Grassegger, M. Diplom thesis, Graz University, 1989.

[25] Schramm, H. W.; Kappel, H. Diplom Thesis, Graz University, 1993.

# Synthesis and Characterization of New 3-Acyl-7-hydroxy-6,8-substituted-coumarin and 3-Acyl-7-benzyloxy-6,8-substituted-coumarin Derivatives

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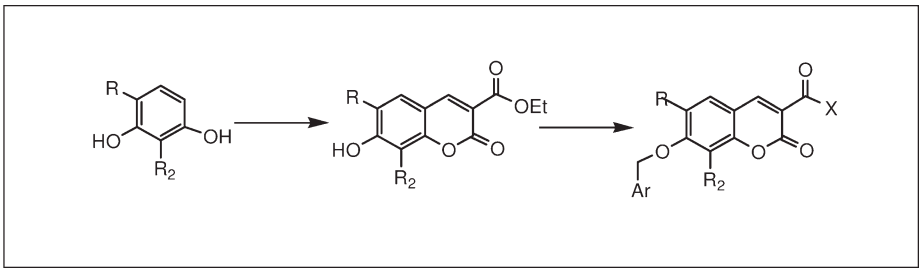


A new series of 3-acyl-6,7,8-substituted coumarin derivatives has been synthesized in high yields (79–99%) and characterized by means of elemental analysis, mass spectrometry, IR, and $^1$H NMR spectroscopy. We examined with particular attention the presence of an acyl group at position 3 (ethyl ester, carboxylic acid, and acyl chloride), and of a hydroxyl group at position 7 or a functionalized one like benzyloxy or phthalimido. The hydroxyl group has been modified by an etherification in presence of crown ether with substituted benzyl bromide or chloride to evaluate the influence on chemical characteristics and lipophilicity of coumarin nucleus. Halogens (Cl, Br) and methyl group were introduced in position 6 and 8 of the coumarin ring, respectively, in order to study their effect on reaction feasibility. Some of these 3-acyl derivatives have been recently assayed as MAO inhibitors and as intermediates (i.e. reactive chloride derivative) to design new anti-*Helicobacter pylori* agents.

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## INTRODUCTION

Coumarins, (2*H*)-1-benzopyran-2-ones, represent a common type of phytochemicals, frequently encountered in plants of the *Apiaceae*, *Rutaceae*, *Fabaceae*, and *Hyppocastanaceae* [1]. Interest in this scaffold arose from the identification of both natural or synthetic pharmacologically active derivatives, which have been found to be useful in photochemotherapy, antitumor [2], and anti-HIV [3] therapy, and as stimulants for central nervous system, antibacterials, antioxidants [4], anti-inflammatory [5], anticoagulants, and dyes according to the nature and the substitution pattern. In particular we recently demonstrated that 3-acyl and 3-carboxyamido coumarins could be considered good lead compounds as reversible and effective human monoamine oxidase (hMAO) inhibitors [6,7].

The interesting biological properties of coumarins made these compounds very attractive for organic synthesis. There are many developed methods of coumarins synthesis, e.g. Pechman reaction, Perkin reaction, Knoevenagel condensation, and many others [1]. However, it is important to highlight that all the reported procedures have some disadvantages, as they lack generality and efficiency making the development of new reliable high-yielding methods for the synthesis of coumarins an important matter. For these reasons, we synthesized many molecules based on the coumarin ring system by utilizing classic and innovative synthetic techniques such as carbon suboxide [8] and microwave [9].

In particular, microwave irradiation usually accelerates some chemical transformations and offers numerous benefits for performing solventless procedures (green chemistry) and improving reaction yields, especially in heterocyclic chemistry [10].

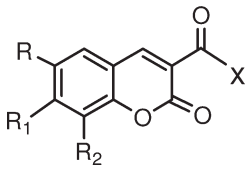
Hence, in this article, we report on synthesis and characterization by spectral data, such as IR, $^1$H NMR, and mass spectroscopy of coumarin analogues bearing an acyl function (ethyl ester, carboxylic acid, and acyl chloride) at position 3, halogens (Cl, Br) at position 6, different unsubstituted or substituted benzyloxy moieties at position 7, and methyl group at position 8 (Table 1).

## RESULTS AND DISCUSSION

Coumarin derivatives were synthesized starting from substituted salicylic aldehydes according to the pathway reported in Scheme 1.

**Table 1**

Structure and CLogP (ChemDraw Ultra 8.0) of synthesized coumarin derivatives.



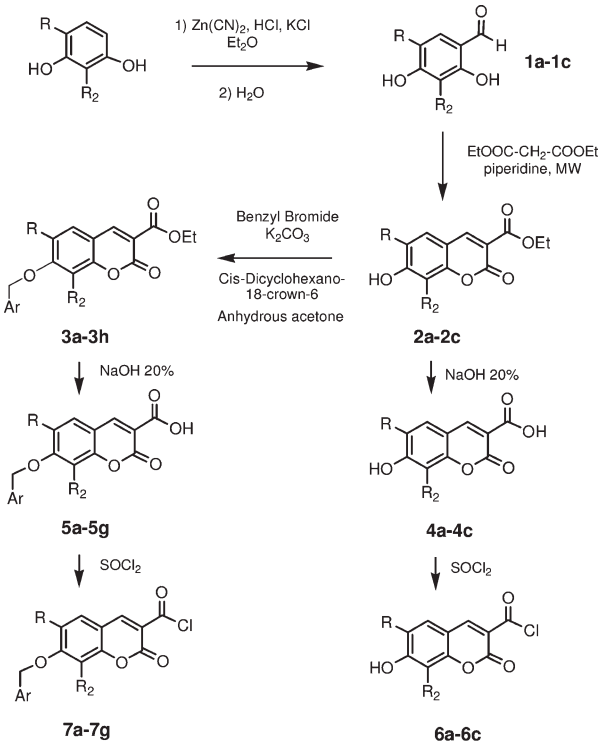

| Comp | R | $R_1$ | $R_2$ | X | ClogP | *m/z* |
|---|---|---|---|---|---|---|
| **3a** | Cl | $CH_2Ph$ | H | OEt | 4.52 | 358.77 |
| **3b** | Br | $OCH_2Ph$ | H | OEt | 4.67 | 403.22 |
| **3c** | H | $OCH_2Ph$ | $CH_3$ | OEt | 4.53 | 338.35 |
| **3d** | H | $OCH_2$(2-Cl-Ph) | H | OEt | 4.74 | 358.77 |
| **3e** | H | $OCH_2$(4-F-Ph) | H | OEt | 4.17 | 342.31 |
| **3f** | H | $OCH_2$(4-Cl-Ph) | H | OEt | 4.74 | 358.77 |
| **3g** | H | $OCH_2$(4-$NO_2$-Ph) | H | OEt | 3.77 | 369.32 |
| **3h** | H | $OCH_2$phtalimido | H | OEt | 3.15 | 393.35 |
| **5a** | Cl | $OCH_2Ph$ | H | OH | 3.80 | 330.71 |
| **5b** | Br | $OCH_2Ph$ | H | OH | 3.95 | 375.17 |
| **5c** | H | $OCH_2Ph$ | $CH_3$ | OH | 3.81 | 310.30 |
| **5d** | H | $OCH_2$(2-Cl-Ph) | H | OH | 4.02 | 330.72 |
| **5e** | H | $OCH_2$(4-F-Ph) | H | OH | 3.45 | 314.26 |
| **5f** | H | $OCH_2$(4-Cl-Ph) | H | OH | 4.02 | 330.72 |
| **5g** | H | $OCH_2$(4-$NO_2$-Ph) | H | OH | 3.05 | 341.27 |
| **6a** | Cl | OH | H | Cl | 1.46 | 259.04 |
| **6b** | Br | OH | H | Cl | 1.66 | 303.49 |
| **6c** | H | OH | $CH_3$ | Cl | 1.49 | 238.32 |
| **7a** | Cl | $OCH_2Ph$ | H | Cl | 3.43 | 349.16 |
| **7b** | Br | $OCH_2Ph$ | H | Cl | 3.58 | 393.61 |
| **7c** | H | $OCH_2Ph$ | $CH_3$ | Cl | 3.43 | 328.74 |
| **7d** | H | $OCH_2$(2-Cl-Ph) | H | Cl | 3.65 | 349.16 |
| **7e** | H | $OCH_2$(4-F-Ph) | H | Cl | 3.08 | 332.71 |
| **7f** | H | $OCH_2$(4-Cl-Ph) | H | Cl | 3.65 | 349.16 |
| **7g** | H | $OCH_2$(4-$NO_2$-Ph) | H | Cl | 2.68 | 359.72 |

The corresponding salicylic aldehydes were obtained by a Gattermann aromatic formylation starting from 2- or 4-substituted resorcinol in a strongly acidic environment (**1a**–**1c**). Ethyl esters of (2*H*)-1-benzopyran-2-one-3-carboxylic acids (**2a**–**2c**), were easily obtained by a Knoevenagel cyclization in 15–20 min (80°C) under microwave irradiation with an automatic single-mode reactor. All reactions were performed solventless in vials of 10 mL, confirming that the focused microwave irradiation was a very effective technique for accelerating thermal organic reactions and limiting solvent wasting, not being affected by substituents. These compounds, bearing a hydroxyl group at position 7, were subsequently functionalized by benzylation in the presence of *N*,*N*′-dicyclohexyl-18-crown-6-ether, which by chelating potassium ion facilitated the nucleophilic attack to improve the yields of the related compounds (**3a**–**3h**). Alkaline hydrolysis with 10% sodium hydroxide gave carboxylic acid compounds (**4a**–**4c** and **5a**–**5f**), which were treated with thionyl chloride at reflux to yield the desired and reactive acyl chloride derivatives (**6a**–**6c** and **7a**–**7g**). In general this synthetic procedure allowed us to obtain the desired compounds in high yields and simplify reaction work up, limiting the presence of by-products.

The compounds, correctly analyzed for their molecular formula, showed in the IR spectrum strong bands at 1695–1720 $cm^{-1}$ due to the presence of a δ-lactone C=O and eventually a carbonyl group, and characteristic bands at 1655, 1615, 1575, and 1500 $cm^{-1}$ (double bonds in the aromatic ring).

The lipophilicity (ClogP) of this coumarin scaffold has been calculated with the suitable algorithm for each molecule by using ChemDraw Ultra 8.0. because of its importance in modulating biological activity and pharmacodynamic profile of the molecules [11]. As expected, the introduction of a benzyloxy group at position 7 of the coumarin ring deeply affects this parameter. All compounds, and above all compound **5g**, which was insoluble in common organic solvents (dimethyl

**Scheme 1.** General synthetic pattern of coumarin derivatives.




## EXPERIMENTAL

Starting materials and reagents were obtained from commercial suppliers and were used without purification. Melting points (mp) were determined by the capillary method on an FP62 apparatus (Mettler-Toledo) and are uncorrected. $^1$H NMR spectra were recorded at 400 MHz on a Bruker spectrometer using DMSO-$d_6$ as solvent. Chemical shifts are expressed as δ units (ppm) relative to TMS. Coupling constants *J* are expressed in hertz (Hz). Elemental analyses for C, H, and N were determined with a PerkinElmer 240 B microanalyzer and the analytical results were within ±0.4% of the theoretical values for all compounds. All reactions were monitored by TLC performed on 0.2 mm thick silica gel plates (60 $F_{254}$ Merck). Preparative flash column chromatography was carried out on silica gel (230–400 mesh, G60 Merck). Organic solutions were dried over anhydrous sodium sulphate. Concentration and evaporation of the solvent after reaction or extraction was carried out on a rotary evaporator (Büchi Rotavapor) operating at reduced pressure. IR spectra were registered on a PerkinElmer FTIR Spectrometer Spectrum 1000 in potassium bromide. Mass spectra (EI) were obtained with a Fisons QMD 1000 mass spectrometer (70 ev, 200 μA, ion source temperature 200°C). The samples were introduced directly into the ion source. Compounds **2a**–**2c**, synthesized with the microwave method, were obtained with a Biotage Initiator$^{TM}$ 2.0.

The synthesis of some compounds (**1a**–**1c**, **2a**–**2c**, and **4a**–**4c**) has been previously described and was performed with slight changes. Their analytical and spectral data were in full agreement with those reported in the literature.

sulfoxide, chloroform, and acetone), have been characterized by mass spectral studies. In the mass spectra the fragment ion at *m*/*z* (%) = 173 (90) corresponding to the 3-acyl coumarin structure was always the most abundant observed. The fragmentation pattern of derivative **5g** was described in Figure 1. This compound showed the fragment at *m*/*z* (%) 341 (10), which likely represented the molecular ion. In fact, the base peak, referred to the 4′-nitro-benzyl fragment, was always present at 134 (100). In addition the mass spectrum revealed ion suggestive at *m*/*z* 297 (5), 250 (5), and 205 (20) because of the loss of COOH, $CO_2$, and $NO_2$.

In this article, we have synthesized, by using readily available and inexpensive reagents, and fully characterized a new series of heterocyclic derivatives (3-acyl-6,7,8-substituted coumarins), which could reveal their potentials as versatile biodynamic agents. The most important results of our approach are the optimization of the yields and of the reaction times using microwave irradiation. In addition, lower amount of solvent was used and a better workup was obtained. The introduction of a substituted benzyloxy group at position 7 could influence not only the physical–chemical properties, but also their biological activity. Halogens (Cl, Br) and methyl group were introduced in position 6 and 8 of the coumarin ring, respectively, to study their effect on reaction feasibility.

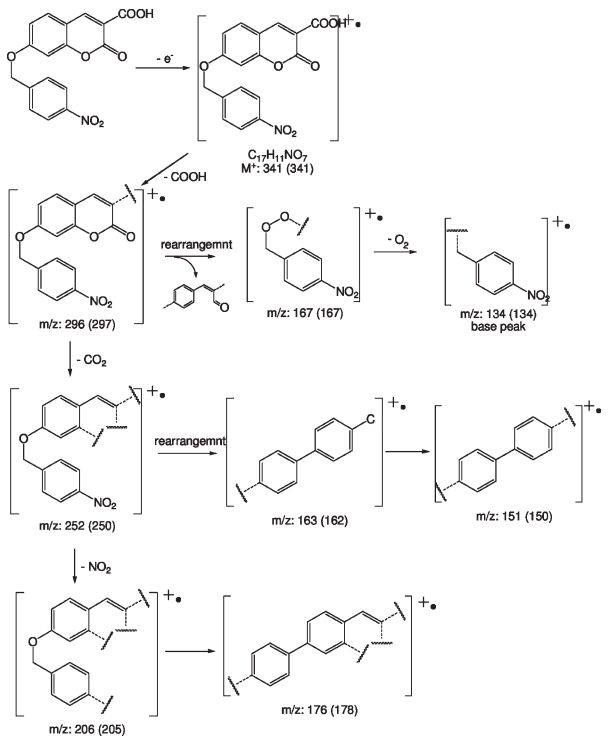



**Figure 1.** The fragmentation pattern of derivative **5g**.

**General procedure for the synthesis of coumarin derivatives 1a–1c.** The substituted salicylic aldehydes were prepared in a 500 mL bottle, fitted with a mechanical stirrer, a reflux water condenser and an inlet tube, with wide mouth to prevent clogging from the precipitate. Resorcinol derivatives (1 mmol), zinc cyanide (2 mmol), and potassium chloride (0.3 mmol) were suspended in anhydrous diethyl ether (40 mL). Gaseous HCl was bubbled inside the bottle and then water was added to hydrolyze the immine product into aldehyde. The zinc chloride, which was produced at the same time, acted as an effective condensing agent.

**General procedure for the synthesis of coumarin derivatives 2a–2c.** The starting ethyl ester of coumarin-3-carboxylic acid was prepared by Knoevenagel reaction between diethyl malonate (1 mmol) and the appropriate salicylic aldehyde (1 mmol) with catalytic amounts of piperidine (0.5 mL) in a 10 mL vial suitable for an automatic single-mode microwave reactor (2.45 GHz high-frequency microwaves, power range 0–300 W). The mixture was prestirred for 30 sec and then heated by microwave irradiation for 15–20 min at 80°C (irradiation power reaches its maximum at the beginning of reaction, then it decreases to lower and quite constant values). The internal vial temperature was controlled by an IR sensor. After cooling with pressurized air, the reaction mixture was poured onto ice, filtered, and dried under vacuum.

**General procedure for the synthesis of coumarin derivatives 3a–3h.** The etherification at position 7 was performed by adding suitable benzyl bromide (1 mmol) and potassium carbonate (1 mmol) in dry acetone (50 mL) for 48 h at room temperature, using *N*,*N*′-dicyclohexyl-18-crown-6-ether (1 mmol) as a chelating agent. The resulting reaction mixture was filtered and the crude product was purified by chromatography.

***Ethyl 7-(benzyloxy)-6-chloro-2-oxo-2H-chromene-3-carboxylate (3a).*** 85% yield; mp 211–212°C; $^1$H NMR (DMSO-$d_6$) δ 1.27–1.29 (t, 3H, $CH_3$), 4.29–4.31 (q, 2H, $CH_2$), 5.31 (s, 2H, $OCH_2Ar$), 7.30 (s, 1H, $C_8$H-chrom.), 7.31–7.50 (m, 5H, Ar), 8.18 (s, 1H, $C_5$H-chrom.), 8.68 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{19}H_{15}ClO_5$: C, 63.61; H, 4.21. Found: C, 63.63; H, 4.22.

***Ethyl 7-(benzyloxy)-6-bromo-2-oxo-2H-chromene-3-carboxylate (3b).*** 87% yield; mp 215–216°C; $^1$H NMR (DMSO-$d_6$) δ 1.30–1.32 (t, 3H, $CH_3$), 4.32–4.34 (q, 2H, $CH_2$), 5.40 (s, 2H, $OCH_2Ar$), 7.19 (s, 1H, $C_8$H-chrom.), 7.21–7.49 (m, 5H, Ar), 8.10 (s, 1H, $C_5$H-chrom.), 8.60 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{19}H_{15}BrO_5$: C, 56.59; H, 3.75. Found: C, 56.57; H, 3.76.

***Ethyl 7-(benzyloxy)-8-methyl-2-oxo-2H-chromene-3-carboxylate (3c).*** 89% yield; mp 154–155°C; $^1$H NMR (DMSO-$d_6$) δ 1.27–1.29 (t, 3H, $CH_3$), 2.20 (s, 3H, $ArCH_3$), 4.22–4.27 (q, 2H, $CH_2$), 5.31 (s, 2H, $OCH_2Ar$), 7.39 (s, 1H, $C_8$H-chrom.), 7.40–7.45 (m, 5H, Ar), 7.46 (s, 1H, $C_5$H-chrom.), 8.72 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.01; H, 5.37.

***Ethyl 7-(2-chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3d).*** 79% yield; mp 126–127°C; $^1$H NMR (DMSO-$d_6$) 1.28–1.30 (t, 3H, $CH_3$), 4.29–4.31 (q, 2H, $CH_2$), 5.44 (s, 2H, $OCH_2Ar$), 7.19 (s, 1H, $C_8$H-chrom.), 7.21–7.22 (m, 1H, $C_6$H-chrom.), 7.23–7.27 (m, 4H, Ar), 7.28–7.29 (m, 1H, $C_5$H-chrom.), 8.70 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{19}H_{15}ClO_5$: C, 63.61; H, 4.21. Found: C, 63.63; H, 4.22.

***Ethyl 7-(4-fluorobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3e).*** 87% yield; mp 159–160 °C; $^1$H NMR (DMSO-$d_6$) 1.29 (t, 3H, $CH_3$), 4.33 (q, 2H, $CH_2$), 5.23 (s, 2H, $OCH_2Ar$), 7.15 (s, 1H, $C_8$H-chrom.), 7.26–7.28 (m, 1H, $C_6$H-chrom.), 7.61–7.65 (m, 2H, $C_3$H-Ar and $C_5$H-Ar), 7.72–7.74 (m, 1H, $C_5$H-chrom.), 7.89–7.92 (m, 2H, $C_2$H-Ar and $C_6$H-Ar), 8.85 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{19}H_{15}FO_5$: C, 66.66; H, 4.42. Found: C, 66.68; H, 4.43.

***Ethyl 7-(4-chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3f).*** 79% yield; mp 160–161°C; $^1$H NMR (DMSO-$d_6$) 1.28 (t, 3H, $CH_3$), 4.23 (q, 2H, $CH_2$), 5.26 (s, 2H, $OCH_2Ar$), 7.19 (s, 1H, $C_8$H-chrom.), 7.25–7.28 (m, 1H, $C_6$H-chrom.), 7.31–7.36 (m, 2H, $C_3$H-Ar and $C_5$H-Ar), 7.41–7.43 (m, 1H, $C_5$H-chrom.), 7.54–7.58 (m, 2H, $C_2$H-Ar and $C_6$H-Ar), 8.80 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{19}H_{15}ClO_5$: C, 63.61; H, 4.21. Found: C, 63.63; H, 4.22.

***Ethyl 7-(4-nitrobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3g).*** 87% yield; mp 210–211°C; $^1$H NMR (DMSO-$d_6$) 1.29 (t, 3H, $CH_3$), 4.33 (q, 2H, $CH_2$), 5.45 (s, 2H, $OCH_2Ar$), 7.26 (s, 1H, $C_8$H-chrom.), 7.30–7.32 (m, 1H, $C_6$H-chrom.), 7.41–7.44 (m, 2H, $C_2$H-Ar and $C_6$H-Ar), 7.51–7.53 (m, 1H, $C_5$H-chrom.), 8.26–8.30 (m, 2H, $C_3$H-Ar and $C_5$H-Ar), 8.83 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.09; N, 3.79. Found: C, 61.77; H, 4.10; N, 3.80.

***Ethyl 7-[(1,3-dioxoisoindolin-2-yl)methoxy]-2-oxo-2H-chromene-3-carboxylate (3h).*** 98% yield; mp 284–285°C; $^1$H NMR (DMSO-$d_6$) 1.27–1.31 (t, 3H, $CH_3$), 4.26-4.28 (q, 2H, $CH_2$), 5.73 (s, 2H, $OCH_2Ar$), 7.29 (s, 1H, $C_8$H-chrom.), 7.33–7.35 (m, 1H, $C_6$H-chrom.), 7.49–7.51 (m, 1H, $C_5$H-chrom.), 7.86–7.92 (m, 4H, Ar), 8.73 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{21}H_{15}NO_7$: C, 64.12; H, 3.84; N, 3.56. Found: C, 64.10; H, 3.83; N, 3.57.

**General procedure for the synthesis of coumarin derivatives 4a–4c and 5a–5g.** All ethyl ester derivatives were dissolved in NaOH 10% (50 mL) and added of HCl 3*N* (50 mL). The resulting suspension was filtered and dried under vacuum.

***7-(Benzyloxy)-6-chloro-2-oxo-2H-chromen-3-carboxylic acid (5a).*** 87% yield; mp 233–234°C; $^1$H NMR (DMSO-$d_6$) δ 5.34 (s, 2H, $OCH_2Ar$), 7.41 (s, 1H, $C_8$H-chrom.), 7.43–7.48 (m, 5H, Ar), 8.18 (s, 1H, $C_5$H-chrom.), 8.43 (s, 1H, $C_4$H-chrom.), 13.24 (bs, 1H, COOH, $D_2O$ exch.). Anal. Calcd. for $C_{17}H_{11}ClO_5$: C, 61.74; H, 3.35. Found: C, 61.76; H, 3.36.

***7-(Benzyloxy)-6-bromo-2-oxo-2H-chromene-3-carboxylic acid (5b).*** 92% yield; mp 255–256°C; $^1$H NMR (DMSO-$d_6$) δ 5.30 (s, 2H, $OCH_2Ar$), 7.30 (s, 1H, $C_8$H-chrom.), 7.41–7.47 (m, 5H, Ar), 8.20 (s, 1H, $C_5$*H*-chrom.), 8.59 (s, 1H, $C_4$H-chrom.), 13.15 (bs, 1H, COOH, $D_2O$ exch.). Anal. Calcd. for $C_{17}H_{11}BrO_5$: C, 54.42; H, 2.96. Found: C, 54.44; H, 2.95.

***7-(Benzyloxy)-8-methyl-2-oxo-2H-chromene-3-carboxylic acid (5c).*** 90% yield; mp 204–205°C; $^1$H NMR (DMSO-$d_6$) δ 2.23 (s, 3H, $ArCH_3$), 5.28 (s, 2H, $OCH_2Ar$), 7.21 (s, 1H, $C_8$H-chrom.), 7.47–7.53 (m, 5H, Ar), 7.77 (s, 1H, $C_5$H-chrom.), 8.70 (s, 1H, $C_4$H-chrom.), 12.98 (bs, 1H, COOH, $D_2O$ exch.). Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.69; H, 4.54.

***7-(2-Chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5d).*** 92% yield; mp 218–219°C; $^1$H NMR (DMSO-$d_6$) 5.32 (s, 2H, $OCH_2Ar$), 7.12 (s, 1H, $C_8$H-chrom.), 7.13–7.15 (m, 1H, Ar) 7.40–7.41 (m, 1H, $C_6$H-chrom.), 7.42–7.44 (m, 1H, Ar), 7.65–7.67 (m, 1H, Ar), 7.77–7.79 (m, 1H, Ar), 7.85–7.86 (m, 1H, $C_5$H-chrom.), 8.72 (s, 1H, $C_4$H-chrom.), 13.12 (bs, 1H,

COOH, $D_2O$ exch.). Anal. Calcd. for $C_{17}H_{11}ClO_5$: C, 61.74; H, 3.35. Found: C, 61.72; H, 3.36.

***7-(4-Fluorobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5e).*** 91% yield; mp 228–229°C; $^1$H NMR (DMSO-$d_6$) 5.33 (s, 2H, $OCH_2Ar$), 7.12 (s, 1H, $C_8$H-chrom.), 7.25–7.27 (m, 1H, $C_6$H-chrom.), 7.37–7.40 (m, 2H, $C_3$H-Ar and $C_5$H-Ar), 7.53–7.56 (m, 2H, $C_2$H-Ar and $C_6$H-Ar), 7.82–7.84 (m, 1H, $C_5$H-chrom.), 8.85 (s, 1H, $C_4$H-chrom.), 13.02 (s, 1H, COOH, $D_2O$ exch.). Anal. Calcd. for $C_{17}H_{11}FO_5$: C, 64.97; H, 3.53. Found: C, 64.98; H, 3.54.

***7-(4-Chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5f).*** 93% yield; mp 251–252°C; $^1$H NMR (DMSO-$d_6$) 5.26 (s, 2H, $OCH_2Ar$), 7.07 (s, 1H, $C_8$H-chrom.), 7.09–7.12 (m, 1H, $C_6$H-chrom.), 7.47–7.53 (m, 4H, Ar), 7.84–7.86 (m, 1H, $C_5$H-chrom.), 8.72 (s, 1H, $C_4$H-chrom.), 13.12 (bs, 1H, COOH, $D_2O$ exch.). Anal. Calcd. for $C_{17}H_{11}ClO_5$: C, 61.74; H, 3.35. Found: C, 61.75; H, 3.34.

***7-(4-Nitrobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5g).*** 89% yield; mp 281–282°C. Insoluble in DMSO, chloroform, and acetone. ms: *m*/*z* 134 (100), 205 (20), 250 (5), 297 (5), 341 (10). Anal. Calcd. for $C_{17}H_{11}NO_7$: C, 59.83; H, 3.25; N, 4.10. Found: C, 59.84; H, 3.26; N, 4.09.

**General procedure for the synthesis of coumarin derivatives 6a–6c and 7a–7g.** Carboxylic acid derivatives were refluxed under magnetic stirring with thionyl chloride (40 mL) for 3 h to give the desired compound. The obtained solutions were added with hexane and the resulting suspensions were then filtered and dried under vacuum.

***6-Chloro-7-hydroxy-2-oxo-2H-chromene-3-carbonyl chloride (6a).*** 95% yield; mp >300°C; $^1$H NMR (DMSO-$d_6$) δ 6.92 (s, 1H, $C_8$H-chrom.), 7.99 (s, 1H, $C_5$H-chrom.), 8.62 (s, 1H, $C_4$H-chrom.), 11.96 (bs, 1H, OH, $D_2O$ exch.). Anal. Calcd. for $C_{10}H_4Cl_2O_4$: C, 46.37; H, 1.56. Found: C, 46.39; H, 1.57.

***6-Bromo-7-hydroxy-2-oxo-2H-chromene-3-carbonyl chloride (6b).*** 91% yield; mp >300°C; $^1$H NMR (DMSO-$d_6$) δ 6.87 (s, 1H, $C_8$H-chrom.), 8.11 (s, 1H, $C_5$H-chrom.), 8.63 (s, 1H, $C_4$H-chrom.), 11.92 (bs, 1H, OH, $D_2O$ exch.). Anal. Calcd. for $C_{10}H_4BrClO_4$: C, 39.57; H, 1.33. Found: C, 39.55; H, 1.32.

***7-Hydroxy-8-methyl-2-oxo-2H-chromene-3-carbonyl chloride (6c).*** 87% yield; mp >300 °C; $^1$H NMR (DMSO-$d_6$) δ 2.16 (s, 3H, $ArCH_3$), 6.96–6.98 (m, 1H, $C_6$H-chrom.), 7.58–7.60 (m, 1H, $C_5$H-chrom.), 8.69 (s, 1H, $C_8$H-chrom.). Anal. Calcd. for $C_{11}H_7ClO_4$: C, 55.37; H, 2.96. Found: C, 55.39; H, 2.95.

***7-(Benzyloxy)-6-chloro-2-oxo-2H-chromene-3-carbonyl chloride (7a).*** 95% yield; mp 214–215°C; $^1$H NMR (DMSO-$d_6$) δ 5.34 (s, 2H, $OCH_2Ar$), 7.41 (s, 1H, $C_8$H-chrom.), 7.43–7.48 (m, 5H, Ar), 8.18 (s, 1H, $C_5$H-chrom.), 8.43 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: C, 58.48; H, 2.89. Found: C, 58.50; H, 2.90.

***7-(Benzyloxy)-6-bromo-2-oxo-2H-chromene-3-carbonyl chloride (7b).*** 85% yield; mp 214–215°C; $^1$H NMR (DMSO-$d_6$) δ 5.30 (s, 2H, $OCH_2Ar$), 7.30 (s, 1H, $C_8$H-chrom.), 7.41–7.47 (m, 5H, Ar), 8.20 (s, 1H, $C_5$H-chrom.), 8.60 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{17}H_{10}BrClO_4$: C, 51.87; H, 2.56. Found: C, 51.89; H, 2.57.

***7-(2-Chlorobenzyloxy)-2-oxo-2H-chromene-3-carbonyl chloride (7d).*** 91% yield; mp 171–172°C; $^1$H NMR (DMSO-$d_6$) δ 5.29 (s, 2H, $ArCH_2$), 7.18 (s, 1H, $C_8$H-chrom.), 7.19–7.21 (m, 1H, Ar), 7.40–7.41 (m, 1H, $C_6$H-chrom.), 7.42–7.44 (m, 1H, Ar), 7.50–7.53 (m, 1H, Ar), 7.59–7.61 (m, 1H, Ar), 7.85–7.86 (m, 1H, $C_5$H-chrom.), 8.73 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: C, 58.48; H, 2.89. Found: C, 58.50; H, 2.90.

***7-(4-Nitrobenzyloxy)-2-oxo-2H-chromene-3-carbonyl chloride (7g).*** 79% yield; mp 220–221°C; $^1$H NMR (DMSO-$d_6$) δ 5.45 (s, 2H, $ArCH_2$), 7.20 (s, 1H, $C_8$H-chrom.), 7.33–7.35 (m, 1H, $C_6$H-chrom.), 7.49–7.52 (m, 2H, $C_2$H-Ar and $C_6$H-Ar), 7.95–7.97 (m, 1H, $C_5$H-chrom.), 8.25–8.29 (m, 2H, $C_3$H-Ar and $C_5$H-Ar), 8.81 (s, 1H, $C_4$H-chrom.). Anal. Calcd. for $C_{17}H_{10}ClNO_6$: C, 56.76; H, 2.80. Found: C, 56.74; H, 2.79.

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## REFERENCES AND NOTES

[1] Borges, F.; Roleira, N.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[2] Musa, M. A.; Cooperwood, J. S.; Khan, M. O. F. Curr Med Chem 2008, 15, 2664.

[3] Kostova, I.; Mojzis, J. Futur HIV Ther 2007, 1, 315.

[4] Kostova, I. Mini Rev Med Chem 2006, 6, 365.

[5] Hadjipavlou-Litina, D. J.; Litinas, K. E.; Kontogiorgis, C. Anti-Inflamm Antiallergy Agents Med Chem 2007, 6, 293.

[6] Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Befani, O.; Turini, P.; Alcaro, S.; Ortuso, F. Bioorg Med Chem Lett 2004, 14, 3697.

[7] Chimenti, F.; Secci, D.; Bolasco, D.; Chimenti, P.; Bizzarri, B.; Granese, A.; Carradori, S.; Yáñez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. J Med Chem 2009, 52, 1935.

[8] Bonsignore, L.; Cottiglia, F.; Lavagna, S. M.; Loy, G.; Secci, D. Farmaco 1998, 53, 693.

[9] Bandgar, B. P.; Uppalla, L. S.; Kurule, D. S. Green Chem 1999, 1, 243.

[10] Carrillo, J. R.; Diaz-Ortiz, A.; De La Hoz, A.; Moreno, A.; Gomez, M. V.; Prieto, P.; Sanchez-Migallon, A.; Vazquez, E. In Targets in Heterocyclic Systems: Chemistry and properties; Attanasi, O. A.; Spinelli, D., Ed.; Italian Society of Chemistry: Rome, 2003; Vol 7, p 64.

[11] (a) Ghose, A. K.; Crippen, G. M. J Chem Inf Comput Sci 1987, 27, 21; (b) Viswanadhan, V. N.; Ghose, A. K.; Revankar, G. R.; Robins, R. K. J Chem Inf Comput Sci,1989, 29, 163; (c) Broto, P.; Moreau, G.; Vandycke, C. Eur J Med Chem,1984, 19, 71.

# A Highly Efficient Methodology for 5-Methyl-3-aryl-2-thiooxazolidin-4-ones Using Lithium Perchlorate in DIPEA Mediated Synthesis



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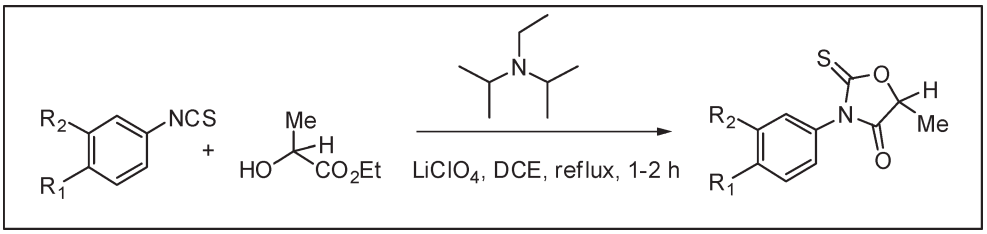


An efficient methodology for the synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-ones from aryl isothiocyanates has been developed. Aryl isothiocyanates, synthesized from various anilines, were converted to the desired compounds by treating with ethyl lactate in presence of DIPEA and catalytic amount of lithium perchlorate. This method provides a convenient and cost-effective strategy, with no specific purification protocol.

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## INTRODUCTION

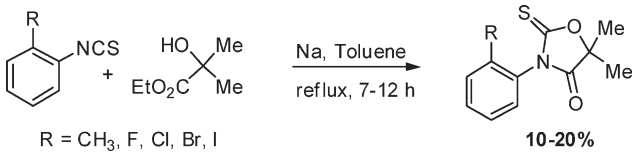
Oxazolidinones and thiooxazolidinones form an integral part of many drugs/intermediates [1,2]. They are well known as chiral directing agents in asymmetric synthesis [3,4]. Thiooxazolidinones were reported for various activities such as potassium channel openers [5], antidiabetics [2], and anticonvulsants [6]. A perusal of the literature shows that there is no report on the synthesis of 3-aryl-2-thiooxazolidin-4-ones having an α-proton, and the available methods in the case of 5,5-dimethyl-3-aryl-2-thiooxazolidin-4-ones, which lack α-protons are poor yielding (Scheme 1) [7–10]. Above all, the reported strategies relied on the kind of isothiocyanates used, and an extrapolation of the methodology to some of the substrates discussed in this article failed primarily due to the harsh reaction conditions [7,8] and the strong base employed [9], leading to the formation of very little of the desired product [10] together with unwanted side-products. The tight legislation on the maintenance of greenness in synthetic pathways and processes demands to prevent waste and minimize energy requirements which unfortunately could not be met in uneconomical low yielding reactions [11].

## RESULTS AND DISCUSSION

Various aryl isothiocyanates 2(a–j) were prepared by previously reported method [12] from corresponding anilines 1(a–j). A model reaction of 4-chlorophenyl isothiocyanate with ethyl lactate was experimented under various reaction conditions like sodium hydride, potassium-*tert*-butoxide, sodium metal, potassium hydroxide, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), and *N*,*N*-diisopropylethylamine (DIPEA) (Experiments 1–6; Table 1), but the yields obtained were quite disappointing. This prompted us to employ an alternate strategy based on the assumption that the condensation between the reactants would become more facile if their reactivity could be enhanced by adequate co-ordination. Quite interestingly, as in agreement with our notion, a stirring solution of 4-chlorophenyl isothiocyanate and ethyl lactate in dichloroethane (DCE) when refluxed in presence of DIPEA and lithium perchlorate (Scheme 2) showed a drastic improvement in the yields (Experiments 8–10; Table 1); though the product was not formed when either of these was solely employed (Experiments 6 and 7; Table 1).

From the results obtained a plausible reaction mechanism could be depicted as shown in Figure 1. Lithium co-ordinates with the hydroxyl group of ethyl lactate forming the O—Li bond and simultaneously generates perchloric acid which reacts with DIPEA to produce the protonated base and perchlorate anion. Further, the alkoxide attacks the thiocarbonyl carbon of the aryl isothiocyanate resulting in an intramolecular cyclization followed by the protonation of the ethoxy group thereby expelling it as a good leaving group to afford

**Scheme 1.** Reported strategy for the synthesis of 5,5-dimethyl-3-aryl-2-thiooxazolidin-4-ones lacking α-proton.




5-methyl-3-aryl-2-thiooxazolidin-4-ones with the regeneration of lithium perchlorate in the final step.

Since lithium shows diagonal relationship with magnesium; magnesium perchlorate was also tested, but the reaction afforded poor results and so was the case with zinc perchlorate (Experiments 12 and 13; Table 1). Surprisingly, comparative results could not be obtained when lithium perchlorate was used with triethylamine (TEA) instead of DIPEA (Experiment 11; Table 1). The reason could be attributed to DIPEA having more basic character over TEA. Also the higher boiling point of DIPEA is advantageous under the reflux conditions. The Lewis acid catalyst lithium perchlorate was chosen based on the well known fact that lithium possess better co-ordination power due to its least ionic radius (0.76 Å) than other alkali metals and therefore the higher charge:size ratio increases its covalent character. Also lithium perchlorate is cheap, commercially available and soluble in various organic solvents. The efficiency of lithium perchlorate is well established in various reactions like Diels-Alder reaction [13,14], Friedel-Crafts acylation [15], aminophosphonation of aldehydes [16], Baylis-Hillman reaction [17], aromatic and heteroatom acylation [18], and Nazarov cyclization [19].

Further studies were carried out to determine the stoichiometric quantity of the functional group activator. Based on percentage conversion calculated from GC-MS traces at various concentrations of 0.1, 0.2, 0.6, and 1.2 equivalent of $LiClO_4$ (Fig. 2); it was ascertained that 0.2 equivalent of the Lewis acid would suffice the purpose. We also observed that solvents have a profound influence over the course of the reaction (Table 2). The reaction failed in polar protic medium. Aprotic solvents like toluene and benzene afforded the product in good yields while 1,2-dichloroethane turned out to be the best.

To generalize the methodology the standardized condition was employed on various substituted aryl isothiocyanates, and the respective products were obtained in good yields though the nature of the substituents was found to affect the course of the reaction.

Electron withdrawing functional groups which generally increase the electrophilicity of aryl isothiocyanate provided better yields (Entries 1–7; Table 3), where as electron donating groups led to longer reaction time

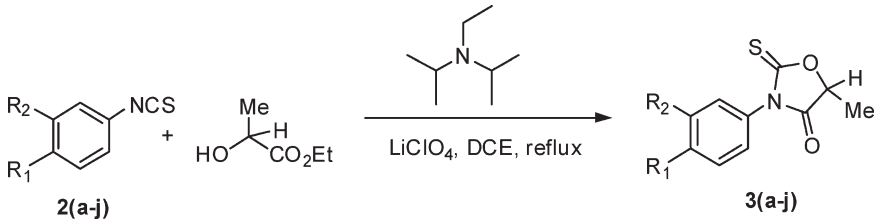
**Table 1**

Effect of reagent/catalyst in the synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-one.[a]

| | Reaction condition | | | | |
|---|---|---|---|---|---|
| Experiment | Reagent[c] | Catalyst[d] | Solvent | % conv. (GC-MS) | Isolated yield (%)[b] |
| 1 | NaH | – | DMF | 15 | 10 |
| 2 | KO*t*Bu | – | DMF | 15 | 12 |
| 3 | Na[d] | – | Toluene | 24 | 23 |
| 4 | KOH | – | DMF | 15 | 10 |
| 5 | DBU | – | DCE | 20 | 10 |
| 6 | DIPEA | – | DCE | 0 | 0 |
| 7 | – | $LiClO_4$ | DCE | 0 | 0 |
| 8 | DIPEA | $LiClO_4$[c] | DCE | 89 | 88 |
| 9 | DIPEA | $LiClO_4$[e] | DCE | 88 | 87 |
| 10 | DIPEA | $LiClO_4$ | DCE | 92 | 90 |
| 11 | TEA | $LiClO_4$ | DCE | 71 | 70 |
| 12 | DIPEA | $Mg(ClO_4)_2$ | DCE | 25 | 20 |
| 13 | DIPEA | $Zn(ClO_4)_2.\ 6H_2O$ | DCE | 40 | 30 |

[a] The reaction was carried out by stirring a mixture of 4-chlorophenyl isothiocyanate (1.18 mmol, 1.0 equiv) and ethyl lactate (1.42 mmol, 1.2 equiv) in presence of reagent and/or catalyst and solvent (10 mL) at room temperature for 10 min and then refluxing for 1 h.
[b] The product was characterized by NMR and mass spectroscopic methods.
[c] 1.2 equiv was used.
[d] 0.2 equiv was used.
[e] 0.6 equiv was used.

**Scheme 2.** Synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-ones.




with lesser yields (Entries 8–10; Table 3). The reaction conditions were also compatible with disubstituted aryl isothiocyanates (Entries 6–7 and 9–10; Table 3).

In conclusion, an efficient and viable synthetic strategy for synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-ones has been developed.

## EXPERIMENTAL

The $^{1}H$ and $^{13}C$ NMR spectra were recorded at 400 MHz and 100 MHz, respectively on a Bruker Avance DPX 400 (400 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. The chemical shifts (δ) for $^{1}H$ and $^{13}C$ are given in ppm relative to residual signals of the solvent ($CHCl_3$). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; m, multiplet; bs, broad signal. The IR spectra were recorded on a Nicolet Impact 400 spectrometer as KBr pellets for solid samples. Mass spectra were recorded on POLARIS Q (Thermo Scientific) GC-MSMS spectrometer and elemental analyses were done by Varion-EL elemental analyzer. The reactions were monitored by TLC (Merck). Evaporation of solvents was performed under reduced pressure using a Buchi rotary evaporator. Melting points are uncorrected.

Commercial grade reagents and solvents were used without further purification; ethyl lactate, lithium perchlorate, zinc perchlorate hexahydrate, magnesium perchlorate, 4-fluoro-3-chloroaniline, 4-chloro-3-trifluoromethylaniline (Aldrich), *N,N*-diisopropylethylamine, triethylamine, 4-bromoaniline, 4-fluoroaniline, 4-aminobenzonitrile, 4-methylaniline, 3,4-dimethylaniline, 3,4-dimethoxyaniline, thiophosgene, sodium metal, sodium hydride (60% suspension in mineral oil), potassium *tert*-butoxide, DBU, 1,4-dioxane, (Spectrochem); 4-chloroaniline (Merck); sodium hydrogen carbonate, THF, toluene (CDH); DCE (Loba Chemie), DME (Sigma), benzene, DMF (SISCO), 3-nitroaniline (S.D. Fine chemicals), potassium hydroxide (Qualigens).

**General procedure for the synthesis of aryl isothiocyanates.** In a 100 mL RB flask, a solution of sodium hydrogen carbonate (5.5 g, 65.7 mmol) in 20 mL water was stirred for 10 min and to it dichloromethane (20 mL) was added followed by 4-chloroaniline (2.0 mL, 21.9 mmol). The reaction mixture was cooled to 0°C, thiophosgene (2.5 mL, 32.85 mmol) was introduced dropwise over a period of 30 min and continuously stirred at room temperature for 1 h. The workup of the reaction mixture was carried out in dichloromethane and dried over anhydrous sodium sulphate. The organic layer upon concentration afforded a crude gummy compound,

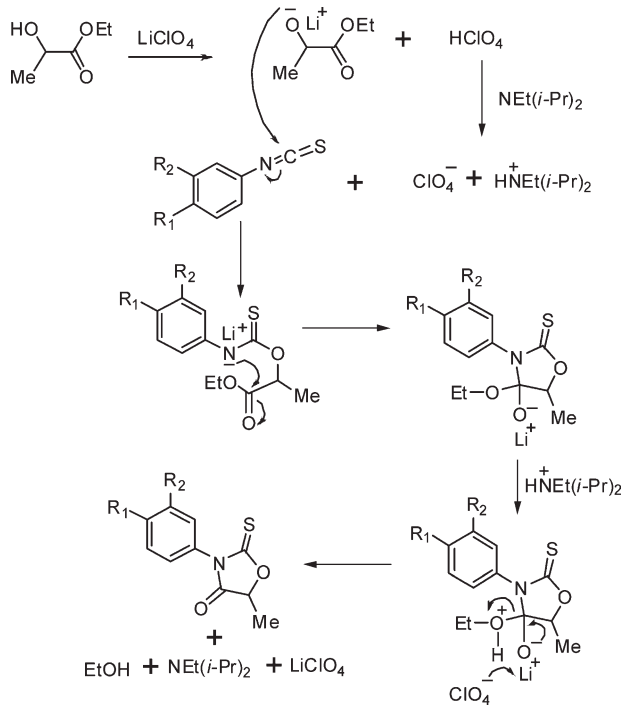



**Figure 1.** A plausible reaction mechanism for the formation of 5-methyl-3-aryl-2-thiooxazolidin-4-ones.

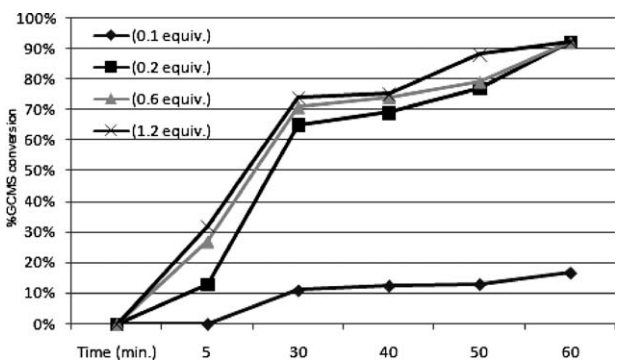



**Figure 2.** GC-MS study of model reaction at various concentrations of $LiClO_4$.

**Table 2**

Effect of solvent in the synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-one.[a]

| Experiment | Reagent[b] | Catalyst[c] | Solvent | % conv. (GC-MS) | Isolated yield (%)[d] |
|---|---|---|---|---|---|
| 1 | DIPEA | $LiClO_4$ | Neat (80°C) | 10 | 10 |
| 2 | DIPEA | $LiClO_4$ | Toluene | 85 | 81 |
| 3 | DIPEA | $LiClO_4$ | Benzene | 86 | 83 |
| 4 | DIPEA | $LiClO_4$ | DME | 70 | 66 |
| 5 | DIPEA | $LiClO_4$ | DCE | 92 | 90 |
| 6 | DIPEA | $LiClO_4$ | Dioxane | 85 | 81 |
| 7 | DIPEA | $LiClO_4$ | THF | 36 | 33 |
| 8 | DIPEA | $LiClO_4$ | DMF | 0 | 0 |
| 9 | DIPEA | $LiClO_4$ | DMSO | 0 | 0 |
| 10 | DIPEA | $LiClO_4$ | Ethanol | 0 | 0 |
| 11 | DIPEA | $LiClO_4$ | Methanol | 0 | 0 |

[a] The reaction was carried out by stirring a mixture of 4-chlorophenyl isothiocyanate (1.18 mmol, 1.0 equiv) and ethyl lactate (1.42 mmol, 1.2 equiv) in presence of reagent and/or catalyst and solvent (10 mL) at room temperature for 10 min and then refluxing for 1 h.
[b] 1.2 equiv was used.
[c] 0.2 equiv was used.
[d] The product was characterized by NMR and mass spectroscopic methods.

which was recrystallized in hexane under cold condition. The precipitate was filtered and dried to get the desired compound (Yield: 3.0 g, 81%, white solid). The formation of the product was confirmed by analytical and spectral methods.

***4-Chlorophenyl isothiocyanate (2a).*** Yield: 81%, white solid; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.16 (d, $J$ = 8.8 Hz, 2H), 7.33 (d, $J$ = 8.8 Hz, 2H); MS (*m*/*z*): 169.03 ($M^+$).

***4-Bromophenyl isothiocyanate (2b).*** Yield: 82%, white solid; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.10 (d, $J$ = 8.8 Hz, 2H), 7.48 (d, $J$ = 8.8 Hz, 2H); MS (*m*/*z*): 213.03 ($M^+$), 215.03 ($M^{+2}$).

***4-Fluorophenyl isothiocyanate (2c).*** Yield: 81%, colourless oil; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.00–7.09 (m, 2H), 7.19–7.24 (m, 2H); MS (*m*/*z*): 153.14 ($M^+$).

***4-Cyanophenyl isothiocyanate (2d).*** Yield: 79%, white solid; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.31 (d, $J$ = 8.8 Hz, 2H), 7.66 (d, $J$ = 8.8 Hz, 2H); MS (*m*/*z*): 160.07 ($M^+$).

***3-Nitrophenyl isothiocyanate (2e).*** Yield: 75%, yellow solid; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.56 (d, $J$ = 8.8 Hz, 2H), 8.06 (s, 1H), 8.10–8.15 (m, 1H); MS (*m*/*z*): 180.09 ($M^+$).

***3-Chloro-4-fluorophenyl isothiocyanate (2f).*** Yield: 75%, colourless oil; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.09–7.16 (m, 2H), 7.29–7.37 (m, 1H); MS (*m*/*z*): 187.01 ($M^+$).

***4-Chloro-3-trifluoromethylphenyl isothiocyanate (2g).*** Yield: 70%, colourless oil; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 7.31–7.34 (m, 1H), 7.42–7.54 (m, 2H); MS (*m*/*z*): 237.07 ($M^+$).

***4-Methylphenyl isothiocyanate (2h).*** Yield: 90%, brownish solid; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.11–7.16 (m, 4H); MS (*m*/*z*): 149.08 ($M^+$).

***3,4-Dimethylphenyl isothiocyanate (2i).*** Yield: 92%, brown oil; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 2.26 (s, 6H), 6.97 (d, $J$ = 8.0 Hz, 1H), 7.02 (s, 1H), 7.09 (d, $J$ = 8.0 Hz, 1H); MS (*m*/*z*): 163.09 ($M^+$).

**Table 3**

Synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-ones.[a]

| Entry | Aryl isothiocyanate | $R_1$ | $R_2$ | Reaction time (h) | Product | % conv. (GC-MS) | Isolated yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | 2a | Cl | H | 1.0 | 3a | 92 | 90 |
| 2 | 2b | Br | H | 1.5 | 3b | 77 | 75 |
| 3 | 2c | F | H | 1.0 | 3c | 87 | 85 |
| 4 | 2d | CN | H | 1.5 | 3d | 82 | 80 |
| 5 | 2e | H | $NO_2$ | 1.5 | 3e | 79 | 75 |
| 6 | 2f | F | Cl | 2.0 | 3f | 70 | 69 |
| 7 | 2g | Cl | $CF_3$ | 2.0 | 3g | 74 | 72 |
| 8 | 2h | Me | H | 1.0 | 3h | 70 | 65 |
| 9 | 2i | Me | Me | 1.5 | 3i | 78 | 70 |
| 10 | 2j | MeO | MeO | 1.5 | 3j | 71 | 70 |

[a] The reaction was carried out by stirring a mixture of aryl isothiocyanate (1.18 mmol, 1.0 equiv) and ethyl lactate (1.42 mmol, 1.2 equiv) in presence of DIPEA (1.42 mmol, 1.2 equiv) and $LiClO_4$ (0.24 mmol, 0.2 equiv) in DCE (10 mL) at room temperature for 10 min and then refluxing for 1–2 h.
[b] The product was characterized by NMR and mass spectroscopic methods.

***3,4-Dimethoxyphenyl isothiocyanate (2j).*** Yield: 88%, white solid; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 3.37 (s, 6H), 6.65 (s, 1H), 6.69–6.75 (m, 2H); MS (*m*/*z*): 195.14 ($M^+$).

**General procedure for the synthesis of 5-methyl-3-aryl-2-thiooxazolidin-4-one.** To a solution of 4-chlorophenyl isothiocyanate (0.2 g, 1.18 mmol, 1.0 equiv) in 1,2-dichloroethane (10 mL), ethyl lactate (0.17 mL, 1.42 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (0.24 mL, 1.42 mmol, 1.2 equiv), and lithium perchlorate (0.026 g, 0.24 mmol, 0.2 equiv) were added. It was refluxed for 1 h, and the reaction mixture was cooled, washed with water, and concentrated. The crude product was dissolved in minimum amount of dichloromethane, precipitated with excess of hexane, filtered, and dried (Yield: 0.26 g, 90%, white solid). The compound was identified by spectral and analytical methods.

***5-Methyl-3-(4-chlorophenyl)-2-thiooxazolidin-4-one (3a).*** Yield: 90%, white solid; mp 111–114°C; FTIR (KBr) ν: 1763 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.77 (d, $J$ = 6.8 Hz, 3H), 5.11–5.17 (m, 1H), 7.30 (d, $J$ = 8.8 Hz, 2H), 7.51 (d, $J$ = 8.8 Hz, 2H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.66, 78.71, 128.86, 129.78, 130.64, 135.84, 172.91, 188.79; MS (*m*/*z*): 241.00 ($M^+$); $C_{10}H_8ClNO_2S$ Calcd: C, 49.69; H, 3.34; N, 5.80; S, 13.27; Found: C, 49.72; H, 3.38; N, 5.85; S, 13.33.

***5-Methyl-3-(4-bromophenyl)-2-thiooxazolidin-4-one (3b).*** Yield: 75%, white solid; mp 144–147°C; FTIR (KBr) ν: 1771 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.78 (d, $J$ = 7.2 Hz, 3H), 5.12–5.17 (m, 1H), 7.24 (d, $J$ = 8.8 Hz, 2H), 7.67 (d, $J$ = 8.8 Hz. 2H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.67, 78.74, 123.96, 129.12, 131.16, 132.77, 172.86, 188.71; MS (*m*/*z*): 285.01($M^+$), 287.01($M^{+2}$); $C_{10}H_8BrNO_2S$ Calcd: C, 41.97; H, 2.82; N, 4.89; S, 11.21; Found: C, 41.95; H, 2.80; N, 4.94; S, 11.23.

***5-Methyl-3-(4-fluorophenyl)-2-thiooxazolidin-4-one (3c).*** Yield: 85%, white solid; mp 93–96°C; FTIR (KBr) ν: 1771 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.76 (d, $J$ = 6.8 Hz, 3H), 5.11–5.16 (m, 1H), 7.19–7.25 (m, 2H), 7.30–7.35 (m, 2H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.63, 78.69, 116.51, 116.74, 129.49, 129.58, 161.66, 164.15, 173.08, 189.16; MS *m*/*z*: 225.10 ($M^+$); $C_{10}H_8FNO_2S$ Calcd: C, 53.32; H, 3.58; N, 6.22; S, 14.24; Found: C, 53.35; H, 3.55; N, 6.27; S, 14.26.

***5-Methyl-3-(4-cyanophenyl)-2-thiooxazolidin-4-one (3d).*** Yield: 80%, white solid; mp 202–205°C; FTIR (KBr) ν: 1774, 2231 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.73 (d, $J$ = 6.8 Hz, 3H), 5.14–5.20 (m, 1H), 7.53 (d, $J$ = 8.8 Hz, 2H), 7.83 (d, $J$ = 8.8 Hz, 2H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.65, 78.83, 113.69, 117.64, 128.49, 133.32, 135.98, 172.46, 187.77; MS (*m*/*z*): 232.10 ($M^+$); $C_{11}H_8N_2O_2S$ Calcd: C, 56.88; H, 3.47; N, 12.06; S, 13.81; Found: C, 56.92; H, 3.51; N, 12.10; S, 13.86.

***5-Methyl-3-(3-nitrophenyl)-2-thiooxazolidin-4-one (3e).*** Yield: 75%, light yellow solid; mp 151–154°C; FTIR (KBr) ν: 1769 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.80 (d, $J$ = 7.2 Hz, 3H), 5.19–5.24 (m, 1H), 7.75 (d, $J$ = 8.0 Hz, 2H), 8.30 (s, 1H), 8.34–8.37 (m, 1H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.67, 78.96, 123.22, 124.51, 130.32, 133.19, 133.70, 148.61, 172.52, 187.93; MS (*m*/*z*): 252.08 ($M^{+1}$); $C_{10}H_8N_2O_4S$ Calcd: C, 47.61; H, 3.20; N, 11.11; S, 12.71; Found: C, 47.67; H, 3.16; N, 11.09; S, 12.68.

***5-Methyl-3-(3-chloro-4-fluorophenyl)-2-thiooxazolidin-4-one (3f).*** Yield: 69%, white solid; mp 98–100°C; FTIR (KBr) ν: 1770 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.77 (d, $J$ = 7.2 Hz, 3H), 5.12–5.17 (m, 1H), 7.24–7.33 (m, 2H), 7.43–7.46 (m, 1H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.62, 78.78, 117.27, 117.50, 127.71, 127.79, 130.18, 157.28, 159.80, 172.74, 188.51; MS (*m*/*z*): 259.05 ($M^+$); $C_{10}H_7ClFN_2O_2S$ Calcd: C, 46.25; H, 2.72; N, 5.39; S, 12.35; Found: C, 46.27; H, 2.75; N, 5.43; S, 12.39.

***5-Methyl-3-(4-chloro-3-trifluoromethylphenyl)-2-thiooxazolidin-4-one (3g).*** Yield: 72%, white solid; mp 178–181°C; FTIR (KBr) ν: 1781 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.80 (d, $J$ = 7.2 Hz, 3H), 5.15–5.20 (m, 1H), 7.52 (d, $J$ = 8.8 Hz, 1H), 7.69 (d, $J$ = 8.8 Hz, 1H), 7.72 (s, 1H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.65, 78.87, 123.42, 127.00, 127.06, 129.92, 130.81, 131.93, 132.61, 172.53, 187.98; MS (*m*/*z*): 309.01 ($M^+$); $C_{11}H_7ClF_3NO_2S$ Calcd: C, 42.66; H, 2.28; N, 4.52; S, 10.35; Found: C, 42.70; H, 2.31; N, 4.55; S, 10.34.

***5-Methyl-3-(4-methylphenyl)-2-thiooxazolidin-4-one (3h).*** Yield: 65%, white solid; mp 109–111°C; FTIR (KBr) ν: 1769 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.76 (d, $J$ = 7.2 Hz, 3H), 2.43 (s, 3H), 5.11–5.16 (m, 1H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.34 (d, $J$ = 8.0 Hz, 2H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.69, 21.34, 78.67, 127.23, 129.60, 130.22, 140.09, 173.35, 189.63; MS (*m*/*z*): 222.09 ($M^{+1}$); $C_{11}H_{11}NO_2S$ Calcd: C, 59.71; H, 5.01; N, 6.33; S, 14.49; Found: C, 59.68; H, 5.04; N, 6.28; S, 14.51.

***5-Methyl-3-(3,4-dimethylphenyl)-2-thiooxazolidin-4-one (3i).*** Yield: 70%, white solid; mp 113–115°C; FTIR (KBr) ν: 1769 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.73 (d, $J$ = 7.2 Hz, 3H), 2.30 (s, 6H), 5.07–5.12 (m, 1H), 7.02 (s, 1H), 7.04 (d, $J$ = 7.6 Hz, 1H), 7.25 (d, $J$ = 7.6 Hz, 1H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.69, 19.69, 19.89, 78.70, 124.76, 128.24, 129.79, 130.69, 138.28, 138.85, 173.46, 189.81; MS (*m*/*z*): 235.09 ($M^+$); $C_{12}H_{13}NO_2S$ Calcd: C, 61.25; H, 5.57; N, 5.95; S, 13.63; Found: C, 61.21; H, 5.61; N, 5.99; S, 13.65.

***5-Methyl-3-(3,4-dimethoxyphenyl)-2-thiooxazolidin-4-one (3j).*** Yield: 70%, white solid, mp 145–147°C; FTIR (KBr) ν: 1768 $cm^{-1}$; NMR ($^1$H, 400 MHz, $CDCl_3$) δ 1.76 (d, $J$ = 6.8 Hz, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 5.09–5.14 (m, 1H), 6.80 (s, 1H), 6.87 (d, $J$ = 8.8 Hz, 1H), 6.97 (d, $J$ = 8.8 Hz, 1H); NMR ($^{13}$C, 100 MHz, $CDCl_3$) δ 16.64, 56.05, 56.13, 78.62, 110.73, 111.20, 120.04, 124.80, 149.55, 150.02, 173.39, 189.76; MS (*m*/*z*): 267.08 ($M^+$); $C_{12}H_{13}NO_4S$ Calcd: C, 53.92; H, 4.90; N, 5.24; S, 12.00; Found: C, 53.94; H, 4.89; N, 5.30; S, 11.95.

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## REFERENCES AND NOTES

[1] Walker, R. B.; Fitz, L. D.; Williams, L. M.; Linton, H.; Smith, C. C. Gen Pharmacol Vasc Syst 1993, 24, 669.

[2] Momose, Y.; Maekawa, T.; Yamano, T.; Kawada, M.; Odaka, H.; Ikeda, H.; Sohda, T. J Med Chem 2002, 45, 1518.

[3] Lin, G. Q.; Li, Y. M.; Chan, A. S. C. Principles and Applications of Asymmetric Synthesis; Wiley Interscience: New York, 2001; p 135.

[4] Aitken, R. A.; Kilenyi, S. N. Asymmetric Synthesis; Blackie Academic & Professional: London, 1992; p 83.

[5] Liang, P.-H.; Hsin, L.-W.; Cheng, C.-Y. Bioorg Med Chem 2002, 10, 3267.

[6] Shapiro, S. L.; Rose, I. M.; Testa, F. C.; Roskin, E.; Freedman, L. J Am Chem Soc 1959, 81, 6498.

[7] Ordu, O. D.; Dogan, I. Tetrahedron: Asymmetry 2004, 15, 925.

[8] Yilmaz, E. M.; Doğan, I. Tetrahedron: Asymmetry 2008, 19, 2184.

[9] Doğan, I.; Burgemeister, T.; Içli, S.; Mannschreck, A. Tetrahedron 1992, 48, 7157.

[10] Ordu, O. D.; Yilmaz, E. M.; Doğan, I. Tetrahedron: Asymmetry 2005, 16, 3752.

[11] Tundo, P.; Anastas, P.; Black, D. S.; Breen, J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. Pure Appl Chem 2000, 72, 1207.

[12] Nair, V. A.; Mustafa, S. M.; Mohler, M. L.; Dalton, J. T.; Miller, D. D. Tetrahedron Lett 2006, 47, 3953.

[13] Reetz, M. T.; Gansäuer, A. Tetrahedron 1993, 49, 6025.

[14] Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. Org Lett 2000, 2, 3611.

[15] Hachiya, I.; Moriwaki, M.; Kobayashi, S. Tetrahedron Lett 1995, 36, 409.

[16] Heydari, A.; Karimian, A.; Ipaktschi, J. Tetrahedron Lett 1998, 39, 6729.

[17] Kawamura, M.; Kobayashi, S. Tetrahedron Lett 1999, 40, 1539.

[18] Chapman, C. J.; Frost, C. G.; Hartleya, J. P.; Whittleb, A. J. Tetrahedron Lett 2001, 42, 773.

[19] Malona, J. A.; Colbourne, J. M.; Frontier, A. J. Org Lett 2006, 8, 5661.

# Mild and Efficient Oxidative Aromatization of 4-Substituted-1,4-dihydropyrimidines Using (Diacetoxyiodo)benzene

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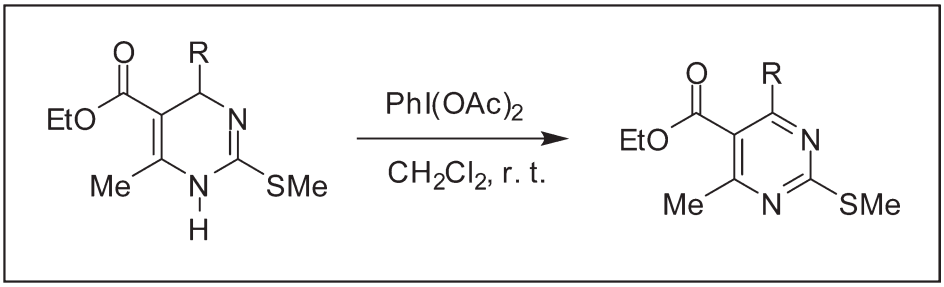


4-Alkyl or aryl-1,4-dihydropyrimidines were readily oxidized by (diacetoxyiodo)benzene under mild reaction conditions to the corresponding pyrimidine derivatives in good to excellent yields.

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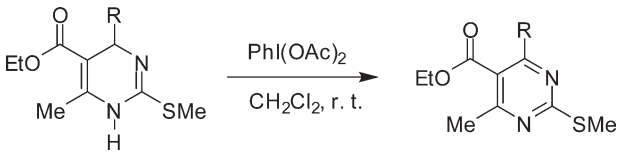
## INTRODUCTION

4-Aryl-3,4-dihydropyrimidin-2(1*H*)-ones (Biginelli compounds, DHPMs) represent an azaheterocyclic system of remarkable pharmacological profile [1]. It was investigated during 1980s and 1990s that DHPMs exhibit a similar pharmacological profile to the Hantzsch's 1,4-dihydropyridine calcium channel modulators of the nifedipine type drugs [2]. In particular, the 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters were investigated by Atwal and coworkers as potent mimics of 1,4-dihydropyridine [3]. The metabolism of these drugs involves an oxidative dehydrogenation of 1,4-dihydro ring nucleus to the corresponding aromatic derivatives, which is catalyzed in the liver by cytochrome P-450 [4]. The chemical oxidation of 4-substituted-1,4-dihydropyrimidine also provides an easy access to multi-substituted pyrimidine derivatives, which are further known to exhibit anti-anoxic and anti-lipid peroxidation activities [5]. Recently, the S-alkylation of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thione followed by oxidative aromatization has been demonstrated for the generation of a variety of 2-substituted pyrimidines via displacement of the reactive sulfonyl group with nitrogen, oxygen, sulfur, and carbon nucleophiles [6]. In contrast to Hantzsch 1,4-dihydropyridine [7], the chemical oxidative aromatization of 1,4-dihydropyrimidine is relatively less investigated reaction. All the reported methods for the chemical oxidation of 4-substituted-1,4-dihydropyrimidine utilize mainly transition metal based oxidizing agents such as $Mn(OAc)_3$ [8], $MnO_2$ [6], $(NH_4)_2Ce(NO_3)_6$ [6], and $CuCl_2/Na_2CO_3$/*tert*-BuOOH [9]. The optimized conditions for the oxidative aromatization of 2-methylthio-1,4-dihydropyrimidine requires four or five equivalents of $Mn(OAc)_3$ or $MnO_2$ respectively under different reaction conditions. Thus, there is a need for the development of an efficient and general method for the oxidative aromatization of 4-aryl or alkyl-1,4-dihydropyrimidine.

Hypervalent iodine reagents are used extensively in organic synthesis as a mild, safe, and economical alternative to heavy metal reagents [10]. A literature survey showed that phenyliodine(III) bis(trifluoroacetate) [$PhI(OCOCF_3)_2$] can be used for the solid state oxidation of Hantzsch's 1,4-dihydropyridines under microwave irradiation conditions [11]. Similarly, (diacetoxyiodo)benzene has been reported for the oxidative aromatization of 1,3,5-trisubstituted pyrazolines [12] and 2-imidazolines [13]. Recently, we have reported a clean and efficient oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones to 1,2-dihydropyrimidines using a combination of (diacetoxyiodo)benzene and *tert*-butylhydroperoxide in $CH_2Cl_2$ [14]. The application of hypervalent iodine reagents for the oxidative aromatization of 1,4-dihydropyrimidines is hitherto unknown in the literature. Herein, we wish to report a simple and highly efficient oxidative dehydrogenation of 4-substituted-1,4-dihydropyrimidine to afford the multi-substituted pyrimidine derivatives by using (diacetoxyiodo)benzene (DIB) as the mild oxidizing agent (Scheme 1).

**Scheme 1**



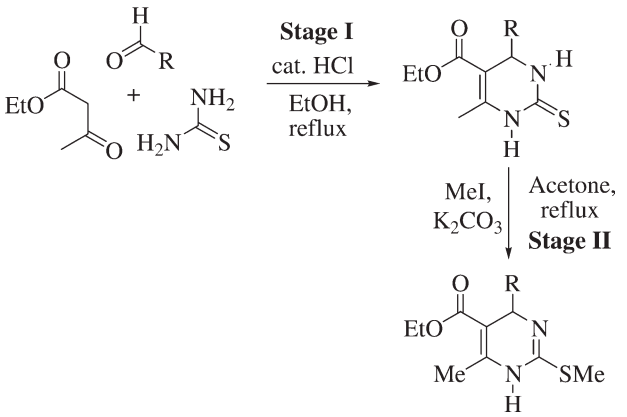

## RESULTS AND DISCUSSION

Variously substituted 4-aryl or alkyl-1,4-dihydropyrimidines precursor were prepared via two steps: (a) the Biginelli reaction involving three component condensation of ethyl acetoacetate, aldehyde and thiourea under reflux conditions in ethanol using a catalytic quantity of HCl to afford 3,4-dihydropyrimidin-2(1*H*)-thiones and (b) the S-methylation reaction of the resulting 3,4-dihydropyrimidin-2(1*H*)-thiones using MeI/$K_2CO_3$/acetone system (Scheme 2). The structures of 4-aryl or alkyl-1,4-dihydropyrimidines were confirmed by IR, $^1$H NMR, and LCMS spectra.

The oxidative aromatization of **1a** (R = $C_6H_5$) was selected as a model reaction using different iodine based oxidizing agents such as $I_2$, $I_2/K_2CO_3$, $KIO_3$, $PhI(OAc)_2$, and Dess-Martin periodinane and the results are summarized in Table 1. The oxidative aromatization using molecular iodine in MeOH was previously reported for the oxidative aromatization of Hantzsch's 1,4-dihydropyridine [15]. It is interesting to mention that molecular iodine and $I_2/K_2CO_3$ (Table 1, entry 1 and 2) did not produce oxidative aromatization of **1a** in satisfactory yields. The oxidation of **1a** to **2a** took place in 63% yield using the pentavalent hypervalent iodine reagent, Dess-Martin periodinane (DMP) but with a relatively long reaction time of 12 h. The trivalent hypervalent iodine reagent, $PhI(OAc)_2$ was found to be the most effective reagent to produce the aromatized product **2a** in 89% yield within 1 h.

With optimal conditions in hand, the reaction of different 4-substituted-1,4-dihydropyrimidines with DIB was examined to explore the scope of the reaction (Table 2). In all the cases, the expected products **2a–l** were obtained in excellent yields. All the reactions were carried out at room temperature using stochiometric use of DIB. 4-Aryl-1,4-dihydropyrimidine containing either an electron-withdrawing group or an electron-donating group all afforded the corresponding products smoothly (Table 2, entries 2a–h). The oxidative aromatization of 4-alkyl-1,4-dihydropyridine is most frequently accompanied by the dealkylation reaction. The side product formation due to the dealkylation reaction was also observed in the DIB mediated oxidative aromatization of 4-alkyl-1,4-dihydropyrimidine (Table 2). Dealkylation was a major pathway in the case of *i*-propyl at 4-position of 1,4-dihydropyrimidine. The aromatized products

**Scheme 2.** Preparation of 1,4-dihydropyrimidine.

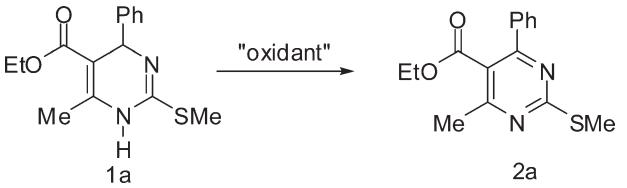



**2a–k** except **2a** are new compounds in the literature and the structures of these products were confirmed from IR, $^1$H, and $C^{13}$ NMR spectroscopy and LCMS analysis. The $^1$H NMR of the precursor 4-aryl-1,4-dihydropyrimidine showed characteristic peak around δ 5.82 due to C-4 proton and a broad peak around δ 6.36 due to N-H proton. These two signals were found to be absent in the $^1$H NMR spectra of the aromatized product **2**. The methyl group at 6-position of 4-aryl-1,4-dihydropyrimidine appears at δ 2.37 which is shifted downfield to δ 2.55 in the case of aromatized product.

A tentative reaction mechanism is shown in Scheme 3. The oxidative aromatization takes place around the coordination sphere of trivalent iodine, DIB **3**. The ligand exchange reaction between 1,4-dihydropyrimidine **1** and DIB **3** forms a resonance stabilized carbocation **4** which is subsequently deprotonated to form **5**. The concomitant reductive elimination of iodobenzene from **5** leads to form aromatized product **2**.

**Table 1**

Optimization of the reaction conditions.

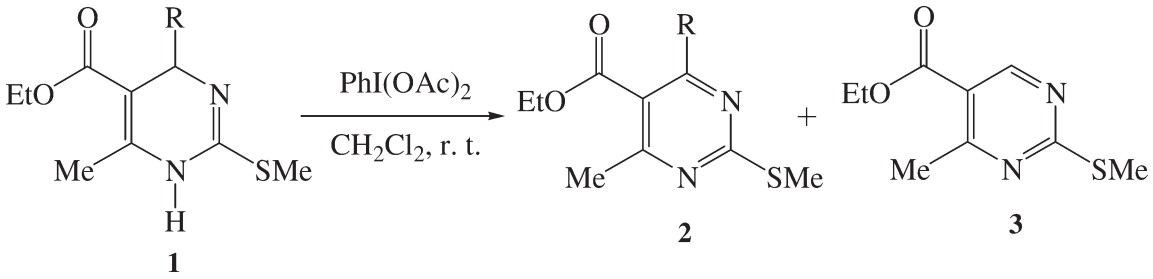



| Entry | Oxidizing agent | Solvent | Reaction time and conditions | Yield of **2a** (%)[a] |
|---|---|---|---|---|
| 1 | $I_2$ | MeOH | 12 h, reflux | 09 |
| 2 | $I_2/K_2CO_3$ | MeOH | 12 h, reflux | 22 |
| 3 | $KIO_3$ | MeOH | 12 h, reflux | 00 |
| 4 | DMP | $CH_2Cl_2$ | 12 h, r.t. | 63 |
| 5 | $PhI(OAc)_2$ | MeOH | 12 h, r.t. | 73 |
| 6 | $PhI(OAc)_2$ | $CH_2Cl_2$ | 1 h, r.t. | 89 |

[a] Isolated yields.

**Table 2**

Oxidative aromatization of 4-substituted-1,4-dihydropyrimidine using (diacetoxyiodo)benzene.




**1** **2** **3**

| Entry | Substrate, **1** R | Yield (%)[a,b] **2** | **3** |
|---|---|---|---|
| a | $C_6H_5$ | 81 | – |
| b | 4—$CH_3C_6H_4$ | 75 | – |
| c | 3—$CH_3OC_6H_4$ | 78 | – |
| d | 4—$CH_3OC_6H_4$ | 79 | – |
| e | 3,4—$(CH_3O)_2C_6H_3$ | 74 | – |
| f | 3,4,5—$(CH_3O)_3C_6H_2$ | 77 | – |
| g | 4—$ClC_6H_4$ | 76 | – |
| h | 3—$NO_2C_6H_4$ | 73 | – |
| i | *i*—$C_3H_7$ | – | 69 |
| j | $(CH_3)_2CHCH_2$ | 66 | – |
| k | $CH_3(CH_2)_5$ | 63 | – |

[a] Isolated yields after chromatography.
[b] All the reactions were carried out at room temperature stirring of 1 h.

## CONCLUSION

In summary we have developed a general and practical route for the oxidative aromatization of 4-substituted-1,4-dihydropyrimidine using (diacetoxyiodo)benzene as the safe oxidizing agent. The salient features of this methodology are: (a) mild reaction conditions, (b) transition metal-free protocol, (c) no excessive use of the oxidant, (d) short reaction time, and (e) an easy experimental procedure.

## EXPERIMENTAL

**General.** All melting points are uncorrected. The glassware was routinely oven-dried at 110°C for a minimum of 4 h. Column chromatography was performed on silica gel 70–230 mesh. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Advance 400 DPX spectrometer ($^1$H at 400 MHz and $^{13}$ C at 100 MHz) in $CDCl_3$ with TMS as the internal standard. FTIR spectra were determined on a PerkinElmer 100 FTIR spectrometer.

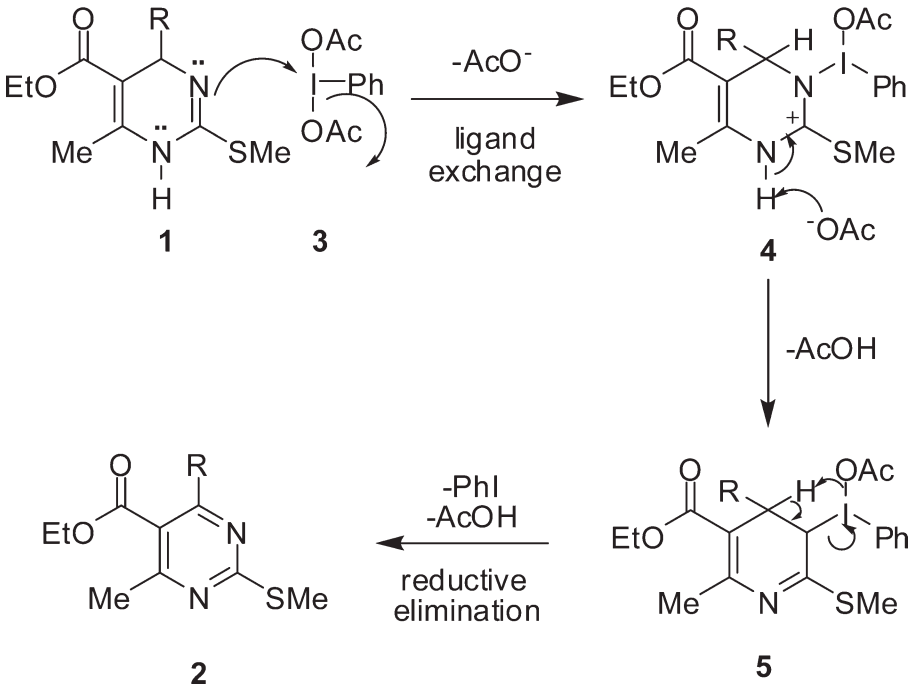
***General procedure for the preparation of 4-substituted-3, 4-dihydropyrimidin-2(1H)-thione.*** A mixture of appropriate aldehyde (20 mmol), ethyl acetoacetate (20 mmol), thiourea (22 mmol), and HCl (2 mL) in EtOH (40 mL) was refluxed for 24 h. The reaction was monitored by TLC. After completion of reaction, the mixture was slowly poured to crushed ice and the resulting solid was filtered off. The crude Biginelli compound was recrystallized from ethanol to afford the product in excellent purity. The products were characterized by the comparison of melting points with the literature value.

***General procedure for the preparation of 4-substituted-1, 4-dihydropyrimidines.*** A suspension of 4-substituted-3,4-dihydropyrimidin-2(1*H*)-thione (3 mmol) in acetone (15 mL) was treated with finely ground potassium carbonate (1.0 g, 7.25 mmol) and methyl iodide (3.5 mmol). The reaction was allowed to stir at room temperature overnight and was diluted with ethyl acetate. It was filtered and the filtrate was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated and the residue was crystallized from ether-hexanes to provide 4-substituted-1,4-dihydropyrimidine as a colorless solid.

***General procedure for the oxidation/aromatization of 4-substituted-1,4-dihydro-(2-methylthio)-pyrimidines.*** To a stirred solution of appropriate 4-substituted-1,4-dihydro-(2-methylthio)-pyrimidine (2 mmol) in $CH_2Cl_2$ (10 mL) was added (diacetoxyiodo)benzene (0.644 g, 2 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h. The progress of the reaction was monitored by TLC. After the completion of reaction, the solvent was removed under vacuum and the crude product was purified using column chromatography (silica gel, petroleum ether-ethyl acetate) to give the corresponding aromatized product in good yield.

*Ethyl 4-methyl-2-(methylthio)-6-phenylpyrimidine-5-carboxylate (2a).* IR (KBr): $\nu_{max}$ = 2926, 1722, 1582, 1534, 1225, 1080, 753, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, $J$ = 9.2 Hz, 3H), 2.57 (s, 3H), 2.62 (s, 3H), 4.18 (q, $J$ = 9.2 Hz, 2H), 7.46 (m, 3H), 7.62 (m, 2H). $^{13}$C NMR (100 MHz,$CDCl_3$): δ 13.55, 14.13, 22.57, 61.64, 120.89, 128.27,

**Scheme 3.** Reaction mechanism.




128.39, 130.03, 137.72, 163.54, 165.42, 168.09, 172.45. LCMS (M+1) = 289.

*Ethyl 4-methyl-2-(methylthio)-6-p-tolylpyrimidine-5-carboxylate (2b).* IR (KBr): $\nu_{max}$ = 2925, 2853, 1722, 1613, 1574, 1532, 1224, 1078, 864, 793 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.00 Hz, 3H), 2.35 (s, 3H), 2.54 (s, 3H), 2.60 (s, 3H), 4.18 (q, *J* = 7.00 Hz, 2H), 7.23 (d, *J* = 8.04 Hz, 2H), 7.56 (d, *J* = 8.28 Hz, 2H). $^{13}C$ NMR (100 MHz,$CDCl_3$): δ 13.72, 14.20, 21.44, 22.62, 61.74, 120.77, 128.34, 129.21, 134.83, 140.49, 163.39, 165.28, 168.40, 172.35. LCMS (M+1) = 303.

*Ethyl 4-(3-methoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2c).* IR (KBr): $\nu_{max}$ = 2928, 2851, 1723, 1601, 1536, 1429, 1223, 1122, 1046, 783, 703 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.08 Hz, 3H), 2.55 (s, 3H), 2.61 (s, 3H), 3.84 (s, 3H), 4.19 (q, *J* = 7.08 Hz, 2H), 7.01 (m, 1H), 7.19 (m, 2H), 7.33 (t, *J* = 7.88 Hz, 1H). $^{13}C$ NMR (100 MHz,$CDCl_3$): δ 13.67, 14.21, 22.63, 55.38, 61.77, 113.55, 116.08, 120.68, 121.06, 129.53, 139.03, 159.65, 163.37, 165.43, 168.15, 172.48. LCMS (M+1) = 319.

*Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2d).* IR (KBr): $\nu_{max}$ = 2928, 1721, 1608, 1580, 1531, 1509, 1402, 1255, 1224, 1079, 865, 797 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 9.6 Hz, 3H), 2.54 (s, 3H), 2.61 (s, 3H), 3.86 (s, 3H), 4.24 (q, *J* = 9.6 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 7.65 (d, *J* = 9.2 Hz, 2H). $^{13}C$ NMR (100 MHz,$CDCl_3$): δ 13.72, 14.07, 22.47, 55.31, 61.63, 113.83, 114.15, 129.98, 161.33, 162.59, 165.09, 168.48, 172.11. LCMS (M+1) = 319.

*Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2e).* IR (KBr): $\nu_{max}$ = 2931, 2836, 1696, 1603, 1513, 1260, 1233, 1141, 1095, 795 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.08 Hz, 3H), 2.54 (s, 3H), 2.62 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.21 (q, *J* = 7.08 Hz, 2H), 6.91 (d, *J* = 8.32 Hz, 1H) 7.27 (m, 2H). $^{13}C$ NMR (100 MHz,$CDCl_3$): δ 13.49, 14.21, 19.99, 55.74, 59.77, 109.81, 110.35, 110.86, 118.72, 137.42, 148.15, 148.64, 166.77. LCMS (M+1) = 349.

*Ethyl 4-(3,4,5-trimethoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2f).* IR (KBr): $\nu_{max}$ = 2935, 2841, 1722, 1587, 1536, 1504, 1415, 1225, 1127, 1006, 797, 710 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.11 (t, *J* = 7.2 Hz, 3H), 2.55 (s, 3H), 2.71 (s, 3H), 3.89 (s, 9H), 4.19 (q, *J* = 7.2 Hz, 2H), 6.90 (s, 2H). $^{13}C$ NMR (100 MHz,$CDCl_3$): δ 13.78, 14.17, 22.50, 29.68, 56.19, 60.94, 61.83, 105.67, 120.94, 133.00, 139.81, 153.26, 163.06, 165.26, 168.37, 172.37. LCMS (M+1) = 379.

*Ethyl 4-methyl-2-(methylthio)-6-(3-nitrophenyl)pyrimidine-5-carboxylate (2h).* $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.2 Hz, 3H), 2.60 (s, 3H), 2.62 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.92 Hz, 1H), 7.19 (m, 1H), 8.34 (m, 1H), 8.53 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$):δ 13.75, 14.24, 22.85, 29.69, 62.12, 120.92, 123.46, 124.69, 129.58, 134.33, 139.28, 148.23, 161.00, 166.21, 167.40, 173.19. LCMS (M+1) = 334.

*Ethyl 4-methyl-2-(methylthio)pyrimidine-5-carboxylate (2i).* IR (KBr): $\nu_{max}$ = 2925, 1724, 1641, 1564, 1528, 1403, 1326, 1281, 1200, 1091, 1045 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.12 Hz, 3H), 2.59 (s, 3H), 2.84 (s, 3H), 4.39 (q, *J* = 7.24 Hz, 2H), 8.94 (s, 1H). LCMS (M+1) = 255.

*Ethyl 4-isobutyl-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2j).* IR (KBr): $\nu_{max}$ = 2958, 2928, 2869, 1725, 1542, 1430, 1274, 1240, 1184, 1100 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 5.96 Hz, 6H), 1.39 (t, *J* = 7.1 Hz, 3H), 2.17 (m, 1H), 2.46 (s, 3H), 2.56 (s, 3H), 2.62 (d, *J* =

7.12 Hz, 3H), 4.41 (q, $J$ = 7.1 Hz, 2H). $^{13}$C NMR (100 MHz,$CDCl_3$): δ 14.05, 14.16, 22.48, 22.87, 28.33, 44.23, 61.62, 122.22, 164.52, 167.19, 167.77, 171.97. LCMS (M+1) = 269.

*Ethyl 4-hexyl-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2k).* IR (KBr): $\nu_{max}$ = 2956, 2928, 2856, 1725, 1652, 1541, 1402, 1228, 1102, 1078 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H), 1.29 (m, 8H), 1.36 (t, $J$ = 7.16 Hz, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 2.71 (t, $J$ = 6.4 Hz, 2H), 4.37 (q, $J$ = 7.16 Hz, 2H). LCMS (M+1) = 297.

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## REFERENCES AND NOTES

[1] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[2] Atwal, K.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. J Med Chem 1990, 33, 1510.

[3] Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satah, F.; Morita, M.; Noguchi, T. J Med Chem 1989, 32, 2399.

[4] (a) Bocker, R.; Guengerich, F. P. J Med Chem 1986, 29, 1596; (b) Guengerich, F. P.; Brian, W. R.; Iwasaki, M.; Sari, M. A.; Baarnhielm, C.; Berntsson, P. J Med Chem 1991, 34, 1838.

[5] (a) Kuno, A.; Sugiyama, Y.; Katsuta, K.; Kamitani, T.; Takasugi, H. Chem Pharm Bull 1992, 6, 1452; (b) Kuno, A.; Sugiyama, Y.; Katsuta, K.; Kamitani, T.; Takasugi, H. Chem Pharm Bull 1992, 9, 2423.

[6] Matloobi, M.; Kappe, C. O. J Comb Chem 2007, 9, 275.

[7] Fang, X.; Liu, Y.-C.; Li, C. J Org Chem 2007, 72, 8608.

[8] Akhtar, M. S.; Seth, M.; Bhaduri, A. P. Ind J Chem 1987, 26B, 556.

[9] Yamamoto, K.; Chen, Y. G.; Buono, F. G. Org Lett 2005, 21, 4673.

[10] Wirth, T. Angew Chem Int Ed 2005, 44, 3656; (b) Moriarty, R. M. J Org Chem 2005, 70, 2893; (c) Zhdankin, V. V.; Stang, P. J Chem Rev 2002, 102, 2523; (d) Varvoglis, A. Hypervalent Iodine in Organic Synthesis; Academic Press: London, 1997.

[11] Varma, R. S.; Kumar, D. J Chem Soc Perkin Trans 1 1999, 12, 1755.

[12] Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. Synth Commun 1997, 27, 2683.

[13] Ishihara, M.; Togo, H. Synlett 2006, 2, 227.

[14] Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Tiwari, G. B. Tetrahedron Lett 2008, 49, 3441.

[15] Yadav, J. S.; Subba Reddy, B. V.; Sabitha, G.; Kiran Kumar Reddy, G. S. Synthesis 2000, 11, 1532.

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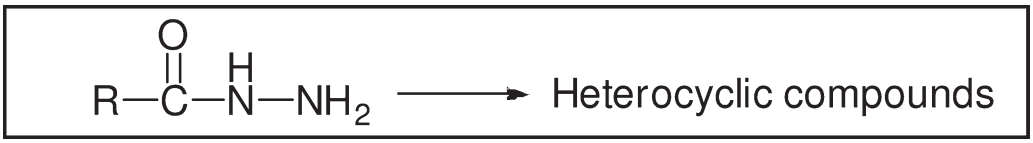


The review summarizes recent literatures dealing with the synthesis of carbohydrazide derivatives, chemical reactions and their applications in the synthesis of important heterocyclic as well as fused heterocyclic compounds.

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**Contents**



## 1. INTRODUCTION

Hydrazide compounds, such as indole-2-carbohydrazide derivatives have been shown to inhibit monoamine oxidase A activity [1]. Furan carbohydrazide, thiophene carbohydrazide, and isonicotinic acid hydrazide react with a series of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-alken-2-ones to give 3-alkyl(aryl)-5-trifluoro-methyl substituted pyrazoles [1]. One-pot reactions between carboxylic hydrazides and 2-isothiocyanato-benzonitrile afforded pharmacologically relevant 1,2,4-triazolo[1,5-*c*]quinazoline-5-thiones [2]. Hydrazide compounds were also converted to triazole-3-thiols [3], imidazopyrazolopyrimidine [3], 1,3,4-oxadiazole [4], 1,3,4-oxadiazine [4], pyrazolotriazolopyrimidine [5,6], and pyrazolotriazoloquinoline derivatives [7]. Bis (pyridinyl-2,3-dihydrooxadiazolyl)benzenes were obtained by heating the corresponding bis(hydrazides) with benzaldehyde [7]. Such compounds have attracted attention not only as model compounds for polymers but also because many biologically active natural and synthetic products have molecular symmetry [7].

The condensation of an acyl hydrazide and an amidine to afford acylamidrazone, followed by thermal cyclization, provides a convenient method for preparing 3,5-disubstituted-1,2,4-triazoles [8].

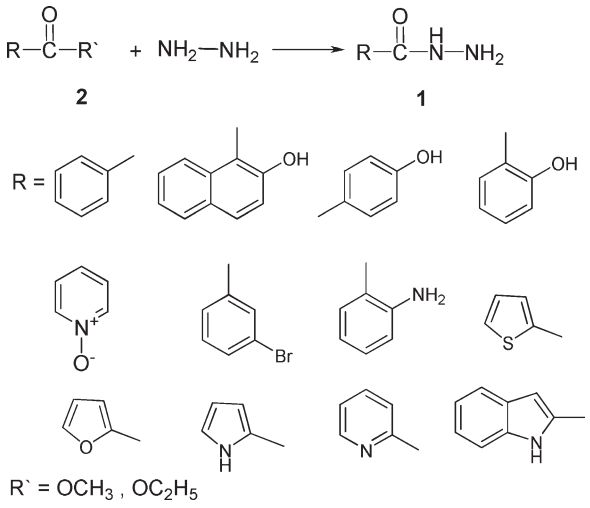
1,2,4-Triazines were formed *via* the condensation of 1,2-diketones with acylhydrazides in the presence of ammonium acetate under both traditional heating and dry media microwave assisted reaction conditions [9].

Carbohydrazides and their derivatives occupy a specific place among the other N,O-containing compounds used in the synthesis of heterocyclic systems because of their accessibility and ability to act as nucleophiles.

Accordingly, it is important to shed more light on the recent literatures dealing with that chemistry, especially in the field of heterocycles. Therefore, the present review was aimed at summarizing and systematizing available published data on the reactions of carbohydrazides with activated ethylenes, ethynes, benzo- and naphthoquinones, compounds containing C=N and C≡N moiety. Several types of reactions involving nucleophilic addition, condensation followed by heterocyclization were observed. Various heterocyclic and fused heterocyclic as well as spiro-heterocyclic compounds have been synthesized from carbohydrazides.

## 2. METHODS OF PREPARATION

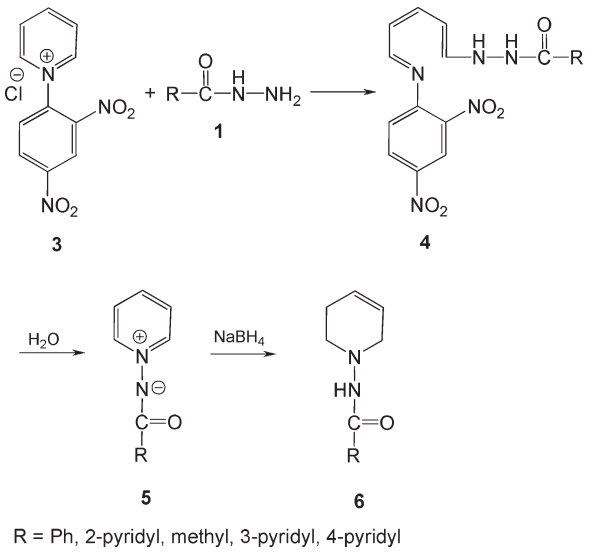
Carbohydrazides **1** can be prepared by refluxing aromatic carboxylic acid methyl or ethyl ester **2** with hydrazine hydrate in neat or in methanol. After cooling to room temperature, the resulting colorless solids were collected by filtration and dried *in vacuo* [10,11].



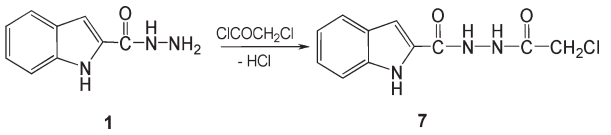

2-Thiophenecarbohydrazide 1 refluxed for 5 h [12], 2-pyridincarbohydrazide 1 refluxed for 4 h [13,14], 2-indolecarbohydrazide 1 refluxed for 15 h [4,15–18], and 2-furancarbohydrazide 1 refluxed for 2 h [19]. Some derivatives of carbohydrazide can be prepared like picolinic-*N*-oxidehydrazide [20] and 2-pyrrolecarbo-hydrazide [21]. Carbohydrazides have been prepared by hydrazinolysis of diethyl carbonate [22] and diphenyl carbonate [23] in satisfactory yields. The interaction of phosgene and hydrazine hydrate in refluxing benzene afforded carbohydrazides as dihydrochloride [24]. Also, hydrazinolysis of carbazic acid [25] and cyanuric acid [26] gave carbohydrazides.

## 3 REACTIONS OF CARBOHYDRAZIDES

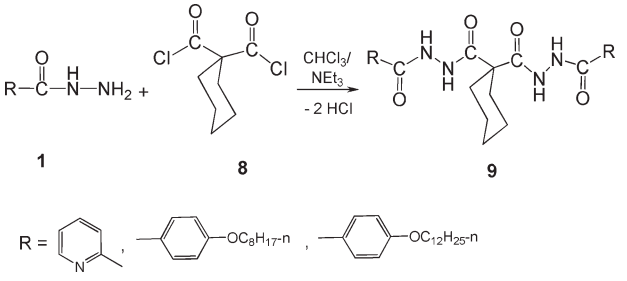
**3.1. Synthesis of linear compounds.** *N*-(2,4-Dinitrophenyl)pyridinium chloride **3** reacted with carbohydrazides **1** in methanol containing triethylamine at room temperature for 12 h to furnish 2,4-dinitroanilino derivatives **4**. Hydrolysis of **4** with water/*p*-1,4-dioxane mixture, at reflux temperature for 2 h, produced substituted carbonyliminopyridinium compounds **5**. Reduction of **5** with sodium borohydride in ethanol at 0°C for 4 h afforded alkyl substituted carbonylamino-1,2,3,6-tetrahydropyridines **6** [27–29].




A solution of chloroacetyl chloride was added dropwise to a solution of 2-indole carbohydrazide **1** in dry dioxane. After stirring at room temperature for 6 h, $N^2$-(2-chloroacetyl)indole-2-carbohydrazide **7** was formed [4].

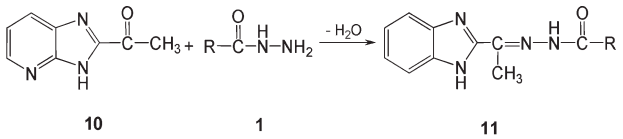



Substituted carbohydrazides **1** reacted with cyclohexane-1,1-dicarbonylchloride **8** in chloroform/triethylamine to yield cyclohexane-1,1-dicarboxylic acid-*N*,*N*′-di(2-octyloxybenzoyl)hydrazide **9** [30].

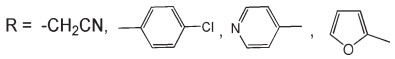



Condensation of carbohydrazides **1** with 2-acetyl-imidazo[4,5-*b*]pyridine **10** in absolute ethanol containing a

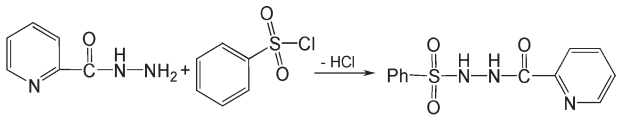
catalytic amount of piperidine afforded the corresponding hydrazones **11** [31].



**10** **1** **11**

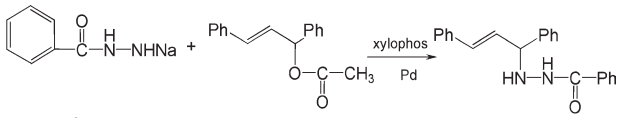


Benzenesulfonyl chloride **12** reacted with 2-pyridinecarbohydrazide **1** to give 1-isonicotinyl-2-benzene-sulfonyl hydrazine **13** [32].



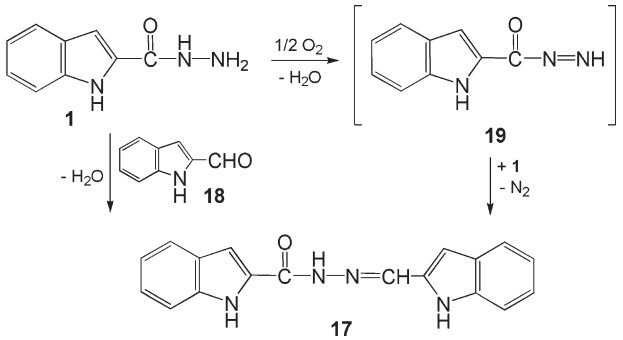
**1** **12** **13**

Allylic substitution of carbohydrazide was prepared by reaction of sodium derivative **14** with 1,3-diphenyl-prop-2-enylacetate **15** to give *N*′-1,3-diphenylallylbenzohydrazide **16** [33].



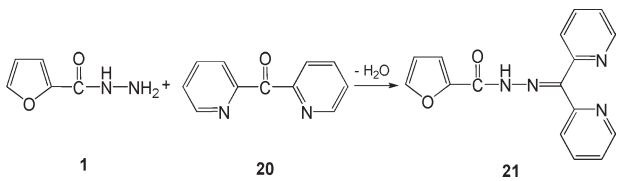
**14** **15** **16**

Hydrazone **17** was formed when 2-indole carbohydrazide **1** was dissolved in ethanol for 3 h at room temperature. On other hand, compound **17** was also obtained by condensing **1** with the aldehyde **18** [34].



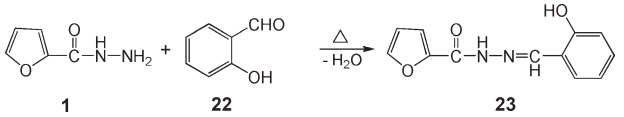
**1** **19** **18** **17**

Refluxing equimolar amounts of di-2-pyridyl ketone **20** and carbohydrazid **1** in ethanol for 3 h afforded di-2-pyridyl ketone 2-furoylhydrazone **21** [35].



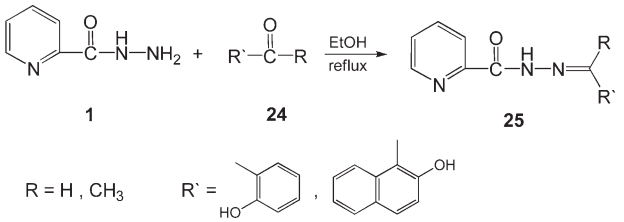
**1** **20** **21**

Refluxing an ethanolic solution of salicylaldehyde **22** and 2-furancarbohydrazide **1** for 30 min gave salicylaldehyde-2-furoic acid hydrazone **23** [36].



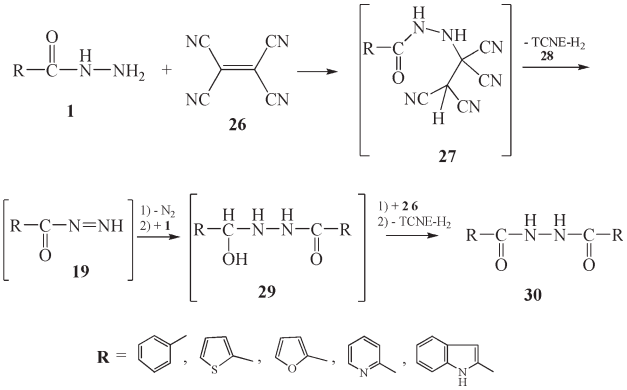
**1** **22** **23**

Condensation of 2-pyridine carbohydrazide **1** with some aldehydes or ketones **24** in ethanol gave the corresponding hydrazones **25** [37].

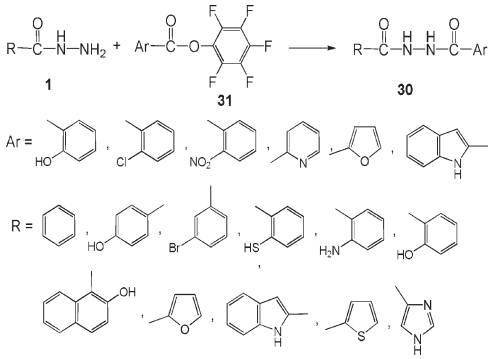


**1** **24** **25**

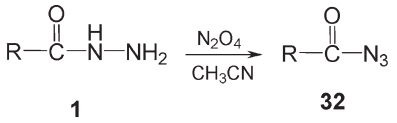
To a stirred solution of ethenetetracarbonitrile (TCNE) (**26**) in dimethylformamide (DMF), carbohydrazides **1** was added to give diaroylhydrazines **30** and 1,1,2,2-tetracyanoethane (TCNE-$H_2$) **28** [38]. Formation of these products may be rationalized *via* the following steps [38].

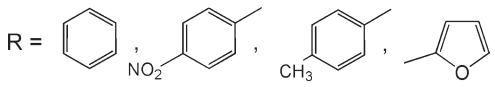


*N*,*N*′-Diaroylhydrazines **30** were formed by using pentafluorophenyl ester to activate arylcarboxylate **31** with carbohydrazides **1**, mild conditions which avoid intermediate were subjected; both symmetrical and unsymmetrical diaroylhydrazines **30** were formed in a high yields [39].

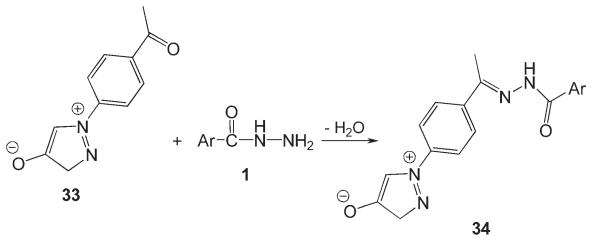


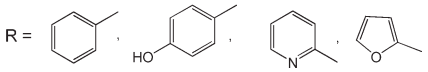
Carbohydrazides **1** reacted rapidly with dinitrogen tetraoxide ($N_2O_4$) [40] in acetonitrile at low temperature (−20 to −40°C) to give the corresponding azides **32** in mostly quantitative yields [41].



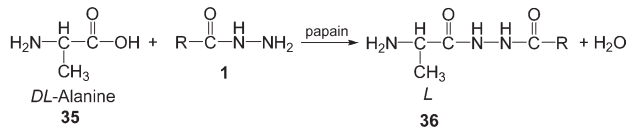


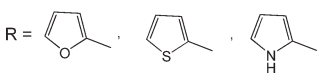
Mixtures of carbohydrazides **1** with 3-(4-acetylphenyl)-sydnone **33** were heated under reflux to produce hydrazone derivatives **34** [42].



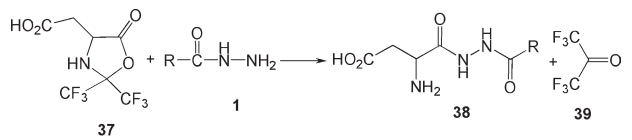


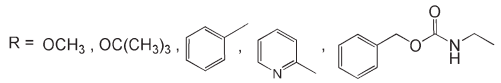
Reaction of carbohydrazides **1** with *DL*-alanine **35** under papain catalysis gave **36**; this represented an example of the power of papain to exert stereochemical preference during catalyzed reaction [43,44].



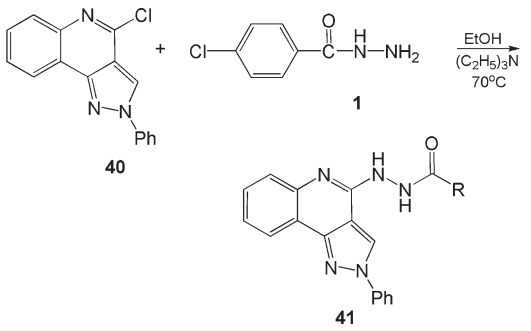


[(4-L)-2,2-Bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl] acetic acid 37 reacted with carbohydrazides 1 in ethyl acetate at room temperature to give 38 [45].

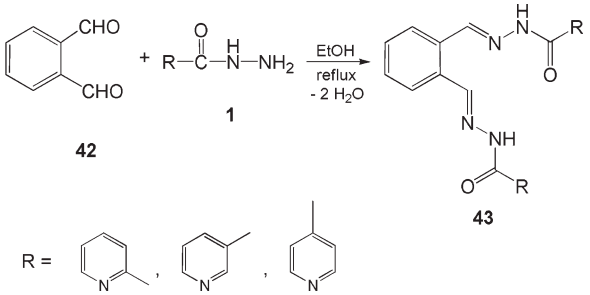




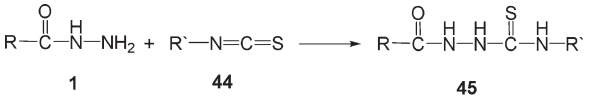
Reaction of carbohydrazides **1** with 4-chloro-2-phenyl-*2H*-pyrazolo[4,3-*c*]quinoline **40** in ethanol and in the presence of triethylamine afforded 4-chloro-*N*′-(2-phenyl-*2H*-pyrazolo[4,3-*c*]quinolin-4-yl)benzohydrazide **41** [46].

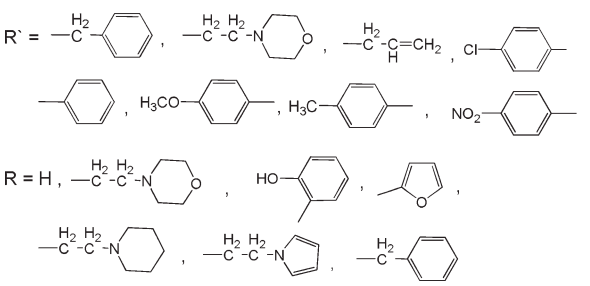


Reaction of phthalaldehyde **42** with carbohydrazides **1** in refluxing ethanol for 2–3 h afforded the corresponding bis(hydrazones) **43** [7].

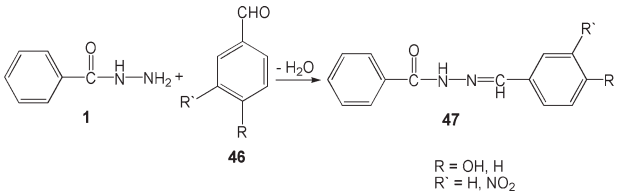


Reaction between an isothiocyanates **44** and carbohydrazides **1** in benzene gave acylthiosemicarbazides **45** in yields ranging from 88 to 95% [47–52].

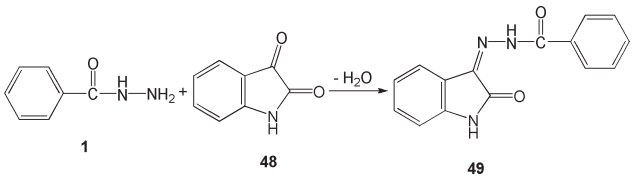




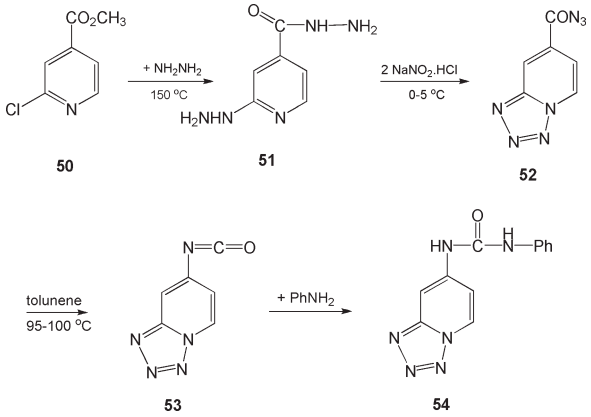
Substituted benzaldehyde **46** reacted with phenyl carbohydrazide **1** in ball-milled for 1 h to give *N*-substituted benzoylhydrazones **47** in spectroscopically pure form [53].



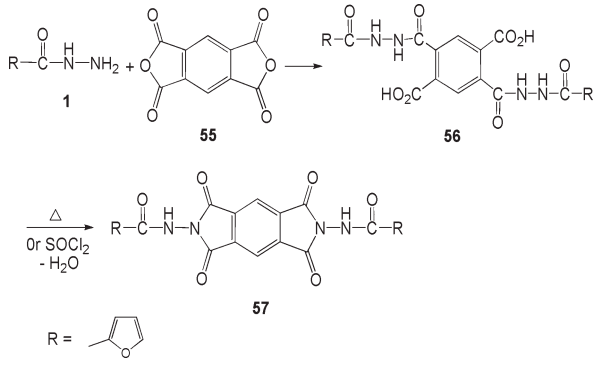
Condensation of isatin **48** with phenyl carbohydrazide **1** required 3 h ball-milling for complete reaction to give isatin-3-benzoylhydrazone **49** [53].



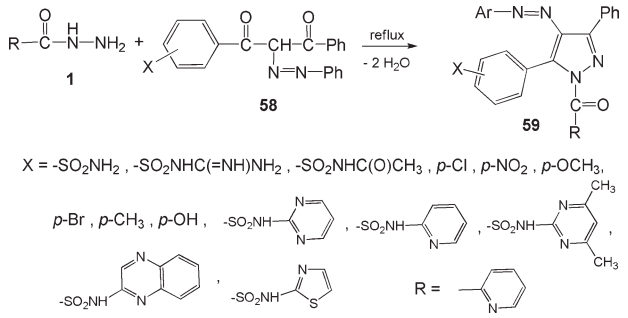
Heating methyl-2-chloroisonicotinate **50** with $N_2H_4.H_2O$ at 150°C in sealed tube gave the substituted carbohydrazide **51** [49]. Treatment of **51** with sodium nitrite in the presence of hydrochloric acid yielded carbonyl azide **52**, which was heated in toluene at 90–100°C for 1 h, sole product to form isocyanate **53** (*Curtius* rearrangement). The later was further reacted *in situ* with aniline at room temperature to give the expected urea derivative **54** [54].



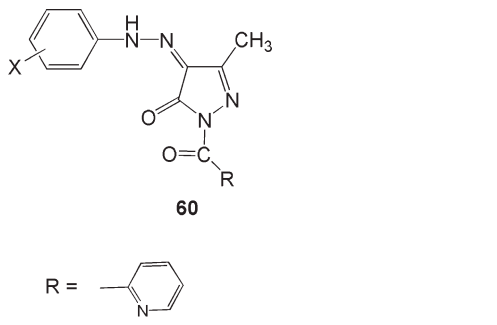
**3.2. Synthesis of pyrrole derivatives.** Reaction of carbohydrazide **1** with acid anhydride **55** to produce pyrrole derivative **57** was carried out *via* thermal cyclodehydration of the dicarboxylic acid **56** at 150°C or during heating with thionyl chloride [55].



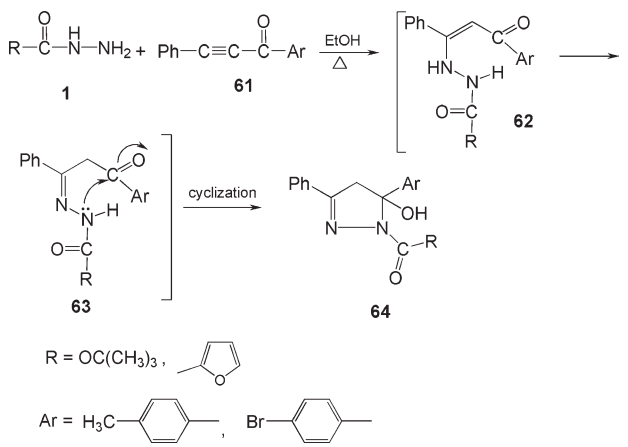
**3.3. Synthesis of pyrazole derivatives.** A mixture of substituted 2-phenylazo-1,3-diphenyl-propane-1,3-dione (**58**) and carbohydrazide **1** in glacial acetic acid was heated under reflux to form *N′*-picolinyl-3-phenyl-5-aryl-4-(substituted phenylazo)pyrazoles **59** [56].



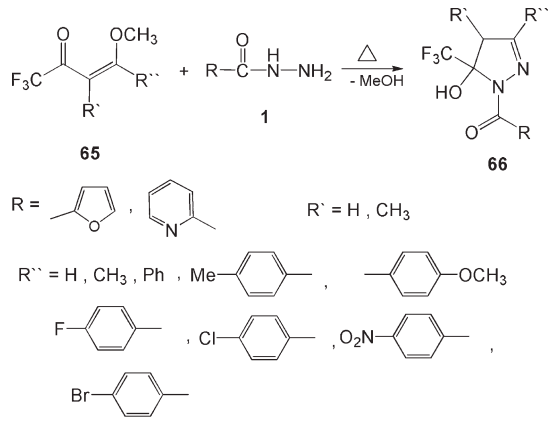
2-Pyridine carbohydrazides **1** reacted with sulpha-substituted phenylhydrazomethyl-2,3-dioxobutyrate in glacial acetic acid to form *N′*-(2-pyridinecarbonyl)-3-methyl-4-(substituted)hydrazono-2-pyrazoline-5-one **60** [57].



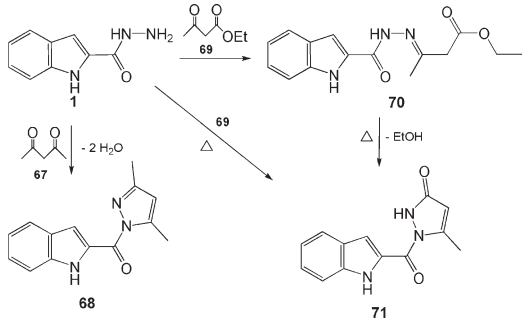
When aroylphenylacetylenes **61** was refluxed with carbohydrazides **1** in ethanol for 5 h, the reaction mixture afforded 5-aryl-4,5-dihydro-5-hydroxy-3-phenyl-1*H*-pyrazole derivatives **64** [58] rather than open chain compounds **63** [59–61].



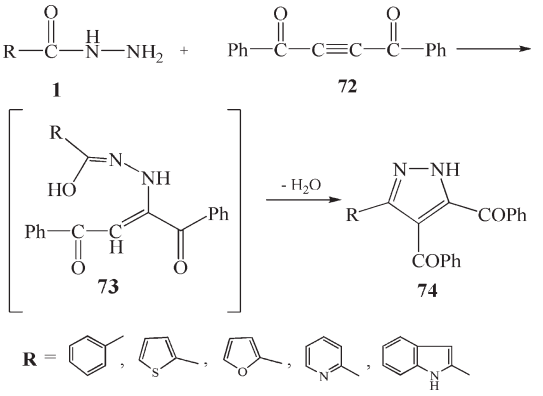
Cyclocondensation reaction of carbohydrazides **1** with a series of 4-methoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-alken-2-one derivatives **65** in refluxing methanol afforded 3-alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1(2-aryl) pyrazoles **66** [62].



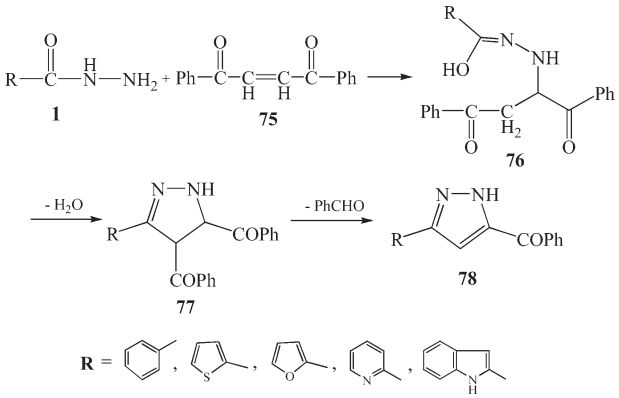
Condensation of 2-indole carbohydrazide **1** with acetyl acetone **67** in ethanol containing a catalytic amount of acetic acid resulted in the formation of the corresponding pyrazole derivative **68** [1]. Carbohydrazides **1** reacted with ethylacetoacetate **69** in the absence of solvent to give the ester derivative **70**, which could be cyclized to pyrazolone derivative **71** by heating above its melting point for 10 min followed by refluxing in methanol for further 2 h. Compound **71** was also obtained independently *via* direct refluxing of **1** with ethylacetoacetate **69** in ethanol/acetic acid mixture for 5 h [1].



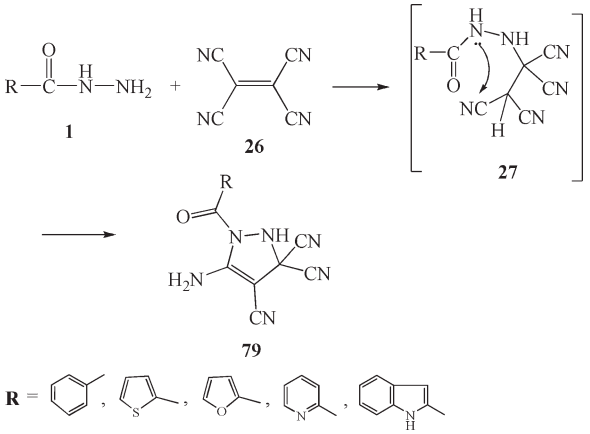
Addition of substituted carbohydrazides **1** to 1,4-dibenzoylacetylene **72** afforded the 4,5-dibenzoyl-3-substituted-1*H*-pyrazole **74** *via* the intermediate **73** [63].



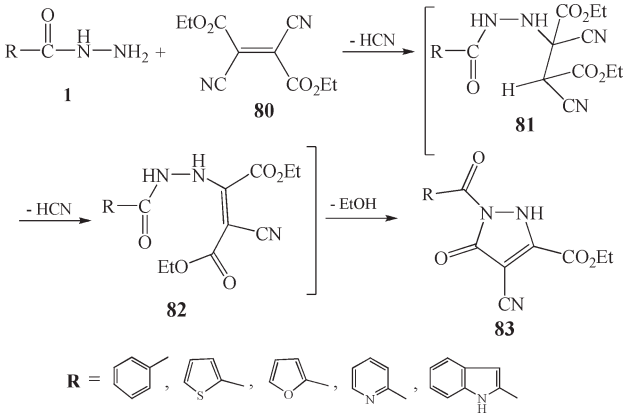
On the other hand, the reaction of substituted carbohydrazides **1** with 1,4-diphenylbut-2-ene-1,4-dione **75** in refluxing acetic acid gave 4-benzoyl-3-substituted pyrazoles **78** [63].



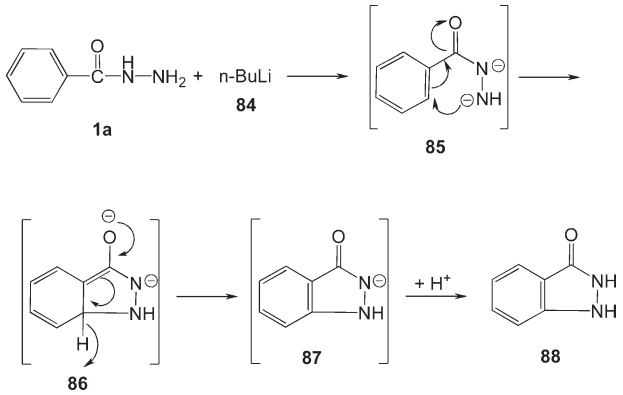
Reaction of substituted carbohydrazides **1** with **26** in DMF afforded 5-amino-1(substituted)-1*H*-pyrazole-3,3,4(2*H*)-tricarbonitriles **79** [38].



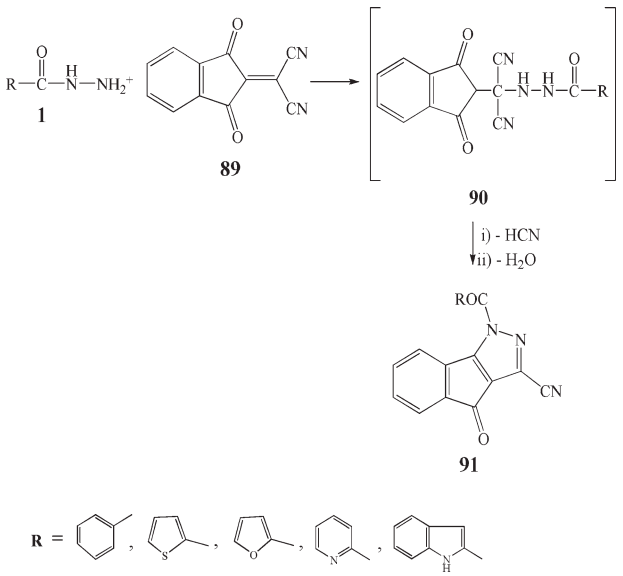
Mixing equimolar amount of carbohydrazides **1** with diethyl(*E*) 2,3-dicyanobutenedioate **80** in ethyl acetate under reflux led to the formation of pyrazole derivatives **83** [38].



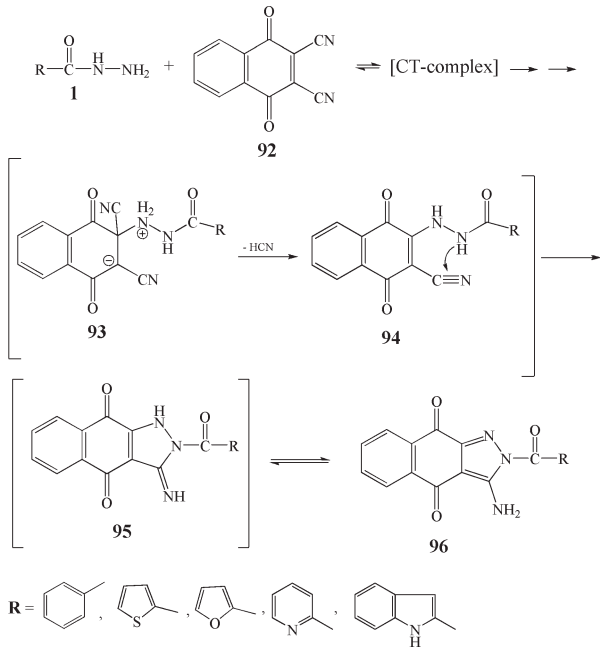
**3.4. Synthesis of fused pyrazole derivatives.** When phenyl carbohydrazide **1** in tetrahydrofuran (THF) was treated with n-butyl-lithium **84** in hexane under nitrogen atmosphere at −78°C for 1.5 h and allowed to reach the room temperature overnight, indazol-3(2*H*)-one **88** was isolated [64].



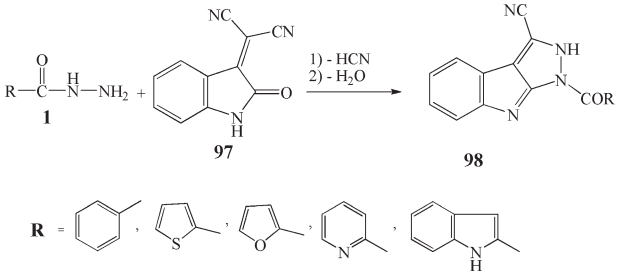

The reaction of (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile **89** and **1** in DMF with admission of air afforded 4-oxo-1-substituted-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonitrile **91** [65].



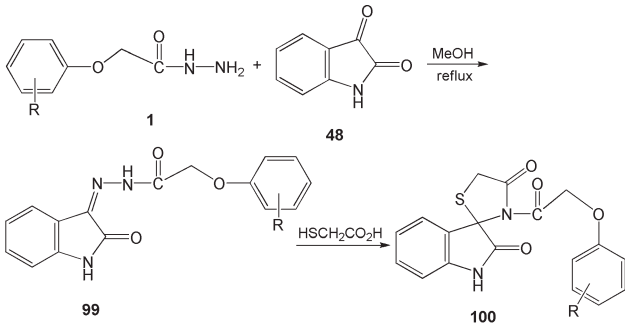

**3.5. Synthesis of indazole derivatives.** In a different manner, 1,4-naphthoquinone-2,3-dicarbonitrile **92** reacted with **1** to give substituted benzo[*f*]indazoledione **96** [66].




Carbohydrazides **1** reacted with 3-(dicyanomethylene)-2-indolone **97** in the presence of pipridine to give substituted carbonylpyrazolo[3,4-*b*]-indole-3-carbonitrile **98** [65].



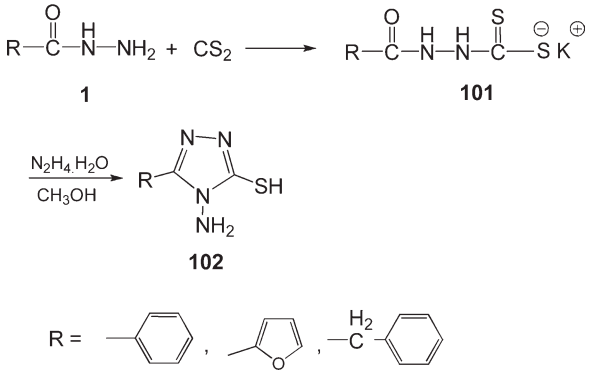

**3.6. Synthesis of thiazolidine derivatives.** Refluxing carbohydrazides **1** with **48** in methanol afforded isatin-β-arylhydrazones **99**, which reacted with 2-mercapto acetic acid in dioxane to furnish the interesting spiro[3*H*-indole-3,2ʾ-thiazolidine] derivatives **100** [67].



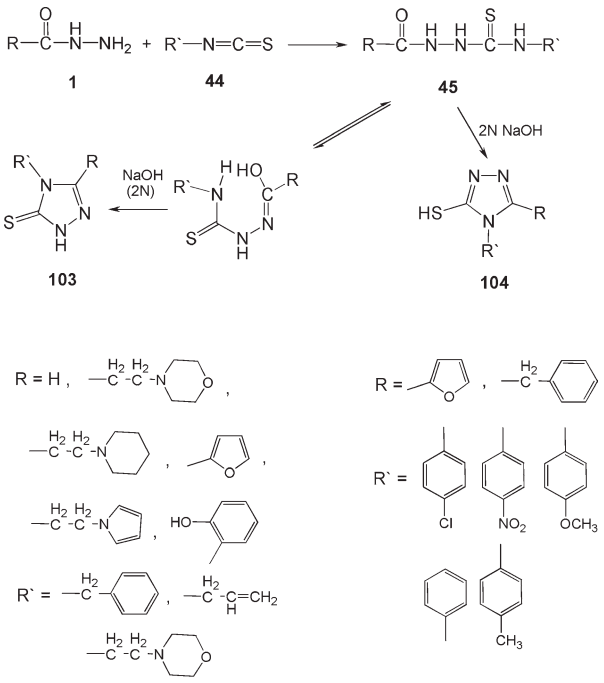

R = 2,4-$(CH_3)_2$ , 4-Cl , 4-$CH_3$ , 2-$CH_3$ , 4-Cl-3-$CH_3$ , 2-Cl , 3,4-$(CH_3)_2$ , 3,5-$(CH_3)_2$ , 2,5-$(CH_3)_2$

**3.7. Synthesis of 1,2,4-triazole derivatives.** Reaction of carbohydrazides **1** with carbon disulfide in ethanolic

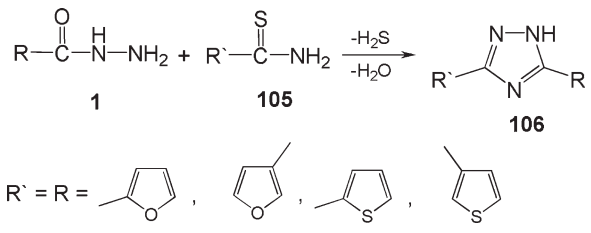
potassium hydroxide gave dithiocarbazate **101**, which reacted with hydrazine hydrate to form 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiol **102** [51].



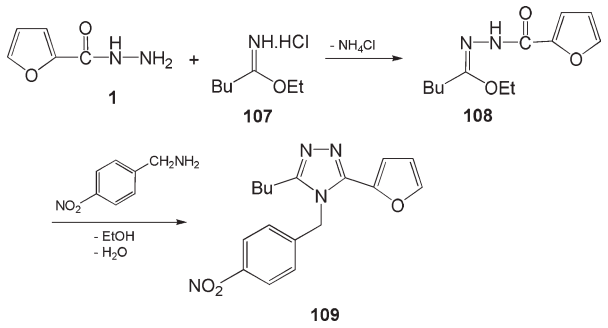
Ring closer acylthiosemicarbazides **45**, prepared by reacting **1** with **44**, in an alkaline medium, led to the formation of 1,2,4-triazole-3-thione derivatives **103** [51] and 1,2,4-triazolethiol derivatives **104** [47,48,68–70].



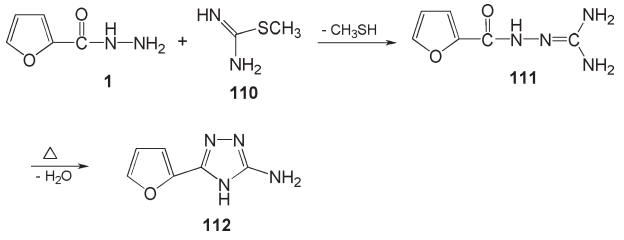
1,2,4-Triazole derivatives **106** were also obtained *via* the reaction of thiocarbamides **105** with carbohydrazides **1** [71].



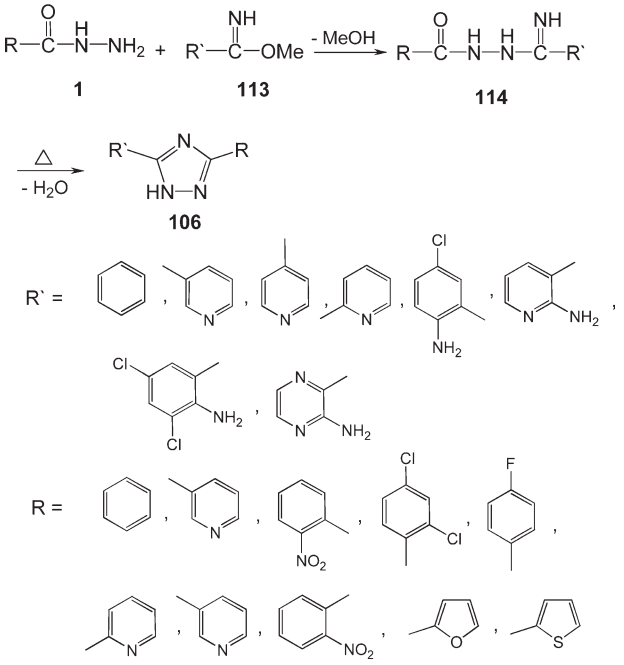
The reaction of carbohydrazide **1** with imidate hydrochloride **107** gave compound **108**, which was converted into 1,2,4-triazole derivative **109** upon heating with 4-nitrobenzylamine [72].



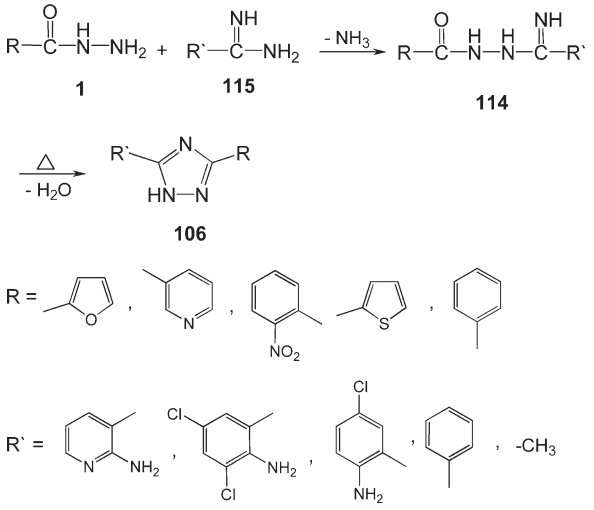
2-Furan carbohydrazide **1** reacted with *S*-methyl-isothiourea **110** to give the corresponding guanidine **111**. Upon heating **111**, 3-amino-1,2,4-triazole derivative **112** was formed [73,74].



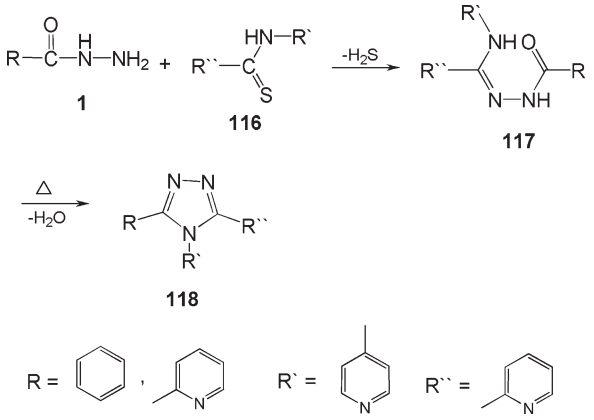
Most of 3,5-disubstituted-1,2,4-triazoles **106** were readily synthesized from imidates **113** and carbohydrazides **1**. For example, condensation of imidates **113** with carbohydrazides **1** gave acylamidrazones **114**, which underwent thermal cyclization to give 3,5-disubstituted-1,2,4-triazoles **106** [75–79].



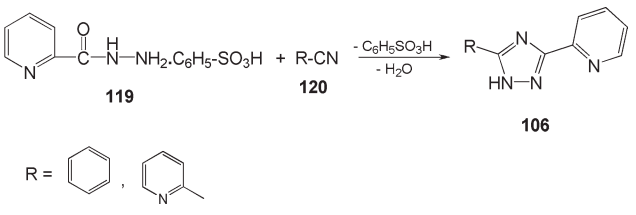
Also, reaction of carbohydrazides **1** with acetamidine or benzamidine **115** afforded 1,2,4-triazole derivatives **106** [80–82].



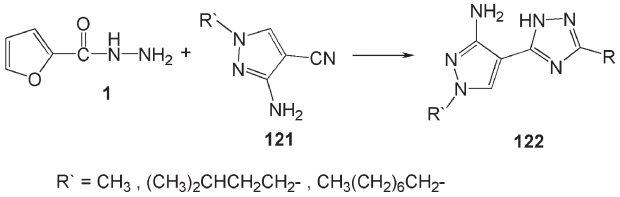
Substituted 1,2,4-triazoles **118** were synthesized by thermal cyclization of $N^3$-substiuted-$N^1$-acylamidrazone derivatives **117**, prepared by the reaction of carbohydrazides **1** with thioamides **116** in ethanol at room temperature [83–85].



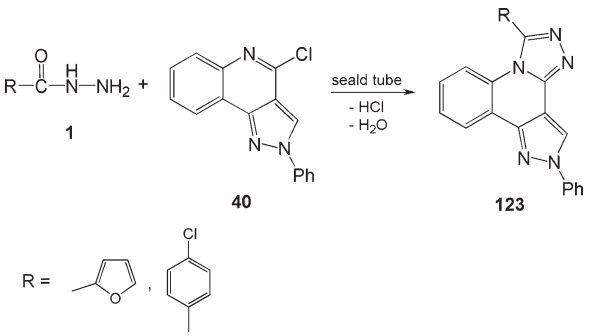
1,2,4-Triazole derivatives **106** were prepared *via* the reaction of 2-pyridine carbohydrazide benzenesulphonate **119** with substituted nitriles **120** [86] according to Pott's method [87–90].



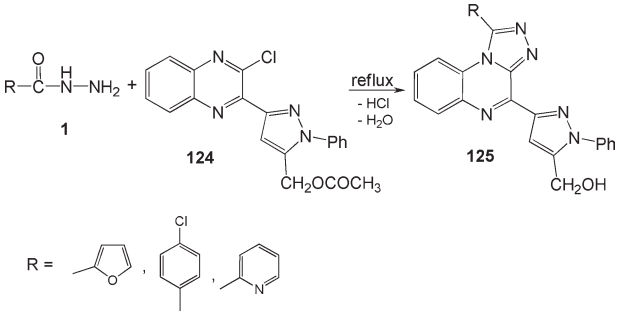
Reaction of pyrazole derivatives **121** with carbohydrazide **1** afforded 1,2,4-triazole derivatives **122** [91]. Also, the reaction of **121** with carbohydrazides **1** in refluxing diphenyl ether gave the 1,2,4-triazole derivatives **122** [3].



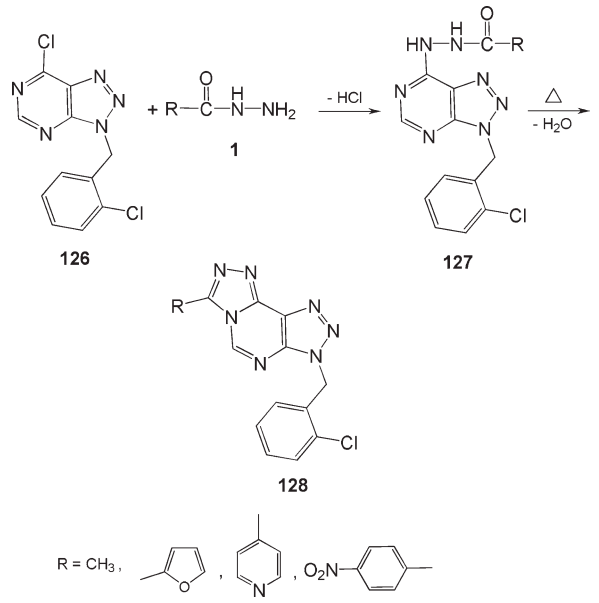
**3.8. Synthesis of fused triazole compounds.** 4-Chloro-2-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline **40** reacted with carbohydrazides **1** in ethanol to form 2-phenyl-6-(furan-2-yl or 4-chlorophenyl)-2*H*-pyrazolo[4,3-*c*]-1,2,4-triazolo[4,3-*a*]quinolines **123** [46].



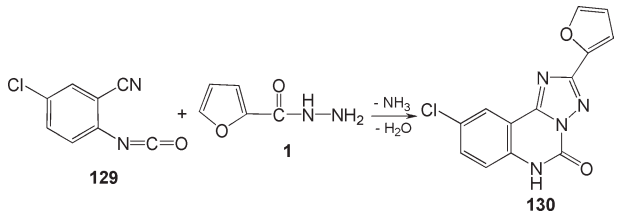
The reaction of carbohydrazides **1** with 2-chloro-3-[5-(acetoxymethyl)-1-phenylpyrazol-3-yl]quinoxaline **124** in boiling n-butanol resulted in the formation of the corresponding 1-aryl-4-[5-(hydroxymethyl-1-phenyl-pyrazol-3-yl]-1,2,4-triazolo[4,3-*a*]quinoxalines **125** [92].



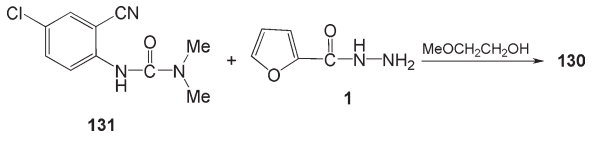
3-(2-Chlorobenzyl)-7-chloro-1,2,3-triazolo[4,5-*d*]-pyrimidine **126** reacted with carbohydrazides **1** in boiling ethanol to give hydrazo derivatives **127**, which underwent intramolecular thermal cyclization to form 3-(2-chlorobenzyl)-7-substituted-1,2,3-triazolo [4,5-*e*]-1,2,4-triazolo[4,3-*c*]-pyrimidine derivatives **128** [93].



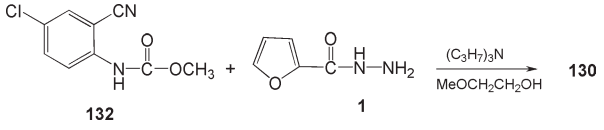

The reaction of carbohydrazide **1** with 5-chloro-2-isocyanatobenzonitrile **129** in presence of tripropylamine and 2-methoxyethanol afforded 9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-*c*]quinazolin-5-(6*H*)-one **130** [94,2].



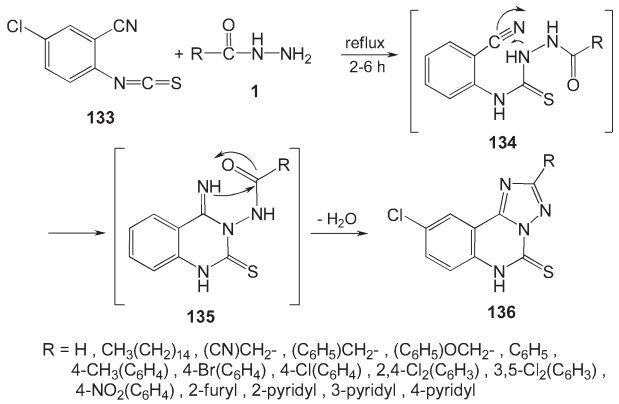

Also, the reaction of *N,N*-dimethyl-*N*\-(4-chloro-2-cyanophenyl)urea **131** with 2-furan carbohydrazide **1** in 2-methoxyethanol gave triazoloquinazolinone derivatives **130** [94].



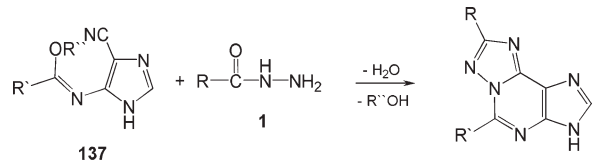

On the other hand, compound **130** was synthesized by the reaction of 5-chloro-2-[(methoxycarbonyl)-amino]-benzonitrile **132** with 2-furan carbohydrazide **1** in tripropylamine and 2-methoxyethanol [94].



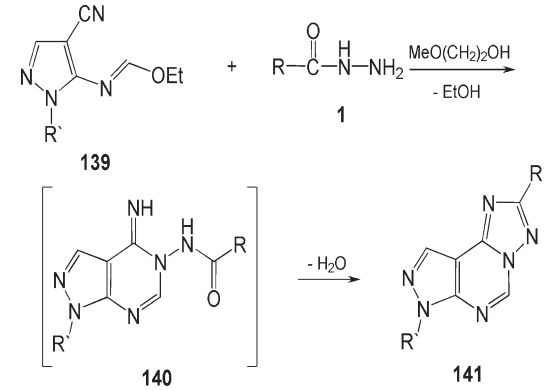

One-pot reaction between carbohydrazides **1** and 5-chloro-2-isothiocyanatobenzonitrile **133** afforded 1,2,4-triazolo[1,5-*c*]quinazoline-5(6*H*)-thiones **136**, in good yields [95].



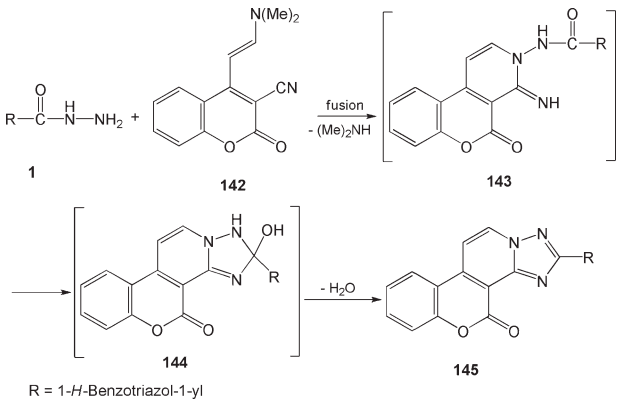

Refluxing alkyl-*N*-[4-cyano-1*H*-imidazol-5-yl]alkyl-imidate **137** with carbohydrazides **1** in DMF gave substituted 3*H*-1,2,4-triazolo[5,1-*i*]purines **138** [96].



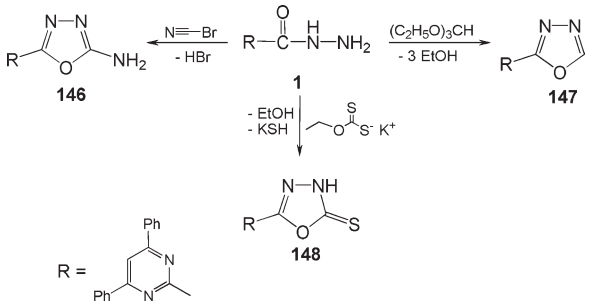

Reaction of 2-furan carbohydrazide **1** with imidate **139** in refluxing 2-methoxyethanol gave pyrazolo[4,3-*e*]-pyrimidine derivatives **140**, the non-isolable which converted *via* a thermally induced cyclization in diphenyl ether into pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine derivatives **141** [5, 6, 97–99].



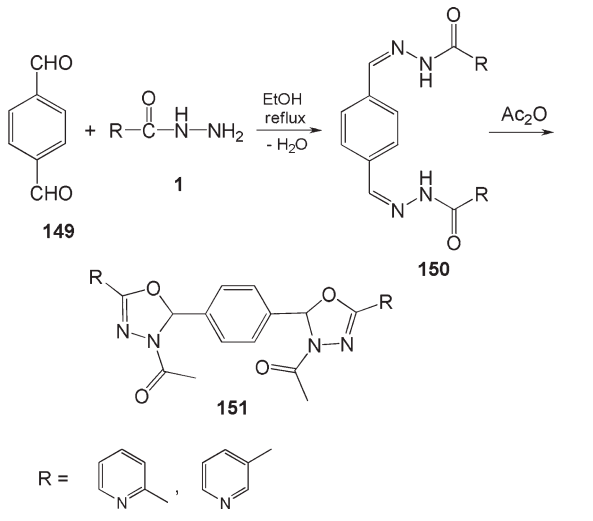

Fusion of *E*-dimethylaminoethylene derivatives **142** with carbohydrazide **1** afforded the corresponding 1,2,4- triazolo[1,5-*a*]pyrido[3\,4\-*c*]coumarin derivative **145** [100].



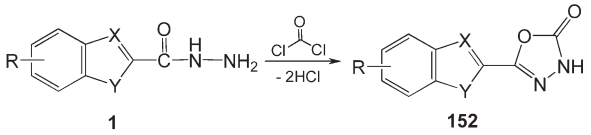

**3.9. Synthesis of oxadiazole derivatives.** Oxadiazole derivative **146** was obtained from the reaction of carbohydrazide **1** with cyanogen bromide [101]. Also, compound **1** reacted with triethoxymethane or potassium *o*-ethylxanthate to give, 1,3,4-oxadiazole and 1,3,4-oxadiazolethione **147** and **148** respectively [47].




Reaction of terephthalaldehyde **149** with carbohydrazides **1** in refluxing ethanol afforded the corresponding bis(carbohydrazone) **150**. Heating **150** in acetic acid/ethanol mixture at reflux temperature afforded bis(dihydroxadiazolyl)benzene derivatives **151** [102].

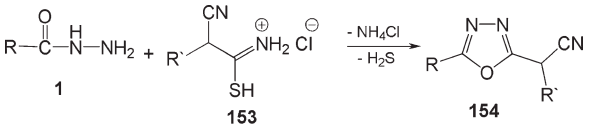



2-(2,3-Dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzo-heterocycles **152** were prepared by treatment of carbohydrazides **1** with excess of phosgene in methylene chloride at room temperature [103].



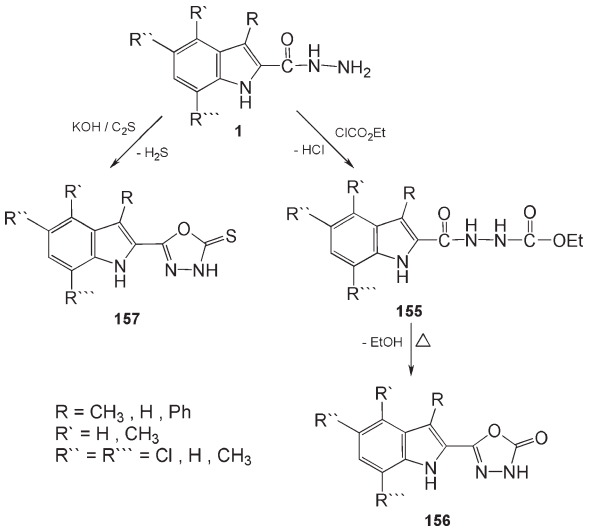

R = H , 5-Cl , 5-$CO_2CH_3$ , 7-$OCH_3$ , 6-$CH_3$
5-$CO_2Et$ , 4-$CH_3$ , 5-$CH_3$ , 6-$CH_3$ , 6-Cl
X = N , C-Cl , C-$CH_3$ , CH
Y = N-$CH_3$ , S , $CH_2$ , NH , O

Carbohydrazides **1** reacted with **153** in refluxing ethanol to give 2-cyanomethyl-5-substituted-1,3,4-oxadiazole **154** [103].

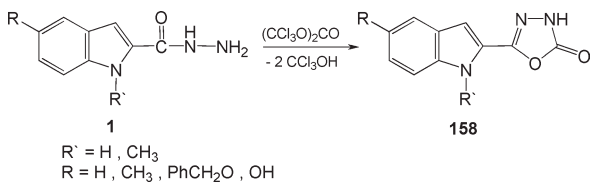



R` = H , n-Bu , $PhCH_2$
R = Ph , n-$C_{11}H_{23}$ , 2-indolyl

Carbohydrazides **1** underwent condensation with ethyl chloroformate to give *N*-carbethoxy-5-substituted indole-2-carbohydrazides **155**, which were refluxed in diethyl ether to give 2-(5′-oxo-1′,3′,4′-oxadiazol-2′-yl)indole derivatives **156** [104].

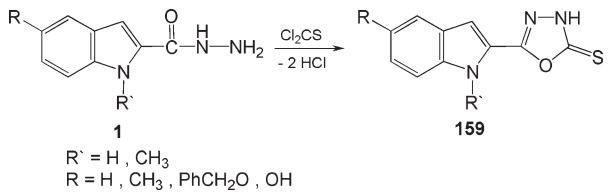



Treatment of carbohydrazides **1** with triphosgene afforded oxadiazolone derivatives **158** in one step [16].

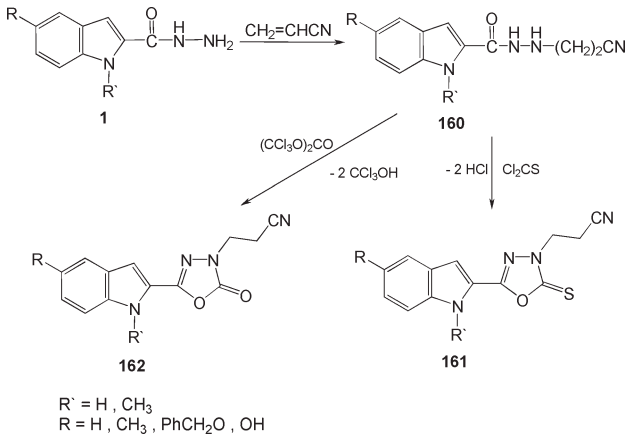



Also, **1** was refluxed with appropriate quantities of KOH and $CS_2$ in ethanol to give oxadiazolethione derivatives **157** [104].

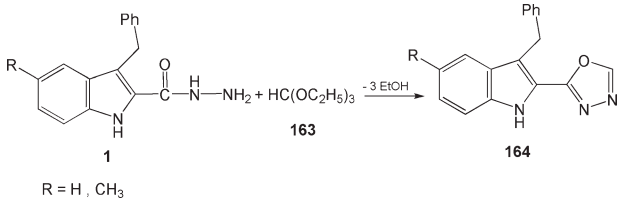
1,3,4-Oxadiazolethiones **159** were generated directly by treatment of the corresponding carbohydrazides **1** with thiophosgene [4].



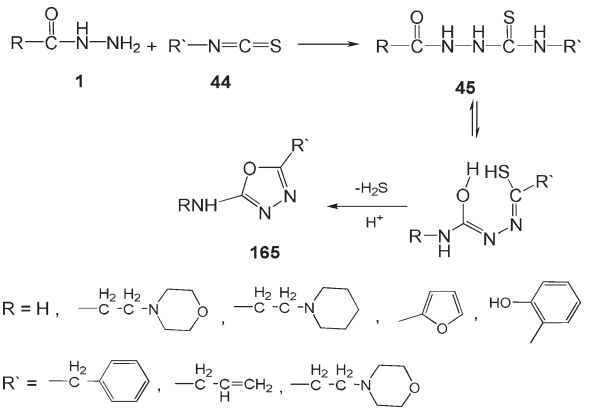

Monosubstituted indole-2-cyanoethylhydrazides **160**, prepared by Michael addition of acrylonitrile on the corresponding carbohydrazides **1**, were used as good precursors for the synthesis of indolyl-1,3,4-oxadiazole-3-(2-cyanoethyl)-2-one derivatives **161** and **162**, during the reaction with thiophosgene and triphosgene, respectively [4].



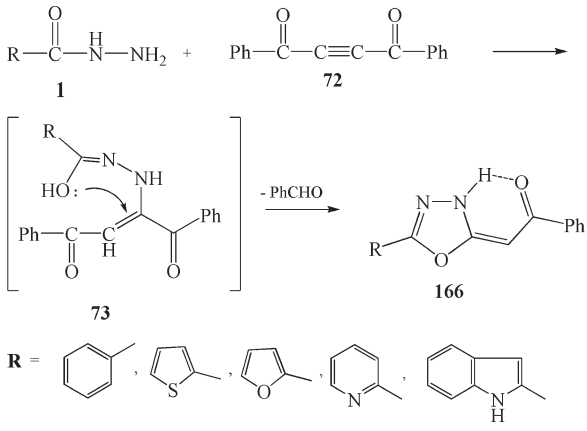

Refluxing carbohydrazides **1** with triethylorthoformate (TEO) **163** afforded 1,3,4-oxadiazole derivatives **164** [105].



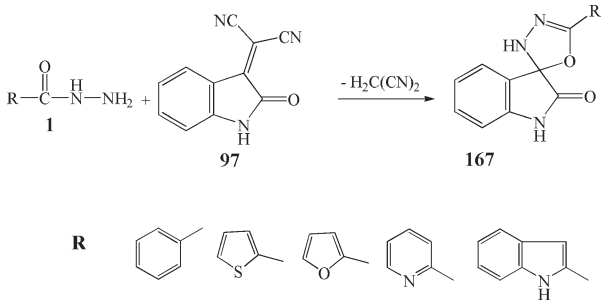

Isothiocyanates **44** reacted with carbohydrazides **1** to form acylthiosemicarbazides **45**. Ring closure of **45** in acidic medium gave 1,3,4-oxadiazole **165** derivatives [47,106].




Reaction of **1** with **72** in acetic acid gave the intermediate **73** which loss a molecule of PhCHO to form 1-phenyl-2-(5-substituted-1,3,4-oxadiazol-2-(3*H*)-ylidene) ethanone **166** [63].

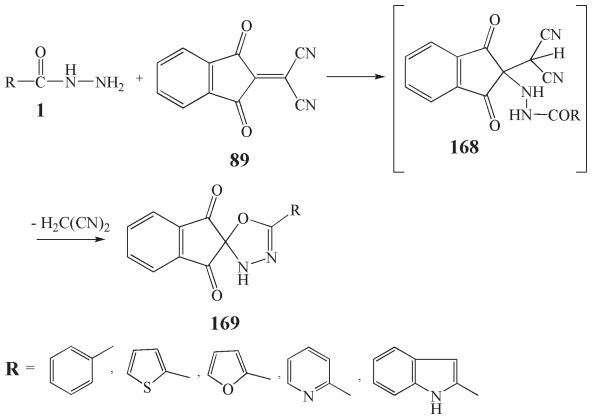



Carbohydrazides **1** reacted with 3-(dicyanomethylene)-2-indolone **97** in the presence of pipridine to give substituted spiro(indoline-3,2\-1,3,4-oxadiazol)-2-one **167**. Nucleophilic attack of **1** on C=C of **97** followed by loss of one molecule of malononitrile afforded **167** [65].

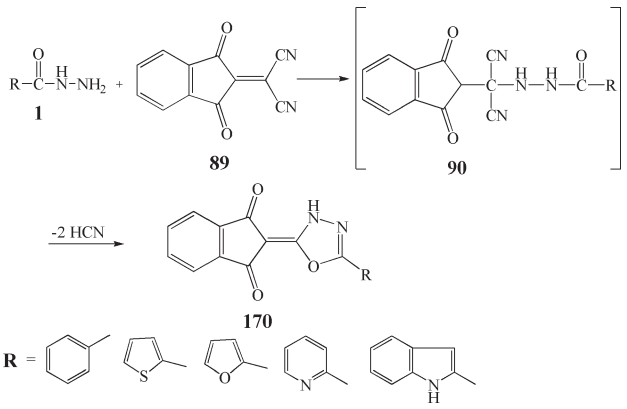



Carbohydrazides **1** reacted with (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile **89** in DMF with

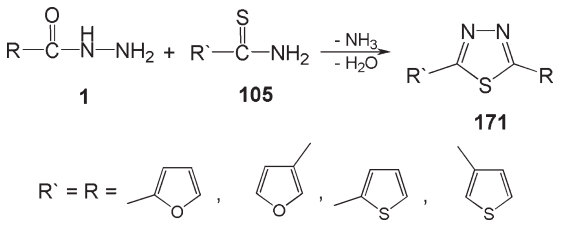
admission of air, to afford 5′-substituted-3′*H*-spiro(indene-2,2′-1,3,4-oxadiazole)-1,3-dione **169** [65].



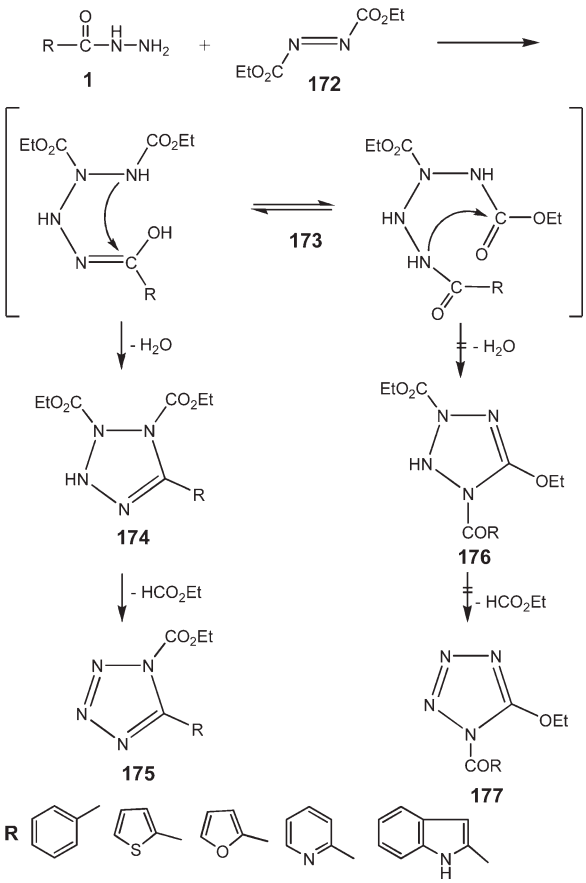
On the other hand, reaction of carbohydrazides **1** with **89** gave 2-(5-substituted-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-diones **170** *via* the formation of the intermediate **90** and elimination of two molecules of HCN [65].



**3.10. Synthesis of thiadiazole derivatives.** Thiadiazole derivatives **17**1 were obtained from the reaction of carbohydrazides **1** and thiocarboxamides **105** [71].



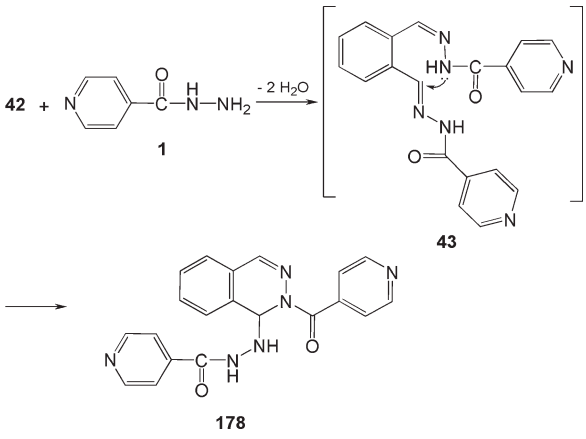
**3.11. Synthesis of tetrazole derivatives.** A mixture of **1** and diethyl diazene-1,2-dicarboxylate **172** in glacial acetic acid was heated at reflux temperature for 6-8 h, during which time tetrazole derivatives **175** were formed [63].



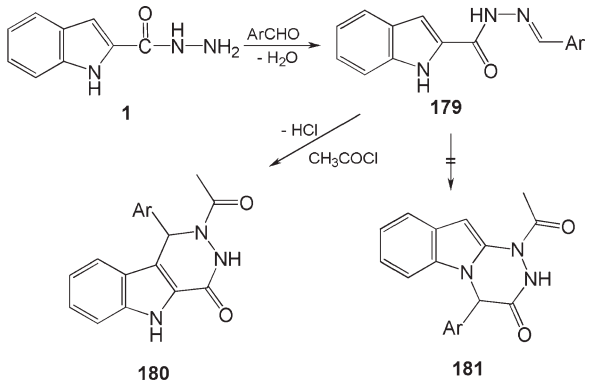
Nucleophilic attack of **1** to **172** with loss one molecule of $H_2O$ followed by elimination of another molecule of ethyl formate afforded tetrazole derivatives **175** rather than the alternative structure **177** [63].

**3.12. Synthesis of diazine derivatives.**

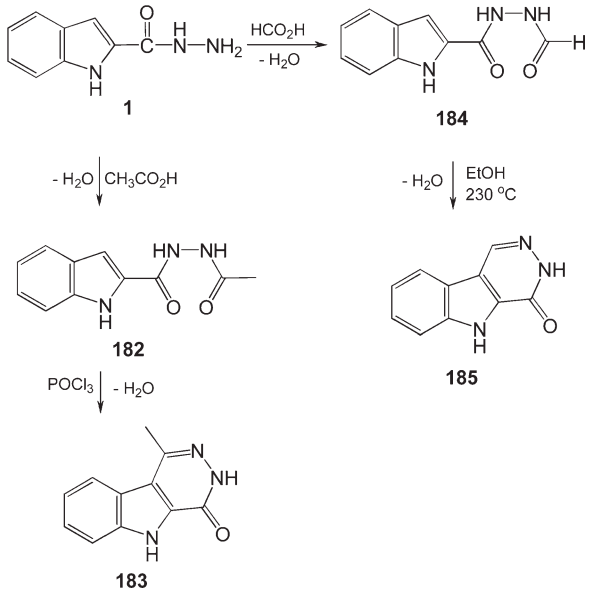
***3.12.1. Synthesis of phthalazine derivatives.*** Reaction of *o*-phthalaldehyde **42** with 4-pyridine carbohydrazide **1** in refluxing ethanol gave a pure sample of hydrazone **43**, which underwent intramolecular cyclization afford the phthalazine derivatives **178** [102].



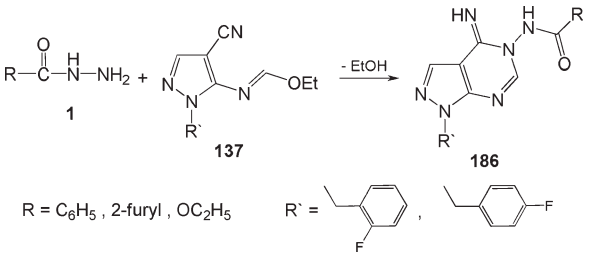
*3.12.2. Synthesis of pyridazine derivatives.* Condensation of indole carbohydrazide **1** with aromatic aldehydes gave the corresponding hydrazone derivatives **179** were obtained in varying yields, which heated to reflux in acetyl chloride to give the interesting tricyclic indolo[2,3-*d*]pyridazine derivatives **180** rather than indenotriazines **181** [64].



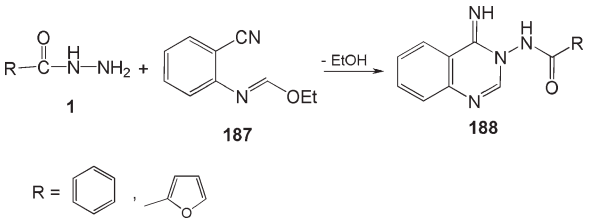

Acetylation of **1** by refluxing in acetic acid afforded 2-acetyl-hydrazinocarbonylindole **182**, in high yield. Compound **182** was cyclized directly by refluxing in dioxane containing $POCl_3$ to the indolo[3,2-*b*]pyradizines **183** [64]. On the other hand, refluxing **1** in formic acid for 5 h afforded the *N*-formyl derivative **184**, which was heated for 10 min in ethanol to afford 2,3-dihydro-indolo[3,2-*b*]pyridazin-1-one **185** [64].



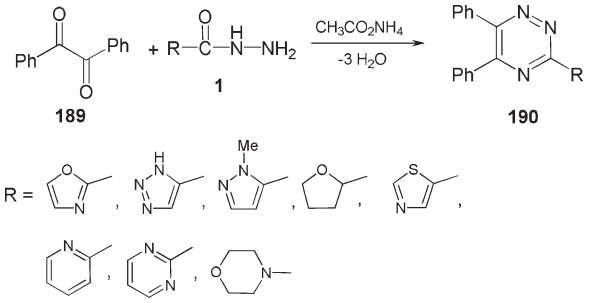

*3.12.3. Synthesis of pyrimidine derivatives.* Carbohydrazides **1** reacted with 4-cyano-5-[(ethoxymethylene)amino]pyrazoles **137** to give 5-acyl-amino-4-imino-4,5-dihydropyrazolo[3,4-*d*]pyrimidines **286** [91].



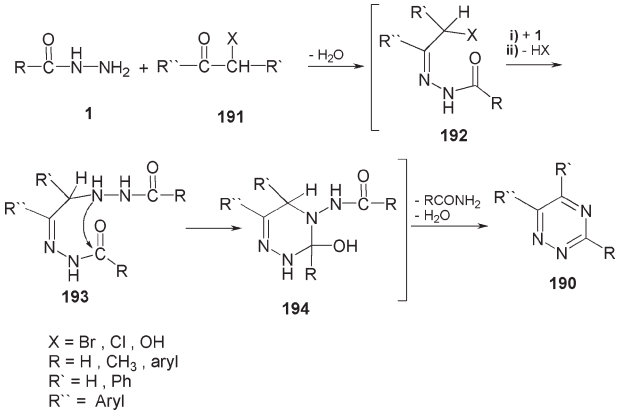

*3.12.4. Synthesis of quinazoline derivatives.* Refluxing of carbohydrazides **1** with *N*-ethoxy-methylene-2-amino-benzonitrile **187** in ethanol gave 3-acylamino-4-imino-3,4-dihydroquinazolines **188** [107].




**3.13. Synthesis of 1,2,4-triazine derivatives.** Benzil **189** reacted with carbohydrazides **1** in the presence ammonium acetate under microwave irradiation to give 1,2,4-triazine derivatives **190** [9,108–110].

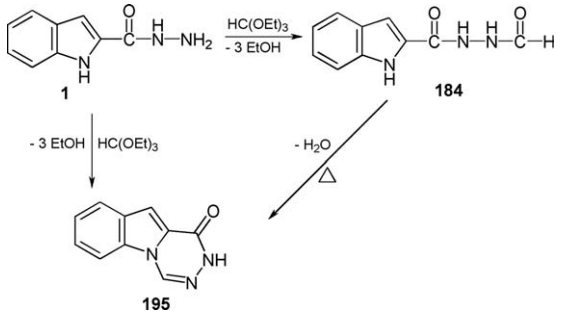



1,2,4-Triazine derivatives **190** were obtained by the reaction of carbohydrazides **1** with halomethyl ketone **191** [111,112].

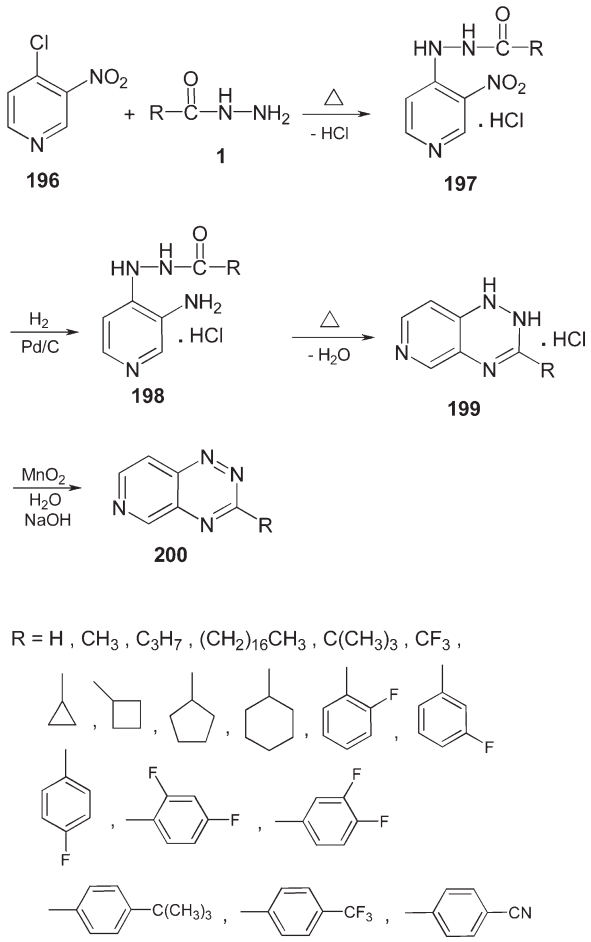



Boiling of 2-indole carbohydrazide **1** with triethyl-orthoformate in DMF, or thermal cyclodehydration of

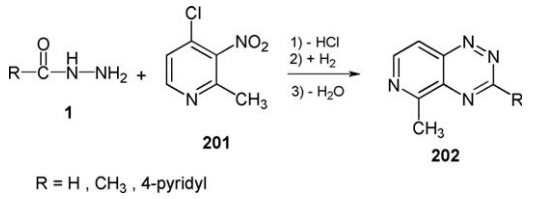
**184** gave 1,2-dihydro-1-oxo-1,2,4-triazino[4,5-*a*]indole **195** [113].



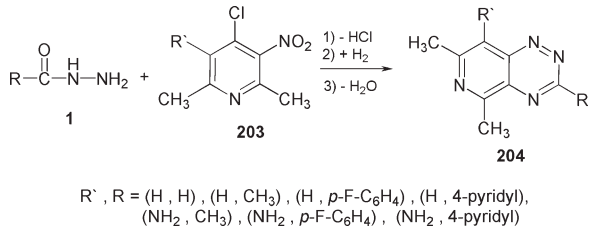
Carbohydrazides **1** reacted with 4-chloro-3-nitropyridine **196** in ethanol to form the acyl derivatives of 4-hydrazino-3-nitropyridine hydrochloride **197**. The nitro group in **197** was rapidly reduced over palladium catalyst to give **198**, ring closure of the latter compound under acidic conditions gave pyrido[3,4-*e*]-1,2,4-triazine derivatives **199**, which was oxidized by $MnO_2$ in presence of alkaline solution to form 3-substiuted pyrido[3,4-*c*]-1,2,4-triazine derivatives **200** [114,115].



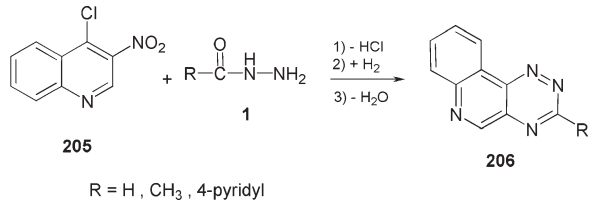
Similarly, carbohydrazides **1** reacted with 4-chloro-2-methyl-3-nitropyridine **201** to give 3,5-disubstituted pyrido[3,4-*c*]-1,2,4-triazine derivatives **202** [114,115].



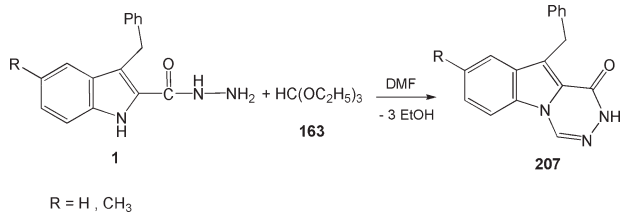
The reaction of carbohydrazides **1** with 5-substituted-4-chloro-2,6-dimethyl-3-nitropyridine **203** afforded pyridotriazine derivatives **204** [114,115].



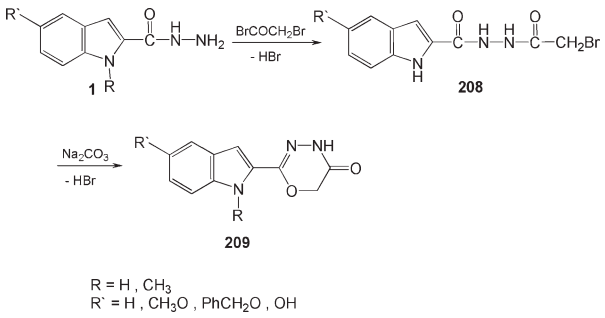
Reaction of 4-chloro-3-nitroquinoline **205** with carbohydrazides **1** gave 1,2,4-triazino[5,6-*c*]quinolines **206** [114,115].



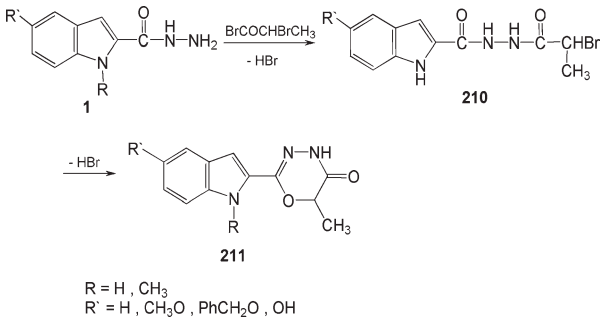
Reaction of carbohydrazides **1** with triethylorthoformate **163** in DMF gave 10-benzyl-1,2-dihydro-1-oxo-1,2,4-triazino[4,5-*a*]indole derivatives **207** [105].



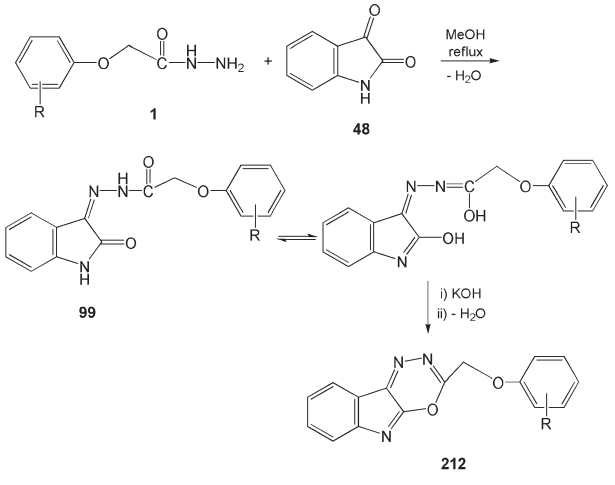
**3.14. Synthesis of 1,3,4-oxadiazine derivatives.** 2-Indolyl-4*H*-1,3,4-oxadiazine-5(6*H*)-one derivatives **209** have been synthesized by reaction of $Na_2CO_3$ with $N^2$-(2-bromoacetyl)indole-2-carbohydrazides **208**, prepared by reaction of carbohydrazides **1** with α-bromoacylbromide [4].



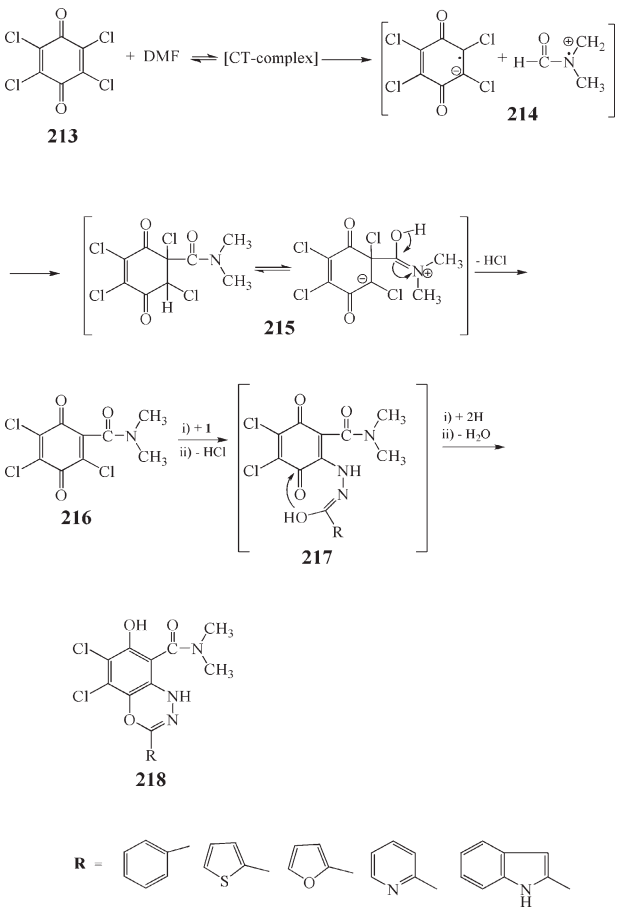

Reaction of carbohydrazides **1** with 2-bromopropanoylbromide gave $N^2$-(2-bromopropanoyl)-indole-2-carbohydrazide **210**, which cyclized to produce 2-indolyl-4*H*-1,3,4-oxadiazine-6-methyl-5-one derivatives **211** [4].



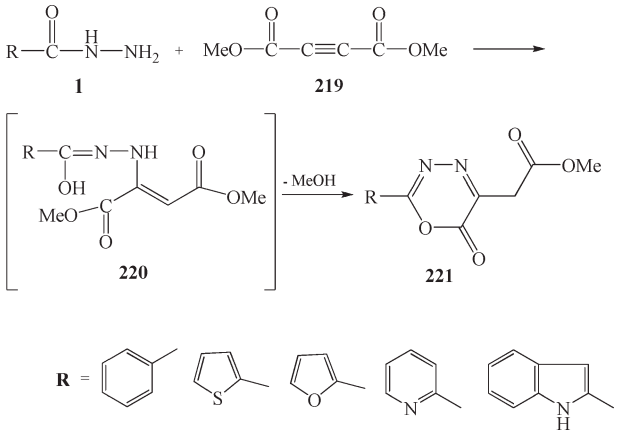

Isatin **48** was refluxed with carbohydrazides **1** in methanol to furnish isatin-β-aroylhydrazones **99**, which heated to reflux in aq. KOH to afford 2-aryl-1,3,4- oxadiazino[5,6-*b*]indole derivatives **212** [67].



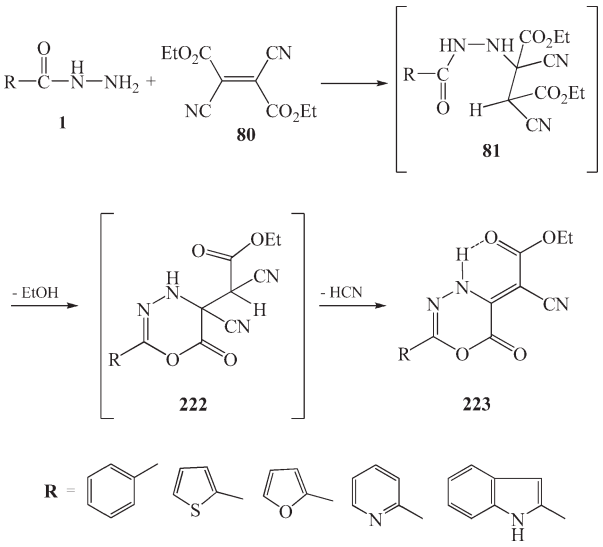

A mixture of 2,3,5,6-tetrachloro-1,4-benzoquinone **213** and **1** in DMF with admission of air afforded substituted benzo[1,3,4]oxadiazinecarboxamide **218** [66].



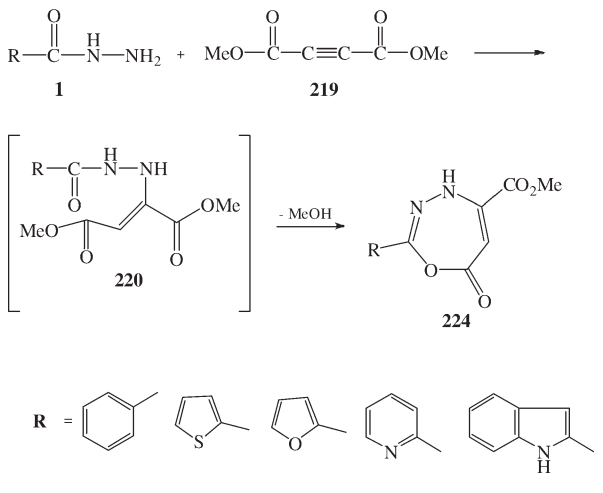

A mixture of dimethyl but-2-ynedicarboxylate **219** and substituted carbohydrazides **1** was refluxed in methanol to afford 1,3,4-oxadiazine derivatives **221** [63].



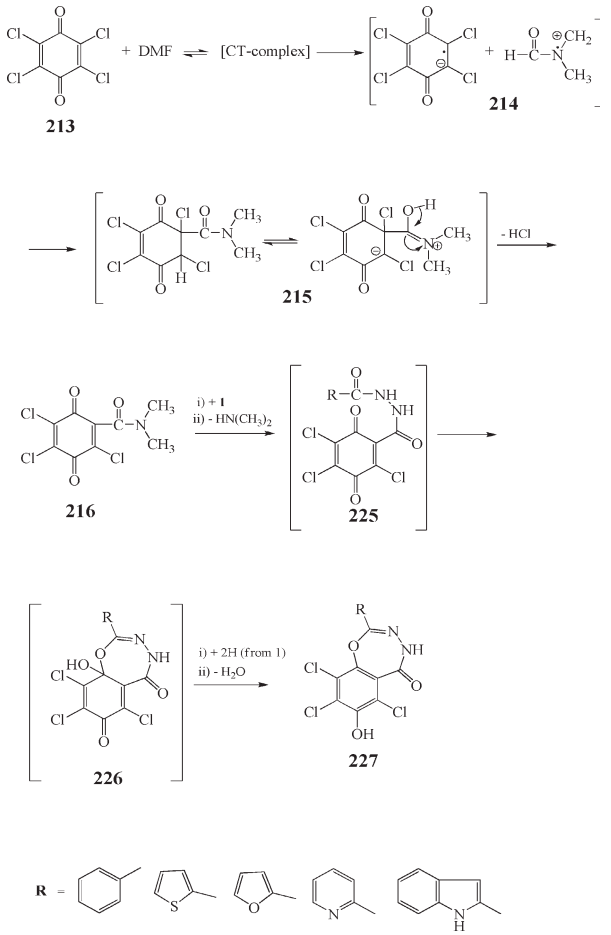

Solutions of diethyl (*E*) 2,3-dicyanobutenedioate **80** and **1** were refluxed for 4–18 h in ethyl acetate to give 1,3,4-oxadiazinone **223**, *via* elimination of one molecule of ethanol follwed by HCN [38].



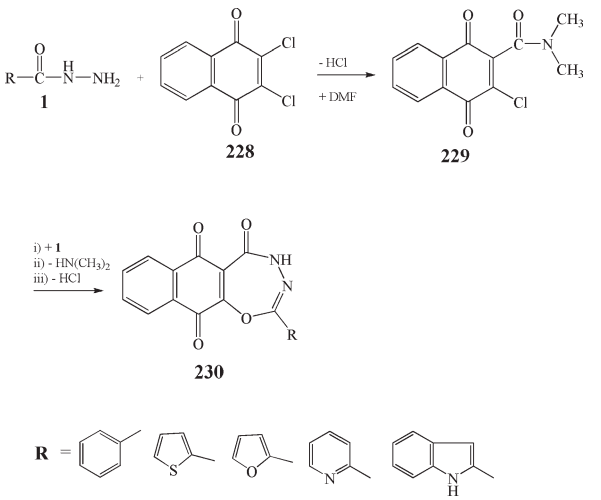
**3.15. Synthesis of oxadiazepine derivatives.** A mixture of dimethyl but-2-ynedicarboxylate **219** and substituted carbohydrazides **1** was heated to reflux in methanol to afford 1,3,4-oxadiazepine derivatives **224**. Nucleophilic attack of the $NH_2$ group of **1** to the triple bond of **219** afforded the adduct **220**, followed by elimination of one molecule of methanol and intramolecular cyclization to give **224** [63].



The reaction of 2,3,5,6-tetrachloro-1,4-benzoquinone **213** and **1** in DMF, with admission of air, afforded substituted benzo[1,3,4]oxadiazepine **227** [66].



On the other hand, the reaction of 2,3-dichloro-1,4-naphthoquinone **228** with **1** in DMF afforded substituted naphtho[2,3-*f*]-1,3,4-oxadiazepine-5,6,11-(4*H*)-trione **230** [66].



## REFERENCES AND NOTES


[1] Sarhan, A. A. O. Monatsh Chem 2001, 132, 753.

[2] Francis, J. E.; Cash, W. D.; Psychoyos, S.; Ghai, G.; Wenk, P.; Friedmann, R. C.; Atkins, C.; Warren, V.; Furness, P.; Hyun, J. L.; Stone, G. A.; Desai, M.; Williams, M. J Med Chem 1988, 31, 1014.

[3] Gatta, F.; Dell Giudice, M. R.; Borioni, A.; Borea, P. A.; Dionisotti, S.; Ongini, E. Eur J Med Chem 1993, 28, 569.

[4] (a) Struve, G. J Prakt Chem 1894, 50, 295; (b) Struve, G. J Prakt Chem 1895, 52, 170.

[5] Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Villatoro, M. J. P.; de las, I.; Zocchi, C.; Dionisotti, S.; Ongini, E. J Med Chem 1996, 39, 1164.

[6] Al-Afaleq, E. I.; Abubshait, S. A. Molecules 2001, 6, 621.

[7] Glwahy, A. H. M.; Ahmed, M. M.; El-Sadek, M. J Chem Res (S), 2001, 175.

[8] Francis, J. E.; Gorczyca, L. A.; Mazzenga, G. C.; Meckler, H. Tetrahedron Lett 1987, 28, 5133.

[9] Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. Tetrahedron Lett 2003, 44, 1123.

[10] Paulsen, H.; Stoye, D. In The Chemistry of Amides; Zabicky, J., Ed.; Interscience: London, 1970, p 515.

[11] Nolan, G.; Samuel, E. L.; Ennis, B. C.; Hinde, R. W. J Chem Soc C, 1967, 30.

[12] Curtius, T.; Thyssen, J. J Prakt Chem 1902, 7, 65.

[13] Iqbal, R.; Malik, F. J Chem Soc Pak 1984, 6, 43.

[14] Cruces, M. A.; Elorriage, C.; Fernandes-Alvarez, E. Eur J Med Chem 1991, 26, 33.

[15] Fernandez-Alvarez, E.; Lone, M.; Monge, A. Bull Soc Chim Fr 1969, 1932.

[16] Marco, J. L. J Heterocycl Chem 1998, 35, 475.

[17] Pêrez, S.; Lasheras, B.; Oset, C.; Monge, A. J. Heterocycl Chem 1997, 34, 1527.

[18] Cruces, M. A.; Elorriage, C.; Fernandes-Alvarez, E. Biochem Pharmacol 1990, 40, 535.

[19] Cook, M. J.; Bes, E. J. Tetrahedron 1968, 24, 4501.

[20] Shimazu, M.; Naito, T.; Ohta, G.; YoshihawaT.; Dohmori, R. J Pharm Soc Jpn 1952, 72, 1474.

[21] Fischer, E.; Van Slyke, D. D. Ber Dtsch Chem Ges 1911, 44, 3166.

[22] Kesting, W. Chem Ber 1924, 57, 1321.

[23] Borsche, W.; Müller, W.; Bodenstein, C. A. Ann Chem 1929, 475, 120.

[24] Lieser, T.; Nischk, G. Chem Ber 1949, 82, 527.

[25] Fichter, F.; Becker, B. Chem Ber 1911, 44, 3481.

[26] (a) Argyle, C. S. (to Whiffen and Sons Ltd.). U.S. Pat.3,258,485 (1966); (b) Argyle, C. S. Chem Abstr 1966, 65, 7067.

[27] Knaus, E. E.; Redda, K. K. J Heterocycl Chem 1976, 13, 1237.

[28] Redda, K. K.; Melles, H.; Rao, K. N. J Heterocycl Chem 1990, 27, 1041.

[29] Rao, K. N.; Redda, K. K.; Onayemi, F. Y.; Melles, H.; Choi, J. J Heterocycl Chem 1995, 32, 307.

[30] Zhao, X.; Wang, X.; Jiang, X.; Chen, Y.; Li, Z.; Chen, G. J Am Chem Soc 2003, 125, 15128.

[31] Bukowski, L.; Janowic, M.; Zwolska-Kwick, Z.; Andrzejczyk, Z. Pharmazie 1999, 9, 54.

[32] Fox, H. H.; Gibas, J. T. J Org Chem 1952, 17, 1653.

[33] Pamies, O.; Ruiz, A.; Net, G.; Claver, C.; Kalchhauser, H.; Widhalm, M. Monatsh Chem 2000, 131, 1173.

[34] Lehmann, J.; Ghoneim, K. M.; Elgendy, A. A. Arch. Pharm (Weinheim), 1984, 317, 188.

[35] Salgado, M.; Garcia Detorres, A.; Cano Pavon, J. M. Talanta 1985, 32, 887.

[36] Syamal, A.; Maurya, M. R. Ind J Chem 1985, 24A, 836.

[37] El-Baradie, K. Y.; Gaber, M.; El-Mehasseb, I. M. Egypt J Chem 1994, 37, 441.

[38] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M. Z. Naturforsch.,2008, 63b, 998.

[39] Zhao, H.; Burke, T. R. Jr. Tetrahedron 1997, 53, 421.

[40] Pedler, A.; Pollard, F. H. Inorganic Synthesis; Mc Graw-Hill: New York, 1957; Vol. 87

[41] Kim, Y. H.; Kim, K.; Shim, S. B. Tetrahedron Lett 1986, 27, 4749.

[42] Moustafa, M. A.; Nasr, M. N.; Gineinah, M. M.; Bayoumi, W. A. Arch Pharm Med Chem 2004, 337, 164.

[43] Abernethy, J. L.; Boebeck, R.; Ledesma, A.; Kemp, R. J Org Chem 1973, 38, 1286.

[44] Abernethy, J. L.; Srulevtch, D.; Ordway, M. J. Jr. J Org Chem 1975, 40, 3445.

[45] Burger, K.; Lange, T.; Rudolph, M. Heterocycles 2003, 59, 1.

[46] Baraldi, P. G.; Tabrizi, M. A.; Preti, D.; Bovero, A.; Fruttarolo, F.; Romagnoli, R.; Abdel Zaid, N.; Moorman, A. R.; Varani, K.; Borea, P. A. J Med Chem 2005, 48, 5001.

[47] Hoggarth, E. J Chem Soc 1949,1163.

[48] Godefroi, E. F.; Wittle, E. L. J Org Chem 1956, 21, 1163.

[49] Buu Hoi, N. P.; Xuong, N. D.; Gazave, J. M.; Schembri, L.; Nam, N. H.; Long, C. T. Bull Soc Chim Fr 1956, 363.

[50] Shah, M. H.; Mhasalkar, M. Y.; Patki, V. M.; Deliwala, C. V.; Sheth, U. K. J Pharm Sci 1969, 58, 1398.

[51] Cansiz, A.; Koparir, M.; Demirdag, A. Molecules 2004, 9, 204.

[52] Mekuskiene, G.; Tumkevicius, S.; Vainilavicius, P. J Chem Res (S) 2002, 231.

[53] Kaupp, G.; Schmeyers, J.; Boy, J. J Prakt Chem 2000, 243, 259.

[54] Dias, M.; Mornet, R.; Laloue, M. Bioorg Med Chem 1995, 3, 361.

[55] Abid, S.; El-Gharbi, R.; Gandini, A. Polymer 2004, 45, 6469.

[56] Gupta, D. R.; Arora, R. K. Rev Roum Chim 1985, 30, 137.

[57] Singh, C. P. J Ind Chem Soc 1985, XII, 222.

[58] Baddar, F. G.; Al-Hajjar, F. H.; El-Rayyes, N. R. J Heterocycl Chem 1976, 13, 257.

[59] Al-Farkh, Y. A.; Al-Hajjar, F. H.; Hamoud, H. S. Chem Pharm Bull (Tokyo) 1978, 26, 1298.

[60] Al-Farkh, Y. A.; Al-Hajjar, F. H.; Hamoud, H. S. J Chem Eng Data 1978, 23, 347.

[61] Al-Hajjar, F. H.; Sabri, S. S. J Heterocycl Chem 1986, 23, 727.

[62] Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; da Silva, L. B.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P. J Heterocycl Chem 2005, 42, 631.

[63] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M. J Chem Res (S), 2008, 468.

[64] Barton, D. H. R.; Lukacs, G.; Wagle, D. J Chem Soc Chem Commun 1982, 450.

[65] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M. J Heterocycl Chem 2009, 46, 616.

[66] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M. J Heterocycl Chem, to appear.

[67] Ali, R.; Mishra, B.;Nizamuddin Ind J Chem 1989, 28B, 526.

[68] Chen, Y. T.; Chang, T. I. Sci Sin 1963, 12, 143; Chem. Abstr. 1963, 58, 13937f.

[69] Bhat, A. K.; Bhamaria, R. P.; Bellare, R. A.; Deliwala, C. V. Ind J Chem 1967, 5B, 397.

[70] Iqbal, R.; Rama, N. H.; Ahmed, N.; Zamani, K.; Ebrahim, S.; Iqbal, N. Ind J Chem 1998, 37B, 506.

[71] Decroix, P. B.; Dubus, P.; Morel, J.; Pastour, P. Bull Soc Chim Fr 1976, 3–4, 621.

[72] Ashton, W. T.; Chang, L. L.; Hutchins, S. M.; Strelitz, R. A.; MacCoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S. J Med Chem 1993, 36, 591.

[73] Srivastava, R. P.; Kumar, V. V.; Bhatia, S.; Sharma, S. Ind J Chem 1995, 34B, 209.

[74] Lipinski, C. A. J Med Chem 1983, 26, 1.

[75] Browne, E. J.; Polya, J. B. J Chem Soc C 1968, 824.

[76] Browne, E. J. Aust J Chem 1971, 24, 393.

[77] Browne, E. J. Aust J Chem 1971, 24, 2389.

[78] Browne, E. J.; Polya, J. B. J Chem Soc C, 1969, 1056.

[79] Browne, E. J. Aust J Chem 1975, 28, 2543.

[80] Poonian, M. S.; Nowoswait, E. F. J Org Chem 1980, 45, 203.

[81] Francis, J. E.; Gorezyca, L. A.; Mazzenga, G. C.; Meckler, H. Tetrahedron Lett 1987, 28, 5133.

[82] Postovskii, I. Y.; Vereshchqngia, N. N.; Obsch, Z. Khim 1959, 229, 2139; Chem. Abstr. 1960, 54, 9898c.

[83] Potts, K. T. Chem Rev 1961, 61, 78.

[84] Kilngele, M. H.; Brooker, S. Eur J Org Chem 2004, 3422.

[85] Santus, M. Liebigs Ann Chem 1988, 179.

[86] Mamolo, M. G.; Vio, L.; Banfi, E.; Cinco, M. Eur J Chem 1986, 21, 467.

[87] Potts, K. T. J Chem Soc 1954, 3461.

[88] Vio, L.; Mamolo, M. G.; Pellizer, G. Arch Pharm (Weinheim) 1988, 321, 713.

[89] Takalo, H.; Mukkala, V.-M.; Meriö, L. Helv Chim Acta 1997, 80, 372.

[90] Lipinski, C. A. J Med Chem 1983, 26, 1.

[91] Moro, S.; Braiuca, P.; Deflorian, F.; Ferrari, C.; Pastorin, G.; Cacciari, B.; Baraldi, P. G.; Varani, K.; Borea, P. A.; Spalluto, G. J Med Chem 2005, 48, 152.

[92] Atta, K. F.; El-Massry, A.; Abdel Hamid, H.; El Ashry, E. H.; Amer, A. J Heterocycl Chem 1994, 31, 549.

[93] Biagi, G.; Giorgi, I.; Livi, O.; Pacchini, F.; Scartoni, V. J Heterocycl Chem 2002, 39, 885.

[94] Francis, J. E.; Cash, W. D.; Baraz, B. S.; Bernard, P. S.; Lovell, R. A.; Mazzenga, G. C.; Friedmann, R. C.; Hyun, J. L.; Braunwalder, A. F.; Loo, P. S.; Bennett, D. A. J Med Chem 1991, 34, 281.

[95] Blank, J.; Kandt, M.; Pfeiffer, W.; Hetzheim, A.; Langer, P. Eur J Org Chem 2003, 182.

[96] Okamura, T.; Kurogi, Y.; Nishikawa, H.; Hashimato, K.; Fujiwara, H.; Nagao, Y. J Med Chem 2002, 45, 3703.

[97] Todde, S.; Moresco, R. M.; Simonelli, P.; Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Varani, K.; Monopoli, A.; Matarrese, M.; Carpinelli, A.; Magni, F.; Kienl, M. G.; Fazio, F. J Med Chem 2000, 43, 4359.

[98] Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Klotz, N.; Leung, E.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P. A. J Med Chem 1999, 42, 4473.

[99] Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Bergonzoni, M.; Dionisotti, S.; Ongini, E.; Varani, K.; Borea, P. A. J Med Chem 1998, 41, 2126.

[100] Al-Omran, F.; Elassar, A.-A.; El-Khair, A. A. J Heterocycl Chem 2003, 40, 249.

[101] Hetzhem, A.; Müller, G.; Vainilavicius, P.; Girdžiunaite, D. Pharmazie 1985, 40, 17.

[102] Musser, J. H.; Brown, R. E.; Love, B.; Bailey, K.; Jones, H.; Kohen, R.; Huang, F.; Khandwala, A.; Leibowitz, M.; Sonnino-Goldman, P.; Donigi-Ruzza, D. J Med Chem 1984, 27, 121.

[103] Yokoyama, M.; Sato, K. Synthesis 1988, 813.

[104] Hiremath, S. P.; Hiremath, D. M.; Purohit, M. G. Ind J Chem 1983, 22B, 571.

[105] Maddirala, S. J.; Gokak, V. S.; Basanagoudar, L. D. J Heterocycl Chem 2004, 41, 7.

[106] Demetrescu, C. Rev Roum Chim 1972, 17, 1013.

[107] Gatta, F.; Dell Giudice, M. R.; Borioni, A. J Heterocycl Chem 1993, 30, 11.

[108] Taylor, E. C.; French, L. G. J Org Chem 1989, 54, 1245.

[109] Rostamizadeh, S.; Sadeghi, K. Synth Commun 2002, 32, 1899.

[110] Mazaahir, K.; Pooja, S.; Bhushan, K.; Pretti, M. Synth Commun 2001, 31, 1639.

[111] Saraswthi, T. V.; Srinivasan, V. R. Tetrahedron Lett 1971, 25, 2315.

[112] Saraswthi, T. V.; Srinivasan, V. R. Tetrahedron Lett 1977, 33, 1043.

[113] Vega, A. M.; Aldana, I.; Rabbani, M. M.; Fernandez-Alvarez, E. J Heterocycl Chem 1980, 17, 77.

[114] Lews, A.; Shepherd, R. G. J Heterocycl Chem 1971, 8, 47.

[115] Reich, M. F.; Fabio, P. F.; Lee, V. J.; Fuck, N. A.; Testa, R. T. J Med Chem 1989, 32, 2474.

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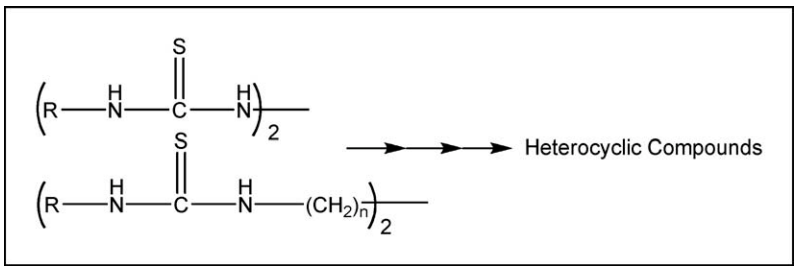


This review summarizes published data on the behavior and reactions of dithiobiurea and thioureidoalkylthiourea derivatives, which lead to the formation of heterocyclic systems, including methods of preparation in addition to synthesis of imidazolidine, thiazole, thioazolidine, triazolidine, thiadiazine, and spiro compounds.

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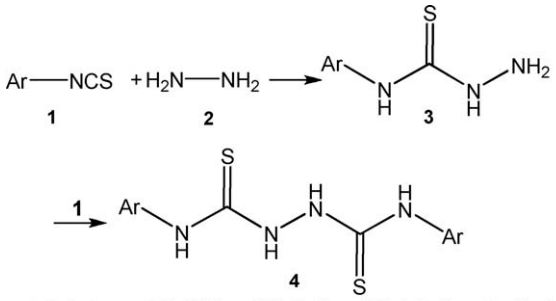
## 1. INTRODUCTION

In recent years, there has been increasing interest in the synthesis of heterocyclic compounds by cyclization of appropriate linear compounds [1–15]. Organosulfur compounds play an important role in modern organic synthesis, not only because they constitute a particularly useful class of synthons [16] but also because they are of great biological interest [17–23] such as fungicidal [24], bactericidal [25–27], insecticidal [28], and antitumor agents for thioureidoalkanethiourea [29–32]. Symmetrical and unsymmetrical 2,5-dithiobiureas have been utilized widely in the synthesis of heterocylic compounds and are considered as very good complexing agents for a variety of materials in the synthesis of complexes [33–39]. Substituted-2,5-dithiobiureas and their derivatives are versatile compounds, which have been extensively used in the preparation of heterocyclic ring systems. Also, oxidation of *S*-alkylisodithiobiureas resulted in the formation of thiadiazole derivatives [40], but oxidation of 1,5-diaryl-2-*S*-alkylisodithiobiuretes led to the formation of benzothiazolylisothiouereas [41]. Alkylation of 1-substituted-2,5-dithiobiureas by refluxing with appropriate alkyl halide in ethanol led to the formation of thiadiazole derivatives [42].

On the other hand, symmetrical 2,5-dithiobiureas underwent cyclization in the presence of alkali to form the corresponding 1,2,4-triazolidine-3,5-thione [43,44], and, therefore, the substituted dithiobiureas and their

**Scheme 1**




derivatives act as a key for the synthesis of many organic heterocyclic ring systems.

## 2. SYNTHESIS OF DITHIOBIUREAS AND THEIR DERIVATIVES

The reaction of aryl isothiocyanates **1** with hydrazine (**2**) in great excess and at low temperature in ethanol readily gave 4-arylthiosemicarbazides **3**, which reacted further with another molecule of **1** to give *N*,*N*′-di(arylthioformyl)hydrazines **4** (Scheme 1) [45].

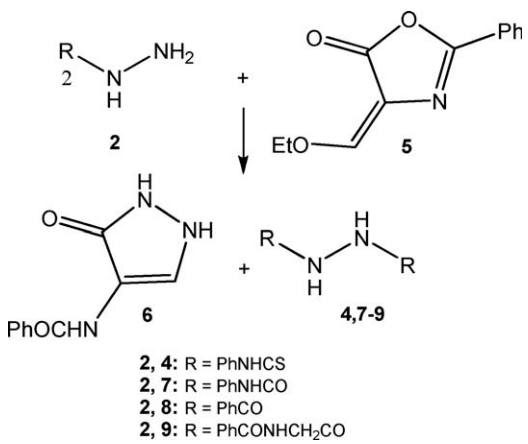
When oxazolone **5** was heated with two equivalents of appropriate hydrazine derivatives **2** in dioxane for 0.5–2 h, the products **6**, **4**, and **7–9** were separated (Scheme 2) [46].

Ammoniumthiocyanate **10** was added to a solution of dilute $H_2SO_4$, and thiosemicarbazide **3** to afford 2,5-dithiobiurea **4** in 52% yield (Scheme 3) [47].

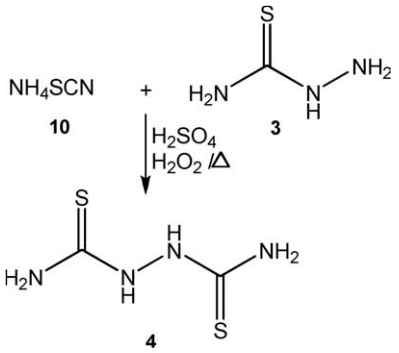
Egri [48,49] reported the synthesis of substituted dithiobiureas by treating $RNH_2$ and $R'NH_2$ with $CSCl_2$ and then with hydrazine hydrate (Figure 1).

Heating naphtho[1,2-*d*]oxazole-2(1*H*)-thione **12** (which was prepared by heating a mixture of 1-imino-2-hyroxynaphthalene hydrochloride **11** and phenyl isothiocyanate **1** in boiling ethanol) with hydrazine hydrate **2** in

**Scheme 2**




**Scheme 3**




ethanol did not give the expected product, 2-hydrazinonaphth[1,2-*d*]oxazole **13**, but the obtained product contained sulfur. This indicates that the reaction of **12** with hydrazine hydrate as nucleophile led to cleavage of the oxazolinethione ring and formation of 3-amino-1,3-dihydro-2*H*-naphth[1,2-*d*]imidazole-2-thione **14** or 4-(2-hydroxy-naphthaien-1-yl)thiosemicarbazide **15**. The spectral data are in agreement with the structure of thiosemicarbazide **15**, which reacted with the appropriate aryl isothiocyanate at room temperature to afford the derivatives of **4** (Scheme 4) [50].

1,2-Bis(thiocarbamoyl)hydrazine **4** was prepared by treating 4-substituted thiosemicarbazide **3** with allyl isothiocyanate **1** (Scheme 5) [51].

1,1-Bis(β-hydroxyethyl)thiocarbohydrazide **16** was heated with isothiocyantes **1** in ethanol to give dithiobiurea derivatives **4** (Scheme 6) [52].

When benzhydryl isothiocyanate was allowed to react with excess of hydrazine, a good yield of 4-benzhydrylthiosemicarbazide was obtained. Equivalent amounts of these reactants, however, gave a dithiobiurea **4** as the major product (Figure 2) [53].

Unsaturated 1,6-disbstituted-2,5-dithiobiureas **4** was obtained from the reaction of substituted isothiocyanates **1** with 4-substituted thiosemicarbazides **3** (Scheme 7) [54].

The reaction of thiocarbohydrazide **17** with 2*M* equivalents of benzaldehyde results in the formation of the monobenzylidene derivatives **18**, which further reacted with isobutyl isothiocyanate and triethylamine in

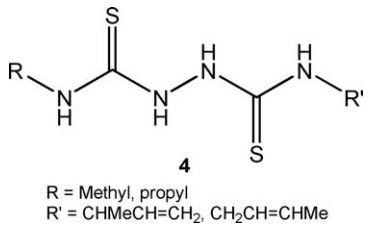
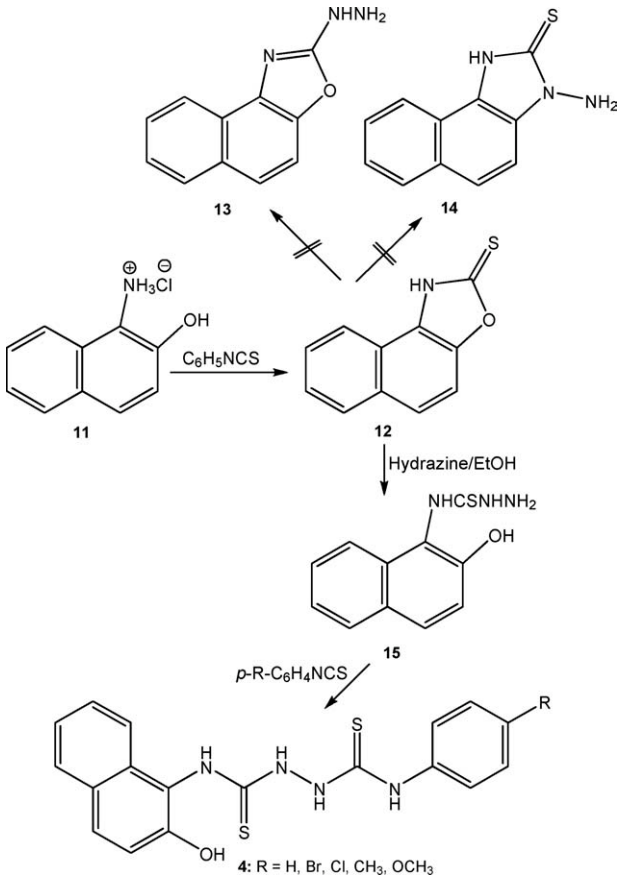



**Figure 1.** Substituted dithiobiureas from primary amines.

**Scheme 4**

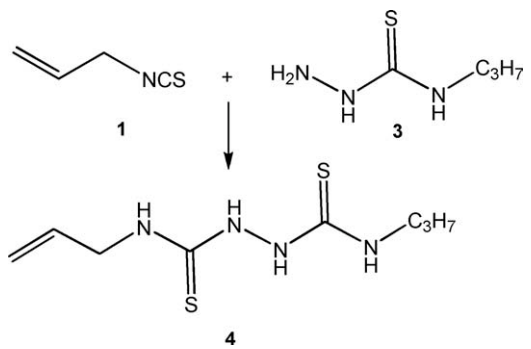



dimethylformamide (DMF) to gave 1-benzylidene-5-(*N*-isobutylthiocarbamoyl)-thiocarbohydrazide **4** (Scheme 8) [55].

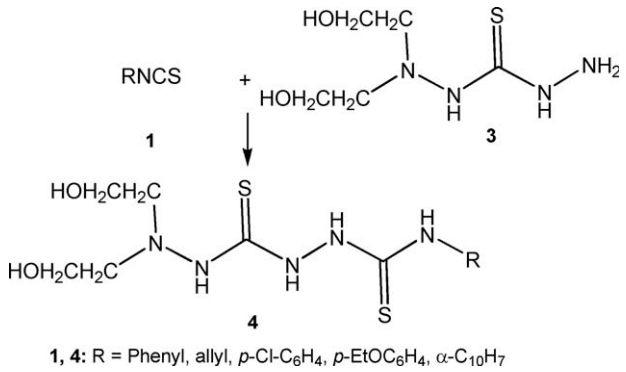
Refluxing phenyl thiosemocarbazide with appropriate isothiocyanates in absolute ethanol gave dithiobiurea derivatives **4** (Figure 3) [56].

The reductive debenzylation of 5-*S*-benzyliso-1-aryl-2-thiohydrazodicarbonamides **19** afforded **4** (Scheme 9) [57,58].

**Scheme 5**




**Scheme 6**



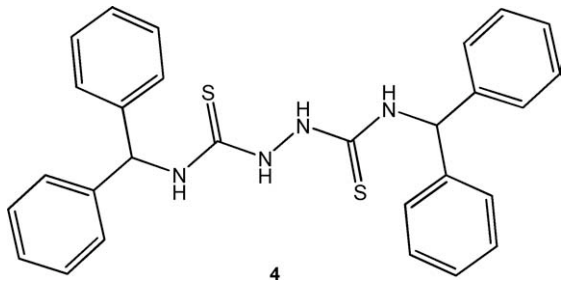



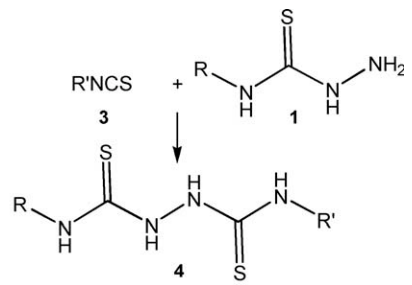

**Figure 2.** Dithiobiurea from benzhydryl isothiocyanate.

The reduction of 6-substituted amino-3-amino-1,2,4,5-dithiadiazines **20** under similar conditions of the above reaction gave **4** in good yields (Scheme 10) [57,58].

Thioureidoalkanethiourea derivatives **21** ($n$ = 2–4, 6, 7) were prepared from the reaction of diamines with isothiocyanates (Figure 4) [59].

When α-mannosyl isothiocyanate **1** was reacted with diamines **22** ($n$ = 2, 6), **21** was formed after deacetylation with sodium methanolate in methanol [24] (Scheme 11).

**Scheme 7**



**Scheme 8**

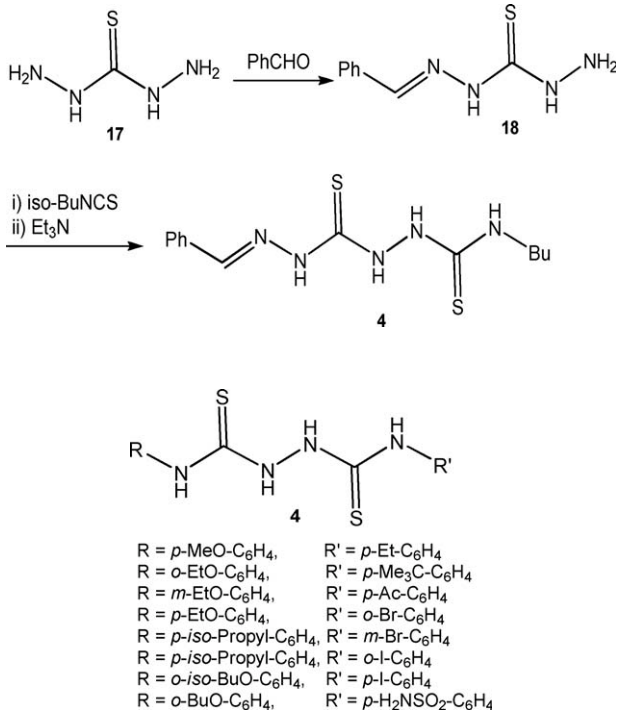
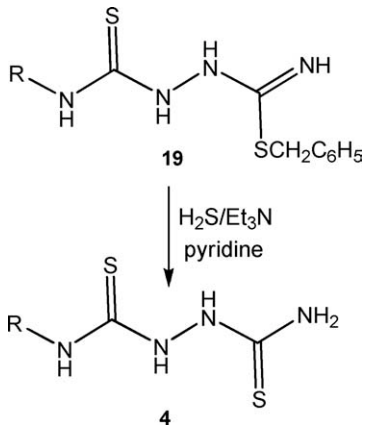
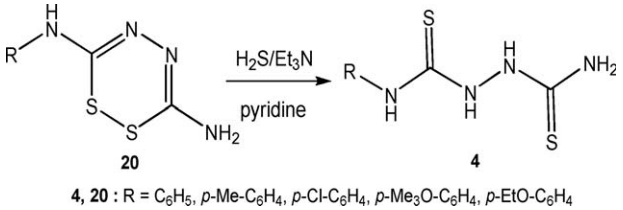



**Figure 3.** Dithiobiurea derivatives from phenyl thiosemicarbazide.

**Scheme 9**




**Scheme 10**



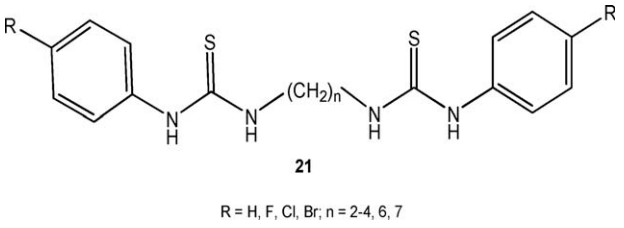
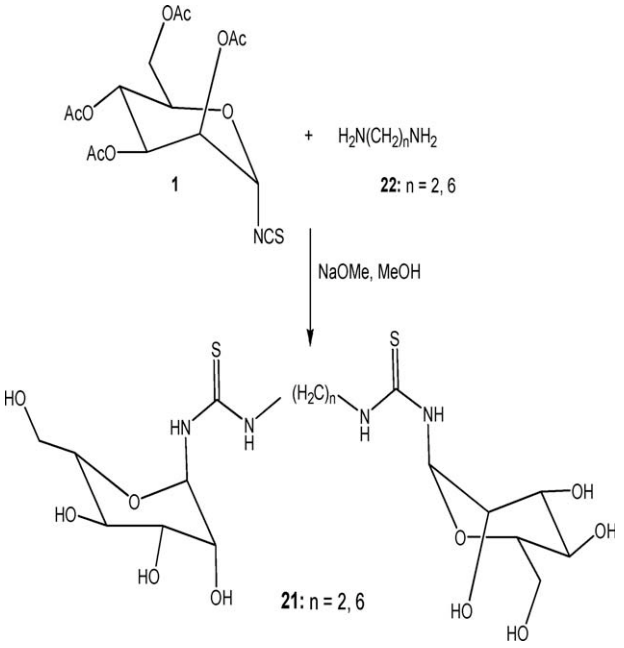




**Figure 4.** Thioureidoalkanethiourea derivatives from diamines.

**Scheme 11**




Page and Roy [26] reported that, when *p*-amino-phenyl 2,3,4,6-tetra-*o*-acetyl-α-D-mannopyranoside **23** was dissolved in dichloromethane containing diisopropylethylamine (DIPEA) and thiophosgene, compound **1** was formed, which when added to a solution of diamine in dichloromethane containing a catalytic amount of DIPEA, derivatives of compounds **21** were formed (Scheme 12).

1,6-Bis(allylthioureido)alkanes **21** were prepared by treating of diamine (1,2-diaminoethane, 1,3-di-amino-propane, 1,4-diaminobutane, 1,5-diaminopentane, and 1,6-diaminohexane) with allyl isothio-cyanate (Figure 5) [60].

Disubstituted thioureidothioureas **21** were obtained from ethylenediamine **22** and isothiocyanates **1** (Scheme 13) [61].

Compound **21** was obtained by refluxing ethylenediamine **22** with EtOH, NaOH, and phenyl isothiocyanate, while when HCl was added to the solution, NaCl was precipitated together with imidazoline derivatives **24** (Scheme 14) [62].

**Scheme 12**

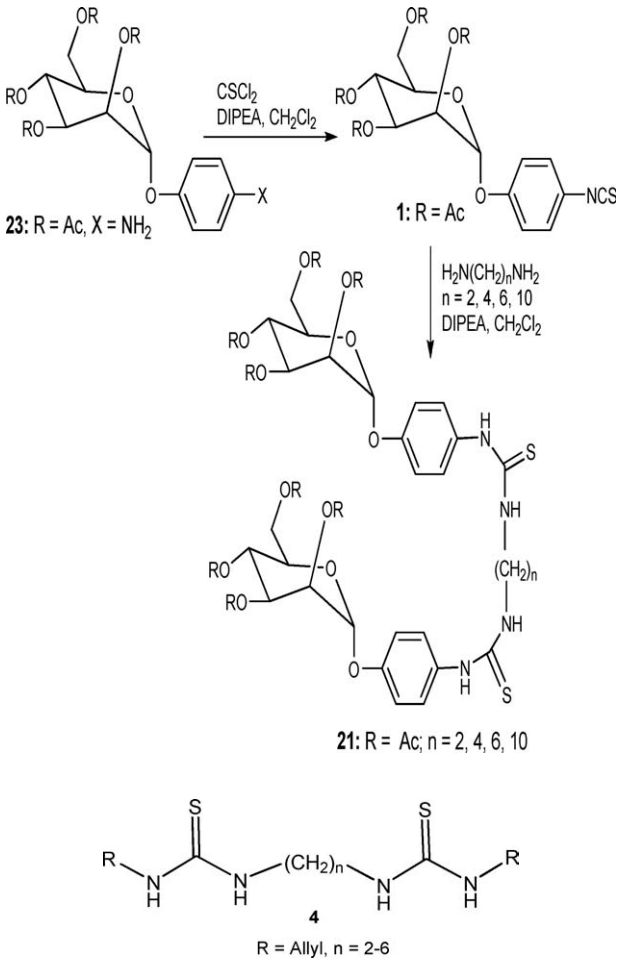
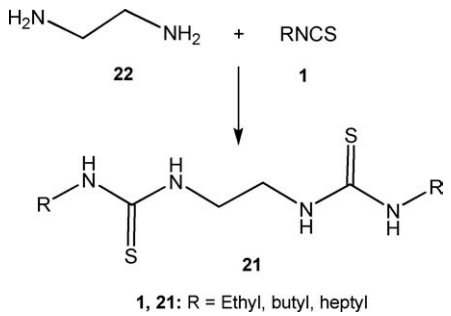



**Figure 5.** 1,6-Bis(allylthioureido)alkanes from different diamines.

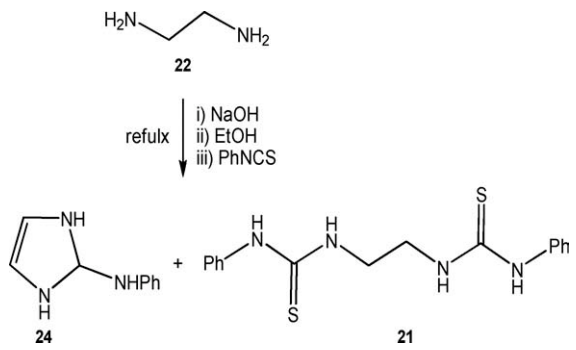
Ethylenediaryldithiocarboamides **21** were prepared by the action of 2 mol of isothiocyanates **1** with ethylenediamine **22** and boiling with concentrated HCl or KOH (Scheme 15) [63].

Ethylene diisothiocyanate **25** gave **21** and imidazolidine derivatives **26** when reacted with a nucleophilie (aniline or marpholine) (Scheme 16) [64].

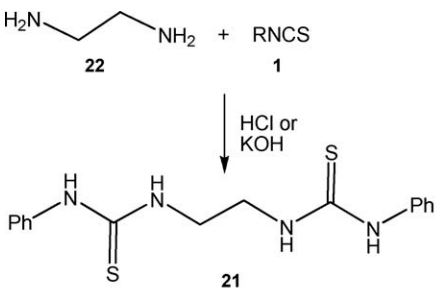
**Scheme 13**




**Scheme 14**




**Scheme 15**

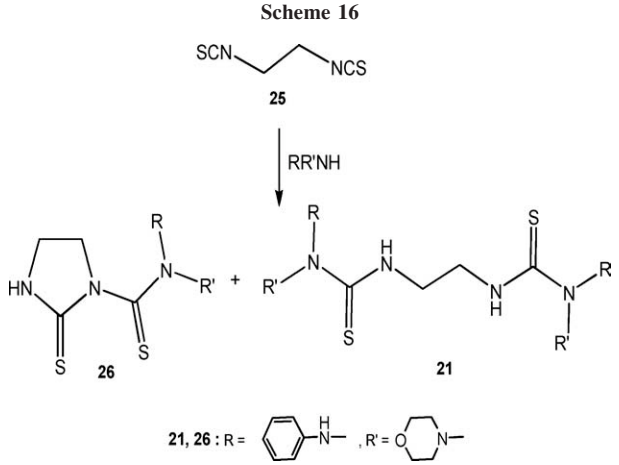



Also, trimethylene diisothiocyanate **27** and tetramethylene diisothiocyanate **28** gave linear mono-addition derivatives **29** and bis-adducts **21** when reacted with aniline or morpholine (Scheme 17) [64].

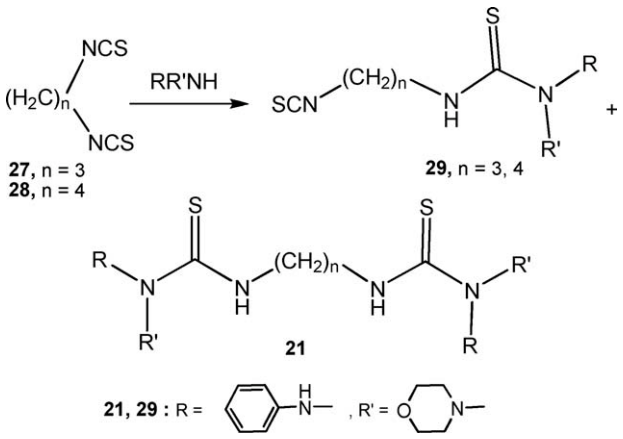
## 3. REACTIONS OF DITHIOBIUREAS AND THIOUREIDOALKYLTHIOUREAS

**3.1. Synthesis of imidazolidine derivatives.** The reaction of thioureidoethyl- and propylthioureas **21** with mercury bis(phenyl acetylide) **30** afforded corresponding

**Scheme 16**



**Scheme 17**




cyclic symmetrical mercaptides **31** and **32**. The thermal decomposition of **31** led to the formation of imidazolidines **35** (Scheme 18) [65].

4-Chloro-*N*′-(4,5-dihydro-1*H*-imidazo-2-yl)-benzene-1,2-diamine **36** was prepared by addition of ethylenediamine **22** to the corresponding 4-chloro-2-nitrophenylisothiocyanate **1** (Figure 6) [66].

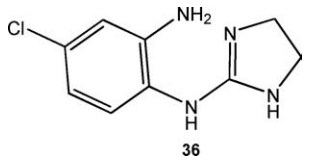
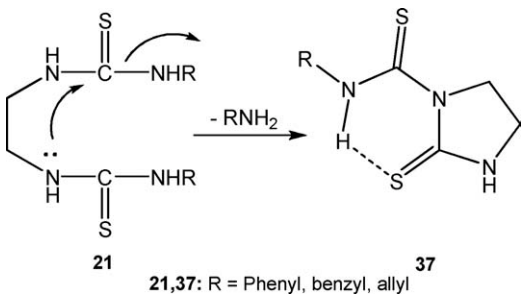



**Figure 6.** Substituted imidazoylbenzendiamine from ethylenediamine.

**Scheme 19**




Hassan *et al*. [67] reported that imidazolidine **37** can be formed on heating or microwave irradiation of thioureidoethylthiourea derivatives **21** (Scheme 19).

**3.2. Synthesis of thiazole, thiazolidine, and thiazolium derivatives.** 2,5-Dithiobiurea **4** reacted with methylphenylchloropyruvate exclusively as thiourea (Hantzsch reaction) forming dimethyl 2,2′-(hydrazine-1,2-diyl)-bis(5-phenylthiazol-4-carboxylate) **38** (Figure 7) [68].

It has been reported that bis(*N*-phenyl)thiourea **4** was cyclized to thiazolidine-4-one **39** when reacted with monochloroacetic acid in the presence of EtOH/AcONa (Scheme 20) [69].

Symmetrical azines of 3-allylthiazolidine-4-one **39** can be obtained by treating allyldithiourea **4** with acid derivatives **40** under reflux in alcohol in the presence of AcOK (Scheme 21) [70].

Trisubstituted thiazoles **42** can be obtained by heating a mixture of **4** and **41** (Scheme 22) [71].

Reaction of ethylenediamine **22** with allyl isothiocyanate **1** followed by treating by aq. HCl gave bisthiazoline **43** (Figure 8) [72].

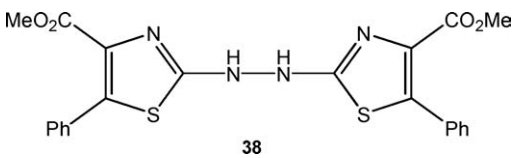
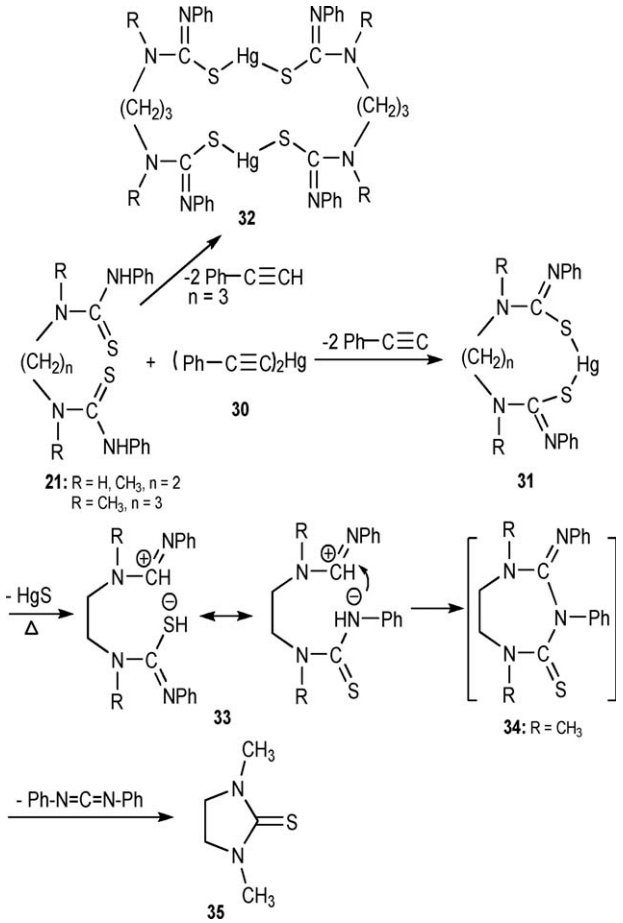
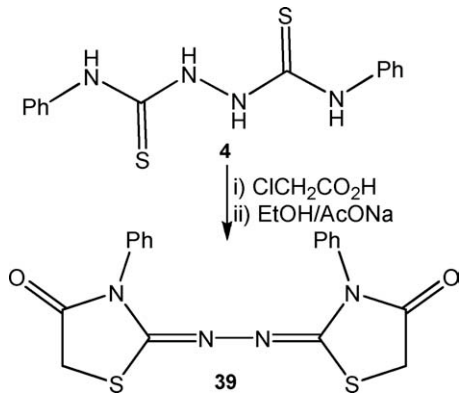



**Figure 7.** (Hydrazine-1,2-diyl)-bis(5-phenylthiazol-4-carboxylate) from dithiobiurea.

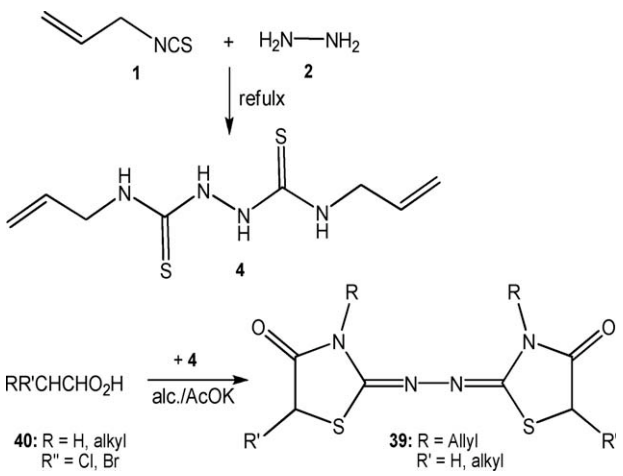
**Scheme 18**



**Scheme 20**




**Scheme 21**




Symmetrical bisthiazolidine **44** was obtained by heating *N*,*N*′-ethane-1,2-diylbis(thiourea) **21** with α-chloroacetic acid in butanol (Scheme 23) [73].

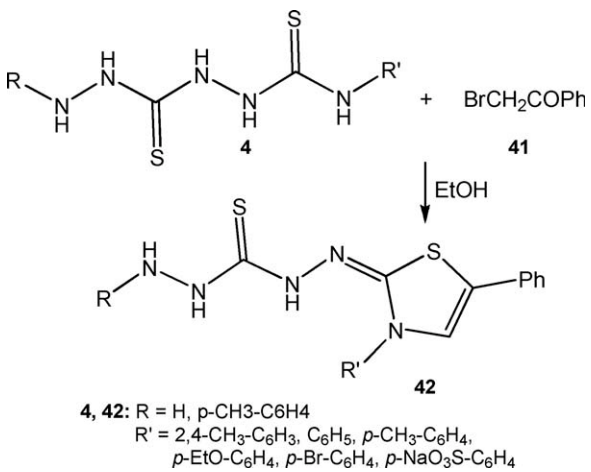
**3.3. Synthesis of thiadiazole derivatives.** 2-Amino-5-mercapto-1,3,4-thiadiazole **45** was obtained *via* cyclization of 2,5-dithiobiurea **4** in refluxing HCl (Scheme 24) [74].

Also, oxidation of 1-substituted-4-*S*-alkyl(aryl)-2,4-isodithiobiuretes **46** afforded 3-alkylmercapto-5-arylamino-1,2,4-thiadiazoles **47** (Scheme 25) [40].

On heating 1-substituted-5-*S*-alkyl(aryl)isodi-thiobiureas **48** in ethanol or water in the presence of hydrochloric acid, 5-alkylmercapto-2-substituted amino-1,3,4-thiadiazoles **49** were obtained (Scheme 26) [42].

On the other hand, alkylation of 1-substituted-2,5-dithiobiureas **4** with alkyl halide in ethanol gave substituted-1,3,4-thiadiazoles **49** (Scheme 27) [42].

**Scheme 22**



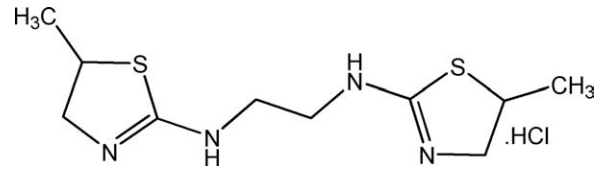
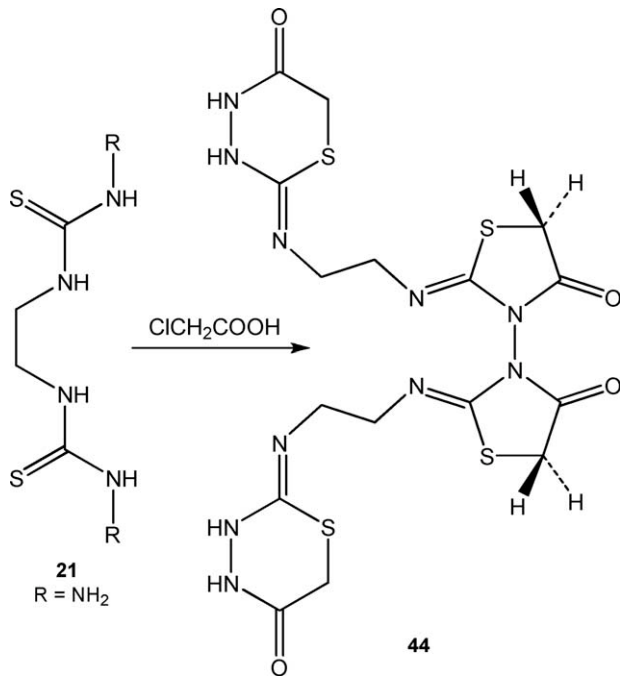
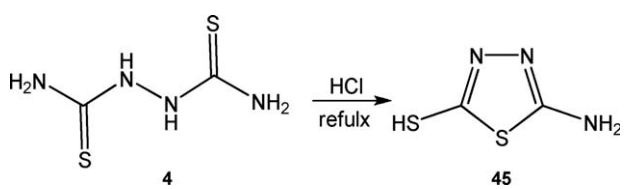




**Figure 8.** Bisthiazoline from ethylenediamine.

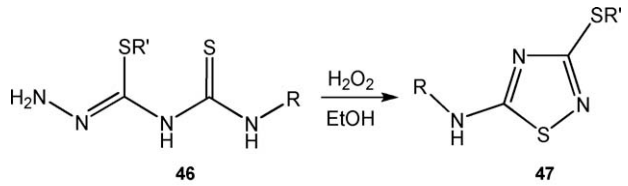
**Scheme 23**




**Scheme 24**

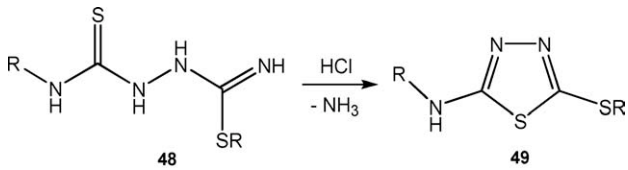


**Scheme 25**



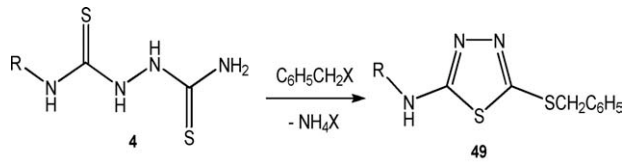
**46, 47:** R = Phenyl, benzyl, R' = phenyl, methyl

**Scheme 26**



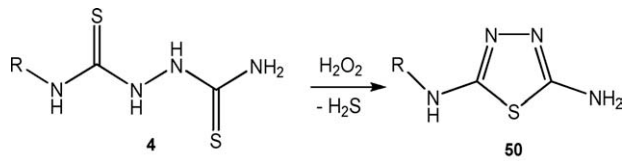
**48, 49:** R = Benzyl, ethyl, methyl

**Scheme 27**



**4, 49:** R = $C_6H_5$, $CH_3$, $C_2H_5$, *p*-Me-$C_6H_4$

**Scheme 28**

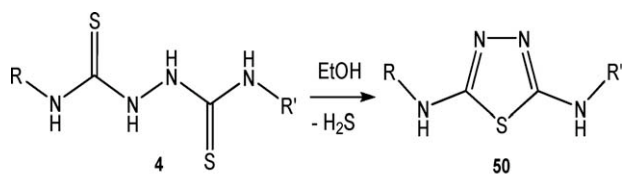


**4, 50:** R = $C_6H_5$, $CH_3$, $C_2H_5$, *p*-Me-$C_6H_4$

Oxidation of substituted-2,5-biueras **4** with either hydrogen peroxide or iodine in warm ethanolic medium afforded 2-amino-5-substituted amino-1,3,4-thiadiazoles **50** (Scheme 28) [42].

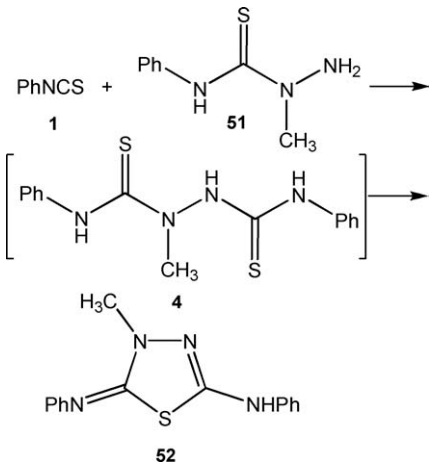
Thiadiazole derivatives **50** can be obtained by cyclization of compounds **4** in an alkaline medium with evolution of hydrogen sulfide (Scheme 29) [75].

**Scheme 29**

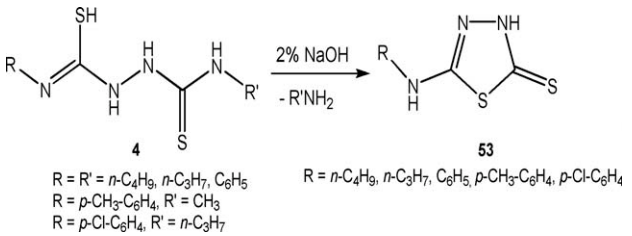


**4, 50:** R = R' = $C_6H_5$, *p*-Me-$C_6H_4$, *p*-Cl-$C_6H_4$, *p*-EtO-$C_6H_4$, *p*-MeO-$C_6H_4$

**Scheme 30**



**Scheme 31**



**4**

R = R' = *n*-$C_4H_9$, *n*-$C_3H_7$, $C_6H_5$
R = *p*-$CH_3$-$C_6H_4$, R' = $CH_3$
R = *p*-Cl-$C_6H_4$, R' = *n*-$C_3H_7$

**53**

R = *n*-$C_4H_9$, *n*-$C_3H_7$, $C_6H_5$, *p*-$CH_3$-$C_6H_4$, *p*-Cl-$C_6H_4$

2,4-Disubstituted thiosemicarbazide **51** was allowed to react with phenyl isothiocyanate **1** to give dithiobiurea **4** as an intermediate, followed by cyclization with elimination of hydrogen sulfide to give 5-anilino-3-methyl-2-phenylimino-2,3-dihydro-1,3,4-thiadiazole **52** (Scheme 30) [76].

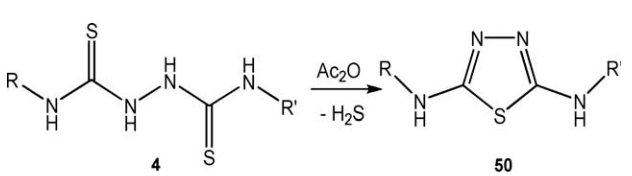
Alkali-catalyzed thermal cyclization of 1-alkyl and 1,6-dialkyl-2,5-dithiobiureas **4** gave 2-alkyl amino-$\Delta^2$-1,3,4-thiadiazoline-5-thiones **53** (Scheme 31) [77].

On the other hand, oxidative cyclization of 1,6-disubstituted-2,5-dithiobiueras **4** was occurred in the presence of $Ac_2O$ to produce the corresponding thiadiazoles **50** (Scheme 32) [78,79].

When 2,5-dithiobiurea **4** treated with $Me_2SO_4$ and hypophosphorous acid in $H_2O$; the reaction underwent formation of 2-amino-5-(methylthio)-1,3,4-thiadiazole **49** (Scheme 33) [80].

Wegner [81] has reported the synthesis of substituted thiadiazoles **54** by the reaction of substituted amine with

**Scheme 32**



**4, 50:** R = $C_2H_5$, R' = $CH_2$=CH-$CH_2$, *p*-F-$C_6H_4$, $C_6H_5$, $CH_2$=C($CH_3$)-$CH_2$

**Scheme 33**

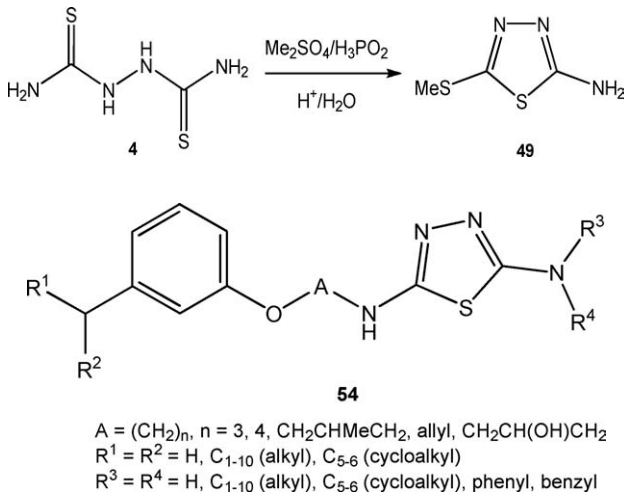



**Figure 9.** Substituted thiazoles from hydrazinecarbothioamide.

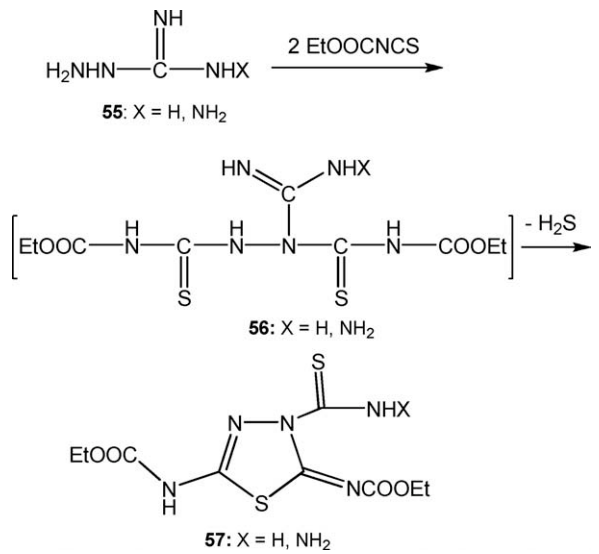
$ClCS_2Ph$, and the resulting product was allowed to react with hydrazine hydrate to form substituted hydrazinecarbothioamide **4**, which further reacted with phenyl isothiocyanate dichloride (Figure 9).

The interaction of guanidine derivatives **55** and ethoxycarbonyl isothiocyanate under mild conditions afforded the thiadiazole derivatives **57** (Scheme 34) [82].

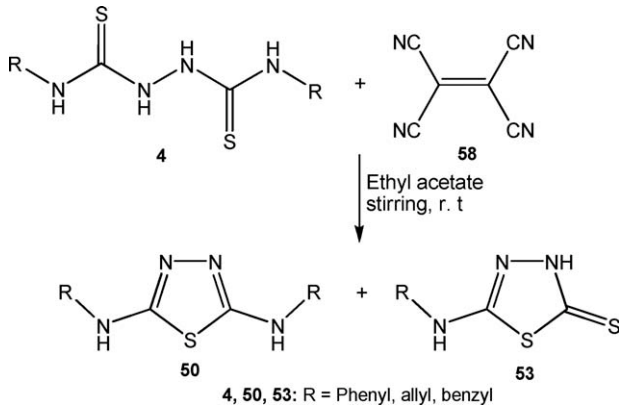
Addition of two equivalents of ethenetetracarbonitrile **58** to a solution of 1,6-disubstituted-2,5-dithiobiureas **4** in ethyl acetate at room temperature led to the formation of thiadiazole derivatives **50** and **53** as side products (Scheme 35) [83].

A phase transfer catalytic oxidation of hydrazinedicarbothioamide leads to a red colored solid **59**, the reduction of **59** with hydrazine or other reductants trans-

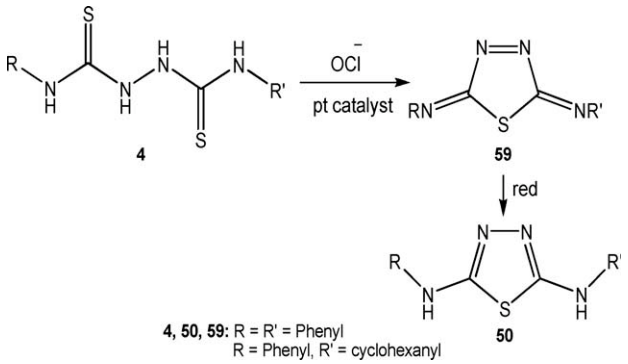
**Scheme 34**




**Scheme 35**




**Scheme 36**



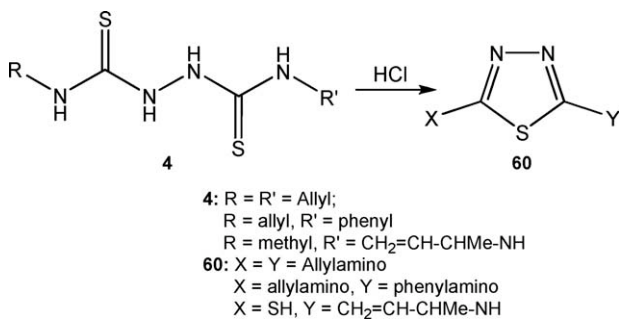

formed it into colorless compound, 2,5-diphenylamino-1,3,4-thiadiazole **50** (Scheme 36) [84].

Cyclization of symmetrical and unsymmetrical 1,6-bis(substituted)-2,5-dithiobiureas **4** in acid media gave 1,3,4-thiadiazoles **60** (Scheme 37) [85].

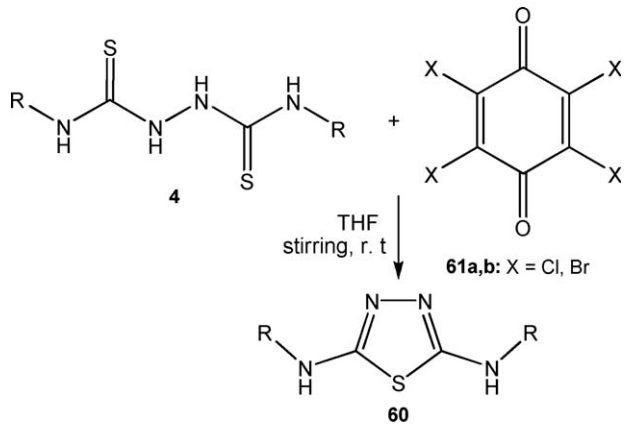
On adding tetrahydrofuran (THF) solution of 1,6-disubstituted-2,5-dithiobiureas **4** to a solution of chloranil or bromanil **61a,b** in the same solvent lead to the formation of thiadiazole derivatives **50** as a side product (Scheme 38) [86].

On the other hand, the addition of THF solution of 1-substituted-2,5-dithiobiureas **4** to a solutions of

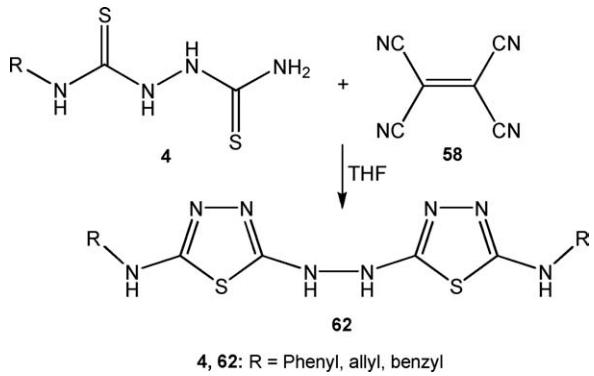
**Scheme 37**



**Scheme 38**



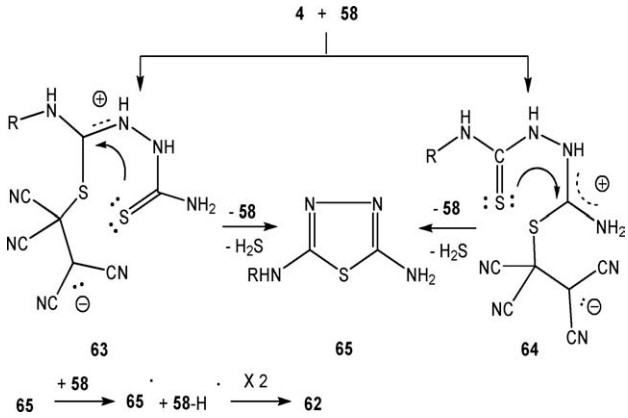

**Scheme 39**



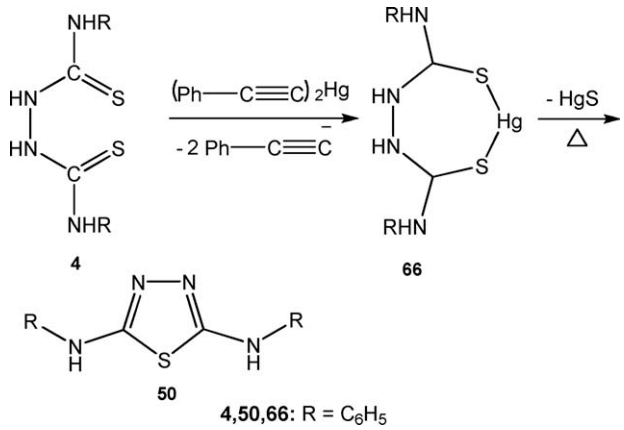

ethenetetracarbonitrile **58** in the same solvent lead to the formation of 1,2-bis[5-(substituted amino)-1,3,4-thiadiazole-2-yl)hydrazines **62** (Scheme 39) [87].

Scheme 40 showed the mechanism of formation of thiadiazole and bisthiadiazole derivatives from **4** by using ethnetetracarbonitrile **58**, which reacted as a mediator.

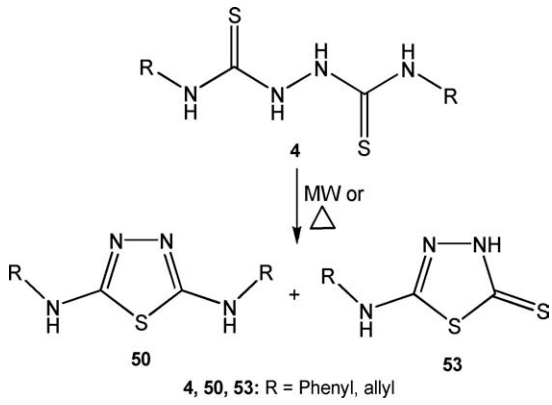
**Scheme 40**




**Scheme 41**




**Scheme 42**




Diphenylhydrazine-1,2-dicarbothioamide **4** reacted with mercury bis(phenyl acetylide) **30** to give the intermediate **66**, which under thermal decomposition afforded the thiadiazole derivatives **50** (Scheme 41) [88].

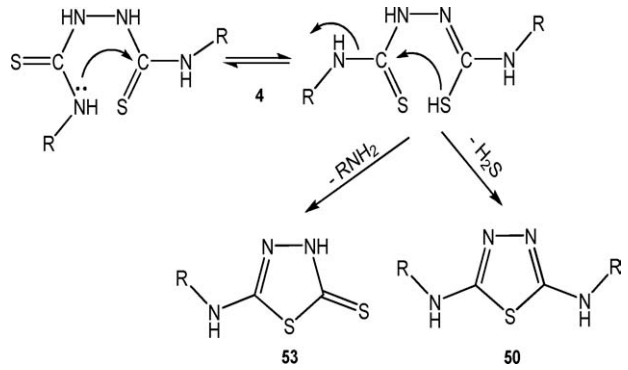
Microwave (MW) and thermal heterocyclization of *N*,*N*′-disubstituted hydrazinecarbothioamide **4** results in formation of 2,5-disubstituted amino[1,3,4]thiadi-azoles **50** and 5-substituted amino[1,3,4]thiadi-azole-2-thiones **53** (Scheme 42) [67].

A mechanism for the formation of thermal or MW irradiation for 1,6-disubstituted hydrazinecarbothio-amide **4** as shown in Scheme 43 [67].

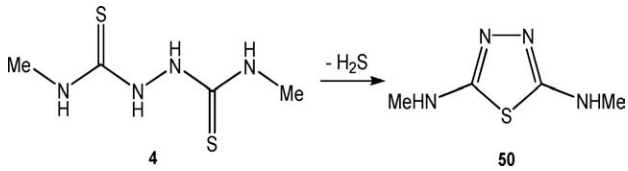
Thiadiazole derivatives **50** was prepared by cyclization of 1,6-dimethyl-2,5-dithiobiurea **4**, which was obtained by the reaction of methyl isothiocyanate with methylthiosemicarbazide (Scheme 44) [89].

1,6-Di(2-pyridyl)hydrazodithiocarbonamide **4** can be obtained from 2-pyridyl isothiocyanate and 2-pyridylthiosemicarbazide, which thermally cyclized to 2,5-di(2-pyridylamino)-1,3,4-thiadiazole **50** (Scheme 45) [90].

**Scheme 43**



**Scheme 44**



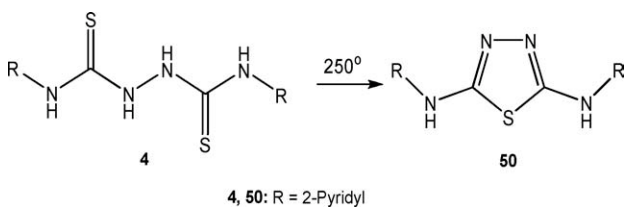
In case of the reaction of **4** with methyl iodide in the absence of the base, 5-acylamino-2-anilinidene-3-methyl-1,3,4-thiadiazoline **68** and 2-acylamino-5-methyl-thio-1,3,4-thidiazole **70** were formed (Scheme 46).

This reaction is presumed to be initiated by *S*- and *N*-methylation to form the intermediate **69**, followed by cyclization through the attack of SH group on C=N with elimination of dimethylaniline to afford **70**. On the other hand, **4** ($R^2 = CH_3$) was merely methylated on the sulfur atom, followed by elimination of $CH_3SH$ to give **68** [91].

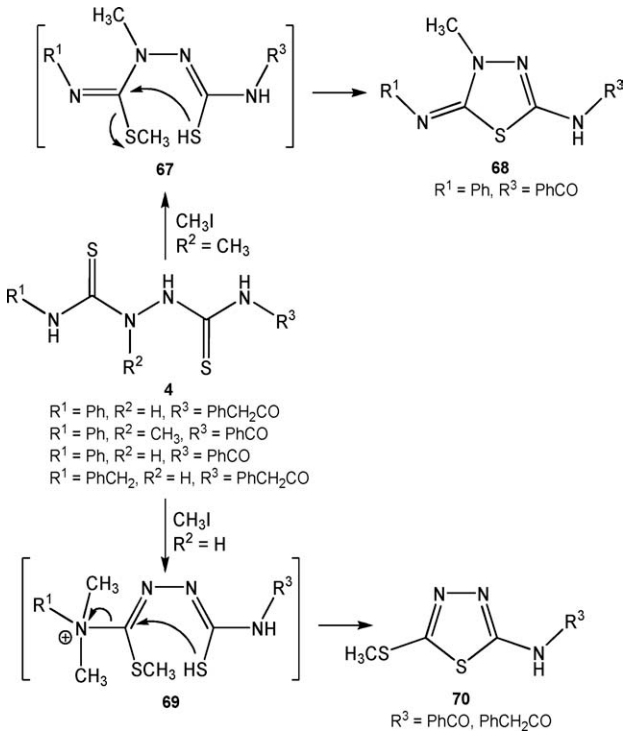
The reaction of trifluoroacetic acid with dithiobiurea **4** (R = $CH_3$) afforded 1,3,4-thiadi-azolineimine **71** and 1,3,4-thiadiazoline-2-thione **72** with loss of hydrogen sulfide and methylamine, respectively. On the other hand, dithiobiurea **4** (R = Ph) underwent ring closure with elimination of hydrogen sulfide and gave 1,3,4-thiadiazolineimine **71** as the only product. The different cyclization behavior of **4** (R = $CH_3$ and R = Ph) under acidic conditions appears to be caused in the different basicity of the R—NH moiety (Scheme 47) [92].

The reaction of ''nonalkylated'' carbothiohydrazide derivatives **73** with substituted isothiocyanates **1** at room

**Scheme 45**

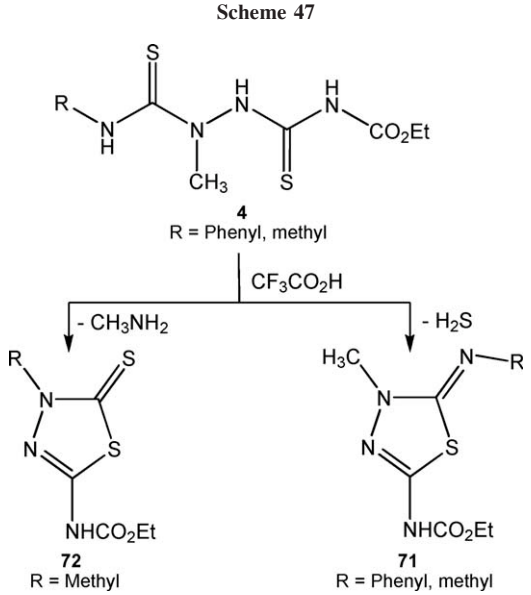


**Scheme 46**

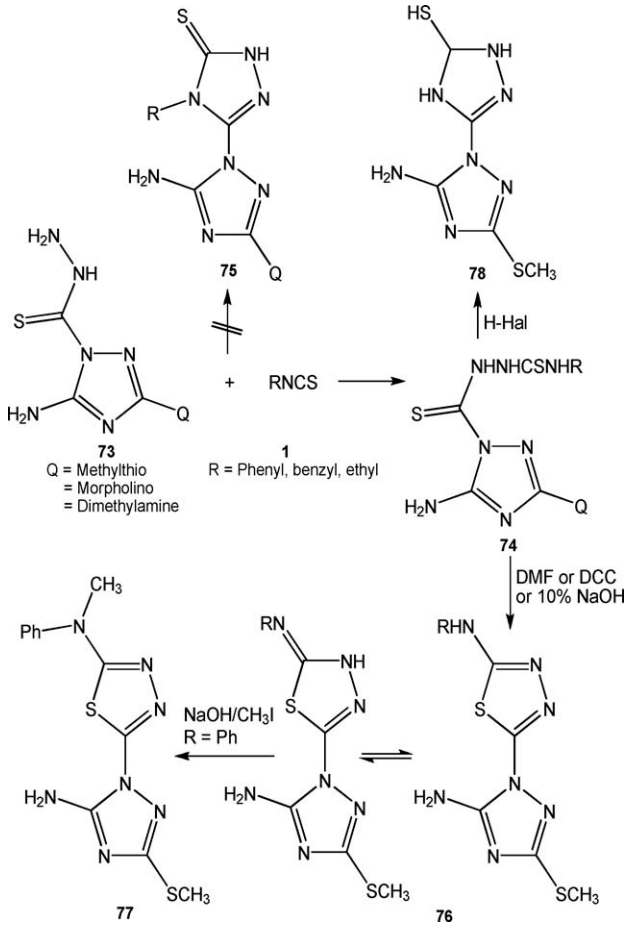


temperature in methanol or (Scheme 48) DMF as a solvent led to the thermally unstable thiocarbamoyl derivatives **74** and not **75** [93]. These were cyclized either in boiling DMF, or by reaction with dicyclohexyl carbodiimide (DCC), or by heating in 10 % sodium hydroxide to **76** and **78**. Compound **76** was changed to **77** after *N*-methylation. The alkylation of the ''nonalkylated'' derivatives **74** with methyl iodide and benzyl bromide in

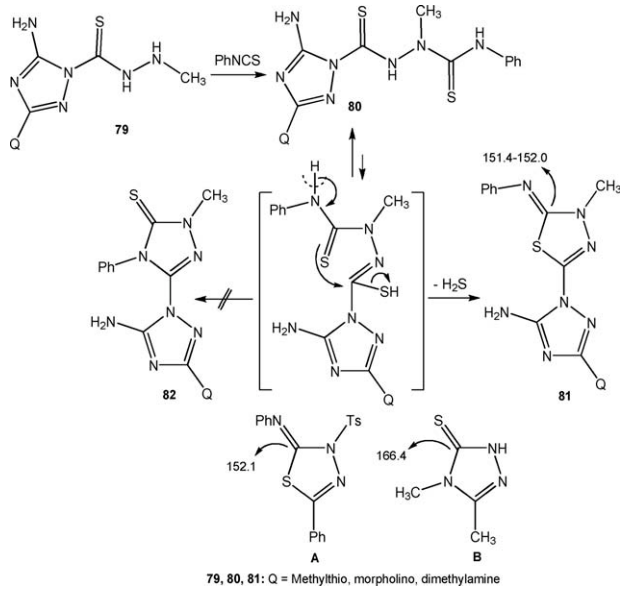
**Scheme 47**



**Scheme 48**




**Scheme 49**




either methanol or DMF afforded the corresponding **78** [94].

The reaction of **79** with phenyl isothiocyanate **1** afforded the expected phenylthiocarbomoyl derivatives **80** (Scheme 49).

The thermally unstable derivatives **80** could by easily cyclized probably through their tautomeric form to the thiadiazoles **81** by their short heating in DMF. It should be mentioned that the loss of $H_2S$ from derivatives **79** may, in principal, also lead to the formation of derivatives **82**, thus, the structure of derivatives **81** formed had to be confirmed [94]. The decision between structure **81**, **82** made possible the comparison of the chemical shifts of the thiadiazole carbon atoms 5 of derivatives **81** (δ C5 = 151.4–152.0 ppm) with those of corresponding carbon atoms of model compounds **A**, **B** (δ C5 = 152.1 and 166.4 ppm, respectively) to prove structure **81** unequivocally.

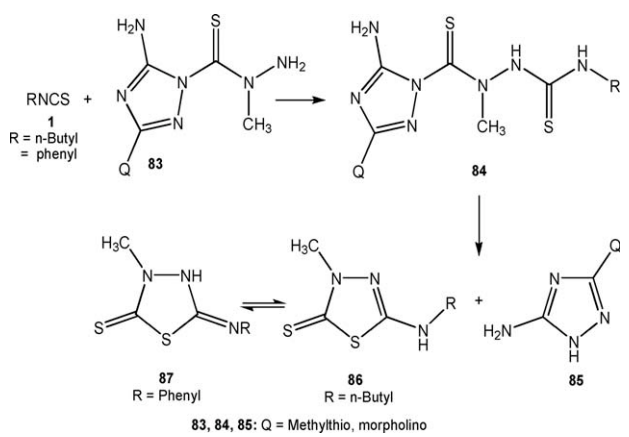
From the reaction of **83** and butyl- or phenyl-isothiocyanate instead of the corresponding thiocarbomoyl derivatives **84**, 2,3-dihydro-3-methyl-5-(*n*-butylamino)-1,3,4-thiadiazole-2-thione **86** or 2,3,4,5-tetrahydro-3-methyl-5-phenylimino-1,3,4-thiadiazole-2-thione **87**, respectively, were isolated besides 5-amino-3-(methylthio and merpholine)-1*H*-1,2,4-triazoles **85** (Scheme 50) [94].

**3.4. Synthesis of triazole, triazoline, and triazolidine derivatives.** Symmetrically substituted-2,5-dithiobiureas **4** lost ammonia or amine in the presence of alkali, giving 1,2,4-triazolidine-3,5-dithione derivatives **88** (Scheme 51) [43].

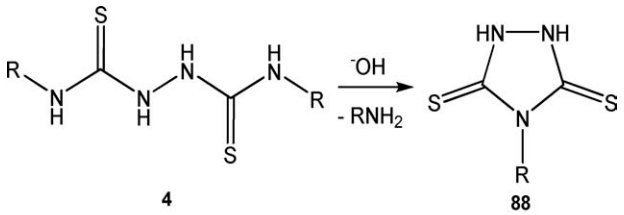
1,6-Dimethyl-2,5-dithiobiurea **4** cyclized under either strong or weak basic conditions to produce compound **88** as the major product and in minor amount of compound 4-methyl-5-methylamino-1,2,4-triazoline-3-thione **89** was also obtained (Scheme 52) [95].

When 1-alkyl-2,5-dithiobiureas **4** were refluxed with sodium methoxide in methanol, the reaction directly

**Scheme 50**

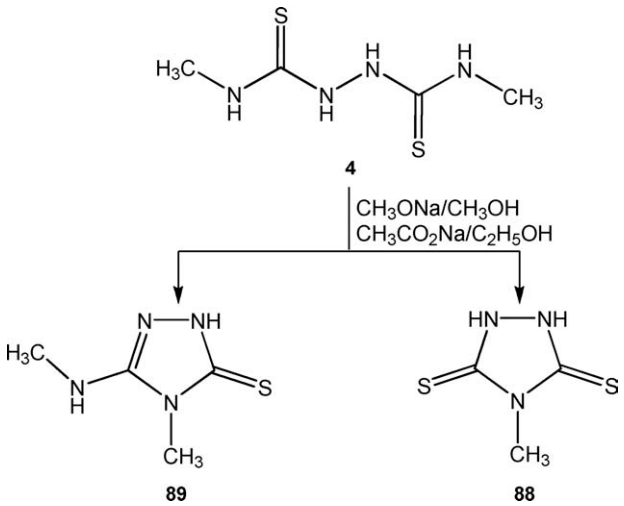


**Scheme 51**



**4, 88:** R = n-Butyl, benzyl, methyl

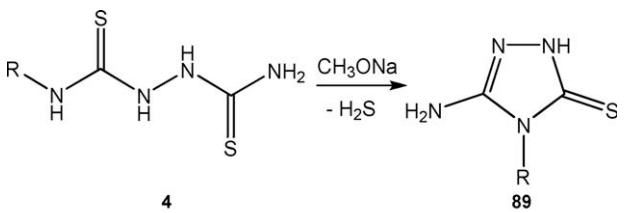
**Scheme 52**



produced 4-alkyl-5-amino-1,2,4-triazoline-3-thiones **89** (Scheme 53) [95].

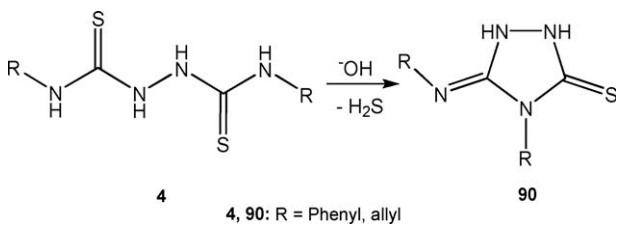
Similarly, cyclization of substituted-2,5-dithiobiueras **4** in alkaline medium took place with the elimination of $H_2S$ to give the 1,2,4-triazoles **90** (Scheme 54) [95].

**Scheme 53**



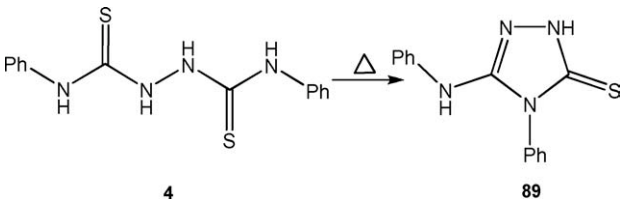
**4, 89:** R = *n*-Butyl, benzyl, methyl

**Scheme 54**

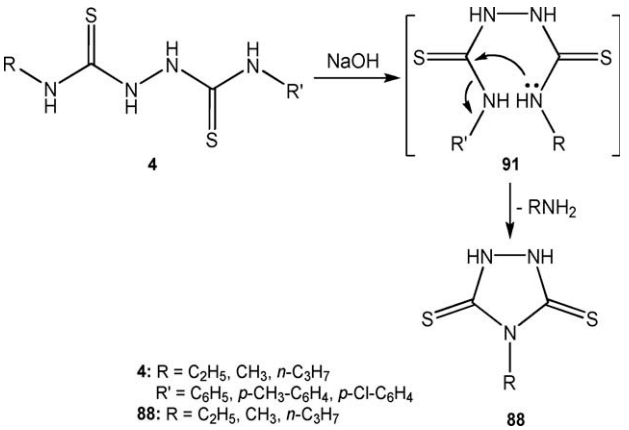


**4, 90:** R = Phenyl, allyl

**Scheme 55**



**Scheme 56**



**4:** R = $C_2H_5$, $CH_3$, *n*-$C_3H_7$
R' = $C_6H_5$, *p*-$CH_3$-$C_6H_4$, *p*-Cl-$C_6H_4$
**88:** R = $C_2H_5$, $CH_3$, *n*-$C_3H_7$

On the other hand, 1,6-diphenyl-2,5-dithiobiurea **4** was heated in the presence of alkali afforded 4-phenyl-3-phenyl amino-$\Delta^2$-1,2,4-triazoline-5-thione **89** (Scheme 55) [44].

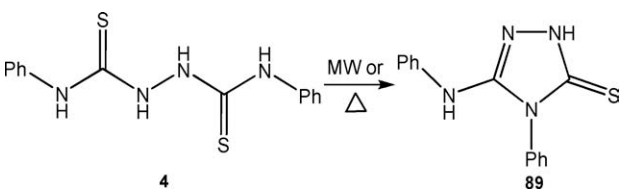
In a different manner, alkali-catalyzed thermal cyclization of 1-alkyl-6-aryl-2,5-dithiobiureas **4** led to the formation of 4-alkyl-1,2,4-triazolidine-3,5-dithiones **88** (Scheme 56) [96,97].

MW and thermal heterocyclization of *N,N′*-disubstituted hydrazinecarbothioamide **4** results in formation of 4-phenyl-5-phenylamino[1,2,4]triazole-3-thione **89** (Scheme 57) [67].

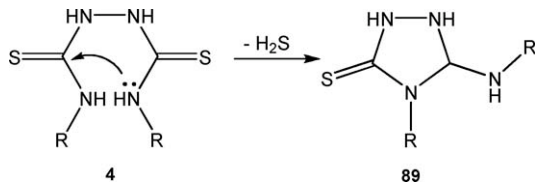
A mechanism for the formation of thermal or MW irradiation for 1,6-disubstituted hydrazinecarbothio-amide **4** to produce 4-phenyl-5-phenylamino[1,2,4]-triazole-3-thione **89** [67] as shown in Scheme 58.

The action of alkali or hydrazine on **4** produced moderate yields 3-amino-5-mercapto-1,2,3-triazole **92** or 4-

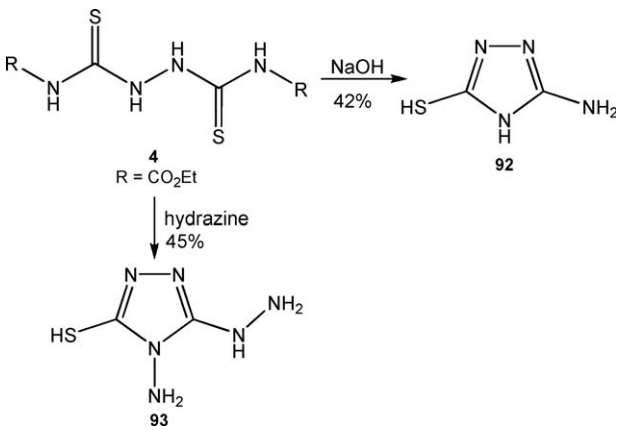
**Scheme 57**



**Scheme 58**



**Scheme 59**



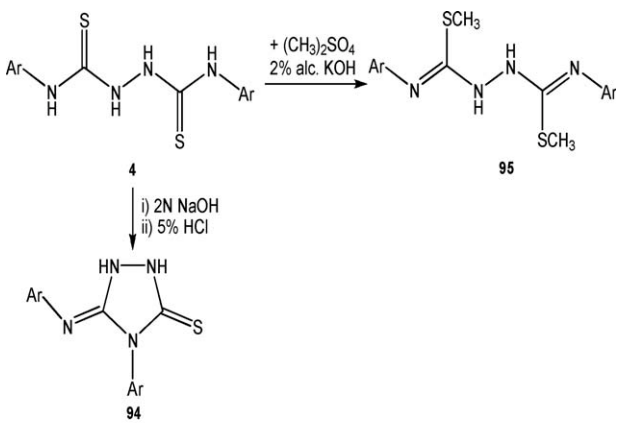
amino-3-hydrazino-5-mercapto-1,2,4-triazole **93** (Scheme 59) [82].

Dubenko *et al*. [98] reported the formation of 4-alkyl/aryl-1,2,4-triazolidine-3,5-dithiones **94**, during alkali-catalyzed thermal cyclization of 1,6-dialkyl/aryl-2,5-dithiobiureas **4**. Treatment of **4** with alcohol/KOH in presence $(CH_3)_2SO_4$ gave **95** (Scheme 60).

Triazolidines **88** and **94** can be obtained by cyclization of **4** with aqueous NaOH (Scheme 61) [99].

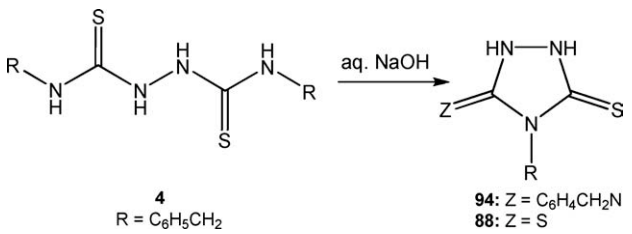
Framm and co-workers [44] reported that when 1,6-diphenyl-2,5-dithiobiurea **4** was heated in the presence

**Scheme 60**



**4, 94, 95:** Ar = *p*-Me-$C_6H_4$, *o*-Cl-$C_6H_4$, *p*-Cl-$C_6H_4$, *p*-Et-$C_6H_4$, *o*-MeO-$C_6H_4$, *p*-MeO-$C_6H_4$, *m*-Cl-$C_6H_4$, *o*-I-$C_6H_4$, $Me_2$-$C_6H_3$

**Scheme 61**



of alkali, the sole product obtained was 4-phenyl-3-phenylamino-$\Delta^2$-1,2,4-triazoline-5-thione **96** (Figure 10).

Alkali catalyzed thermal cyclization of 1,6-dialkyl-2,5-dithiobiureas **4** (R = R' = alkyl) results in the formation of 4-alkyl-1,2,4-triazolidine-3,5-dithiones **88** (alkyl = Me or Et) and 2-alkylamino-$\Delta^2$-1,3,4-thidiazoline-5-thione **52** (alkyl = *n*-Pr or *n*-Bu) (Scheme 62).

The anions **97** and **98**, respectively, formed from **4** carry a negative charge on the nitrogen and sulfur atoms and these can undergo cyclization by nucleophilic attack on the carbon atom at the other end, displacing

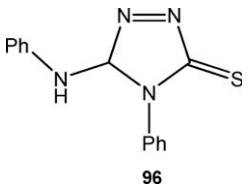
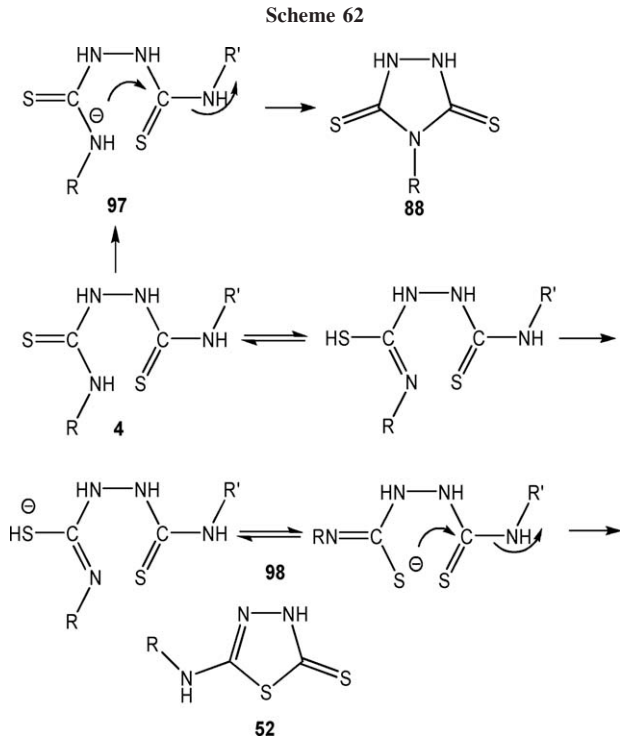
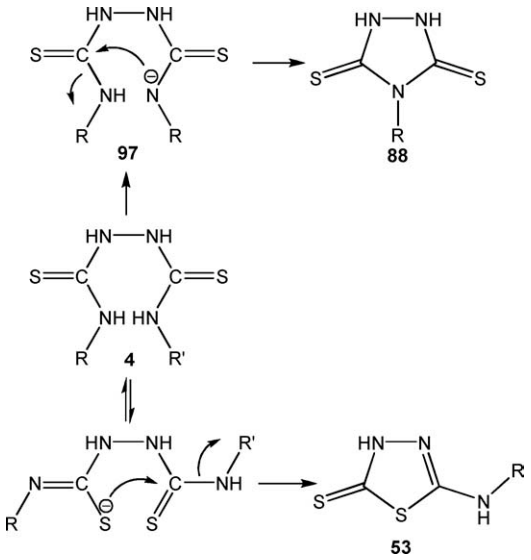


**Figure 10.** Triazolinethione from dithiobiurea.

**Scheme 62**

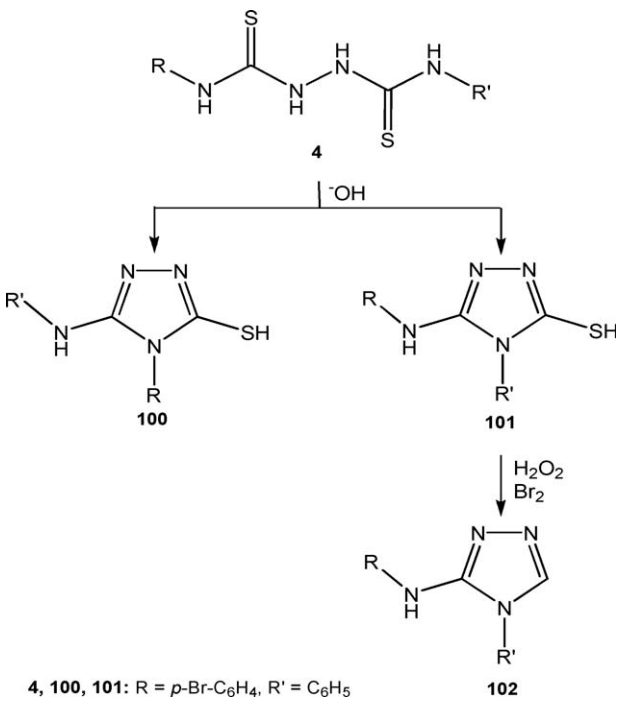


**Scheme 63**



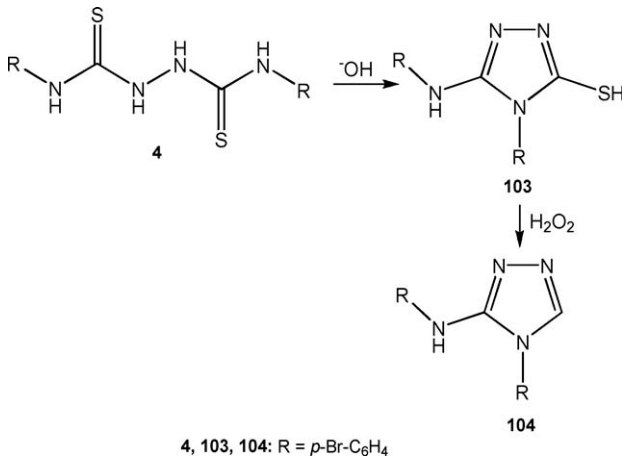
alkylamine. The formation of the different products during cyclization can be explained on the basis of the electronic and steric effects of the alkyl groups. When the alkyl groups are methyl or ethyl the electronic effect of the alkyl group is the major factor governing the mode of cyclization and the attack by the nitrogen atom carrying the alkyl substituent always occurs resulting in the formation of 4-ethyl/methyl-1,2,4-triazolidine-3,5-dithiones **88**. While going from methyl, ethyl, *n*-propyl to *n*-butyl, the inductive effect increase in the order

**Scheme 64**



**4, 100, 101:** R = *p*-Br-$C_6H_4$, R' = $C_6H_5$

**Scheme 65**

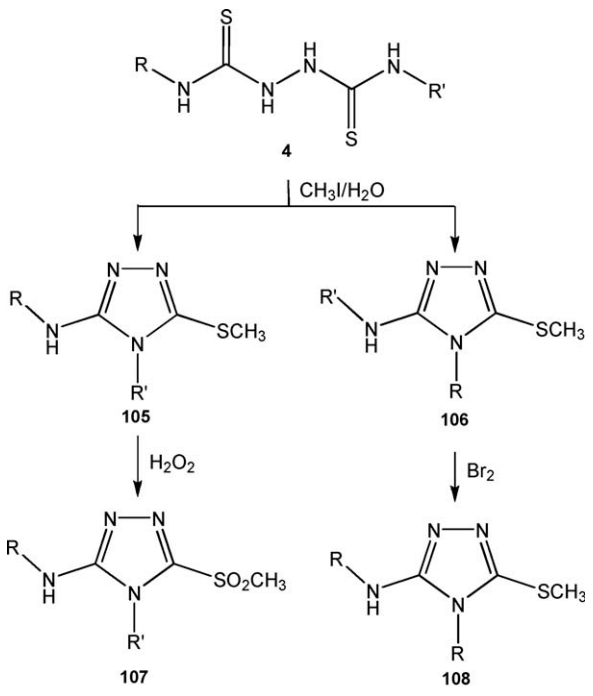


**4, 103, 104:** R = *p*-Br-$C_6H_4$

given. However, the steric effect of the alkyl group also increases and it exerts some influence on the mode of cyclization as follows [77].

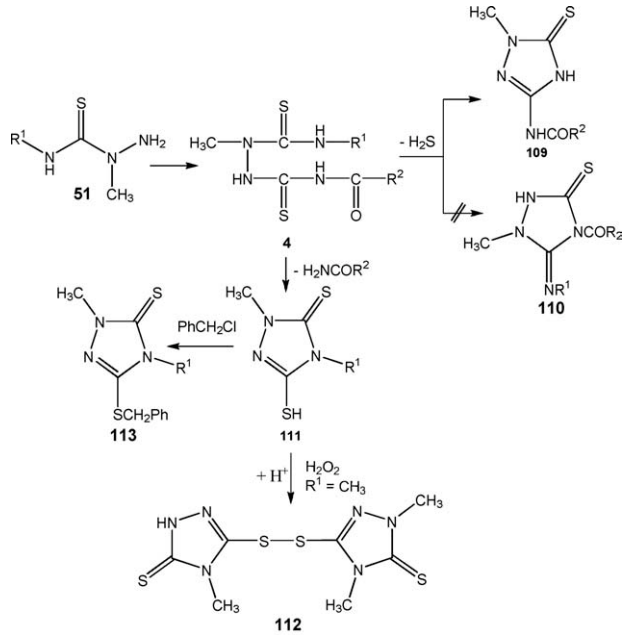
In view of the different modes of cyclization observed with alkyl substituted derivatives, a few 1-alkyl-6-aryl-2,5-dithiobiureas **4** (R = alkyl, R' = aryl) were also subjected to this cyclization reaction. The aryl groups chosen were; phenyl, 4-methylphenyl, *p*-chlorophenyl, and *p*-anisyl. When the alkyl group was methyl or ethyl, two products were obtained; one of the products was identified as 2-arylamino-$\Delta^2$-1,3,4-thiadiazolidine-5-thiones **53**, the other product was identified as 4-ethyl/

**Scheme 66**



**4, 105-108:** R = *p*-Br-$C_6H_4$, R' = $C_6H_5$

**Scheme 67**



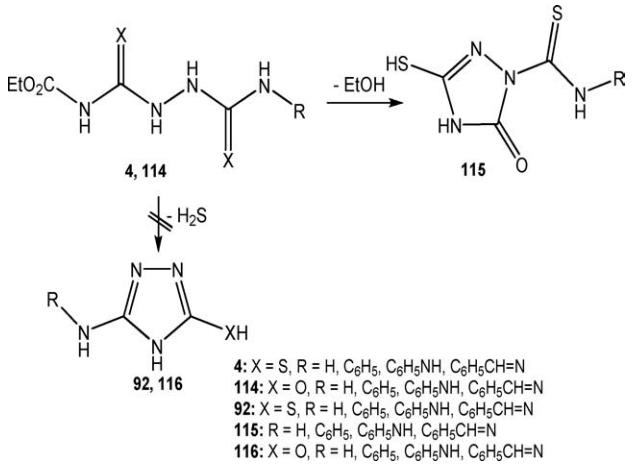
**4,109** : $R^1$ = Methallyl, phenyl, $R^2$ = Ethoxy, phenyl

methyl-1,2,4-triazoline-3,5-dithione **88** [77]. When the alkyl group was *n*-propyl or *n*-butyl, the sole product obtained was characterized as 2-arylamino-$\Delta^2$-1,3,4-thiadiazolidine-5-thion **53**. It was presumably formed by the elimination of alkylamine (Scheme 63).

Simiti and Marie [100] studied the behavior of symmetrical and asymmetrical *p*-bromodianilide of *N,N′*-bisthiocarbonic acid **4** toward —OH and $CH_3I$/—OH. The isomeric triazole **100** and **101** were formed from **4** in NaOH. Oxidation of **101** by $H_2O_2$ gave **102** (Scheme 64).

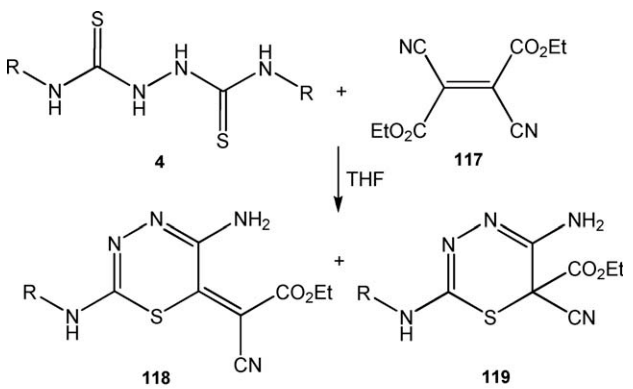
On the other hand, the action of NaOH on symmetrical **4** gave **103**, which oxidized by $H_2O_2$ to give **104** (Scheme 65) [100].

**Scheme 68**



**4:** X = S, R = H, $C_6H_5$, $C_6H_5NH$, $C_6H_5CH$=N
**114:** X = O, R = H, $C_6H_5$, $C_6H_5NH$, $C_6H_5CH$=N
**92:** X = S, R = H, $C_6H_5$, $C_6H_5NH$, $C_6H_5CH$=N
**115:** R = H, $C_6H_5$, $C_6H_5NH$, $C_6H_5CH$=N
**116:** X = O, R = H, $C_6H_5$, $C_6H_5NH$, $C_6H_5CH$=N

**Scheme 69**

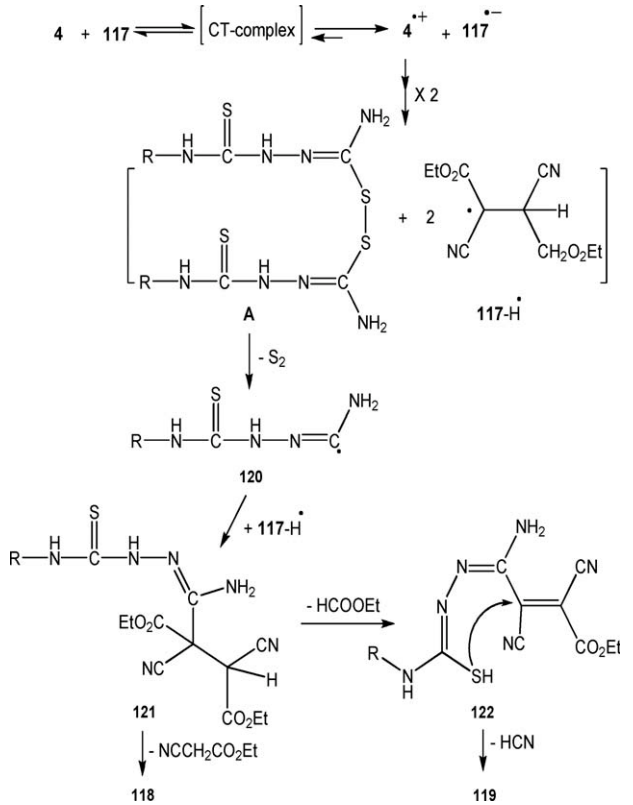


**4,118,119:** R = Phenyl, allyl, benzyl

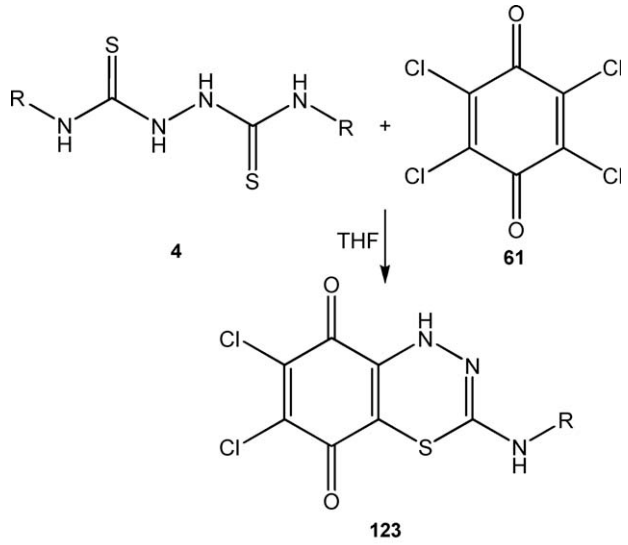
Also the action of NaOH and MeI, respectively, on **4** gave **105** and **106**. Oxidation of **105** by $H_2O_2$ gave **107**, while bromonation of **106** gave **108** (Scheme 66) [100].

2,4-Disubstituted thiosemicarbazides **51** reacted with acyl isothiocyanates to give dithiobiureas **4**, which cyclized to 1,2,4-triazoline-3-thiones **109** (not **110**) and 5-mercapto-1,2,4-triazoline-3-thiones **111** by the action of sodium ethanolate (Scheme 67).

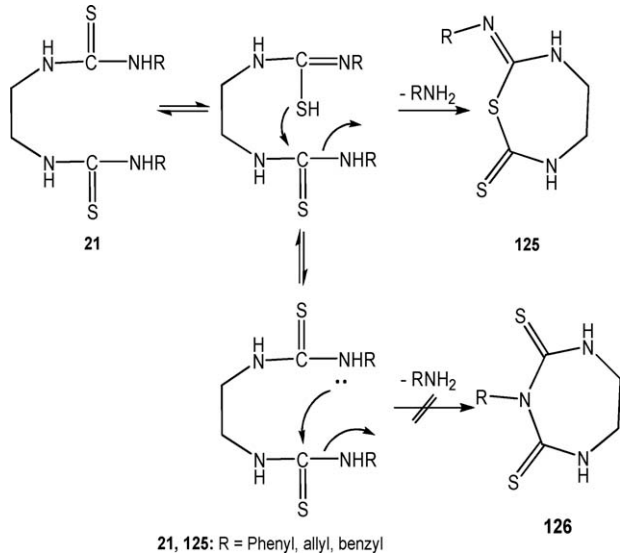
**Scheme 70**



**Scheme 71**




**Scheme 73**




Compound **111** was converted to the more stable *S*-benzyl derivatives **113**. However, **111** were oxidized by hydrogen peroxide to disulfide **112** [92].

Cyclization of dithiobiurea and thiobiurea derivatives involving the usual loss of hydrogen sulfide or $H_2O$ and did not convert compounds of type **4** and **114** into **92** or **116**, but occurs in fact with elimination of ethanol and formation of 1*H*-(thio)amide-1,2,4-triazoles **115** (Scheme 68) [101–103].

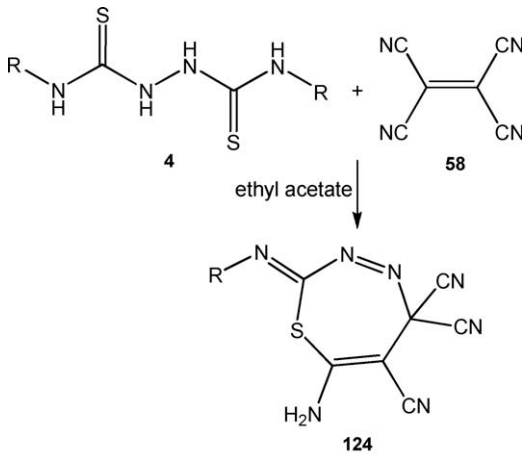
**3.5. Synthesis of thiadiazine derivatives.** 1-Substituted hydrazinecarbothioamide **4** reacted with ditheyl (*E*)-2,3-dicyanobutenedioate **117** in THF at room temperature to give ethyl (*Z*)-2-[-2-amino-2-(substituted amino)-6*H*-1,3,4-thiadiazine]-2-cyanoacetate **118** and ethyl 5amino-6-cyano-2-(substituted amino-6*H*-1,2,4-thiadiazine-6-carboxylate **119** (Scheme 69) [87].

A rationalization for the formation of thiadiazines compounds is given in Scheme 70 [87].

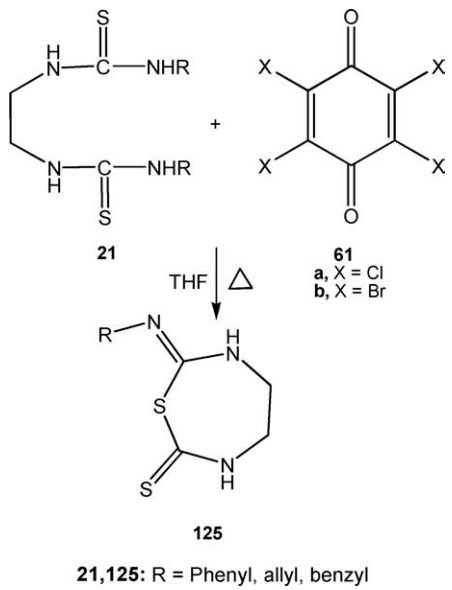
The interaction between 1,6-disubstituted hydrazinearbothioamides **4** and chloranil **61** in THF led to the formation of 3-substituted amino-6,7-dichloro-1*H*-benzo[*e*][1,3,4]thiadiazine-5,8-diones **123** (Scheme 71) [86].

**3.6. Synthesis of thiadiazepine and thiadiazepane derivatives.** Addition of two equivalents of ethenetetracarbonitrile **58** to 1,6-disubstituted-2,5-dithiobiureas **4** in ethyl acetate lead to the formation of 7-amino-2-

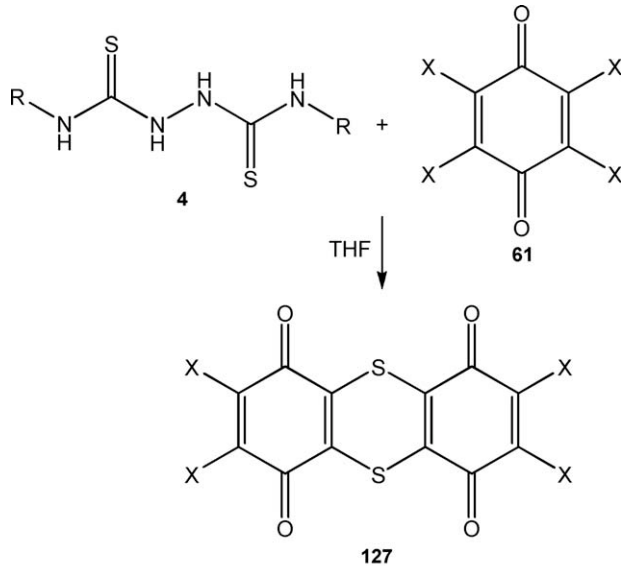
**Scheme 72**




**Scheme 74**



**Scheme 75**



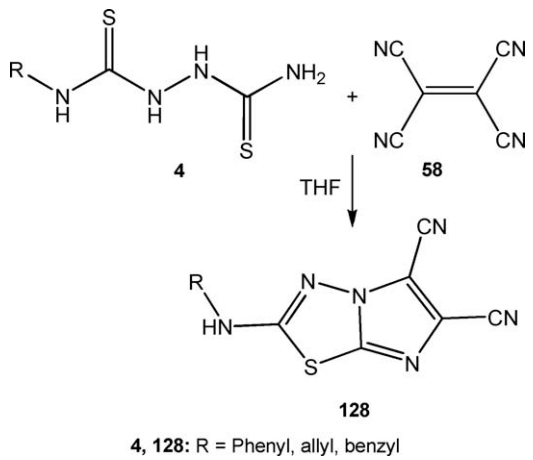

substituted imino-2*H*-[1,3,4]thiadiazepine-5,5,6-tri-carbonitriles **124** (Scheme 72) [83].

1,3,6-Thiadiazepane-2-thione **125** can be obtained on heating or microwave irradiation of thioureido-thioureas **21** [67]. The formation of **125** can be explained by nucleophilic attack of SH on C═S with elimination of a molecule of amine. The alternative structure **126** could be ruled out on the basis of spectral data of **125** (Scheme 73).

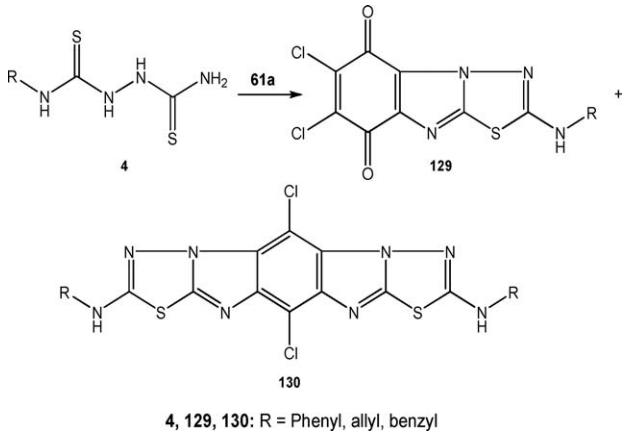
Also, 1,3,6-thiadiazepane-2-thione **125** was formed *via* interaction between thioureidothioureas **21** with chloranile or bromanile **61a,b** in boiling THF (Scheme 74) [86].

**3.7. Synthesis of thiantherne derivatives.** On adding 1,6-disubstituted-2,5-dithiobiureas **4** to chloranil or bromanil **61a,b**, 2,3,7,8-tetrahalothia-anthrene derivatives **127** were formed (Scheme 75) [86].

**Scheme 76**



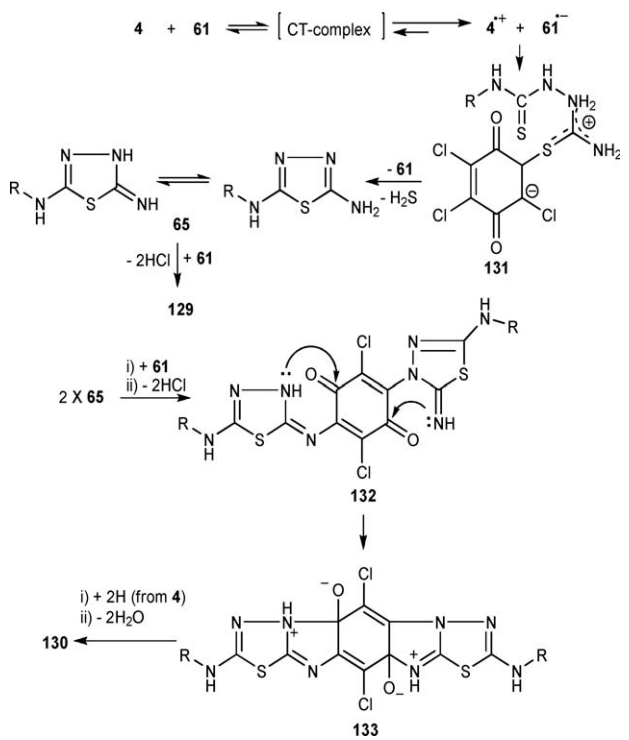

**Scheme 77**



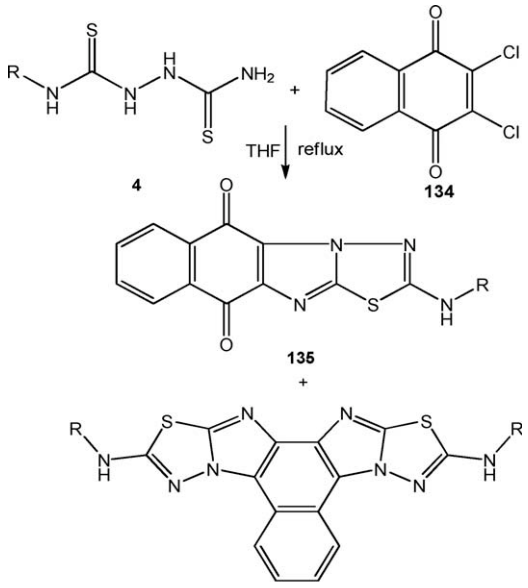

**3.8. Synthesis of imidazothiadiazole derivatives.** 2-(Substituted amino)imidazo[2,1-*b*][1,3,4]thiadi-azole-5,6-dicarbonitriles **128** were formed during the interaction between 1-substituted-2,5-dithiobiureas **4** with ethenete-tracarbonitrile **58** (Scheme 76) [87].

On the other hand, the reaction of chloranil **61a** with 1-substituted-2,5-dithiobiureas **4**, 2-substituted amino-6,7-dichlorobenzo[4,5]imidazo[2,1-*b*][1,3,4]-thiadiazole-5,8-diones **129** and 5,11-dichloro-2,8-disubstituted

**Scheme 78**



**Scheme 79**




**4,135,136:** R = Phenyl, allyl, benzyl

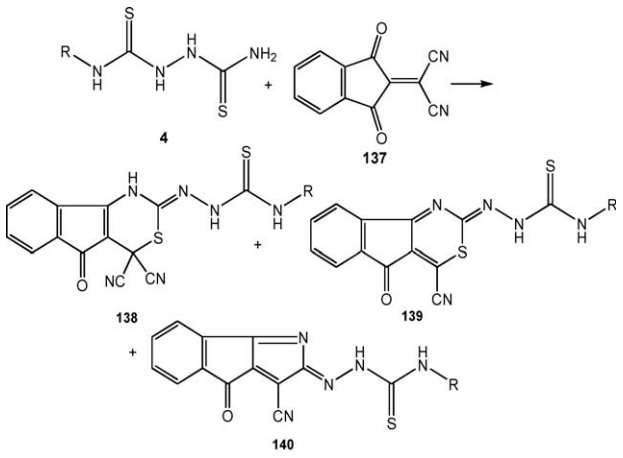
aminobenzo[21,3-*d*:6,5-*d*']bis(imidazo-[2,1-*b*][1,3,4]thiadiazoles) **130** were formed (Scheme 77) [104].

The formation of products **129** and **130** as in Scheme 78 [104]:

Also, the reaction between 1-substituted-2,5-dithiobiureas **4** and 2,3-dichloro-1,4-naphthoquinone **134** gave 2-substituted aminonaphtho[4,5]imidazo-[2,1-*b*][1,3,4] thiadiazole-5,10-diones **135** and 2,11-disubstituted aminonaphtho[1,2-*d*:4,3-*d*']bis-(imidazo[2,1-*b*][1,3,4]thidiazoles) **136** (Scheme 79) [104].

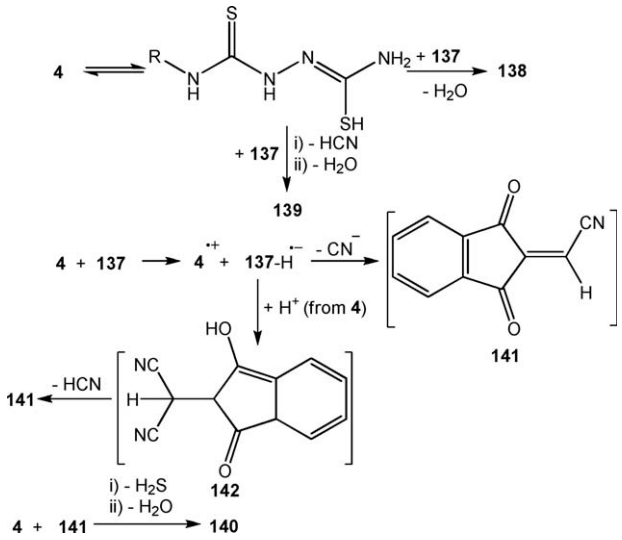
**3.9. Synthesis of oxoindenothiazine and oxoindenopyrrole derivatives.** (1,3-Dioxo-2,3-dihydro-1*H*-inden-2ylidene)-propanedinitrile **137** reacted with 1-substi-

**Scheme 80**




**4,138,140:** R = Phenyl, allyl, benzyl

**Scheme 81**

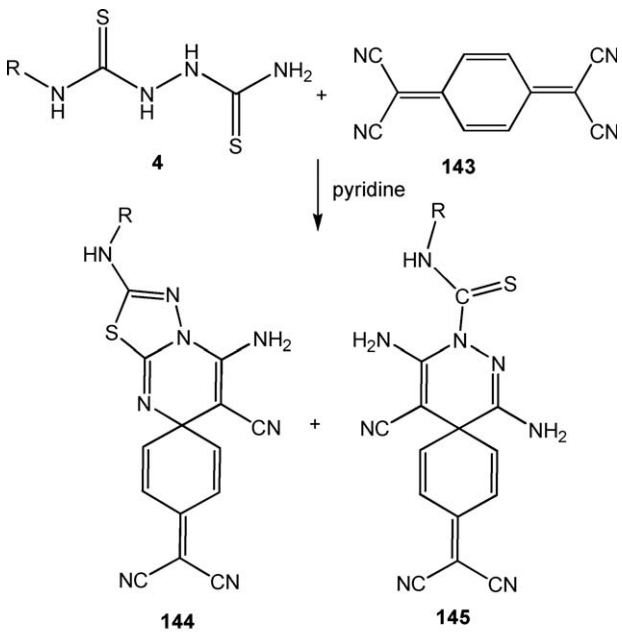



tuted-2,5-dithiobiureas **4** in ethyl acetate to give *N*-substituted-2(4,4-dicyano-5-oxoindeno[1,2-*d*][1,3]thiazin-2-(1*H*,4*H*,5*H*)-ylidene)hydrazinecarbothioamides **138**, *N*-substituted-2(4-cyano-5-oxoindeno-[1,2-*d*][1,3]-thiazin-2-(5*H*)-ylidene)hydrazinecarbothioamides **139** and *N*-substituted-2(3-cyano-4-oxoindeno[1,2-*b*]pyrrol-2-(4*H*)-ylidene)hydrazinecarbothioamides **140** (Scheme 80) [104].

A rationalization for the formation of products **138**–**140** is shown in Scheme 81 [104].

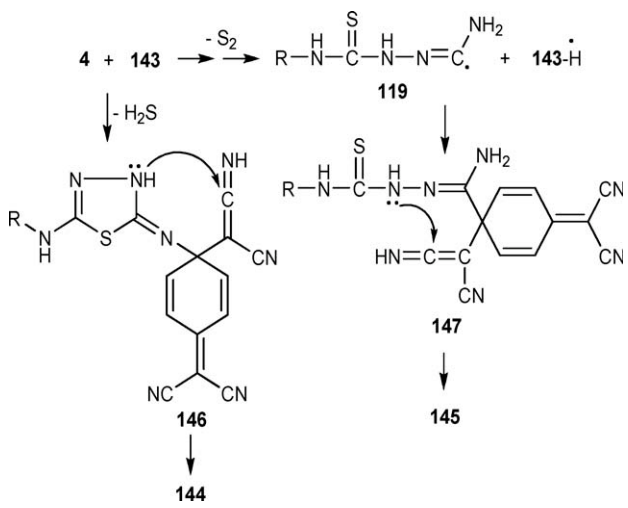
**3.10. Synthesis of spiro compounds.** The reaction of 1-substituted-2,5-dithiobiureas **4** with 7,7′,8,8′-

**Scheme 82**




**4,144,145:** R = Phenyl, allyl, benzyl

**Scheme 83**



tetracyanoquinodimethane **143** in dry pyridine lead to the formation of {5-amino-6-cyano-2-(substituted amino)spiro[1,3,4]thiadiazolo[3,2-*a*]-pyrimidine-7,1′-cyclohexa[2,5]diene-4′-ylidene}malononitriles **144** and 1,4-diamino-5-cyano-9-(dicyanomethylene)-*N*-substituted-2,3-diazospiro-[5,5′]undeca-1,4,7,10-tetraene-9-thioamides **145** (Scheme 82) [87].

The formation of compounds **144** and **145** can be rationalized by the following mechanism (Scheme 83) [87].

## REFERENCES AND NOTES


[1] Hassan A. A. Bull Soc Fr 1994, 131, 424.

[2] Hassan, A. A.; Ibrahim, Y. R.; Semida, A. A.; Mourad, A. E. Liebigs Ann Chem 1994, 989.

[3] Hassan, A. A. Phosphorus, Sulfur, Silicon and Rel. Elements, 1995, 101, 189.

[4] Hassan, A. A.; Ibrahim, Y. R.; El-Tamany, E. H.; Semida, A. A.; Mourad, A. E. Phosphorus Sulfur Silicon Relat Elements 1995, 106, 167.

[5] Hassan, A. A.; Mohamed, N. K.; Aly, A. A.; Mourad, E. A. Monatsh Chem 1997, 128, 61.

[6] Hassan, A. A.; Mohamed, N. K.; Shawky, A. M.; Döpp, D. Arkivoc 2003, i, 118.

[7] Doyle, K. M.; Kurzer, F. Tetrahedron 1976, 32, 2347.

[8] Noto, R.; Buccheri, F.; Cusmano, G.; Gruttadauria, M.; Werber, G. J Heterocyclic Chem 1991, 28, 1421.

[9] Werber, G.; Buccheri, F.; Vivona, N.; Gentile, M. J Heterocyclic Chem 1977, 14, 1433.

[10] Gruttadauria, M.; Buccheri, F.; Buscemi, S.; Noto, R.; Werber, G. J Heterocyclic Chem 1992, 29, 233.

[11] Beckert, R.; Gruner, M.; Seidal, I.; Kuban, R. Monatsh Chem 1989, 120, 1125.

[12] Singh, H.; Yadav, L. D. S.; Singh, A. K. J Indian Chem 1985, LXII, 147.

[13] Reynolds, G. A.; Van Allan, J. A. J Org Chem 1959, 24, 1478.

[14] Hassaneen, H. M.; Shetta, A. H.; Elwan, N. M.; Shawali, A. S. Heterocycles 1982, 19, 1477.

[15] Dobosz, M.; Pitucha, M.; Wujec, M. Acta Pol Pharm 1996, 53, 31.

[16] Trost, B. M. Chem Rev 1978, 78, 363.

[17] Roman, L.; Floreav, E.; Marcu, P. Pharmazie 1972, 27, 690.

[18] Oettel, M.; Huebler, D.; Grass, M.; Chemmitia, K. H.; Eberhardt, U. Pharmazie 1975, 30, 321.

[19] Winkelmann, E.; Wagener, W. H.; Wirth, H. Arzneim-Forsch 1977, 27, 950.

[20] Craciuneanu, R.; Florean, E. Rev Roum Chim 1968, 13, 105.

[21] Popper, E.; Craciuneanu, R.; Ariton, N. Rev Roum Chim 1961, 9, 537.

[22] Eggensperger, H.; Berscheid, R. Sofw J 1994, 120, 289.

[23] Runti, C.; Collino, F. Bull Chim Farm 1961, 100, 837.

[24] Lindhorst, K. T.; Kieburg, C.; Krallmann-Wenzel, U. Glycoconjugate J 1998, 15, 605.

[25] Sondhi, S. M.; Verma, R. P.; Nidhi, S.; Shukla, R.; Raghubir, R.; Dubey, M. P. Indian Drugs 1999, 36, 50.

[26] Page, D.; Roy, R. Glycoconjugate J 1997, 14, 345.

[27] Page, D.; Roy, R. Bioconjugate Chem 1997, 8, 714.

[28] Fedorova, O. V.; Mordavaski, G. G.; Rusiov, G. L.; Zueva, M. N.; Ovchinnikova, I. G. Khim-Farm Zh 1996, 30, 6; Chem Abstr 1997, 126, 152416y.

[29] Simanenkova, L. B.; Donstov, A. A.; Novitskaya, S. P.; Kiro, Z. B. Kauch Rezina 1981, 9, 19; Chem Abstr 1981, 95, 188416d.

[30] Yonova, P.; Guleva, E. Bulgarian J Plant Physiol 1997, 23, 72; Chem Abstr 1999, 131, 195741.

[31] Davarski, K.; Schuster, G.; Vasilev, G. J Phytopathol 1989, 125, 133.

[32] Krivenko, L. V.; Cherezova, E. N.; Mukmeneva, N. A. Zh Prikl Khim 2000, 73, 1193; Chem Abstr 2001, 134, 148330p.

[33] Lipowska, M.; Hayes, B. L.; Hansen, Lory; Taylar, A.; Marzilli, L. G., Jr. Inorg Chem 1996, 35, 4227.

[34] Navoratna, M. R.; Lyer, C. S. P. Talanta 1977, 24, 396.

[35] Furloni, C.; Tarantelli, T. Gazz Chim Ital 1973, 103, 951.

[36] Sensarm, K. P.; Pal, H. K.; Saha, M. B. J Indian Chem Soc 1984, 61, 823.

[37] Abrams, M. J.; Davison, A.; Faggiami, R.; Jones, A. G.; Lock. C. J. L. Inorg Chem 1984, 23, 3284.

[38] Watson, P. L.; Albanese, J. A.; Calabrese, J. C.; Ovenall, D. W.; Smith, R. G. Inorg Chem 1991, 30, 4638.

[39] Bodensieok, U.; Carraus, Y.; Stoeckli-Evans, H.; Suss-Fink, G. Inorg Chim Acta 1992, 195, 135.

[40] Kurzer, F.; Taylor, J. J Chem Soc 1959, 1064.

[41] Joshua. C. P. J Indian Chem Soc 1961, 38, 155.

[42] Indukumari, P. V.; Josshva, C. P.; Rajan, V. P. Indian J Chem 1981, 20B, 384.

[43] Whitera, B. R. D.; Fry, D. J. British Patent 1, 049,053, November 23, 1966; Chem Abstr 1967, 66, 65474q.

[44] Framm, E.; Layer, E. Nerzk Liebigs Ann Chem 1923, 1, 433.

[45] Buu-Hoï, N. P.; Xuong, N. D.; Nam, N. H. J Prakt Chem 1955, 216.

[46] Kepe, V.; Pozgan, F.; Golobic, A.; Polanc, S.; Kočevar, M. J Chem Soc Perkin Trans 1998, 1, 2813.

[47] Song J. (to American Cyanamid Co.). US 3,033,901, May 8, 1962, US Pat. Appl. October 27, 1955; Chem Abstr 1962, 56, 11030i.

[48] Egri, J.; Magyar, K.; Majerko, B.; Rakoczi, J.; Varhegyi, I. Hung. Telies 5801 (CI. C 07c); Chem Abstr 1973, 79, 78152b.

[49] Egri, J.; Magyar, K.; Majerko, B.; Rakoczi, J.; Varhegyi, I. Hung. Telies 5660 (CI. C 07c); Chem Abstr 1973, 79, 78156f.

[50] Aboulwafa, O. M.; El-Khawass, E. M.; El-Shamy, H. A. Alexandria J Pharm Sci 1991, 5, 69.

[51] Paget, G. E.; Richardson, D. N.; Walpole, A. L. Ger. Pat. 1,468,071 (Cl. C 07c, A 61K); Chem Abstr 1972, 77, 151530p.

[52] Podgornaya, I. V.; Postovskii, I. Ya Zh Obshch Khim 1963, 33, 2037; Chem Abstr 1963, 59, 9858h.

[53] Winthrop, S. O.; Sybulski, S.; Gavin, G.; Grant, G. A. J Am Chem Soc 1970, 79, 3496.

[54] Somolanka, I. V.; Ershova, I. I. Ukr. Khim. Zh., 1970, 36, 273; Chem Abstr 1970, 73, 34368y.

[55] Barba, N. A.; Shur, A. M. Zh. Vses. Khim. Obshchest, 1969, 44, 464; Chem Abstr 1969, 71, 112585s.

[56] Nikolaeva, I. V.; Tsurkan, A. A.; Levshin, I. B.; V'yunov, K. A.; Ginak, A. I. Zh. Prikl. Khim., 1985, 58, 1189; Chem Abstr 1985, 103, 177952h.

[57] Katritzky, A. R. Physical Methods in Heyerocyclic Chemistry, Vol. 2; Academic Press: New York, 1963; p 325.

[58] Singh, A. P.; Singh, R.; Verma, V. K. Heterocycles 1988, 27, 2373.

[59] Ionova, R. A.; Ionov, L. R. Dokl Bulg Akad Nauk 1999, 52, 57; Chem Abstr 2000, 133, 237647u.

[60] Maussulli, F. S. US 3,632,363 (Cl. 106/86; C 08b); Chem Abstr 1972, 76, 128704u.

[61] Stautland, O.; Helgen, L.; Agre, C. L. J Org Chem 1959, 24, 818.

[62] Farbenfabriken Bayer, A.-G. Ger. Pat. 842,065 (Cl. 12p, 9); Chem Abstr 1952, 50, 10207h.

[63] Nathghosh, I. T. J Indian Chem Soc 1933, 10, 583.

[64] D'Angel, F.; Di Bello, C.; Giormani, V. Gazz Chim Ital 1996, 96, 954.

[65] Wegner, K.; kraemer, I.; Schichaneder, H.; Schunak, W.; Scelenyi, I.; Ahrens, K. H. Ger. Offen. De 3,441,086 (Cl. C07D417/12); Chem Abstr 1986, 105, 133878a.

[66] Haerter, H. P.; Stauss, U.; Schindler, O. Helv Chim Acta 1971, 54, 2144.

[67] Hassan, A. A.; Mourad, A. F. E.; El-Shaieb, K. M.; Abou-Zied, A. H. Heteroatom Chem 2003, 14, 535.

[68] Mamedov, V. A.; Nurkhametova, I. Z.; Gubaidullin, A. T.; Litvino, I. A.; Levin, Y. A. Chem Heterocycl Compd 1999, 35, 1357.

[69] Sead, M.; Abdel-Rahman, R. M.; Abdel-Megid, M. Indian J Heterocyclic Chem 1993, 3, 96.

[70] Levshin, I. B.; Nikolaeva, I. V.; Tsurkan, A. A. Otkrytiya Izobret 1985, 6, 75; Chem Abstr 1985, 69, 22582p.

[71] Dubenko, R. G.; Bazavova, I. M.; Pel'kis, P. S. Zh Org Khim 1968, 4, 1057; Chem Abstr 1968, 69, 43841s.

[72] Mizrakh, L. T.; Polanskaya, L. Yu.; Gvozdetskii, A. N.; Vasil've, A. M.; Ivanova, T. M.; Lisina, N. I. Khim-Farm Zh 1987, 21, 322; Chem Abstr 1988, 108, 21771r.

[73] Hanefeld, W.; Martin, S. J Heterocyclic Chem 1994, 31, 391.

[74] Hu, P.; Chéng, K.; Huang, L.; Hu, C.; Ts'ao, C.; Liang, H.; Liu, W. Yao Hsüeh Hsüeh Pao, Patent, 1959, 7, 222; Chem Abstr 1961, 54, 11004f.

[75] Jooshua, C. P., Annie, V. J Indian Chem Soc 1990, 67, 759.

[76] Tomita, Y.; Kabashima, S.; Okawara, T.; Yamasaki, T.; Furukawa, M. J Heterocyclic Chem 1990, 27, 707.

[77] Raphael, E.; Joshua, C. P.; Kosky, L. Indian J Chem 1989, 28B, 635.

[78] Shen, T. Y.; Clark, R. L.; Arsenio, A. P. (Merck and Co., Inc.) S. African 7,503,527, March 22, 1974; US Pat. Appl. 491,205, July 24, 1974; Chem Abstr 1977, 86, 72662r.

[79] Tao, E. V. P.; Rolski, S. (Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN 46285 USA). Org. Prep. Proced. Int. Patent, 1986, 18, 272; Chem Abstr 1987, 106, 213838y.

[80] Chamberlin, K. S. US 4,374,993, February 22, 1983, US Pat. Appl. 271,323, June 8, 1981, 3 pp.; Chem Abstr 98, 198248b, 1983.

[81] Wegner, K.; Kraemer, I.; Schickaneder, H.; Schunak, W.; Scelenyi, I.; Ahrens, K. H. Ger. Offen. Df 3,441,086 (Cl. C07D41/12); Chem Abstr 1986, 105, 133878a.

[82] Kurzer, F.; Secker, J. L. J Heterocyclic Chem 1989, 26, 355.

[83] Hassan, A. A.; Mourad, A. E.; El-Shaieb, K. M.; Abou-Zied, A. H. Z. Naturforsch 2004, 59B, 910.

[84] Broda, W.; Dehmlow, E. V. Isr J Chem 1985, 26, 219.

[85] Richardson, D. N. Ind Chim Belge 1967, 32, 330; Chem Abstr 1969, 70, 77891u.

[86] Hassan, A. A.; Mourad, A. E.; El-Shaieb, K. M.; Abou-Zied, A. H. J Heterocyclic Chem 2006, 43, 471.

[87] Hassan, A. A.; Aly, A. A.; El-Sheref, E. M. J Chem Res 2008, 1, 9.

[88] Ried, W.; Oxenius, R. Chem Ber 1973, 106, 484.

[89] Tao, E. V.; Rolski, S. Org Prep Int 1986, 18, 272; Chem Abstr 1987, 106, 213838y.

[90] Marchalin, M.; Povazonoc, F.; Martvon, A. Collect Czech Chem Commum 1982, 47, 877.

[91] Okawara, T.; Tateyama, Y.; Yamasoki, T.; Furukawa, M. J Heterocyclic Chem 1988; 47, 1071.

[92] Ernst, S.; Richter, C.; Hobert, A.; Marian, G. G.; Schulze, K. J Heterocyclic Chem 1995, 32, 275.

[93] Reiter, J.; Barkoczy, J. J Heterocyclic Chem 1992, 29, 1677.

[94] Reiter, J.; Barkoczy, J. J Heterocyclic Chem 1993, 30, 333.

[95] Altland, H. W.; Graham, A. P. J Heterocyclic Chem 1978, 15, 377.

[96] Silberg, A.; Simiti, I.; Cosma, N.; Proinov, I. Acad Rep Populare Romine Filiala Cluj Studii Cercetări Chim 1957, 8, 315; Chem Abstr 1961, 54. 17625e.

[97] Dubenko, R. G.; Pelkis, P. S. Zh Obshsh Khim 1963, 33, 2220; Chem Abstr 1963, 59, 13985f.

[98] Dubenko, R. G.; Bazavova, I. M.; Pel'kis, P. S. Zh Org Khim 1963, 33, 2220; Chem Abstr 1963, 59, 13985.

[99] Bazavova, I. M.; Dubenko, R. G.; Shevchenko, L. I.; Pel'-kis, P. S. Ukr Khim Zh 1980, 46, 286; Chem Abstr 1980, 93, 71237p.

[100] Simiti, I.; Marie, A. Arch Pharm 1973, 306, 659.

[101] Esmail, R.; Kurzer, F. Tetrahedron 1977, 33, 2007.

[102] Kurzer, F. J Chem Soc C 1971, 2927.

[103] Kurzer, F. J Chem Soc C 1971, 1805.

[104] Hassan, A. A.; Aly, A. A.; El-Sheref, E. M. Arckivoc 2007, xiv, 229.

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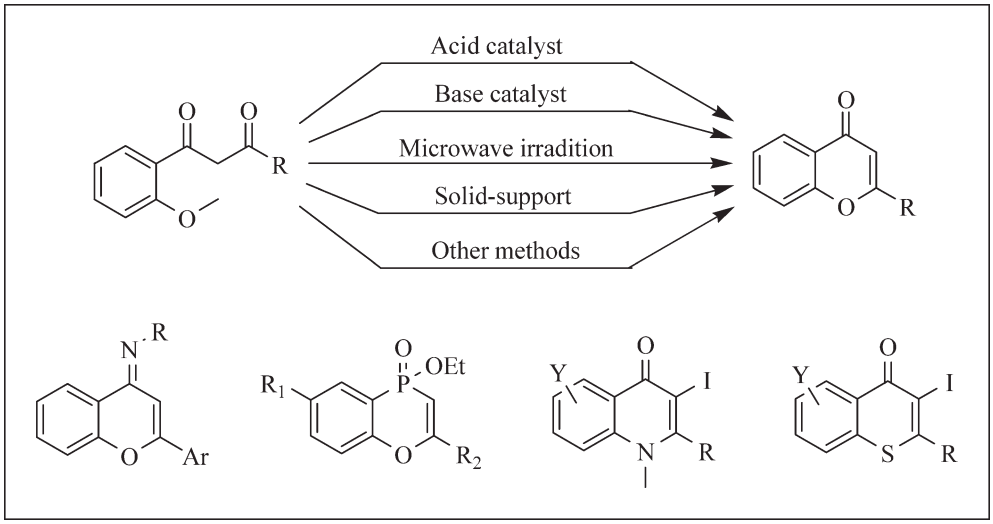


Because of important biological applications of chromones, some synthetic strategies leading to more complex derivatives have been widely explored in the past years. Thus, the purpose of this review is to report some recent improvements of the classical synthetic methods and of some nonclassical methods to obtain simple oxygenated chromones. The strategies for synthesis of heterocycle analogs containing phosphorus, nitrogen, and sulfur are also summarized.

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## INTRODUCTION

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [1]. Chemically, chromones (4*H*-chromen-4-ones) are heterocyclic compounds with the benzo-γ-pyrone framework (Fig. 1). Molecules containing the chromone or benzopyranone ring have a wide range of biological activities. They have been shown to be tyrosine and protein kinase inhibitors [2–4], as well as anti-inflammatory [5], antiviral [6], antioxidant [7,8], and antihypertensive agents [6]. Chromone derivatives are also active at benzodiazepine receptors [9], and on lipoxygenase and cyclooxygenase [10]. In addition to this, they have been shown to be anticancer agents [11], possessing antimutagenic properties [12] and the ability to inhibit electron transport through inhibition at NADH: ubiquinone oxidoreductase and phorbol ester-inducedornithinedecarboxylase [13,14]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator [15]. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure [16]. The main objectives of chromones syntheses are not only for the development of more diverse and complex bioactive compounds for biological activity and structure-activity relationship (SAR) studies but also for other applications in Medicinal Chemistry, such as preparation of fluorescence probes, due to photochemical properties of chromones [17].

One of the first methods for the synthesis of chromones was introduced by Heywang and Kostanecki, which involved the decarboxylation of chromone-2-carboxylic acid [18]. Since then, several other routes with higher yields and less drastic experimental conditions have been developed.

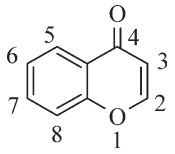


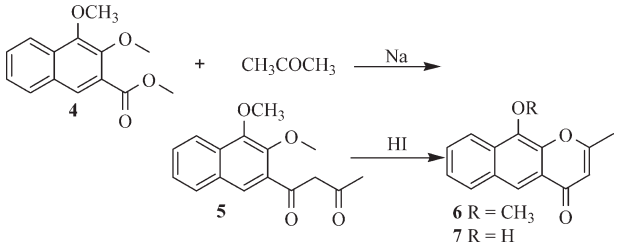
**Figure 1.** Chromone nucleus and numbering.

Chromones could be synthesized under either acidic or basic conditions. The classical 2,3-disubstituted benzopyranone (**3**) synthesis utilized acidic conditions (Scheme 1) and was by far the most common method [19]. It proceeded through an intramolecular condensation of molecules such as **2**, which were usually obtained through a Baker–Venkataraman rearrangement of compound **1**, or via a Claisen ester condensation (Scheme 1). Most synthesis required harsh acidic conditions as the final step. On the other hand, synthesis utilizing basic conditions typically consisted of piperidine in refluxing pyridine for several hours to affect ring closure. This was far less common [19]. Recently, microwave heating has also been used to affect ring cyclization [20]. In this review, our aim is to provide a comprehensive summary till the March 2009, with special emphasis on the synthesis of chromone ring based on different methods, and the same reactive condition in chromone ring closure will be cited along with the latest reported literature.

**Acid as catalyst in chromone ring closure.** Acid comprised a major catalyst in chromone ring closure, and many acids can be used including hydriodic acid, polyphosphoric acid (PPA), acetic acid, methanesulfonylchloride, hydrochloric acid, para toluene sulfonic acid (PTS), triflic anhydride, phosphorus oxychloride, perchloric acid, and sulfuric acid.

***Hydriodic acid as a catalyst.*** In 1952, Wawzonek and Ready [21] reported the synthesis of chromone using hydriodic acid as a catalyst in the ring closure (Scheme 2). Methyl 1,2-dimethoxy-3-naphthoate (**4**), which was prepared from 1,2-dihydroxy-3-naphthoic acid by a two-step methylation process, was condensed with acetone in the desired fashion to afford **5**. Cyclization of the diketone (**5**) with hydriodic acid gave products which depended upon the time of refluxing. A period of 7 h gave a mixture of 2-methyl-8-hydroxy-6,7-benzochromon (**7**) and 2-methyl-8-methoxy-6,7-benzochromone (**6**). Complete demethylation was achieved only after 24 h of heating. This chromone ring closure using hydriodic acid as a catalyst was not common because it required high temperature and long reaction time, and sometimes the reactant might decompose under these conditions.

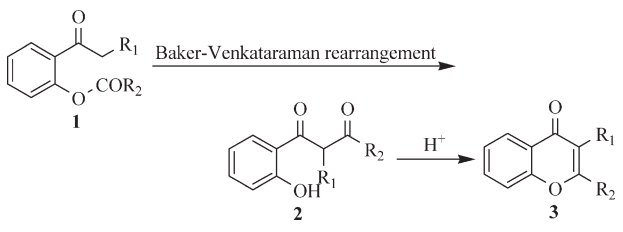
**Scheme 2**



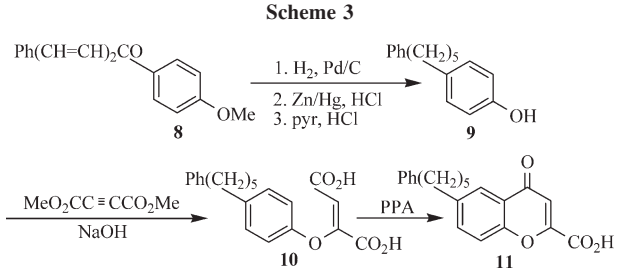
***Polyphosphoric acid as a catalyst.*** In 1977, Lee and coworkers [22] took PPA as a catalyst in the chromone ring closure; in their synthetic route (Scheme 3), they firstly applied a two-step reduction procedure to the chalcone **8** with subsequent demethylation provided the aralkylphenol **9**, which, by modification [23] of the process described by Ruhemann and Stapleton [24] for the formation of chromone-2-carboxylic acids from phenols, was converted to the chromone **11** through PPA as the catalyst in the last step. This method was more suitable in the phenolic hydroxyl side chain in a carboxylic acid of the cyclization.

***Acetic acid as a catalyst.*** In 1990, Harvey *et al*. [25] described a new synthesis of chromones and flavones based on the ortho-directed metalation of methoxymethyl aryl ethers with alkyllithium reagents (Scheme 4), and they applied acetic acid as a catalyst in the chromone ring closure. Their synthetic route entailed reaction of the ortho-lithiated intermediates **12** with a conjugated unsaturated aldehyde followed by oxidation of the allylic alcohol product **13** with ''periodinane'' to yield an ortho-allylic ketone **14**. The latter on heating in acetic acid undergoes loss of the methoxymethyl protecting group and cyclization to a chromanone (or flavanone, if a β-phenyl substitutent is present) **15**. Dehydrogenation by treatment with pyrrolidone hydrotribromide in dimethyl sulfoxide yielded the corresponding chromones

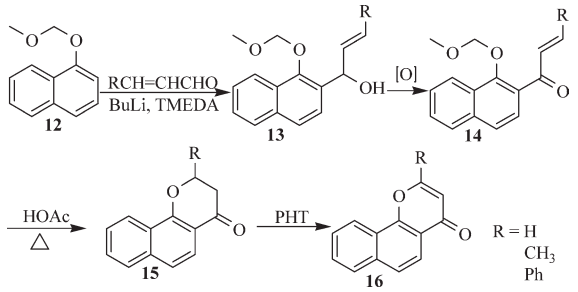
**Scheme 1**



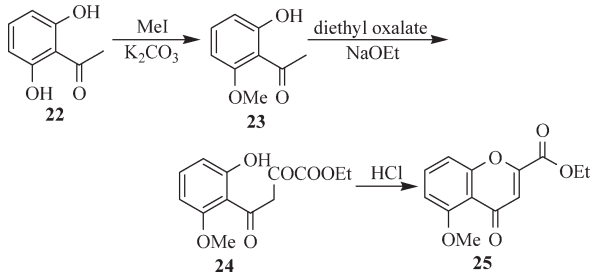
**Scheme 3**



**Scheme 4**




**Scheme 6**




(or flavones) **16**. This synthetic approach appeared general in its applicability. It has been applied to the synthesis of a series of polycyclic chromone and flavone compounds containing the naphthalene and pyrene ring systems that hold promise as agents for the chemoprevention of cancer.

***Methanesulfonylchloride as a catalyst.*** In 2001, Ismail and Abd El Aziem [26] reported the synthesis of the new 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones (**21**) starting from 2-hydroxy-4-methoxyacetophenone (**17**) according to Scheme 5. The key step in this synthesis involved the alkylation with alkyl halide using potassium tertiary butoxide of 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**18**) which was prepared by the protection of the hydroxyl group of **17** using *t*-butyldimethylsilylchloride. The *O*-silyl protected alkylacetophenone derivatives (**19**) were, therefore, treated with tetra-*n*-butylammonium fluoride to produce the corresponding 2′-alkyl-2-hydroxy-4-methoxyacetophenone (**20**) in good yield. Cyclization of the alkyl derivatives **20** was achieved via methanesulfonylchloride using boron trifluoride diethyl etherate at 0°C [27] to give the desired 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones (**21**). This reaction conditions was relatively mild, and the reaction yield was also relatively high.

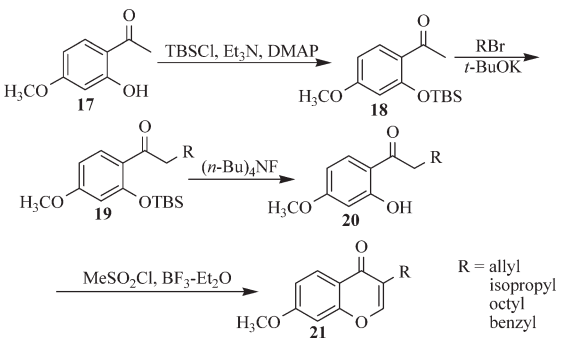
***Hydrochloric acid as a catalyst.*** In 2003, Boumendjel and coworkers [28] obtained chromone **25** in three steps starting from 2,6-dihydroxyacetophenone (Scheme 6); this time they used concentrated hydrochloric acid as a catalyst in the ring closure. Treatment of the 2,6-dihydroxyacetophenone (**22**) with methyl iodide gave 2-hydroxy-6-methoxyacetophenone (**23**). Condensation of **23** with diethyl oxalate in the presence of sodium ethoxide in EtOH and then concentrated HCl catalysted cyclization afforded ester **25**, and a lot of reactions have adopted this approach [29–32].

***Para toluene sulfonic acid as a catalyst.*** In 2004, Sabui and Venkateswaran [33] synthesized the chromone using PTS as a catalyst in the ring closure (Scheme 7). Condensation of the acetophenone **26** [34] with ethyl formate in the presence of sodium hydride followed by dehydration of the resulting chromanol furnished the 6-methoxy-7-methyl chromone **28** in an overall yield of 85%. This catalyst was especially suitable in the phenolic hydroxyl and aldehyde condensation cyclization.

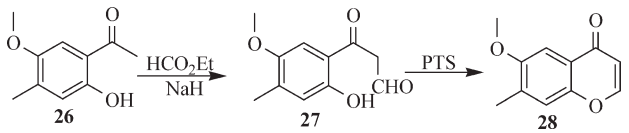
***Triflic anhydride as a catalyst.*** In 2005, Griffin *et al*. [4] used triflic anhydride as a catalyst to construct the chromone ring (Scheme 8). Reaction of the appropriate 2-hydroxyarylcarboxylate esters **31**, which were prepared by carboxylation-esterification of the corresponding phenols **30** by standard methods, with *N*-acetylmorpholine, *N*-acetylthiomorpholine, or *N*-acetylpiperidine afforded the β-ketoamides **32**, and ring closure to the required chromones **33** was readily effected with triflic anhydride. Although the effect of this catalyst was better, but higher prices due to trifluoroacetic anhydride, making its practical application being limited.

***Phosphorus oxychloride as a catalyst.*** This catalyst is most widely used in the chromone ring closure, and there are two ways in construction the chromone ring. One approach is that phenolic compounds and carbonyl compounds are refluxed in phosphorus oxychloride, another approach is that the phenolic compounds with the acyl side chain is refluxed in phosphorus oxychloride. In 2005, Balbi and coworkers [35] synthesized the

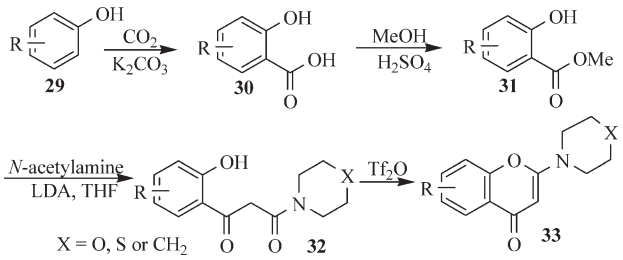
**Scheme 5**




**Scheme 7**



**Scheme 8**



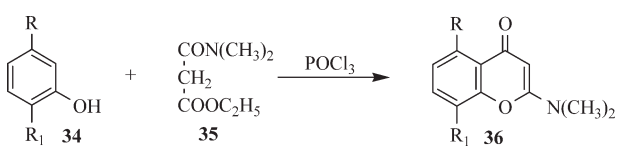

chromone ring via $POCl_3$ as a catalyst (Scheme 9). **36** was obtained by following their well-established method from substituted phenols and *N*,*N*′-(dimethyl)malonamide in the presence of phosphorus oxychloride [36,37].

In 2008, Yang and coworkers [38] prepared the 6-hydroxy-3-carbaldehyde chromone via a Vilsmeier reaction in another way (Scheme 10). 6-hydroxy-4-chromone-3-carbaldehydes **40** were easily prepared by the reaction of 2,5-dihydroxy-acetophenone **39** with DMF in $POCl_3$ solution [39–45].

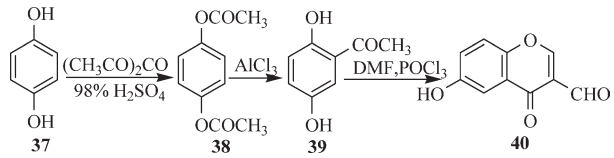
***Perchloric acid as a catalyst.*** In 2006, Langer and coworkers [46] synthesized chromone using perchloric acid as a catalyst (Scheme 11). The reaction of 3-formylchromones **41** with $Me_3SiOTf$ (**42**) and 1,3-bis(silyl enol ether) **43** afforded the 4-(2-hydroxybenzoyl)phenols **44**. The formation of the products could be explained by a domino ''Michael–retro-Michael–Aldol'' reaction. Compounds **44** were transformed into the novel chromones **45** by treatment with triethyl orthoformate and perchloric acid [47–49].

***Sulfuric acid as a catalyst.*** In 2007, Cushman and coworkers [50] reported the synthesis of chromone using $H_2SO_4$ as a catalyst (Scheme 12). Commercially available 2-hydroxy-6-methoxyacetophenone (**23**) was subjected to Elbs oxidation using sodium persulfate and aqueous sodium hydroxide to yield the substituted acetophenone **46**, followed by regioselective methylation using anhydrous potassium carbonate and dimethyl sulfate in acetone to afford 6-hydroxy-2,3-dimethoxyacetophenone (**47**) in 53% yield in two steps. The generation of the dilithium dianion **48** of the acetophenone **47** was ensured by treatment with four equivalents of lithium hexamethyldisilylazide in THF. Treatment of dilithium dianion **48** with commercially available 2,6-dimethoxybenzoyl chloride, followed by acidification, afforded the

**Scheme 9**




**Scheme 10**



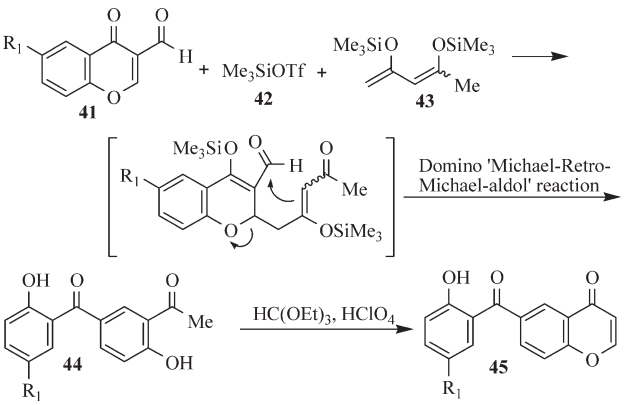

β-diketone intermediate **49**, which was used without purification for cyclization to zapotin (**50**) with the catalyst of $H_2SO_4$ [51–55]. This $H_2SO_4$ as catalyst and HCl as catalyst means were basically the same.

**Base as catalyst in chromone ring closure.** Although base as catalyst in the chromone ring closure is not common compared with acid, sometimes it can really bring some satisfactory results.

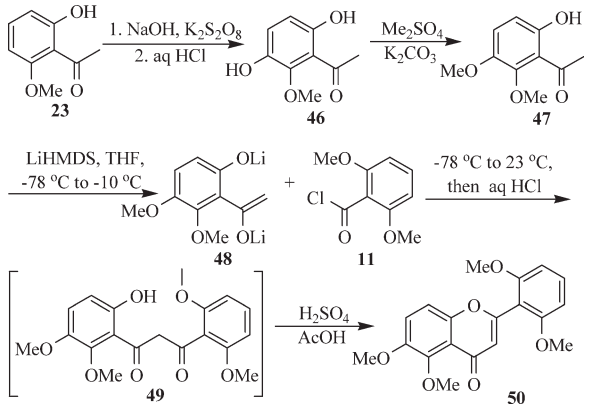
***Sodium formate as a catalyst.*** In 2001, Wallace and coworkers [56] reported the synthesis of enantiomerically pure (*S*)-2-methylchroman-4-one **53** based on the following procedure (Scheme 13): Treating methyl 5-methyl-salicylate **51** with an excess of lithium diisopropylamide followed by the lithium derivative of (*R*)-(+)-methyl *p*-tolyl sulfoxide gave the desired ketosulfoxide (*R*)-**52** directly and in good yield. Then, the formation of the chromone **53** was achieved conventionally using acetic formic anhydride and sodium formate [57,58]. But this method is only applicable to compounds with ketosulfoxide.

***Sodium methoxide as a catalyst.*** In 2001, Khan and coworkers [59] synthesized the chromone ring via cyclization on treating with 0.1*M* NaOMe solution (Scheme 14). The compounds **54** on bromination with the same reagent in $CH_2Cl_2$ gave the brominated products **55** in good yields. Various flavones (**57**) were obtained in good yields from the brominated products **55** by dehydrobromination followed by cyclization on treatment with 0.1*M* sodium methoxide solution. The main feature

**Scheme 11**



**Scheme 12**

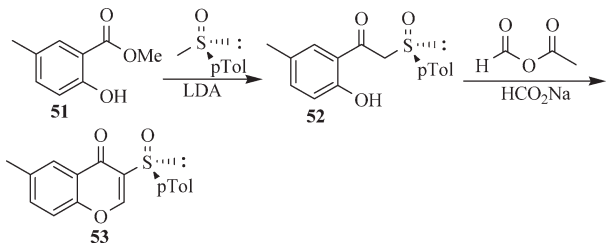


of this reaction was the bromination of the unsaturated olefinic bond.

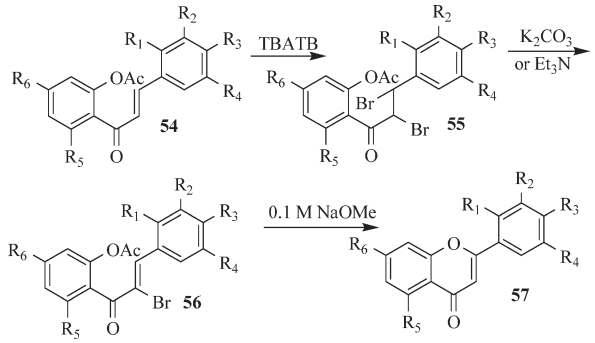
***Sodium hydride as a catalyst.*** In 2003, Samat and coworkers [60] developed the synthesis of a series of new nine 3-benzoyl-2-benzylchromones through a classical and an optimized Kostanecki–Robinson method involving an *o*-hydroxyphenyl-β-diketone **59** and an acid anhydride **61** (Scheme 15). Most of the *o*-hydroxyphenyl-β-diketones **59** were obtained using a traditional method involving a reaction between *o*-hydroxy acetophenone **58** and acid chloride, followed by a Baker–Venkataraman rearrangement. The homoveratric anhydride **61** prepared from the reaction of dicyclohexylcarbodiimide with the corresponding acid **60** had been used to perform the Kostanecki–Robinson reaction. In this last reaction, Sodium hydride was used also as base to favor the formation of the expected chromone **62** instead of byproducts. However, this method had one drawback, the anhydride was not easy to prepare, especially for the aromatic acid anhydride.

***Pyridine as a catalyst.*** In 2005, Lee *et al*. [61] synthesized the chromone using pyridine as a catalyst in the ring closure (Scheme 16). Dioxane-fused propiophenone (**64**) was prepared by Fries rearrangement of compound **63**, which was obtained from benzodioxane via two-step sequence, Friedel-Craft acylation with propionyl chloride and Bayer–Villiger oxidation. Chromone rings were

**Scheme 13**



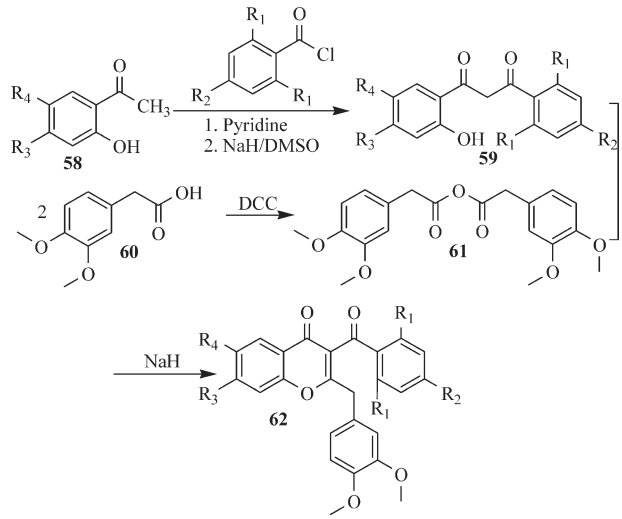
**Scheme 14**



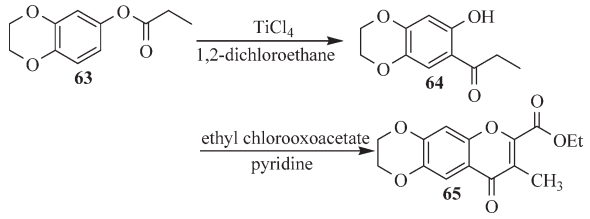
constructed by acylation of 2-hydroxyphenones **64** with ethyl chlorooxoacetate followed by *in situ* cyclization of the resulting esters in the presence of pyridine to provide compounds **65** [62]. This method of using pyridine as a catalyst was more suitable to acyl phenols and chloroacetyl carboxylic acid esters in the chromone ring closure.

***Sodium acetate as a catalyst.*** In 2005, Gabbutt and coworkers [63] synthesized 3-acylchromones by acylation of 2′-hydroxydibenzoylmethane with acid anhydrides in the presence of sodium acetate (Scheme 17). The requisite starting materials, 2′-hydroxydibenzoylmethanes **67**, were easily available by *O*-acylation of 2′-hydroxyacetophenone followed by Baker–Venkataraman (BV) rearrangement under standard conditions [64]. Acylation of the 1,3-diketones **67** with acetic anhydride gave the 2-alkyl-3-aroylchromones **68** in high yields [65]. This condensation reaction was not only applicable to acetic anhydride but also for other acid anhydride such as propionic anhydride and butyric anhydride.

**Scheme 15**



**Scheme 16**

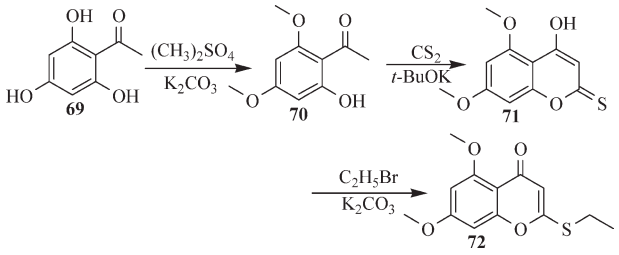



***Potassium tert-butoxide as a catalyst.*** In 2007, Wu and coworkers [66] prepared the chromone ring using potassium *tert*-butoxide in the ring closure during their total synthesis 6-demethoxycapillarisin (Scheme 18). Methylation of **69** with dimethyl sulfate in the presence of $K_2CO_3$ in $CH_3COCH_3$ afforded **70**. The intermediate **70** was readily reacted with $CS_2$ in the presence of *t*-BuOK in toluene to provide **71**. Without purification, the lactone **71** reacted with $C_2H_5Br$ and $K_2CO_3$ in $CH_3COCH_3$ to afford the key product **72** [67,68]. This reaction was very useful, which laid the foundation to expand the SAR of chromone ring with sulfur atom in the side chain.

***$Cs_2CO_3$ as a catalyst.*** In 2008, Arai *et al*. [69] described a practical and useful synthesis of heterocyclic-substituted chromones (Scheme 19) and also developed a one-pot synthesis by Michael aldol reaction of chromone derivatives bearing heterocycle units. The 2,3-heterocyclic-substituted chromones **75** were obtained in one step, as shown in scheme 19, 4′-benzyloxy-2′-hydroxyacetophenone (**73**) reacted with heterocyclic aldehydes **74** to give 2,3-disubstituted chromone **75** in high yield under $Cs_2CO_3$ conditions.

***Potassium carbonate as a catalyst.*** In 2009, Anwar and Hansen [70] used $K_2CO_3$ as a catalyst in the chromone ring closure during their first total synthesis of the marine natural product *all*-(*Z*)-5,7-dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl)chromone (Scheme 20). In their synthetic route, aldehyde **76** was transformed to the terminal alkyne **77** in a Colvin rearrangement in 58% yield. Addition of aldehyde **78** in THF to the anion of **77** at −78°C yielded the secondary alcohol **79** in 60% yield. Oxidation of **79** with $MnO_2$ yielded MOM-protected ketone **80** in 88% yield. Mild deprotection of **80** with HCl in EtOH at ambient temperature, followed by intramolecular Michael addition under lenient basic conditions ($K_2CO_3$, acetone), afforded the natural product **81** in 49% yield for the latter two steps [71]. This reaction using phenol hydroxyl addition to the alkyne bond was relatively classical.

**Scheme 18**

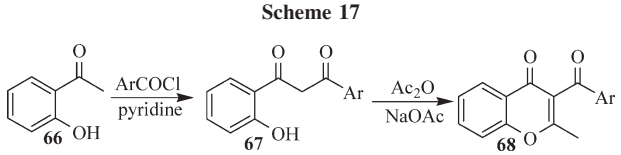



**Chromone ring closure under the microwave irradiation.** Recently, microwave irradiation [72,73] offers a considerable advantage over conventional heating because it results in substantial rate enhancements in a wide range of organic reactions. Cleaner reactions are also commonly achieved, together with improvements in yield and selectivity [74]. The increasing demand for clean and ''green'' chemical syntheses has resulted in increased use of microwave irradiation, so there have been several recent reports, describing the application of microwave irradiation to the synthesis of flavonoids.

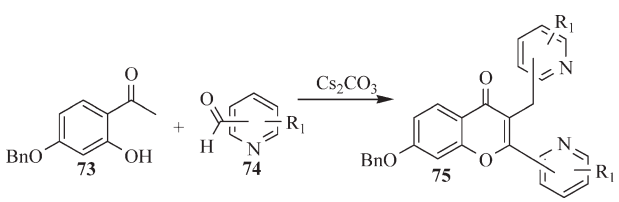
In 2005, Seijas *et al*. [75] reported an eco-friendly direct solvent-free synthesis of functionalized flavones **84** under microwave irradiation (Scheme 21). This method was valid for flavones with or without substitution in the B ring. Thus, the flavonoids were prepared from the corresponding ethyl benzoyl acetates **83** and phloroglucinol for 2–12 min of irradiation in 66–96% yields. The successful use of microwave irradiation in providing this rapid and direct route to flavones in comparison to classical procedures contributes to confirming the participation of specific effects in some microwave-assisted organic synthesis.

In 2005, Kabalka and Mereddy [76] reported a facile microwave synthesis of functionalized flavones and chromones via the cyclization of 1-(2-hydroxyaryl)-3-aryl-1,3-propanedione (Scheme 22). In their study, the intermediate 1,3-propanediones **85** were synthesized in 5 min via dehydrative cyclization to the corresponding flavones and chromones **86** in ethanol, in the presence of $CuCl_2$ under microwave irradiation.

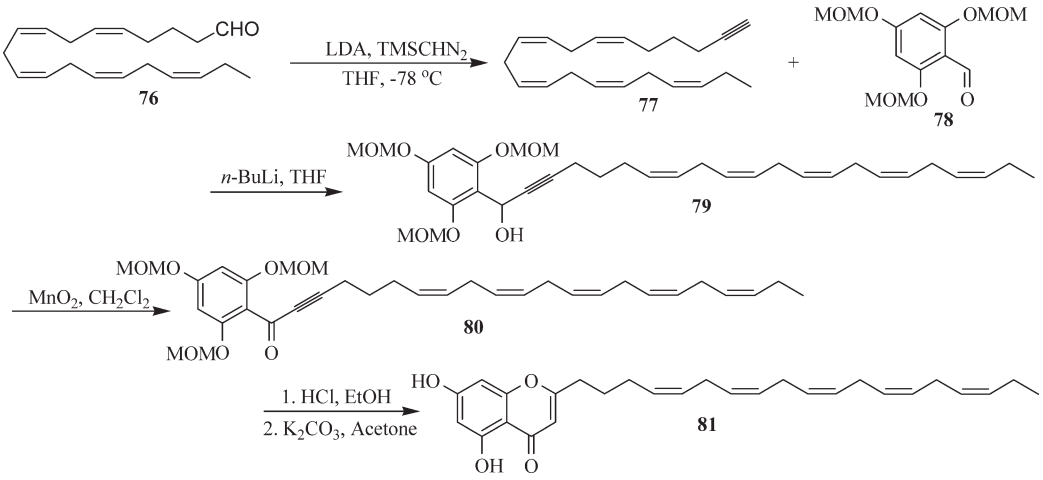
**Scheme 17**




**Scheme 19**



**Scheme 20**




In 2009, Luthman and coworkers. [77] reported a base-promoted condensation between 2-hydroxyacetophenones **87** and aliphatic aldehydes **88** (Scheme 23); they optimized the reaction to afford 2-alkyl-substituted 4-chromanones **89** in an efficient manner using microwave heating. Performing the reaction using diisopropylamine in EtOH at 170°C for 1 h gave high yield in 88%. The 4-chromanones could be further converted into highly functionalized 2,3,6,8-tetrasubstituted chromones in which a 3-substituent (acetate, amine, or bromine) was introduced via straightforward chemical transformations.

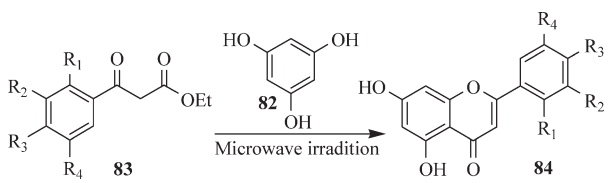
**Chromone ring closure via solid-support.** In recent years, solid-phase chemical reaction has appeared many advantages including good selectivity, high yield, simple operation, and no pollution, and some researcher has applied this method in chromone synthesis.

***Via solid-support catalysts.*** In 2002, Blanco and coworkers [78] studied the catalytic performance of MPA ($(H_3PMo_{12}O_{40}\cdot nH_2O)$ and TPA ($H_3PW_{12}O_{40}\cdot nH_2O$) (Scheme 24), both bulk or supported on silica (S), to obtain flavones and substituted chromones **96** from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones **95**, using glacial acetic acid as solvent at 90°C. The result showed that the conversion to flavones and substituted chromones was in general higher in homogeneous phase than that observed for the supported catalysts. Nevertheless, the use of the supported catalysts enabled an easy separation and recovery of the catalyst for its immediate reuse without any important decrease of the catalytic activity. In addition, the unchanged starting material may be recycled to the reactor because it was almost quantitatively recovered and secondary products were not practically formed.

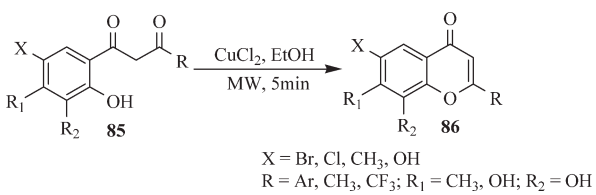
In 2005, van Lier and coworkers [79] explored silica gel-supported $InBr_3$ or $InCl_3$ (15–20 mol %) as a new solid-support catalysts for the facile and efficient oxidation, under solvent free conditions (Scheme 25), of 2′-hydroxychalcones **97** to yield the corresponding flavones **98** in >80% yield. The catalysts were easily prepared, stable, and efficient under mild reaction conditions.

Trifluoromethanesulfonic acid (TFMS) is known to be a strong acid, and it is used in many organic reactions such as Friedel Crafts reactions, polymerization, Koch carbonylation, among others [80]. However, the recovery of the triflic acid from the reaction mixture results in the formation of large amounts of waste [80]. So, in 2007, Romanelli and coworkers described the synthesis and characterization of TFMS supported on mesoporous titania [81] using urea as a low-cost, pore-forming agent (Scheme 26), via HCl catalyzed sol–gel reactions. The acidic characteristics of the solids were determined by potentiometric titration with *n*-butylamine. The use of these solid catalysts provided interesting yields in the cyclization reaction of 1-(2-hydroxyphenyl)-3-aryl-1,3-

**Scheme 21**

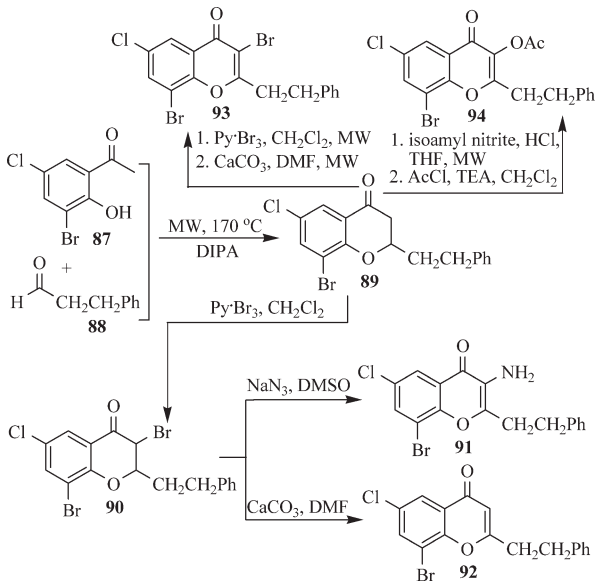



**Scheme 22**




X = Br, Cl, $CH_3$, OH
R = Ar, $CH_3$, $CF_3$; $R_1 = CH_3$, OH; $R_2$ = OH

**Scheme 23**

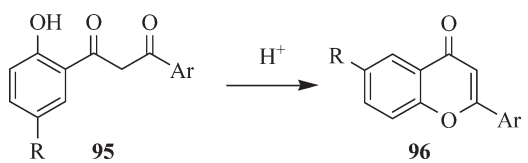



propanediones **99** to flavone **100**, also leading to an easy separation and recovering of the catalysts for further use.

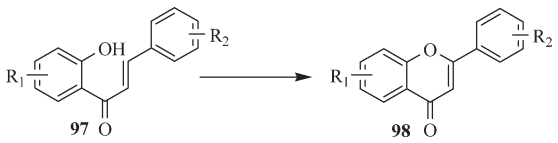
In 2009, Romanelli and coworkers [82] also prepared the $TFMSC_1$ and $TFMSC_2$ catalysts by adsorption of TFMS on two activated carbons with different textural properties used as supports (Scheme 27). The $TFMSC_2$ catalyst used as solid catalyst provided interesting yields in the cyclization reaction of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones **101** to flavones and chromones **102**, also leading to an easy separation and recovery of the catalysts for further use. Moreover, as a significant decrease of the catalytic activity was not observed, they can be recycled without any activity loss.

***Solid-supported synthesis.*** In 2001, Borrell *et al*. [83] developed procedures for the synthesis of the solid-supported synthetic equivalents of chromones (Scheme 28). Treatment of the Wang chloro resin in DMA with 3 equiv of *o*-hydroxyacetophenone **103** and 3 equiv of NaOMe at 80°C overnight quantitatively afforded **104**. Compound **104** was then treated with DMF and $POCl_3$ under Vilsmeier–Haack reaction conditions affording chromone **105** as the major product. In this way, heterocyclic libraries could be effectively and rapidly synthesized.

**Scheme 24**

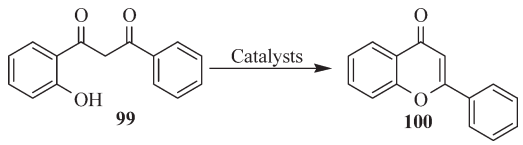



**Scheme 25**

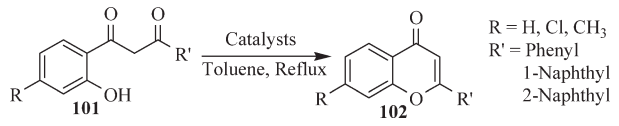


In 2004, Albericio and coworkers [84] described an effective solid-phase preparation of the pharmaceutically interesting 4*H*-2-(3-hydroxy-4-methoxyphenyl)-naphtho [1,2-*b*]pyran-1-one system from an anchored bisarylacetylene (Scheme 29). The coupling reaction between the resin **107** and acetylene **106** with $PdCl_2(PPh_3)_2$, CuI as catalyst, $Et_3N$ as base, and THF as solvent cleanly afforded the resin **108**. Then *O*-silylation of the MOM methoxy group with $Me_3SiBr$ followed by demethylation via nucleophilic attack of bromide gave the *O*-trimethylsilyl derivative. This compound was susceptible to further electrophilic addition by the triple bond and trapping of the resulting carbocation intermediate by atmospheric $H_2O$ then generated the keto group. Further oxidation gave the anchored compound **109**. Final cleavage with $AlCl_3$ rendered **110**. Through this solid-phase strategy, the quite rare 2-(aryl)naphtho[1,2-*b*]pyran-1-one was effectively synthesized. These compounds, like other polycondensed heterocyclic systems bearing electrondonating substituents, are of undoubted pharmaceutical interest. This solid-phase synthetic strategy will facilitate the preparation of libraries with applications in drug discovery.

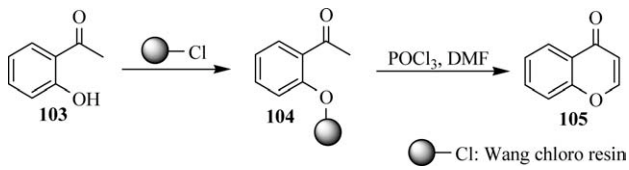
**Scheme 26**



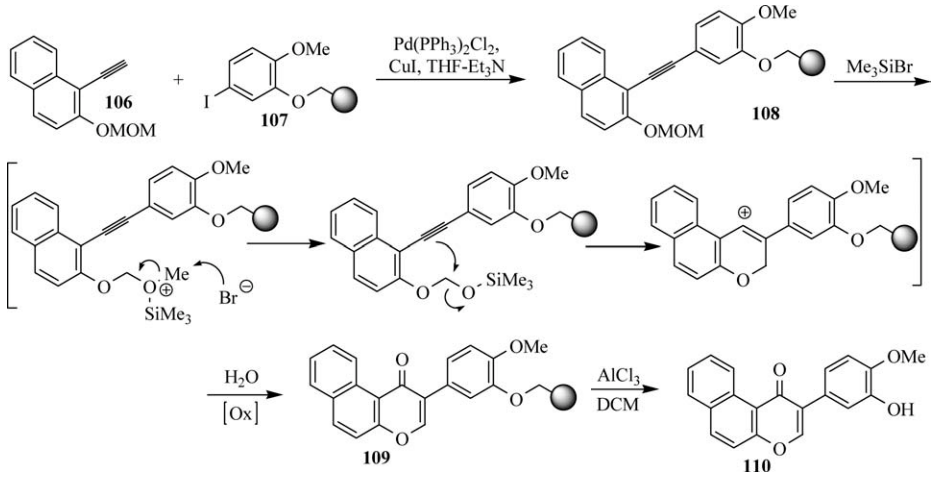

**Scheme 27**




**Scheme 28**



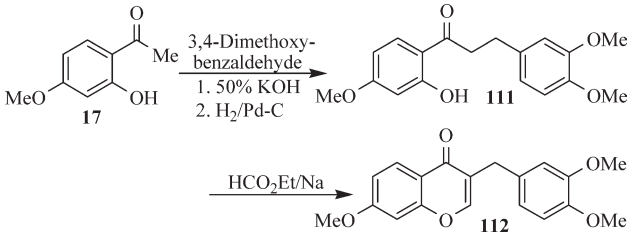
**Scheme 29**



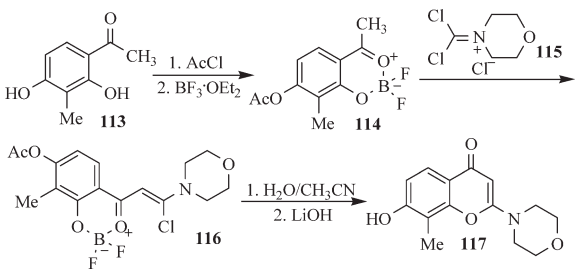
**Chromone ring closure through other methods.** Besides the above acid catalyst, base catalyst, microwave irradiation, and solid-supported synthesis in ring closure, there are many other catalysts and reaction conditions in this chromone construction.

***Sodium as a catalyst.*** In 1993, Davis and Chen [85] synthesized the chromone through a highly efficient procedure catalysted by sodium sand (Scheme 30). Heating 2-hydroxy-4-methoxyacetophenone (**17**) with 3,4-dimethoxybenzaldehyde in methanol using 50% aqueous KOH followed by hydrogenation over 10% palladium on activated carbon gave 2′-hydroxy-4′,3,4-trimethoxydihydrochalcone (**111**) in 89% overall yield. Treatment of **111** in ethyl formate with sodium sand at 0°C afforded chromone **112** in high yield. However, this reaction was not practical because the hot sodium sand was very dangerous during the reaction.

**Scheme 30**



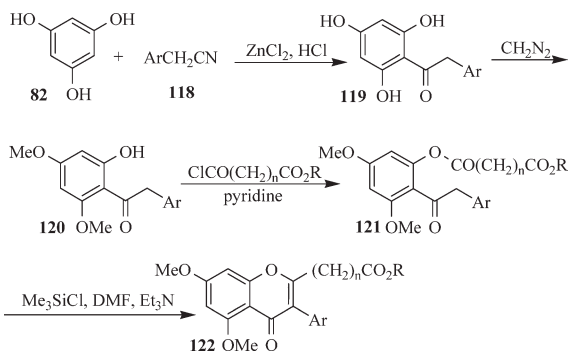
**Scheme 31**



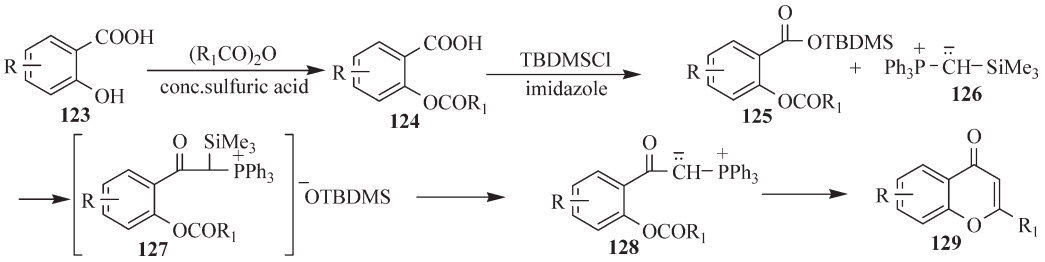
***Through basic hydrolysis.*** In 1993, Morris *et al*. [86] accomplished the preparation of chromone utilizing a novel synthesis of 2-aminochromones **117** via the condensation of $BF_2$ complexes of 2'-hydroxyacetophenones with phosgeniminium salts [87] (Scheme 31). Acetylation of **113** followed by treatment with $BF_3{\cdot}OEt_2$ afforded the $BF_2$ complex **114** in 76% overall yield. Reaction of **114** with 4-(dichloromethylene)morpholinium chloride (**115**) (65°C, 24 h) produced **116**. Liberation of the $BF_2$ complex ($H_2O$, $CH_3CN$) promoted cyclization to afford chromone **117** upon basic hydrolysis of the acetate protecting group (67% from **114**). Through this method, a side chain containing nitrogen atoms could be introduced into the chromone ring.

***$Me_3SiCl$ as a catalyst.*** In 1999, Pelter *et al*. [88] reported the synthesis of chromone ring via $Me_3SiCl$/DMF/$Et_3N$ (Scheme 32). Phloroglucinol **82** was reacted with 4-methoxybenzyl cyanide **118** by a modified procedure using catalytic $ZnCl_2$ to give **119** in 91% yield. Methylation of **119** with diazomethane in methanol readily gave **120** in which only the 2-hydroxyl group

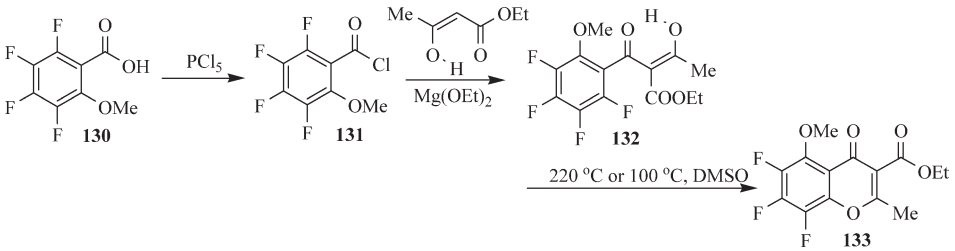
**Scheme 32**



**Scheme 33**



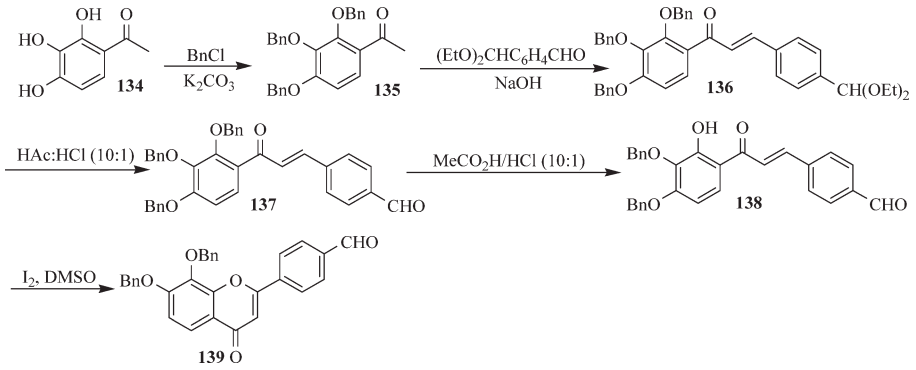
**Scheme 34**



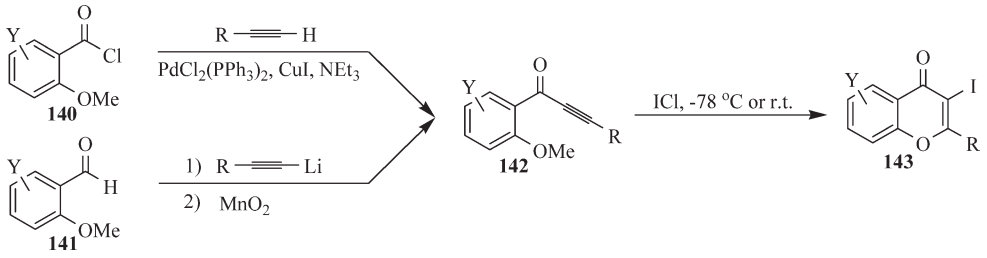
was free. Acylation of **120** gave the required esters **121**. A simple modification using $Me_3SiCl/DMF/Et_3N$ converted **121** to **122** in high yield.

***Via intramolecular ester carbonyl olefination.*** In 2000, Kumar and Bodas [89] reported a new and simple route to 4*H*-chromen-4-ones via intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane (Scheme 33). Salicylic acid or its substituted derivative **123** was converted into its *O*-acyl(aroyl) derivatives **124** by reaction with the corresponding anhydride. Compound **124** was then treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole to furnish the corresponding silyl ester **125** in excellent yields. When a mixture of compound **125** and

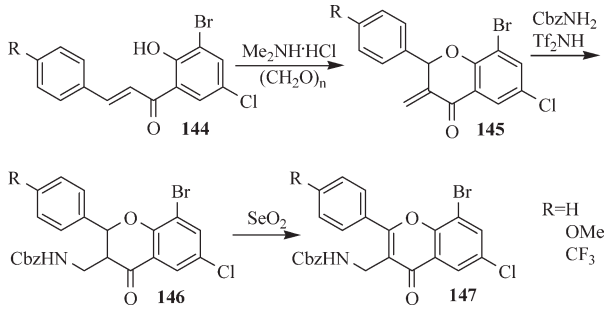
**Scheme 35**



**Scheme 36**



**Scheme 37**



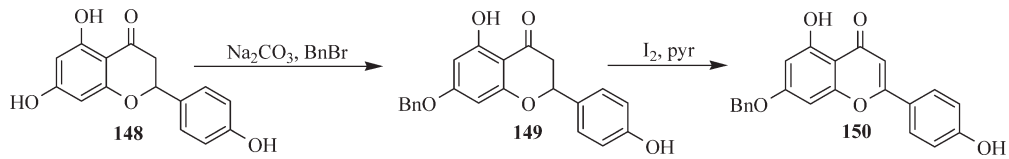

(trimethylsilyl)methylenetriphenylphosphorane **126** was heated in refluxing THF, the desired chromones **129** was obtained in 55–80% yields. This is the first report of chromone synthesis via intramolecular Wittig ester carbonyl olefination using (trimethylsilyl) methylenetriphenyl-phosphorane.

***Via heating.*** In 2001, Saloutin and coworkers [90] described the acylation of ethyl acetoacetate by the fluorobenzoyl chloride and synthesis of novel flurobenzopyran-2(4)-one (Scheme 34). 2-Dimethoxy-3,4,5,6-tetrafluorobenzoyl chloride **131** was obtained by heating the corresponding acid **130** with an excess of phosphorus pentachloride. Then, the interaction of fluorobenzoyl chloride **131** with ethyl acetoacetate in the presence of magnesium ethoxide resulted in β,β′-dioxaester **132**, which readily cyclized into chromone **133** on heating in the absence of solvents or in DMSO. The cyclization proceeded through intramolecular substitution of the *o*-fluorine atom in the fluorophenyl substituent.

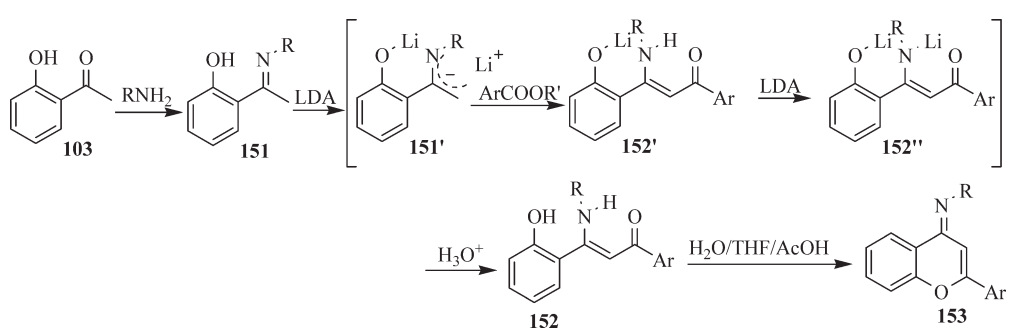
***Iodine as a catalyst.*** In 2004, Tomé and coworkers [91] reported the synthesis of chromone through iodine as a catalyst (Scheme 35). Benzylation of 2′,3′,4′-trihydroxyacetophenone **134** with benzyl chloride in the presence of potassium carbonate afforded the corresponding 2′,3′,4′-tribenzyloxy-acetophenone **135** in 90% yield. This compound was condensed with terephthalaldehyde mono(diethyl acetal) to give chalcone **136**. Hydrolysis of the acetal group furnished the formylchalcone **137**. Selective debenzylation of the 2-benzyloxy group was achieved by the treatment of **137** with a mixture of acetic acid and concentrated hydrochloric acid (10:1) for 1 h at 40°C. Finally, formylflavone **139** was obtained by oxidative cyclization of **138** in refluxing dimethylsulfoxide with a catalytic amount of iodine. This approach was widely used in chromone ring closure, and many synthesis have adopted this approach [92–95].

***Via ICl-induced cyclization.*** In 2006, Larock and coworkers [96] described the ICl-induced cyclization of heteroatom-substituted alkynones **142** (Scheme 36); this method provided a simple, highly efficient approach to various 3-iodochromones **143**. The 2-methoxyaryl-containing alkynones required were readily prepared in one or two steps by two complementary methods: (1) the palladium/copper-catalyzed Sonogashira coupling of an acid chloride **140** with a terminal acetylene at room temperature or 50°C [97] or (2) the addition of a lithium acetylide to an aldehyde **141**, followed by oxidation of the resulted secondary alcohol by activated $MnO_2$ [98]. This process was run under mild conditions, tolerated various functional groups, and generally provided chromones in good to excellent yields.

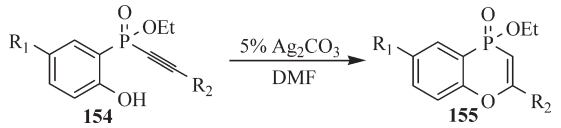
**Scheme 38**




**Scheme 39**



**Scheme 40**




***Under Mannich conditions.*** In 2007, Luthman and coworkers [99] developed an efficient synthetic route to Cbz-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromones **147** (Scheme 37). In their synthetic route, 3-Aryl-1-(3-bromo-5-chloro-2-hydroxyphenyl)-2-propen-1-one **144** was reacted under Mannich conditions yielding 2-aryl-8-bromo-6-chloro-3-methylenechroman-4-one **145**, which was further converted to the target compound **147** via an aza-Michael reaction followed by an $SeO_2$ oxidation [100–103]. This procedure represented a new method to introduce a primary aminomethyl group at the 3-position of a 2-arylchromone scaffold.

***Through base-induced elimination.*** In 2009, Rizzacasa and coworkers [104] described the synthesis of chromone through Iodination of naringenin followed by base-induced elimination (Scheme 38). This began with selective benzylation of naringenin (**148**) on the more acidic C7 phenol to afford benzyl ether **149**. Iodination followed by base-induced elimination gave the flavone **150** in a reasonable yield for the two steps.

**Synthesis of heterocycle analog of chromone.** The chromones have gained considerable synthetic and pharmacological interest for a long time because of their diverse biological activities, and recent studies have indicated that a lot of natural heterocycle analog containing phosphorus, sulphur, and nitrogen also show the expected bioactivity, so many synthesis of heterocycle analog of chromone have been reported with high regioselectivity and good yields.

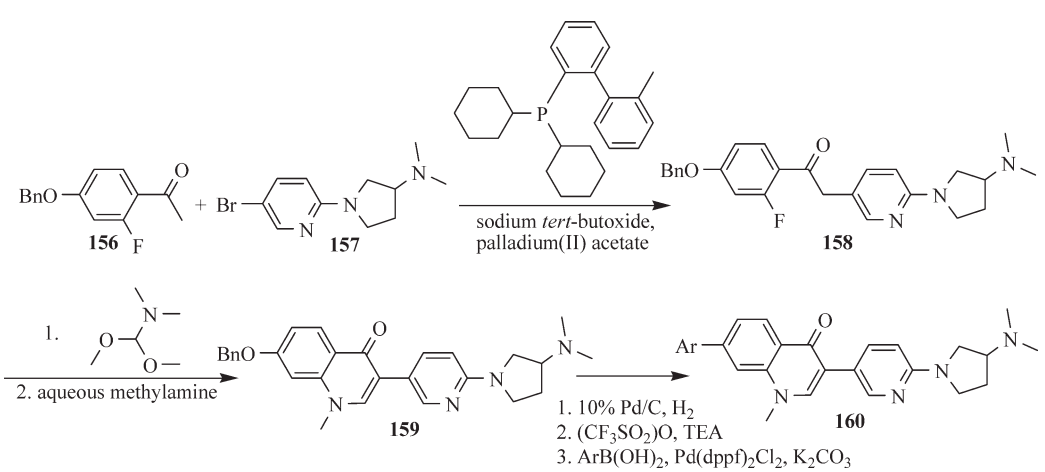
***Synthesis of 4H-Chromen-4-ylidenamines.*** 4*H*-Chromen-4-ylidenamines **153** were derivatives of chromones, that have awakened new interest because the simplest of them (2-phenyl-*4H*-chromen-4-imine), has been used [105] for treatment of cell proliferative diseases and for its antihypoxic, hypotensive, and antiallergic properties. So, in 2000, Palmieri's group [106] described a method to obtain 4*H*-chromen-4-ylidenamines **153** (Scheme 39). The reaction of *o*-imidoyl phenol dianions **151′** with aromatic esters and subsequent acid cyclization of the 3-(2-hydroxyphenyl)-3-(amino)-1-phenylprop-2-en-1-ones **152** afforded *4H*-chromen-4-ylidenamines **153** in satisfactory yields, a class of compounds of renewed interest.

***Synthesis of phosphachromones.*** Because there was a remarkable similarity in reactivity and bioactivities between the carbon species and their phosphorus counterparts [107,108], one can anticipate that the phosphachromone analog of chromone would have potential bioactivities similar to those of chromones, so in 2008, Ding and coworkers [109] reported a novel $Ag_2CO_3$-catalyzed cyclization reaction of *O*-hydroxyphenylethynylphosphinates **154** to phosphachromones **155** with high regioselectivity and good yields (Scheme 40), which provided an effective approach to synthesize the new kind of phosphorus heterocycles.

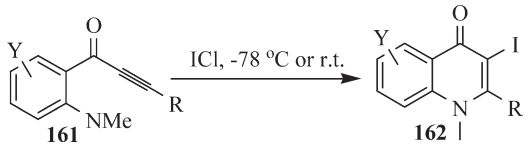
***Synthesis of quinolones.*** In 2006, Dyck and coworkers [110] reported the synthesis of the quinolone derivatives (Scheme 41). Bromopyridine **157** was coupled to 4′-benzyloxy-2′-fluoroacetophenone **156** to provide **158**. Aminomethylenation with dimethylformamide dimethyl acetal provided the precyclization intermediate which, upon reaction with methylamine, provided the quinolone core (**159**). Removal of the benzyl protecting group gave the phenol, which was converted to the triflate and coupled with aryl boronic acids to provide the target quinolones **160**.

In 2006, Larock and coworkers [96] described the ICl-induced cyclization of nitrogen-substituted alkynones **161** to afford the quinolones **162** in good to excellent yields (Scheme 42).

**Scheme 41**



**Scheme 42**




In 2008, Nam and coworkers [111] reported the synthesis of quinolinone as they designed and synthesized the 4-quinolinone 2-carboxamides as calpain inhibitors (Scheme 43). Diethyl oxalpropionate (**163**) was condensed with aniline in acetic acid to give anilino-maleate **164**. Compound **164** was heated at 250°C in mineral oil to form the cyclized product, quinolinone **165**.

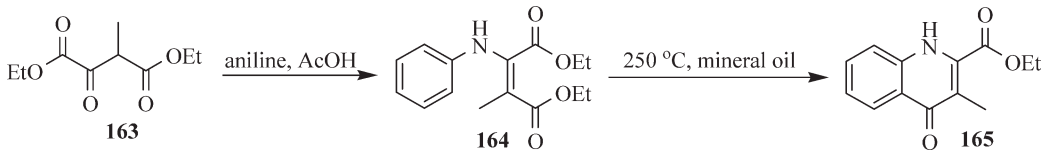
***Synthesis of thioflavones.*** In 2004, Kataoka *et al*. [112] reported the synthesis of thioflavones as they studied the SARs of thioflavone derivatives as specific inhibitors of the ERK-MAP kinase signaling pathway (Scheme 44). Condensation of benzaldehydes **166** with α-benzoyl sulfoxide **167** gave α-sulfinyl enones **168** in good yields. Cyclization of **168** followed by debenzylation was performed by the treatment with formic acid at 5°C to give 3-(methylsulfinyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-ones **169** as a mixture of diastereoisomers. Refluxing the diastereomer mixtures of **169** in benzene caused the elimination of methanesulfenic acid to form thioflavones **170**.

In 2006, Larock and coworkers [96] described the ICl-induced cyclization of sulphur-substituted alkynones **171** to give various 3-iodo-thiochromones **172** in good to excellent yields (Scheme 45).

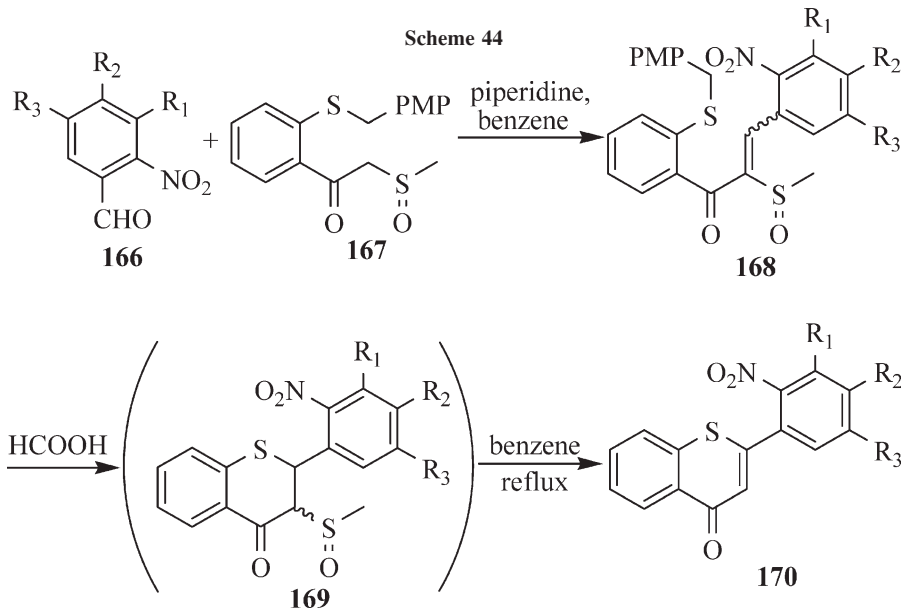
## CONCLUSIONS

Chromone derivatives have high potential in drug discovery. Synthesis of large compound libraries is a general trend in a modern drug discovery process. Furthermore, computer-aided drug design can be used to perform virtual screening before the compounds are synthesized. Both methodologies require rapid synthesis of the compounds preferably from a limited number of starting materials. So, in recent years, a lot of synthetic method to construct the chromone ring appeared. In this review, some recent improvements of the classical synthetic methods and of some nonclassical methods to obtain simple oxygenated chromones have been reported, which includes acid as catalyst, base as catalyst, microwave irradiation assisted synthesis, solid-supported synthesis, and other methods. Furthermore, recent studies have indicated that a lot of natural heterocycle analog containing phosphorus, sulphur, and nitrogen also show the expected bioactivity, so many synthesis of heterocycle analog of chromone have been reported with high regioselectivity

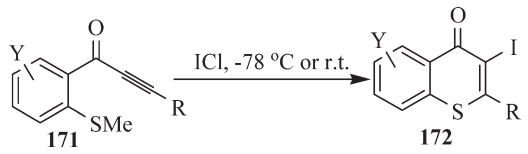
**Scheme 43**




**Scheme 44**



**Scheme 45**




and good yields. So, the strategies for synthesis of heterocycle analog containing phosphorus, nitrogen, and sulfur are also summarized in this review. We hope this review will stimulate interest in the synthesis of chromone with biological activities in the near future.

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## REFERENCES AND NOTES

[1] Hepworth, J. D. In Comprehensive Heterocyclic Chemistry; Boulton A. J., McKillop, A., Ed.; Pergamon Press: Oxford, 1984; Vol.3, pp 835–840.

[2] Kaur, G.; Stetler-Stevenson, M.; Sebers, S.; Worland, P.; Sedlacek, H.; Myers, C.; Czech, J.; Naik, R.; Sausville, E. J Natl Cancer Inst 1992, 84, 1736.

[3] Leahy, J. J. J.; Golding, B. T.; Griffin, R. J.; Hardcastle, I. R.; Richardson, C.; Rigoreau, L.; Smith, G. C. M. Bioorg Med Chem Lett 2004, 14, 6083.

[4] Griffin, R. J.; Fontana, G.; Golding, B. T.; Guiard, S.; Hardcastle, I. R.; Leahy, J. J. J.; Martin, N.; Richardson, C.; Rigoreau, L.; Stockley, M.; Smith, G. C. M. J Med Chem 2005, 48, 569.

[5] Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. J Pharmacol Sci 2004, 96, 229.

[6] Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W. Tetrahedron Lett 1999, 40, 2469.

[7] Bennett, C. J.; Caldwell, S. T.; McPhail, D. B.; Morrice, P. C.; Duthie, G. G.; Hartley, R. C. Bioorg Med Chem 2004, 12, 2079.

[8] Krishnamachari, V.; Levine, L. H.; Zhou, C.; Pare, P. W. Chem Res Toxicol 2004, 17, 795.

[9] Marder, M.; Viola, H.; Bacigaluppo, J. A.; Colombo, M. I.; Wasowski, C.; Wolfman, C.; Medina, J. H.; Rúveda, E. A.; Paladini, A. C. Biochem Biophys Res Commun 1998, 249, 481.

[10] Hoult, J. R. S.; Moroney, M. A.; Payá, M. Methods Enzymol 1994, 234, 443.

[11] Parmar, V. S.; Bracke, M. E.; Philippe, J.; Wengel, J.; Jain, S. C.; Olsen, C. E.; Bisht, K. S.; Sharma, N. K.; Courtens, A.; Sharma, S. K.; Vennekens, K.; van Marck, V.; Singh, S. K.; Kumar, N.; Kumar, A.; Malhotra, S.; Kumar, R.; Rajwanshi, V. K.; Jain, R.; Mareel, M. M. Bioorg Med Chem 1997, 5, 1609.

[12] Wall, M. E. J Nat Prod 1992, 55, 1561.

[13] Fang, N.; Casida, J. E. Proc Natl Acad Sci USA 1998, 95, 3380.

[14] Fang, N.; Casida, J. E. J Nat Prod 1999, 62, 205.

[15] Galietta, L. J. V.; Springsteel, M. F.; Eda, M.; Niedzinski, E. J.; By, K.; Haddadin, M. J.; Kurth, M. J.; Nantz, M. H.; Verkman, A. S. J Biol Chem 2001, 276, 19723.

[16] Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893.

[17] Protti, S.; Mezzetti, A.; Lapouge, C.; Cornard, J. P. Photochem Photobiol Sci 2008, 7, 109.

[18] Heywang, R.; Kostanecki, S.von. Ber Dtsch Chem Ges 1902, 35, 2887.

[19] Harikrishnan, L. S.; Showalter, H. D. H. Tetrahedron 2000, 56, 515.

[20] Varma, R. S. J Heterocycl Chem 1999, 36, 1565.

[21] Wawzonek, S.; Ready, H. A. J Org Chem 1952, 17, 1419.

[22] Appleton, R. A.; Bantick, J. R.; Chamberlain, T. R.; Hardern, D. N.; Lee, T. B.; Pratt, A. D. J Med Chem 1977, 20, 371.

[23] Cairns, H.; Fitzmaurice, C.; Hunter, D.; Johnson, P. B.; King, J.; Lee, T. B.; Lord, G. H.; Minshull, R.; Cox, J. S. G. J Med Chem 1972, 15, 583.

[24] Ruhemann, S.; Stapleton, H. E. J Chem Soc 1900, 77, 1179.

[25] Harvey, R. G.; Hahn, J.-T.; Bukowska, M.; Jackson, H. J Org Chem 1990, 55, 6161.

[26] Ismail, K. A.; Abd El Aziem, T. Eur J Med Chem 2001, 36, 243.

[27] Bass, R. J. J Chem Soc Chem Commun 1976, 78.

[28] Hadjeri, M.; Barbier, M.; Ronot, X.; Mariotte, A.-M.; Boumendjel, A.; Boutonnat, J. J Med Chem 2003, 46, 2125.

[29] Koo, J. J Org Chem 1961, 26, 2440.

[30] Witiak, D. T.; Stratford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. R. J Med Chem 1971, 14, 758.

[31] Ellis, G. P.; Shaw, D. J Med Chem 1972, 15, 865.

[32] Bantick, J. R.; Cairns, H.; Chambers, A.; Hazard, R.; King, J.; Lee, T. B.; Minshull, R. J Med Chem 1976, 19, 817.

[33] Sabui, S. K.; Venkateswaran, R. V. Tetrahedron Lett 2004, 45, 983.

[34] Sabui, S. K.; Venkateswaran, R. V. Tetrahedron 2003, 59, 8375.

[35] Sottofattori, E.; Anzaldi, M.; Mazzei, M.; Miele, M.; Balbi, A.; Pyshnyi, D. S.; Zakharovab, O. D.; Abramova, T. V. Bioorg Med Chem 2005, 13, 1515.

[36] Ermili, A.; Balbi, A.; Di Braccio, M.; Roma, G. II Farmaco 1977, 32, 713.

[37] Balbi, A.; Roma, G.; Ermili, A.; Ambrosini, A.; Passerini, N. II Farmaco 1982, 37, 582.

[38] Wang, B.-D.; Yang, Z.-Y.; Qin, D.-D.; Chen, Z.-N. J Photochem Photobiol A Chem 2008, 194, 49.

[39] Harnisch, H. Liebigs Ann Chem 1972, 765, 8.

[40] Bruno, O.; Schenone, S.; Ranise, A.; Bondavalli, F.; Barocelli, E.; Ballabeni, V.; Chiavarini, M.; Bertoni, S.; Tognolini, M.; Impicciatore, M. Bioorg Med Chem 2001, 9, 629.

[41] Ishar, M. P. S.; Singh, G.; Singh, S.; Sreenivasan, K. K.; Singh, G. Bioorg Med Chem Lett 2006, 16, 1366.

[42] Wang, B.-D.; Yang, Z.-Y.; Li, T.-R. Bioorg Med Chem 2006, 14, 6012.

[43] Kumar, S.; Singh, B. K.; Pandey, A. K.; Kumar, A.; Sharma, S. K.; Raj, H. G.; Prasad, A. K.; Eycken, E. V. d.; Parmar, V. S.; Ghosh, B. Bioorg Med Chem 2007, 15, 2952.

[44] Wang, B.-D.; Yang, Z.-Y.; Crewdson, P.; Wang, D.-Q. J Inorg Biochem 2007, 101, 1492.

[45] Zhao, P.-L.; Li, J.; Yang, G.-F. Bioorg Med Chem 2007, 15, 1888.

[46] Lubbe, M.; Appel, B.; Flemming, A.; Fischer, C.; Langer, P. Tetrahedron 2006, 62, 11755.

[47] Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Pugsley, T. A.; Meltzer, L. T. J Med Chem 1991, 34, 248.

[48] Yu, D.-L.; Brossi, A.; Kilgore, N.; Wild, C.; Allaway, G.; Lee, K.-H. Bioorg Med Chem Lett 2003, 13, 1575.

[49] Ullah, E.; Appel, B.; Fischer, C.; Langer, P. Tetrahedron 2006, 62, 9694.

[50] Maiti, A.; Cuendet, M.; Kondratyuk, T.; Croy, V. L.; Pezzuto, J. M.; Cushman, M. J Med Chem 2007, 50, 350.

[51] Adams, R.; Mecorney, J. W. J Am Chem Soc 1944, 66, 802.

[52] Schönberg, A.; Sina, A. J Am Chem Soc 1950, 72, 3396.

[53] Ares, J. J.; Outt, P. E.; Randall, J. L.; Johnston, J. N.; Murray, P. D.; O'Brien, L. M.; Weisshaar, P. S.; Ems, B. L. Bioorg Med Chem Lett 1996, 6, 995.

[54] Malolanarasimhan, K.; Lai, C. C.; Kelley, J. A.; Iaccarino, L.; Reynolds, D.; Young, H. A.; Marquez, V. E. Bioorg Med Chem 2005, 13, 2717.

[55] Ono, M.; Maya, Y.; Haratake, M.; Nakayama, M. Bioorg Med Chem 2007, 15, 444.

[56] Hodgetts, K. J.; Maragkou, K. I.; Wallace, T. W.; Wootton, R. C. R. Tetrahedron 2001, 57, 6793.

[57] Krimen, L. I. Org Synth 1970, 50, 1.

[58] Solladié, G.; Gehrold, N.; Maignan, J. Tetrahedron Asymmetry 1999, 10, 2739.

[59] Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. Tetrahedron Lett 2001, 42, 8907.

[60] Rossollin, V.; Lokshin, V.; Samat, A.; Guglielmetti, R. Tetrahedron 2003, 59, 7725.

[61] Lee, K. S.; Seo, S. H.; Lee, Y. H.; Kim, H. D.; Son, M. H.; Chung, B. Y.; Lee, J. Y.; Jin, C.; Lee, Y. S. Bioorg Med Chem Lett 2005, 15, 2857.

[62] Hauser, F. M.; Dorsch, W. A. Org Lett 2003, 5, 3753.

[63] Clarke, D. S.; Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. Tetrahedron Lett 2005, 46, 5515.

[64] Wheeler, T. S. Org Syn 1963, Coll 4, 479.

[65] Huffman, K. R.; Burger, M.; Henderson, W. A.; Loy, M.; Ullman, E. F. J Org Chem 1969, 34, 2407.

[66] Tong, Y. F.; Chen, S.; Cheng, Y. H.; Wu, S. Chin Chem Lett 2007, 18, 407.

[67] Roma, G.; Braccio, M. D.; Carrieri, A.; Grossi, G.; Leoncini, G.; Signorello, M. G.; Carotti, A. Bioorg Med Chem 2003, 11, 123.

[68] Braccio, M. D.; Grossi, G.; Roma, G.; Marzano, C.; Bacchichetti, F.; Simonato, M.; Bordin, F. Il Farmaco 2003, 58, 1083.

[69] Arai, M. A.; Sato, M.; Sawada, K.; Hosoya, T.; Ishibashi, M. Chem Asian J 2008, 3, 2056.

[70] Anwar, H. F.; Hansen, T. V. Org Lett 2009, 11, 587.

[71] McGarry, L. W.; Detty, M. R. J Org Chem 1990, 55, 4349.

[72] Loupy, A. Microwave in Organic Synthesis; Wiley: New York, 2003.

[73] Varma, R. S. Green Chem 1999, 1, 43.

[74] Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. Synthesis 1998, 9, 1213.

[75] Seijas, J. A.; Vázquez-Tato, M. P.; Carballido-Reboredo, R. J Org Chem 2005, 70, 2855.

[76] Kabalka, G. W.; Mereddy, A. R. Tetrahedron Lett 2005, 46, 6315.

[77] Fridén-Saxin, M.; Pemberton, N.; Andersson, K. da S.; Dyrager, C.; Friberg, A.; Grøtli, M.; Luthman, K. J Org Chem 2009, 74, 2755.

[78] Vázquez, P.; Pizzio, L.; Romanelli, G.; Autino, J.; Cáceres, C.; Blanco, M. Appl Catal A-Gen 2002, 235, 233.

[79] Ahmed, N.; Ali, H.; van Lier, J. E. Tetrahedron Lett 2005, 46, 253.

[80] Chidambaram, M.; Curulla-Ferre, D.; Singh, A. P.; Anderson, B. G. J Catal 2003, 220, 442.

[81] Bennardi, D. O.; Romanelli, G. P.; Autino, J. C.; Pizzio, L. R. Appl Catal A-Gen 2007, 324, 62.

[82] Bennardi, D. O.; Romanelli, G. P.; Autino, J. C.; Pizzio, L. R. Catal Commun 2009, 10, 576.

[83] Borrell, J. I.; Teixidó, J.; Schulera, E.; Michelotti, E. Tetrahedron Lett 2001, 42, 5331.

[84] Cironi, P.; Albericio, F.; Álvarez, M. Tetrahedron Lett 2004, 45, 7311.

[85] Davis, F. A.; Chen, B. C. J Org Chem 1993, 58, 1751.

[86] Morris, J.; Wishka, D. G.; Lin, A. H.; Humphrey, W. R.; Wiltse, A. L.; Gammill, R. B.; Judge, T. M.; Bisaha, S. N.; Olds, N. L.; Jacob, C. S.; Bergh, C. L.; Cudahy, M. M.; Williams, D. J.; Nishizawa, E. E.; Thomas, E. W.; Gorman, R. R.; Benjamin, C. W.; Shebuski, R. J. J Med Chem 1993, 36, 2026.

[87] Morris, J.; Wishka, D. G.; Fang, Y. J Org Chem 1992, 57, 6502.

[88] Pelter, A.; Ward, R. S.; Whalley, J. L. Environ Toxicol Pharmacol 1999, 7, 217.

[89] Kumar, P.; Bodas, M. S. Org Lett 2000, 2, 3821.

[90] Kisil, S. P.; Burgart, Y. V.; Saloutin, V. I.; Chupakhin, O. N. J Fluorine Chem 2001, 108, 125.

[91] de la Torre, M. D. L.; Rodrigues, A. G. P.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. Tetrahedron 2004, 60, 3581.

[92] Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro J. A. S. Tetrahedron Lett 1994, 35, 5899.

[93] Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. J Heterocycl Chem 1996, 33, 1887.

[94] Silva, A. M. S.; Pinto, D. C. G. A.; Tavares, H. R.; Cavaleiro, J. A. S.; Jimeno, M. L.; Elguero, J. Eur J Org Chem 1998, 2031.

[95] Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. Tetrahedron 1999, 55, 10187.

[96] Zhou, C. X.; Dubrovsky, A. V.; Larock, R. C. J Org Chem 2006, 71, 1626.

[97] Tohda, Y.; Sonogashira, K.; Hagihara, N. Synthesis 1977, 11, 777.

[98] Lin, C.-F.; Lu, W.-D.; Wang, I.-W.; Wu, M.-J. Synlett 2003, 13, 2057.

[99] Wallén, E. A.; Dahlén, K.; Grøtli, M.; Luthman, K. Org Lett 2007, 9, 389.

[100] Mahal, H. S.; Rai, H. S.; Venkataraman, K. J Chem Soc 1935, 866.

[101] Mahal, H. S.; Venkataraman, K. J Chem Soc 1936, 569.

[102] Chakravarti, D.; Dutta, J. J Indian Chem Soc 1939, 16, 639.

[103] Shah, D. N.; Parikh, S. K.; Shah, N. M. J Am Chem Soc 1955, 77, 2223.

[104] Adams, T. E.; Sous, M. El.; Hawkins, B. C.; Hirner, S.; Holloway, G.; Khoo, M. L.; Owen, D. J.; Savage, G. P.; Scammells, P. J.; Rizzacasa, M. A. J Am Chem Soc 2009, 131, 1607.

[105] Oganesyan, E. T.; Ivchenko, A. V.; Ivashev, M. N.; Lysenko, T. A.; Saraf, A. S. Izobreteniya 1994, 18, 213.

[106] Cimarelli, C.; Palmieri, G. Tetrahedron 2000, 56, 475.

[107] Dillon, K. B.; Mathey, F.; Nixon FRS, J. F. Phosphorus: The Carbon Copy; Wiley: Chichester, 1998.

[108] Quin, L. D. A Guide to Organophosphorus Chemistry; Wiley: New York, 2000. Chapter 11.

[109] Xie, L.; Ma, J.; Ding, Y.-X. Tetrahedron Lett 2008, 49, 847.

[110] Dyck, B.; Zhao, L.; Tamiya, J.; Pontillo, J.; Hudson, S.; Ching, B.; Heise, C. E.; Wen, J.; Norton, C.; Madan, A.; Schwarz, D.; Wade, W.; Goodfellow, V. S. Bioorg Med Chem Lett 2006, 16, 4237.

[111] Nam, D. H.; Lee, K. S.; Kim, S. H.; Kim, S. M.; Jung, S. Y.; Chung, S. H.; Kim, H. J.; Kim, N. D.; Jin, C.; Lee, Y. S. Bioorg Med Chem Lett 2008, 18, 205.

[112] Kataoka, T.; Watanabe, S.; Mori, E.; Kadomoto, R.; Tanimura, S.; Kohno, M. Bioorg Med Chem 2004, 12, 2397.

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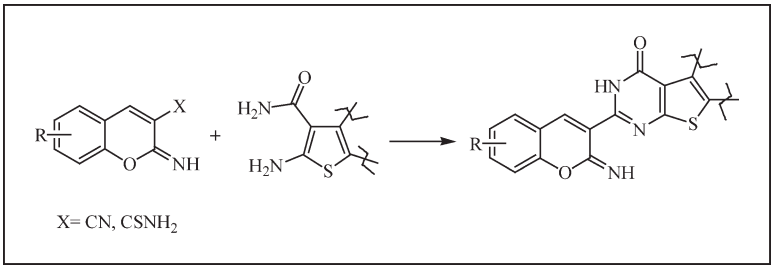


The interaction of both 2-iminocoumarin-3-carbonitriles and 2-iminocoumarin-3-carbothioamides with 2-aminothiophen-3-carboxamides lead to formation of 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins in two steps. The simplicity of the procedure, as well as the high yields of the target products make this method to be a good alternative of Knoevenagel condensation for the synthesis of 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins.

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## INTRODUCTION

3-Substituted-2-iminocoumarins are known not only due to their versatile biological activity, such as anti-inflammatory [1,2], antimicrobial, antifungal [3,4], and antitumor [5–9], but also as luminescent indicators [10] and laser dyes [11–13]. They can also be useful as effective reagents for 2-substituted 2*H*-1-benzopyrans syntheses [14]. Therefore, the development of a simple methodology for synthesis 2-iminocoumarins substituted with heterocyclic moiety at position 3 is important problem of benzopyrans chemisrty.

With regard to the pharmacological potential of thieno[2,3-*d*]pyrimidines [15–24] as the part of our research work on the synthesis of 3-heteryl-2-iminocoumarins [25,26], we focused our efforts on the synthesis of 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins.

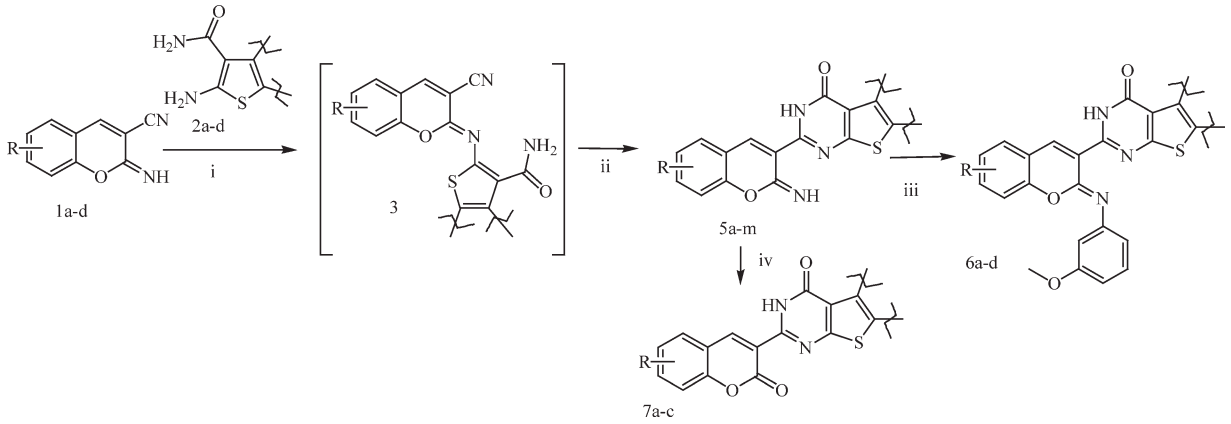
The most commonly used method for synthesis of 3-heteryl-2-iminocoumarins is the Knoevenagel condensation of salicylic aldehydes with nitriles of heterylacetic acids [27–30]. However, for synthesis of 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins this approach is not convenient enough due to the difficulties in the starting building-blocks, the corresponding 2-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)acetonitriles, preparation [31]. With the aim to develop more suitable method, we tested the alternative route for synthesis of 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins based on intramolecular rearrangement of 2-iminocoumarins, so-called ''recyclization'' approach.

Recently it was shown that ''recyclization'' of 2-iminocoumarin-3-carboxamides under the action of binucleophlic reagents results in various 3-heterylcoumarins [25,26,32–37]. According to the proposed mechanism of these reactions the carboxamide group of 2-iminocoumarin-3-carboxamide serves as precursor of lactone C=O group of the resulting 3-heterylcoumarin. Thus, it was worthy to assume that utilization of 2-iminocoumarin-3-carbonitriles in a similar rearrangement would lead to the formation of products with the C=NH moiety in the 2 position of benzopyran ring. Therefore, we studied the interaction between 2-iminocoumarin-3-carbonitriles and 2-aminothiophen-3-carboxamides as the possible convenient approach for synthesis of desired 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins.

## RESULTS AND DISCUSSION

It is known that the interaction of 2-iminocoumarin-3-carboxamides with arylamines in the glacial acetic acid leads to formation of 2-*N*-aryliminocoumarin-3-carboxamides [34–38]. We applied a similar reaction to obtain the key-intermediates, which apparently were 2-(3-carbamoyl-2-thienylimino)-coumarin-3-carbonitriles **3** by interaction between 2-iminocoumarin-3-carbonitriles 1

**Scheme 1**



and 2-aminothiophen-3-carboxamides 2. The compounds **3** were isolated from glacial acetic acid as red solids and used without any additional purification.

The ''recyclization'' of 2-(3-carbamoyl-2-thienylimino)coumarin-3-carbonitriles **3** was performed by heating in DMF. The anhydrous solvent was used to avoid hydrolysis of the imino group of product **5** formed (Scheme 1). The proposed mechanism of ''recyclization'' reaction is depicted on the Scheme 2.

The compounds **5a–m** were obtained in the high yields (65–89%) (Method A).

In the $^1$H NMR spectra of the compounds **5a–m**, the signal of proton in the position 4 of coumarin resonate in the range δ 8.66–8.83 ppm, as well as the signal of imino group proton (δ 9.31–9.51 ppm) and aromatic protons (δ 7.20–7.94 ppm) are present. All these spectra also contain signal of thieno[2,3-*d*]pyrimidine fragment NH (14.08–14.50 ppm). Though the LC/MS spectra for compound **5** show their high purity, in most cases the $^1$H NMR spectra of derivatives **5** in DMSO-$d_6$ contain some additional signals, possibly from the open form of the iminolactone ring.

The IR-spectra (KBr) of the compounds **5a–m** have the strong absorption bands of υ C=O and υ C=N at 1700–1621 cm$^{-1}$, the broad band of υ N—H (pyrimidine and imino-group) at 3500–3150 cm$^{-1}$. In the spectra of the products **5**, the signal of υ CN is absent comparatively with the spectra of intermediates 3 (2240–2220 cm$^{-1}$).

Unfortunately the compounds **5** appeared to be slightly soluble in the suitable solvents to measure $^{13}$C NMR spectra. Thus with the aim to prove the presence of imino-group in the molecule of these derivatives we performed their acidic hydrolysis (HCl) in 2-propanol-water mixture. The obtained products appeared to be the same as previously reported 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)coumarins **7a–c** [34–36] (Table 1).

Also the presence of the imino group in the structure of **5** allowed us to obtain 2-*N*-aryliminoproducts **6** (using reaction of **5** with *m*-anisidine in glacial acetic acid) as crystalline substances.

In the $^1$H NMR spectra of the compounds **6a–d** the signals of methoxygroup (3.76–3.78 ppm) and aromatic protons (6.73–7.53 ppm) of 3-methoxyphenyl substituent appear.

The crystals of compound **6a** appeared to be suitable for X-ray diffraction analysis after the crystallization from DMF. In the crystal phase of the compound **6** was observed as hemisolvate with DMF.

According to X-ray diffraction data the 2-minocoumarin fragment and 4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin fragment are coplanar within 0.04 Å (Fig. 1). Such arrangement of these fragments relatively each other is stabilized by the formation of the N(2)—H(2N)...N(3) intramolecular hydrogen bond (H...N 1.96 Å N—H...N 138°) and the H(19)...N(1) attractive interaction (2.39 Å when compared with the van der Waals radii sum [39] 2.67 Å). The

**Scheme 2**

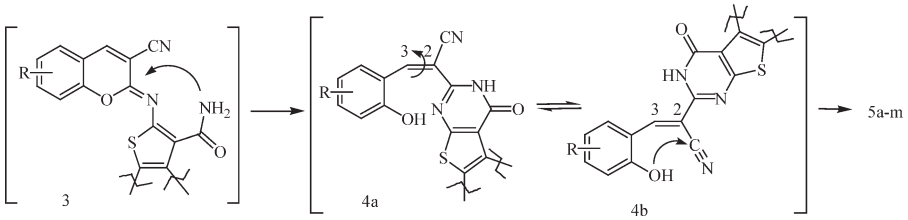
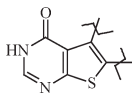
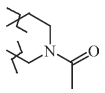
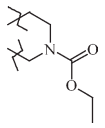


**Table 1**

Synthesis of compounds **5a–m**, **6a–d**, and **7a–c**.

| No. |  | R | Yield[a] (%) |
|---|---|---|---|
| **5a** | | H | 74 |
| **5b** |  | 6-Cl | 65 |
| **5c** | | 8-OMe | 84 |
| **5d** | | 8-OEt | 88 |
| **6a** | | 6-Cl | 83 |
| **6b** | | 8-OMe | 90 |
| **6c** | | 8-OEt | 92 |
| **7a** | | H | 90 |
| **5e** |  | H | 66 |
| **5f** | | 6-Cl | 69 |
| **5g** | | 8-OMe | 75 |
| **5h** | | 8-OEt | 78 |
| **6d** | | 8-OMe | 89 |
| **7b** | | H | 88 |
| **7c** | | 8-OMe | 89 |
| **5i** |  | H | 68 |
| **5j** |  | H | 85 |
| **5k** | | 6-Cl | 65 |
| **5l** | | 8-OMe | 79 |
| **5m** | | 8-OEt | 80 |

[a] Isolated yields of **5** based on **1** used (Method A); Isolated yields of **6** and **7** based on **5** used.

tetrahydrocycle is disordered over two half-chair conformation (A and B) with population 75:25%. Deviations of the C(4) and C(5) atoms from the mean plane of the remaining atoms of the ring are −0.50 and 0.19 Å, respectively for conformer A and 0.31 and −0.47 Å, respectively for B. The methoxyphenyl substituent is located in the cis-conformation relatively the C(12)—O(2) bond [the C(20)—N(3)—C(12)—O(2) torsion angle is 1.7(5)°] and it adopts –sc conformation relatively the C(12)—N(3) bond [the C(12)—N(3)—C(20)—C(25) torsion angle is -43.4(5)°]. The methoxy group is coplanar to the plane of the aromatic ring [the C(26)—O(3)—C(24)—C(25) torsion angle is 2.0(6)°].

The structures of the products 6 have been also confirmed using elemental analyses, IR, and LC/MS-spectra.

Following the mechanism of ''recyclization'' reaction, we tested whether the 2-iminocoumarin-3-carbothioamides were suitable precursors for 2-thiocoumarins synthesis. We obtained the intermediate 2-(3-carbamoyl-2-thienylimino)-coumarin-3-carbothioamides **9** by reaction of 2-iminocoumarin-3-carbothioamides **8** [40] with 2-aminothiophen-3-carboxamides **2** in glacial acetic acid. Further ''recyclization'' have been performed by heating compounds **9** in DMF. Though instead of the desired 2-(2-thiocoumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **10** 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins **5** were isolated (Scheme 3). Thus it can be deduced that in this case the hydrogen sulfide cleavage is preferable way for recyclization the 2-iminocoumarin-3-carbothioamides (Scheme 4) (Method B).

## CONCLUSION

It was established that interaction of both 2-iminocoumarin-3-carbonitriles and 2-iminocoumarin-3-carbothioamides with 2-aminothiophen-3-carboxamides after the rearrangement of arylimino intermediates lead to formation of 3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-iminocoumarins. The simplicity of the proposed procedure as well as the high yields of the target products make this method to be a good alternative of Knoevenagel condensation for the synthesis of derivatives **5**. The further reaction of **5** with *m*-anisidine allowed us to obtain 2-(2-(3-methoxyphenylimino)-coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **6**.

## EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Elemental analyses were within ± 0.4% of the theoretical value. IR spectra were recorded on Specord M80 spectrometers in KBr. $^1$H NMR spectra were recorded on Varian Mercury-200 spectrometer in DMSO-$d_6$ and $CDCl_3$ using TMS as an internal standard. Mass spectral analyses were obtained on a PE SCIEX API 150EX mass spectrometer.

**X-ray study.** The colourless crystals of 6a ($C_{26}H_{20}N_3O_3SCl$ 0.5 $C_3H_7NO$) are triclinic. At 293 K, $a$ = 8.760(1), $b$ = 11.321(1), $c$ = 13.895(1) Å, α = 86.85(1)°, β = 83.36(1)°, γ = 85.46(1)°, $V$ = 1363.0(3) Å$^3$, $M_r$ = 562.0, $Z$ = 2, space

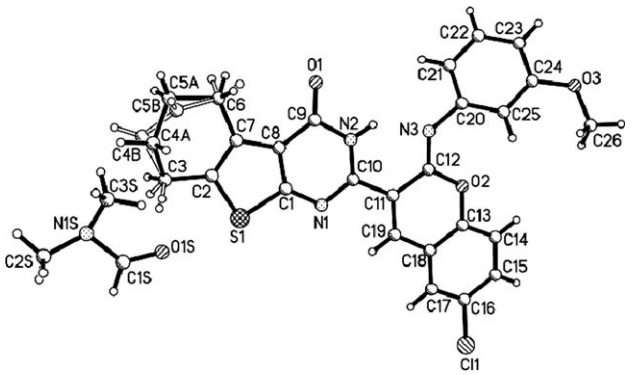
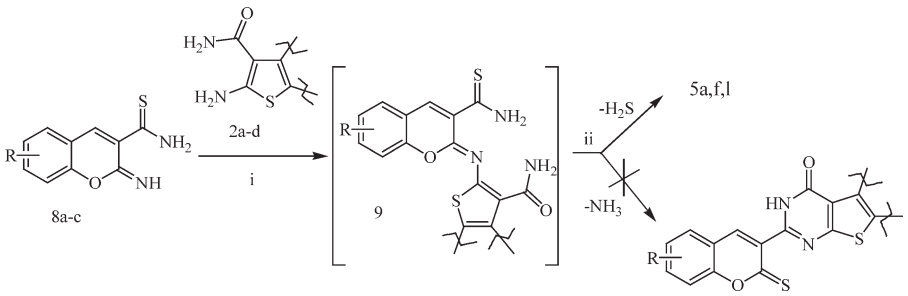



**Figure 1.** The molecular structure of the compound 6a according to X-ray diffraction data.

**Scheme 3**



group $P\bar{1}$, $d_{calc}$ = 1.282 g/cm$^3$, μ(MoK$_\alpha$) = 0.253 mm$^{-1}$, $F(000)$ = 547. Intensities of 7751 reflections (4600 independent, $R_{int}$ = 0.038) were measured using the ''Xcalibur-3'' diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, ω-scanning, $2T_{max}$ = 50°). The structure was solved by direct method using SHELXTL package [41]. The restrains for bond lengths in the disordered fragment were applied during refinement ($Csp^2$—$Csp^3$ 1.51 Å, $Csp^3$—$Csp^3$ 1.54 Å). Positions of the hydrogen atoms were located from electron density difference maps and refined by ''riding'' model with $U_{iso}$ = $nU_{eq}$ of the carrier atom ($n$ = 1.5 for methyl group and $n$ = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against $F^2$ in anisotropic approximation for nonhydrogen atoms using 4517 reflections was converged to $wR_2$ = 0.191 ($R_1$ = 0.063 for 2815 reflections with F > 4σ($F$), $S$ = 1.156). The final atomic coordinates, and crystallographic data for molecule 6a have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK and are available on request quoting the deposition numbers CCDC 705029.

**2-Iminocoumarin-3-carbonitriles.** 1a–d were obtained starting of malononitrile by interaction with corresponding salicylic aldehydes [42]. 2-Iminocoumarin-3-carbothioamides **8a-c** were synthesized by interaction of salicylic aldehydes of 2-cyanoethanethioamide [40].

**2-Iminocoumarin-3-carbonitrile (1a).** This compound was obtained in 65% yield as a yellow solid, mp 160–162°C; IR (cm$^{-1}$): 3293, 3038, 2228, 1651, 1601, 1450; $^1$H NMR ($CDCl_3$): δ 7.12 (m, 2 H), 7.32 (d, $J$ = 6.41 Hz, 1 H), 7.46 (t, $J$ = 7.63 Hz, 1 H), 7.64 (br.s, 1 H), 7.70 (br.s, 1 H); Anal. calcd. for $C_{10}H_6N_2O$: H, 3.34; C, 55.36; N, 10.33. Found: H, 3.20; C, 55.08; N, 10.14.

**6-Chloro-2-Iminocoumarin-3-carbonitrile (1b).** This compound was obtained in 72% yield as a yellow solid, mp 172–174°C; IR (cm$^{-1}$): 3307, 3046, 2233, 1649, 1599, 1478; $^1$H NMR ($CDCl_3$): δ 7.09 (d, $J$ = 8.85 Hz, 1 H), 7.37 (d, $J$ = 2.14 Hz, 1 H), 7.47 (dd, $J$ = 8.85, 2.44 Hz, 1 H), 7.69 (br.s, 1 H), 7.80 (br.s, 1 H); Anal. calcd. for $C_{10}H_5ClN_2O$: H, 3.15; C, 53.66; N, 10.01. Found: H, 3.22; C, 53.33; N, 9.77.

**2-Imino-8-methoxy-coumarin-3-carbonitrile (1c).** This compound was obtained in 70% yield as a yellow solid, mp 165–167°C; IR (cm$^{-1}$): 3287, 3054, 2226, 1651, 1607, 1477; $^1$H NMR ($CDCl_3$): δ 3.84 (s, 3 H), 6.89 (d, $J$ = 6.71 Hz, 1 H), 7.05 (m, 2 H), 7.67 (br.s, 1 H), 7.78 (br.s, 1 H); Anal. calcd. for $C_{11}H_8N_2O_2$: H, 3.44; C, 54.95; N, 10.05. Found: H, 3.40; C, 54.70; N, 9.82.

**8-Ethoxy-2-iminocoumarin-3-carbonitrile (1d).** This compound was obtained in 78% yield as a yellow solid, mp 161–163°C; IR (cm$^{-1}$): 3320, 3036, 2228, 1655, 1604, 1467; $^1$H NMR ($CDCl_3$): δ 1.36 (t, $J$ = 6.71 Hz, 3 H), 4.03 (q, $J$ = 6.71 Hz, 2 H), 6.84 (m, 1 H), 6.98 (m, 2 H), 7.61 (br.s, 1 H) 7.71 (br.s, 1 H); Anal. calcd. for $C_{12}H_{10}N_2O_2$: H, 3.57; C, 55.33; N, 9.93. Found: H, 3.31; C, 55.25; N, 9.67.

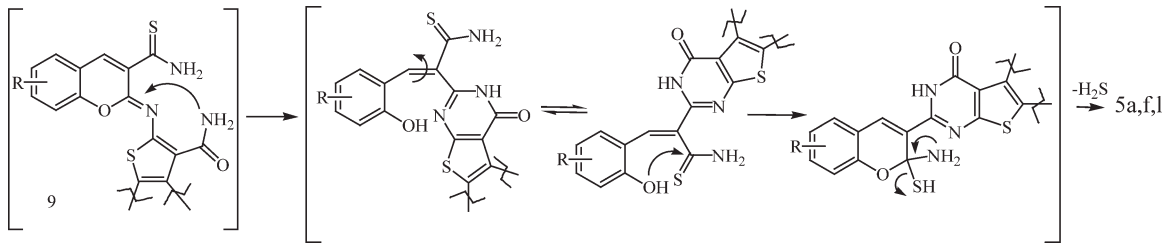
**2-Aminothiophene-3-carboxamides.** 2a–d were obtained from cyclohexanone, 4-methyl-cyclohexanone, and *N*-substituted piperidin-4-ones according to the Gewald procedure [43–45].

**2-Amino-6-methyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide 2(b).** This compound was obtained in 62% yield as a colorless solid, mp 187–189°C; IR (cm$^{-1}$): 3400, 3259, 3180, 2944, 1632, 1584, 1561, 1499; $^1$H NMR (DMSO-$d_6$): δ 0.97 (t, $J$ = 6.22 Hz, 3 H), 1.25 (m, 1 H), 1.74 (m, 2 H), 2.05 (m, 1 H), 2.58 (m, 2 H), 3.31 (br.s, 1 H), 6.49 (br.s, 2 H), 6.87 (s, 2 H).

**6-Acetyl-2-amino-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide 2(c).** This compound was obtained in 65% yield as a colorless solid, mp 250–252°C; IR (cm$^{-1}$): 3497, 3394, 3280, 3159, 1651, 1563, 1480; $^1$H NMR (DMSO-$d_6$): δ 2.01, 2.05 (s, 3 H), 2.63 (br.s, 2 H), 2.73 (br.s, 2 H), 3.57 (br.s, 2 H), 4.35, 4.39 (s, 2 H), 6.56 (br.s, 2 H), 6.92 (s, 1 H), 6.98 (s, 1 H).

**Ethyl 2-amino-3-(aminocarbonyl)-4,7-dihydrothieno[2,3-*c*] pyridine-6(5*H*)-carboxylate 2(d).** This compound was obtained in 60% yield as a colorless solid, mp 185–187°C; IR

**Scheme 4**



($cm^{-1}$): 3431, 3365, 3319, 3172, 1690, 1638, 1572, 1427; $^1H$ NMR (DMSO-$d_6$): δ 1.18 (t, $J$ = 7.32 Hz, 3 H), 2.68 (t, $J$ = 5.49 Hz, 2 H), 3.55 (t, $J$ = 5.49 Hz, 2 H), 4.06 (q, $J$ = 7.32 Hz, 2 H), 4.29 (s, 2 H), 6.48 (s, 2 H), 6.88 (s, 2 H).

**General procedure for the preparation of 2-(2-iminocoumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones 5a–m.** To the warm (40–50°C) solution of 2-aminothiophene-3-carboxamide 2 (2 mmol) in glacial acetic acid (3 mL) the solution of either 2-iminocoumarine-carbonitrile 1 (Method A) or 2-iminocoumarine-3-carbothioamide 8 (Method B) (2 mmol) in glacial acetic acid (3 mL) was added and the mixture was heated at 70–80°C for 30 min. Then the reaction mixture was cooled. The precipitate that formed was collected by filtration and dried. The product **3** (Method A) or **9** (Method B) was dissolved in DMF (5 mL) at 140–150°C and heated for 3 h. The precipitate of **5** formed after cooling was filtered out, washed with 2-propanol and dried.

**2-(2-Iminocoumarin-3-yl)-5,6,7,8-tetrahydro-benzo[4,5]-thieno[2,3-*d*]pyrimidin-4-one (5a).** This compound was obtained in 74% yield (Method A) and 72% (Method B) as a red solid, mp 280–282°C; IR ($cm^{-1}$): 3451, 3156, 2932, 2846, 1654, 1615, 1535, 1473; $^1H$ NMR (DMSO-$d_6$): δ 1.72 (br.s, 4 H), 2.63 (br.s, 2 H), 2.79 (br.s, 2 H), 7.21 (m, 2 H), 7.53 (t, $J$ = 6.7 Hz, 1 H), 7.79 (d, $J$ = 6.4 Hz, 1 H), 8.71 (s, 1H, H-4), 9.31 (br.s, 1H, =NH), 14.17 (br.s, 1H, -NHCO); lcms: m/z ($MH^+$) 350. Anal. calcd. for $C_{19}H_{15}N_3O_2S$: H, 4.33; C, 65.31; N, 12.03. Found: H, 4.12; C, 65.55; N, 11.72.

**2-(6-Chloro-2-iminocoumarin-3-yl)-5,6,7,8-tetrahydro-benzo [4,5]thieno[2,3-*d*]pyrimidin-4-one (5b).** This compound was obtained in 65% yield as a orange solid, mp 294–296°C; IR ($cm^{-1}$): 3450, 3232, 2932, 2854, 1679, 1651, 1592, 1554, 1477; $^1H$ NMR (DMSO-$d_6$): δ 1.74 (br.s, 4 H), 2.67 (br.s, 2 H), 2.82 (br.s, 2 H), 7.20 (d, $J$ = 8.9 Hz, 1 H), 7.54 (d, $J$ = 8.9 Hz, 1 H), 7.89 (s, 1 H), 8.68 (s, 1H, H-4), 9.45 (br.s, 1H, =NH), 14.10 (br.s, 1H, -NHCO); lcms: *m/z* ($MH^+$) 384. Anal. calcd. for $C_{19}H_{14}ClN_3O_2S$: H, 3.68; C, 59.45; N, 10.95. Found: H, 3.40; C, 59.28; N, 10.57.

**2-(2-Imino-8-methoxycoumarin-3-yl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (5c).** This compound was obtained in 84% yield as a yellow solid, mp 275–277; IR ($cm^{-1}$): 3436, 3326, 2925, 2842, 1679, 1660, 1605, 1574, 1533; $^1H$ NMR (DMSO-$d_6$): δ 1.76 (br.s, 4 H), 2.74 (br.s, 2 H), 2.88 (br.s, 2 H), 3.89 (s, 3 H), 7.32 (m, 3 H), 8.81 (s, 1H, H-4), 9.49 (br.s, 1H, =NH), 14.32 (br.s, 1H, -NHCO); lcms: m/z ($MH^+$) 379. Anal. calcd. for $C_{20}H_{17}N_3O_3S$: H, 4.52; C, 63.31; N, 11.07. Found: H, 4.22; C, 63.65; N, 10.73.

**2-(8-Ethoxy-2-iminocoumarin-3-yl)-5,6,7,8-tetrahydro-benzo [4,5]thieno[2,3-*d*]pyrimidin-4-one (5d).** This compound was obtained in 88% yield as a yellow solid, mp 278–280°C; IR ($cm^{-1}$): 3442, 3188, 2985, 2936, 1651, 1603, 1573, 1484; $^1H$ NMR (DMSO-$d_6$): δ 1.37 (t, $J$ = 7.0 Hz, 3 H), 1.75 (br.s, 4 H), 2.69 (br.s, 2 H), 2.83 (br.s, 2 H), 4.17 (q, $J$ = 7.0 Hz, 2 H), 7.26 (m, 3 H), 8.74 (s, 1H, H-4), 9.38 (br.s, 1H, =NH), 14.25 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 394. Anal. calcd. for $C_{21}H_{19}N_3O_3S$: H, 4.87; C, 64.11; N, 10.68. Found: H, 4.68; C, 64.25; N, 10.30.

**2-(2-Iminocoumarin-3-yl)-7-methyl-5,6,7,8-tetrahydro-benzo [4,5]thieno[2,3-*d*]pyrimidin-4-one (5e).** This compound was obtained in 66% yield as a yellow solid, mp 282–284°C; IR ($cm^{-1}$): 3446, 3165, 2944, 2921, 1654, 1613, 1602, 1535, 1475; $^1H$ NMR (DMSO-$d_6$): δ 1.02 (d, $J$ = 6.4 Hz, 3 H), 1.36 (m, 1 H), 1.85 (m, 2 H), 2.31 (m, 1 H), 2.78 (m, 2 H), 3.06 (m, 1 H), 7.26 (m, 2 H), 7.57 (t, $J$ = 7.6 Hz, 1 H), 7.85 (d, $J$ = 7.3 Hz, 1 H), 8.80 (s, 1H, H-4), 9.35 (br.s, 1H, =NH), 14.23 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 364. Anal. calcd. for $C_{20}H_{17}N_3O_2S$: H, 4.71; C, 66.10; N, 11.56. Found: H, 4.52; C, 65.84; N, 11.32.

**2-(6-Chloro-2-iminocoumarin-3-yl)-7-methyl-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (5f).** This compound was obtained in 69% yield (Method A) and 63% (Method B) as a yellow solid, mp 290–292; IR ($cm^{-1}$): 3440, 3251, 2931, 2823, 1671, 1595, 1552, 1492, 1446; $^1H$ NMR (DMSO-$d_6$): δ 1.01 (d, $J$ = 6.1 Hz, 3 H), 1.31 (m, 1 H), 1.82 (m, 2 H), 2.25 (m, 1 H), 2.72 (m, 2 H), 3.00 (m, 1 H), 7.20 (d, $J$ = 8.9 Hz, 1 H), 7.53 (d, $J$ = 8.9 Hz, 1 H), 7.90 (s, 1 H), 8.66 (s, 1H, H-4), 9.42 (br.s, 1H, =NH), 14.08 (br.s, 1H, NHCO); lcms: *m/z* ($MH^+$) 399. Anal. calcd. for $C_{20}H_{16}ClN_3O_2S$: H, 4.05; C, 60.37; N, 10.56. Found: H, 3.91; C, 60.11; N, 10.22.

**2-(2-Imino-8-methoxycoumarin-3-yl)-7-methyl-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (5g).** This compound was obtained in 75% yield as a yellow solid, mp 268–270°C; IR ($cm^{-1}$): 3446, 3328, 2930, 1681, 1658, 1604, 1576, 1479; $^1H$ NMR (DMSO-$d_6$): δ 1.03 (d, $J$ = 6.4 Hz, 3 H), 1.38 (m, 1 H), 1.86 (m, 2 H), 2.23 (m, 1 H), 2.79 (m, 2 H), 3.07 (m, 1 H), 3.89 (s, 3 H), 7.25 (m, 2 H), 7.42 (dd, $J$ = 7.3 Hz, 1 H), 8.79 (s, 1H, H-4), 9.43 (br.s, 1H, =NH), 14.31 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 394. Anal. calcd. for $C_{21}H_{19}N_3O_3S$: H, 4.87; C, 64.11; N, 10.68. Found: H, 4.68; C, 64.29; N, 10.42.

**2-(8-Ethoxy-2-iminocoumarin-3-yl)-7-methyl-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (5h).** This compound was obtained in 78% yield as a yellow solid, mp 265–267°C; IR ($cm^{-1}$): 3445, 3169, 2976, 2950, 1685, 1656,1603, 1573,1467; $^1H$ NMR (DMSO-$d_6$): δ 1.01 (d, $J$ = 6.4 Hz, 3 H), 1.37 (t, $J$ = 6.7 Hz, 3 H), 1.81 (m, 2 H), 2.24 (m, 1 H), 2.72 (m, 2 H), 3.02 (m, 1 H), 4.14 (q, $J$ = 7.0 Hz, 2 H), 7.25 (m, 3 H), 8.67 (s, 1H, H-4), 9.36 (br.s, 1H, =NH), 14.24 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 408. Anal. calcd. for $C_{22}H_{21}N_3O_3S$: H, 5.19; C, 64.85; N, 10.31. Found: H, 5.00; C, 64.72; N, 10.04.

**7-Acetyl-2-(2-iminocoumarin-3-yl)-3,4,5,6,7,8-hexa-hydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4-one (5i).** This compound was obtained in 68% yield as a brown solid, mp 284–286°C; IR ($cm^{-1}$): 3442, 3317, 3050, 2930, 1650, 1599, 1565, 1453, 1427; $^1H$ NMR (DMSO-$d_6$): δ 2.11 (s, 3 H), 2.99 (m, 2 H), 3.73 (s, 2 H), 4.71 (m, 2 H), 7.27 (m, 2 H), 7.58 (t, $J$ = 7.3 Hz, 1 H), 7.84 (d, $J$ = 7.3 Hz, 1 H), 8.83 (s, 1H, H-4), 9.32 (br.s, 1H, =NH), 14.31 (br.s, 1H, —NHCO); lcms: *m/z* (M) 392. Anal. calcd. for $C_{20}H_{16}N_4O_3S$: H, 4.11; C, 61.21; N, 14.28. Found: H, 4.04; C, 61.39; N, 14.03.

**Ethyl 4-oxo-2-(2-iminocoumarin-3-yl)-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (5j).** This compound was obtained in 85% yield as a yellow solid, mp 274–276°C; IR ($cm^{-1}$): 3437, 3261, 2979, 2929, 1673, 1653, 1537, 1693, 1429; $^1H$ NMR (DMSO-$d_6$): δ 1.21 (t, $J$ = 6.8 Hz, 3 H), 2.88 (s, 2 H), 3.64 (t, $J$ = 5.1 Hz, 2 H), 4.09 (q, $J$ = 6.8 Hz, 2 H), 4.58 (s, 2 H), 7.23 (m, 2 H), 7.55 (td, $J$ = 7.7 Hz, 1 H), 7.81 (d, $J$ = 6.8 Hz, 1 H), 8.78 (s, 1H, H-4), 9.36 (br.s, 1H, =NH), 14.34 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 423. Anal. calcd. for $C_{21}H_{18}N_4O_4S$: H, 4.29; C, 59.71; N, 13.26. Found: H, 4.17; C, 59.46; N, 12.96.

**Ethyl 4-oxo-2-(6-chloro-2-iminocoumarin-3-yl)-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (5k).** This compound was obtained in 65% yield as a yellow solid, mp 287–289°C; IR ($cm^{-1}$): 3440, 3322, 2914,

2853, 1675, 1649,1592, 1563, 1698, 1452; $^1$H NMR (DMSO-$d_6$): δ 1.22 (t, $J$ = 7.3 Hz, 3 H), 2.96 (m, 2 H), 3.68 (s, 2 H), 4.10 (q, $J$ = 6.8 Hz, 2 H), 4.64 (s, 2 H), 7.25 (d, $J$ = 9.0 Hz, 1 H), 7.57 (dd, $J$ = 8.5, 2.6 Hz, 1 H), 7.94 (s, 1 H), 8.78 (s, 1H, H-4), 9.43 (br.s, 1H, =NH), 14.15 (br.s, 1H, —NHCO); lcms: *m/z* (M) 457. Anal. calcd. for $C_{21}H_{17}ClN_4O_4S$: H, 3.75; C, 55.20; N, 12.26. Found: H, 3.65; C, 55.52; N, 11.88.

**Ethyl 4-oxo-2-(2-imino-8-methoxycoumarin-3-yl)-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (5l).** This compound was obtained in 79% yield (Method A) and 70% (Method B) as a yellow solid, mp 280–282°C; IR (cm$^{-1}$): 3449, 3328, 2974, 2929, 1672, 1653, 1604, 1574,1697, 1472; $^1$H NMR (DMSO-$d_6$): δ 1.19 (t, $J$ = 6.8 Hz, 3 H), 2.94 (s, 2 H), 3.66 (t, $J$ = 5.1 Hz, 2 H), 3.89 (s, 3 H), 4.08 (q, $J$ = 7.3 Hz, 2 H), 4.62 (s, 2 H), 7.25 (m, 2 H), 7.40 (d, $J$ = 7.3 Hz, 1 H), 8.81 (s, 1H, H-4), 9.51 (br.s, 1H, =NH), 14.44 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 453. Anal. calcd. for $C_{22}H_{20}N_4O_5S$: H, 4.46; C, 58.40; N, 12.38. Found: H, 4.31; C, 58.24; N, 12.17.

**Ethyl 4-oxo-2-(2-imino-8-ethoxycoumarin-3-yl)-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (5m).** This compound was obtained in 80% yield as a yellow solid, mp 273–275°C; IR (cm$^{-1}$): 3452, 3159, 2979, 2928, 1651, 1603, 1546, 1698, 1425; $^1$H NMR (DMSO-$d_6$): δ 1.20 (t, $J$ = 7.3 Hz, 3 H), 1.39 (t, $J$ = 6.8 Hz, 3 H), 2.97 (br.s, 2 H), 3.67 (t, $J$ = 6.4 Hz, 2 H), 4.08 (q, $J$ = 7.3 Hz, 2 H), 4.19 (q, $J$ = 6.4 Hz, 2 H), 4.65 (s, 2 H), 7.25 (m, 2 H), 7.42 (dd, $J$ = 7.7 Hz, 1 H), 8.86 (s, 1H, H-4), 9.50 (br.s, 1H, =NH), 14.50 (br.s, 1H, —NHCO); lcms: *m/z* ($MH^+$) 467. Anal. calcd. for $C_{23}H_{22}N_4O_5S$: H, 4.75; C, 59.22; N, 12.01. Found: H, 4.61; C, 59.43; N, 11.66.

**General procedure for the preparation of 2-(2-(3-methoxyphenylimino)-coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones 6a-d.** To a solution of corresponding 2-(2-iminocoumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones 5 (2mmol) in glacial acetic acid (10 mL) 3-methoxy-phenylamine (2 mmol) was added at 40–50°C. The reaction mixture was heated at 70–80°C and stirred for 30 min. After cooling down to room temperature the precipitate was filtered out, washed with 2-propanol and recrystallized form DMF.

**2-(6-Chloro-2-(3-methoxyphenylimino)-coumarin-3-yl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (6a).** This compound was obtained in 83% yield as a yellow solid, mp >300°C; IR (cm$^{-1}$): 3450, 2935, 2835, 1672, 1645, 1587, 1566; $^1$H NMR (DMSO-$d_6$): δ 1.75 (br.s, 4 H), 2.74 (br.s, 2 H), 2.86 (br.s, 2 H), 3.77 (s, 3H, 3-$OCH_3$), 6.74 (d, $J$ = 7.3 Hz, 1 H), 6.84 (m, 2 H), 7.25 (m, 2 H), 7.53 (dd, $J$ = 8.3 Hz, 1 H), 8.00 (s, 1 H), 8.79 (s, 1H, H-4), 13.50 (br.s, 1H, NHCO). Anal. calcd. for $C_{26}H_{20}ClN_3O_3S$: H, 4.11; C, 63.73; N, 8.58. Found: H, 3.88; C, 63.46; N, 8.33.

**2-(2-(3-Methoxyphenylimino)-8-methoxycoumarin-3-yl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (6b).** This compound was obtained in 90% yield as a yellow solid, mp >300°C; IR (cm$^{-1}$): 3442, 2925, 2836, 1672, 1647, 1588, 1572; $^1$H NMR (DMSO-$d_6$): δ 1.71 (br.s, 4 H), 2.67 (br.s, 2 H), 2.82 (br.s, 2 H), 3.74 (s, 3 H), 3.76 (s, 3H, 3-$OCH_3$), 6.75 (dd, $J$ = 7.5 Hz, 1 H), 6.98 (d, $J$ = 7.8 Hz, 1 H), 7.26 (m, 5 H), 8.72 (s, 1H, H-4), 13.88 (br.s, 1H, —NHCO—). Anal. calcd. for $C_{27}H_{23}N_3O_4S$: H, 4.77; C, 66.79; N, 8.65. Found: H, 4.65; C, 66.95 N, 8.33.

**2-(8-Ethoxy-2-(3-methoxyphenylimino)-coumarin-3-yl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (6c).** This compound was obtained in 92% yield as a yellow solid, mp >300°C; IR (cm$^{-1}$): 3440, 2931, 2833, 1667, 1642, 1604, 1587; $^1$H NMR (DMSO-$d_6$): δ 1.30 (t, $J$ = 7.0 Hz, 3 H), 1.73 (br.s, 4 H), 2.68 (br.s, 2 H), 2.83 (br.s, 2 H), 4.04 (q, $J$ = 7.0 Hz, 2 H), 3.78 (s, 3H, 3-$OCH_3$), 6.76 (d, $J$ = 7.4 Hz, 1 H), 7.23 (m, 6 H), 8.72 (s, 1H, H-4), 13.82 (br.s, 1H, —NHCO—). Anal. calcd. for $C_{28}H_{25}N_3O_4S$: H, 5.04; C, 67.32; N, 8.41. Found: H, 5.80; C, 67.21; N, 8.22.

**2-(2-(3-Methoxyphenylimino)-8-methoxycoumarin-3-yl)-7-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (6d).** This compound was obtained in 89% yield as a yellow solid, mp >300°C; IR (cm$^{-1}$): 3426, 2931, 2833, 1676, 1640, 1603, 1526; $^1$H NMR (DMSO-$d_6$): δ 1.00 (d, $J$ = 6.4 Hz, 3 H), 1.31 (m, 1 H), 1.79 (m, 2 H), 2.20 (m, 1 H), 2.71 (m, 2 H), 3.03 (m, 1 H), 3.77 (s, 3 H), 3.77 (s, 3H, 3-$OCH_3$), 6.73 (d, $J$ = 7.4 Hz, 1 H), 6.97 (d, $J$ = 7.6 Hz, 1 H), 7.25 (m, 5 H), 8.70 (s, 1H, H-4), 13.83 (br.s, 1H, —NHCO—). Anal. calcd. for $C_{28}H_{25}N_3O_4S$: H, 5.04; C, 67.32; N, 8.41. Found: H, 4.82; C, 67.13; N, 8.09.

**General procedure for the preparation of 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones 7a–c.** Corresponding 2-(2-iminocoumarin-3-yl)thieno[2,3-d]pyrimidin-4-ones 5a, e, g (2 mmol) was dissolved at 60–70°C in mixture of 2-propanol (10 mL) and concentrated hydrochloric acid (1 mL). The reaction mixture was heated with reflux for 20 min, then cooled and the precipitate was collected by filtration and dried.

**2-(Coumarin-3-yl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (7a).** This compound was obtained in 92% yield as a yellow solid, mp >300°C.

**2-(Coumarin-3-yl)-7-methyl-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (7b).** This compound was obtained in 88% yield as a yellow solid, mp 235–237°C.

**2-(8-Methoxy-coumarin-3-yl)-7-methyl-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (7c).** This compound was obtained in 89% yield as a yellow solid, mp 277–279°C.

## REFERENCES

[1] Bylov, I. E.; Vasylyev, M. V.; Bilokin, Y. V. Eur J Med Chem 1999, 34, 997; CAN 132: 166094.

[2] Ukhov, S. V.; Kon'shin, M. E.; Odegova, T. F. Pharm Chem J 2001, 35, 364; CAN 136: 309779.

[3] Manrao, M. R.; Goel, R.; Sethi, R. K.; Kalsi, P. S. Indian J Heterocycl Chem 1995, 4, 231; CAN 123: 83152.

[4] Manrao, M. R.; Singh, B.; Sharma, J. R.; Kalsi, P. S. J Indian Council Chem 1996, 12, 38; CAN 127: 190618.

[5] Hadfield, J. A.; Pavlidis, V. H.; Perry, P. J.; McGown, A. T. Anticancer Drugs 1999, 10, 591; CAN 131: 295226.

[6] O'Callaghan, C. N. Proc R Ir Acad 1973, 73, 291. CAN 80: 78349.

[7] O'Callaghan, C. N.; Conalty, M. L. Proc R Ir Acad 1983, 83B, 241; CAN 100: 103286.

[8] Burke, Terrence R.; Lim, Benjamin; Marquez, Victor E.; Li, Zhen Hong; Bolen, Joseph B.; Stefanova, Irena; Horak, Ivan D. J Med Chem 1993, 36, 425.

[9] Huang,Chi-Kuang; Wu, Feng-Ying; Ai, You-Xi. Bioorg Med Chem Lett 1995, 5, 2423.

[10] Liepouri, F.; Foukaraki, E.; Deligeorgiev, T. G.; Katerinopoulos, H. E. Cell Calcium 2001, 30, 331; CAN 136: 213001.

[11] Nikolov, P.; Tyutyulkov, N.; Dryanska, V. Z. Naturforsch.1987, 42, 987; CAN 109: 72859.

[12] Asimov, M. M.; Nikitchenko, V. M.; Novikov, A. I.; Rubinov, A. N.; Bor, Z.; Gaty, L. Chem Phys Lett 1988, 149, 140; CAN 109: 179828.

[13] Yu, J.; Shirota, Y. Chem Lett 2002, 10, 984; CAN 138: 114681

[14] Gorobets, N. Yu.; Borisov, A. V.; Silin, A. V.; Nikitchenko, V. M.; Kovalenko, S. N. Chem Heterocycl Compd (Engl Transl) 2002, 38, 1389.

[15] Romeo, G.; Russo, F.; Caruso, A.; Cutuli, V.; Amico-Roxas, M. Arzneim-Forsch Drug Res 1998, 48, 167.

[16] Pathak, U. S.; Gandhi, N. V.; Singh, S.; Warde, R. P.; Jain, K. S. Indian J Chem Sect B: Org Chem Incl Med Chem 1992, 31, 223.

[17] Cho, N.; Nara, Y.; Harada, M.; Sugo, T.; Masuda, Y.; Abe, A.; Kusumoto, K.; Itoh, Y.; Ohtaki, T.; Watanabe, T.; Furuya, S. Chem Pharm Bull 1998, 46, 1724.

[18] Ismail, M. M. F.; Zahran, M. A.; El-Gaby, M. S. A.; Ammar, Y. A. Al-Azhar Bull Sci 1999, 10, 41.

[19] Modica, M.; Santagati, M.; Guccione, S.; Russo, F.; Cagnotto, A.; Goegan, M.; Mennini, T. Eur. J Med Chem 2000, 35, 1065.

[20] El-Kerdawy, M. M.; Yousif, M. Y.; El-Emam, A. A.; Moustafa, M. A.; El-Sherbeny, M. A. Boll Chim Farm 1996, 135, 301.

[21] Pathak, U. S.; Singh, S.; Padh, J. Indian J Chem B Org Chem Incl Med Chem 1991, 30, 618.

[22] Kretzschmar, E.; Laban, G.; Meisel, P.; Lohmann, D.; Grupe, R. GDR Patent DD 272090, 1989.

[23] Mkrtchyan, A. P.; Kazaryan, S. G.; Noravyan, A. S.; Akopyan, R. A.; Dzhagatspanyan, I. A.; Akopyan, N. E.; Akopyan, A. G. Khim-Farm Zh 1986, 20, 1312.

[24] Terricabras Belart, E.; Segarra Matamoros, V. M.; Alvarez-Builla Gomez, J.; Vaquero Lopez, J. J.; Minguez Ortega, J. M. Patent WO 2004065391, 2004; Chem Abstr 2004, 141, 157133.

[25] Kovalenko, S. M.; Bylov, I. E.; Sytnik, K. M.; Chernykh, V. P.; Bilokin, Y. V. Molecules 2000, 5, 1146.

[26] Kovalenko, S. N.; Vasil'ev, M. V.; Sorokina, I. V.; Chernykh, V. P.; Turov, A. V.; Rudnev, S. A. Chem Heterocycl Comp (New York) (Khim Geterotsikl Soed).1998, 34, 1664.

[27] Kuzmierkiewicz, W. Justus Liebigs Ann Chem 1987, 6, 541.

[28] Osman, S. A. M.; Hammad, M.; Swellem, R.; Shalaby A. M. Egypt J Chem 1988, 31, 735.

[29] Bukowski, L. Polish J Pharmacol Pharm 1986, 38, 91.

[30] Bukowski, L.; Janowiec, M. Pharmazie 1990, 45, 904.

[31] Hosni, Hanaa M.; Basyouni, Wahid M.; El-Bayouki,Khairy A. M.Acta Pol Pharm 1999, 56, 49.

[32] Kovalenko, S. N.; Zubkov, V. A.; Chernykh, V. P.; Turov A. V.; Ivkov, S. M. Chem Heterocycl Comp (New York) (Khim Geterotsikl Soed).1996, 32, 186.

[33] Kovalenko, S. N.; Sytnik, K. M.; Nikitchenko, V. M.; Rusanova, S. V.; Chernykh, V. P. Porokhnyak, A. O. Chem Heterocycl Comp (New York) (Khim Geterotsikl Soed) 1999, 35, 190.

[34] Vasylyev, M. V.; Bilokin, Y. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. Heterocycl Comm 1999, 5, 241.

[35] Bilokin, Y. V.; Vasylyev, M. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. Tetrahedron 1999, 55, 13757.

[36] Kovalenko, S. M.; Vlasov, S. V.; Chernykh, V. P. Synthesis 2006, 5, 847.

[37] Kovalenko, Sergiy M.; Vlasov, Sergiy V.; Chernykh, Valentin P. Heteroatom Chem 2007, 18, 341.

[38] O'Callaghan, C. N.; McMurry, T. B. H.; O'Brien, J. E. J Chem Soc Perkin Trans 2 1998, 2, 425.

[39] Zefirov Yu. V. Kristallografiya (Russian) 1997, 42, 936.

[40] Borisov, A. V.; Dzhavakhishvili, S. G.; Zhuravel, I. O.; Kovalenko, S. M.; Nikitchenko, V. M. J Comb Chem 2007, 9, 5.

[41] Sheldrick, G. M. SHELXTL PLUS. PC Version. A system of computer programs for the determination of crystal structure from X-ray diffraction data, 1998, Rev.5.1.

[42] Schiemenz, G. P. Chem Ber 1962, 95, 483.

[43] Mohareb, R. M.; Sherif, S. M.; Gaber, H. M.; Ghabrial, S. S.; Aziz, S. I. Heteroat Chem 2003, 14, 459.

[44] Shaban, M. A.; Mohamed, M. S.; Kamel, M. M.; El-Zanfally, S. H. Bull Fac Pharm 1990, 28, 17.

[45] Pech, R.; Schleiermacher, E.; Boehm, R. Sekt. Pharm., Martin-Luther-Univ., Halle/Saale, Ger Dem Rep Pharmazie 1989, 44, 860.

# Synthesis and Reactions of 4-Hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol-6-ones



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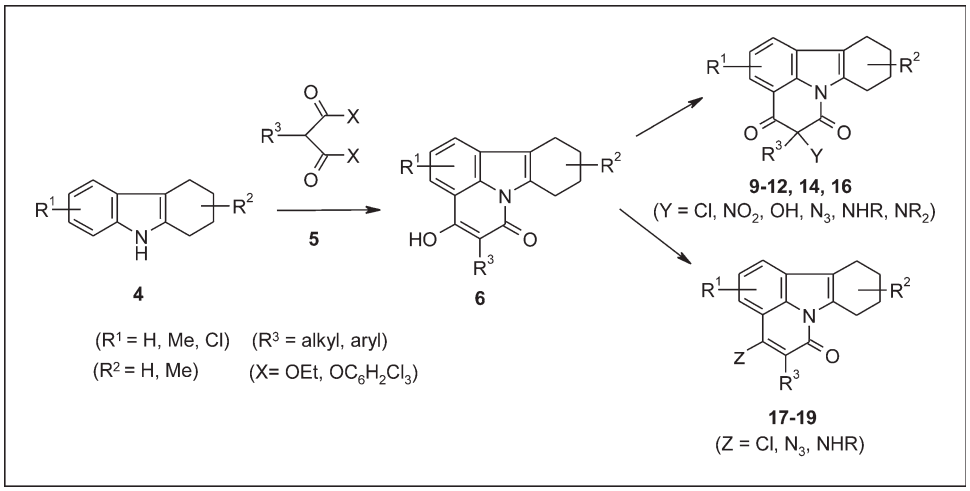


Tetrahydrocarbazoles **4** obtained from phenylhydrazines and cyclohexanones gave by cyclocondensation with 2-substituted malonates **5** in all cases 4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol-6-ones **6** by attack at the nitrogen and the aromatic ring of tetrahydrocarbazoles **4**; the direction of the cyclization was not dependent on substituents either in the aromatic or the saturated ring; isomeric pyridocarbazoles could not be isolated. Electrophilic substitutions of pyridocarbazoles **6** under mild conditions took place exclusively at the 5-position and gave pyridocarbazolediones **9**-**11** with 5-nitro-, 5-hydroxy or 5-chloro-substituents. Exchange of the chloro substituent in **11** gave 5-azido- and 5-amino products **12**, **14** or **16**. Reactions at the aromatic ring were not observed. Chlorination of 4-hydroxypyridocarbazoles **6** with phosphoryl chloride by nucleophilic substitution took place exclusively at the 4-position and gave 4-chloropyridocarbazolones **17**, which were further reacted to azides and amines **18, 19**.

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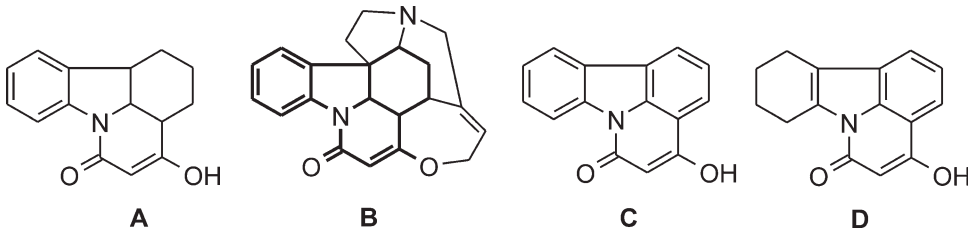
## INTRODUCTION

Tetrahydropyrido[3,2,1-*jk*]carbazol-6-one **A** is part of the heterocyclic skeleton of many natural products (*e.g.* strychnos alkaloids such as strychninolones **B** [1] and derivatives such as brucinolones [2] and vomicin [3]). It possesses the biologically interesting combination of an indole and a 2-pyridone structure. Moreover, some derivatives have found interest in pharmacological investigations [4]. Recently, we published the synthesis and reactions of pyrido[3,2,1-*jk*]carbazol-6-ones **C** with two aromatic rings [5]. In this article, we report about the synthesis and reactions of tetrahydropyrido [3,2,1-*jk*]carbazol-6-ones **D** having partial structures more similar to the natural products (Scheme 1).

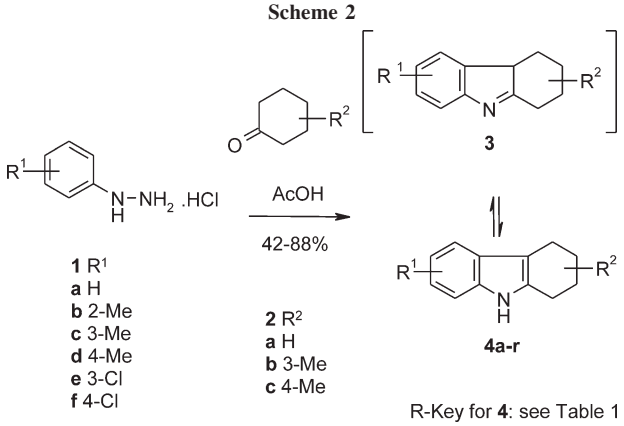
## RESULTS AND DISCUSSION

Our approach to the tetrahydro-pyridocarbazole system started with the synthesis of 2,3,4,5-tetrahydro-1*H*-carbazoles **4** with suitable substituents at the desired positions. Despite numerous reactions and catalysts described in the literature, such as the cyclization of cyclohexanone phenylhydrazones [6] or 2-phenylcyclohexanone oxime [7], the reaction of 2-chlorocyclohexanone [8] or 2-hydroxycyclohexanone with aniline [9], or the hydrogenation of carbazole [10], we found that an adapted version of a long-known procedure from Ref. [11] gave the best and simplest approach. Our synthetic approach started from phenylhydrazines **1** and cyclohexanones **2** in acetic acid as solvent without isolation of

**Scheme 1**




**Scheme 2**




phenylhydrazones, and we combined this reaction with a one-pot release of chloro- and methyl substituted phenylhydrazines **1**, which are commercially available only as hydrochlorides. The cumbersome release of oily and sensitive free phenylhydrazine bases could be skipped, when sodium acetate was added to the reaction mixture which gave *in situ* the desired phenylhydrazines. Excess sodium acetate and formed sodium chloride was removed at the end of the reaction during work-up by precipitation with diethyl ether.

To study the influence of substituents at the aromatic ring, chloro- and methyl-phenylhydrazines **1** were reacted with cyclohexanones **2** to synthesize a series of

**Scheme 3**

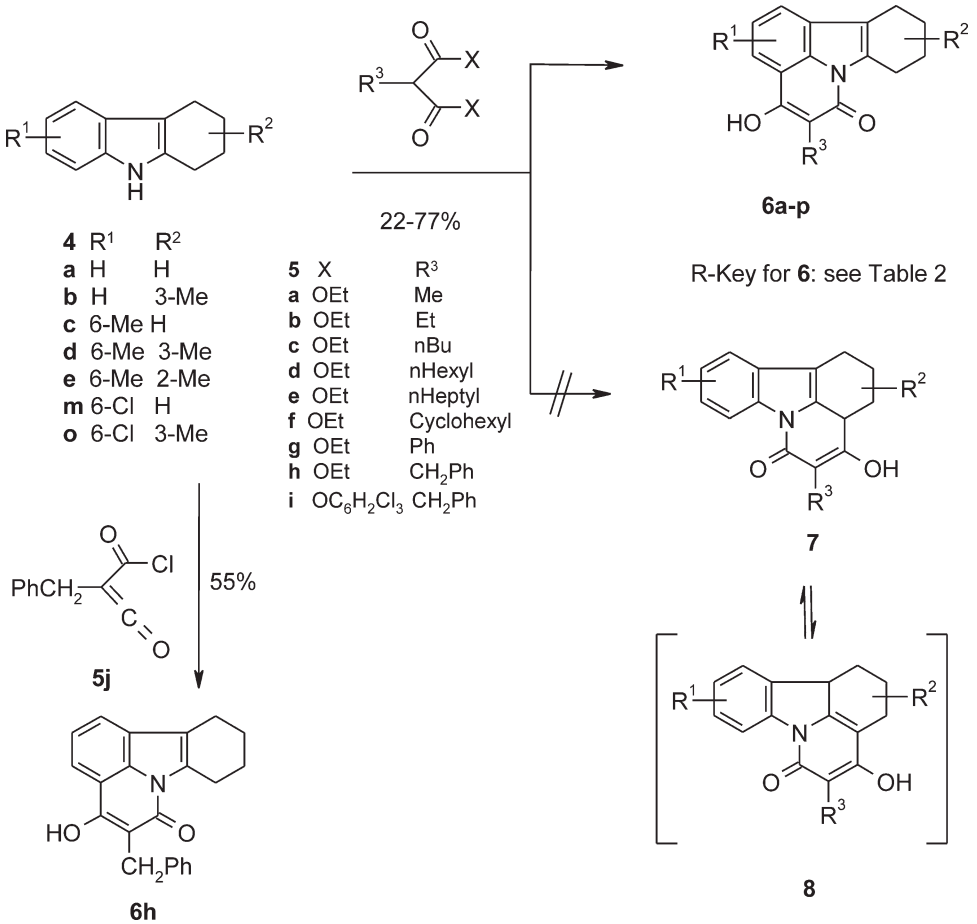


**Table 1**

2,3,4,9-Tetrahydro-1*H*-carbazoles (**4**).

| Compound | $R^1$ | $R^2$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$), δ | Elemental formula (molecular mass), Elemental analysis (calculated/found) |
|---|---|---|---|---|---|---|---|---|
| **4a** | H | H | 2,3,4,9-Tetrahydro-1*H*-carbazole | B:88 (**1a**, **2a**) | 115–117(ethanol) lit. 116 [11,20,21] | | | |
| **4b** | H | 3-Me | 3-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole | B:85 (**1a**, **2c**) | 109–110 (cyclohexane) lit. 109–110 [22] | | | |
| **4c** | 6-Me | H | 6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole | B:80 (**1d**, **2a**) | 146 (ethanol) lit. 145–147 [23,24] | | | |
| **4d** | 6-Me | 3-Me | 3,6-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole | A:66 (**1d**, **2c**) | 113 (ethanol) lit. 112 [20,21] | 3395 s, 2951 m, 2915 s, 2863 m, 1588 s | 1.07 (d, $J$ = 6.5 Hz, 3 H, 3-Me), 1.37–1.42 (m, 1 H, 3-CH), 1.86–1.89 (m, 2 H, 2-$CH_2$), 2.26–2.31 (m, 1 H, 4-$CH_2$), 2.34 (s, 3 H, 6-Me), 2.54–2.58 (m, 1 H, 4-$CH_2$), 2.63–2.68 and 2.72–2.79 (2 m, 2 H, 1-$CH_2$), 6.79 (d, $J$ = 8.3 Hz, 1 H, 7-H), 7.09–7.12 (m, 2 H, 5-H, 8-H), 10.43 (s, 1 H, NH) | |
| **4e** | 6-Me | 2-Me | 2,6-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 63 (**1d**, **2b**) | 147 (ethanol), lit. 137-146 [21,24] | 3395 s, 2952 m, 2915 s, 2863 m, 1588 s, 1457 s | 1.07 (d, $J$ = 6.5 Hz, 3 H, 2-Me), 1.36–1.46 (m, 1 H, 2-CH), 1.86-1.95 (m, 2 H, 3-$CH_2$), 2.26–2.30 (m, 1 H, 4-$CH_2$), 2.34 (s, 3 H, 6-Me), 2.54–2.58 (m, 1 H, 4-$CH_2$), 2.63-2.68 (m, 1 H, 1-CH2), 2.72–2.78 (m, 1 H, 1-$CH_2$), 6.78 (d, $J$ = 8.3 Hz, 1 H, 7-H), 7.09–7.11 (m, 2 H, 5-H, 8-H), 10.43 (s, 1 H, NH). | |
| **4f** | 7-Me | 3-Me | 3,7-Dimethyl- 2,3,4,9-tetrahydro-1*H*-carbazole | A: 60 (**1c**, **2c**)[a] | 98 (ethanol) | 3387 s, 2923 s, 1629 m, 1458 m | 1.08 (d, $J$ = 6.5 Hz, 3 H, 3-Me), 1.39–1.45 (m, 1 H, 3-CH), 1.84–1.87 (m, 2 H, 2-$CH_2$), 2.34 (s, 3 H, 7-Me), 2.41–2.45 and 2.53–2.56 (2 m, 2 H, 4-$CH_2$), 2.67–2.69 and 2.74–2.79 (2 m, 2 H, 1-$CH_2$), 6.73 (d, $J$ = 8.0 Hz, 1 H, 6-H), 7.50 (s, 1 H, 8-H), 7.19 (d, J = 8.0 Hz, 1 H, 5-H), 10.44 (s, 1 H, NH) | $C_{14}H_{17}N$ (199.30)<br>C 84.37/84.64<br>H 8.60/8.67<br>N 7.03/7.38 |

(*Continued*)

**Table 1**
(*Continued*)

| Compound | $R^1$ | $R^2$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$), δ | Elemental formula (molecular mass), Elemental analysis (calculated/found) |
|---|---|---|---|---|---|---|---|---|
| **4g** | 5-Me | 3-Me | 3,5-Dimethyl- 2,3,4,9-tetrahydro-1*H*-carbazole | A: 5 (**1c**, **2c**)[a] | 94 (ethanol) | 3386 s, 2921 s, 1565 w, 1457 w | 1.08 (d, $J$ = 6.5 Hz, 3 H, 3-Me), 1.42–1.47 (m, Hz, 1 H, 3-CH), 1.87–1.92 (m, 2 H, 2-$CH_2$), 2.30–2.35 (m, 1 H, 4-$CH_2$), 2.68 (s, 3 H, 5-$CH_3$), 2.55–2.59 (m, 1 H, 4-$CH_2$), 2.60-2.65 and 2.74–2.78 (2 m, 2 H, 1-$CH_2$), 6.60 (d, $J$ = 7.0 Hz, 1 H, 6-H), 6.82 (t, $J$ = 7.6 Hz, 1 H, 7-H), 7.02 (d, $J$ = 7.0 Hz, 1 H, 8-H), 10.54 (s, 1 H, NH) | $C_{14}H_{17}N$ (199.30)<br>C 84.37/84.72<br>H 8.60/8.36<br>N 7.03/6.75 |
| **4h** | 7-Me | 2-Me | 2,7-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 63 (**1c**, **2b**)[a] | 97 (ethanol) | 3406s, 3380 s, 2945 m, 2921 s, 1460 w, 1454 w | 1.07 (d, $J$ = 6.5 Hz, 3 H, 2-Me), 1.37–1.42 (m, 1 H, 2-CH), 1.85–1.89 (m, 2 H, 3-$CH_2$), 2.24–2.32 (m, 1 H, 4-$CH_2$), 2.34 (s, 3 H, 7-Me), 2.53–2.58 (m, 1 H, 4-$CH_2$), 2.63–2.67 and 2.71–2.77 (2 m, 2 H, 1-$CH_2$), 6.72 (d, $J$ = 8.0 Hz, 1 H, 6-H), 7.00 (s, 1 H, 8-H), 7.18 (d, $J$ = 8.0 Hz, 1 H, 5-H), 10.41 (s, 1 H, NH) | $C_{14}H_{17}N$ (199.30)<br>C 84.37/84.03<br>H 8.60/8.24<br>N 7.03/7.35 |
| **4i** | 5-Me | 2-Me | 2,5-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 4 (**1c**, **2b**)[a] | 95 (ethanol) | 3405 s, 3380 s, 2945 m, 2920 s, 2359 m, 1460 w, 1452 m | 1.08 (d, $J$ = 6.5 Hz, 3 H, 2-Me), 1.36–1.42 (m, 1 H, 2-CH), 1.85–1.89 (m, 2 H, 3-$CH_2$), 2.25–2.32 (m, 1 H, 4-$CH_2$), 2.53 (s, 3 H, 5-Me), 2.56–2.58 (m, 1 H, 4-$CH_2$), 2.63–2.66 and 2.72–2.77 (2 m, 2 H, 1-$CH_2$), 6.60 (d, $J$ = 7.0 Hz, 1 H, 6-H), 6.80 (t, $J$ = 7.6 Hz, 1 H, 7-H), 7.02 (d, $J$ = 7.0 Hz, 1 H, 8-H), 10.52 (s, 1 H, NH) | $C_{14}H_{17}N$ (199.30)<br>C 84.37/84.76<br>H 8.60/8.98<br>N 7.03/6.66 |
| **4j** | 8-Me | H | 8-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 43 (**1b**, **2a**) | 95 (ethanol) lit. 96–98 [23,25] | | | |

(*Continued*)

**Table 1**
(*Continued*)

| Compound | $R^1$ | $R^2$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$), δ | Elemental formula (molecular mass), Elemental analysis (calculated/found) |
|---|---|---|---|---|---|---|---|---|
| **4k** | 8-Me | 2-Me | 2,8-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 46 (**1b**, **2b**) | 102 (ethanol) lit. 103 [21,24] | 3391 s, 2948 s, 2915 s, 2838 s, 1617 m $cm^{-1}$ | 1.09 (d, $J$ = 6.7 Hz, 3 H, 2-Me), 1.36–1.47 (m, 1 H, 2-CH), 1.87–1.94 (m, 2 H, 3-$CH_2$), 2.29–2.36 (m, 1 H, 4-CH2), 2.40 (s, 3 H, 8-Me), 2.56–2.61 (m, 1 H, 4-$CH_2$), 2.66–2.70 (m, 1 H, 1-$CH_2$), 2.77–2.83 (m, 1 H, 1-$CH_2$), 6.75–6.83 (m, 2 H, 6-H, 7-H), 7.15 (d, $J$ = 7.5 Hz, 1 H, 5-H), 10.48 (s, 1 H, NH) | |
| **4l** | 8-Me | 3-Me | 3,8-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 48 (**1b**, **2c**) | 106 (ethanol) (lit. 108–109.6 [25]) | 3432 s, 3279 s, 2946 m, 2915 s, 2832 m, 1618 m | 1.19 (s, 3 H, 3-Me), 1.45–1.53 (m, 1 H, 3-CH), 1.88–1.92 (m, 2 H, 2-$CH_2$), 2.142.21 (m, 1 H, 4-$CH_2$), 2.40 (s, 3 H, 8-Me), 2.72–2.75 (m, 3 H, 4-$CH_2$), 2.68–2.70 and 2.81–2.83 (2 m, 2 H, 1-$CH_2$), 6.75–6.83 (m, 2 H, 6-H, 7-H), 7.14 (d, $J$ = 7.5 Hz, 1 H, 5-H), 10.52 (s, 1 H, NH) | |
| **4m** | 6-Cl | H | 6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole | B: 81 (**1f**, **2a**) | 149 (ethanol) (lit. 142–147 [26] | | | |
| **4n** | 6-Cl | 2-Me | 6-Chloro-2-methyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 86 (**1f**, **2b**) | 142 (ethanol) | 3402 s, 2922 s, 1580 m | 1.07 (d, $J$ = 6.5 Hz, 3 H, 2-Me), 1.36–1.45 (m, 1 H, 2-CH), 1.85–1.91 (m, 2 H, 3-$CH_2$), 2.27–2.34 and 2.49–2.57 (2 m, 2 H, 4-$CH_2$), 2.64–2.68 and 2.75–2.79 (2 m, 2 H, 1-$CH_2$), 6.84–6.97 (d, $J$ = 8.5 Hz, 1 H, 8-H), 7.24 (d, $J$ = 8.5 Hz, 1 H, 7-H), 7.33 (s, 1 H, 5-H), 10.82 (s, 1 H, NH) | $C_{13}H_{14}ClN$ (219.72) C 71.07/70.76 H 6.42/6.70 N 6.37/6.33 C |
| **4o** | 6-Cl | 3-Me | 6-Chloro-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 84 (**1f**, **2c**) | 115 (ethanol) | 3399 s, 2932 m, 2919 m, 2833 m, 1579 m | 1.08 (d, $J$ = 6.5 Hz, 3 H, 3-Me), 1.44–1.49 (m, 1 H, 3-CH), 1.87–1.90 (m, 2 H, 2-$CH_2$), 2.11–2.18 and 2.70–2.75 (2 m, 2 H, 4-$CH_2$), 6.95 (d, $J$ = 8.5 Hz, 1 H, 8-H), 7.22 (d, $J$ = 8.5 Hz, 1 H, 7-H), 7.32 (s, 1 H, 5-H), 10.85 (s, 1 H, NH) | $C_{13}H_{14}ClN$ (219.72) C 71.07/70.68 H 6.42/6.24 N 6.37/6.19 |

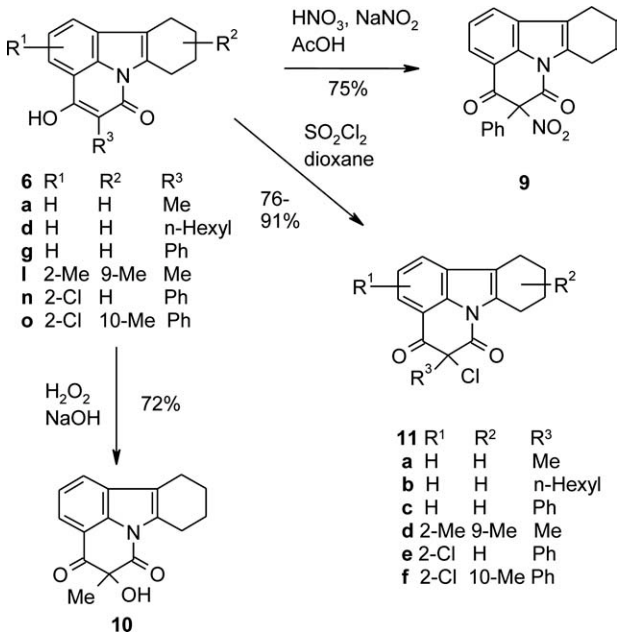
(*Continued*)

**Table 1**
(*Continued*)

| Compound | $R^1$ | $R^2$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$), δ | Elemental formula (molecular mass), Elemental analysis (calculated/found) |
|---|---|---|---|---|---|---|---|---|
| **4p** | 7-Cl | H | 7-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole | B: 52 (**1e**, **2a**) | 160.3 (cyclohexane) lit. 178–180 [27] | | | |
| **4q** | 7-Cl | 2-Me | 7-Chloro-2-methyl-2,3,4,9-tetrahydro-1*H*-carbazole | A: 59 (**1e**, **2b**) | 147 (ethanol) | 3391 s, 2948 m, 2919 s, 1619 m | 1.07 (d, $J$ = 6.5 Hz, 3 H, 2-Me), 1.36–1.45 (m, 1 H, 2-CH), 1.86–1.90 (m, 2 H, 3-$CH_2$), 2.26–2.33 and 2.55–2.59 (2 m, 2 H, 4-$CH_2$), 2.65–2.68 and 2.73–2.79 (2 m, 2 H, 1-$CH_2$), 6.91 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.24 (s, 1 H, 8-H), 7.31 (d, $J$ = 8.3 Hz, 1 H, 6-H), 10.79 (s, 1 H, NH) | $C_{13}H_{14}ClN$ (219.72) C 71.07/71.03 H 6.42/6.54 N 6.37/6.29. |
| **4r** | 7-Cl | 3-Me | 7-Chloro-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol | A 42 (**1e**, **2c**) | 144 (ethanol) | 3393 s, 2955 m, 2927 s, 2830 m, 1619 m | 1.08 (d, $J$ = 6.5 Hz, 3 H, 3-Me), 1.43–1.51 (m, 1 H, 3-CH), 1.86–190 (m, 2 H, 2-$CH_2$), 2.08–2.19 and 2.70–2.75 (2 m, 2 H, 4-$CH_2$, 1-$CH_2$), 6.91 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.25 (s, 1 H, 8-H), 7.30 (d, $J$ = 8.3 Hz, 1 H, 6-H), 10.81 (s, 1 H, NH) | $C_{13}H_{14}ClN$ (219.72) C 71.07/70.97 H 6.42/6.44 N 6.37/6.32 |

[a] The separation of compounds **4f/4g** and **4h/4i** was achieved by dry column flash chromatography (toluene/acetone as gradients).

**Scheme 4**




tetrahydrocarbazoles with methyl- and chloro substituents in the aromatic ring and methyl substituents in the saturated ring. The structure could be assigned to **4**, as evident from $^1$H NMR spectra with clear 9-NH signals ranging between 10.4 and 10.8 ppm, and no hydrogen signal of a 4a-proton present in the possibly formed isomeric structure **3**. 2-Methylcyclohexanone (**2**, $R^2$ = 2-Me) gives, depending on the reaction conditions, a mixture of both isomers of **3** and **4**, 1- or 4a-methyl-tetrahydrocarbazole [12]; the work on these topics is in progress [13]. 3-Methylcyclohexanone (**2b**) gave 2-methyl-tetrahydrocarbazoles **4e, h, i, k, n, q**, as evident from the $^1$H NMR signal of 4-$CH_2$ at ~2.6 ppm and of the 2-CH at ~1.4 ppm; the corresponding 4-methyl isomer could not be isolated. From 3-methylphenylhydrazine (**1c**) we isolated both isomers, 7-methyl-tetrahydrocarbazoles **4f,h** and 5-methyl derivatives **4g,i** in a ratio of about 10:1 (Scheme 2).

The cyclocondensation reaction of **4** was performed with ethyl 2-alkyl- and 2-phenylmalonates **5a-h**. $^1$H NMR spectral data revealed that in all cases the ring closure was directed to the aromatic ring to produce 4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol-6-ones **6** as evident from the ratio of aromatic: aliphatic protons and unaffected $CH_2$ groups in position 8. 6-Chloro-tetrahydrocarbazoles **4m-o** did not show significant influence on the synthesis and gave 2-chloro-pyridocarbazoles **6n-p**. 7-Chloro-tetrahydrocarbazoles **4p-r** gave, probably by deactivation of the aromatic nucleus, very low yields or unseparable mixtures which did not allow the isolation of pure 3-chloro-pyridocarbazoles **6**; the isolation of possibly formed isomers **7/8** was not achieved.

6-Methyl-tetrahydrocarbazoles **4c-e** formed in reasonable yields 2-methyl-pyridocarbazoles **6k-m**. 8-Methyl-tetrahydrocarbazoles **4j-l** prevented the formation of pyridocarbazoles **6** by steric hindrance, but gave again no reaction to isomeric pyridocarbazoles **7/8**.

The yields of pyridocarbazoles **6a-j** without substituents in the aromatic carbazole nucleus were ranging from 20 to 80%. The cyclization reaction proceeds in two steps via an initial malono-monoamide followed by formation of a thermally produced ketene derivative which cyclizes in an electrophilic substitution towards the aromatic carbazole ring [14]. The differing yields can be explained by both a competing malono-diamide formation and side-reactions during the ketene reaction.

There are some other reaction sequences known using highly reactive malonic acid derivatives, which avoid the high temperatures of the second ketene forming step: one of these derivatives is the well established *bis*(2,4,6-trichlorophenyl) malonate (active malonate, magic malonate) [15], another one is (chlorocarbonyl)ethylketene (chlorocarbonylketene, in older literature also named as malonyldichloride) [16]. We compared the reactions of *bis*(2,4,6-trichlorophenyl) 2-benzylmalonate (**5i**) and 2-benzyl-2-(chlorocarbonyl)ethylketene (**5j**) with tetrahydrocarbazole **4a** to 5-benzyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1:*jk*]carbazol-6-one (**6h**). Both reactions gave the desired product **6h**, trichlorophenylester **5i** in 30% and chlorocarbonylketene **5j** in 55% yield, which is better than the yield of the thermal method, but does not counterbalance the disadvantages of time-consuming and expensive syntheses of **5i** and **5j** (Scheme 3; Table 1).

Tetrahydro-pyridocarbazoles **6** possess besides the biologically interesting indole structure a 4-hydroxy-pyridone structure element, which is susceptible for many reactions. It can exist in tautomeric structures: the 4-hydroxy-6-oxo-structure as drawn in **6** is the predominant structure as evident in all spectroscopic investigations (*e.g.* shown by the hydroxy signal at 10.6–10.9 ppm in the $^1$H NMR spectra, and a single IR signal for the amide-CO at position 6 at about 1650 $cm^{-1}$). A reversed 4-oxo-6-hydroxy structure can be excluded because of its missing 4-pyridone signal in IR spectra [17]. However, during reactions with suitable reagents, the molecule can react from its 4,6-dioxo tautomer giving fixed dioxo-derivatives. The carbon at position 5 behaves due to the neighborship of two carbonyl groups as reactive CH acidic moiety, and electrophilic reactions such as nitration are directed first to this position. Therefore, it is possible to nitrate **6a** in position 5 by a gentle reaction with concentrated nitric acid in the presence of sodium nitrite as catalyst in glacial acetic acid already

**Table 2**

4-Hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol-6-ones (**6**).

| Compound | $R^1$ | $R^2$ | $R^3$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$ unless otherwise stated), δ | Elemental formula (molecular mass), elemental analysis (calculated./ found) |
|---|---|---|---|---|---|---|---|---|---|
| **6a** | H | H | Me | 4-Hydroxy-5-methyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*]carbazol- 6-one | B: 77 (**4a**, **5a**) | 144 (ethanol) | 3435 s, 2934 s, 1649 m (6-C=O), 1610 s, 1591 w | 1.76–1.79 and 1.84–1.86 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.03 (s, 3 H, 5-$CH_3$), 2.67 (t, $J$ = 7.1 Hz, 2 H, 8-$CH_2$), 3.08 (t, $J$ = 7.1 Hz, 2 H, 11-$CH_2$), 7.39 (t, $J$ = 7.7 Hz, 1 H, 2-H), 7.66 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.85 (d, $J$ = 7.7 Hz, 1 H, 3-H), 10.69 (s, 1 H, OH) | $C_{16}H_{15}NO_2$ (253.30) C 75.87/75.59 H 5.97/5.91 N 5.53/5.57 |
| **6b** | H | H | Et | 5-Ethyl-4-hydroxy-8,9,10,11-tetrahydro-pyrido [3,2,1-*jk*] carbazol-6-one | B: 46 (**4a**, **5b**) | 232 (ethanol) | 3440 s, 2930 s, 1650 m (6-C=O), 1610 s, 1590 w | 0.95 (s, 3 H, Me), 1.75-1.80 and 1.83–1.90 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.58 (q, 2 H, 5-$CH_2$), 2.65 (t, $J$ = 7.1 Hz, 2 H, 8-$CH_2$), 3.10 (t, $J$ = 7.1 Hz, 2 H, 11-$CH_2$), 7.40 (t, $J$ = 7.7 Hz, 1 H, 2-H), 7.65 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.85 (d, $J$ = 7.7 Hz, 1 H, 3-H), 10.70 (s, 1 H, OH) | $C_{17}H_{17}NO_2$ (267.33) C 76.38/75.92 H 6.41/6.40 N 5.24/5.10 |
| **6c** | H | H | n-Bu | 5-Butyl-4-hydroxy-8,9,10,11-tetrahydro-pyrido [3,2,1-*jk*] carbazol-6-one | B: 37 (**4a**, **5c**) | 210 (ethanol) | 3400–3350 b, m, 2960 m, 1640 s (6-C=O), 1615 m, 1595 m | 0.91 (t, $J$ = 7.0 Hz, 3 H, Me), 1.32–1.42 (m, 2 H, $CH_2$), 1.47–1.51 (m, 2 H, $CH_2$), 1.75–1.79 and 1.84–1.90 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.69 (t, $J$ = 7.0 Hz, 5-$CH_2$), 7.42 (t, $J$ = 7.7 Hz, 1 H, 2-H), 7.66 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.84 (d, $J$ = 7.7 Hz, 1 H, 3-H), 10.80 (s, 1 H, OH) | $C_{19}H_{21}NO_2$ (295.38): C 77.26/77.54 H 7.17/6.82 N 4.74/4.35 |

(*Continued*)

**Table 2**
(*Continued*)

| Compound | $R^1$ | $R^2$ | $R^3$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$ unless otherwise stated), δ | Elemental formula (molecular mass), elemental analysis (calculated./ found) |
|---|---|---|---|---|---|---|---|---|---|
| **6d** | H | H | n-Hexyl | 5-Hexyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol- 6-one | A: 30 (**4a**, **5d**) | 162 (ethanol) | 3300-3100 b, 2930 m, 1645 m (6-C=O), 1605 s, 1590 s | 0.85 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), 1.20-1.60 (m, 4 H, 2 hexyl-$CH_2$), 1.70–1.90 (m, 4 H, 9-$CH_2$ and 10-$CH_2$), 2.50-2.70 (m, 4 H, 4-$CH_2$, 11-$CH_2$), 3.10 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 7.40 (t, $J$ = 7.1 Hz, 1 H, 2-H), 7.65 (d, $J$ = 7.1 Hz, 1 H, 1-H), 7.90 (d, $J$ = 7.1 Hz, 1 H, 3-H), 10.60 (s, OH) | $C_{21}H_{25}NO_2$ (323.44): C 77.99/77.87 H 7.79/7.73 N 4.33/4.46 |
| **6e** | H | H | n-Heptyl | 5-Heptyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol-6-one | A: 37 (**4a**, **5e**) | 144 (toluene) | 3300-3000 b, 2920 s, 1650 m (6-C=O), 1610 s, 1590 s | 0.80 (t, $J$ = 7.0 Hz, 3 H, Me), 1.15–1.60 (m, 5 heptyl-$CH_2$), 1.80–2.00 (m, 4 H, 9-$CH_2$ and 10-$CH_2$), 2.50-2.80 (m, 4 H, 4-$CH_2$, 11-$CH_2$), 3.10 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 7.40 (t, $J$ = 7.1 Hz, 1 H, 2-H), 7.70 (d, $J$ = 7.1 Hz, 1 H, 1-H), 7.90 (d, $J$ = 7 Hz, 1 H, 3-H), 10.65 (s, 1 H, NH) | $C_{22}H_{27}NO_2$ (337.47): C 78.30/78.68 H 8.06/7.78 N 4.15/4.02. |
| **6f** | H | H | Cyclohexyl | 5-Cyclohexyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-*jk*] carbazol-6-one | A: 22 (**4a**, **5f**) | 245 (ethanol) | 3300–3100 b, 2920m, 1740 w, 1660 s (6-C=O), 1600 s, 1590 sh | 1.10–1.50 (m, 4 H, 2 $CH_2$), 1.60–2.10 (m, 10 H, 5 $CH_2$), 2.15–2.20 (m, 1 H, CH), 2.60–2.80 (m, 1 H, 8-$CH_2$), 3.10 (t, $J$ = 7.0 Hz, 11-$CH_2$), 7.45 (t, $J$ = 7.1 Hz, 1 H, 2-H), 7.70 (d, $J$ = 7.1 Hz, 1 H, 1-H), 8.04 (d, $J$ = 7 Hz, 1 H, 3-H), 10.65 (s, 1 H, NH) | $C_{21}H_{23}NO_2$ (321.42) C 78.47/68.69 H 7.21/ 5.80 N 4.36/ 4.34. |
| **6g** | H | H | Ph | 4-Hydroxy-5-phenyl-8,9,10,11-tetrahydropyrido[3,2,1-*jk*]carbazol-6-one | B: 37 (**4a**, **5g**) | 207 (ethanol); lit 210°C [28,29] | | | |

(*Continued*)

**Table 2**
(*Continued*)

| Compound | $R^1$ | $R^2$ | $R^3$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$ unless otherwise stated), δ | Elemental formula (molecular mass), elemental analysis (calculated./ found) |
|---|---|---|---|---|---|---|---|---|---|
| **6h** | H | H | $CH_2Ph$ | 5-Benzyl-4-hydroxy-8,9,10,11-tetrahydropyrido [3,2,1-*jk*]carbazol-6-one | B: 27 (**4a**, **5h**) Methods C and D:[b] | 240 (glacial acetic acid/ water) lit. 240–245 [28] | | | |
| **6i** | H | 10-Me | Et | 5-Ethyl-4-hydroxy- 10-methyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*] carbazol-6-one | A: 26 (**4b**, **5b**) | 240 (ethanol) | 3400–3200 m, 2960 m, 2920 m, 1650 m (6-C=O), 1610 s | 1.05 (t, $J$ = 7.0 Hz, Me), 1.4–1.6 and 1.7–2.0 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.20 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 2.60 (q, $J$ = 7.0 Hz, 2 H, 5-$CH_2$), 2.95 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 7.35 (t, $J$ = 6.8 Hz, 1 H, 2-H), 7.6 (d, $J$ = 6.8 Hz, 1 H, 1-H), 7.90 (d, $J$ = 6.8 Hz, 1 H, 3-H), 10.70 (s, 1 H, OH) | $C_{18}H_{19}NO_2$ (281.36): C 76.84/76.72 H 6.81/6.72 N 4.98/ 4.83 |
| **6j** | H | 10-Me | n-Bu | 5-Butyl-4-hydroxy-10-methyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*] carbazol-6-one | A: 62 (**4b**, **5c**) | 220 (ethanol) | 3400–3200 m, 2930 m, 1645 m (6-C=O), 1620 sh, 1600 s | 0.80 (t, $J$ = 7.0 Hz, 3 H, butyl-Me), 1.05 (d, $J$ = 7.0 Hz, 3 H, 10-Me), 1.20-1.70 (m, 6 H, 3 $CH_2$), 1.80–2.00 (m, 2 H, 10-H), 2.20, (t, $J$ = 7.0 Hz, 5-$CH_2$), 2.55 (t, $J$ = 7 Hz, 2 H, 11-$CH_2$), 2.95 (t, $J$ = 7 Hz, 2 H, 8-$CH_2$), 7.35 (t, $J$ = 6.9 Hz, 1 H, 2-H), 7.65 (d, $J$ = 6.9 Jz, 1 H, 1-H), 7.85 (d, $J$ = 6.9 Hz, 1 H, 3-H), 10.90 (s, 1 H, OH) | $C_{20}H_{23}NO_2$ (309.41): C 77.64/77.98 H 7.49/7.21 N 4.53/4.17 |
| **6k** | 2-Me | H | Ph | 4-Hydroxy-2-methyl-5-phenyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*] carbazol-6-one | A: 52 (**4c**, **5g**) | 181 (ethanol) | 3450 s, 2950 s, 1650 s (6-C=O), 1610 m | 1.75–2.00 (m, 4 H, 9-$CH_2$ and 10-$CH_2$), 2.65 (s, 3 H, 2 Me)2.75 (t, $J$ = 7.0 Hz, 8-$CH_2$), 3.10 (t, $J$ = 7.0 Hz, 11-$CH_2$), 7.25–7.50 (m, 6 H, ArH), 7.80 (s, 1-H), 8.05 (s, 1 H, 3-H), 10.85 (s, OH) | $C_{22}H_{19}NO_2$ -329.4 C 80.22/80.54 H 5.81/5.59 N 4.25/3.89 |

(*Continued*)

**Table 2**
(*Continued*)

| Compound | $R^1$ | $R^2$ | $R^3$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$ unless otherwise stated), δ | Elemental formula (molecular mass), elemental analysis (calculated./ found) |
|---|---|---|---|---|---|---|---|---|---|
| **6l** | 2-Me | 9-Me | Me | 4-Hydroxy-2,5,9-trimethyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*] carbazol-6-one | B: 63 (**4e**, **5a**) | 262 (ethanol) | 3435 s, 2922 m, 1649 m (6-C=O), 1627 m, 1613 m | 1.11 (d, $J$ = 7.0 Hz, 3 H, 9-Me), 1.42–1.47 (m, 1 H, 9-H), 1.87–1.92 (m, 2 H, 10-$CH_2$), 2.03 (s, 3 H, 5-Me), 2.08 (s, 3 H, 2-Me), 2.56-2.73 (m, 4 H, 8-$CH_2$, 11-$CH_2$), 7.50 (d, $J$ = 7.0 Hz, 1 H, 1-H), 7.67 (d, $J$ = 7.0 Hz, 1 H, 3-H), 10.70 (s, 1 H, OH) | $C_{18}H_{19}NO_2$ (281.36) C 76.84/76.49 H 6.81/6.64 N 4.98/4,89 |
| **6m** | 2-Me | 10-Me | Ph | 4-Hydroxy-2,10-dimethyl-5-phenyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*]carbazol-6-one | A 49 (**4d**, **5g**) | 217 (toluene) | 3450 s, 2920 s, 1650 s (6-C=O), 1605 m | 1.10 (d, $J$ = 7.0 Hz, 3 H, 10-Me), 1.45–1.50 (m, 1 H, 9-H), 1.85–1.95 (m, 2 H, 9-$CH_2$), 2.05 (s, 3 H, 2-Me), 2.55-2.75 (m, 4 H, 8-$CH_2$, 11-$CH_2$), 7.20–7.70 (m, 5 Ph-H), 7.80 (d, $J$ = 2 Hz, 1 H, 1-H), 8.00 (d, $J$ = 7.0 Hz, 1 H, 3-H), 10.80 (s, 1 H, OH) | $C_{23}H_{21}NO_2$ (343.43) C 80.44/80.28 H 6.16/5.69 N 4.08/4.03 |
| **6n** | 2-Cl | H | Ph | 2-Chloro-4-hydroxy- 5-phenyl-8,9,10,11-tetrahydropyrido [3,2,1-*jk*] carbazol-6-one | A: 23 (**4m, 5g**) | 200 (ethanol) | 3500–3000 m, 2940 m, 1650 m (6-C=O), 1620 s, 1590 sh | 1.75–1.95 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.75 and 3.10 (2 t, $J$ = 7.0 Hz, 11-$CH_2$ and 8-$CH_2$), 7.20–7.70 (m, 5 Ph-H), 7.80 (d, $J$ = 2.0 Hz, 1 H, 1-H), 8.00 (d, $J$ = 7.0 Hz, 1 H, 3-H), 11.00 (s, 1 H, OH) | $C_{21}H_{16}ClNO_2$ (349.82): C 72.10/72.45 H 4.61/4.52 N 4.00/3.73 |
| **6o** | 2-Cl | 10-Me | Ph | 2-Chloro-4-hydroxy-10-methyl-5-phenyl-8,9,10,11-tetrahydro-pyrido [3,2,1-jk]carbazol-6-one | A: 31 (**4o**, **5g**) | 268 (toluene) | 3200–2800 w, 1650 m (6-C=O), 1625 s, 1595 m | 1.05 (d, $J$ = 7.0 Hz, 3 H, 10-Me), 1.30–1.55 (m, 1 H, 10-H), 1.75–2.00 (m, 2 H, 9-$CH_2$), 2.65 (d, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 2.90–3.05 (m, 2 H, 8-$CH_2$), 7.10–7.60 (m, 5 H, PhH), 7.7 (d, $J$ = 1.5 Hz, 1 H, 1-H), 7.95 (d, $J$ = 1.5 Hz, 1 H, 3-H) | $C_{22}H_{18}ClNO_2$ (363.85): C 72.63/73.01 H 4.99/5.05 N 3.85/3.70 |

(*Continued*)

**Table 2**
(*Continued*)

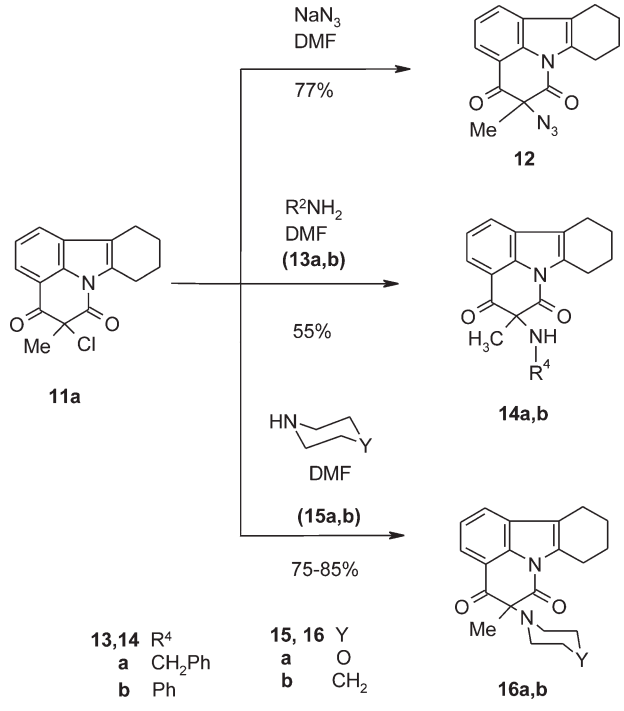
| Compound | $R^1$ | $R^2$ | $R^3$ | Chemical name | Method: yield(%) (starting material) | mp (°C) solvent | IR (KBr-discs, $cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$ unless otherwise stated), δ | Elemental formula (molecular mass), elemental analysis (calculated./ found) |
|---|---|---|---|---|---|---|---|---|---|
| **6p** | 2-Cl | 10-Me | Me | 2-Chloro-5,10-dimethyl-4-Hydroxy-8,9,10,11- tetrahydropyrido [3,2,1-*jk*]carbazol-6-one | B 66 (**4o**, **5a**) | 275 (ethanol) | 3432 s, 2919 m, 1649 m (6-C=O), 1624 s, 1561 s | 1.07 (d, $J$ = 6.0 Hz, 3 H, 10-Me), 1.44–1.46 (m, 1 H, 10-H), 1.85–1.93 (m, 2 H, 9-$CH_2$), 2.00 (s, 3 H, 5-H), 2.11–2.18 and 2.73–2.76 (2 m, 2 H, 11-$CH_2$), 2.88– 2.93 and 3.15–3.20 (2 m, 2 H, 8-$CH_2$), 7.63 (s, 1 H, 5-H), 7.79 (s, 1 H, 7-H), 10.81 (s, 1 H, OH) | $C_{17}H_{16}ClNO_2$ (301.78): C 67.66/67.76 H 5.34/4.97 N 4.64/4.26 |

[b]Methods C and D for 6h are described in the experimental part.

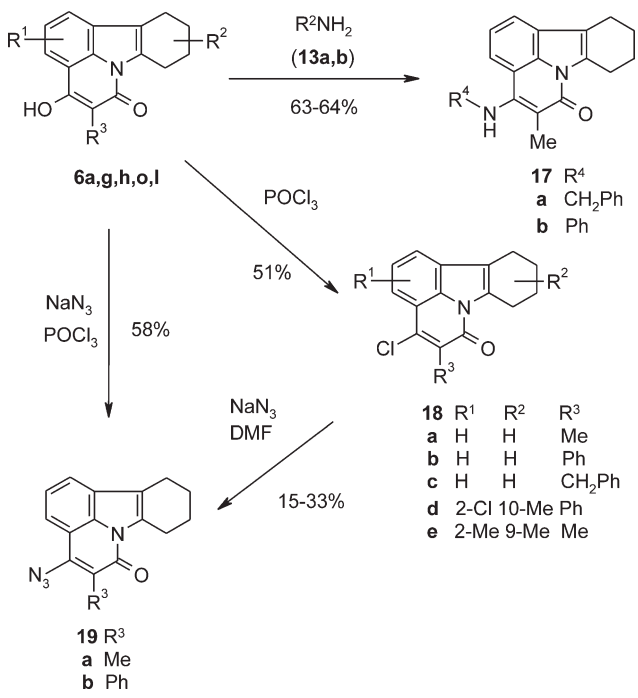
at room temperature. All other aromatic positions (1,2, and 3) remain unaffected, and 5-nitro-pyridocarbazoledione **9** is obtained in 75% yield. Hydroxylation of **6a** with hydrogenperoxide in buffered slightly alkaline aqueous solution gives in good yields 5-hydroxy-pyridocarbazoledione **10**, which contains the 3-hydroxy-2,4-dioxoquinoline structure element present in contents of some *Pseudomonas* bacteria (Scheme 4; Table 2) [18].

Electrophilic chlorination of **6** in position 5 could be performed with sulfuryl chloride. Because of the reactivity of this reagent, 2,5-dimethyl- and 2,5,9-trimethyl derivatives **6a** and **6k** had to be brought to reaction at room temperature, otherwise polychlorinated by-products were formed. The formed 5-chloro-pyridocarbazolediones **11**, which were obtained in excellent yields, serve as starting material for further substitution reactions: as examples an azidation and aminations are shown. The azidation of **11a** proceeds by simple halogen exchange at the aliphatic C-5 position at 50°C and gives in excellent yields 5-azido-pyridocarbazoledione **12**. Amination was performed with primary and secondary amines: **11a** gave with benzylamine (**13a**) the corresponding 5-benzylamino-pyridocarbazoledione **14a** in excellent yields; with aniline (**13b**) as the amino component, the yield of the corresponding 5-phenylamino-pyridocarbazoledione **14b** was slightly lower. Reaction of **1a** with secondary amines such as morpholine (**15a**) or piperidine (**15b**) gave in excellent yields 5-morpholino- and 5-piperidino-pyridocarbazolediones **16a**,**b** (Scheme 5).

**Scheme 5**



**Scheme 6**




In contrast to the electrophilic reactions shown above, a nucleophilic displacement takes place at the 4-position of the pyridocarbazolone. The 4-hydroxy group of **6** can be easily displaced by a chloro function, using phosphoryl chloride as reagent, or by substituted amino groups. Amination of **6a** at position 4 can be achieved by reaction of the reactive 4-hydroxy group with benzylamine (**13a**) and gives 4-benzylamino-pyridocarbazolones **17a** in excellent yield. The amination of **6a** with aniline (**13b**) needed the addition of aniline hydrochloride as acidic catalyst and gave in exellent yields 4-anilinopyridocarbazolone **17b**. Chlorination with phosphoryl chloride gave 4-chloropyridocarbazolones **18** in moderate to excellent yields. The nucleophilic exchange of the chloro substituent in 4-chloro-5-methylpyridocarbazolone **18a** against the azide group gave 4-azidopyrido[3,2,1-*jk*]carbazolones **19a** in only 15% yield. 4-Chloro-5-phenylpyridocarbazolone **18b** gave slightly better yields of 33% of the corresponding 4-azidopyrido[3,2,1-*jk*]carbazolone **19b**. To improve the yield, we used our recently developed one-pot synthesis [5] starting from 4-hydroxypyridocarbazolone **6a**, which reacted with a mixture of sodium azide and phosphoryl chloride (probably via reactive phosphoric esters) in dimethylformamide to obtain in this one-pot reaction **19a** in 58% yield (Scheme 6).

## CONCLUSION

Our results show that cyclization reactions of 2,3,4,5-tetrahydro-1*H*-carbazoles **1** with malonic acid derivatives give solely the 8,9,10,11-pyrido[3,2,1-*jk*]carbazole system **6**. Attempts to force a cyclization to 1,2,3,3a-tetrahydro-pyrido[3,2,1-jk]carbazole or its tautomeric ring system (**7/8**) by deactivation of the aromatic nucleus by electronic or steric influences failed. Electrophilic and nucleophilic substitution reactions with suitable reagents and conditions took place exclusively at the fused pyridone ring at position 5 or 4, respectively.

## EXPERIMENTAL

**General.** Melting points were determined using a Stuart SMP3 Melting Point Apparatus in open capillary tubes. IR spectra were recorded using a Mattson Galaxy Series FTIR 7020 instrument with potassium bromide discs. NMR spectra were recorded on a Bruker AMX 360 instrument (360 MHz $^1$H, 90 MHz $^{13}$C) or on a Bruker Avance DRX 500 instrument (500 MHz $^1$H, 125 MHz $^{13}$C). Chemical shifts are given in ppm (δ) from the internal TMS standard. Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna, Austria. Mass spectra were obtained from a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen). Dry column flash chromatography [19] was carried out on Merck Kieselgel 60 H (5–40 μm). All reactions were monitored by thin layer chromatography on 0.2 mm silica gel F 254 (Merck, Darmstadt, Germany) plates using UV light (254 and 366 nm) for detection. Analytical HPLC was performed on a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 μm) column, running an acetonitrile/water gradient (30–100% acetonitrile). Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

***General methods for the Fischer indole synthesis of 2,3,4,9-tetrahydro-1H-carbazoles (4).*** *Method A (one pot procedure).* To a mixture of anhydrous sodium acetate (2.46 g, 30 mmol) in glacial acetic acid (40 mL) the appropriate cyclohexanone **2** (30 mmol) was added at 90°C, then the corresponding phenylhydrazine hydrochloride **1.HCl** (25 mmol) was added in small portions during 1 h. The reaction mixture was further heated under reflux for 1 h, cooled to room temperature and diluted with diethyl ether (100 mL). The precipitated solid (inorganic salts) was separated by suction filtration and washed with diethyl ether. The combined filtrates were taken to dryness in vacuo, the residue diluted with a mixture of ethanol/water (7:3, 100 mL) and after standing for 3 h, the precipitated product isolated by suction filtration. The product was dried in vacuo at room temperature, then recrystallized from the appropriate solvent using charcoal.

*Method B (2-step procedure).* The corresponding phenylhydrazine hydrochloride **1.HCl** (27 mmol) was suspended in 0.5*M* aqueous sodium hydroxide (100 mL) and stirred at 70°C for 30 min. After cooling the precipitated oil was separated (loss ~5–10%) and added without further purification to a solution of the appropriate cyclohexanone **2** (30 mmol) in glacial acetic acid (70 mL) in small portions during 1 h. The reaction mixture was then heated under reflux for 1 h and cooled to room temperature under stirring until a solid precipitated. The

mixture was cooled to 5°C, the precipitated solid isolated by suction filtration and the filtrate cooled again to isolate a second crop. The combined solids were washed with water (100 mL) and ethanol/water (7:3, 100 mL), air-dried and then recrystallized from the appropriate solvent using charcoal.

R-key and data of **4a-r**: Table 1.

***General Methods for the cyclization of tetrahydrocarbazoles 4 to 4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazol-6-ones (6).*** *Method A (thermal neat method).* A mixture of the appropriate diethyl malonate **5** (30 mmol) and the corresponding tetrahydrocarbazole **4** (25 mmol) was heated for 2–3 h to 280–300°C in a metal bath using a Vigreux column equipped with a distillation bridge. During this time the first equivalent of ethanol (25 mmol, about 0.9 mL) was liberated. When the liberation of ethanol had stopped, the reaction mixture was heated for about 30 min to a bath temperature of 330–350°C; during this time the second equivalent of ethanol (0.9 mL, 25 mmol) was liberated. The reaction mixture was cooled to about 80°C, methanol (30 mL) was added, the mixture cooled to room temperature and filtered by suction. The solid was taken up in aqueous sodium hydroxide solution (0.25*M*, 100 mL) and extracted with toluene (100 mL). The aqueous layer was decolorized with charcoal at 50 to 80°C and filtered. Concentrated hydrochloric acid was added to the filtrate until pH ~3, the precipitate filtered by suction, washed acid-free with water, dried and recrystallized from the appropriate solvent.

*Method B (thermal solution method).* A solution of the appropriate diethyl malonate **5** (30 mmol) and the corresponding tetrahydrocarbazole **4** (25 mmol) in diphenylether (25 mL) was heated under reflux at 250°C in a metal bath using a Vigreux column equipped with a distillation bridge for about 12 h. During this time, 2 equivalents of ethanol were liberated (50 mmol, about 1.8 mL). After cooling to room temperature, diethyl ether (50 mL) was added, and the solid which precipitated was filtered by suction, washed with diethyl ether and dried. The collected solid was taken up in aqueous sodium hydroxide solution (0.25*M*, 100 mL) and filtered by suction. Concentrated hydrochloric acid was added to the filtrate until pH ~3, the precipitate filtered by suction, washed acid-free with water, dried and recrystallized from the appropriate solvent.

R-key and data of **6a-p**: Table 2.

***5-Benzyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazol-6-one (6h).*** From tetrahydrocarbazole **4a** and *bis*(2,4,6-trichlorophenyl) 2-benzylmalonate (**5i**) (Method C, ''active malonate'' method [15]):

Bis*(2,4,6-trichlorophenyl) 2-benzylmalonate (**5i**).* A mixture of dry 2-benzylmalonic acid (**5**, $R^3 = CH_2Ph$, X = OH) (38.8 g, 0.2 mol), 2,4,6-trichlorophenol (63.2 g, 0.32 mol) and phosphoryl chloride (64.4 g, 0.42 mol) was heated under reflux until the evolution of hydrogen chloride gas had stopped (about 4–6 h). The reaction mixture was then poured onto crushed ice (600 mL), filtered by suction, the solid washed with ice-water, dissolved in toluene (400 mL) and washed with aqueous sodium hydrogencarbonate solution (5%) and water. The organic layer was dried with sodium sulfate and the solvent removed under reduced pressure. The residue was triturated with hexane, filtered and dried at room temperature. The yield was 44.6 g (50%), light yellowish prisms, mp 104°C (lit. mp 106–107°C [15a]).

*5-Benzyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1:jk]carbazol-6-one (**6h**).* An intimate mixture of tetrahydrocarbazole **4a** (3.75 g, 22 mmol) and *bis*(2,4,6-trichlorophenyl) 2-benzylmalonate (**5i**) (12.1 g, 22 mmol) was heated without solvent for 60 min to 250°C. The 2,4,6-trichlorophenol vapors were removed *via* a funnel into the water pump. After cooling the dark reaction mixture was washed with hexane until the product became semi-solid. Then the product was stirred overnight with aqueous sodium hydroxide solution (0.5*M*, 500 mL), filtered, the filtrate extracted with toluene (2 × 100 mL) and the aqueous phase acidified with concentrated hydrochloric acid. The precipitate was washed with water, recrystallized from glacial acetic acid/water and dried. The yield was 2.17 g (30%).

***From tetrahydrocarbazole 4a and 2-benzyl-2-(chlorocarbonyl)ethylketene (5j) (Method D, ''(chlorocarbonyl)ethylketene''-method [16]).*** *2-Benzyl-2-(chlorocarbonyl)ethylketene (5j).* To a solution of 2-benzylmalonic acid (**5**, $R^3 = CH_2Ph$, X = OH) (38.8 g, 0.2 mol) in toluene (50 mL), thionyl chloride (59.5 g, 0.6 mol) was added dropwise under stirring in a nitrogen atmosphere. The mixture was heated for 24 h under reflux, then toluene and excess thionyl chloride were removed by distillation under reduced pressure (60°C, 130 mm Hg). The residue was distilled under reduced pressure (134–140°C, 15 mm Hg). The yield was 27.2 g (70%) yellowish oil; lit. bp 110–112°C (1.5 mm Hg) [16b].

*5-Benzyl-4-hydroxy-8,9,10,11-tetrahydropyrido[3,2,1:jk]carbazol-6-one (6h).* To a solution of tetrahydrocarbazole **4a** (5.12 g, 30 mmol) in dry ethyl acetate (150 mL), 2-benzyl-2-(chlorocarbonyl)ketene (**5j**) (6.5 g, 33 mmol) and dry triethylamine (4.5 mL) was added at 40–50°C. The yellow reaction mixture turned red and viscous and a small amount of a dark solid precipitated. The reaction mixture was kept for 30 min at room temperature, then the precipitate was filtered off, the filtrate taken to dryness under reduced pressure and triturated with xylene. The resulting precipitate was filtered by suction and dried. The yield was 5.42 g (55%), yellowish prisms. Data of **6h**: Table 2.

***5-Nitro-5-phenyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (9).*** A solution of 4-hydroxy-pyridocarbazole **6a** (2.00 g, 6.3 mmol) in glacial acetic acid (12 mL) was treated with concentrated nitric acid (1.2 mL) and sodium nitrite (0.03 g). The mixture was stirred for 30 min at room temperature, then diluted with ice/water (45 mL), the formed yellow precipitate separated by suction filtration and washed with water until acid-free. The yield was 1.70 g (75%), yellow prisms, mp 164°C (methanol). IR: 2960–2860 w, 1730 s (4-C=O), 1695 s (6-C=O), 1660 sh, 1625 w, 1590 w, 1570 s $cm^{-1}$; $^1H$ NMR ($CF_3COOH$): δ 1.80–2.10 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.70 (t, $J = 7.0$ Hz, 2 H, 11-$CH_2$), 3.15 (t, $J = 7.0$ Hz, 2 H, 8-$CH_2$), 7.25 (t, $J = 7.1$ Hz, 1 H, 2-H), 7.35–7.50 (m, 3 H, PhH), 7.55–7.60 (m, 2 H, PhH), 7.70 (d, $J = 7.1$ Hz, 1-H), 7.90 (d, $J = 7.1$ Hz, 1 H, 8-H). Anal. calcd. for $C_{21}H_{16}N_2O_4$ (360.37): C, 69.99; H, 4.48; N, 7.77. Found: C, 70.34; H, 4.71; N, 7.45.

***5-Hydroxy-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazol-4,6-dione (10).*** A solution of 4-hydroxy-pyridocarbazole **6a** (0.68 g, 2.7 mmol) in aqueous sodium hydroxide solution (0.25*M*, 60 mL) was slowly brought to pH ~8 with aqueous potassium dihydrogenphosphate solution (1*M*, ~10 mL), then hydrogenperoxide (30%, 20 mL) was added. The reaction mixture was stirred for 6 h at 40°C. After cooling to room temperature, the mixture was poured onto crushed ice/water (100

mL), the solid filtered by suction and washed with water. The yield was 0.52 g (72%), yellow prisms, mp 189°C (ethanol). IR: 3395 s, 2945 m, 1711 s (4-C=O), 1684 s (6-C=O), 1630 w, 1593 m $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.49 (s, 3 H, 5-Me), 1.82–1.88 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.68 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.06 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 6.15 (s, 1 H, 5-OH), 7.41 (t, $J$ = 7.6 Hz, 1 H, 2-H), 7.69 (d, $J$ = 7.6 Hz, 1 H, 1-H), 7.82 (d, $J$ = 7.6 Hz, 1 H, 3-H); MS [APCI, pos]: m/e (%) = 271 (11), 270 (M, 100). Anal. calcd. for $C_{16}H_{15}NO_3$ (269.30): C, 71.36; H, 5.61; N, 5.20. Found: C, 71.20; H, 5.86; N, 5.22.

***5-Chloro-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazol-4,6-dione (11a).*** To a suspension of 4-hydroxy-pyridocarbazole **6a** (2.30 g, 9 mmol) in dioxane (50 mL) at 20°C, sulfuryl chloride (0.8 mL, 10 mmol) was added slowly. The reaction mixture was stirred for 5 h at room temperature and then poured onto crushed ice/water (200 mL). The solid was filtered and washed with water. The yield was 2.00 g (76%), yellow needles, mp 182°C (ethanol). IR: 3432 s, 2936 m, 1722 s (4-C=O), 1689 s (6-C=O), 1629 w, 1592 w $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.74–1.82 and 1.86–1.94 (2 m, 4 H, 9-$CH_2$ and 10-$CH_2$), 1.98 (s, 3 H, 5-Me), 2.70 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.06 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 7.45 (t, $J$ = 7.6 Hz, 1 H, 2-H), 7.78 (d, $J$ = 7.6 Hz, 1 H, 1-H), 7.81 (d, $J$ = 7.6 Hz, 1 H, 3-H). Anal. calcd. for $C_{16}H_{14}ClNO_2$ (287.75): C, 66.79; H, 4.90; N, 4.87. Found: C, 66.90; H, 4.92; N, 4.85.

***5-Chloro-5-phenyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (11b).*** To a suspension of 4-hydroxy-pyridocarbazole **6g** (1.65 g, 5.2 mmol) in dioxane (25 mL) at 50°C, sulfuryl chloride (1.70 g ~1.01 mL, 12.6 mmol) was added slowly. The mixture was stirred for 10 min, heated to boiling for a few min and then poured onto crushed ice/water (50 mL). The oily product was stirred and washed several times with water until solid. The yellow-orange precipitate was crushed, filtered by suction and washed with water. The yield was 1.79 g (97%), yellow prisms, mp 116°C (ethanol). IR: 3430 s, 2935 m, 1720 s (4-C=O), 1690 s (6-C=O), 1630 w $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.75–1.83 and 1.85–1.93 (2 m, 4 H, 9-$CH_2$ and 10-$CH_2$), 2.71 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.05–3.09 (m, 2 H, 8-$CH_2$), 7.37–7.50 (m, 4 H, 3 PhH, 2-H), 7.55–7.60 (m, 2 H, PhH), 7.75–7.85 (m, 2 H, 1-H, 3-H). Anal. calcd. for $C_{21}H_{16}ClNO_2$ (349.82): C, 72.10; H, 4.61; N, 4.00. Found: C, 72.36; H, 4.32; N, 4.25.

***5-Chloro-2,5,9-trimethyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (11c).*** From 4-hydroxy-pyridocarbazole **6l** (5.06 g, 18 mmol) in dioxane (100 mL) and sulfuryl chloride (2.7 g ~1.61 mL, 20 mmol) as described for **11a**. Work-up was performed as described for **11b**. The yield was 4.56 g (80%) orange-yellow needles, mp 151°C (ethanol). IR: 3435 s, 2949 m, 2923 m, 1719 s (4-C=O), 1690 s (6-C=O), 1630 w, 1604 w $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.12 (d, $J$ = 7.0 Hz, 3 H, 9-Me), 1.46–1.50 (m, 1 H, 9-H), 1.96–1.98 (m, 5 H, 5-Me, 10-$CH_2$), 2.51 (s, 3 H, 2-Me), 2.59–2.70 and 2.72–2.83 (2 m, 4 H, 11-$CH_2$, 8-$CH_2$), 7.58 (s, 1 H, 1-H), 7.67 (s, 1 H, 3-H). Anal. calcd. for $C_{18}H_{18}ClNO_2$ (315.80): C, 68.46; H, 5.75; N 4.44. Found: C, 68.58; H, 5.59; N 4.39.

***2,5-Dichloro-5-phenyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (11d).*** From 4-hydroxy-pyridocarbazole **6n** (1.50 g, 4.3 mmol) in dioxane (25 mL) and sulfuryl chloride (0.70 g–0.42 mL, 5.2 mmol) as described for **11b**. The yield was 1.42 g (86%) yellow prisms, mp 100°C (ethanol). IR: 3430 s, 2950 m, 2920 m, 1720 s (4-C=O), 1690 s (6-C=O), 1630 w, 1605 w $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.75–1.82 and 1.85–1.92 (2 m, 4 H, 9-$CH_2$ and 10-$CH_2$), 2.70 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.05–3.08 (m, 2 H, 8-$CH_2$), 7.35–7.50 (m, 3 H, 3 PhH), 7.55–7.60 (m, 2 H, PhH), 7.80–8.00 (m, 2 H, 1-H, 3-H). Anal. calcd. for $C_{21}H_{15}Cl_2NO_2$ (384.27): C, 65.64; H, 3.93; N. 3.65. Found: C, 65.28; H, 3.95; N 3.27.

***2,5-Dichloro-10-methyl-5-phenyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole- 4,6-dione (11e).*** From 4-hydroxy-pyridocarbazole **6o** (1.10 g, 3 mmol) in dioxane (20 mL) and sulfuryl chloride (0.49 g, 0.30 mL, 3.7 mmol) as described for **11b**. The yield was 1.10 g (91%), yellow prisms, mp 105°C (ethanol). IR: 3420 s, 2940 m, 2910 m, 1715 s (4-C=O), 1690 s (6-C=O), 1625 w, 1605 w $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.06 (d, $J$ = 7.0 Hz, 3 H, 10-Me), 1.30–1.55 (m, 1 H, 10-H), 1.75–2.00 (m, 2 H, 9-$CH_2$), 2.70 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.03–3.08 (m, 2 H, 8-$CH_2$), 7.35–7.50 (m, 3 H, 3 PhH), 7.55–7.60 (m, 2 H, PhH), 7.81 (d, $J$ = 2.0 Hz, 1 H, 1-H), 8.02 (d, $J$ = 7.0 Hz, 1 H, 3-H). Anal. calcd. for $C_{22}H_{17}Cl_2NO_2$ (398.29): C, 66.34; H, 4.30; N, 3.52; Found: C, 66.25; H, 4.28; N, 3.24.

***5-Azido-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (12).*** A suspension of 5-chloropyridocarbazole **11a** (1.20 g, 4.2 mmol) and sodium azide (1.00 g, 15.3 mmol) in dimethylformamide (40 mL) was stirred and heated for 1 h at 50°C. After cooling to room temperature, the mixture was poured onto crushed ice/water (100 mL), filtered by suction and washed with water. The yield was 0.95 g (77 %) yellow needles, mp 131°C (ethanol). IR: 3432 s, 2929 m, 2144 sh, 2106 s ($N_3$), 1722 s (4-C=O), 1688 s (6-C=O), 1626 w, 1592 m $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.70 (s, 3 H, 5-Me), 1.81–1.83 and 1.85–1.88 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.69 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.05–3.09 (m, 2 H, 8-$CH_2$), 7.43 (t, $J$ = 7.6 Hz, 1 H, 2-H), 7.72 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.85 (d, $J$ = 7.5 Hz, 1 H, 3-H). Anal. calcd. for $C_{16}H_{14}N_4O_2$ (294.32): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.24; H, 4.78; N, 18.65.

***5-Benzylamino-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (14a).*** A solution of 5-chloropyridocarbazole **11a** (1.20 g, 4.2 mmol) and benzylamine (**13a**) (0.50 mL, 4.5 mmol) in dimethylformamide (3 mL) was heated and stirred for 15 h at 50°C. After cooling to room temperature, the mixture was poured onto ice/water (100 mL), filtered by suction and washed with water. The yield was 1.22 g (81%), yellow prisms, mp 73°C (ethanol). IR: 3395 m, 2932 m, 2853 w, 1720 s (4-C=O), 1681 s (6-C=O), 1628 w, 1591 m $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.50 (s, 3 H, 5-Me), 1.79–1.83 and 1.86–2.08 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.67 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.04–3.14 (m, 2 H, 8-$CH_2$), 3.51 (s, 2 H, benzyl-$CH_2$), 7.17–7.30 (m, 5 H, PhH), 7.43 (t, $J$ = 7.7 Hz, 1 H, 2-H), 7.70 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.81 (d, $J$ = 7.6 Hz, 1 H, 3-H); MS [APCI, pos]: m/e (%) = 360 (11), 359 (100, M). Anal. calcd. for $C_{23}H_{22}N_2O_2$ (358.44): C, 77.07; H, 6.19; N, 7.82. Found: C, 77.35; H, 5.99; N, 7.54.

***5-Methyl-5-phenylamino-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (14b).*** From a solution of 5-chloropyridocarbazole **11a** (1.00 g, 3.4 mmol) and aniline (**13b**) (0.5 mL, 5.5 mmol) in dimethylformamide (20 mL) as described for **14a**. The yield was 0.63 g (54 %), yellow prisms, mp 115°C (ethanol). IR: 3395 m, 2932 m, 2856 w, 1724 s (4-C=O), 1686 s (6-C=O), 1603 m, 1592 m $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.65 (s, 3 H, 5-Me), 1.83–1.91 (m, 4 H, 9-$CH_2$, 10-

$CH_2$), 2.73 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.06 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 6.12 (d, $J$ = 8.0 Hz, 2 H, PhH), 6.51 (t, $J$ = 7.3 Hz, 1 H, PhH), 6.86 (s, 1 H, NH, $D_2O$-exchangeable), 6.94 (t, $J$ = 7.8 Hz, 2 H, PhH), 7.51 (t, $J$ = 7.6 Hz, 1 H, 2-H), 7.76 (d, $J$ = 7.6 Hz, 1 H, 1-H), 7.93 (d, $J$ = 7.6 Hz, 1 H, 3-H). Anal. calcd. for $C_{22}H_{20}N_2O_2$ (344.42): C, 76.72; H, 5.85; N, 8.13. Found: C, 76.39; H, 5.67; N, 8.36.

***5-Methyl-5-morpholino-8,9,10,11-tetrahydropyrido[3,2,1-jk] carbazole-4,6-dione (16a).*** A solution of 5-chloropyridocarbazole **11a** (1.60 g, 5.5 mmol) and morpholine (**15a**) (0.5 mL, 5.7 mmol) in dimethylformamide (20 mL) was stirred for 5 h at 50°C. After cooling to room temperature, the mixture was poured into water (100 mL), the solid was filtered by suction, washed with water and dried at room temperature in vacuo. The yield was 1.40 g (75%), yellow prisms, mp 72°C (ethanol). IR: 3425 m, 2936 s, 2853 s, 1713 s (4-C=O), 1681 s (6-C=O), 1631 w, 1591 m $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 1.49 (s, 3 H, 5-Me), 1.78–1.81 and 1.86–1.89 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.55–2.60 (m, 4 H, 2x 5-morpholino-$CH_2$), 2.67 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.09 (s, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 3.49 (t, $J$ = 4.2 Hz, 4 H, 2x 5-morpholino-$CH_2$), 7.40 (t, $J$ = 7.6 Hz, 1 H, 2-H), 7.66 (d, $J$ = 7.6 Hz, 1 H, 1-H), 7.82 (d, $J$ = 7.6 Hz, 1 H, 3-H); MS [APCI, pos]: m/e (%) = 340 (28), 339 (100, M), 337 (12). Anal. calcd. for $C_{20}H_{22}N_2O_3$ (338.41): C, 70.99; H, 6.55; N, 8.28. Found: C, 71.24; H, 6.32; N, 8.01.

***5-Methyl-5-piperidino-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-4,6-dione (16b).*** From 5-chloropyridocarbazole **11a** (1.50 g, 5.2 mmol) and piperidine (**15b**) (0.6 mL, 6 mmol) in dimethylformamide (20 mL) as described for **16a**. The yield was 1.45 g (84%), yellow prisms, mp 87°C (ethanol). IR: 3421 m, 2934 s, 2851 m, 1714 s (4-C=O), 1681 s (6-C=O), 1630 w, 1591 m $cm^{-1}$: $^1H$ NMR (DMSO-$d_6$): δ = 1.31–1.33 and 1.38–1.40 (2 m, 6 H, 3 5-piperidino-$CH_2$), 1.47 (s, 3 H, 5-Me), 1.77–1.80 and 1.85–1.87 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.54–2.57 (m, 4 H, 5-piperidine-$CH_2$), 2.67 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.09 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 7.39 (t, $J$ = 7.6 Hz, 1 H, 2-H), 7.65 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.80 (d, $J$ = 7.6 Hz, 1 H, 3-H); MS [APCI, pos]: m/e (%) = 338 (20%), 337 (M, 100%). Anal. calcd. for $C_{21}H_{24}N_2O_2$ (336.44): C, 74.97; H, 7.19; N, 8.33. Found: C, 75.35; H, 7.01; N, 8.04.

***4-Benzylamino-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk] carbazol-6-one (17a).*** A solution of 4-hydroxy-pyridocarbazole **6a** (2.53 g, 10 mmol) and excess benzylamine (**13a**) (20 mL) was heated for 6 h at 180°C using an air condenser to remove water formed during the reaction, cooled and the excess benzylamine removed by distillation in vacuo. To the liquid residue petroleum ether (bp 60–90°C, 50 mL) was added and stirred. The solid precipitated, was filtered by suction and washed with petroleum ether (bp 60–90°C). Then toluene (50 mL) was added and the solid was filtered by suction and washed with ethanol (20 mL). The yield was 2.15 g (63 %), yellow prisms, mp 128°C (ethanol). IR: 3442 m, 3386 s, 3357 s, 2934 m, 1642 m (6-C=O), 1618 s, 1536 s $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.89–1.90 and 1.96–1.97 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.18 (s, 3 H, 5-Me), 2.76 (t, $J$ = 6.0 Hz, 2 H, 11-$CH_2$), 3.27 (t, $J$ = 6.0 Hz, 2 H, 8-$CH_2$), 4.43 (s, 1 H, NH), 4.82 (d, $J$ = 3.8 Hz, 2 H, benzyl-$CH_2$), 7.30–7.36 (m, 3 H, PhH, 2-H), 7.38–7.40 (m, 3 H, PhH), 7.61 (d, $J$ = 7.5 Hz, 1 H, 1-H), 7.67 (d, $J$ = 8.0 Hz, 1 H, 3-H). $^{13}C$ NMR ($CDCl_3$): δ 11.2, 21.2 and 22.4 (C9, C10), 23.0 and 24.9 (C11, C8), 52.5 (Me), 108.5, 113.7, 117.4, 118.5, 120.4, 122.4, 127.5, 128.1, 129.9, 131.2 (13 ArC), 137.7, 139.1, 150.2 (3 C—N), 161.6 (C=O); MS [APCI, pos]: m/e (%) = 344 (25), 343 (100), 341(5), 241 (33), 108 (39). Anal. calcd. for $C_{23}H_{22}N_2O$ (342.44): C, 80.67; H, 6.48; N, 8.18. Found: C, 80.38; H, 6.47; N, 8.27.

***5-Methyl-4-phenylamino-8,9,10,11-tetrahydropyrido[3,2,1-jk] carbazole-6-one (17b).*** From 4-hydroxy-pyridocarbazole **6a** (2.53 g, 10 mmol), aniline hydrochloride (2.50 g, 19 mmol) and aniline (**13b**) (20 mL) as described for **17a**. The yield was 2.10 g (64 %), yellowish prisms, mp 167°C (ethanol). IR: 3462 m, 3342 m, 2934 m, 1648 m (6-C=O), 1630 s, 1601 m, 1555 w $cm^{-1}$; $^1H$ NMR($CDCl_3$): δ 1.89–1.93 and 1.96–2.00 (2 m, 4 H, 9-$CH_2$. 10-$CH_2$), 2.15 (s, 3 H, 5-Me), 2.78 (t, $J$ = 6.0 Hz, 2 H, 11-$CH_2$), 3.31 (t, $J$ = 6.0 Hz, 2 H, 8-$CH_2$), 6.02 (s, 1 H, NH), 6.94 (d, $J$ = 7.6 Hz, 2 H, PhH), 7.01 (t, $J$ = 7.4 Hz, 1 H, 2-H), 7.15–7.29 (m, 3 H, PhH), 7.38 (d, $J$ = 7.8 Hz, 1 H, 1-H), 7.58 (d, $J$ = 7.5 Hz, 1 H, 3-H); $^{13}C$ NMR ($CDCl_3$): δ 12.4, 21.3, 22.4, (C9, C10), 22.9, 24.8 (C8, C11), 42.0 (Me), 114.9, 117.8, 118.4, 118.7, 119.2, 120.5, 127.9, 129.2, 131.3 (12 ArC), 137.6, 143.5, 144.3 (3 C—N), 161.8 (C=O); MS [APCI, pos]: m/e (%) = 330 (28), 329 (100). Anal. calcd. for $C_{22}H_{20}N_2O$ (328.42): C, 80.46; H, 6.14; N, 8.53. Found: C, 80.20; H, 6.26; N, 8.68.

***4-Chloro-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-6-one (18a).*** A solution of 4-hydroxy-pyridocarbazole **6a** (2.53g, 10 mmol) in phosphoryl chloride (30 mL) was heated under reflux for 1 h. The excess phosphoryl chloride was removed i. vac., the residue cooled to room temperature and poured onto crushed ice/water (100 mL). Caution: strong exothermic reaction. The product was brought to pH ~4 to 6 with 2*M* aqueous sodium hydroxide solution, the solid filtered by suction and washed with water. The yield was 1.40 g (51 %), ash–grey powder, mp 165°C (ethanol). IR: 3453 m, 2930 s, 1659 s (6-C=O), 1628 m, 1597 w $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.87–2.01 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.41 (s, 3 H, 5-Me), 2.76 (t, $J$ = 6.0 Hz, 2 H, 11-$CH_2$), 3.24 (t, $J$ = 6.0 Hz, 2 H, 8-$CH_2$), 7.42 (t, $J$ = 7.7 Hz, 1 H, 2-H), 7.63 (d, $J$ = 7.6 Hz, 1 H, 1-H), 7.73 (d, $J$ = 7.8 Hz, 1 H, 3-H); MS [APCI, pos]: *m/z* (%) = 274 (35), 273 (15), 272 (100, M). Anal. calcd. for $C_{16}H_{14}ClNO$ (271.75): C, 70.72; H, 5.19; N, 5.00. Found: C, 70.49; H, 5.26; N, 5.15

***4-Chloro-5-phenyl-8,9,10,11-tetrahydro-pyrido[3,2,1-jk]carbazol-6-one (18b).*** From 4-hydroxy-pyridocarbazole **6g** (3.15 g, 10 mmol) and phosphoryl chloride (30 mL) as described for **18a**. The yield was 2.20 g (66%), light brownish needles, mp 154°C (ethanol). IR: 2960–2840 w, 1660 s (6-C=O), 1625 w, 1595 w $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.85–2.00 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.75 (t, $J$ = 6.0 Hz, 2 H, 11-$CH_2$), 3.20–3.25 (m, 2 H, 8-$CH_2$), 7.35–7.50 (m, 4 H, 3 PhH, 2-H), 7.55–7.60 (m, 2 H, PhH), 7.65–7.75 (m, 2 H, 1-H, 3-H). Anal. calcd. for $C_{21}H_{16}ClNO$ (333.82): C, 75.56; H, 4.83; N, 4.20. Found: C, 75.39; H, 5.06; N, 4.05.

***5-Benzyl-4-chloro-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazol-6-one (18c).*** From 4-hydroxy-pyridocarbazole **6h** (3.29 g, 10 mmol) and phosphoryl chloride (30 mL) as described for **18a**. The yield was 0.79 g (24%), yellow prisms, mp 106°C (ligroin). IR: 2950-2850 w, 1655 s (6-C=O), 1615 w, 1590 w; $^1H$ NMR (DMSO-$d_6$): δ 1.70–1.90 (m, 4 H, 2 $CH_2$), 2.70 (s, 2 H, 11-$CH_2$), 3.10 (s, 2 H, 8-$CH_2$), 4.00 (s, benzyl-$CH_2$), 7.10–7.50 (m, 6 H, 5 benzyl-H, 2-H), 7.70 (d, $J$ = 6.0 Hz, 1-H), 8.05 (d, $J$ = 6.0 Hz, 3-H). Anal. calcd. for $C_{22}H_{18}ClNO$

(347.85): C, 75.97; H, 5.22; N, 4.03. Found: C, 76.32; H, 4.91; N, 3.65.

***2,4-Dichloro-10-methyl-5-phenyl-8,9,10,11-tetrahydro-pyrido [3,2,1-jk]carbazol-6-one (18d).*** From 4-hydroxy-pyridocarbazole **6o** (3.63 g, 10 mmol) and phosphoryl chloride (30 mL) as described for **18a**. The yield was 3.28 g (86%), colorless prisms, mp 190°C (ethanol). IR: 2930–2800 w, 1660 s, 1610 w, 1590 w $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.85–2.05 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.73 (t, $J$ = 6.0 Hz, 2 H, 11-$CH_2$), 3.20–3.25 (m, 2 H, 8-$CH_2$), 7.35–7.45 (m, 3 H, 3 PhH), 7.55–7.60 (m, 2 H, PhH), 7.65–7.75 (m, 2 H, 1-H, 3-H). Anal. calcd. for $C_{22}H_{17}Cl_2NO$ (382.29): C, 69.12; H, 4.48; N, 3.66. Found: C 69.18; H, 4.81; N 3.80.

***4-Chloro-2,5,9-trimethyl-8,9,10,11-tetrahydropyrido[3,2,1-jk] carbazol-6-one (18e).*** From 4-hydroxy-pyridocarbazole **6l** (2.81 g, 10 mmol) and phosphoryl chloride (30 mL) as described for **18a**. The yield was 1.85 g (62%), colorless prisms, mp 157°C (ethanol). IR: 3450 m, 2922 m, 1662 s (6-C=O), 1627 m, 1588 w $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 1.15 (d, 3 H, 9-Me), 1.41–1.46 (m, 1 H, 9-H), 1.89–2.19 (m, 2 H, 10-$CH_2$), 2.41 (s, 3 H, 5-Me) 2.58 (s, 3 H, 2-$CH_3$), 2.68–2.84 (m, 4 H, 8-$CH_2$, 11-$CH_2$), 7.46 (d, $J$ = 6.5 Hz, 1 H, 1-H), 7.55 (d, $J$ = 6.5 Hz, 1 H, 3-H). Anal. calcd. for $C_{18}H_{18}ClNO$ (299.80): C, 72.11; H, 6.05; N, 4.67. Found: C, 71,81; H, 5,94; N, 4,51.

***4-Azido-5-methyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazole-6-one (19a).*** *Method A*. A mixture of 4-chloro-pyridocarbazole **18a** (1.36 g, 5 mmol) and sodium azide (0.98 g, 15 mmol) in dimethylformamide (30 mL) was intensively stirred and heated for 36 h at 50°C. After cooling to room temperature, the mixture was poured onto crushed ice/water (250 mL). This solution was kept for 3 h at room temperature, filtered by suction and dried in vacuum with phosphorouspentoxide. Tlc check showed a mixture of starting **18a** and azide **19a**, which were separated by dry column flash chromatography (hexane/ethyl acetate as gradients). The yield of **19a** was 0.33 g (15%). *Method B*. A mixture of 4-hydroxy-pyridocarbazole **6a** (0.50 g, 2 mmol) and sodium azide (0.65 g, 10 mmol) in excess phosphoryl chloride (3 mL ~5 g, 30 mmol) was intensively stirred and heated for 12 h at 60°C. The excess phosphoryl chloride was removed by vacuum distillation. After cooling to room temperature, the solid was poured into crushed ice/water (50 mL), and filtered by suction. The yield was 0.32 g (58 %), yellowish crystals, mp 104°C (dec.) (methanol). IR: 3432 m, 2390 m, 2855 w, 2114 s ($N_3$), 1661 s (6-C=O), 1626 m, 1598 w $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.88–1.82 and 1.87–1,89 (2 m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.32 (s, 3 H, 5-Me), 2.72 (t, $J$ = 7.0 Hz, 2 H, 11-$CH_2$), 3.10 (t, $J$ = 7.0 Hz, 2 H, 8-$CH_2$), 7.48 (t, $J$ = 7.7 Hz, 1 H, 2-H), 7.72 (d, $J$ = 7.6 Hz, 1 H, 1-H), 7.78 (d, $J$ = 7.8 Hz, 1 H, 3-H). Anal. calcd. for $C_{16}H_{14}N_4O$ (278.32): C, 69.05; H, 5.07; N, 20.13. C, 69.41; H, 5.44; N, 19.75.

***4-Azido-5-phenyl-8,9,10,11-tetrahydropyrido[3,2,1-jk]carbazol-6-one (19b).*** To a solution of 4-chloro-pyridocarbazole **18b** (0.60 g, 1.8 mmol) in dimethylformamide (30 mL) at 50°C, sodium azide (0.5 g, 7.2 mmol) was added and the mixture stirred for 12 h at room temperature, and then for about 60 min at 80°C until the reaction was finished (tlc check). The yield was 0.20 g (33%), brownish prisms, mp 107°C (dec.). IR: 3430 m, 2350 m, 2850 w, 2115 s ($N_3$), 1660 s (6-C=O), 1625 m, 1595 w $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.85–2.05 (m, 4 H, 9-$CH_2$, 10-$CH_2$), 2.70 (t, $J$ = 6.0 Hz, 2 H, 11-$CH_2$), 3.20–3.25 (m, 2 H, 8-$CH_2$), 7.35–7.50 (m, 4 H, 3 PhH, 2-H), 7.55–7.62 (m, 2 H, PhH), 7.67–7.80 (m, 2 H, 1-H, 3-H). Anal. calcd. for $C_{21}H_{16}N_4O$ (340.39): C, 74.10; H, 4.74; N, 16.46. Found: C, 74.35; H, 4.52; N, 16.28.

## REFERENCES AND NOTES


[1] (a) Budavari, S., Ed. The Merck Index; Merck & Co Inc: Rahway, 1996; Vol. 12, p 9020; (b) Smith, G. F. In The Alkaloids; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. VIII, p 591; (c) Prelog, V.; Szpilfogel, S.; Battegay, J. Helv Chim Acta 1947, 30, 366; (d) Beifuss, U. Angew Chem 1994, 196, 1204.

[2] Budavari, S., Ed. The Merck Index; Merck & Co Inc: Rahway, 1996; Vol. 12, p 1476.

[3] Budavari, S., Ed. The Merck Index; Merck & Co Inc: Rahway, 1996; Vol. 12, p 10170.

[4] (a) Ziegler, E.; Rossmann, U.; Litvan, F.; Meier, H. Monatsh Chem 1962, 93, 26; (b) Ziegler, E.; Litvan, F. (Geigy Chemical Corp.), US Pat. 1959, 3,052,678; (c) Ziegler, E.; Litvan, F. Chem Abstr 1963, 58, 3437e; (d) Geigy Chemical Corp. Brit. Pat. 1960, 912,289; (e) Geigy Chemical Corp. Chem Abstr 1963, 59, 645; (f) Harfenist, M.; Magnien, E. J Org Chem, 1963, 28, 538.

[5] Dang, V. H.; Knobloch, B.; Habib, N. S.; Kappe, T.; Stadlbauer W. J Heterocycl Chem 2005, 42, 85.

[6] (a) Drechsel, E. J Prakt Chem 1888, 38, 68; (b) Yamada, S.; Chibata, I.; Tsurui, R. Pharm Bull Japan 1953, 1, 14; (c) Yamada, S.; Chibata, I.; Tsurui, R. Chem Abstr 1954, 48, 12078; (d) Yamada, S. (Tanabe Drug Manfacturing Co) Jpn. Pat. 1954, 1284; (e) Yamada, S. Chem Abstr 1955, 49, 11720.

[7] Loffler, A.; Ginsburg, D. Nature 1953, 172, 820.

[8] (a) Friederich, H. H.; Henkel, E. (BASF AG) Ger. Pat. 1956, 947,068; (b) Friederich, H. H.; Henkel, E. Chem Abstr 1959, 53, 6250i.

[9] Jones, N. A.; Tomlinson, M. L. J Chem Soc 1953, 4114.

[10] Adkins, H.; Coonradt, H. L. J Am Chem Soc 1941, 63, 1563.

[11] (a) Rogers, C. U.; Corson, B. B. J Am Chem Soc 1947, 69, 2910; (b) Rogers, C. U.; Corson, B. B. Organic Syntheses; Wiley: New York, London, 1950; Vol. 30, p 90; (c) Rogers, C. U.; Corson, B. B. Organic Syntheses; Wiley: New York, London, 1963; Coll Vol. IV, p 884.

[12] (a) Plancher, G. Gazz Chim Ital 1900, 30 II, 558; (b) Pausacker, K. H.; Schubert, C. I. Nature 1949, 163, 289; (c) Pausacker, K. H.; Schubert, C. I. J Chem Soc 1949, 1384; (d) Fritz, H.; Stock, E. Liebigs Ann Chem 1969, 721, 82.

[13] (a) Stadlbauer, W.; Dang, V. H.; Deeb, A.; Schuiki, B.; Kappe, T. Proceedings of ECSOC-12, The Twelvth International Electronic Conference on Synthetic Organic Chemistry, http://www.usc.es/congresos/ecsoc/12/ECSOC12.htm, November 1–30, 2008; J. A. Seijas, Shu-Kun Lin, Vázquez Tato, M. P., Eds; CD-ROM edition, ISBN 3–906980-20–0; MDPI: Basel, 2008; (b) Stadlbauer, V. H.; Deeb, A.; Schuiki, B.; Kappe, T. in preparation.

[14] Stadlbauer, W.; Badawey, E.-S.; Hojas, G.; Roschger, P.; Kappe, Th. Molecules 2001, 6, 338.

[15] (a) Kappe, Th. Monatsh Chem 1967, 98, 874; (b) Kappe, Th. In Encylopedia of Reagents for Organic Synthesis; Paquette, L. A., Ed.; John Wiley & Sons: Chichester—New York—Brisbane—Toronto—Singapore, 1995; Vol. 1, p 577.

[16] (a) Kappe, Th. In Encylopedia of Reagents for Organic Synthesis; Paquette, L. A., Ed.; John Wiley & Sons: Chichester—New York—Brisbane—Toronto—Singapore, 1995; Vol. 2, p 1098; (b) Nakanishi, S.; Butler, K. Org Prep Proc Int 1975, 7, 155.

[17] (a) Knops, H. J.; Born, L. Tetrahedron Lett 1983, 24, 2973; (b) Bellamy, L. J.; Rogasch, R. E. Spectrochim Acta 1960, 16, 30; (c) Katritzky, A. R.; Jones, R. A. J Chem Soc 1960, 2947.

[18] (a) Budzikiewicz, H.; Schaller, U.; Korth, H.; Pulverer, G. Monatsh Chem 1979, 110, 947; (b) Kitamura, S.; Hashizume, K.; Ida, T.; (c) Miyashita, E.; Shirata, K.; Kase, H. J Antibiot 1986, 39, 1160.

[19] Harwood, L. M. Aldrichim Acta 1985, 18, 25.

[20] Oakeshott, S. H.; Plant, S. G. P. J Chem Soc 1926, 1210.

[21] Borsche, W.; Witte, A.; Bothe, W. Liebigs Ann Chem 1908, 359, 49.

[22] Scott, T. L.; Burke, N.; Carrero-Martinez, G.; Soederberg, B. C. G.; Bennett, C. E. Tetrahedron 2006, 63, 1183.

[23] Kuroki, M; Tsunashima, Y. J Heterocycl Chem 1981, 18, 709.

[24] Bhattacharya, D.; Gammon, D. W.; Van Steen, E. Catalysis Lett 1999, 61, 93.

[25] (a) Martynov, V. F., J Org Chem 1957, 27, 1191; (b) Barclay, B. M.; Campbell, N. J Chem Soc 1945, 530.

[26] (a) Lalloz, L.; Caubere, P. J Chem Soc Chem Comm 1975, 745; (b) Welch, W. M. Synthesis 1977, 645.

[27] (a) Campbell, N.; McCall, E. B. J Chem Soc 1950, 2870; (b) Chen, J.; Hu, Y. Synth Comm 2006, 36, 1485; (c) Roth, H. J.; Lepke, P. Arch Pharm 1972, 305, 159.

[28] Ziegler, E.; Junek, H.; Rossmann, U. Monatsh Chem 1961, 92, 809.

[29] (a) Baumgarten, P.; Riedel, M. Ber Dtsch Chem Ges 1942, 75, 984; (b) Clemo, G. R.; Perkin, W. H. J Chem Soc 1924, 125, 1608.

# *E*,*E*-Bis(Styryl)Sulfones—Synthons for a New Class of Bis(heterocycles)



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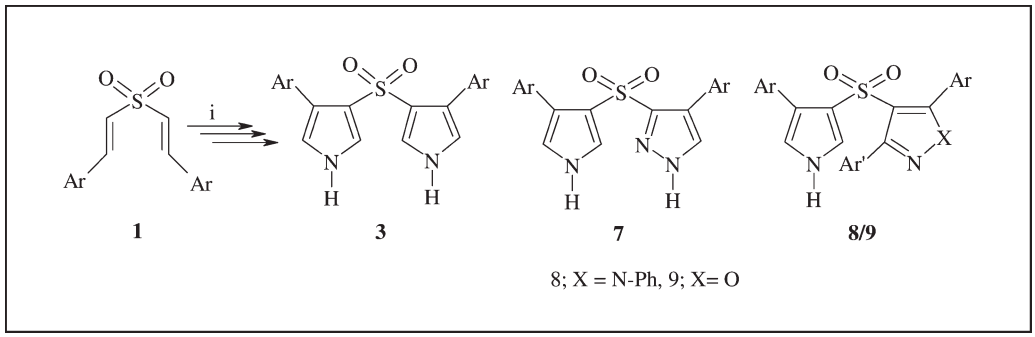


A new class of bis heterocycles having two different heterocyclic rings *viz*., pyrroles in combination with pyrazolines and isoxazolines were synthesized. All the compounds were characterized by elemental and spectral analysis.

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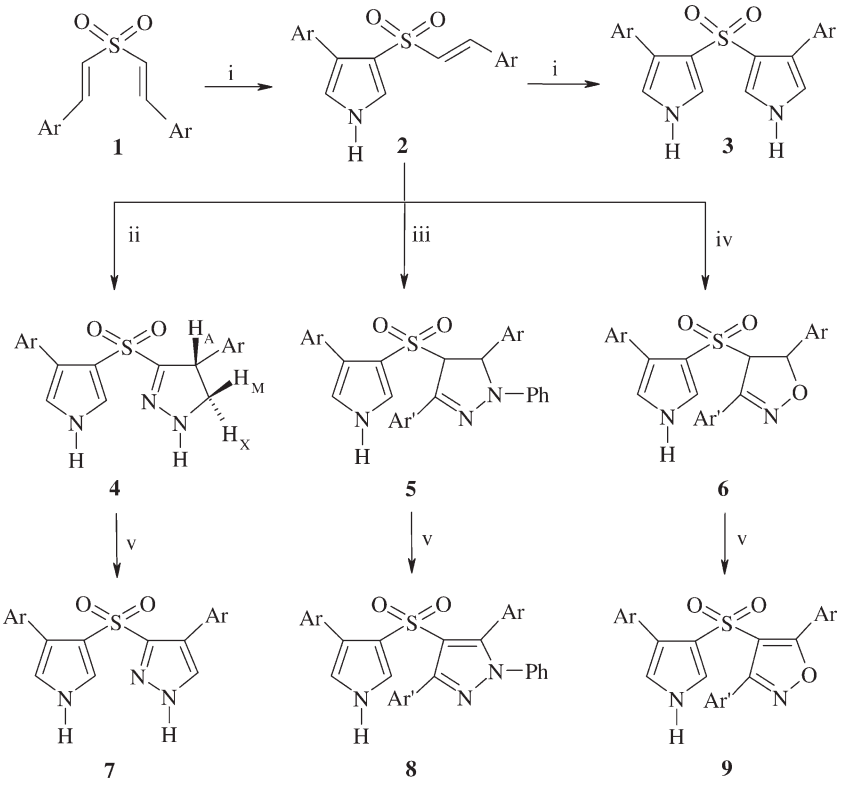
## INTRODUCTION

Heterocyclic chemistry has attracted a lot of interest during recent years as many useful drugs have emerged in this branch. In fact, the development of simple, facile, and efficient synthetic methodologies for the development of five membered heterocycles has been a challenging task in organic synthesis. Amongst five membered heterocycles, pyrroles, pyrazoles, and isoxazoles have gained importance because of their varied physiological activities. As constituents of cytotoxic drugs, such as netrospin and distamycin, 4-aminopyrrole-2-carboxylates, have been used as the main compounds in the construction of a diverse series of DNA-binding ligands exhibiting antibiotic, antiviral, and oncolytic properties [1]. The related 3-amino pyrroles also exhibit anticonvulsant activity by blocking sodium channels [2]. In addition, pyrazolines and isoxazolines have gained importance due to their various chemotherapeutic properties. In fact, Celecoxib, a pyrazole derivative and Valdecoxib, an isoxazole derivative, have been widely used in the market as anti-inflammatory drugs [3]. Hence, it was considered worthwhile to prepare molecules having both pyrrole and pyrazole/isoxazole rings. In the literature, 3,4-disubstituted pyrroles were reported either by coupling imines and nitroalkanes or by using Friedel-Craft's acylation in the presence of an electron-withdrawing group on the pyrrole nitrogen or on 3,4-silylated precursors [4]. However, these synthetic routes were often complicated and limited to only some substituents. Previously, 3,4-disubstituted pyrroles were synthesized from Michael acceptors and tosylmethyl isocyanide (TosMIC) [5]. Following this synthetic methodology, we have reported recently a new regioselective one step procedure using phenyl vinyl sulfone, aryl styryl sulfones, benzyl styryl sulfones and TosMIC, leading to a series of 3,4-disubstituted pyrroles in good yields [6]. Similarly, pyrazolines and isoxazolines were prepared by 1,3-dipolar cycloaddition of an ylide to an alkene involving the 3+2 cycloaddition principle [7]. Among the ylides, diazomethane, nitrile imines, and nitrile oxides were used extensively as reactive intermediates. These nitrile imines and nitrile oxides can be generated by the dehydrogenation of araldehyde phenylhydrazones and araldoximes with lead tetraacetate [8], mercury acetate [9], 1-chlorobenzotriazole [10], chloramine-T [11] etc. Use of the latter for *in situ* generation of dipolar reagents has enthused many organic chemists. In fact, we have reported the 1,3-dipolar cycloaddition reaction of Chloramine-T catalysed dipolar reagents with variety of activated mono and bis(olefins) [12]. Apart from these, bis heterocycles, bis pyrroles and pyrrolyl pyrazoles were prepared from 1-arylsulfonyl-2-styrylsulfonyl ethenes by 1,3-dipolar cycloaddition methodology [13]. The present communication deals with the synthesis of hitherto unknown sulfonelinked bis (heterocycles) having pyrrole together with pyrazole or

**Scheme 1**



i) TosMIC / NaH/ $Et_2O$ + DMSO ii) $CH_2N_2$ / $Et_2O$
iii) Ar'-CH=NNHPh / Chloramine-T.$3H_2O$ / MeOH
iv) Ar'-CH=NOH / Chloramine-T.$3H_2O$ / MeOH
v) Chloranil / Xylene

| | Ar | Ar' |
|---|---|---|
| **2a/3a/4a/7a** | $C_6H_5$ | - |
| **2b/3b/4b** | 4-$OMeC_6H_4$ | - |
| **2c/3c/4c** | 4-$ClC_6H_4$ | - |
| **5a/6a/ 8a/ 9a** | $C_6H_5$ | $C_6H_5$ |
| **5b/6b** | 4-$OMeC_6H_4$ | $C_6H_5$ |
| **5c/6c** | $C_6H_5$ | 4-$ClC_6H_4$ |
| **5d/6d** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ |

isoxazole units, from 1,3-dipolar cycloaddition of TosMIC, nitrile imines and nitrile oxides to sulfonyl activated olefins.

## RESULTS AND DISCUSSION

The synthetic scheme was based on the reactivity of *E*,*E*-bis(styryl)sulfone (**1**) towards 1,3-dipolar reagents *viz*., TosMIC, diazomethane, nitrile imines and nitrile oxides. When **1** was treated with TosMIC in the presence of sodium hydride in a mixture of ether and dimethylsulfoxide, a solid was obtained which was identified as 4-aryl-3-(2′-arylethenesulfonyl)-1*H*-pyrrole (**2**) by spectral studies (Scheme 1; Table 1). Compound **2a** exhibited two singlets at δ 6.85 and 7.48 ppm, assigned to $C_2$-H and $C_5$-H of pyrrole ring protons. Two doublets were observed at δ 6.96 and 7.63 ppm corresponding to olefinic protons, in addition to the signals of aromatic protons (Table 3). The $^{13}C$ nuclear mass spectroscopy (NMR) spectra of **2a** showed signals at δ 119.8, 125.7, 125.9, and 127.3 for pyrrole ring carbons, C-4, C-3, C-5, C-2 and at δ 124.2, 141.3 ppm for olefinic carbons, C-1′, C-2′ (Table 3). Thus the formation of **2** indicates that the reaction was regiospecific. Attempts to prepare bis (4-aryl-1*H*-pyrrol-3-yl)sulfone (**3**) by treating **1** with

**Table 1**

Physical and analytical data of compounds **2–9**.

| Compound | Mp (°C) | Yield (%) | Ar | Ar' | Molecular formula | Analysis % calculated/ found | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **2a** | 221–223 | 72 | $C_6H_5$ | – | $C_{18}H_{15}NO_2S$ (309.40) | 69.88 | 4.89 | 4.53 |
| | | | | | | 69.80 | 4.94 | 4.50 |
| **2b** | 243–245 | 69 | 4-$OMeC_6H_4$ | – | $C_{20}H_{19}NO_4S$ (369.45) | 65.02 | 5.18 | 3.79 |
| | | | | | | 64.92 | 5.24 | 3.85 |
| **2c** | 265–267 | 66 | 4-$ClC_6H_4$ | – | $C_{18}H_{13}Cl_2NO_2S$ (378.29) | 57.15 | 3.46 | 3.70 |
| | | | | | | 57.08 | 3.44 | 3.67 |
| **3a** | 232–234 | 76 | $C_6H_5$ | – | $C_{20}H_{16}N_2O_2S$ (348.43) | 68.94 | 4.63 | 8.04 |
| | | | | | | 68.85 | 4.68 | 8.11 |
| **3b** | 225–227 | 80 | 4-$OMeC_6H_4$ | – | $C_{22}H_{20}N_2O_4S$ (408.48) | 64.69 | 4.93 | 6.86 |
| | | | | | | 64.76 | 4.96 | 6.92 |
| **3c** | 270–272 | 82 | 4-$ClC_6H_4$ | – | $C_{20}H_{14}Cl_2N_2O_2S$ (417.32) | 57.56 | 3.38 | 6.71 |
| | | | | | | 57.50 | 3.35 | 6.66 |
| **4a** | 242–244 | 68 | $C_6H_5$ | – | $C_{19}H_{17}N_3O_2S$ (351.43) | 64.94 | 4.87 | 11.96 |
| | | | | | | 65.00 | 4.92 | 12.05 |
| **4b** | 230–232 | 70 | 4-$OMeC_6H_4$ | – | $C_{21}H_{21}N_3O_4S$ (411.49) | 61.29 | 5.14 | 10.21 |
| | | | | | | 61.37 | 5.20 | 10.33 |
| **4c** | 256–258 | 65 | 4-$ClC_6H_4$ | – | $C_{19}H_{15}Cl_2N_3O_2S$ (420.33) | 54.29 | 3.60 | 9.99 |
| | | | | | | 54.20 | 3.58 | 10.08 |
| **5a** | 282–284 | 68 | $C_6H_5$ | $C_6H_5$ | $C_{31}H_{25}N_3O_2S$ (503.63) | 73.93 | 5.00 | 8.34 |
| | | | | | | 74.00 | 5.06 | 8.27 |
| **5b** | 270–272 | 64 | 4-$OMeC_6H_4$ | $C_6H_5$ | $C_{33}H_{29}N_3O_4S$ (563.68) | 70.32 | 5.18 | 7.45 |
| | | | | | | 70.43 | 5.14 | 7.38 |
| **5c** | 288–290 | 71 | $C_6H_5$ | 4-$ClC_6H_4$ | $C_{31}H_{24}ClN_3O_2S$ (538.07) | 69.20 | 4.49 | 7.81 |
| | | | | | | 69.27 | 4.53 | 7.92 |
| **5d** | 296–298 | 65 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | $C_{31}H_{22}Cl_3N_3O_2S$ (606.96) | 61.34 | 3.65 | 6.92 |
| | | | | | | 61.25 | 3.69 | 7.00 |
| **6a** | 277–278 | 70 | $C_6H_5$ | $C_6H_5$ | $C_{25}H_{20}N_2O_3S$ (428.52) | 70.07 | 4.70 | 6.54 |
| | | | | | | 70.14 | 4.68 | 6.60 |
| **6b** | 264–266 | 65 | 4-$OMeC_6H_4$ | $C_6H_5$ | $C_{27}H_{24}N_2O_5S$ (488.57) | 66.38 | 4.95 | 5.73 |
| | | | | | | 66.32 | 5.00 | 5.67 |
| **6c** | 252–254 | 68 | $C_6H_5$ | 4-$ClC_6H_4$ | $C_{25}H_{19}ClN_2O_3S$ (462.96) | 64.86 | 4.14 | 6.05 |
| | | | | | | 64.78 | 4.10 | 6.13 |
| **6d** | 280–282 | 72 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | $C_{25}H_{17}Cl_3N_2O_3S$ (531.85) | 56.46 | 3.22 | 5.27 |
| | | | | | | 56.52 | 3.18 | 5.22 |
| **7a** | 274–276 | 66 | $C_6H_5$ | - | $C_{19}H_{15}N_3O_2S$ (349.42) | 65.31 | 4.33 | 12.02 |
| | | | | | | 65.26 | 4.31 | 12.12 |
| **8a** | 296–298 | 65 | $C_6H_5$ | $C_6H_5$ | $C_{31}H_{23}N_3O_2S$ (501.61) | 74.23 | 4.62 | 8.38 |
| | | | | | | 74.33 | 4.67 | 8.46 |
| **9a** | 287–289 | 68 | $C_6H_5$ | $C_6H_5$ | $C_{25}H_{18}N_2O_3S$ (426.50) | 70.40 | 4.25 | 6.57 |
| | | | | | | 70.52 | 4.28 | 6.51 |

two equivalents of TosMIC were not successful. However, **3** was obtained by treating **2** with one equivalent of TosMIC, as confirmed by NMR spectroscopy. Compound **3a** exhibited two sharp singlets at δ 6.84 and 7.08 ppm corresponding to $C_{2,2'}$-H and $C_{5,5'}$-H. The $^{13}C$ NMR spectra of **3a** exhibited signals at 119.2 (C-4,4′), 122.6 (C-3,3′), 126.2 (C-5,5′), 127.4 (C-2,2′). This indicates that the molecule was highly symmetrical.

The olefin in **2** was utilized in the synthesis of pyrazolines and isoxazolines. When **2** was subjected to 1,3-dipolar cycloaddition reaction with diazomethane, (4′-aryl-4′,5′-dihydro-1′*H*-pyrazol-3′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-sulfone (**4**) was obtained (Scheme 1; Table 1). The $^1H$ NMR spectra of **4a** showed an *AMX* splitting pattern of the pyrazoline ring protons at δ 4.48 ($H_A$), 3.86 ($H_M$) and 3.48 ppm ($H_X$) respectively, in addition to the signals of the pyrrole ring protons. The observed coupling constant values $J_{AM} = 12.6$, $J_{AX} = 5.5$ and $J_{MX} = 10.0$ Hz indicated that $H_A$ and $H_M$ were *cis*, $H_A$ and $H_X$ were *trans* and $H_M$ and $H_X$ were *geminal*. The $^{13}C$ NMR spectrum of **4a** exhibited signals at δ 46.9, 57.2, 119.4, 120.3, 124.8, 125.6 and 152.3 ppm for the carbons C-4′, C-5′, C-4, C-3, C-5, C-2, and C-3′, respectively (Table 2).

In addition, the reaction of **2** with nitrile imines and nitrile oxides generated from araldehyde phenylhydrazones and araldoximes in the presence of chloramine-T resulted in (1′,3′,5′-triaryl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-sulfones (**5**) and (3′,5′-diaryl-

**Table 2**

Infrared data of compounds **2–9**.

| Compound | IR (KBr) $cm^{-1}$ | | | |
|---|---|---|---|---|
| | $SO_2$ | C=C | C=N | NH |
| **2a** | 1130, 1300 | 1635 | – | 3175 |
| **2b** | 1145, 1297 | 1632 | – | 3170 |
| **2c** | 1132, 1295 | 1630 | – | 3180 |
| **3a** | 1140, 1294 | – | – | 3182 |
| **3b** | 1128, 1305 | – | – | 3168 |
| **3c** | 1124, 1296 | – | – | 3172 |
| **4a** | 1125, 1325 | – | 1570 | 3185 |
| **4b** | 1132, 1320 | – | 1575 | 3180 |
| **4c** | 1128, 1325 | – | 1572 | 3190 |
| **5a** | 1126, 1295 | – | 1558 | 3195 |
| **5b** | 1130, 1292 | – | 1568 | 3188 |
| **5c** | 1132, 1304 | – | 1560 | 3178 |
| **5d** | 1125, 1310 | – | 1562 | 3182 |
| **6a** | 1140, 1305 | – | 1574 | 3200 |
| **6b** | 1135, 1315 | – | 1562 | 3205 |
| **6c** | 1124, 1296 | – | 1578 | 3210 |
| **6d** | 1132, 1315 | – | 1566 | 3205 |
| **7a** | 1120, 1300 | 1625 | 1573 | 3198 |
| **7b** | 1124, 1298 | 1628 | 1558 | 3186 |
| **7c** | 1128, 1310 | 1630 | 1574 | 3198 |

4′,5′-dihydroisoxazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-sulfone (**6**), respectively (Scheme 1; Table 1). The $^1$H NMR spectrum of **5a** and **6a** displayed two doublets at δ 5.25, 5.19 and 5.63, 5.67 ppm, respectively, which were assigned to $C_{4'}$-H and $C_{5'}$-H, the two methine protons of the pyrazoline and isoxazoline rings. The *J* values indicated that they were in *trans* geometry (Table 3). The $^{13}$C NMR spectra of **5a** and **6a** displayed signals at 63.0, 64.9 (C-4′), 87.4, 83.7 (C-5′), 119.2, 119.4 (C-4), 121.0, 121.9 (C-3), 124.4, 124.3 (C-5), 126.8, 126.3 (C-2) and 154.9, 151.7 (C-3′), respectively (Table 3). Compounds **4a**, **5a** and **6a** on oxidation with chloranil in xylene, gave the corresponding pyrazoles and isoxazoles **7a**, **8a** and **9a**. The disappearance of two doublets corresponding to pyrazoline/isoxazoline ring protons in the $^1$H NMR spectra confirmed their formation.

## CONCLUSION

A simple dipolarophile, bis(styryl)sulfone was exploited to get a new and novel sulfone-linked bis(heterocycles) containing two different heterocyclic rings adopting simple and versatile 1,3-dipolar cycloaddition methodology.

## EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by thin layer chromatography (Silica gel H, BDH, ethyl acetate-hexane, 1:3). The infrared (IR) spectra were recorded on a Thermo Nicolet IR 200 FT-IR in KBr pellets and the wave numbers were given in $cm^{-1}$. The $^1$H NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$ on a Jeol JNM λ-300 MHz. The $^{13}$C NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$ on a Jeol JNM spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. Elemental analyses were performed using Perkin-Elmer 240C elemental analyser. The starting substrates *E,E*-bis(styryl)sulfones were prepared according to the literature procedure [14]. Araldehyde phenylhydrazones and araldoximes were prepared by standard procedures [15].

**4-Aryl-3-(2-arylethenesulfonyl)-1*H*-pyrroles (2).** ***General procedure.*** A mixture of TosMIC (5 mmol) and **1** (5 mmol) in $Et_2O$/DMSO (2:1) was added dropwise under stirring to a suspension of NaH (50 mg) in $Et_2O$ (10 mL) at room temperature. Stirring was continued for about 6 h. Then it was diluted with $H_2O$ and extracted with $Et_2O$. The ethereal layer was dried over anhydrous $Na_2SO_4$. The solvent was removed *in vacuo*. The resultant solid was purified by recrystallization from MeOH.

**Bis(4-aryl-1*H*-pyrrol-3yl)-sulfones (3).** ***General procedure.*** A mixture of TosMIC (5 mmol) and **2** (5 mmol) in $Et_2O$/DMSO (2:1) was added dropwise under stirring to a suspension of NaH (50 mg) in $Et_2O$ (10 mL) at room temperature. Stirring was continued for about 7 h. Then, $H_2O$ was added and the product was extracted with $Et_2O$ and dried over anhydrous $Na_2SO_4$. The solvent was removed *in vacuo*. The resultant solid was purified by column chromatography [Silica gel, hexane-ethyl acetate (1:4)].

**(4′-Aryl-4′,5′-dihydro-1′*H*-pyrazol-3′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-sulfones (4).** ***General procedure.*** To a cooled solution of **2** (5 mmol) in $CH_2Cl_2$ (20 mL), an ethereal solution of diazomethane (40 mL, 0.4*M*) and triethylamine (0.12 g) were added. The reaction mixture was kept at −20 to −15°C for 48–56 h. The solvent was removed under reduced pressure. The resultant solid was purified by recrystallization from MeOH.

**(1′,3′,5′-Triaryl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-sulfones (5).** ***General procedure.*** A mixture of **2** (1 mmol), araldehyde phenylhydrazone (2 mmol) and chloramine-T (2 mmol) in MeOH (20 mL) was refluxed for 20–22 h. over a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with $CH_2Cl_2$. The organic phase was washed with water, brine and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure. Recrystallization of the crude product from ethanol resulted in pure **5**.

**(3′,5′-Diaryl-4′,5′-dihydro-isoxazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)-sulfones (6).** ***General procedure.*** A mixture of **2** (1 mmol), araldoxime (2 mmol) and chloramine-T (2 mmol) in MeOH (20 mL) was refluxed for 16–18 h. over a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with $CH_2Cl_2$. The organic phase was washed with water, brine and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure. Recrystallization of the crude product from ethanol resulted in pure **6**.

**(4′-Phenyl-1′*H*-pyrazol-3′-yl)-(4-phenyl-1*H*-pyrrol-3-yl)-sulfone (7a)/(4-phenyl-1*H*-pyrrol-3-yl)-(1′,3′,5′-triphenyl-1′*H*-pyrazol-4′-yl)-sulfone (8a)/(3′,5′-diphenyl-isoxazol-4′-yl)-(4-phenyl-1*H*-pyrrol-3-yl)-sulfone (9a).** ***General procedure.*** A solution of **4a/5a/6a** (1 mmol) and chloranil (1.04 mmol) in

**Table 3**

$^{1}$H and $^{13}$C NMR data of compounds **2–9**.

| Compound | $^{1}$H NMR ($CDCl_3$/DMSO-$d_6$) δ, ppm | $^{13}$C NMR ($CDCl_3$/DMSO-$d_6$) δ, ppm |
|---|---|---|
| **2a** | 6.85 (s, 1H, $C_2$-H), 6.96 (d, 1H, $C_1'$-H, $J$ = 15.6 Hz), 7.48 (s, 1H, $C_5$-H), 7.15-7.62 (m, 10H, Ar-H), 7.63 (d, 1H, $C_2'$-H, $J$ = 15.6 Hz), 9.04 (bs, 1H, NH) | 119.8 (C-4), 124.2 (C-1′), 125.7 (C-3), 125.9 (C-5), 127.3 (C-2), 141.3 (C-2′) |
| **2b** | 3.72 (s, 6H, Ar-$OCH_3$), 6.79 (s, 1H, $C_2$-H), 6.89 (d, 1H, $C_1'$-H, $J$ = 16.2 Hz), 7.41 (s, 1H, $C_5$-H), 6.95-7.58 (m, 8H, Ar-H), 7.65 (d, 1H, $C_2'$-H, $J$ = 16.2 Hz), 9.12 (bs, 1H, NH) | 55.2 (Ar-$OCH_3$), 118.7 (C-4), 123.6 (C-1′), 124.9 (C-3), 125.6 (C-5), 126.8 (C-2), 140.3 (C-2′) |
| **2c** | 6.88 (s, 1H, $C_2$-H), 6.89 (d, 1H, $C_1'$-H, $J$ = 16.3 Hz), 7.45 (s, 1H, $C_5$-H), 7.24-7.59 (m, 8H, Ar-H), 7.60 (d, 1H, $C_2'$-H, $J$ = 16.3 Hz), 9.11 (bs, 1H, NH) | 119.6 (C-4), 124.6 (C-1′), 125.8 (C-3), 126.3 (C-5), 127.6 (C-2), 140.3 (C-2′) |
| **3a** | 6.84 (s, 2H, $C_{2,2'}$-H), 7.08 (s, 2H, $C_{5,5'}$-H), 7.02-7.48 (m, 10H, Ar-H), 9.05 (bs, 2H, NH) | 122.6 (C-3,3′), 119.2 (C-4,4′), 126.2 (C-5,5′), 127.4 (C-2,2′) |
| **3b** | 3.69 (s, 6H, Ar-$OCH_3$), 6.88 (s, 2H, $C_{2,2'}$-H), 7.06 (s, 2H, $C_{5,5'}$-H), 6.95-7.45 (m, 8H, Ar-H), 9.12 (bs, 2H, NH) | 121.9 (C-3,3′), 55.5 (Ar-$OCH_3$), 118.6 (C-4,4′), 125.8 (C-5,5′), 127.6 (C-2,2′) |
| **3c** | 6.89 (s, 2H, $C_{2,2'}$-H), 7.11 (s, 2H, $C_{5,5'}$-H), 7.15-7.44 (m, 8H, Ar-H), 9.11 (bs, 2H, NH) | 122.5 (C-3,3′), 120.2 (C-4,4′), 124.6 (C-5,5′), 127.8 (C-2,2′) |
| **4a** | 3.48 (dd, 1H, $H_X$, $J_{AX}$ = 5.5, $J_{MX}$ = 10.0 Hz), 3.86 (t, 1H, $H_M$) 4.48 (dd, 1H, $H_A$, $J_{AM}$ = 12.6 Hz), 6.85 (s, 1H, $C_2$-H), 7.14-7.32 (m, 10H, Ar-H), 7.74 (s, 1H, $C_5$-H), 8.26 (bs, 1H, NH), 10.45 (bs, 1H, NH) | 46.9 (C-4′), 57.2 (C-5′), 119.4 (C-4), 120.3 (C-3), 124.8 (C-5), 125.6 (C-2), 152.3 (C-3′) |
| **4b** | 3.46 (dd, 1H, $H_X$, $J_{AX}$ = 5.7, $J_{MX}$ = 10.1 Hz), 3.67 (s, 6H, Ar-$OCH_3$), 3.89 (t, 1H, $H_M$), 4.45 (dd, 1H, $H_A$, $J_{AM}$ = 12.8 Hz), 6.81 (s, 1H, $C_2$-H), 7.01-7.32 (m, 8H, Ar-H), 7.73 (s, 1H, $C_5$-H), 8.23 (bs, 1H, NH), 10.52 (bs, 1H, NH) | 46.8 (C-4′), 55.3 (Ar-$OCH_3$), 56.4 (C-5′), 118.3 (C-4), 119.6 (C-3), 123.6 (C-5), 125.7 (C-2), 151.6 (C-3′) |
| **4c** | 3.54 (dd, 1H, $H_X$, $J_{AX}$ = 5.7, $J_{MX}$ = 10.2 Hz), 3.84 (t, 1H, $H_M$), 4.45 (dd, 1H, $H_A$, $J_{AM}$ = 12.9 Hz), 6.81 (s, 1H, $C_2$-H), 7.12-7.45 (m, 8H, Ar-H), 7.69 (s, 1H, $C_5$-H), 8.23 (bs, 1H, NH), 10.45 (bs, 1H, NH) | 47.2 (C-4′), 56.8 (C-5′), 119.2 (C-4), 119.9 (C-3), 122.8 (C-5), 126.4 (C-2), 152.3(C-3′) |
| **5a** | 5.25 (d, 1H, $C_4'$-H, $J$ = 7.8 Hz), 5.63 (d, 1H, $C_5'$-H, $J$ = 7.2 Hz), 6.79 (s, 1H, $C_2$-H), 6.85 (s, 1H, $C_5$-H), 7.22-7.54 (m, 20H, Ar-H), 8.85 (bs, 1H, NH) | 63.6 (C-4′), 87.4 (C-5′), 119.2 (C-4), 121.0 (C-3), 124.4 (C-5), 126.8 (C-2), 154.9 (C-3′) |
| **5b** | 3.74 (s, 6H, Ar-$OCH_3$), 5.27 (d, 1H, $C_4'$-H, $J$ = 6.6 Hz), 5.63 (d, 1H, $C_5'$-H, $J$ = 6.6 Hz), 6.74 (s, 1H, $C_2$-H), 6.87 (s, 1H, $C_5$-H), 7.04-7.83 (m, 18H, Ar-H), 8.86 (bs, 1H, NH) | 55.2 (Ar-$OCH_3$), 64.8 (C-4′), 87.3 (C-5′), 120.4 (C-4), 121.6 (C-3), 123.8 (C-2), 127.2 (C-5), 154.8 (C-3′) |
| **5c** | 5.24 (d, 1H, $C_4'$-H, $J$ = 6.9 Hz), 5.62 (d, 1H, $C_5'$-H, $J$ = 6.9 Hz), 6.73 (s, 1H, $C_2$-H), 6.85 (s, 1H, $C_5$-H), 7.12-7.80 (m, 19H, Ar-H), 8.91 (bs, 1H, NH) | 62.8 (C-4′), 85.9 (C-5′), 118.6 (C-4), 122.6 (C-3), 123.8 (C-2), 125.8 (C-5), 154.6 (C-3′) |
| **5d** | 5.26 (d, 1H, $C_4'$-H, $J$ = 6.4 Hz), 5.65 (d, 1H, $C_5'$-H, $J$ = 6.4 Hz), 6.76 (s, 1H, $C_2$-H), 6.92 (s, 1H, $C_5$-H), 7.18-7.82 (m, 17H, Ar-H), 8.93 (bs, 1H, NH) | 63.9 (C-4′), 84.6 (C-5′), 119.3 (C-4), 121.8 (C-3), 124.6 (C-2), 124.9 (C-5), 153.7 (C-3′) |
| **6a** | 5.19 (d, 1H, $C_4'$-H, $J$ = 5.9 Hz), 5.67 (d, 1H, $C_5'$-H, $J$ = 5.9 Hz), 6.76 (s, 1H, $C_2$-H), 6.85 (s, 1H, $C_5$-H), 7.08-7.93 (m, 15H, Ar-H), 8.83 (bs, 1H, NH) | 64.9 (C-4′), 83.7 (C-5′), 119.4 (C-4), 121.9 (C-3), 124.3 (C-5), 126.3 (C-2), 151.7 (C-3′) |
| **6b** | 3.74 (s, 6H, Ar-$OCH_3$), 5.21 (d, 1H, $C_4'$-H, $J$ = 5.8 Hz), 5.66 (d, 1H, $C_5'$-H, $J$ = 5.8 Hz), 6.75 (s, 1H, $C_2$-H), 6.87 (s, 1H, $C_5$-H), 7.01-7.94 (m, 13H, Ar-H), 8.86 (bs, 1H, NH) | 55.6 (Ar-$OCH_3$), 63.6 (C-4′), 84.5 (C-5′), 118.7 (C-4), 122.3 (C-3), 125.7 (C-5), 126.7 (C-2), 152.6 (C-3′) |
| **6c** | 5.23 (d, 1H, $C_4'$-H, $J$ = 6.0 Hz), 5.72 (d, 1H, $C_5'$-H, $J$ = 6.0 Hz), 6.74 (s, 1H, $C_2$-H), 6.83 (s, 1H, $C_5$-H), 7.14-7.92 (m, 14H, Ar-H), 8.91 (bs, 1H, NH) | 64.6 (C-4′), 83.3 (C-5′), 119.8 (C-4), 122.6 (C-3), 125.5 (C-5), 126.1 (C-2), 153.8 (C-3′) |
| **6d** | 5.24 (d, 1H, $C_4'$-H, $J$ = 5.7 Hz), 5.70 (d, 1H, $C_5'$-H, $J$ = 5.7 Hz), 6.78 (s, 1H, $C_2$-H), 6.86 (s, 1H, $C_5$-H), 7.18-7.89 (m, 12H, Ar-H), 8.94 (bs, 1H, NH) | 64.7 (C-4′), 83.9 (C-5′), 119.6 (C-4), 121.8 (C-3), 125.3 (C-5), 125.9 (C-2), 152.7 (C-3′) |
| **7a** | 6.36 (bs, 1H, NH), 6.75 (s, 1H, $C_2$-H), 6.94 (s, 1H, $C_5$-H), 6.96-7.84 (m, 11H, $C_5'$-H & Ar-H), 8.94 (bs, 1H, NH). | 116.8 (C-4), 122.3 (C-3), 125.8 (C-5), 127.6 (C-2), 134.7 (C-5′), 140.9 (C-4′), 156.8 (C-3′) |
| **8a** | 6.76 (s, 1H, $C_2$-H), 6.83 (s, 1H, $C_5$-H), 7.10-8.02 (m, 20H, Ar-H), 8.83 (bs, 1H, NH) | 118.3 (C-4), 124.6 (C-3), 125.3 (C-5), 126.5 (C-2), 144.8 (C-3′), 147.8 (C-4′), 150.4 (C-5′) |
| **9a** | 6.76 (s, 1H, $C_2$-H), 6.86 (s, 1H, $C_5$-H), 7.02-7.94 (m, 15H, Ar-H), 8.92 (bs, 1H, NH) | 117.3 (C-4), 122.6 (C-3), 125.6 (C-5), 127.8 (C-2), 146.3 (C-4′), 147.4 (C-3′), 152.5 (C-5′) |

xylene (10 mL) was refluxed for 30–35 h. Then it was treated with 5% sodium hydroxide solution. The organic layer was separated and repeatedly washed with water, dried over anhydrous $Na_2SO_4$ and was removed on a rotary evaporator. The solid obtained was purified by recrystallization in isopropanol to give pure **7a/8a/9a** respectively.

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## REFERENCES AND NOTES

[1] [a] Wang, C. C. C.; Dervan, P. B. J Am Chem Soc 2001, 123, 8657; [b] Wellenzohn, B.; Flader, W.; Winger, R. H.; Hallbrucker, A.; Mayer, E. Liedl, K.R. J Am Chem Soc 2001, 123, 5044; and references 1–33 therein; [c] Sharma, S. K.; Tandon M.; Lown, J. W. J Org Chem 2001, 66, 1030; [d] Wurtz, N. R.; Turner, J. M.; Baird, E. E.; Dervan, P. B. Org Lett 2001, 3, 1201; [e] Dyatkina, N. B.; Roberts, C. D.; Keicher, J. D.; Dai, Y.; Nadherny, J. P.; Zhang, W.; Schmitz, U.; Kongpachith, A.; Fung, K.; Nokikov, A. A.; Lou, L.; Velligan, M.; Khorlin, A. A.; Chen, M. S. J Med Chem 2002, 45, 805.

[2] Unverferth, K.; Engel, J.; Hofgen, N.; Rostock, A.; Gunther, R.; Lankau, H. J.; Menzer, M.; Rolfs, A.; Liebscher, J.; Muller, B.; Hofmann, H. J. J Med Chem 1998, 41, 63.

[3] Dannahardt, G.; Kiefer, W.; Kramer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. Eur J Med Chem 2000, 35, 499.

[4] [a] Shiraishi, H.; Nishitani, T.; Nishihara, T.; Sakaguchi, S.; Ishii, Y. Tetrahedron 1999, 55, 13957; [b] Zelikin, A.; Shastri, V. R.; Langer, R. J Org Chem 1999, 64, 3379; [c] Liu, J. H.;Chan H. W.Wong, H. N. C. J Org Chem 2000, 65, 3274.

[5] [a] Van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; Van Leusen, D. Tetrahedron Lett 1972, 13, 5337; [b] Pavri, N. P.; Trudell, M. L. J Org Chem 1997, 62, 2649.

[6] Padmavathi, V.; Jagan Mohan Reddy, B.; Rajagopala Sarma, M.; Thriveni, P. J Chem Res (S) 2004, 79.

[7] [a] Lee, A. G. Synthesis 1982, 508; [b] Bao-Xiang, Z.; Yang, Y.; Shoji, E. Tetrahedron 1996, 52, 12049.

[8] Just, G.; Dahl, K. Tetrahedron 1968, 24, 5251.

[9] Lokanath Rai, K. M.; Liganna, N.; Hassner, A.; Murthy, C. A. Org Prep Proced Int 1992, 24, 91.

[10] Khim, J. N.; Ryu, J. N. Synth Commun 1990, 20, 1373.

[11] [a] Lokanath Rai, K. M.; Hassner, A. Indian J Chem 1997, 36B, 242; [b] Lokanath Rai, K. M.; Hassner, A. Synth Commun 1997, 27, 467; [c] Hassner, A.; Lokanath Rai, K. M. Synthesis 1989, 57; [d] Lokanath Rai, K. M.; Hassner, A. Synth Commun 1989, 19, 2799.

[12] [a] Padmavathi, V.; Bhaskar Reddy, A. V.; Sumathi, R. P.; Bhaskar Reddy, D. Indian J Chem 1998, 37B, 1286; [b] Padmavathi, V.; Sumathi, R. P.; Chandrasekhar Babu, N.; Bhaskar Reddy, D. J Chem Res (S) 1999, 610; [c] Padmavathi, V.; Sumathi, R. P.; Venugopal Reddy, K.; Somasekhar Reddy, A.; Bhaskar Reddy, D. Synth Commun 2000, 30, 4007; [d] Padmavathi, V.; Venugopal Reddy, K.; Padmaja, A.; Bhaskar Reddy, D. Synth Commun 2002, 32, 1227; [e] Padmavathi, V.; Venugopal Reddy, K.; Balaiah, A.; Ramana Reddy, T. V.; Bhaskar Reddy, D. Heteroatom Chem 2002, 13, 677.

[13] Padmavathi, V.; Radha Laksmi, T.; Sudhakar Reddy, G.; Padmaja, A. J Heterocyclic Chem 2008, 45, 1579.

[14] Baliah, V.; Ananthapadmanabhan, S. Indian J Chem 1971, 9, 1167.

[15] Vogel, A. I. A Text Book of Practical of Organic Chemistry, 5th ed.; Longman's Green & Co. Ltd.: London, 1989.

# An Efficient One-Pot Synthesis of *N*-(1,3-Diphenyl-1*H*-Pyrazol-5-yl)amides



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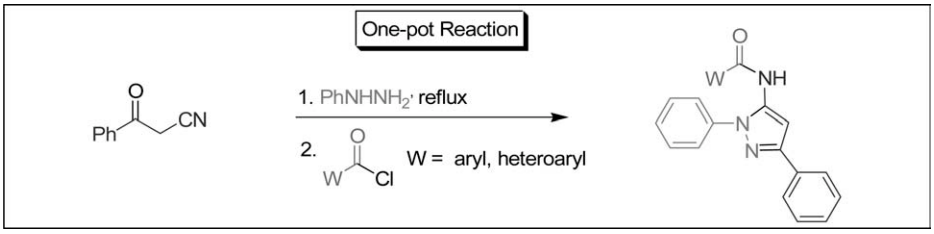


A ''one-pot'' method for the synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides was developed by cyclization of benzoylacetonitrile (**1**) and phenylhydrazine in neat condition followed by acylation. The corresponding *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides were provided in good to excellent yields (70–90%). The significant advantages of the new synthetic method are excellent yields and simple work-up procedure without isolation and purification of intermediary 5-amino-1,3-diphenyl pyrazol (**2**).

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## INTRODUCTION

Pyrazole compounds have aroused great interest in recent years because of their wide spectrum of biological activities, including anti-inflammatory, antipyretic, gastric secretion stimulatory, antidepressant, antibacterial, anticonvulsant, antifilarial agents, and as analytical reagents [1–4].

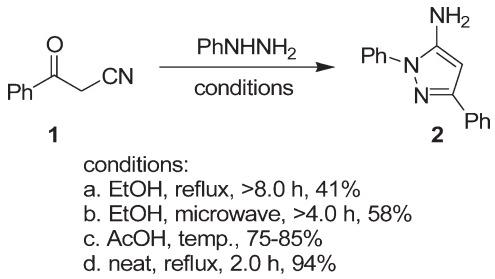
A recently reported pyrazole, 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (**16**, CDPPB), was developed as the first centrally active positive allosteric modulator of rat and human metabotropic glutamate receptor $mGluR_5$ subtype [5–7]. The receptors play an important role in controlling neuronal excitability and synaptic transmission in the central nervous system of the mammalian brain [8,9]. *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives are also considered as potential targets for therapeutic intervention in a variety of neurological and psychiatric illnesses [10]. The detailed structure–activity relationship studies of CDPPB analogs were reported by de Paulis *et al*. in 2006 [11]. Herein, we provided an efficient and convenient one-pot method to synthesize *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides for the large-scale preparation.

## RESULTS AND DISCUSSION

The traditional method for the synthesis of analog **2** [12,13] was the reaction of benzoylacetonitrile (**1**) with phenylhydrazine under different conditions to provide the key intermediate 5-amino-1,3-diphenyl pyrazole (**2**). The conditions include: (1) heated in EtOH [14], (2) microwave radiation [15], and (3) heated in acetic acid (Scheme 1) [15]. Compound **2** was then subjected to acylation to provide model compound **5** [*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide]. These methods all involve two steps, and it is necessary to purify aminopyrazole **2**. To develop a better synthetic methodology for expanding the structural variation of compound **5**, we developed an efficient and convenient ''one-pot'' method for their syntheses. Benzoylacetonitrile (**1**) was allowed to react with neat phenylhydrazine. The resultant **2**, needless to be purified, was subjected to acylation to generate model compound **5** in good to excellent yields (Scheme 1).

We first tried to prepare 5-amino-1,3-diphenyl pyrazole (**2**) by traditional methods to study their feasibility for one-pot reaction of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide derivatives. The first method was refluxing benzoylacetonitrile (**1**) with the same equivalent of

**Scheme 1**




phenylhydrazine in EtOH for >8.0 h (see Scheme 1, path a) [14]. Compound **2** was generated in only 41% yield *via* tandem condensation and thermal cyclization. Another method was the use of microwave irradiation of 1 with hydrazine in EtOH solution for >4.0 h to provide compound **2** in 58% yield (see Scheme 1, path b) [15]. The two literature-reported methods did not provide compound **2** in satisfactory yield, as a result, not suitable for direct acylation for a one-pot preparation. Use of acetic acid as the solvent could provide **2** in 75–85% yield (see Scheme 1, path c). However, the residual acetic acid should be distilled before acylation. Those methods were troublesome for removing EtOH or acetic acid, especially in large-scale preparation.

We then carried out the reaction in neat condition. Benzoylacetonitrile (**1**) was allowed to react with phenylhydrazine in neat condition at reflux for 2.0 h (see Scheme 1, path d). The desired 5-amino-pyrazole **2** was successfully generated in 94% yield. Compound **2** was fully characterized by spectroscopic method, and the results were consistent with the reported data of previous literature [14,15]. This method is able to promote the cyclization yield and provide the one-pot approach for *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives.

For searching a better acylation agent to generate **3**, compound **2** was treated with various acylation agents, including acetyl chloride, acetic anhydride, and ethyl acetate (EtOAc) at room temperature or at reflux for 3.0–4.0 h in THF (see Table 1). The corresponding acylated products were obtained in 85%, 83%, and trace yields, respectively. When compound **2** was reacted with ethyl benzoate or ethyl phenylacetate, the reaction gave the corresponding compounds **4** and **5** in 89% and 93% yields (see Table 1).

We then tried to combine the two-step process into a one-pot reaction. Compound **1** was refluxed with the same equivalent amount of phenylhydrazine in neat condition for 2 h. After the reaction was completed, the resultant compound **2** was dissolved in $CH_2Cl_2$ and stirred in ice-bath. The acylation agents, including acetyl chloride, benzoyl chloride, and phenylacetyl chloride, were diluted with anhydrous $CH_2Cl_2$, and THF was slowly added to the reaction mixture at 0–10°C. The reaction was stirred for 3–4 h from 0–10°C to the room temperature under $N_2$, and the corresponding acylation products *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide **3–5** were successfully provided in 78–90% yields in the one-pot reaction (see Table 1).

We then tried to apply this new method to synthesize *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide derivatives by use of different monosubstituted benzoyl halides containing Cl, F, $CH_3$, $CF_3$, OMe, CN, and $NO_2$ functionalities as the acylation agents (Scheme 2 and Table 2). The corresponding *N*-(1,3-diphenyl-1-*H*-pyrazol-5-yl)benzamide **6–19**, which were reported as a novel class of positive allosteric modulation of $mGluR_5$ [5,11], could be obtained in 70–90% yields (Table 2). Use of 2,4-difluorobenzoyl chloride also provided the corresponding product **15** in 88% yields. Compounds **6–19** were fully characterized by spectroscopic methods, and the data were consistent with reported [5,11]. For example, the pyrazole ring in compound **16** presented a peak at δ 6.79 ppm for NH—C=C—$^1$H and a peak at δ 95.7 ppm for NH—$^{13}$C=C in NMR. Its IR spectrum showed absorption at 2232 $cm^{-1}$ for —CN stretching and 3308 $cm^{-1}$ for —N—H stretching [14]. Being the first centrally active positive allosteric modulator of $mGluR_5$, compound **16** was synthesized by this one-pot method in 73% yield.

The method can also be applied to the synthesis of quinoline-8-sulfonyl and heteroarylaminopyrazoles. Use of quinoline-8-sulfonyl chloride, 2-benzofurancarbonyl chloride, 2-furoyl chloride, isoxazole-5-carbonyl chloride, 2-thiophenecarbonyl chloride, and trimellitic anhydride chloride could successfully provide the corresponding *N*-(1,3-diphenyl-1*H*-pyrazol-5yl)amide **20–25** in 70–90% yields (see Scheme 3 and Table 3).

In conclusion, we have successfully developed a newly one-pot method by treating benzoylacetonitrile (**1**) and phenylhydrazine with various acylation agents,

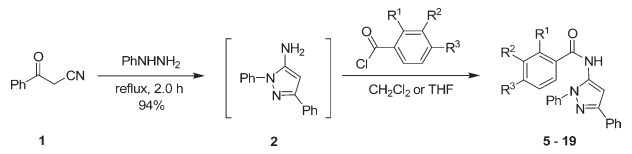
**Table 1**

The results of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives **3–5** *via* step-by-step and one-pot synthesis.

| Acylation agents | *N*-(1,3-Diphenyl-1 *H*-pyrazol-5-yl)amides | Yields (%) |
|---|---|---|
| Acetyl chloride | **3** | 85[a], 78[b] |
| Acetic anhydride | **3** | 83[a] |
| Ethyl acetate | **3** | Trace[a] |
| Ethyl benzoate | **4** | 89[a] |
| Ethyl phenylacetate | **5** | 93[a] |
| Phenylacetylchloride | **4** | 90[b] |
| Benzoyl chloride | **5** | 78[b] |

[a] The step-by-step synthesis.
[b] The one-pot synthesis reaction.

**Scheme 2**




including acetyl chloride, aryl chloride, heteroaryl chloride, quinoline-8-sulfonyl chloride, and trimellic anhydride chloride to give *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides **3–25** in 70–90% yields. The new strategy has been demonstrated to substantially promote the productive yields in the generation of substituted *N*-(1,3-diphenyl-1-*H*-pyrazol-5-yl)benzamides **6–19** compounds.

## EXPERIMENTAL

**General procedure.** All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Dichloromethane, ethyl acetate, hexanes, and methanol were purchased from ECHO Chemical (USA). Dry tetrahydrofuran (reagent grade) and 3-fluorobenzoyl chloride were purchased from Aldrich (USA). The following compounds were purchased from Acoros Chemical (Japan): acetyl chloride, benzoyl chloride, 3-cyanobenzoic acid, 2,4-difluorobenzoyl chloride, 4-fluorobenzoyl chloride, 3-methylbenzoyl chloride, and 4-methylbenzoyl chloride. Benzoylacetonitrile, 2-chlorobenzoyl chloride, 3-chlorobenzoyl chloride, 4-cyanobenzoyl chloride, 3-methoxylbenzoyl chloride, phenylhydrazine, and quinoline-8-sulfonyl chloride were purchased from TCI Chemical (Japan). Isoxazole-5-carbonyl chloride 2-nitrobenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, and trimellitic anhydride chloride were purchased from Alfa Chemical. 2-Furoyl chloride was purchased from Merck Chemical (Germany). Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 $cm^{-1}$ absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of $CDCl_3$ and $d_6$-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by the use of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

**Table 2**

The results of the one-pot synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide derivative.

| Acid chloride | | | Products | |
|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | *N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl) benzamides | Yields (%) |
| H | H | H | **5** | 78 |
| H | F | H | **6** | 77 |
| H | H | F | **7** | 70 |
| Cl | H | H | **8** | 85 |
| H | Cl | H | **9** | 71 |
| Me | H | H | **10** | 84 |
| H | H | Me | **11** | 76 |
| H | H | $CF_3$ | **12** | 78 |
| OMe | H | H | **13** | 90 |
| H | OMe | H | **14** | 72 |
| F | H | F | **15** | 88 |
| H | CN | H | **16 (CDPPB)** | 73 |
| H | H | CN | **17** | 78 |
| $NO_2$ | H | H | **18** | 76 |
| H | H | $NO_2$ | **19** | 89 |

**Standard procedure for condensation–cyclization to prepare 5-amino-1,3-diphenyl pyrazole (2).** [15] Benzoylacetonitrile (**1**, 5.08 g, 35.1 mmol, 1.0 equiv) and phenylhydrazine (3.80 g, 35.1 mmol, 1.0 equiv) were mixed and heated at reflux for 2.0 h. The mixture was purified by column chromatography on silica gel ($CH_2Cl_2$ as eluant) to give pure 5-amino-1,3-diphenyl pyrazole (**2**, 7.81 g, 33.3 mmol) as yellow solids in 94% yield: mp 129–131°C (lit. [15] mp 129–130°C); $^1$H-NMR ($CDCl_3$, 200 MHz) δ 3.82 (s, 2 H, $NH_2$), 5.88 (s, 1 H, Py-H), 7.32–7.49 (m, 6 H, ArH), 7.58 (dd, 2 H, $J$ = 6.6, 1.2 Hz, ArH), 7.80 (dd, 2 H, $J$ = 6.6, 1.2 Hz, ArH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 88.1, 124.2, 125.6, 127.5, 127.8, 128.5, 129.5, 133.5, 138.7, 145.8, 151.5; IR (KBr) 3427 (brs, NH), 3337 (brs, NH), 3059, 1616, 1598, 1558, 1505, 1456, 1375, 1070, 952, 758, 698 $cm^{-1}$; MS *m*/*z* (relative intensity) 235 ($M^+$, 100), 207 (20), 192 (3), 180 (3), 131 (7), 117 (4), 104 (11), 102(10), 92 (7), 77 (17), 65 (3), 51 (8); Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.21; H, 5.79; N, 18.03.

**Standard procedure for one-pot synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5yl)amide derivatives (3–25).** [4,8–10] Benzoylacetonitrile (**1**, 501 mg, 3.45 mmol, 1.0 equiv) and phenylhydrazine (374 mg, 3.46 mmol, 1.0 equiv) were mixed and stirred at reflux for 2.0–3.0 h. After the reaction was completed, the resultant compound **2** was dissolved in $CH_2Cl_2$ (10 mL) and stirred in ice-bath. Acetyl chloride, benzoxyl chloride, benzyl chloride, or heteroaryl chloride (4.14 mmol, 1.2 equiv)

**Scheme 3**

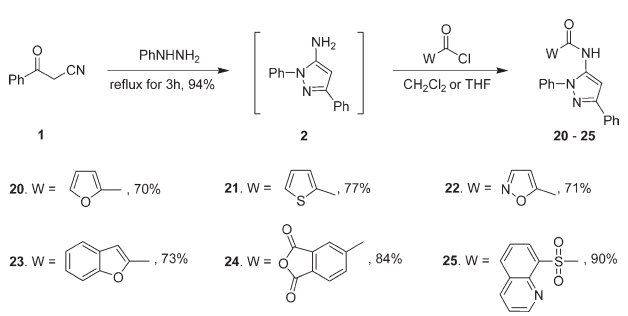


**Table 3**

The results of the one-pot synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives.

| Acylation agents | *N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl)amides | Yields (%) |
|---|---|---|
| 2-Furoyl chloride | **20** | 70 |
| 2-Thiophenecarbonyl chloride | **21** | 77 |
| Isoxazole-5-carbonyl chloride | **22** | 71 |
| 2-Benzofurancarbonyl chloride | **23** | 73 |
| Trimellitic anhydride chloride | **24** | 84 |
| Quinoline-8-sulfonyl chloride | **25** | 90 |

in 10 mL of $CH_2Cl_2$ or THF were slowly added to the reaction mixture at 0°C under $N_2$, respectively. The reaction was stirred at 0–10°C for 3–4 h. The reaction mixture was washed with water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel or recrystallization to give the corresponding acylation product *N*-(1,3-diphenyl-1*H*-pyrazol-5yl)amide **3**–**25** in 70–90% yields.

***N-(1,3-Diphenyl-1H-pyrazol-5-yl)acetamide (3).*** mp (purified by column chromatography on silica gel) 148–150°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 3 H, Me), 6.95 (s, 1 H, Py-H), 7.32–7.84 (m, 8 H, ArH), 7.81 (dd, 2 H, $J$ = 6.6, 1.7 Hz, ArH), 10.89 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 23.7, 96.4, 124.2, 125.0, 125.7 (2 × CH), 128.1 (2 × CH), 128.6 (2 × CH), 129.8 (2 × CH), 133.0, 136.5, 137.9, 151.8, 167.0; IR (KBr) 3230 (brs, NH), 3061, 1681, 1595, 1560, 1505, 1496, 1468, 1367, 1267, 1072, 954, 763, 692 cm$^{-1}$; MS *m*/*z* (relative intensity) 277 ($M^+$, 14), 235 (24), 207 (6), 180 (2), 131 (5), 102 (23), 77 (45), 65 (5), 51 (34), 43 (100); Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.52; H, 5.64; N, 15.49.

***2-Phenyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)acetamide (4).*** mp (purified by column chromatography on silica gel) 132–134°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 3.69 (s, 2 H, $CH_2$), 7.05 (s, 1 H, Py-H), 7.09–7.43 (m, 13 H, ArH), 7.83 (d, 2 H, $J$ = 6.6 Hz, ArH), 9.83 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 29.7, 94.9, 123.66 (2 × CH), 124.2, 125.7 (2 × CH), 128.1 (2 × CH), 128.6, 129.5 (4 × CH), 129.6, 129.8 (2 × CH), 132.9, 133.5, 136.5, 137.4, 151.8, 167.3; IR (KBr) 3268 (brs, NH), 3064, 2924, 1700, 1559, 1486, 1458, 1368, 1158, 1073, 954 cm$^{-1}$; MS *m*/*z* (relative intensity) 353 ($M^+$, 8), 269 (1), 235 (18), 207 (3), 180 (1), 167 (1), 131 (3), 102 (17), 91 (100), 77 (40), 65 (29), 51 (18); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.01; H, 5.34; N, 11.69.

***N-(1,3-Diphenyl-1H-pyrazol-5-yl)benzamide (5).*** [11] mp (purified by column chromatography on silica gel) 171–173°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.20 (s, 1 H, Py-H), 7.30–7.64 (m, 9 H, ArH), 7.88 (dd, 2 H, $J$ = 6.6, 1.6 Hz, ArH), 7.87 (dd, 2 H, $J$ = 6.6, 1.6 Hz, ArH), 8.06 (dd, 2 H, $J$ = 6.6, 1.6 Hz, ArH), 9.42 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 95.9, 124.9 (2 × CH), 125.8 (2 × CH), 127.1 (2 × CH), 128.2, 128.5 (2 × CH), 129.0 (2 × CH), 129.3, 130.1 (2 × CH), 130.2, 132.5, 133.0, 133.7, 136.7, 137.9, 171.1; IR (KBr) 3275 (brs, NH), 3062, 1645, 1558, 1365, 1258, 1072, 954, 763, 711, 698 cm$^{-1}$; MS *m*/*z* (relative intensity) 339 ($M^+$, 74), 234 (2), 206 (2), 105 (100), 77 (45), 51 (5); Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.56; H, 5.24; N, 12.47.

***3-Fluoro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (6).*** [12] mp (recrystallized from $CH_2Cl_2$/MeOH) 175–177°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.18 (s, 1 H, Py-H), 7.31–7.41 (m, 8 H, ArH), 7.57 (dd, 4 H, $J$ = 4.2, 1.4 Hz, ArH), 7.88 (dd, 2 H, $J$ = 6.6, 1.4 Hz, ArH), 8.21 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 96.4, 114.5, 114.9, 119.4, 119.8, 122.4 (2 × CH), 124.7 (2 × CH), 125.8, 128.6, 128.7 (2 × CH), 130.1 (2 × CH), 130.6, 130.8, 132.9, 135.3, 135.4, 136.3,137.8, 152.0, 160.4, 162.6, 165.3; IR (KBr) 3269 (brs, NH), 3064, 1684, 1589, 1458, 1365, 1290, 1072, 956, 692 cm$^{-1}$; MS *m*/*z* (relative intensity) 357 ($M^+$, 15), 356 (15), 206 (2), 123 (100), 101 (18), 95 (35), 77 (17), 51 (10); Anal. Calcd. for $C_{22}H_{16}FN_3O$: C, 73.94; H, 4.51; N, 11.76. Found: C, 73.66; H, 4.46; N, 11.41.

***4-Fluoro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (7).*** [14] mp (recrystallized from $CH_2Cl_2$/MeOH) 187–189°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.12 (t, 1 H, $J$ = 8.7 Hz, ArH), 7.18 (s, 1 H, Py-H), 7.32–7.48 (m, 4 H, ArH), 7.55–7.58 (m, 4 H, ArH), 7.70–7.77 (m, 2H, ArH), 7.88 (dd, 4 H, $J$ = 7.9, 1.3 Hz, ArH), 8.12 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 96.0, 116.0, 116.4, 124.8 (2 × CH), 125.8 (2 × CH), 128.2, 128.6 (2 × CH), 128.7, 129.4, 129.6, 130.1 (2 × CH), 132.9, 136.5, 137.9, 146.2, 152.1, 162.6; IR (KBr) 3217 (brs, NH), 3045, 1685, 1529, 1504, 1460, 1367, 1286, 1234, 1072, 918, 760, 694 cm$^{-1}$; MS *m*/*z* (relative intensity) 357 ($M^+$, 15), 234 (1), 206 (1), 123 (100), 102 (24), 95 (46), 77 (24), 51 (12); Anal. Calcd. for $C_{22}H_{16}FN_3O$: C, 73.94; H, 4.51; N, 11.76. Found: C, 73.75; H, 4.61; N, 11.43.

***2-Chloro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (8).*** [14] mp (purified by column chromatography on silica gel) 147–149°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.14 (s, 1 H, Py-H), 7.22–7.68 (m, 11 H, ArH), 7.70–7.94 (m, 3 H, ArH), 8.64 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 96.2, 125.5 (2 × CH), 125.8 (2 × CH), 127.5, 128.2, 128.6 (2 × CH), 128.9, 129.5 (2 × CH), 130.5, 131.2, 132.0,132.5,132.9,136.6, 137.6, 151.9, 162.7, 168.9; IR (KBr) 3256 (brs, NH), 3066, 1666, 1566, 1502, 1460, 1369, 1263, 1117, 1051, 765, 696 cm$^{-1}$; MS *m*/*z* (relative intensity) 373 ($M^+$, 10), 338 (18), 234 (1), 206 (2), 141 (44), 139 (100), 111 (36), 102 (34), 77 (36), 51 (16); Anal. Calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.29; H, 4.51; N, 11.14.

***3-Chloro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (9).*** [14] mp (purified by column chromatography on silica gel) 168–170°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.14 (s, 1 H, Py-H), 7.22–7.61 (m, 10 H, ArH), 7.65–7.94 (m, 3 H, ArH), 8.04 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 96.4, 124.8 (2 × CH), 124.9, 125.8 (2 × CH), 127.7, 128.2, 128.6 (2 × CH), 128.8, 130.1 (2 × CH), 130.3, 132.6, 133.7, 134.9, 136.2, 137.8, 152.1, 162.6, 169.6; IR (KBr) 3248 (brs, NH), 3052, 1675, 1573, 1498, 1455, 1431, 1358, 1292, 1252, 1061, 758, 692 cm$^{-1}$; MS *m*/*z* (relative intensity) 373 ($M^+$, 15), 343 (1), 234 (2), 206 (3), 141 (33), 139 (100), 111 (46), 102 (32), 77 (33), 75 (27), 51 (19). Anal. Calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.41; H, 4.24; N, 11.48.

***2-Methyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (10).*** mp (recrystallized from $CH_2Cl_2$/hexane) 187–189°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3 H, $CH_3$), 6.82 (s, 1 H, Py-H), 6.91–7.56 (m, 12 H, ArH), 7.86 (dd, 2 H, $J$ = 7.1, 1.0 Hz,

ArH), 10.4 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 19.7, 102.8, 125.2, 125.7, 125.9, 127.3, 128.2, 128.6, 129.1, 129.4, 131.3 (5 × CH), 132.8, 134.3 (2 × C), 137.6, 138.3 (2 × C), 151.8, 172.1; IR (KBr) 3064 (brs, NH), 1718, 1683, 1599, 1549, 1501, 1458, 1383, 1319, 1233, 1140, 1108, 1078, 953, 901, 841 $cm^{-1}$; MS *m*/*z* (relative intensity) 354 ($M^+$, 14), 336 (13), 307 (11), 289 (11), 262 (8), 235 (9), 219 (12), 178 (9), 154 (68), 136 (65), 119 (100), 107 (36), 91 (79), 77 (50), 69 (43), 55 (50); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.19; H, 5.47; N, 11.69.

***4-Methyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (11).*** [11] mp (recrystallized from $CH_2Cl_2$/hexane) 181–183°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3 H, $CH_3$), 7.19 (s, 1 H, Py-H), 7.24–7.65 (m, 12 H, ArH), 7.89 (dd, 2 H, $J$ = 7.3, 1.4 Hz, ArH), 8.12 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 21.5, 95.7, 124.8 (2 × CH), 125.8 (2 × CH), 127.1 (2 × CH), 128.1, 128.6 (2 × CH), 129.6, 129.7 (2 × CH), 130.0 (2 × CH), 130.3, 133.0, 136.8, 137.9, 143.3, 152.0, 163.6; IR (KBr) 3277 (brs, NH), 1654, 1558, 1505, 1459, 1387, 1282, 1074, 1018, 953, 915, 834 $cm^{-1}$; MS *m*/*z* (relative intensity) 354 ($M^+$, 6), 233 (2), 205 (2), 177 (1), 167 (1), 130 (3), 119 (100), 102 (19), 91 (56), 77 (19), 65 (8), 51 (5); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.05; H, 5.34; N, 11.71.

***3-Trifluoromethyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (12).*** [11] mp (recrystallized from $CH_2Cl_2$/ hexane) 196–198°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.19 (s, 1 H, Py-H), 7.29–7.49 (m, 4 H, ArH), 7.56–7.58 (m, 4 H, ArH), 7.71 (d, 2 H, $J$ = 8.7 Hz, ArH), 7.82–7.91 (m, 4 H, ArH), 8.21 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 96.4, 124.0, 124.7 (2 × CH), 125.8 (2 × CH), 126.1, 127.6 (2 × CH), 128.3, 128.6 (2 × CH), 128.6, 128.8, 129.4, 130.1 (2 × CH), 130.5, 131.1, 133.8, 136.1, 1 137.8, 152.1, 162.6; IR (KBr) 3205 (brs, NH), 3051, 1658, 1593, 1556, 1537, 1498, 1460, 1367, 1303, 1168. 1066, 854, 758, 688 $cm^{-1}$; MS *m*/*z* (relative intensity) 407 ($M^+$, 30), 377 (2), 234 (4), 206 (4), 173 (100), 145 (54), 131 (6), 102 (38), 77 (38), 51 (15); Anal. Calcd. for $C_{23}H_{16}F_3N_3O$: C, 67.81; H, 3.96; N, 10.31. Found: C, 68.12; H, 4.10; N, 10.21.

***2-Methoxy-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (13).*** mp (purified by column chromatography on silica gel) 196–198°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 3.52 (s, 3 H, Me), 6.91 (d, 1 H, $J$ = 6.9 Hz, ArH), 7.10 (t, 1 H, $J$ = 6.4 Hz, ArH), 7.13 (s, 1 H, Py-H), 7.33–7.89 (m, 8 H, ArH), 7.91 (dd, 2 H, $J$ = 6.7, 1.3 Hz, ArH), 8.43 (dd, 1 H, $J$ = 6.7, 1.3 Hz, ArH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 55.6, 94.6, 111.4, 120.1, 121.8, 125.8 (2 × CH), 125.9 (2 × CH), 128.0, 129.8 (2 × CH), 132.7 (2 × CH), 133.1, 133.9, 135.1, 136.7, 138.1, 152.1, 157.2, 161.2; IR (KBr) 3306 (brs, NH), 3062, 2924, 1674, 1598, 1570, 1496, 1483, 1371, 1296, 1244, 1163. 1018, 759, 694 $cm^{-1}$; MS *m*/*z* (relative intensity) 369 ($M^+$, 2), 206 (1), 135 (100), 120 (3), 102 (15), 92 (25), 77 (49), 63 (7), 51 (11); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.98; H, 5.43; N, 11.48.

***3-Methoxy-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (14).*** [11] mp (purified by column chromatography on silica gel) 175–177°C (lit. [11] mp 177–179°C); $^1$H-NMR ($CDCl_3$, 200 MHz) δ 3.84 (s, 3 H, $CH_3$), 7.19 (s, 1 H, Py-H), 7.28–7.72 (m, 12 H, ArH), 7.88 (d, 2 H, $J$ = 8.0 Hz, ArH), 8.21 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 55.5, 96.1, 112.6, 118.6, 118.7, 124.4 (2 × CH), 124.8, 125.9 (2 × CH), 128.2, 128.6 (2 × CH), 129.6, 130.0 (2 × CH), 133.0, 134.6, 136.6, 137.9, 152.0, 160.1, 163.7; IR (KBr) 3257 (brs, NH), 3066, 2843, 1667, 1597, 1560, 1502, 1460, 1369, 1284, 1230, 1041, 769, 702 $cm^{-1}$; MS *m*/*z* (relative intensity) 369 ($M^+$, 1), 234 (2), 206 (2), 135 (100), 107 (27), 92 (25), 77 (52), 64 (13), 51 (12); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.56; H, 5.42; N, 11.61.

***2,4-Difluoro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (15).*** mp (recrystallized from $CH_2Cl_2$/hexane) 162–164°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 6.74–6.89 (m, 1 H, ArH), 7.92–7.10 (m, 1 H, ArH), 7.26 (s, 1 H, Py-H), 7.31–7.51 (m, 4 H, ArH), 7.55–7.59 (m, 4 H, ArH), 7.88 (dd, 2 H, $J$ = 6.7, 1.4 Hz, ArH), 8.14–8.39 (m, 1 H, ArH), 8.74 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 95.5, 104.0, 104.5, 105.0, 112.9, 113.3, 116.7, 116.9, 117.0, 125.1 (2 × CH), 125.8 (2 × CH), 128.2, 128.6 (2 × CH), 128.8, 130.0 (2 × CH), 132.9, 134.2, 134.4, 136.7, 152.0, 158.2, 164.3; IR (KBr) 3423 (brs, NH), 3061, 1693, 1614, 1570, 1494, 1289, 1111, 970, 766, 694 $cm^{-1}$; MS *m*/*z* (relative intensity) 376 ($M^+$, 100), 358 (3), 336 (3), 304 (3), 282 (5), 262 (3), 234 (6), 219 (4), 207 (5), 154 (5), 141 (98), 113 (7), 92 (4), 77 (12), 57 (4). Anal. Calcd. for $C_{22}H_{15}F_2N_3O$: C, 70.39; H, 4.03; N, 11.19. Found: C, 70.64; H, 4.23; N. 11.46.

***3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (16, CDPPB).*** [11,14,15] mp (purified by column chromatography on silica gel) 207–208°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 6.90 (s, 1 H, Py-H), 7.26–7.45 (m, 11 H, ArH), 7.79–7.92 (m, 3 H, ArH), 8.86 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 100.5, 112.7, 117.1, 124.3 (2 × CH), 125.3 (2 × CH), 128.3 (2 × CH + CH), 128.7, 129.0, 129.5 (2 × CH), 129.6, 131.2, 131.8, 134.4, 135.3, 135.7, 138.6, 151.7, 164.3; IR (KBr) 3309 (brs, NH), 3068, 2922, 2852, 2232 (s, C≡N), 1689, 1654, 1560, 1498, 1458, 1363, 1292, 1190, 1072, 916 $cm^{-1}$; MS *m*/*z* (relative intensity) 364 ($M^+$, 59), 234 (11), 207 (6), 147 (8), 130 (100), 102 (49), 91 (2), 77 (15), 64 (1), 51 (8); Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 75.49; H, 4.65; N, 15.18.

***4-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (17).*** [11] mp (purified by column chromatography on silica gel) 207–209°C (lit. [11] mp 207–208°C); $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.02 (s, 1 H, Py-H), 7.35–7.49 (m, 6 H, ArH), 7.66–7.72 (m, 3 H, ArH), 7.90–7.95 (m, 3 H, ArH), 8.12–8.20 (m, 2 H, ArH), 8.27 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 99.7, 112.7, 117.7, 124.0 (2 × CH), 125.3 (2 × CH), 127.7, 127.9, 128.6 (2 × CH), 129.9 (2 × CH), 129.9, 131.3, 132.1, 133.4, 134.9, 135.3, 136.8, 139.2, 150.7, 163.8; IR (KBr) 3250 (brs, NH), 3087, 2308 (s, C[tbond]N), 1686, 1578, 1501, 1296, 769, 699 $cm^{-1}$; MS *m*/*z* (relative intensity) 364 ($M^+$, 100), 335 (6), 262 (3), 234 (12), 206 (7), 130 (98), 102 (44), 77 (16), 51 (5); Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 76.12; H, 4.42; N, 15.14.

***2-Nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (18).*** [11] mp (recrystallized from $CH_2Cl_2$/hexane) 229–231°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.00 (s, 1 H, Py-H), 7.36–7.89 (m, 12 H, ArH), 8.08–8.26 (m, 3 H, ArH + NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 100.1, 124.4 (2 × CH), 124.8, 125.7 (2 × CH), 128.6, 129.2 (2 × CH), 129.7, 130.2 (2 × CH), 132.0, 133.1, 134.6, 135.6, 137.0, 138.9, 144.4, 147.0, 150.8, 167.8; IR (KBr) 3261 (brs, NH), 3061, 1718, 1533, 1502, 1354, 1249, 757, 690 $cm^{-1}$; MS *m*/*z* (relative intensity) 385 ($M^+$, 66), 370 (27), 339 (22), 323 (10), 307 (45), 289 (39), 285 (18), 262

(15), 234 (32), 206 (22), 178 (31), 165 (48), 154 (100); Anal. Calcd. for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58. Found: C, 68.81; H, 4.15; N, 14.81.

***4-Nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (19).*** [11] mp (recrystallized from $CH_2Cl_2$/hexane) 221–223°C (lit. [11] mp 221–223°C); $^1$H-NMR ($CDCl_3$, 200 MHz) δ 6.95 (s, 1 H, Py-H), 7.21–7.89 (m, 9 H, ArH + NH), 8.18 (d, 2 H, $J$ = 6.5 Hz, ArH), 8.34 (d, 2 H, $J$ = 6.5 Hz, ArH), 8.39–8.54 (m, 1 H, ArH) 9.64 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 100.1, 122.9 (2 × CH), 123.0 (2 × CH), 124.7 (2 × CH), 126.9, 127.5, 128.1 (2 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 132.3, 136.1, 138.3, 138.5, 150.5, 162.0, 164.2; IR (KBr) 3250 (brs, NH), 3087, 1686, 1578, 1501, 1296, 769, 699 cm$^{-1}$; MS $m/z$ (relative intensity) 364 ($M^+$, 100), 335 (6), 262 (3), 234 (12), 206 (7), 130 (98), 102 (44), 77 (16), 51 (5); Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 76.12; H, 4.42; N, 15.14.

***N-(2-Furancarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (20).*** mp (purified by column chromatography on silica gel) 143–145°C; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 6.54 (dd, 1 H, $J$ = 3.6, 1.7 Hz, Furan-H), 7.18 (s, 1 H, Py-H), 7.25 (d, 1 H, $J$ = 3.6 Hz, Furan-H), 7.32–7.51 (m, 6 H), 7.56–7.60 (m, 3 H), 7.89 (dd, 2 H, $J$ = 8.0, 1.3 Hz, ArH), 8.34 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 95.4, 112.8, 116.4, 124.7 (2 × CH), 125.8 (2 × CH), 128.1, 128.6 (3 × CH), 130.0 (2 × CH), 133.0, 136.0, 137.9, 144.8, 146.8, 152.0, 154.2; IR (KBr) 3400 (brs, NH), 3277, 3138, 3061, 1672, 1587, 1556, 1537, 1500, 1471, 1415, 1365, 1288, 1228, 1157, 1074, 1012, 954, 883, 763, 692 cm$^{-1}$; MS $m/z$ (relative intensity) 330 ($M^+$, 100), 315 (9), 262 (11), 236 (14), 221 (16), 207 (12), 154 (28), 121 (42), 119 (58), 95 (95), 79 (57), 69 (100), 55 (99); HRMS Calcd. for $C_{20}H_{15}N_3O_2$: 329.1164, Found 329.1167.

***N-(2-Thiophenecarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (21).*** [14] $^1$H-NMR ($CDCl_3$) δ 7.04 (dd, 1 H, $J$ = 4.9, 3.8 Hz, thiophene-H), 7.13 (s, 1 H, Py-H), 7.36–7.66 (m, 10 H, ArH), 7.86–7.90 (m, 2 H, thiophene-H), 7.90 (b, 1 H, NH); $^{13}$C-NMR ($CDCl_3$) δ 96.0, 124.7 (2 × CH), 125.8 (2 × CH), 128.1, 128.2, 128.6 (2 × CH + CH), 129.2, 130.1 (2 × CH), 131.8, 132.9, 136.2, 137.4, 137.8, 152.0, 158.1. IR (KBr) 3061 (brs, NH), 2922, 2851, 1654, 1554, 1537, 1504, 1365, 1283, 1214, 1171, 1065, 1038, 888 cm$^{-1}$; MS $m/z$ (relative intensity) 345 ($M^+$, 42), 236 (4), 207 (3), 111 (100), 102 (11), 83 (2), 77 (10), 51 (3); HRMS Calcd. for $C_{20}H_{15}N_3OS$: 345.0936, Found 345.0939.

***N-Isoxazole-5-carbonyl-1,3-diphenyl-5-amino-1H-pyrazole (22).*** mp (purified by column chromatography on silica gel) 153–155°C; $^1$H-NMR ($CDCl_3$) δ 7.04 (d, 1H, $J$ = 1.8 Hz, Isoxazole-H), 7.19 (s, 1 H, Py-H), 7.35–7.58 (m, 8 H, ArH), 7.87 (dd, 2 H, $J$ = 6.6, 1.4 Hz, ArH), 8.35 (d, 1 H, $J$ = 1.8 Hz, Isoxazole-H), 8.51 (b, 1 H, NH); $^{13}$C-NMR ($CDCl_3$) δ 96.2, 107.9, 124.7 (2 × CH), 125.8 (2 × CH), 128.3, 128.6 (2 × CH), 128.9, 130.2 (2 × CH), 132.7, 135.0, 137.5, 151.4, 151.7, 152.0, 161.5; IR (KBr) 3399 (brs, NH), 3306, 3151, 3085, 1700, 1559, 1498, 1457, 1418, 1364, 1330, 1270, 1204, 1162, 1073, 1018, 825 cm$^{-1}$; MS $m/z$ (relative intensity) 331 ($M^+$, 62), 262 (15), 236 (11), 203 (11), 169 (12), 154 (22), 121 (21), 119 (41), 95 (74), 79 (53), 69 (96), 55 (100); HRMS Calcd. for $C_{19}H_{14}N_4O_2$: 330.1117, Found 330.1187; Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.68; H, 4.27; N, 16.96. Found: C, 69.58; H, 4.15; N, 16.86.

***N-(2-Benzofurancarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (23).*** mp (purified by column chromatography on silica gel) 164–166°C; $^1$H-NMR ($CDCl_3$) δ 7.24–7.72 (m, 14 H, ArH), 7.90 (dd, 2 H, $J$ = 8.1, 1.6 Hz, ArH), 8.62 (b, 1 H, NH); $^{13}$C-NMR ($CDCl_3$) δ 95.8, 111.9, 112.5, 123.0, 124.2, 124.7 (2 × CH), 125.8 (2 × CH), 127.3, 127.5, 127.7 (2 × CH + CH), 128.2, 128.6 (2 × CH), 130.1, 132.9, 135.8, 137.8, 147.2, 152.1, 154.8; IR (KBr) 3061 (brs, NH), 2922, 2850, 1554, 1504, 1365, 1282, 1170, 1142 cm$^{-1}$; MS $m/z$ (relative intensity) 379 ($M^+$, 47), 351 (16), 246 (4), 233 (2), 206 (3), 180 (1), 145 (100), 131 (4), 102 (15), 89 (33), 77 (14), 63 (5), 51 (4); HRMS Calcd. for $C_{24}H_{17}N_3O_2$: 379.1321, Found 379.1318.

***N-(5-Isobenzofurancarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (24).*** $^1$H-NMR ($CDCl_3$) δ 6.78 (s, 1 H, Py-H), 6.95 (s, 1 H, isobenzofurane-H), 7.27–7.50 (m, 10 H, ArH), 7.72–7.89 (m, 3 H, ArH), 8.06 (d, 1 H, $J$ = 6.4 Hz, isobenzofurane-H), 8.5 (b, 1 H, NH); $^{13}$C-NMR ($CDCl_3$) δ 97.6, 104.1, 122.7, 124.4 (2 × CH), 124.8, 125.7 (2 × CH), 128.5, 128.7, 129.4 (2 × CH + CH), 129.8, 130.0, 131.8, 132.4, 133.9, 135.7, 137.9, 139.4, 151.9, 152.1 165.0; IR (KBr) 3062 (brs, NH), 2924, 1735, 1674, 1558, 1497, 1458, 1367, 1087 cm$^{-1}$; MS $m/z$ (relative intensity) 409 ($M^+$, 4), 364 (100), 336 (5), 313 (6), 262 (4), 234 (12), 206 (12), 180 (5), 131 (4), 103 (10), 91 (9), 77 (27), 55 (6); Anal. Calcd. for $C_{24}H_{15}N_3O_4$; C, 70.41; H, 3.69; N, 10.26. Found: C, 70.34; H, 3.57; N, 10.22.

***N-Quinoline-8-sulfonyl-1,3-diphenyl-5-amino-1H-pyrazole (25).*** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 6.38 (s, 1 H, Py-H), 7.25–7.68 (m, 12 H, ArH + quinoline-H), 8.01 (dd, 1 H, $J$ = 8.4, 1.4 Hz, quinoline-H), 8.20 (dd, 1 H, $J$ = 8.4, 1.7 Hz, quinoline-H), 8.35 (dd, 1 H, $J$ = 7.3, 1.4 Hz, quinoline-H), 8.47 (dd, 1 H, $J$ = 4.3, 1.7 Hz, quinoline-H), 10.2 (b, 1 H, NH); $^{13}$C-NMR (50 MHz, $CDCl_3$) δ 96.4, 122.3, 123.7, 125.2 (2 × CH), 125.5 (2 × CH), 125.7, 127.4, 128.1, 128.3, 128.5 (2 × CH), 129.3 (2 × CH), 131.5, 132.6, 134.0, 135.0, 136.4, 137.1, 137.8, 151.0, 151.4; IR (KBr) 3450 (brs, NH), 3061, 1597, 1544, 1502, 1460, 1379, 1173, 1146, 766, 696 cm$^{-1}$; MS $m/z$ (relative intensity) 427 ($M^+$, 86), 395 (59), 337 (13), 289 (13), 281 (20), 235 (59), 221 (23), 207 (28), 194 (15), 185 (46), 176 (38), 165 (32), 154 (80), 109 (86), 83 (100), 71 (100), 57 (100); HRMS Calcd. for $C_{24}H_{18}N_4O_2S$: 427.1150, Found 427.1123; Anal. Calcd. for $C_{24}H_{18}N_4O_2S$: C, 67.59; H, 4.25; N, 13.14. Found: C, 67.25; H, 4.56; N, 12.97.

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## REFERENCES AND NOTES

[1] Cralg, P. N. In Comprehensive Medicinal Chemistry; Drayton, C. J., Ed.; Pergamon Press: New York, 1991; Vol. 8.

[2] Southon, I. W.; Buckinggham, J. In Dictionary of Alkaloids; Saxton, J. E., Ed.; Chapman and Hall: London, 1989.

[3] Negwer, M. In Organic-Chemical Drugs and Their Synonyms (An International Survey), 7th ed.; Akademie Verlag GmbH: Berlin, 1994.

[4] For the biological activities of pyrazole derivatives, see: Singh, P.; Paul, K.; Holzer, W. Bioorg Med Chem 2006, 6, 5061 and references cited therein.

[5] Lindsley, C. W.; Wisonoski, D. D.; Leister, W. H.; O'Brien, J. A.; Lemaire, W.; Williams, D. L., Jr.; Burno, M.; Sur, C.; Kinney, G. G.; Pettibone, D. J.; Tiller, P. R.; Smith, S.; Duggan, M. E.; Hartman, G. D.; Conn, P. J.; Huff, J. R. J Med Chem 2004, 47, 5825.

[6] Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.;

Varney, M. A.; Prasit, P.; Cosford, N. D. P. J Med Chem 2004, 47, 4645.

[7] Poon, S. F.; Eastman, B. W.; Chapman, D. F.; Chung, J.; Cramer, M.; Holtz, G.; Cosford, N. D. P.; Smith, N. D. Bioorg Med Chem Lett 2004, 14, 5477.

[8] Conn, P. J.; Pin, J. P. Annu Rev Pharmacol Toxicol 1997, 37, 205.

[9] Marino, M. J.; Conn, P. J. Curr Opin Pharmacol 2006, 6, 98.

[10] Ritzen, A.; Mathiesen, J. M.; Thomsen, C. Basic Clin Pharmacol Toxicol 2005, 97, 202.

[11] de Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; Baldwin, R. M.; Tamagnan, G. D.; Conn, P. J. J Med Chem 2006, 49, 3332.

[12] Elnagdi, M. H.; Khalifa, M. A. E. J Heterocycl Chem 1981, 18, 877.

[13] For the synthesis of pyrazole derivatives, see: (a) Elguero, J. In Comprehensive Heterocyclic Chemistry; Katrizky, A., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, p 277; (b) Elguero, J. In Comprehensive Heterocyclic Chemistry II; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol. 3, p 3; (c) Elguero, J. In Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds; Katrizky, A. R., Rees, C. W., Ed.; Pergamon: New York, NY, 1996; Vol. 5, p 111.

[14] Pinkerton, A. B.; Huang, D.; Cube, R. V.; Hutchinson, J. H.; Struthers, M.; Ayala, J. M.; Vicario, P. P.; Patel, S. R.; Wisniewski, T.; DeMartino, J. A.; Vernier, J.-M. Bioorg Med Chem Lett 2007, 17, 807.

[15] Our spectroscopic data are consistent with the literature: Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. J Org Chem 2004, 69, 5578.

# Green Synthesis of 5-Substituted-1,3,4-thiadiazole-2-thiols as New Potent Nitrification Inhibitors [1]



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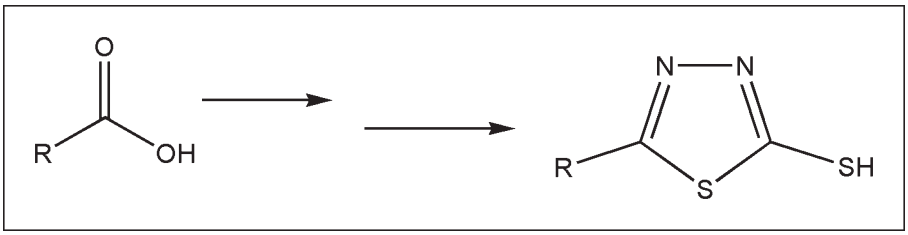


A fast, efficient synthesis of 5-substituted-1,3,4-thiadiazole-2-thiols was successfully developed, assessed using green chemistry matrices, and compounds were screened for their *in vitro* nitrification inhibitory activity. The greener method was superior with higher energy efficiency, E(nvironmental) factor, atom economy, atom efficiency, carbon efficiency, and reaction mass efficiency.

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## INTRODUCTION

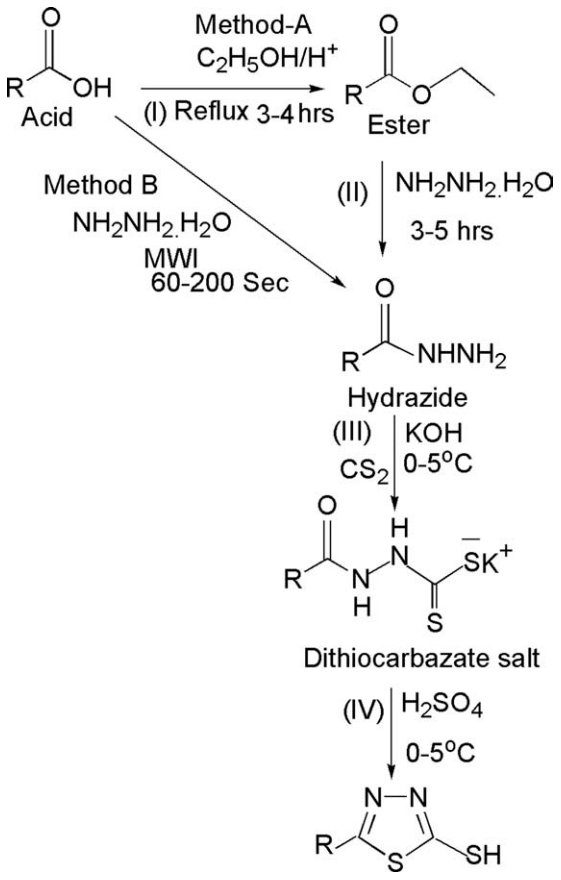
With increasing global population, demands have been increased to meet the requirements and consequently the industrial pollution. To control this detrimental phenomenon, the term ''green chemistry'' has come into existence [2]. Green chemistry is a package of technologies, design principles, and tools to reduce toxicity, resource energy use, and pollution of chemicals [2,3]. Due to environmental awareness [4], chemists have focused their attention to examine bioactive products such as heterocycles and processes in terms of environment friendliness. The 1,3,4-thiadiazoles are important bioactive heterocyclic moieties and have been reported to have wide range of bioactivities [5] such as neuroprotective, antibacterial, antidepressant, and antituberculour. One of the title compound, 5-methyl-1,3,4-thiadiazole-2-thiol is the side chain at C-3 position of a well known antibiotic Cefazolin sodium [6].

The low nitrogen use efficiency accounts to US$ 17 Billion annual nitrogen losses worldwide along with environmental and health hazards [7,8]. There is, thus, an urgent call for improving the efficiency of N-fertilizer use to achieve higher food production for catering the ever increasing population and also to minimize fertilizer related pollution of the environment [9]. Despite a great interest in the development and use of nitrification inhibitors to date, only a few compounds have been adopted for agricultural use [10]. The main problems associated with these inhibitors are the high cost involved in the development, subsequent registration of effective nitrification inhibitors, and the economics of their use in field conditions [11]. Various heterocyclics being an important bioactive class are used as nitrification inhibitors [12], but their use is restrained because of the complex synthetic procedures involving hazardous chemicals and subsequent cost. This problem can be solved by synthesizing potential nitrification inhibiting heterocyclics with minimum cost in an environment friendly manner. Keeping in view the aforementioned consideration, this study was taken up to design and synthesize 5-substituted-1,3,4-thiadiazole-2-thiols in a greener and cost effective way as potential nitrification inhibitors.

## RESULTS AND DISCUSSION

5-Substituted-1,3,4-thiadiazole-2-thiols have been synthesized starting from carboxylic acids following the conventional (protocol 1) and improved greener synthetic protocol (protocol 2). Reaction pathway is depicted in Scheme 1. In protocol 1, carboxylic acids were esterified by refluxing with ethyl alcohol for 3–4 h in the presence of sulfuric acid. These ester yielded corresponding hydrazide on refluxing with hydrazine hydrate for 3–5 h [13]. The analytical and spectral data of hydrazides were in complete agreement with those given in literature [13–17]. Hydrazides on reaction with carbon disulphide and potassium hydroxide afforded thiocarbazate salts, which are cyclized in the presence of concentrated sulfuric acid to afford 5-substituted-1,3,4-

**Scheme 1.** Synthesis of 5-substituted-1,3,4-thiadiazole-2-thiols.




thiadiazole-2-thiols. In protocol 2, our new greener one-pot method was used for the synthesis of acid hydrazides [18], and hydrazides were further processed similarly as in protocol 1 to yield 5-substituted-1,3,4-thiadiazole-2-thiols. This innovation improved the overall synthetic protocol for 5-substituted-1,3,4-thiadiazole-2-thiols in terms of yield, time, energy, atom economy and efficiency, number of steps, and other green chemistry measures (Table 3). All these compounds were characterized by analytical and spectral data (Tables 1 and 2).

The structures of 5-substituted-1,3,4-thiadiazole-2-thiols were established on the basis of their IR, $^1$H-NMR, $^{13}$C-NMR, CHNS data. The analytical and spectral data of 5-substituted-1,3,4-thiadiazole-2-thiols are given in Tables 1 and 2. The structure was supported by the absence of IR bands at 3200–3300, 1650–1670 $cm^{-1}$ due to $NHNH_2$ and CONH groups, respectively, and appearance of 1550–1590 $cm^{-1}$ due to C=N groups. It was also supported by the $^1$H-NMR data showing signals at δ 11.0–14.2 due to SH and $^{13}$C-NMR data showing signals at δ 160.0–174.0 and 176–192 due to 5 C—N and 2 C—N, respectively.

Both conventional and greener synthetic protocols for 5-substituted-1,3,4-thiadiazole-2-thiols were assessed using various green chemistry measures [19–21]. The developed greener protocol showed 4.7–11.4% increase in overall yield (Table 1). 5-Phenyl-1,3,4-thiadiazole-2-thiol was taken as a case for all calculations and related data for both the protocols (1 and 2) are described in Table 3.

The overall yield, *i.e.*, starting from benzoic acid to 5-phenyl-1,3,4-thiadiazole-2-thiol, following protocol 2 was 69.3% as compared with 59.6% from conventional protocol. There was 9.7% increase in the yield. The number of steps was also reduced to three as compared with four in protocol 1. This resulted in the higher energy efficiency and reduction of time, as total heating time was just 60–200 s under microwaves in protocol 2 as compared with 6–9 h in protocol 1. Among the various green chemistry matrices, *E*-factor values for protocols 1 and 2 were 20.1 and 14.8 kg waste/kg product, respectively, showing the reduction of 26.4% in the waste produced over the production of 1 kg of the product. Atom economy was increased by 5% as it was 43.3 and 48.3% for protocols 1 and 2, respectively. Atom efficiency, which considers both atom economy and yield parameters, showed an improvement of 7.7%. Carbon efficiency was found to be 28.5 and 34.7% for protocols 1 and 2, respectively, and it was improved by 6.2%. Reaction mass efficiency possessed the values of 31.5 (protocol 1) and 36.1 (protocol 2) as well as an increase of 4.6% was observed.

Results obtained in the *in vitro* soil incubation study are described in the Table 4. All the test compounds showed significantly higher ammonium-N and lower nitrate-N content as compared with urea alone The nitrite-N content remained insignificant (<0.5 mg/kg) in all the samples on all the sampling days.

All the compounds have been found to be effective nitrification inhibitors showing 49.5–79.7%, 36.8–78.8%, 42.4–78.5%, and 24.6–76.85% nitrification inhibition (NI) at 7th, 14th, 21st, and 28th days, respectively (Table 4). 4-Amino-1,2-4-triazole (ATC), the reference inhibitor at 10% dose, showed 75.3%, 75.7%, 77.2%, and 73.7% inhibitory activity on 7th, 14th, 21st, and 28th days, respectively, whereas the corresponding data on 5% dose were 65.9%, 65.5%, 65.3%, and 59.2% as well as at 1% dose were 60.9%, 57.4%, 54.6%, and 39.0% on 7th, 14th, 21st, and 28th days, respectively.

Among the series, 5-heptyl-1,3,4-thiadiazole-2-thiol (**ii**), 5-(2-chloro phenyl)-1,3,4-thiadiazole-2-thiol (**vi**), 5-(2,4,-dichloro phenyl)-1,3,4-thiadiazole-2-thiol (**vii**), 5-(2-methyl phenyl)-1,3,4-thiadiazole-2-thiol (**viii**), 5-(3-methyl phenyl)-1,3,4-thiadiazole-2-thiol (**ix**), 5-(3,4,-dimethoxy phenyl)-1,3,4-thiadiazole-2-thiol (**xii**), 5-(2-hydroxy phenyl)-1,3,4-thiadiazole-2-thiol (**xiii**), and 5-(4-hydroxy-3-methoxy phenyl)-1,3,4-thiadiazole-2-thiol

**Table 1**

Physical and spectral data of 5-substituted-1,3,4-thiadiazole-2-thiols.

| S. no. | Melting Point Obs./Lit. | % Yield Protocol 1 (Protocol 2) | IR ($cm^{-1}$) (C=N) | $^1$H NMR (DMSO-$d_6$ + $CDCl_3$ δ, ppm) | $^{13}$C NMR (DMSO-$d_6$ + $CDCl_3$ δ, ppm) |
|---|---|---|---|---|---|
| i. | 182–184/184–187 [22] | 53.1 (79.9) | 1553 | 2.43 (s, 3H, $CH_3$), 14.16 (s,1H, 2-SH) | 19.9 ($CH_3$), 160 (5 C=N), 190 (2 C=N) |
| ii. | 97–98/95–96 [22] | 58.4 (63.2) | 1548 | 0.89 (t, 3H, 7′-$CH_3$), 1.29 (m, 8H, 4 × $CH_2$), 1.63 (m, 2H, 2′-$CH_2$), 2.35 (t, 2H, 1′-$CH_2$), 12.9 (s, 1H, 2-SH) | 14.0 ($CH_3$), 23.1 ($CH_2$), 32.5 ($CH_2$), 30.0 ($CH_2$), 29.9 ($CH_2$), 32.1 ($CH_2$), 29.6, ($CH_2$) 155 (5 C=N), 187 (2 C=N) |
| iii. | 105–108/105–107 [22] | 49.5 (65.4) | 1540 | 0.88 (t, 3H, 9′$CH_3$), 1.27 (m, 12H, 6 × $CH_2$), 1.61 (m, 2H, 2′-$CH_2$), 2.34 (t, 2H, 1′-$CH_2$), 12.8 (s, 1H, 2-SH) | 14.2 ($CH_2$), 23.3 ($CH_2$), 32.6 ($CH_2$), 30.0 ($CH_2$), 29.3 ($CH_2$), 30.2 ($CH_2$), 31.2 ($CH_2$), 31.5 ($CH_2$), 34.1 ($CH_2$), 154 (5C=N), 182 (2 C=N) |
| iv. | 123–126/123–125 [22] | 51.7 (60.3) | 1535 | 0.88 (t, 3H, 11′-$CH_3$), 1.26 (m, 16H, 8 × $CH_2$), 1.62 (m, 2H, 2′-$CH_2$), 2.34 (t, 2H, 1′ $CH_2$), 12.7 (s, 1H, 2-SH) | 15.1 ($CH_3$), 24.1 ($CH_2$), 30.1 ($CH_2$), 31.2 ($CH_2$), 29.5 ($CH_2$), 31.2 ($CH_2$), 33.0 ($CH_2$), 31.2 ($CH_2$), 30.5 ($CH_2$), 32.1 ($CH_2$), 34.1 ($CH_2$), 151 (5 C=N), 180 (2 C=N) |
| v. | 214–216/215–216 [23] | 59.4 (77.0) | 1572 | 7.51–7.55 (m, 1H, Ar—H), 7.59 (dd, 2H, Ar—H, $J$ = 8.0 MHz), 7.94–7.96 (m, 2H, Ar—H) 11.0 (s, 1H, SH) | 122.81 (Ar—C), 126.42 (Ar—C) 126.91(Ar—C), 129.82 (Ar—C), 132.0 (Ar—C), 160.90 (Ar—C), 177.8 (5 C=N), 192 (2 C=N) |
| vi. | 212–214/210–212 [24] | 57.9 (68.3) | 1575 | 7.90 (d, 2H, Ar—H), 7.48 (d, 2H, Ar—H), 13.16 (s, 1H, SH) | 129.1 (Ar—C), 130.0 (2 Ar—C), 131.5 (2 Ar—C), 138.2 (Ar—C), 166.9 (5 C=N), 179.23 (2 C=N) |
| vii. | 197–201 | 57.1 (60.2) | 1581 | 7.32–7.39 (m, 1H, Ar—H), 7.57 (d, 1H, Ar—H), 8.2 (d, 1H, Ar—H), 13.98 (s, 1H, SH) | 126.58 (Ar—C), 127.20 (Ar—C), 131.47 (Ar—C), 133.55 (Ar—C), 136.02 (Ar—C), 139.62 (Ar—C), 169.60 (5 C=N), 182.46 (2 C=N) |
| viii. | 142–143 | 54.5 (59.3) | 1574 | 2.70 (s, 3H, $CH_3$), 8.12–8.31 (m, 1H, Ar—H), 7.92–8.1 (m, 1H, Ar—H), 7.46–7.49 (m, 1H, Ar—H), 7.29–7.32 (m, 1H, Ar—H), 12.28 (s, 1H, SH) | 21.19 ($CH_3$), 125.59 (Ar—C), 129.71 (Ar—C), 131.98 (2Ar—C), 132.79 (Ar—C), 141.4 (Ar—C), 173.76 (5 C=N), 186.43 (2 C=N) |
| ix. | 161–162 | 53.3 (61.2) | 1569 | 2.43 (s, 3H,$CH_3$), 7.26 (d, H, Ar—H), 7.41 (dd, Ar—H, $J$ = 9.6 MHZ) 7.49 (d, 1H, Ar—H), 7.94 (d, 1H, Ar—H), 12.68 (s, 1H, SH) | 21.28 ($CH_3$), 127.39 (Ar—C), 128.39 (Ar—C), 129.22 (Ar—C), 130.72 (Ar—C), 134.63 (Ar—C), 138.32 (Ar—C), 172.65 (5 C=N), 183.24 (2 C=N) |
| x. | 180–183 | 57.1 (67.4) | 1561 | 2.28 (s, 3H, $CH_3$), 7.19 (d, 2H, Ar—H), 7.81 (d, 2H, Ar—H), 12.65 (s, 1H, SH) | 21.42 ($CH_3$), 128.48 (Ar—C), 129.43 (2 Ar—C), 129.75 (2 Ar—C), 143.34 (Ar—C), 167.8 (5 C=N), 176.34 (2 C=N) |
| xi. | 223–225/222–224 [24] | 56.2 (65.3) | 1573 | 3.72 (s, 3H, $CH_3$), 7.31 (d, 2H, Ar—H), 7.68 (d, 2H, Ar—H), 12.36 (s, 1H, SH) | 48.24 ($OCH_3$), 111.30 (2 Ar—C), 121.35 (2 Ar—C), 139.75 (Ar—C), 147.34 (Ar—C), 164.8 (5 C=N), 178.34 (2 C=N) |
| xii. | 240–242 | 53.6 (58.2) | 1577 | 3.9 (s, 3H, $OCH_3$), 4.8 (s, 3H, $OCH_3$), 6.92 (d, 1H, Ar—H), 7.59 (s, 1H, Ar—H), 7.76–7.78 (dd, Ar—H, $J$ = 6.81), 12.76 (s, 1H, SH) | 55.98 ($OCH_3$), 56.04 ($OCH_3$), 110.30 (Ar—C), 112.22 (Ar—C), 121.70 (Ar—C), 124.59 (Ar—C), 148.61 (Ar—C), 153.45 (Ar—C), 172.03 (5C=N), 183.23 (2 C=N) |
| xiii. | 232–235 | 55.5 (67.3) | 1582 | 5.2 (s, 1H, OH), 6.83–6.91 (m, 1H, Ar—H), 7.41–7.45 (m, 1H, Ar—H), 7.76 (d, 1H, Ar—H), 7.78 (d, 1H, Ar—H), 11.38 (s, 1H, SH) | 113.26 (Ar—C), 117.20 (Ar—C), 119.47 (Ar—C), 130.67 (Ar—C), 135.96 (Ar—C), 161.16 (Ar—C), 172.47 (5 C=N), 183.24 (2 C=N) |

(*Continued*)

**Table 1**
(*Continued*)

| S. no. | Melting Point Obs./Lit. | % Yield Protocol 1 (Protocol 2) | IR ($cm^{-1}$) (C=N) | $^1$H NMR (DMSO-$d_6$ + $CDCl_3$ δ, ppm) | $^{13}$C NMR (DMSO-$d_6$ + $CDCl_3$ δ, ppm) |
|---|---|---|---|---|---|
| xiv. | 210–214 | 57.9 (59.3) | 1579 | 3.89 (s, 1H, Ar—OH), 3.8 (s, 3H, $OCH_3$), 6.63 (d, 1H, Ar—H), 6.83–6.99 (m, 1H), 7.03 (d, 1H), 9.82 (s, 1H, OH), 12.43 (s, 1H, SH) | 55.87 ($CH_3$), 113.05 (Ar—C), 115.46 (Ar—C), 122.03 (Ar—C), 151.45 (Ar—C), 167.72 (5C=N), 188.7 (2C=N) |
| xv. | 167–169 | 53.3 (60.9) | 1576 | 1.34 (s, 9H, *t*-$C_4H_9$), 7.46 (d, 2H, Ar—H), 8.03 (d, 2H, Ar—H), 13.39 (s, 1H, SH) | 14.3 (Aliph-C), 29.7 (Aliph-C), 31.1 (Aliph-C), 35.2 (Aliph-C), 125.3 (Ar—C), 125.5 (Ar—C), 126.5 (Ar—C), 129.4 (Ar—C), 130.1 (Ar—C), 157.58 (Ar—C), 172.15 (5 C=N), 183.92 (2 C=N) |

(**xiv**) were found to be the promising nitrification inhibitors.

Among the active series, 5-(3-methyl phenyl)-1,3,4-thiadiazole-2-thiol (**ix**) was most active at 10% dose with NI 78.2%, 77.1%, 77.3%, and 76.8% on 7th, 14th, 21st, and 28th days, respectively. The next active compound was 5-(2-chloro phenyl)-1,3,4-thiadiazole-2-thiol (**vi**) with activity at 10% was 79.7%,78.8%, 77.7%, and 75.1% on 7th, 14th, 21st and 28th days, respectively (Table 4).

Other active compounds (**vii**), (**xii**), (**xiii**), (**viii**), (**ii**), and (**xiv**) were statistically at par with ATC as evident from least significant difference (LSD) values. Compound (**xv**) showed 77.3%, 76.6%, 78.5%, and 68.4% NI on 7th, 14th, 21st, and 28th days, respectively. It performed statistically at par with ATC on 7th, 14th, 21st, but its activity was lower on 28th day. Rest of the compounds was less active at 10% doses than the reference inhibitor ATC. Among them, least active was compound (**iv**) with activity of 58% on the 28th day at 10% dose.

Among the active series compound (**vi**) was most active at 5% dose with NI 74.1, 73.5, 72.3, and 65.4 on 7th, 14th, 21st, and 28th days, respectively (Table 4). It performed better than ATC (5%) and statistically at par with ATC (10%) on 7th and 14th day. The next active compound was (**vii**) at 5% dose with NI 72.5%, 71.5%, 72.1%, and 63.1% on 7th, 14th, 21st, and 28th days, respectively. Other active compounds showed NI in the range of 56.1–73.8% during the entire period of incubation. All these compounds were statistically similar to ATC (5%). Remaining compounds were found to be inferior to reference inhibitor ATC (5%).

Compound (**vi**) at 5% dose performed best with NI 66.3%, 62.9%, 54.4%, and 41.4% on 7th, 14th, 21st, and 28th days, respectively. The next in performance were (**x**), (**xiv**), (**viii**), (**vii**), (**ii**), and (**xii**). All these

**Table 2**
Elemental-analytical data of 5-substituted-1,3,4-thiadiazole-2-thiols.

| | | | C (%) | | H (%) | | N (%) | | S (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| S. no. | Molecular formula | FW | Cal | Obs | Cal | Obs | Cal | Obs | Cal | Obs |
| i. | $C_3H_4N_2S_2$ | 132 | 27.25 | 28.2 | 3.04 | 2.99 | 21.19 | 20.83 | 48.51 | 47.21 |
| ii. | $C_9H_{16}N_2S_2$ | 216 | 49.96 | 47.73 | 7.45 | 7.23 | 12.95 | 13.32 | 29.64 | 30.12. |
| iii. | $C_{11}H_{20}N_2S_2$ | 244 | 54.05 | 52.5 | 8.25 | 8.99 | 11.46 | 11.21 | 26.24 | 27.16 |
| iv. | $C_{13}H_{24}N_2S_2$ | 272 | 57.30 | 59.29 | 8.88 | 7.59 | 10.28 | 9.73 | 23.54 | 22.24 |
| v. | $C_8H_6N_2S_2$ | 194 | 46.46 | 44.70 | 3.11 | 2.97 | 14.42 | 13.63 | 33.01 | 31.42 |
| vi. | $C_8H_5N_2S_2Cl$ | 228.5 | 42.01 | 40.26 | 2.20 | 2.09 | 12.25 | 12.85 | 28.04 | 26.52 |
| vii. | $C_8H_4N_2S_2Cl_2$ | 263 | 36.51 | 34.76 | 1.53 | 1.60 | 10.64 | 9.83 | 24.37 | 23.56 |
| viii. | $C_9H_8N_2S_2$ | 208 | 51.89 | 50.36 | 3.87 | 3.19 | 13.45 | 14.05 | 30.79 | 29.23 |
| ix. | $C_9H_8N_2S_2$ | 208 | 51.89 | 49.12 | 3.87 | 3.64 | 13.45 | 12.86 | 30.79 | 31.03 |
| x. | $C_9H_8N_2S_2$ | 208 | 51.89 | 49.64 | 3.87 | 3.61 | 13.45 | 12.32 | 30.79 | 31.63 |
| xi. | $C_9H_8ON_2S_2$ | 224 | 48.19 | 46.21 | 3.59 | 3.32 | 12.49 | 12.93 | 28.59 | 26.35 |
| xii. | $C_{10}H_{10}O_2N_2S_2$ | 254 | 47.23 | 45.06 | 3.96 | 3.41 | 11.01 | 12.51 | 25.22 | 24.89 |
| xiii. | $C_8H_6ON_2S_2$ | 210 | 45.69 | 44.26 | 2.88 | 3.19 | 13.32 | 14.26 | 30.50 | 29.12 |
| xiv. | $C_9H_8O_2N_2S_2$ | 240 | 44.98 | 42.91 | 3.36 | 2.98 | 11.66 | 12.59 | 26.69 | 25.36 |
| xv. | $C_{12}H_{14}N_2S_2$ | 250 | 57.56 | 55.63 | 5.64 | 5.31 | 11.19 | 10.70 | 25.61 | 25.13 |

**Table 3**

Comparative assessment of protocols 1 and 2 using green chemistry measures.

| Matrix | Protocol 1 (Conventional) | Protocol 2 (Greener) | Improvement |
|---|---|---|---|
| Overall yield (%) | 59.6 | 69.3 | 9.7% increase |
| Number of steps | Four | Three | 25% reduction |
| Heating time | 6–9 h | 60–200 s | 162–360 times decrease |
| Energy consumption (KWh) | 6–9 | 0.015–0.050 | 180–400 times reduction |
| E(nvironmental) factor (Kg waste/Kg product) | 20.1 | 14.8 | 26.4% reduction |
| Atom economy (%) | 43.3 | 48.3 | 5% increase |
| Atom efficiency (%) | 25.8 | 33.5 | 7.7% increase |
| Carbon efficiency (%) | 28.5 | 34.7 | 6.2% increase |
| Reaction mass efficiency (%) | 31.5 | 36.1 | 4.6% increase |

compounds were statistically at per with each other (Table 4). All the compounds showed an increase in NI with the increase in dose. Enhancement in NI is more from 1 to 5% increases in dose as compared with 5 to 10%.

**Structure-activity relationship.** In general, aryl substituted thiadiazoles performed better than the alkyl substituted 1,3,4-thiadiazole-2-thiols at all the doses. The 5-substitution in the 1,3,4-thiadiazole with aliphatic chains of 1, 7, 9, and 11 carbon atoms were used. The chain aliphatic seven of carbon atoms performed the best as evident from their performance on 28th day of incubation. The overall effect in minimizing NI was significantly higher with seven carbon atoms with 69.8 and 63.1% as compared with 58.1–64.4% and 52.9–56.2% with others at 10 and 5% doses, respectively (Fig. 1). At 1% dose, maximum NI, 36.2%, was observed with seven carbon atoms, but it was superior to NI with one carbon atom, 25.7% only and performed at par with others.

5-Aryl substitution in the 1,3,4-thiadiazole ring with chloro atoms in phenyl ring was used. Introduction of chlorine atoms in the phenyl ring resulted in the increase of activity and found to be significantly superior to phenyl substitution with no chlorine atom (Fig. 2). Their effect on NI was similar for both mono and dichloro phenyl derivatives (Fig. 2), which were superior to phenyl derivative. Both chloro derivative showed 36.2–41.4%, 63.8–65.4%, and 73.6–75.1% NI at 1, 5, and 10% dose, respectively. The phenyl derivative showed 24.6%, 43.6%, and 60.8% NI at respective 1, 5 and 10% doses.

5-(3-Methyl phenyl)-1,3,4-thiadiazole-2-thiol, 5-(4-chloro phenyl)-1,3,4-thiadiazole-2-thiol and 5-(2,4-dichlorophenyl)-1,3,4-thiadiazole-2-thiol emerged as potent nitrification inhibitors. The study revealed the cost effective and environment friendly synthesis of the potent 1,3,4-thiadizole-2-thiols. These compounds hold promise to be used as nitrification inhibitors and also as prototypes for the discovery of potent analogues through the process of compound library design and screening.

## EXPERIMENTAL

Thin layer chromatography was performed on 200-μm thick aluminum sheets having silica gel 60 $F_{254}$ as adsorbent. Different solvent systems were used for developing the TLC plates. Spots were visualized either by UV-light or iodine vapors. Melting points were determined by using electro thermal melting point apparatus and are uncorrected. Microwave irradiation was carried out by using Samsung microwave oven model CE118KF operating at 2450 MHz. A Christ Lypholizer model Alpha 1-2 LD was used for lyophilizing purpose. Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker Abamce, 400 MHz instrument, after dissolving the samples in $CDCl_3$/DMSO($d_6$) using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in δ values relative to TMS and the notations used are s-singlet, d-doublet, t-triplet, m-multiplet, and brs-broad singlet. Infrared (IR) spectra were recorded on a Nicolet Fourier Transform Infrared Spectrophotometer, Model Impact 400 (FTIR) in either nujol mull or KBr disc. A Varian, Series 634, UV–Vis double beam spectrophotometer was used. Elemental analysis was carried out using EuroVector CHNS analyzer. All the chemicals and reagents were purchased from S D Fine Chemicals, Qualigens Fine Chemicals, and Merck India.

**Synthesis of test chemicals.** 5-Substituted-1,3,4-thiadiazole-2-thiols were synthesized following the Scheme 1 using the both conventional (protocol 1) and greener synthesis (protocol 2). Protocol 2 used the new greener method [18] for synthesizing the intermediate hydrazides which otherwise required 6–9 h heating under protocol 1 [13].

***Conventional method of synthesis of carboxylic acid hydrazides (Method-A).*** The organic acids were esterified in the presence of ethyl alcohol and catalytic amount of sulfuric acid. The resulted esters were hydrazinolysed with hydrazine hydrate to afford the hydrazides [13].

***Greener method for synthesis of carboxylic acid hydrazides (Method B).*** Carboxylic acid (0.01 mol) and hydrazine hydrate (0.012 mol) were irradiated under microwaves for 60–200 s at 900 W. Then, the reaction mixture was cooled to −20°C and lyophilized at −50°C. The product obtained was recrystallized from methyl alcohol. The hydrazides were characterized on the basis of physical and spectral data [13–17].

**Preparation of 5-substituted-1,3,4-thiadiazole-2-thiols.** Potassium hydroxide (0.11 mol) was dissolved in minimum amount of ethanol, and hydrazide (0.1 mol) was added to it. The reaction mixture was cooled to 0–5°C followed by

**Table 4**

Effect of 5-substituted-1,3,4-thiadiazole-2-thiols on nitrification inhibition (NI).

| | | | Nitrification inhibition (%) | | | |
|---|---|---|---|---|---|---|
| Comp. | R | Dose | 7th Day | 14th Day | 21st Day | 28th Day |
| i. | $CH_3$— | 1 | 54.7 | 36.8 | 44.1 | 25.7 |
| | | 5 | 69.3 | 66.9 | 63.9 | 56.1 |
| | | 10 | 76.8 | 74.1 | 75.4 | 64.4 |
| ii. | $CH_3(CH_2)_5CH_2$— | 1 | 59.1 | 53.9 | 51.2 | 36.2 |
| | | 5 | 70.1 | 67.9 | 68.6 | 63.1 |
| | | 10 | 76.1 | 76.0 | 77.0 | 69.8 |
| iii. | $CH_3(CH_2)_7CH_2$— | 1 | 52.7 | 46.3 | 46.9 | 32.8 |
| | | 5 | 65.3 | 61.1 | 59.0 | 52.9 |
| | | 10 | 73.9 | 69.4 | 68.0 | 63.0 |
| iv. | $CH_3(CH_2)_9CH_2$— | 1 | 49.5 | 40.6 | 42.4 | 32.8 |
| | | 5 | 69.8 | 64.7 | 57.8 | 56.2 |
| | | 10 | 75.8 | 73.0 | 74.7 | 58.1 |
| v. | $C_6H_5$— | 1 | 58.0 | 44.3 | 48.0 | 24.6 |
| | | 5 | 61.9 | 58.4 | 56.3 | 43.6 |
| | | 10 | 65.5 | 65.0 | 67.6 | 60.8 |
| vi. | 4-$ClC_6H_4$— | 1 | 66.3 | 62.9 | 54.4 | 41.4 |
| | | 5 | 74.1 | 73.5 | 72.3 | 65.4 |
| | | 10 | 79.7 | 78.8 | 77.7 | 75.1 |
| vii. | 2,4-$(Cl)_2C_6H_3$— | 1 | 61.3 | 54.1 | 53.5 | 36.2 |
| | | 5 | 72.5 | 71.5 | 72.1 | 63.8 |
| | | 10 | 78.4 | 76.6 | 76.7 | 73.6 |
| viii. | 2-$CH_3C_6H_4$— | 1 | 65.8 | 61.2 | 54.6 | 37.9 |
| | | 5 | 64.6 | 64.4 | 65.3 | 59.0 |
| | | 10 | 72.4 | 71.2 | 72.4 | 70.4 |
| ix. | 3-$CH_3C_6H_4$— | 1 | 63.4 | 60.1 | 52.7 | 39.1 |
| | | 5 | 72.9 | 72.3 | 70.7 | 63.7 |
| | | 10 | 78.2 | 77.1 | 77.3 | 76.8 |
| x. | 4-$CH_3C_6H_4$— | 1 | 68.5 | 62.2 | 55.1 | 33.2 |
| | | 5 | 73.7 | 72.3 | 68.7 | 61.7 |
| | | 10 | 79.4 | 77.7 | 76.0 | 67.1 |
| xi. | 4-$CH_3C_6H_4$— | 1 | 53.8 | 51.7 | 48.8 | 29.7 |
| | | 5 | 62.6 | 64.2 | 63.0 | 52.8 |
| | | 10 | 68.0 | 69.4 | 71.6 | 67.0 |
| xii. | 3,4-$(CH_3O)_2C_6H_3$— | 1 | 58.9 | 52.9 | 51.3 | 34.4 |
| | | 5 | 70.6 | 68.7 | 68.1 | 63.2 |
| | | 10 | 77.3 | 75.1 | 75.7 | 71.9 |
| xiii. | 2-$HOC_6H_4$— | 1 | 58.3 | 51.6 | 49.4 | 32.7 |
| | | 5 | 72.3 | 69.9 | 67.0 | 59.2 |
| | | 10 | 73.3 | 71.4 | 71.2 | 70.2 |
| xiv. | 4-HO, 3-$CH_3OC_6H_3$— | 1 | 65.3 | 57.0 | 51.5 | 38.3 |
| | | 5 | 68.8 | 67.7 | 61.3 | 62.5 |
| | | 10 | 76.9 | 75.3 | 72.4 | 70.0 |
| xv. | 4-*t*-$C_4H_9C_6H_4$— | 1 | 58.1 | 51.6 | 44.8 | 32.9 |
| | | 5 | 73.8 | 71.5 | 69.8 | 60.1 |
| | | 10 | 77.3 | 76.6 | 78.5 | 68.4 |
| ATC | – | 1 | 60.9 | 57.4 | 54.6 | 39.0 |
| | | 5 | 65.9 | 65.5 | 65.3 | 59.2 |
| | | 10 | 75.3 | 75.7 | 77.2 | 73.7 |
| LSD (5%) | | – | 4.7 | 5.0 | 4.6 | 5.0 |

drop wise addition of carbon disulphide (0.11 mol). After addition, the reaction mixture was stirred for 30 min to afford solid potassium dithiocarbazate salt. It was filtered, washed with chilled acetone, dried, and used as such for further reaction. Potassium dithiocarbazate salt (0.1 mol) was added slowly in small lots to conc sulfuric acid (2.5 times of salt) at 5°C with constant stirring. The reaction mixture was stirred for 30 min, and the resulting viscous liquid was poured over crushed ice slowly. The solid obtained was filtered and washed with excess of water till the filtrate become neutral to litmus paper. The wet solid was suspended in water at 40°C and 25% sodium hydroxide solution was added slowly with stirring to adjust the pH of the solution in the range of 8.0–9.0. The resulting solution was filtered through a charcoal bed, and pH was adjusted

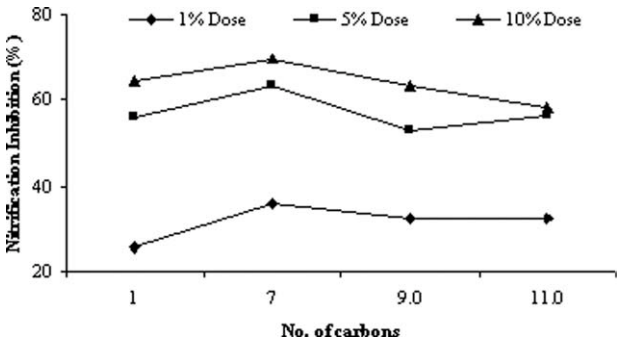



**Figure 1.** Effect of number of aliphatic C-atoms at 5-position of 1,3,4-thiadiazole-2-thiol on nitrification inhibition.

to 3.0–5.0 by drop wise addition of 50% hydrochloric acid. White solid obtained was filtered, washed with water, and dried. All the compounds were characterized on the basis of physical and spectral data as depicted in Tables 1 and 2.

**Assessment by green chemistry matrices.** The developed synthetic protocol for 5-substituted-1,3,4-thiadiazole-2-thiols was assessed by following green chemistry matrices, which were calculated as reported [19–21].

**Nitrification inhibitory activity.** The soil with following properties was collected from the farm of the institute for *in vitro* incubation experiments. Sand 60.8%, silt 18.7%, clay 20.5%, water holding capacity 35.5%, bulk density 1.51 mg/kg, organic C 0.5%, available N 553.72%, ammonium-N 3.2 mg/kg, nitrite-N traces, nitrate-N 8.54 mg/kg, pH (soil: water::1:2.5) 7.9, and EC at 25°C 0.35 $dSm^{-1}$.

The test chemicals (5-substituted-1,3,4-thiadiazole-2-thiols) and reference inhibitor, ATC, were tested at three doses (1, 5 and 10% of applied urea-N) along with urea alone control.

The experiments were laid following completely randomized design with three replicates. Fifty grams of air dried, finely ground, and sieved (10 mesh) soil was taken in 100 mL capacity plastic beakers. Calculated amount of the test chemical (0.1, 0.5, and 1.0 mg for 1, 5, and 10% dose of applied urea-N, respectively) in acetone was added to each beaker and mixed thoroughly. In all the treatments including control, same volume of acetone was added. After mixing, 10 mg urea-N (200 mg urea-N per kg of soil) in aqueous solution was added, mixed thoroughly, and distilled water was added to each beaker for maintaining the moisture at 50% of water holding capacity [25] of the soil. The experiment was conducted in triplicate with concomitant controls. For ATC, the soil was prepared in similar way. All the beakers were accurately weighed, labeled, and incubated in a BOD incubator at 28 ± 1°C, and 98% relative humidity. Soil moisture was maintained by adding distilled water every alternate day (if required) after taking the difference of weight. Samples (5 g) were drawn on 7th, 14th, 21st, and 28th day of incubation. Before sampling, distilled water was added to make up for the loss in weight because of evaporation of water and mixed thoroughly. Ammonium, nitrite, and nitrate-N were extracted in 50 mL 2*M* aqueous sodium sulfate solution. The soil with extracting solution was shaken for an hour on a reciprocal shaker and filtered. Ammonium, nitrite, and nitrate-N were estimated following Indophenol blue, sulfanilic acid, and phenol disulfonic acid method, respectively [26,27].

The contents of ammonium nitrate and nitrite-N were obtained from the standard curves and expressed in mg $kg^{-1}$. The nitrification rate for a constant period of incubation was calculated using Sahrawat's [28] formula. The data were statistically analyzed following the procedure laid out by Gomez and Gomez [29]. The analysis of variance was computed using Statistical Package for Social Services (SPSS version 10.0), and treatment means were compared by LSD at 5% levels.

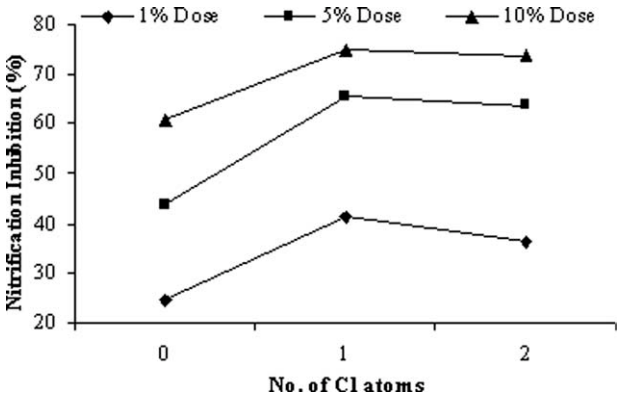



**Figure 2.** Effect of number of chlorine atoms in phenyl ring at 5-position of 1,3,4-thiadiazole-2-thiol on nitrification inhibition.

## REFERENCES AND NOTES

[1] Contribution number 992.

[2] (a) Kidwai, M. Pure Appl Chem 2006, 78, 1983; (b) Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice; Oxford University Press: New York, 2000; p 135; (c) Ahluwalia, V. K.; Kidwai, M. New Trends in Green Chemistry; Kluwer Academic Publishers: Netherland, 2004; p 292; (d) Matlack, A. S. Introduction to Green Chemistry; Marcel Dekker Inc., CRC Press: New York, 2001; p 551; (e) Lancester, M. Green Chemistry: An Introductory Text; Royal Society of Chemistry: Cambridge, 2002; p 310; (f) Clark, J. H.; Macquarrie, D. Handbook of Green Chemistry and Technology; Blackwell Publishers: Oxford, 2002; p 540.

[3] Cusumano, J. A. J Chem Educ 1995, 72, 959.

[4] Iles, A. Bus Strat Env 2008, 17, 524.

[5] (a) Jaquith, J. B.; Villeneuve, G.; Boudreault, A.; Morris, S. J.; Durkin, J.; Gillard, J. W.; Hewitt, K. E.; Marsh, H. N. U.S. Patent 2009/0042953 A1, February 12, 2009; (b) Pattanayak, P.; Sharma, R.; Sahoo, P. K. Med Chem Res 2009, 18, 351; (c) Sainy, J.; Mishra, G. P.; Sharma, R.; Chaturvedi, S. C. Pharmaceut Chem J 2009, 43, 19; (d) Matysiak, J. Chem Pharm Bull (Tokyo) 2006, 54, 988; (e) Schenone, S.; Brullo, C.; Bruno, O.; Bondavalli, F.; Ranise, A.; Filippelli, W.; Rinaldi, B.; Capuano, A.; Falcone, G. Bioorg Med Chem 2006, 14, 1698. (f) Foroumadia, A.; Emamic, S.; Hassanzadehb, A.; Rajaeeb, M.; Sokhanvarb, K.; Hassan, M.; Shafieea, A. Bioorg Med Chem Lett 2005, 15, 4488; (g) Oruc, E. E.; Rollas, S.; Kandemirli, F.; Shvets, N.; Dimoglo, A. S. Bioorg Med Chem Lett 2004, 12, 5651; (h) Clerici, F.; Pocar, D. J. Med Chem 2001, 44, 931; (i) Chapleo, C. B.; Myers, M.; Myers, P. L.; Saville, J. F.; Smith, A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S.; Welbourn, A. P. J Med Chem 1986, 29, 2273; (j) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J. J Med Chem 1993, 36, 1090.

[6] Kariyone, H.; Harada, M.; Kurita, T.; Takana, J. J Antibiot 1970, 23, 131.

[7] Subbarao, G. V.; Ito, O.; Sahrawat, K. L.; Berry, W. L.; Nakahara, K.; Ishikawa, T.; Watanabe, T.; Suenaga, K.; Rondon, M.; Rao, I. M. Crit Rev Plant Sci 2006, 25, 305.

[8] Raun, W. R.; Johnson, G. V. Agron J 1999, 91, 357.

[9] Rao, E. V. S. P.; Puttana, K. Curr Sci 2006, 91, 1335.

[10] Prasad, R.; Power, J. F. Adv Agron 1995, 54, 233.

[11] Sahrawat, K. L.; Keeney, D. R. Commun Soil Sci Plant Anal 1985, 16, 517.

[12] McCarty, G. W. Biol Fertil Soil 1999, 29, 1.

[13] Furniss, B. S.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. Vogel's Textbook of Practical Organic Chemistry, 5th ed.; Longman Scientific and Technical: Essex England, 1989; pp 1342–1349.

[14] Jain, A. K.; Gupta, K. P.; Ganesan, K.; Pande, A.; Malhotra, R. C. Defence Sci J 2007, 57, 267.

[15] Toda, F.; Hyoda, S.; Okada, K.; Hirotsu, K. J Chem Soc Chem Commun 1995, 1531.

[16] Wagner, R. B.; Zook, H. D. Synthetic Organic Chemistry; Wiley: New York, 1953, p 569.

[17] Yale, H. L.; Losee, K.; Martins, J.; Holsing, M.; Perry, F. M.; Bernstein, J. J Am Chem Soc 1953, 75, 1933.

[18] Saha, A.; Kumar, R.; Kumar, R.; Devakumar, C. Towards green agrochemicals: Green synthesis of hydrazides. National Seminar on Green Chemistry and Natural Products, 26–27 November, Department of Chemistry, University of Delhi, Delhi, 2007, p 20.

[19] Constable, D. J. C.; Curzons, A. D.; Freitas dos Santos, L. M.; Geen, G. R.; Hannah, R. E.; Hayler, J. D.; Kitteringham, J.; McGuire, M. A.; Richardson, J. E.; Smith, P.; Webb, R. L.; Yu, M. Green Chem 2001, 3, 7.

[20] Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. Green Chem 2002, 4, 521.

[21] Curzons, A.; Constable, D.; Mortimer, D.; Cunningham, V. Green Chem 2001, 3, 1.

[22] Kidwai, M.; Kumar, R.; Goel, Y. Main Gp Met Chem 1997, 20, 367.

[23] Kidwai, M.; Bhushan, K. R. Indian J Chem 1998, 37B, 427.

[24] Baron, M.; Wilson, C. V. J Org Chem 1958, 28, 1021.

[25] Dastane, N. G. A Practical Manual for Water Use Research; Navbharat Prakashan: Poona (India), 1967; p 105.

[26] Keeney, D. R.; Nelson, D. W. anic forms. In Methods of Soil Analysis, Part 2: Chemical and Microbiological Properties; Page, A. L., Ed.; Soil Science Society of America and American Society of Agronomy: Madison, WI, 1989; pp 643–698.

[27] Prasad, R. A Practical Manual for Soil Fertility; National Professor's Unit, Division of Agronomy, IARI, ICAR: New Delhi, India, 1998; pp 26–31.

[28] Sahrawat, K. L. Plant Soil 1980, 55, 487.

[29] Gomez, K. A.; Gomez, A. A. Statistical Procedures for Agricultural Research; Wiley: New York, 1984.

# Synthesis of Novel 2,3-Dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-Dioxides and Their Epoxidation Ability



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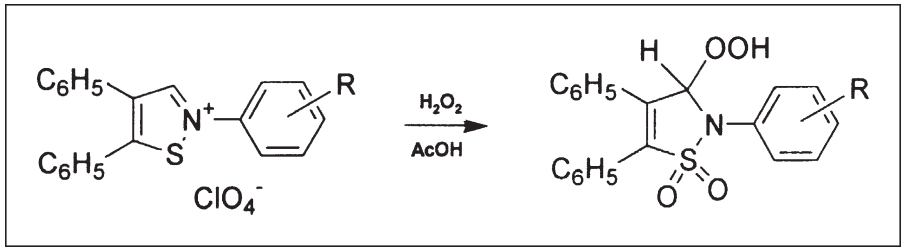


The novel hydroperoxy sultams, 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides, were synthesized by the oxidation of the 2-aryl-4,5-diphenyl substituted isothiazolium salts with $H_2O_2$. These hydroperoxy sultams were investigated as epoxidation agents in the epoxidation reaction of *cis*-cyclooctene catalyzed by MoB. 2-(2-Chlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide was found to have the highest epoxidation ability.

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## INTRODUCTION

The cyclic sulfonamides (sultams) have been shown to be highly useful heterocycles for medicinal chemistry [1,2] as well as for chemical methodology [3,4]. They show biological activities such as antibacterial [5,6], anticonvulsant [7,8], sedative-hypnotic [9], and peptidomimetic [10,11]. Sultams have found application as chiral auxiliaries in several asymmetric processes such as Diels-Alder reactions [12,13], alkylation [14], and dihydroxylation [15] and are used in enantioselective catalysis [16]. Hydroperoxy sultams can also serve as oxidants in oxidation of heteroatoms (N, S, P) [17,18] and in epoxidation of double bonds [19].

We now report the synthesis of novel hydroperoxy sultams, 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides, and studies of their epoxidation ability in the epoxidation reaction of *cis*-cyclooctene catalyzed by molybdenum boride MoB.

## RESULTS AND DISCUSSION

Our approach to hydroperoxy sultams started from isothiazolium salts (1) (Scheme 1) which were prepared for the first time by intramolecular cyclocondensation of β-thiocyanatovinyl aldehydes and the suitably substituted anilines in the presence of perchloric acid in acetic acid in moderate-to-good yields: 1a (61%), 1b (62%), and 1c (51%) according to already reported synthesis [20,21]. The oxidation of the 2-aryl-4,5-diphenyl substituted isothiazolium salts in glacial acetic acid with 30% $H_2O_2$ at r.t. gave stable 3-hydroperoxysultams (2) in good yields: 2-(2-chlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2a) (70%), 2-(2,6-dichlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2b) (70%) and 2-(2,6-dichloro-4-nitrophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2c) (72%) after 72, 72 and 96 h stirring, respectively.

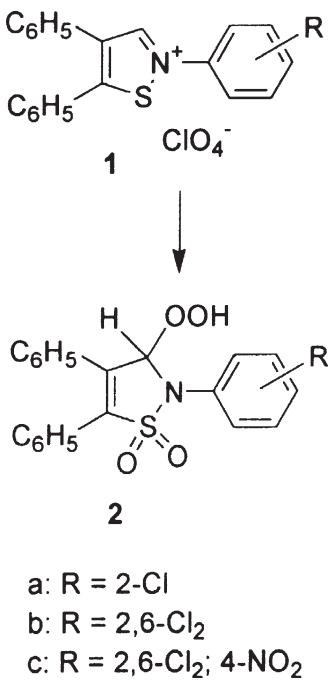
The structures of the 3-hydroperoxysultams 2a, 2b, and 2c were established by IR and NMR spectroscopy and composition was confirmed by mass spectrometry and elemental analysis.

The IR spectra of compounds 2 show two absorption bands at 1302–1316 and 1146–1160 $cm^{-1}$ for the $SO_2$ groups which are characteristic for the antisymmetric and symmetric vibrations of the 1,1-dioxides, respectively. The two absorption bands for the $NO_2$ group are observed at 1335 and 1537 $cm^{-1}$ in the spectrum of compound 2c.

In $^1H$ NMR spectra of 3-hydroperoxysultams 2, the typical absorption of the 3-H atom appears at 6.49–6.60 ppm. The $^{13}C$ NMR signals for C-3 at 92.5–95.0 ppm are characteristic for compounds 2.

The 2 were investigated as epoxidation agents in the epoxidation reaction of cyclooctene in the presence of molybdenum boride. The kinetic curves of 2 consumption and 1,2-epoxycyclooctane accumulation in the

**Scheme 1**



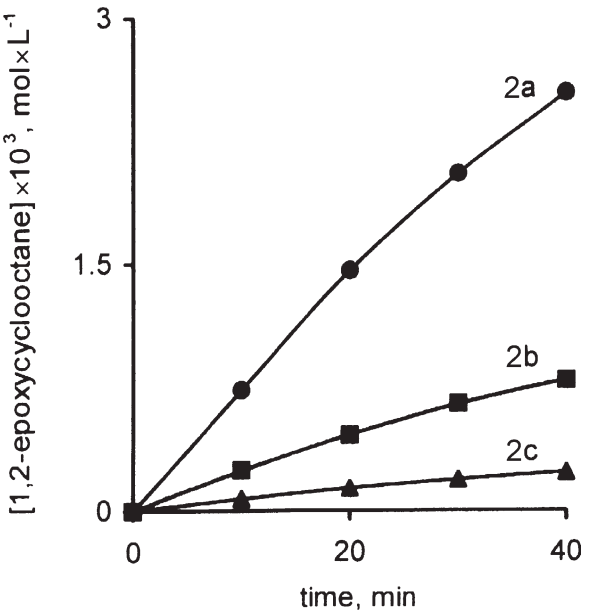




**Figure 2.** The kinetic curves of the 1,2-epoxycyclooctane accumulation in the catalytic epoxidation reaction of cyclooctene by **2**.

epoxidation process are presented in Figures 1 and 2, respectively. It is evident that epoxidation ability of investigated 2 is different and is defined by the nature of the substituents on the aromatic ring connected at nitrogen atom of hydroperoxide molecule.

The highest value of hydroperoxy sultam consumption in the catalytic epoxidation process was observed for 2a containing only one *ortho*-chlorine atom and conversion of this hydroperoxide was equal to 73% after 40 min of reaction. In the case of 2b with two chlorine atoms in ortho-position to bond of nitrogen with aromatic ring, the hydroperoxide consumption was the lowest and hydroperoxide conversion was 41%. The value of hydroperoxide conversion for 2c which contains three substituents—two chlorine atoms and one $NO_2$ group—is 47% so it is between 2a and 2b.

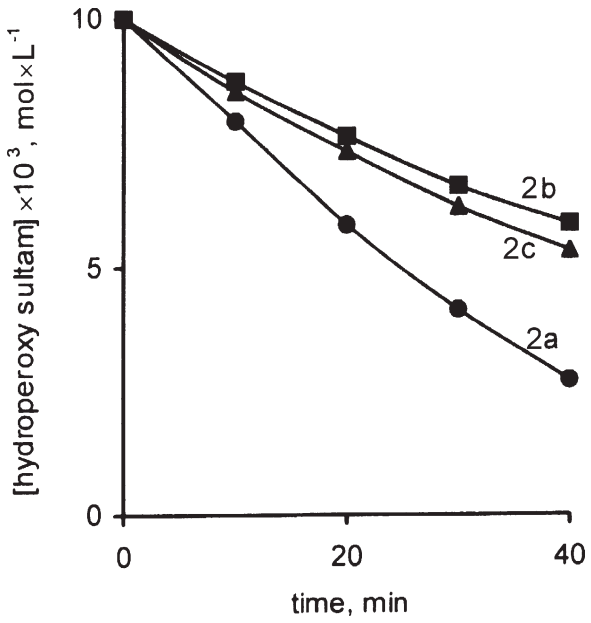



**Figure 1.** The kinetic curves of the consumption of **2** in the catalytic epoxidation reaction of cyclooctene.

The epoxide is formed in the presence of all investigated hydroperoxy sultams. This fact indicates on possibility of their application as epoxidation agents in the catalytic reaction with cyclooctene. The highest epoxidation ability exhibits 2a, the selectivity of epoxide formation (calculated as ratio of formed epoxide quantity to consumed hydroperoxide quantity) in its presence is 35%. The lowest epoxidation ability demonstrates 2c in the case of which the selectivity of epoxide formation is only 5%. 2b shows intermediate selectivity 19%.

From the obtained results, one can conclude that the most effective oxidant in the catalytic epoxidation reaction of cyclooctene is 2a, which molecule contains only one substituent—chlorine atom in α-position to bond of nitrogen with aromatic ring. Introduction of another one chlorine atom and especially $NO_2$ group leads to decrease of the parameters of the epoxidation reaction. It is probably caused by dominant influence of a steric factor. The increase in quantity of substituents complicates possibility of the simultaneous coordination of hydroperoxy sultam and cyclooctene on catalyst and formation of intermediate triple complex which is

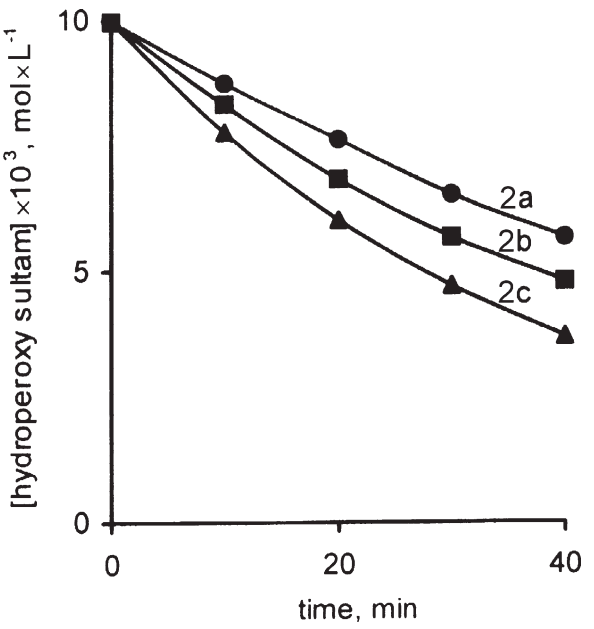



**Figure 3.** The kinetic curves of the consumption of **2** in the catalytic decomposition reaction.

responsible for epoxide formation [22–24]. Accordingly, the efficiency of the epoxidation reaction decreases.

Taking into account the significant contribution of unproductive 2 consumption into overall process of the cyclooctene epoxidation, it is reasonable to study the decomposition process of investigated hydroperoxy sultams catalyzed by MoB at the same reaction conditions in the absence of cyclooctene in the reaction system. Figure 3 shows the kinetic curves of 3-hydroperoxysultams consumption in the process of catalytic decomposition. One can see that the decomposition process most actively occurs in the case of 2c with hydroperoxide conversion 63%. One may suggest that presence of $NO_2$ group in a para-position to bond of nitrogen with aromatic ring favors the proceeding of the catalytic decomposition process. The values of conversions of 2b and 2a are smaller and are equal to 52% and 43%, correspondingly.

Comparing the data of the decomposition process with the data of the epoxidation process, it is possible to conclude that the highest epoxidation ability in the epoxidation process has 2a which is the least active in the decomposition reaction. At the same time, the 2c, which is the most actively consumed in the decomposition process, has the lowest epoxidation ability in the reaction with cyclooctene.

In summary, we have described the synthesis of novel 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides by oxidation of the 2-aryl-4,5-diphenyl substituted isothiazolium salts with $H_2O_2$. We have shown that these hydroperoxy sultams can act as epoxidation agent in the epoxidation reaction of cyclooctene catalyzed by MoB.

## EXPERIMENTAL

Melting points were determined on Boetius micro-melting-point apparatus and are corrected. IR spectra are expressed in $cm^{-1}$ and were recorded on Genisis FTIR Unicam Analytical System (ATI Mattson) using KBr pellets. $^1H$ NMR spectra were recorded on 200- (Varian Gemini-200) and 300-MHz (Varian Gemini-300). Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) as internal standard. $^{13}C$ NMR spectra were received on the named spectrometers. Electron impact mass spectra (EI-MS) were recorded on a Quadrupol-MS VG 12-250 at an ionizing voltage of 70 eV. Elemental analysis was determined on Heraeus CHNO Rapid Analyzer.

**Synthesis of 2,3-dihydro-3-hydroperoxy-2-aryl-4,5-diphenylisothiazole 1,1-dioxides (2).** $H_2O_2$ (0.7 mL, 30%) was added to a stirred suspension of **1** (0.26 mmol) in AcOH (0.7 mL) at room temperature. After dissolution of salts **1**, colorless precipitates of **2** were obtained after 72–96 h and isolated. The crude products were washed with water.

***2-(2-Chlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2a).*** Mp 197–201°C; IR (KBr) 1157, 1302 ($SO_2$) $cm^{-1}$; $^1H$ NMR (200 MHz, acetone-$d_6$) δ 6.60 (s, 1H, 3–H), 7.37–7.96 (m, 14H, ArH), 11.38 (s, 1H, OOH); $^{13}C$ NMR (50 MHz, acetone-$d_6$) δ = 92.5, 128.1, 128.9, 129.5, 129.9, 130.0, 130.4, 130.7, 130.9, 131.6, 131.7, 131.8, 135.0, 135.6, 139.1; EI-MS m/z 413.0 ($M^{+\bullet}$). Anal. Calcd. for $C_{21}H_{16}ClNO_4S$: C, 60.94; H, 3.90; N, 3.38; O, 15.46. Found: C, 60.60; H, 4.01; N, 3.55; O, 15.80.

***2-(2,6-Dichlorophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2b).*** Mp 124–127°C; IR (KBr) 1160, 1313 ($SO_2$) $cm^{-1}$; $^1H$ NMR (300 MHz, acetone-$d_6$) δ 6.49 (s, 1H, 3–H), 7.25–7.64 (m, 13H, ArH), 11.23 (s, 1H, OOH); $^{13}C$ NMR (50 MHz, acetone-$d_6$) δ 95.0, 130.1, 130.3, 130.6, 130.7, 130.9, 131.0, 131.1, 131.3, 131.5, 131.7, 132.4, 132.9, 138.2, 139.4, 140.8; EI-MS m/z 447.0 ($M^{+-}$). Anal. Calcd. for $C_{21}H_{15}Cl_2NO_4S$: C, 56.26; H, 3.37; N, 3.12; O, 14.27. Found: C, 55.40; H, 3.56; N, 3.13; O, 14.00.

***2-(2,6-Dichloro-4-nitrophenyl)-2,3-dihydro-3-hydroperoxy-4,5-diphenylisothiazole 1,1-dioxide (2c).*** Mp 148–151°C; IR (KBr) 1146, 1316 ($SO_2$), 1335, 1537 ($NO_2$) $cm^{-1}$; $^1H$ NMR (200 MHz, acetone-$d_6$) δ 6.58 (s, 1H, 3–H), 7.38–7.50 (m, 10H, ArH), 8.14 (s, 1H, ArH), 8.45 (s, 1H, ArH), 11.55 (s, 1H, OOH); $^{13}C$ NMR (50 MHz, acetone-$d_6$) δ 94.8, 125.6, 125.7, 126.1, 128.2, 130.1, 130.2, 130.4, 130.5, 130.6, 130.8, 131.0, 131.2, 131.7, 131.9, 139.4; EI-MS m/z 474.0 $(M-H_2O)^{+\bullet}$. Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O_6S$: C, 51.13; H, 2.86; N, 5.68; O, 19.46. Found: C, 50.83; H, 2.89; N, 5.72; O, 19.20.

**General experimental procedure for the catalytic epoxidation of cyclooctene by 2.** The epoxidation process was carried out in a thermostated glass reactor fitted with a reflux condenser and a magnetic stirrer under an argon atmosphere at temperature 23°C. The reactor was loaded with 0.01 g of MoB (Alfa Aesar) as a heterogeneous catalyst, 0.3 mL of *cis*-cyclooctene (Acros Organics), 3.5 mL chloroform as solvent, and 0.01 mol $L^{-1}$ of **2**. It is established that **2** does not decompose in the absence of catalyst in the reaction system and 1,2-epoxycyclooctane is not formed under the reaction conditions. The concentration of **2** was determined by iodometric titration [25]. The reaction mixtures were analyzed by using a Hewlett Packard HP 6890 N chromatograph, a capillary column DB-1 (60 m × 0.32 mm × 0.5 μm) packed with dimethylsiloxane. The

column temperature was changed from 50 up to 250°C with rate of 10° in 1 min.

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## REFERENCES AND NOTES

[1] Bowman, W. C.; Ram, M. J. Textbook of Pharmacology, 2nd ed.; Blackwell: London, 1979; Chapter 34.

[2] Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. R. Bioorg Med Chem Lett 2000, 11, 1159.

[3] Elghamry, I.; Dopp, D. Tetrahedron Lett 2001, 42, 5651.

[4] Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. Tetrahedron Lett 2002, 43, 917.

[5] Vree, T. B.; Hekstar, Y. A. Antibiol Chemother 1987, 37, 1.

[6] Enders, D.; Wallert, S. Tetrahedron Lett 2001, 42, 5651.

[7] Obniska, J.; Jurczyk, S.; Zeic, A.; Kaminski, K.; Tatarczynska, E.; Stachowicz, K. Pharm Rep 2005, 57, 170.

[8] Davis, M. Adv Heterocycl Chem 1985, 38, 105.

[9] De, A. Prog Med Chem 1981, 18, 117.

[10] Gennari, C.; Nestlei, H. P.; Salon, B.; Still, W. C. Angew Chem Int Ed Engl 1995, 34, 176.

[11] Gennari, C.; Salon, B.; Potenza, D.; Williams, A. Angew Chem Int Ed Engl 1994, 33, 2067.

[12] Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Frohlich, R.; Wibbeling, B.; Metza, P. Tetrahedron Lett 2002, 43, 4753.

[13] Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. Tetrahedron Lett 2002, 43, 917.

[14] Alvarez-Ibarra, C.; Csaky, A. G.; Gomez de la Oliva, C.; Rodriguez, E. Tetrahedron Lett 2001, 42, 2129.

[15] Lee, A. W. M.; Chan, W. H.; Yuen, W. H.; Xia, P. F.; Wong, W. Y. Tetrahedron Asymmetry 1999, 10, 1421.

[16] Trentmann, W.; Mehler, T.; Martens, J. Tetrahedron Asymmetry 1997, 8, 2033.

[17] Gelalcha, F. G.; Schulze, B. J Org Chem 2002, 67, 8400.

[18] Gelalcha, F. G. Chem Rev 2007, 107, 3338.

[19] Makota, O.; Wolf, J.; Trach, Yu.; Schulze, B. Appl Catal A 2007, 323, 174.

[20] Schulze, B.; Obst, U.; Zahn, G.; Friedrich, B.; Cimiraglia, R.; Hofmann, H.-J. J Prakt Chem/Chem Ztg 1995, 337, 17.

[21] Fahrig, J.; Freysoldt, T. H. E.; Hartung, C.; Sieler, J.; Schulze, B. J Sulfur Chem 2005, 26, 211.

[22] Sheldon, R. A. J Mol Catal 1980, 7, 107.

[23] Sobczak, J. M.; Ziolkowski, J. J. Appl Catal A 2003, 248, 261.

[24] Trach, Yu.; Makota, O. Int J Chem Kinet 2009, 41, 623.

[25] Kokatnur, V. R.; Jelling, M. J Am Chem Soc 1941, 63, 1432.

# Synthesis, Cytotoxic Activity, and Thermal Studies of Novel *N*-[(1,3-Diphenylpyrazol-4-yl)methyl] α-Amino Acids

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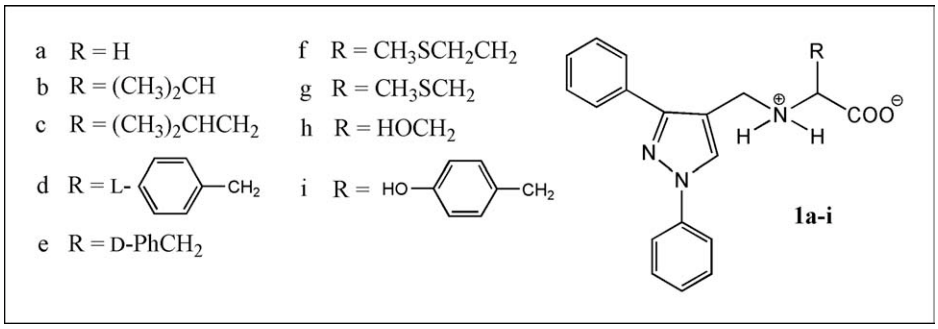


New *N*-[(1,3-diphenylpyrazol-4-yl)methyl]α-amino acids (**1a–i**) have been synthesized and tested *in vitro* for their antiproliferative activity against human myelogenous leukemia K562, colon adenocarcinoma HT-29, cervix carcinoma HeLa, and normal fetal lung fibroblasts, MRC-5. Compounds derived from both phenylalanine enantiomer precursors appeared to be the most active against myelogenous leukemia K562 cell lines with a high cytotoxic potential.

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## INTRODUCTION

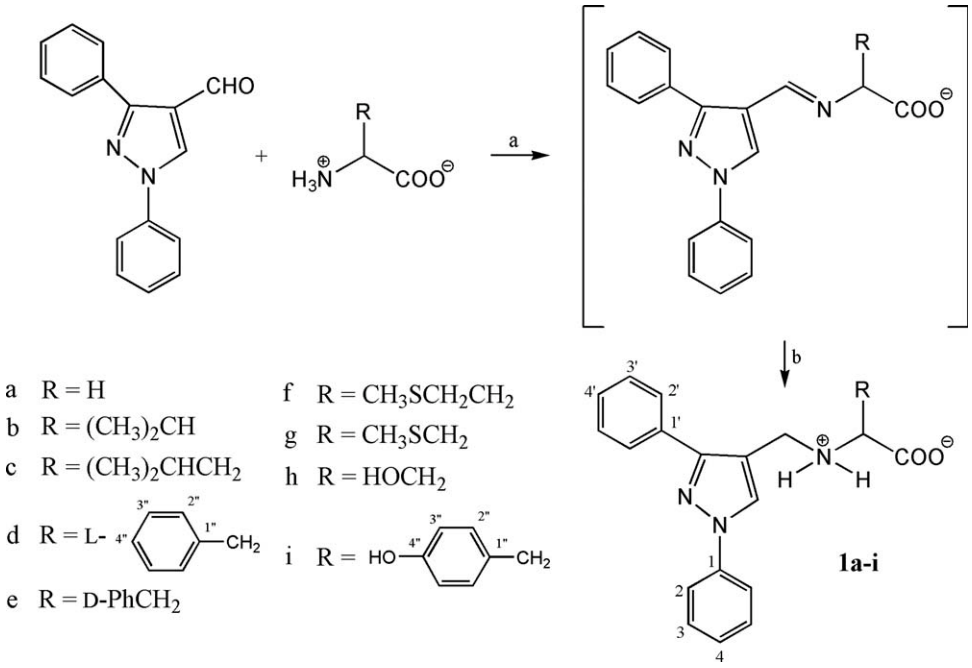
Arylpyrazole derivatives play an important role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. These compounds displayed diverse biological properties such as antiparasitic [1], antifungal [2], antibacterial [3], and antidiabetic [4]. Moreover, arylpyrazole derivatives have shown several biological activities as seen in cyclooxygenase-2 [5], p38 MAP kinase [6], and nonnucleoside HIV-1 reverse transcriptase inhibitors [7]. In the research for antitumor agents, arylpyrazole derivatives exhibited promising antiproliferative properties against several kinds of human tumor cell lines [8–10].

The cytotoxic drugs, such as doxorubicin, 5-fluorouracil, and camptothecins, can damage DNA or affect cellular metabolic pathways causing indirect block of the cell cycle. Unfortunately, these agents produce an irreversible damage to both normal and tumor cells, resulting in a significant toxicity and side effects [11–13]. In this respect, it is desirable to synthesize new highly specific antitumor agents with comparable efficacy and reduced toxicity than the currently available drugs. In view of these observations and as a continuation of our interest toward synthesis and biological activity of arylpyrazole derivatives [14,15], some new *N*-[(1,3-diphenylpyrazol-4-yl)methyl] α-amino acids were prepared with the aim to have promising antiproliferative properties against several kinds of human tumor cell lines.

## RESULTS AND DISCUSSION

In this work, condensation of the optically active L- and D-amino acids (except **1a**) with 1,3-diphenylpyrazole-4-carboxaldehyde in the presence of NaOH led to the formation of Schiff base intermediates. As α-amino acids are sparingly soluble in alcoholic solvents, the Schiff base formation takes long time, and the reaction gives lower yields even under reflux conditions. Thus, the condensation reaction was accelerated using solventless method [16] combining aldehyde, α-amino acids, and NaOH in a porcelain mortar with pestle and aggregating the dry solid mixture until a white powder was formed. The condensation was completed by an additional heating at reflux for 2 h in dry methanol (Scheme 1).

**Scheme 1.** Reagents and conditions: (a) NaOH, continuous aggregating at rt, then MeOH, reflux, 2 h; (b) $NaBH_4$, 0–5°C, then rt, 12 h, AcOH.




The stability of the formed Schiff base products depends on several factors such as amino acid side chain polarity [17], the metal, pH, solvent, and temperature [18]. The problem with Schiff base instability can be overcome by their reduction to give a more flexible amine and not constrained compounds. In the light of these facts, we have performed out the reduction with an excess of $NaBH_4$ without isolation of Schiff base to afford the novel *N*-[(1,3-diphenylpyrazol-4-yl)methyl] α-amino acids.

The structures of the new compounds were confirmed using different spectral data (IR, $^1H$, and $^{13}C$ NMR) and elemental analysis. The IR spectra revealed the presence of $NH_2^+$ stretching frequencies between 2650 and 2300 $cm^{-1}$ in the form of broad band with multiple peaks on the low frequency wing, which continue until about 2200 $cm^{-1}$, confirming their zwitterionic nature. The $\nu_{as}$ (COO) was related to the strong absorption band appearing in the spectra between 1619 and 1601 $cm^{-1}$, whereas the symmetric carboxylate stretches $\nu_s$ (COO) correspond to the medium–strong peaks about 1410 $cm^{-1}$ [19]. The other characteristic very strong absorption bands in the IR spectra were those attributed to the pyrazole ring: ν (C=C) and ν (C=N) between 1601 and 1547 $cm^{-1}$ as well as δ (C=C) about 1505 $cm^{-1}$ [20].

The $^1H$ NMR spectra of all compounds exhibited a characteristic AB system except **1a** and ABX system for **1d**, **1e**, **1g**, **1h**, and **1i**. The $^1H$ NMR spectra revealed the presence of characteristic singlet peak attributed to pyrazole ring proton appeared between 7.97 and 8.67 depending on the applied solvent system. The complete assignment of all reported signals ($^1H$ and $^{13}C$) in the experimental part was carried out by means of 1D and 2D homo- and heteronuclear correlated NMR spectroscopy.

The newly synthesized compounds **1a–i** were evaluated *in vitro* for their antiproliferative activity against human myelogenous leukemia K562, colon adenocarcinoma HT-29, cervix carcinoma HeLa, and normal fetal lung fibroblasts, MRC-5 using sulforhodamine B (SRB) assay [21] and doxorubicin (Dox) as reference drug. The results are presented in Table 1.

The malignant cell line K562 was the most sensitive, where the pronounced cytotoxicity was achieved by seven of nine tested samples. The compounds with benzyl group **1d** and **1e** showed the most potent cytotoxic activity against human myelogenous leukemia K562 cell lines. The replacement of the benzyl group in **1d** by a hydrophobic isobutyl group leading to **1c** would retain potential hydrophobic bonding while creating spatial property differences between the benzyl and isobutyl group. The comparison of the cytotoxicity of **1d** or **1e** with **1c** indicates that **1d** and **1e** are more active in inhibition of these cells. When the side chain was replaced with an isopropyl group **1b**, a complete inactivity against K562 was observed. The moderate activity was achieved when an additional heteroatom was

**Table 1**

*In vitro* cytotoxicity of compounds **1a–i**.

| Compounds | $IC_{50}$ ($\mu M$)[a] | | | |
|---|---|---|---|---|
| | K562 | HeLa | HT29 | MRC-5 |
| **1a** | 8.89 | >100 | >100 | >100 |
| **1b** | >100 | 9.21 | >100 | >100 |
| **1c** | 4.17 | >100 | 72.31 | >100 |
| **1d** | 1.02 | 14.43 | 8.31 | >100 |
| **1e** | 0.97 | 11.97 | 6.45 | >100 |
| **1f** | 6.37 | >100 | >100 | >100 |
| **1g** | >100 | 7.64 | >100 | >100 |
| **1h** | 4.69 | 96.34 | >100 | >100 |
| **1i** | 3.25 | >100 | 67.32 | >100 |
| Dox | 0.36 | 1.17 | 0.51 | 0.32 |

[a] $IC_{50}$ is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control.

incorporated into the side chain **1f**. These differences in cytotoxicity could be related to their conformation and size of the substitutes. The bulky isopropyl group **1b** and voluminous sulfur atom **1g** closely to aminocarboxylate skeleton induce the decrease of cytotoxic activity, probably preventing the formation of intermolecular interaction with cell receptors. Comparison of the cytotoxicity of compounds derived from different enantiomers of phenylalanine indicates that D-phenylalanine demonstrated similar activity with respect to L-phenylalanine analog. We could also suggest that **1d** and **1e** are the most cytotoxic compounds because of their planarity and hydrophobic properties. These results indicate that spatial effects and side chain length should be an important factor in the design of future molecules. It is interesting to note that the compounds **1h** and **1i** having polar hydroxyl groups proved to be less active than **1d** and **1e**, suggesting that electronic character could be diminished in comparison with hydrophobic requirements of amino acid part of molecule. Compounds **1g** and **1e** were also active against HeLa and HT29 cell lines, respectively, but their activity was significantly lower compared with doxorubicin. On the other hand, all compounds were devoid of any cytotoxicity against the normal fetal lung fibroblasts MRC-5. Generally, the hydrophobic character and steric effects in amino acid moiety appear to be the main factors for the growth suppressing potential against K562 cell lines. Further modification of compounds **1d** and **1e**, especially the transformation of carboxylate group and identification of its molecular target, is under investigation.

**Thermal analysis.** Thermal analysis of pharmaceutical compounds is a very reliable method for purity control, and it is a necessary part of the characterization of new compounds with potential bioactivity [22,23]. As amino acid–water–protein interface interactions are very important in biological systems [24]; the thermal properties of these new amino acid derivatives may be of special interest.

In the series of nine new compounds, two of them are pure N-substituted amino acids, whereas the others crystallize with different number of water molecules.

Thermal measurements reveal that the stability of N-substituted amino acids **1a** and **1b** is rather high in both atmospheres (in $N_2$ 200 and 205°C, respectively). Most probably as a consequence of some sensitivity toward oxidation, in air the thermal stability of the compounds is somewhat less. The decomposition mechanism in inert and oxidative atmosphere also differs (see Fig. 1).

The dehydration pattern of the hydrates does not depend on the atmosphere. The dehydrated compounds **1c**, **1g**, **1h**, and **1i** are stable to above 200°C, with the previous remark: their stability in air is less with about 5°C. Compounds **1d**, **1e**, and **1f** decompose further after dehydration, without giving a stable anhydrous intermediate.

The decomposition of all samples was accompanied by melting, observed visually. The decomposition mechanism of the first decomposition step of dry compounds is proposed only on the basis of the mass loss. The fragmentation begins with that of the side chain, *e.g.*, the mass loss to the minimum in DTG curve of **1a** amounts 14.5% in $N_2$ that agrees well with the loss of $CO_2$ molecule (calcd. 14.32%). The valine **1b** derivative most probably decomposes by the loss of the methyl groups. However, it is pointless to give a decomposition mechanism in lack of coupled measurements. It is more important to have a closer look to the dehydration process of the hydrates from both the theoretical and practical point of view. The mass loss with the corresponding temperature of the dehydration is given in Table 2 together with the decomposition temperature of the anhydrous compound.

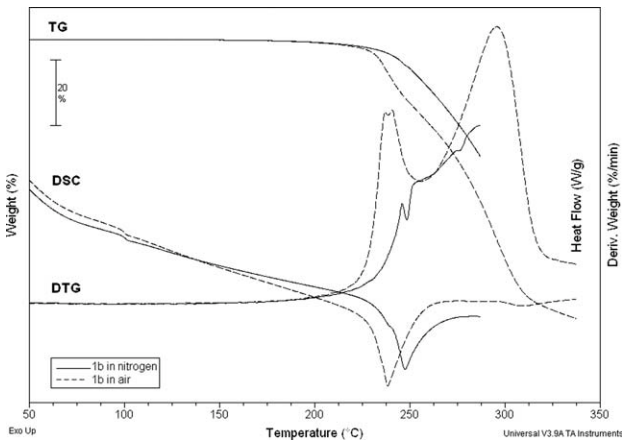



**Figure 1.** Thermal decomposition curves of **1b** in air and nitrogen.

**Table 2**

Mass loss of the dehydration, the dehydration temperature, and the onset temperature of the decomposition of the anhydrous compound in $N_2$.

| Compound | Dehydration, $\Delta m$ (%) | | $t_{DEHYD.}$ (°C) | $t_{DECOMP.}$ (°C) | Comments |
|---|---|---|---|---|---|
| | Exp. | Calcd. | | | |
| **1c** | 4.2 | 4.72 | <105 | 215 | Stable anhydrous compound |
| **1d, 1e** | 7.3 | 8.31 | <130 | – | Stepwise dehydration, continuous decomposition |
| **1f** | 10.4 | 10.17 | <135 | – | Stepwise dehydration, continuous decomposition |
| **1g** | 1.3 | 4.67 | <50 | 203 | Crystal water |
| **1h** | 2.2 | 5.34 | <150 | 225 | Structural water |
| **1i** | 0.5 | 4.36 | <30 | 235 | Loosely bond crystal water |

As the decomposition of the compounds **1d**, **1e**, and **1f** is continuous to obtain better separated decomposition steps, quasi-isothermal [25] (SWI) measurement was carried out. Figure 2 illustrates SWI curve of the compound **1f**. The five water molecules evaporate to 150°C (exp. 15.8%, calcd. 16.95%) in five clearly distinguished steps, not one by one, but through a complex process governed by macroscopic properties of the sample (*e.g.*, the rate of the diffusion) as well as by their different bonding energy. The dehydration of this compound is most probable followed by the evaporation of $CH_3COOH$ molecule. The difference in experimentally determined mass loss and the theoretical one is most probable because of the evaporation of the crystal water at room temperature. The dehydration of **1d** and **1e** derivatives shows similar complexity of the dehydration. Derivative **1h**, according to elemental analysis data, contains both crystal and structural water, belonging to more than one molecule. By TA only the structural water is detected, because in air the compound lost its crystal water completely. Compound **1i** has some crystal water left, while most of it has evaporated during the storage time.

Taking into account the importance of the interactions in the relation of amino acid–water–protein, the cytotoxicity of the compounds might be related to H-bond-forming capability in the molecules. This, indirectly, may be investigated using TA data of hydrates. However, the correlation is not straightforward. TA data may refer only to the preferences of an amino acid to bind water molecules and the strength of the bond between them [26].

## CONCLUSIONS

In summary, a new class of *N*-[(1,3-diphenylpyrazol-4-yl)methyl] α-amino acids were synthesized, and their antiproliferative activity against human myelogenous leukemia K562, colon adenocarcinoma HT-29, cervix carcinoma HeLa, and normal fetal lung fibroblasts, MRC-5 was evaluated. The nature, spatial effects and the distance of bulky substitutes from aminocarboxylate part of molecule appeared to play an important role in antiproliferative activity against different malignant cell lines. The dehydration temperature is related to the water bond energy and might be connected with the active sites of some bioactive molecules.

## EXPERIMENTAL

All chemicals were obtained from commercial sources (Aldrich) and used as supplied. 1,3-Diphenylpyrazole-4-carboxaldehyde was synthesized by Vilsmeier-Haack reaction [27].

Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001, and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical automatic polarimeter Autopol IV. Elemental (C, H, N, and S) analysis of the samples was carried out by standard micromethods in the Center for Instrumental Analysis, Faculty of Chemistry, Belgrade. IR spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer with a KBr disc. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini 200 (200 MHz) and a Bruker Avance III spectrometer operating at 500 MHz. As a consequence of the poor solubility in DMSO-$d_6$, the NMR spectra were recorded in pyridine-$d_5$/$D_2O$ and NaOD/$D_2O$ solvent system for **1h** and **1i**. Thermal measurements were conducted using SDT Q600 TA Instruments'

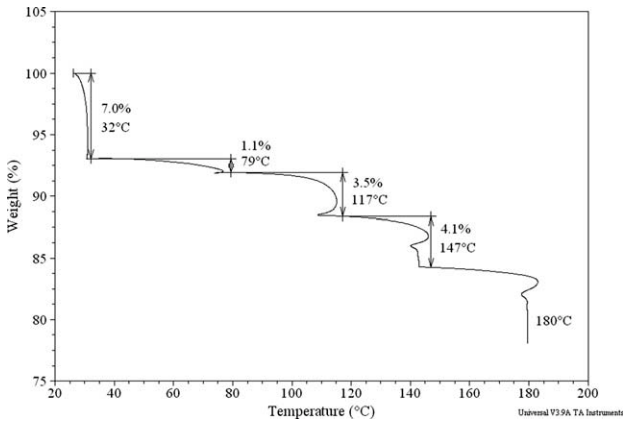



**Figure 2.** SWI decomposition curve of **1g**, illustrating the complexness of its dehydration.

thermal analyzer with about 2 mg sample masses and a heating rate of 20°C/min in air and nitrogen atmospheres. The sample holder and the reference cells were made of alumina.

**General procedure for the preparation of 1a–i.** 1,3-Diphenylpyrazole-4-carboxaldehyde (0.62 g, 2.5 mmol), α-amino acid (2.75 mmol), and NaOH (0.11 g, 2.75 mmol, for **1i** 0.22g, 5.50 mmol) were milled using a porcelain mortar and pestle to obtain a homogenous white powder until the release of water was observed. This mixture was transferred into 50 $cm^3$ of dry methanol and heated to reflux for 2 h. After cooling in an ice bath, sodium borohydride (0.11 g, 3 mmol) was added in several portions with stirring. The solution was stirred for additional 2 h at room temperature, then diluted with 50 $cm^3$ of deionized water, and left for 12 h, after which time the white precipitate had formed by addition of glacial acetic acid. The crude product was purified by dissolving in 1*M* NaOH and precipitation with glacial acetic acid. Recrystallized compound was collected by filtration, washed with plenty of water, and dried over anhydrous $CaCl_2$.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]glycine (1a).*** White powder; yield: 0.56 g (73%); mp 190–191°C (Dec.); IR (KBr, $cm^{-1}$): 3063 ν (C—H)$_{Ar}$, 2960 and 2820 ν (C—H)$_{Al}$, 2650–2400 ν ($NH_2^+$), 1626 $\nu_{as}$ ($COO^-$), 1601 ν (C=C)$_{Ar}$, 1547 ν (C=N)$_{Ar}$, 1502 δ (C=C)$_{Ar}$, 1453 δ (C=N)$_{Ar}$, 1412 $\nu_s$ ($COO^-$), 1066 δ (C—H)$_{ip}$, 758 δ (C—H)$_{oop}$; $^1$H NMR (200 MHz, pyridine-$d_5$/$D_2O$, 9/1 v/v): 4.19 (s, 2H, $CH_2$—COO), 4.74 (s, 2H, Pz—$CH_2$), 7.40–7.71 (m, 6H, 1H at C-4, 1H at C-4′, 2H at C-3/5, and 2H at C-3′/5′), 7.97 (d, 2H at C-2/6, $J$ = 8.00 Hz), 8.00 (d, 2H at C-2′/6′, $J$ = 8.00 Hz), 8.94 (s, 1H, Pz); $^{13}$C NMR (pyridine-$d_5$/$D_2O$, 9/1 v/v): 41.87 (Pz—$CH_2$), 50.13 (*C*$H_2$—COO), 113.09 (C-4, Pz), 119.15 (C-2/6), 127.31 (C-4), 128.66 (C-2′/6′), 129.08 (C-4′), 129.46 (C-3′/5′), 130.02 (C-3/5), 130.40 (C-5, Pz), 132.42 (C-1′), 139.72 (C-3, Pz), 152.50 (C-1), 170.83 (COO); Anal. Calcd. for $C_{18}H_{17}N_3O_2$ (307.35 g/mol): C, 70.34; H, 5.58; N, 13.67; Found: C, 70.12; H, 5.62; N, 13.55.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-L-valine (1b).*** White powder; yield: 0.72 g (82%); mp 198°C (Dec.); $[\alpha]_D^{20}$ = +12.77 ($c = 1.096 \times 10^{-3}$ g/$cm^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, $cm^{-1}$): 3059 ν (C—H)$_{Ar}$, 2965 and 2876 ν (C—H)$_{Al}$, 2600–2400 ν ($NH_2^+$), 1614 $\nu_{as}$ ($COO^-$), 1600 ν (C=C)$_{Ar}$, 1550 ν (C=N)$_{Ar}$, 1504 δ (C=C)$_{Ar}$, 1451 δ (C=N)$_{Ar}$, 1411 $\nu_s$ ($COO^-$), 1069 δ (C—H)$_{ip}$, 756 δ (C—H)$_{oop}$; $^1$H NMR (200 MHz, pyridine-$d_5$/$D_2O$, 9/1 v/v): 1.16 (d, 3H, $J$ = 6.62 Hz, $CH_3$), 1.19 (d, 3H, $J$ = 6.56 Hz, $CH_3$), 2.31 (m, 1H, $(CH_3)_2$C*H*), 3.55 (d, 1H, $J$ = 5.46 Hz, CH—COO), $\delta_A$ = 4.31 and $\delta_B$ = 4.01 (AB system, 2H, $J_{AB}$ = 13.50 Hz, Pz—C$H_2$), 7.33–7.62 (m, 6H, 1H at C-4, 1H at C-4′, 2H at C-3/5, and 2H at C-3′/5′), 8.02 (d, 2H at C-2/6, $J$ = 8.00 Hz,), 8.36 (d, 2H at C-2′/6′, $J$ = 8.00 Hz), 8.55 (s, 1H, Pz); $^{13}$C NMR (pyridine-$d_5$/$D_2O$, 9/1 v/v): 18.81 ($CH_3$), 19.95 ($CH_3$), 31.78 ($(CH_3)_2$C*H*), 43.25 (Pz—$CH_2$), 67.49 (*C*H—COO), 118.80 (C-2/6), 120.14 (C-4, Pz), 126.46 (C-4), 128.33 (C-4′), 128.56 (C-2′/6′), 128.98 (C-3′/5′), 129.14 (C-5, Pz), 129.85 (C-3/5), 134.13 (C-1′), 140.46 (C-3, Pz), 151.93 (C-1), 177.01 (COO); Anal. Calcd. for $C_{21}H_{23}N_3O_2$ (349.43 g/mol): C, 72.18; H, 6.63; N, 12.03; Found: C, 72.02; H, 6.68; N, 11.86.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-L-leucine monohydrate (1c).*** White powder; yield: 0.82 g (86%); mp 184°C (Dec.); $[\alpha]_D^{20}$ = −6.09 ($c = 1.313 \times 10^{-3}$ g/$cm^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, $cm^{-1}$): 3065 ν (C—H)$_{Ar}$, 2956 and 2869 ν (C—H)$_{Al}$, 2550–2300 ν ($NH_2^+$), 1612 $\nu_{as}$ ($COO^-$), 1600 ν (C=C)$_{Ar}$, 1560 ν (C=N)$_{Ar}$, 1503 δ (C=C)$_{Ar}$, 1454 δ (C=N)$_{Ar}$, 1412 $\nu_s$ ($COO^-$), 1076 δ (C—H)$_{ip}$, 755 δ (C—H)$_{oop}$; $^1$H NMR (200 MHz, pyridine-$d_5$/$D_2O$, 9/1 v/v): 0.92 (d, 3H, $J$ = 6.72 Hz, $CH_3$), 0.96 (d, 3H, $J$ = 6.74 Hz, $CH_3$), 1.89 (m, 2H, CH—C$H_2$—CH), 2.16 (m, 1H, $(CH_3)_2$C*H*), 3.87 and 3.90 (2d, 1H, $J$ = 6.36 Hz and $J$ = 6.60 Hz, NH—C*H*—COO), $\delta_A$ = 4.42 and $\delta_B$ = 4.15 (AB system, 2H, $J_{AB}$ = 13.50 Hz, Pz—$CH_2$), 7.32–7.61 (m, 6H, 1H at C-4, 1H at C-4′, 2H at C-3/5, and 2H at C-3′/5′), 8.03 (d, 2H at C-2/6, $J$ = 8.00 Hz), 8.36 (d, 2H at C-2′/6′, $J$ = 8.00 Hz), 8.67 (s, 1H, Pz); $^{13}$C NMR (pyridine-$d_5$/$D_2O$, 9/1 v/v): 21.17 ($CH_3$), 21.94 ($CH_3$), 24.14 (($CH_3$)$_2$*C*H), 41.38 (CH—*C*$H_2$—CH), 41.62 (Pz—*C*$H_2$), 59.50 (*C*H—COO), 117.67 (C-2/6), 118.20 (C-4, Pz), 125.36 (C-4), 127.23 (C-4′), 127.43 (C-2′/6′), 127.67 (C-3′/5′), 128.22 (C-5, Pz), 128.71 (C-3/5), 132.66 (C-1′), 139.28 (C-3, Pz), 150.78 (C-1), 176.47 (COO); Anal. Calcd. for $C_{22}H_{27}N_3O_3$ (381.48 g/mol): C, 69.27; H, 7.13; N, 11.02; Found: C, 68.99; H, 7.21; N, 10.89.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-L-phenylalanine dihydrate (1d).*** White powder; yield: 0.95 g (88%); mp 185–186°C (Dec.); $[\alpha]_D^{20}$ = −1.82 ($c = 1.100 \times 10^{-3}$ g/$cm^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, $cm^{-1}$): 3062 ν (C—H)$_{Ar}$, 2972 and 2853 ν (C—H)$_{Al}$, 2620–2380 ν ($NH_2^+$), 1619 $\nu_{as}$ ($COO^-$), 1599 ν (C=C)$_{Ar}$, 1553 ν (C=N)$_{Ar}$, 1503 δ (C=C)$_{Ar}$, 1453 δ (C=N)$_{Ar}$, 1412 $\nu_s$ ($COO^-$), 1072 δ (C—H)$_{ip}$, 754 δ (C—H)$_{oop}$; $^1$H NMR (200 MHz, pyridine-$d_5$/$D_2O$, 9/1 v/v): $\delta_A$ = 3.42, $\delta_B$ = 3.21, and $\delta_X$ = 4.04 (ABX system, 3H, $J_{AB}$ = 13.59 Hz, $J_{AX}$ = 5.15 Hz, $J_{BX}$ = 8.26 Hz, C*H*—C$H_2$), $\delta_A$ = 4.29 and $\delta_B$ = 3.99 (AB system, 2H, $J_{AB}$ = 13.50 Hz, Pz—$CH_2$), 7.28–7.62 (m, 11H, Ar—H), 7.93 (d, 2H at C-2/6, $J$ = 8.00 Hz), 8.20 (d, 2H at C-2′/6′, $J$ = 8.00 Hz), 8.29 (s, 1H, Pz); $^{13}$C NMR (pyridine-$d_5$/$D_2O$, 9/1 v/v): 40.10 (Ph—$CH_2$), 42.88 (Pz—$CH_2$), 63.30 (*C*H—COO), 118.77 (C-2/6), 120.66 (C-4, Pz), 126.36 (C-4″), 126.78 (C-4), 128.19 (C-4′), 128.50 (C-2′/6′), 128.69 (C-3″/5″), 128.75 (C-5, Pz), 128.96 (C-3′/5′), 129.78 (C-3/5), 130.05 (C-2″/6″), 134.18 (C-1′), 139.35 (C-1″), 140.48 (C-3, Pz), 151.76 (C-1), 176.98 (COO); Anal. Calcd. for $C_{25}H_{27}N_3O_4$ (433.51 g/mol): C, 69.27; H, 6.28; N, 9.69; Found: C, 69.51; H, 6.31; N, 9.74.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-D-phenylalanine dihydrate (1e).*** Yield: 0.93 g (86%); $[\alpha]_D^{20}$ = +1.82 ($c = 1.100 \times 10^{-3}$ g/$cm^3$, pyridine/$H_2O$, 9/1 v/v).

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-L-methionine acetate pentahydrate (1f).*** White powder; yield: 1.18 g (89%); mp 185–186°C (Dec.); $[\alpha]_D^{20}$ = −6.94 ($c = 1.296 \times 10^{-3}$ g/$cm^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, $cm^{-1}$): 3291 ν (O—H, broad), 3060 ν (C—H)$_{Ar}$, 2916 and 2853 ν (C—H)$_{Al}$, 2600–2440 ν ($NH_2^+$), 1681 ν (C=O), 1607 $\nu_{as}$ ($COO^-$), 1598 ν (C=C)$_{Ar}$, 1558 ν (C=N)$_{Ar}$, 1504 δ (C=C)$_{Ar}$, 1452 δ (C=N)$_{Ar}$, 1412 $\nu_s$ ($COO^-$), 1067 δ (C—H)$_{ip}$, 756 δ (C—H)$_{oop}$; $^1$H NMR (200 MHz, pyridine-$d_5$/$D_2O$, 9/1 v/v): 2.04 (s, 3H, $CH_3$—S), 2.43 (s, 3H, $CH_3$—COO), 2.53 (m, 2H, CH—C$H_2$), 3.00 (t, 2H, $J$ = 6.09 Hz, $CH_2$—S); 4.13 (t, 1H, $J$ = 5.60 Hz, C*H*—$CH_2$), $\delta_A$ = 4.58 and $\delta_B$ = 4.35 (AB system, 2H, $J_{AB}$ = 13.50 Hz, Pz—$CH_2$), 7.36–7.70 (m, 6H, 1H at C-4, 1H at C-4′, 2H at C-3/5, and 2H at C-3′/5′), 8.03 (d, 2H at C-2/6, $J$ = 8.00 Hz), 8.21 (d, 2H at C-2′/6′, $J$ = 7.52 Hz); 8.66 (s, 1H, Pz); $^{13}$C NMR (pyridine-$d_5$/$D_2O$, 9/1 v/v): 14.92 ($CH_3$—S), 23.38 (*C*$H_3$—COO), 30.91 (S—$CH_2$), 32.70 (S—$CH_2$—*C*$H_2$), 42.28 (Pz—$CH_2$), 62.92 (*C*H—COO), 117.35 (C-4, Pz), 118.95 (C-2/6), 126.74 (C-4), 128.59 (C-2′/6′), 128.64 (C-4′), 129.18

(C-3′/5′), 129.90 (C-3/5), 130.05 (C-5. Pz), 133.35 (C-1′), 140.11 (C-3, Pz), 152.10 (C-1), 177.02 (COO), 177.39 ($CH_3$—*C*OO); Anal. Calcd. for $C_{23}H_{37}N_3O_9S$ (531.63 g/mol): C, 51.96; H, 7.02; N, 7.90; S, 6.03; Found: C, 51.86; H, 6.94; N, 7.82; S, 5.93.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-S-methyl-L-cysteine monohydrate (1g).*** White powder; yield: 0.88 g (92%); mp 187°C (Dec.); $[\alpha]_D^{20} = -11.04$ ($c = 1.177 \cdot \times 10^{-3}$ g/cm$^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, cm$^{-1}$): 3051 ν (C—H)$_{Ar}$, 2923 and 2853 ν (C—H)$_{Al}$, 2601–2388 ν ($NH_2^+$), 1628 $\nu_{as}$ ($COO^-$), 1599 ν (C=C)$_{Ar}$, 1549 ν (C=N)$_{Ar}$, 1504 δ (C=C)$_{Ar}$, 1451 δ (C=N)$_{Ar}$, 1413 $\nu_s$ ($COO^-$), 1067 δ (C—H)$_{ip}$, 757 δ (C—H)$_{oop}$; $^1$H NMR (500 MHz, pyridine-$d_5$/$D_2O$, 9/1 v/v): 2.20 (s, 3H, $CH_3$—S), $\delta_A = 3.25$, $\delta_B = 3.16$, and $\delta_X = 4.01$ (ABX system, 3H, $J_{AB} = 13.50$ Hz, $J_{AX} = 5.73$ Hz, $J_{BX} = 7.27$ Hz, C*H*—C$H_2$), $\delta_A = 4.34$ and $\delta_B = 4.14$ (AB system, 2H, $J_{AB} = 13.50$ Hz, Pz—C$H_2$), 7.29 (t, 1H, $J = 7.50$ Hz, C-4), 7.44 (t, 1H, $J = 7.50$ Hz, C-4′), 7.50 (t, 2H, $J = 7.50$ Hz, C-3/5), 7.57 (t, 2H, $J = 7.50$ Hz, C-3′/5′), 8.01 (d, 2H, $J = 8.00$ Hz, C-2/6), 8.35 (d, 2H, $J = 8.00$ Hz, C-2′/6′), 8.53 (s, 1H, Pz); $^{13}$C NMR (pyridine-$d_5$/$D_2O$, 9/1 v/v): 16.35 ($CH_3$—S), 38.08 (S—$CH_2$), 43.02 (Pz—$CH_2$), 61.60 (CH), 118.93 (C-2/6), 120.69 (C-4, Pz), 126.52 (C-4), 128.41 (C-4′), 128.74 (C-2′/6′), 128.98 (C-5, Pz), 129.12 (C-3′/5′), 129.95 (C-3/5), 134.43 (C-1′), 140.75 (C-3, Pz), 151.96 (C-1), 175.98 (COO); Anal. Calcd. for $C_{20}H_{23}N_3O_3S$ (385.48 g/mol): C, 62.32; H, 6.01; N, 10.90; S, 8.32; Found: C, 62.49; H, 5.99; N, 10.92; S, 8.35.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-L-serine monohydrate (1h).*** White powder; yield: 0.71 g (80%); mp 190–191°C (Dec.); $[\alpha]_D^{20} = +3.96$ ($c = 1.263 \cdot \times 10^{-3}$ g/cm$^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, cm$^{-1}$): 3445 ν (O—H, broad), 3055 ν (C—H)$_{Ar}$, 2961 and 2853 ν (C—H)$_{Al}$, 2600–2390 ν ($NH_2^+$), 1628 $\nu_{as}$ ($COO^-$), 1600 ν (C=C)$_{Ar}$, 1547 ν (C=N)$_{Ar}$, 1504 δ (C=C)$_{Ar}$, 1452 δ (C=N)$_{Ar}$, 1417 $\nu_s$ ($COO^-$), 1074 δ (C—H)$_{ip}$, 752 δ (C—H)$_{oop}$; $^1$H NMR (500 MHz, NaOD/$D_2O$): $\delta_A = 3.71$, $\delta_B = 3.65$, and $\delta_X = 3.17$ (ABX system, 3H, $J_{AB} = 11.50$ Hz, $J_{AX} = 4.66$ Hz, $J_{BX} = 6.09$ Hz, CH—$CH_2$), $\delta_A = 3.37$ and $\delta_B = 3.62$ (AB system, 2H, $J_{AB} = 13.50$ Hz, Pz—$CH_2$), 7.35 (t, 1H, $J = 7.50$ Hz, C-4), 7.44–7.52 (m, 5H, 2H at C-3/5, 1H at C-4′, and 2H at C-3′/5′), 7.58 (d, 2H at C-2/6, $J = 8.00$ Hz), 7.60 (d, 2H at C-2′/6′, $J = 8.00$ Hz), 8.05 (s, 1H, Pz); $^{13}$C NMR (NaOD/$D_2O$): 43.88 (Pz—*C*$H_2$); 65.67 ($CH_2$—OH), 67.22 (CH), 121.65 (C-4, Pz), 122.09 (C-2/6), 129.75 (C-4), 130.69 (C-2′/6′), 131.32 (C-4′), 131.58 (C-3′/5′), 132.13 (C-5, Pz), 132.33 (C-3/5), 134.68 (C-1′), 141.78 (C-3, Pz), 154.57 (C-1), 181.84 (COO); Anal. Calcd. for $C_{19}H_{21}N_3O_4$ (355.39 g/mol): C, 64.21; H, 5.96; N, 11.82; S, 8.32; Found: C, 64.40; H, 5.94; N, 11.81.

***N-[(1,3-Diphenylpyrazol-4-yl)methyl]-L-tyrosine monohydrate (1i).*** White powder; yield: 0.85 g (79%); mp 190–191°C (Dec.); $[\alpha]_D^{20} = -6.00$ ($c = 1.166 \cdot \times 10^{-3}$ g/cm$^3$, pyridine/$H_2O$, 9/1 v/v); IR (KBr, cm$^{-1}$): 3418 ν (O—H, broad), 3061 ν (C—H)$_{Ar}$, 2957 and 2812 ν (C—H)$_{Al}$, 2622–2400 ν ($NH_2^+$), 1611 $\nu_{as}$ ($COO^-$), 1597 ν (C=C)$_{Ar}$, 1559 ν (C=N)$_{Ar}$, 1504 δ (C=C)$_{Ar}$, 1451 δ (C=N)$_{Ar}$, 1410 $\nu_s$ ($COO^-$), 1072 δ (C—H)$_{ip}$, 757 δ (C—H)$_{oop}$; $^1$H NMR (500 MHz, NaOD/$D_2O$): $\delta_A = 2.80$, $\delta_B = 2.63$, and $\delta_X = 3.28$ (ABX system, 3H, $J_{AB} = 13.75$ Hz, $J_{AX} = 5.67$ Hz, $J_{BX} = 7.83$ Hz, CH—$CH_2$), $\delta_A = 3.75$ and $\delta_B = 3.54$ (AB system, 2H, $J_{AB} = 13.50$ Hz, Pz—$CH_2$), 6.54 (d, 2H at 3″, $J = 8.00$ Hz), 6.91 (d, 2H at 2″, $J = 8.50$ Hz), 7.37 (t, 1H at C-4, $J = 7.50$ Hz), 7.49 (m, 7H, 2H at C-3/5, 1H at C-4′, 2H at C-3′/5′, and 2H at C-2/6), 7.61 (d, 2H at C-2′/6′, $J = 8.00$ Hz), 7.97 (s, 1H, Pz); $^{13}$C NMR (500 MHz, NaOD/$D_2O$): 40.84 (Ph—$CH_2$), 43.62 (Pz—$CH_2$), 67.60 (CH), 121.38 (3″), 121.64 (C-4, Pz), 122.24 (C-2/6), 126.28 (1″), 129.81 (C-4), 130.72 (C-2′/6′), 131.35 (C-4′), 131.63 (C-3′/5′), 132.15 (C-5, Pz), 132.39 (C-3/5), 133.03 (2″), 134.60 (C-1′), 141.83 (C-3, Pz), 154.77 (C-1), 167.28 (4″), 184.13 (COO); Anal. Calcd. for $C_{25}H_{25}N_3O_4$ (431.48 g/mol): C, 69.59; H, 5.84; N, 9.74; Found: C, 69.69; H, 5.82; N, 9.74.

**Biological evaluation.** Three human tumor cell lines and one human nontumor cell line were used in this study: K562 (chronic myelogenous leukemia), HeLa (epitheloid carcinoma of cervix), HT-29 (colon adenocarcinoma), and MRC5 (lung fetal fibroblasts). The cells were grown in RPMI 1640 (K562 cells) or Dulbecco's modified Eagle's medium (DMEM) with 4.5% of glucose (HeLa, HT-29, and MRC5 cells). Media were supplemented with 10% of fetal calf serum (FCS, NIVNS) and antibiotics: 100 IU/mL of penicillin and 100 μg/mL of streptomycin (ICN Galenika). All cell lines were cultured in flasks (Costar, 25 cm$^2$) at 37°C in the 100% humidity atmosphere and 5% of $CO_2$. Only viable cells were used in the assay. Viability was determined by dye exclusion assay with Trypan blue.

Cytotoxicity was evaluated by colorimetric SRB assay as described by Skehan et al. [21]. Briefly, single cell suspension was plated into 96-well microtiter plates (Costar, flat bottom): $1 \times 10^4$ of K562 and $5 \times 10^3$ of HeLa, HT29, and MRC5 cells, per 180 mL of medium. Plates were preincubated for 24 h at 37°C, 5% $CO_2$. Tested substances at concentration ranging from $10^{-8}$ to $10^{-4}M$ were added to all wells except to the control ones. After incubation period (48 h/37°C/5% $CO_2$), SRB assay was carried out as follows: 50 μL of 80% trichloroacetic acide (TCA) was added to all wells; an hour later, plates were washed with distillate water, and 75 μL of 0.4% SRB was added to all wells; half an hour later, plates were washed with citric acid (1%) and dried at room temperature. Finally, 200 μL of 10 mmol TRIS (pH = 10.5) basis was added to all wells. Absorbance was measured on the microplate reader (Multiscan MCC340, Labsystems) at 540/690 nm. The wells without cells, containing compete medium only, acted as blank.

Cytotoxicity was calculated according to the formula:

$$(1 - A_{TEST}/A_{CONTROL}) \times 100$$

and expressed as a percent of cytotoxicity (CI %).

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## REFERENCES AND NOTES

[1] Rathelot, P.; Azas, N.; El-Kashef, H.; Delmas, F.; Di Giorgio, C.; Timon-David, P.; Maldonado, J.; Vanelle, P. Eur J Med Chem 2002, 37, 671.

[2] Prakash, O.; Kumar, R.; Parkash, V. Eur Med Chem 2008, 43, 435.

[3] Finn, J.; Mattia, K.; Morytko, M.; Ram, S.; Yang, Y.; Wu, X.; Mak, E.; Gallant, P.; Keith, D. Bioorg Med Chem Lett 2003, 13, 2231.

[4] Bebernitz, G. R.; Argentieri, G.; Battle, B.; Brennan, C.; Balkan, B.; Burkey, B. F.; Eckhardt, M.; Gao, J.; Kapa, P.; Strohschein, R. J.; Schuster, H. F.; Wilson, M.; Xu, D. D. J Med Chem 2001, 44, 2601.

[5] Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. J Med Chem 2001, 44, 3039.

[6] Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. J Med Chem 2002, 45, 2994.

[7] Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. J Med Chem 2000, 43, 1034.

[8] Wei, F.; Zhao, B. X.; Huang, B.; Zhang, L.; Sun, C. H.; Dong, W. L.; Shin, D. S.; Miao, J. Y. Bioorg Med Chem Lett 2006, 16, 6342.

[9] Rostom, S. A. F.; Shalaby, M. A.; El-Demellawy, M. A. Eur J Med Chem 2003, 38, 959.

[10] Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I. Bioorg Med Chem Lett 2005, 15, 3307.

[11] Van de Vrie, W.; Jonker, A. M.; Marquet, R. L.; Eggermont, A. M. M. J Cancer Res Clin Oncol 1994, 120, 533.

[12] Longhi, A.; Ferrari, S.; Bacci, G.; Specchia, S. Anticancer Drugs 2007, 18, 737.

[13] Kimura, Y.; Okuda, H. Jpn J Cancer Res 1999, 90, 765.

[14] Joksović, M. D.; Marković, V.; Juranić, Z. D.; Stanojković, T.; Jovanović, L. S.; Damljanović, I. S.; Mészáros Szécsényi, K.; Todorović, N.; Trifunović, S.; Vukićević, R. D. J Organomet Chem 2009, 694, 3935.

[15] Leovac, V. M.; Bombicz, P.; Mészáros Szécsényi, K.; Joksović, M. Aust J Chem 2007, 60, 615.

[16] Cave, G. W. V.; Raston, C. L. J Chem Soc Perkin Trans 1 2001, 3258.

[17] Casella, L.; Gullotti, M. Inorg Chem 1983, 22, 2259.

[18] Wagner, M. R.; Walker, F. A. Inorg Chem 1983, 22, 3021.

[19] Colthup, N. B.; Daly, L. H.; Wiberley, S. E. Introduction to Infrared and Raman Spectroscopy, 2nd ed.; Academic Press: London, 1975; Chapter 9, p 304.

[20] Pons, J.; Chadghan, A.; Casabó, J.; Alvarez-Larena, A.; Piniella, J. F.; Ros, J. Polyhedron 2001, 20, 2531.

[21] Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. J Natl Cancer Inst 1990, 82, 1107.

[22] Kiss, D.; Zelkó, R.; Novák, C.; Éhen, Z. J Therm Anal Calorim 2006, 84, 447.

[23] Presswala, L.; Matthews, M. E.; Atkinson, I.; Najjar, O.; Gerhardstein, N.; Moran, J.; Wei, R.; Riga, A. T. J Therm Anal Calorim 2008, 93, 295.

[24] Thanki, N.; Thornton, J. M.; Goodfellow, J. M. J Mol Biol 1988, 202, 637.

[25] Paulik, J.; Paulik, F. Simultaneous Thermoanalytical Examinations by Means of the Derivatograph, Comprehensive Analytical Chemistry, Vol. 12: Thermal Analysis; Wendlandt, W. W., Ed.; Elsevier Scientific Publishing Company: Amsterdam, 1981; p 47.

[26] Hritz, J.; Žoldák, G.; Sedlák, E. Proteins 2006, 64, 465.

[27] Kira, M. A.; Abdel-Rahman, M. O.; Gadalla, K. Z. Tetrahedron Lett 1969, 10, 109.

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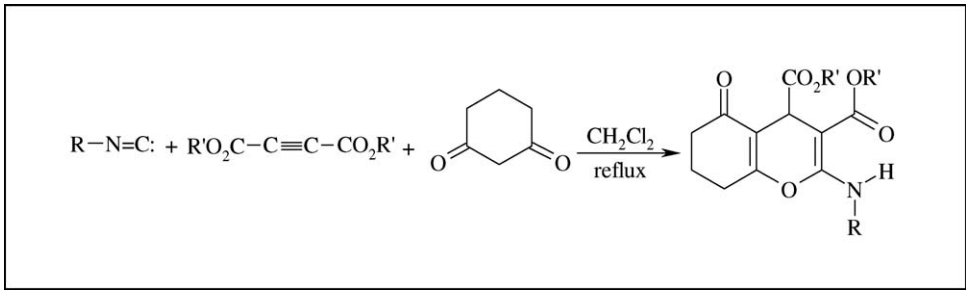


Cyclohexyl isocyanides react with dialkyl acetylenedicarboxylates in the presence of CH-acids such as cyclohexane-1,3-dione or *N*,*N*′-dimethylbarbituric acid in one-pot to afford 4*H*-pyran annulated heterocyclic systems in fairly high yields.

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## INTRODUCTION

In the meantime multicomponent reactions are well established as a powerful tool for the rapid construction of complex and structurally diverse compounds from relatively simple building blocks [1]. High atom-economy, chemical efficiency, and convergence are typical features of such one-pot condensations of at least three different starting materials. Because of the remarkable high purity of libraries, multicomponent reactions are well-suited for both combinatorial chemistry [2] and high-speed parallel synthesis and therefore possess high exploratory power [3]. Amongst the known multicomponent reactions, isocyanide based MCRs such as the versatile Ugi and Passerini reactions are especially valuable [4]. Especially isocyanide-based [5] and asymmetric [6] multicomponent reactions have been emerging fields of interest in the last decade, but the construction of heterocycles via multicomponent reactions was also in the focus recently [7]. However, there are only a few applications of multicomponent reactions in dihydroindeno[1,2-b]pyran so far [8]. In our Laboratory, isocyanide-based multicomponent reactions of CH-acids have just recently been key instruments for the rapid synthesis of the novel pyran ring systems of pyrimidine, indeno, and 4*H*-chromene. Herein we report how such reactions contributed significantly to the synthesis of the novel heterocyclic compounds.

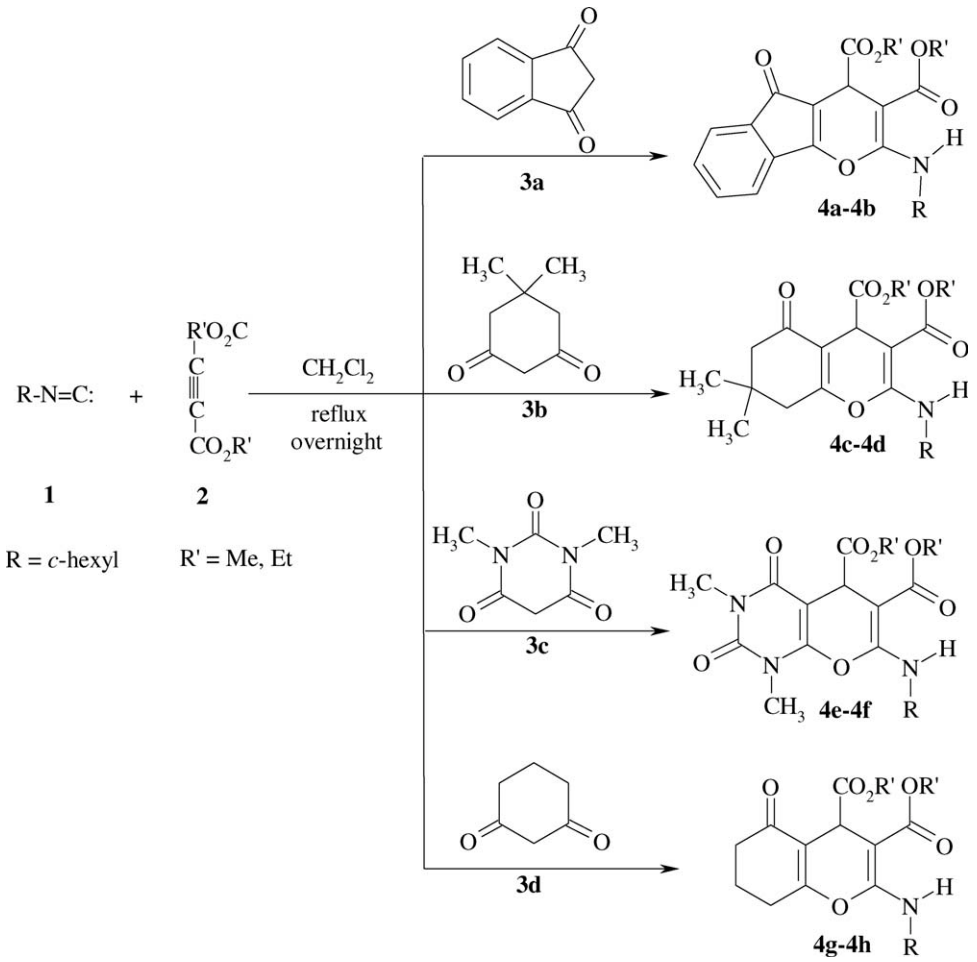
## RESULTS AND DISCUSSION

The one-pot three component condensation reactions of alkyl isocyanides **1** with electron-deficient acetylenic esters **2** in the presence of CH-acids **3a–d** proceeded in anhydrous dichloromethane and was completed after 12 h to afford corresponding heterocyclic systems **4a–h**, in moderate to good yields (65–90%). $^1$H NMR and $^{13}$C NMR spectra of the crude products clearly indicated the formation of heterocyclic compounds **4a–h**. The structures of the products **4a–h** were deduced from their elemental analyses, IR, $^1$H NMR, and $^{13}$C NMR spectra. The mass spectra of compounds **4a–h** displayed molecular ion peak at appropriate *m*/*z* values. Initial fragmentations involved loss from or complete loss of the side chains and scission of heterocyclic system.

The $^1$H NMR spectrum of **4a** consisted of a multiplet of signals for the cyclohexyl ring ($\delta$ = 1.13–1.90 ppm) and two single sharp lines for methoxy groups ($\delta$ = 3.70 and 3.73 ppm). A multiplet resonance is observed for the N—CH group ($\delta$ = 3.82 ppm), and a single sharp line for methine proton ($\delta$ = 4.38 ppm). A fairly broad singlet ($\delta$ = 8.90 ppm) was observed for the NH group. The presence of an amine proton was confirmed by exchange with $D_2O$. The chemical shift of the N—H group indicates that this moiety must have participated in a six-member intramolecular hydrogen bond formation with the vicinal carbonyl group as shown in Scheme 1.

The $^1$H decoupled $^{13}$C NMR spectrum of **4a** showed 20 sharp signals in agreement with proposed structure. Compound **4a** possesses a highly polarized carbon-carbon double bond. The β-carbon of this enaminone system appears about 72–77 ppm. These signals along with the downfield shift of the NH proton, support the enaminone structure **4**. The $^1$H NMR and $^{13}$C NMR spectra of

**Scheme 1**

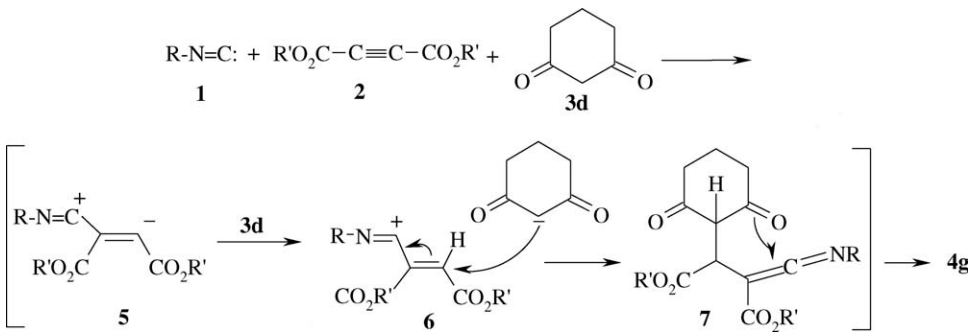



**4b–h** are similar to those of **4a**, except for the CH-acids and ester moieties. Partial assignments of these resonances are given in the experimental section.

The structural assignments made on the basis of the $^{1}H$ NMR and $^{13}C$ NMR spectra of **4a** was supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorption at 3420, 1737, and 1678 $cm^{-1}$ due to the N—H and carbonyls groups.

A plausible mechanism for formation of **4g** is shown in Scheme 2. On the basis of the well established chemistry of isocynides [4] it is reasonable to assume that compound **4g** results from initial addition of alkyl isocyanide **1** to the acetylenic ester to form intermediate **5**. Protonation of **5** by **3d** and subsequent attack of the resulting nucleophile generated to the positively charged ion **6** afforded ketenimine **7** (Scheme 2). Such an

**Scheme 2**



addition product may tautomerize and cyclize, under the reaction conditions employed, to produce **4g**.

In conclusion, the three-component reaction of alkyl isocyanides with electron-deficient acetylenic esters in the presence of CH-acids provides a simple entry into the synthesis of 4*H*-pyran annulated heterocyclic systems of potential synthetic interest. The present procedure carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification.

## EXPERIMENTAL

Dialkyl acetylenedicarboxylates, alkyl isocyanides, and other reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification. NMR spectra were recorded with a Bruker DRX-300 AVANCE instrument (299.9 MHz for $^1$H and 75.4 MHz. for $^{13}$C) with $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constant (*J*) are reported in hertz (Hz). Melting points were measured with an electrotherma1 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed favorably with the calculated values. Mass spectra were recorded with a Shimadzu QP-GC Mass 5050 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured with Bruker Tensor 27 spectrometer.

**Typical procedure for preparation of compounds 4a–h.** To a stirred solution of 0.145 g indan-1,3-dione (1 mmol) and 0.142 g dimethyl acetylendicarboxylate (1 mmol) in 10 mL dichloromethane, was added, 0.109 g *c*-hexyl isocyanide (1 mmol) in 2 mL dichloromethane at room temperature over 4 min via a syringe. The reaction mixture was heated at reflux for 12 h. The solvent was removed and the residue was purified by silica gel (Merck silica gel 60, 70–230 mesh) column chromatography using hexane/ethyl acetate (8:2) as eluent.

**Data.** ***Dimethyl 2-(cyclohexylamino)-5-oxo-4,5-dihydroindeno [1,2-b]pyran-3,4-dicarboxylate (4a)*** Dark brown powder (0.258 g, 65%), mp 212–214°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3420 (NH), 1737, 1678, and 1670 (C=O), 1235 and 1215 (C—O). $^1$H NMR: δ = 1.13–1.90 (10 H, m, 5 $CH_2$), 3.70 (3 H, s, $OCH_3$), 3.71 (3 H, s, $OCH_3$), 3.73 (1 H, m, N—CH), 4.38 (1 H, s, CH), 7.17 (1 H, m, CH), 7.34 (1 H, m, CH), 7.40 (1 H, m, CH), 7.48 (1 H, m, CH), 8.90 (1 H, br d, $^3J_{HH}$ = 5.6 Hz, NH). $^{13}$C NMR: δ = 24.5, 25.5, 33.9 (5 CH2), 43.5 (CH), 50.5 (CHN), 51.2 and 52.5 (2 OCH3), 72.6 (N—*C*=C), 107.8 (O—C=*C*), 118.1 (CH), 122.4 (CH), 130.7 (CH), 131.8 (C), 132.6 (CH), 135.9 (C) 159.4 and 167.2 (2 O—*C*=C), 169.9, 173.3 and 190.7 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 397 (M$^+$, 8), 384 (65), 348 (100), 289 (35), 108 (23), 59 (31). Anal. Calcd. for $C_{22}H_{23}NO_6$ (397.4): C, 66.49; H, 5.83; N, 3.52%; Found: C, 66.98; H, 5.78; N, 3.59.

***Diethyl 2-(cyclohexylamino)-5-oxo-4,5-dihydroindeno[1,2-b]pyran-3,4-dicarboxylate (4b).*** Black oil (0.297 g, 70%). IR (KBr) ($\nu_{max}$ /cm$^{-1}$): 3418 (NH), 1728, 1683, and 1660 (C=O), 1607 (C=O), 1241 (C—O). $^1$H NMR: δ = 1.26 and 1.27 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 $CH_3$), 1.38–2.10 (10 H, m, 5 $CH_2$), 3.80 (1 H, m, N—CH), 4.15 and 4.19 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 $OCH_2$), 4.39 (1 H, s, CH), 7.18 (1 H, m, CH), 7.35 (1 H, m, CH), 7.40 (1 H, m, CH), 7.46 (1 H, m, CH), 8.19 (1 H, br d, $^3J_{HH}$ = 5.5 Hz, NH). $^{13}$C NMR: δ = 14.2 and 14.5 (2 $CH_3$), 24.5, 25.5, 33.9 (5 $CH_2$), 43.5 (CH), 50.5 (CHN), 59.6 and 60.9 (2 $OCH_2$), 72.5 (N—*C*=C), 107.6 (O—C=*C*), 118.1 (CH), 122.4 (CH), 130.7 (CH), 131.8 (C), 132.6 (CH), 135.9 (C), 159.4 and 167.3 (2 O—*C*=C), 169.9, 173.3 and 190.7 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 425 (M$^+$, 5), 409 (12), 352 (100), 342(94), 83 (55), 73 (47). Anal. Calcd. for $C_{24}H_{27}NO_6$ (425.47): C, 67.75; H, 6.40; N, 3.29%; Found: C, 67.8; H, 6.5; N, 3.3.

***Dimethyl 2-(cyclohexylamino)-5-oxo-7,7-dimethyl 5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4c).*** Yellow powder (0.294 g, 0.75%), mp 140–142°C. IR (KBr) ($\nu_{max}$ /cm$^{-1}$): 3423, (N—H) 1761, and 1726 (C=O), 1605 (C=C). $^1$H NMR ($CDCl_3$): δ = 1.10 and 1.12 (6 H, 2 s, 2 $CH_3$), 1.18–1.90 (10 H, m, 5 $CH_2$), 2.25 and 2.42 (4 H, 2 s, 2 $CH_2$), 3.58 and 3.61 (6 H, 2 s, 2 $OCH_3$), 3.70 (1 H, m, NCH), 4.49 (1 H, s, CH), 8.58 (1 H, d, $^3J_{HH}$ = 7.2 Hz, NH). $^{13}$C NMR ($CDCl_3$): δ = 24.4, 25.5 and 33.6 (5 $CH_2$), 27.1 and 29.3 (2 $CH_3$), 32.3 (*C*$M_2$), 34.4 (CH), 40.7 and 50.8 (2 $CH_2$), 49.9 (N—CH), 50.5 and 52.2 (2 $OCH_3$), 72.3 (N—*C*=C), 112.3 (O—C=*C*), 158.9 and 173.8 (2 O—*C*=C), 163.4 and 169.6 (2 C=O ester), 195.2 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 391 (M$^+$, 6), 333 (100), 251 (44), 218 (64), 52 (25). Anal. Calcd. for $C_{21}H_{29}NO_6$ (391.47): C, 64.43; H, 7.47; N, 3.58%. Found: C, 64.4; H, 7.5; N, 3.9%.

***Diethyl 2-(cyclohexylamino)-5-oxo-7,7-dimethyl 5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4d).*** Light yellow oil (0.302 g, 0.72%). IR (KBr) ($\nu_{max}$ /cm$^{-1}$): 3228 (N—H), 1720, and 1680 (C=O), 1610 (C=C). $^1$H NMR ($CDCl_3$): δ = 1.12 and 1.16 (6 H, 2 s, 2 $CMe_2$), 1.17 and 1.25 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 $CH_3$), 1.20–1.90 (10 H, m, 5 $CH_2$), 2.29 and 2.42 (4 H, 2 s, 2 $CH_2$), 3.61 (1 H, m, NCH), 4.10 and 4.19 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 $OCH_2$), 4.50 (1 H, s, CH), 8.60 (1 H, d, $^3J_{HH}$ = 7.4 Hz, NH). $^{13}$C NMR ($CDCl_3$): δ = 14.2 and 14.6 (2 $CH_3$), 24.4, 25.5 and 33.8 (5 $CH_2$), 27.2 and 29.4 (C*Me*$_2$), 32.5 (*C*$M_2$), 34.4 (CH), 40.9 and 50.6 (2 $CH_2$), 49.9 (N—CH), 59.7 and 61.1 (2 $OCH_2$), 72.9 (N—*C*=C), 112.6 (O—C=*C*), 159.4 and 173.8 (2 O—*C*=C), 163.2 and 169.6 (2 C=O ester), 195.2 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 419 (M$^+$, 4), 347 (100), 264 (75), 83 (25). Anal. Calcd. for $C_{23}H_{33}NO_6$ (419.51): C, 65.85; H, 7.93; N, 3.34%. Found: C, 65.9; H, 7.9; N, 3.3%.

***Dimethyl 7-(cyclohexylamino)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (4e).*** Yellow oil (0.346 g, 85%). IR (KBr) ($\nu_{max}$ /cm$^{-1}$): 3370 (N—H), 1741 and 1681 (C=O), 1537 (C=C). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.11–2.10 (10 H, m, 5 $CH_2$), 3.34 and 3.41 (6 H, 2 s, 2 $NCH_3$), 3.65 (1 H, br m, NCH); 3.70 and 3.79 (6 H, 2 s, 2 $OCH_3$), 4.59 (1 H, s, CH), 8.60 (1 H, br d, $^3J_{HH}$ = 5.7 Hz, NH). $^{13}$C NMR ($CDCl_3$): δ = 24.1, 25.2 and 33.5 (5 $CH_2$), 28.4 and 29.6 (2 N—$CH_3$), 35.3 (CH), 50.1 (HN—CH), 51.5 and 52.1 (2 $OCH_3$), 72.2 (N—C=*C*), 88.9 (O—C=*C*), 150.1 and 151.9 (2 C=O), 151.9 and 174.0 (2 O—*C*=C), 161.2 and 169.5 (2 C=O ester),. MS (EI, 70 eV): *m*/*z* (%) = 407 (M$^+$, 12), 348 (100), 324 (65), 316 (50), 83 (35), 59 (46). Anal. Calcd. for $C_{19}H_{25}N_3O_7$ (407.42): C, 56.01; H, 6.18; N, 10.31%; Found: C, 56.1; H, 6.2; N, 10.2.

***Diethyl 7-(cyclohexylamino)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (4f).*** Yellow oil (0.382 g, 88%). IR (KBr) ($\nu_{max}$ /$cm^{-1}$): 3375 (N—H), 1697 (C=O), 1541 (C=C). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.10 and 1.12 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 $CH_3$), 1.20–2.94 (10 H, m, 5 $CH_2$), 3.34 and 3.42 (6 H, 2 s, 2 $NCH_3$), 3.65 (1 H, br m, NCH), 4.10 and 4.15 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 $OCH_2$), 4.55(1 H, s, CH), 8.70 (1 H, br d, $^3J_{HH}$ = 5.6 Hz, NH). $^{13}$C NMR ($CDCl_3$): δ = 13.1 and 14.2 (2 $CH_3$), 24.2, 25.1 and 32.9 (5 $CH_2$), 28.9 and 33.1 (2 N—$CH_3$), 33.9 (CH), 54.1 (HN—CH), 59.1 and 60.0 (2 $OCH_2$), 73.1 (N—C=*C*), 88.7 (O—C=*C*), 150.2 and 151.9 (2 C=O), 157.9 and 171.5 (2 O—*C*=C), 161.2 and 169.5 (2 C=O ester),. MS (EI, 70 eV): *m*/*z* (%) = 435 ($M^+$, 5), 352 (100), 337 (65), 73 (50). Anal. Calcd. for $C_{21}H_{29}N_3O_7$ (435.47): C, 57.92; H, 6.71; N, 9.65%; Found: C, 57.9; H, 6.8; N, 9.7.

***Dimethyl 2-(cyclohexylamino)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4g).*** Yellow paste (0.327 g, 0.90%). IR (KBr) ($\nu_{max}$ /$cm^{-1}$): 3405 (N—H), 1735, and 1686 (C=O), 1603 (C=C). $^1$H NMR ($CDCl_3$): δ = 1.18–2.10 (10 H, m, 5 $CH_2$), 2.26–2.59 (4 H, m, 3 $CH_2$), 3.64 and 3.68 (6 H, 2 s, 2 $OCH_3$), 3.70 (1 H, m, NCH), 4.48 (1 H, s, CH), 8.57 (1 H, d, $^3J_{HH}$ = 7.2 Hz, NH). $^{13}$C NMR ($CDCl_3$): δ = 20.2, 24.4, 25.5 33.6, 33.7 and 36.2 (8 $CH_2$), 34.4 (CH), 49.9 (N—CH), 50.5 and 52.2 (2 $OCH_3$), 77.1 (N—*C*=C), 112.9 (O—C=*C*), 158.1 and 173.8 (2 O—*C*=C), 164.0 and 169.5 (2 C=O ester), 196.1 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 363 ($M^+$, 10), 331 (16), 305 (28), 280 (60), 190 (100), 43 (35). Anal. Calcd. for $C_{19}H_{25}NO_6$ (363.40): C, 62.80; H, 6.93; N, 3.85%; Found: C, 62.8; H, 6.9; N, 3.9.

***Diethyl 2-(cyclohexylamino)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4h).*** Yellow oil (0.313 g, 0.80%), mp 140–142°C. IR (KBr) ($\nu_{max}$ /$cm^{-1}$): 3428, (N—H), 1726 and 1761 (C=O), 1182 (C—O). $^1$H NMR ($CDCl_3$): δ = 1.17 and 1.25 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 $CH_3$), 1.20–1.92 (10 H, m, 5 $CH_2$), 2.29–2.69 (6 H, m, 6 $CH_2$), 3.69 (1 H, m, NCH), 4.15 and 4.21 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 $OCH_2$), 4.42 (1H, s, CH), 8.65 (1 H, d, $^3J_{HH}$ = 7.4 Hz, NH). $^{13}$C NMR ($CDCl_3$): δ = 14.1, 14.2, 24.4, 25.5, 33.7 and 36.5 (8 $CH_2$), 27.2 and 29.4 (C$Me_2$), 32.5 (*C*$M_2$), 36.3 (CH), 49.9 (N—CH), 59.3 and 60.2 (2 $OCH_2$), 72.2 (N—*C*=C), 113.1 (O—C=*C*), 158.2 and 173.8 (2 O—*C*=C), 164.0 and 169.6 (2 C=O ester), 196.1 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 391 ($M^+$, 5), 362 (14), 308 (100), 190 (82), 83 (29). Anal. Calcd. for $C_{21}H_{29}N_3O_6$ (391.46): C, 64.43; H, 7.47; N, 3.58%; Found: C, 64.5; H, 7.5; N, 3.6

## REFERENCES AND NOTES

[1] (a) Zhu, J.; Bienayme, H. Multicomponent Reactions, 1st ed.; Wiley-VCH: Weinheim, Germany, 2005; (b) Dondoni, A.; Massi, A. Acc Chem Res 2006, 39, 451; (c) Hulme, C.; Gore, V. Curr Med Chem 2003, 10, 151; (d) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Chem Eur J 2000, 6, 3321.

[2] (a) Hoffmann, P.; Gokel, G.; Marquarding, D.; Ugi, I. In Isonitrile Chemistry; Ugi, I., Ed.; Academic Press: New York, 1971; (b) Ugi, I. Pure Appl Chem 2001, 73, 187; (c) Ugi, I.; Werner, B.; Domling, A. Molecules 2003, 8, 53.

[3] (a) Hulme, C.; Nixey, T. Curr Opin Drug Discov Devel 2003, 6, 921; (b) Ugi, I.; Domling, A. In Combinatorial Chemistry: A Practical Approach; Fenniri, H., Ed.; Oxford University Press: Oxford, 2000, p 287; (c) Weber, L.; Illgen, K.; Almstetter, M. Synlett 1999, 3, 366; (d) Ugi, I. J Prakt Chem 1997, 339, 499; (e) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Acc Chem Res 1996, 29, 123.

[4] (a) Ugi, I. Angew Chem Int Ed Engl 1982, 21, 810; (b) Ugi, I.; Lohberger, S.; Karl, R. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1083; (c) Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168; (d) Walborsky, H. M.; Periasamy, M. P. In The Chemistry of Functional Groups, Supplement C; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; Chapter 20, p 835; (e) Marcaccini, S.; Torroba, T. Org Prep Proced Int 1993, 25, 141.

[5] (a) Domling, A. Chem Rev 2006, 106, 17; (b) Banfi, L.; Riva, R. Org React 2005, 65, 1; (c) Domling, A. Curr Opin Chem Biol 2000, 4, 318.

[6] (a) Ramon, D. J.; Yus, M. Angew Chem Int Ed Engl 2005, 44, 1602.

[7] (a) Orru, R. V. A.; de Greef, M. Synthesis 2003, 10, 1471; (b) Zhu, J. Eur J Org Chem 2003, 7, 1133; (c) Ugi, I.; Domling, A.; Werner, B. J Heterocycl Chem 2000, **37**, 647; (d) Ugi, I.; Werner, B.; Domling, A. Targets Heterocycl Syst 2000, 4, 1.

[8] Pailer, M.; Worther, H.; Meller, A. Monatsh Chem 1961, 92, 1037.

# Studies on the Acetylation of 3,6-Diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile Derivatives



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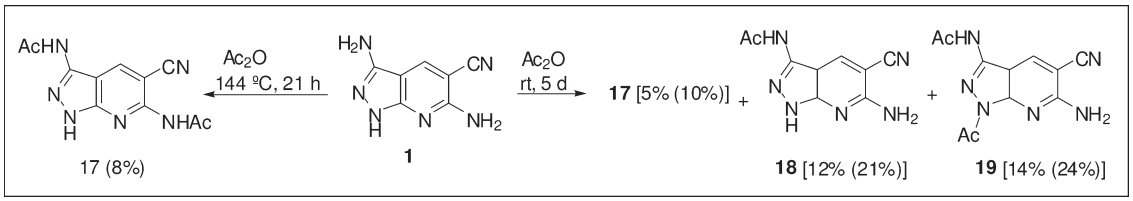


The acetylation reaction of the differently substituted 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile derivatives **1**–**6** is reported. The structure of the resulting acetamides has been investigated and confirmed by analytical, spectroscopic, and chemical transformations. From these studies, we conclude that, in general, under mild conditions, and using acetic anhydride, when free, the *N*(1)H moiety is a more reactive center respect to the C(3)$NH_2$ and C(6)$NH_2$ groups. This trend is reversed when no steric hindrance due to presence of a phenyl group at C4 drives the preferred acetylation to C(3)$NH_2$, as it is evident by comparing the observed results from precursor **1** with **3**. When N1 is blocked, the (C3)$NH_2$ group undergoes preferential acetylation over the (C6)$NH_2$ site, which only has been mono (or diacetylated) at reflux. Computational analyses based on DFT studies have been extensively used to explain the observed reactivities.

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## INTRODUCTION

The pyrazolo[3,4-*b*]pyridine ring system [1] is present in a number of pharmaceutically important compounds targeted to inhibit VEGFR/PDGFR kinases [2] or GSK-3 [3]. In a current project aimed at the synthesis, design, and biological evaluation of new GSK-3 inhibitors, we have recently synthesized a series of known and new 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridines [4] (**A**) (Chart 1). To carry out basic SAR studies, we decided to explore the acylation reaction of 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridines (**1**–**6**) (Chart 2) to get presumably more potent inhibitors as previously demonstrated by other authors [3].

In this context, previous reports from other laboratories have described that the acylation ($C_3H_7COCl$, pyridine, reflux) of precursor **7** gave the C(3)$NH_2$ acetylated derivative **8** in 80% yield (Chart 3). Note, however, that the carbamoylation of the free amino groups on the fused pyrazole ring system in compound **9** showed a reversed regioselectivity, providing compound **10** (Chart 3) [5]. In addition, it has been also shown that under mild conditions, 5-substituted 3-aminopyrazoles are almost simultaneously acylated at N1 and at C(3)$NH_2$ to give diacylated derivatives [6]. Substituted 3-amino-1*H*-pyrazolo[3,4-*b*]quinoxalines have been selectively N-acylated at N1 [7]. Compound **2** has been reported to give exclusively the C(3)-*N*-formyl derivative **11** or the acetamide **13** from related amide **12** (Chart 3) [8]. Finally, a more complex situation was described for 4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine (**14**) [9] when using acetyl chloride. Depending on the base used, the acetylation goes to C(3)$NH_2$ to give compound **15** (for triethylamine as base) or to **16** (for pyridine as base) (Chart 3) [9]. Note also that the position of the acetyl residue at N1 was not unambiguously confirmed by X-ray analysis neither discussed in depth; however, 4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazines have been regioselectively N-alkylated at N1 [9], a result that is in good agreement with similar reaction on 3-amino-1*H*-pyrazolo[3,4-*b*]quinoxalines [7].

In summary, all these data confirm that a simple reaction such as the acetylation in a complex, polyfunctionalized, heterocyclic framework can be more complicated than presumed at first glance [10]. This is in fact what we have observed in the acetylation of 3,6-diamino-pyrazolopyridines **1**–**6** (Chart 2), and in this work, we report our results.

## RESULTS AND DISCUSSION

**Synthesis, structural analysis, and reactivity.** The synthesis of 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**1**) (Chart 2) proceeded uneventually as described by reacting 2-amino-6-chloropyridine-3,5-

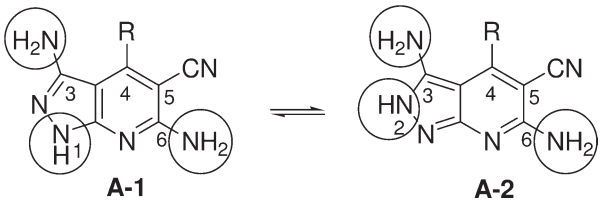



**Chart 1.** 3-6 Diamino-1*H*-pyrazolo[3,4-*b*]pyridines.

dicarbonitrile with hydrazine hydrate [8]. In the HMBC experiment of pyrazolopyridine **1**, we assigned the chemical shifts for the protons at C(3)N$H_2$ and C(6)N$H_2$, at δ 5.56 and 6.70, as cross-peaks were observed with the signals at δ 99.8 (C3a) and 83.0 (C5), respectively; in agreement with this, the signal at 99.8 ppm (C3a) showed a cross-peak with the signal at δ 11.60, corresponding to N(1)H. Similar chemical shifts and effects have been observed for protons in the other related compounds described here, and this trend [δ C(6)N$H_2$ >> δ C(3)N$H_2$] has served as diagnostic for proton assignments and structure determination (see later).

The reaction of compound **1** [8] with acetic anhydride, after 21 h, at 144°C, was complete, but extensive decomposition was observed by TLC analysis, and only *N*,*N*′-(5-cyano-3a,7a-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-3,6-diyl)diacetamide (**17**) could be isolated in 8% yield (Chart 4). Based on the analytical (MS/elemental analysis) and the NMR spectra, compound **17** was clearly a diacetamide derivative of precursor **1**, showing in its $^1$H NMR spectrum two acetyl groups integrating for six protons (2xNHCOC$H_3$), as a singlet at δ 2.12; the singlet at δ 10.96 was assigned to C(3)N*H*COCH$_3$ as it showed cross-peaks in the HMBC spectrum with C3a (δ 104.7) and NH*C*OCH$_3$ (δ 169.2); consequently, the singlet at δ 10.79 corresponded to the proton at C(6)N*H*COCH$_3$; finally, the singlet for one proton at δ 13.62 was assigned to N(1)*H*. In this reaction, we detected traces of a second compound that was identical to the compound isolated when the reaction was carried at out at room temperature for 5 days and identified as *N*-(6-amino-5-cyano-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)acetamide (**18**), isolated in 12% yield (21% taking into account the recovered starting material); in this reaction, we also isolated diacetamide **19** [14% (24%)] and compound **17** [5% (10%)] (Chart 4). In the $^1$H NMR spectrum of monoacetamide **18**, we could analyzed only one singlet for two protons at δ 6.95, indicating that the only free $NH_2$ group was at C6, leaving free the N(1)H (δ 12.66), the acetamido group being thus at C3, as in the $^1$H NMR spectrum the signals for NHCOCH$_3$ appeared at δ (NH) 10.69 and δ (COCH$_3$) 2.12. These assignments were confirmed in the HMBC experiment, as the signal at δ 12.66 showed cross-peaks with C3a, C3, and C7a, while the singlet at δ 10.69 showed cross-peaks with C3a and NH*C*OCH$_3$. In the $^1$H NMR spectrum of compound **19**, in addition to similar signals to those described for compound **18** (see Experimental), no N(1)H resonance was observed at low field, but a new singlet appeared for three protons at 2.77 ppm, characteristic for N(1)COCH$_3$ (see compound **16** in Chart 3) [9]. In summary, we conclude that the acetylation of 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**1**) is relatively complex, and a number of differently substituted acetamido derivatives were isolated and characterized. Under mild reaction conditions, preferent acetylation at C(3)$NH_2$ followed at N(1) positions was observed; the acetylation at C(6)$NH_2$ being also possible, at reflux, to give diacetamide **17** (Chart 4), as the only detected, in a poor chemical yield. Overall, these facts are in good agreement with the previous results [5–7] on the acylation of related substrates (see Chart 3) and strongly point to the absence of a substituent at C4, the key to favor the acetylation at C(3)$NH_2$ (see later).

The acetylation of 3,6-diamino-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**2**) [8], under mild conditions, gave only monoacetamide **20** in good yield (Chart 4). In the $^1$H MNMR of this compound, we could

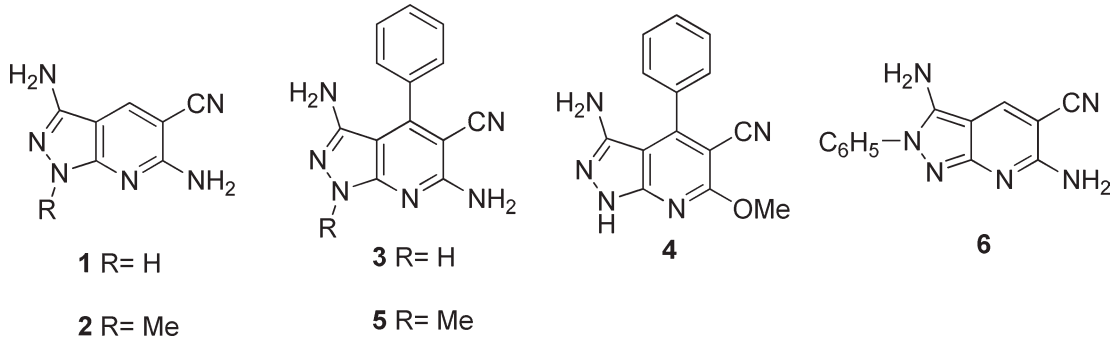



**Chart 2.** Structure of compounds **1–6**.

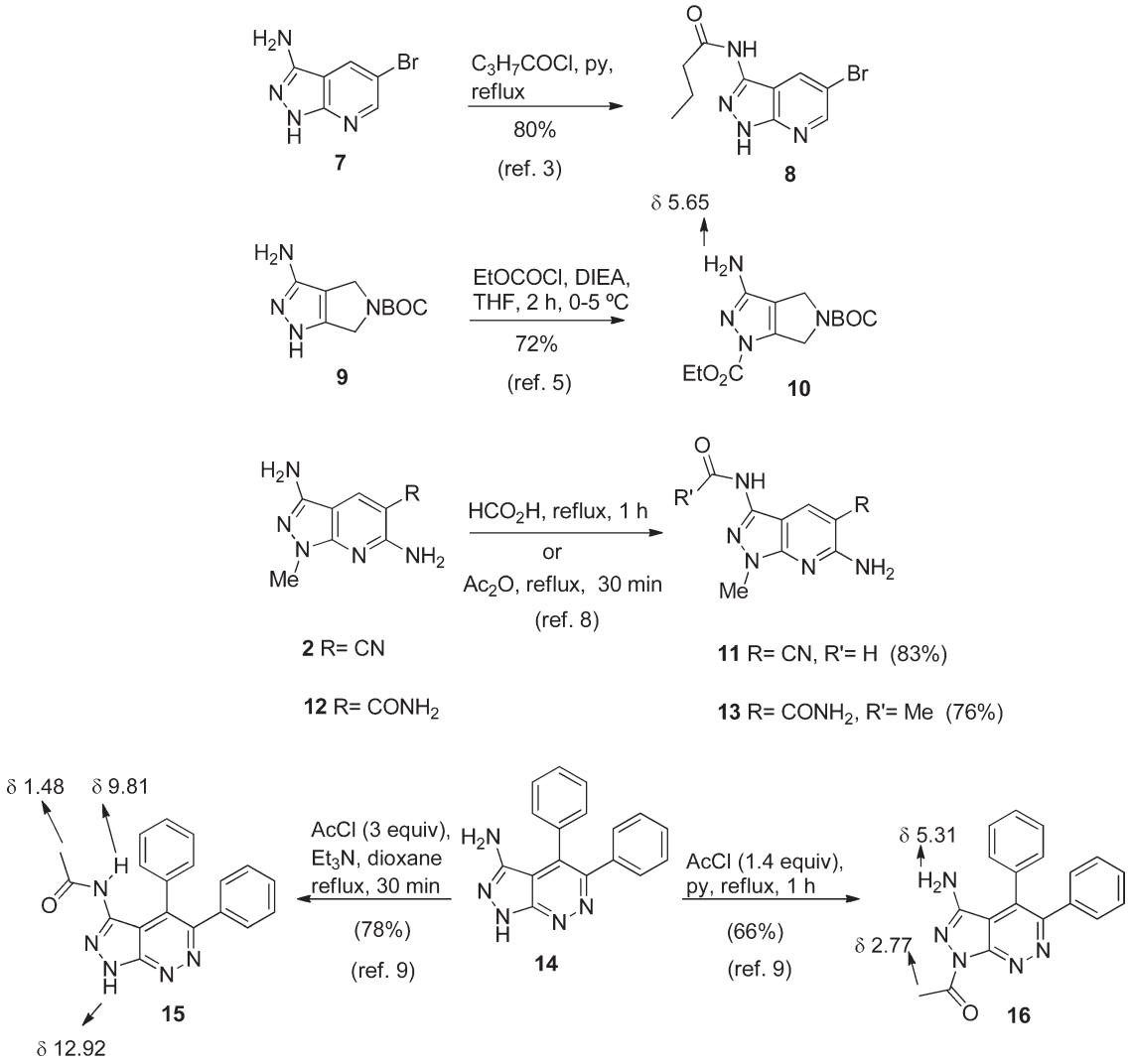



**Chart 3.** Transformation of compounds **2**, **7**, **8**, **12**, and **14**.

analyze two singlets for proton at δ 10.74 and for two protons at δ 7.08, corresponding to (C3)N*H*COCH$_3$ and (C6)NH$_2$ protons, respectively. In agreement with this assignment, in the HMBC-NMR experiment of this pyrazolopyridine, the NH proton at C(3)N*H*COCH$_3$ resonated at δ 10.74 and showed cross-peaks with C3a (100.3 ppm) and NH*C*OCH$_3$ (168.1 ppm), whereas for the proton at C(6)NH$_2$ (δ 7.08) cross-peaks appeared with the signals at δ 86.4 (C5), 158.3 (C6), and 150.7 (C7a). In addition, a small but evident selective nOe experiments between the NH proton at δ 10.74 [(C3)N*H*COCH$_3$] and H4 (δ 8.57) confirmed the position of the acetyl group on the nitrogen at C3. This result and reactivity is thus also in good agreement with the reported reactivity of precursor **2** in the formylation reaction (Chart 3) [8].

The small nOe observed between both protons in the N*H*COC*H*$_3$ group and H4 in compound **20** could be rationalized after computational analysis, which showed that, in fact, rotamer **20b** was 7.0 kcal/mol more stable than conformer **20a** (Fig. 1), possibly because of the lone pair–lone pair electronic repulsion between the carbonylic oxygen and the N2 present in conformer **20a**. On the other hand, the calculated chemical shifts for protons in NHCOC*H*$_3$ are in good agreement with the experimental values.

The reaction of 2-amino-6-chloro-4-phenylpyridine-3,5-dicarbonitrile [11] with hydrazine hydrate [4] gave 3,6-diamino-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**3**) (Chart 2) [12]. In the acetylation of compound **3** with Ac$_2$O, at 0°C, for 20 h (Method A, see Experimental), a solid was formed; it was filtered, washed with cold water/EtOH, and recrystallized from ethanol to give compound **21** in 25% yield (Chart 4). The analytical and spectroscopic data of this molecule

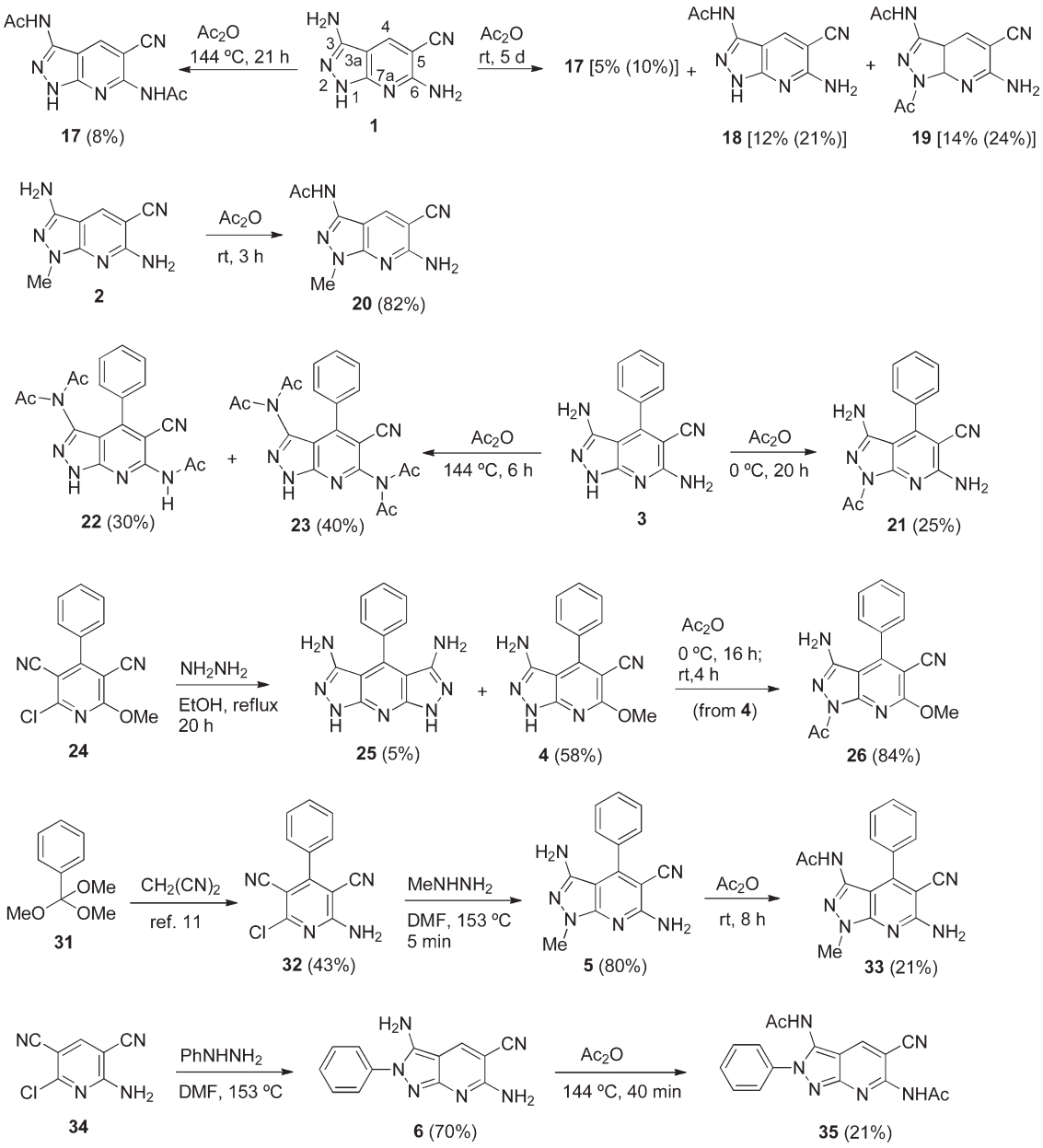



**Chart 4.** The acetylation reaction of compounds **1**–**6**.

clearly showed that **21** was a monoacetamide, as in the $^1$H NMR, a methyl group was observed at an anomalous low field (δ 2.58) and two broad singlets (7.40 and 4.82 ppm) for two protons, each one corresponding to the $NH_2$ groups at carbons C6 and C3, respectively. These data along with the absence of a free NH, or a NH resonance for a N*H*COCH$_3$ moiety, clearly supported the structure of **21** as 1-acetyl-3,6-diamino-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile.This structure has also been confirmed by the data obtained in the $^{13}$C NMR, HMQC, and HMBC experiments.

To improve the chemical yield, the acetylation reaction was carried out with $Ac_2O$ at rt for 5 h or with AcCl, in pyridine, at 0°C for 5 days, but the yields (21 and 24%, respectively) of compound **21** were not better. Finally, the acetylation reaction was performed with $Ac_2O$ at reflux for 6 h; after work-up and purification, peracetylated derivatives **22** (30%) and **23** (40%) were isolated (Chart 4). The structure of compound **22** was established as a triacetamide derivative of precursor **3** by its analytical and spectroscopic data. As in the $^1$H NMR spectrum, we observed a broad singlet for one

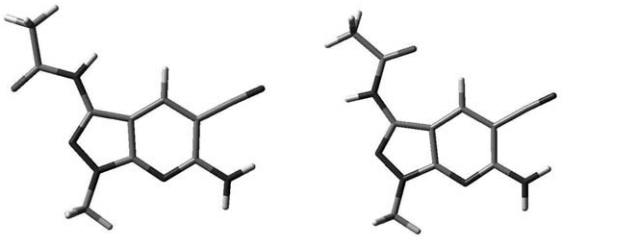



**Figure 1.** Conformers for compound **20**.

proton at 14.45 ppm, and three acetyl groups [δ 2.15 (singlet, one acetyl) and 1.91 (singlet, two acetyl groups)]; we concluded that N(1) was free, the only structural problem that remained to be established was to determine if the $NHCOCH_3$ group was at C3 or at C6. In the HMBC spectrum, the signal al δ 10.98 (N*H*$COCH_3$) showed cross-peaks with signals at 100.0, 152.3, and 169.5 (N*C*$OCH_3$). In the case that the group $NHCOCH_3$ was at C6, the signals at 100.0 and 152.3 should be assigned to C5 and C6, respectively, the signal appearing at 106.5 ppm corresponding thus to C3a, an assignment that seems reasonable, as we have routinely observed in the compounds investigated here that in the $^{13}C$ NMR spectrum δ C3a >> C5. To prove this hypothesis, a series of nOe experiments were carry out. When the N*H*$COCH_3$ was irradiated, only the singlet at 2.15 ppm showed a weak effect; the irradiation of this signal also showed only a weak effect at 10.98 ppm. However, the irradiation of the singlet at 1.91 ppm integrating for six protons (two $NHCOCH_3$ groups) produced a sharp effect on the aromatic protons; the reverse irradiation also produced the same effect. From these experiments, we conclude that the two acetamido groups should be in the same carbon (C3). For compound **23**, as in the $^1H$ MNR spectrum, we observed a broad singlet at δ 14.93 for one proton, clearly assigned to N(1)H, the location of the four acetamido groups present in the molecule at C3 and C6 was evident.

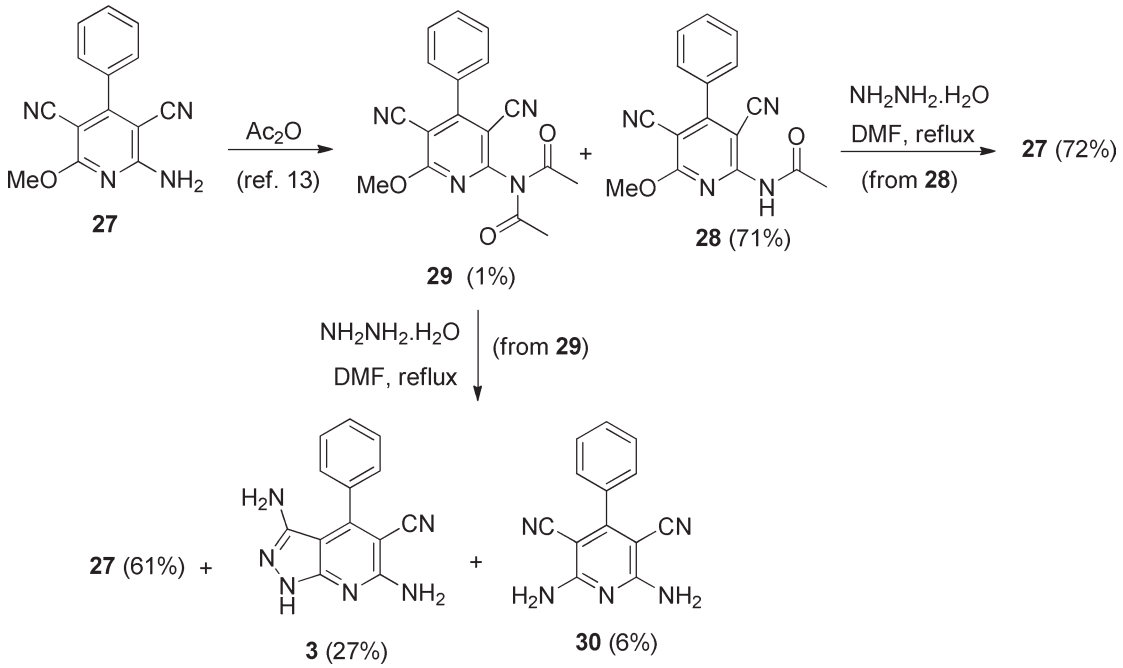
The regioselective acetylation at N1 in compound **3**, respect to both $NH_2$ groups at C3 and C6, under mild conditions, prompted us to investigate the same reaction on precursor **4**, where only two positions at N1 and C(3)$NH_2$ were available for the acetylation. This compound has been prepared from readily available 2-chloro-6-methoxy-4-phenylpyridine-3,5-dicarbonitrile (**24**) [13] after reaction with hydrazine hydrate; in this reaction, we isolated also traces of the bis-pyrazolopyridine **25** (Chart 4). When compound **4** was acetylated with $Ac_2O$ (see Experimental) compound **26** was isolated in good yield (84%) (Chart 4). The analytical and spectroscopic data clearly showed that compound **26** is a monoacetamide bearing the acetyl group at N1, as a broad singlet appeared at 5.10 ppm integrating for two protons [C(6)$NH_2$], and the singlet for the acetyl groups integrating for three protons resonated at δ 2.69, a value that we have found in compound **21** (see earlier) and in compound **16** [9] (Chart 3).

In view of these results, and as we were interested in the synthesis of the monoacetamide at C6 in these pyrazolopyridines, we considered an alternative synthetic route based on the acetylation of 2-amino-6-methoxy-4-phenylpyridine-3,5-dicarbonitrile (**27**) [13] (Scheme 1). Carrying out the reaction as reported [13], we obtained a mixture of monoacetamide **28** (71%) and imide **29** (1%) (Scheme 1) that were easily separated by column chromatography and submitted to reaction with hydrazine hydrate, in DMF at reflux, aiming at the ''one-pot'' methoxy displacement and simultaneous pyrazolopyridine formation. For compound **28**, we obtained compound **27** in 72% yield (Scheme 1). For compound **29**, we isolated and characterized compounds **27**, **30**, and **3** (Scheme 1). The formation of these compounds is the result of a series of deacetylation reactions followed by pyrazolo formation. The structure of compound **30** has been unequivocally established by comparison of the reported data in literature [11] and with an authentic sample prepared in the reaction of DMF [14] with 6-amino-2-chloro-4-phenylpyridine-3,5-dicarbonitrile (**32**) [11,15] (see Experimental), obtained from the reaction of trimethylorthobenzoate (**31**) with malononitrile [11] (see Experimental) (Chart 4).

Next, we have investigated the acetylation of precursor **5**, prepared as usual from compound 6-amino-2-chloro-4-phenylpyridine-3,5-dicarbonitrile (**32**) [11] and *N*-methylhydrazine (Chart 4). As expected, in the $^1H$ NMR spectrum of compound **5**, a positive nOe effect between the broad singlet at δ 4.36 and the aromatic protons allowed us to assign this chemical shift for protons at C(3)$NH_2$, the signal at 6.90 ppm corresponding to C(6)$NH_2$. The acetylation of pyrazolopyridine **5** ($Ac_2O$, rt, 8 h) provided compound **33** in low yield (Chart 4). Not unexpectedly, in the $^1H$ NMR of compound **33**, the singlet for two protons at δ 7.12 [(C6)$NH_2$] clearly demonstrated that the acetylation has taken place in the C(3)$NH_2$ group. Selective nOe experiments also showed the small but evident effect between the protons at the acetamide group (CON*H*$CH_3$).

For compound **33** (Fig. 2), rotamer **b** is 1.8 kcal/mol more stable than **a**, possibly because of the electronic repulsion between the carbonylic oxygen and the N2 present in conformer **a**, as previously shown for compound **20**, although the effect here should be less strong, because the presence of the phenyl ring prevents a coplanar arrangement between the amide group and the azole plane, being rotated with a dihedral angle of 58°.

**Scheme 1.** Synthesis of compounds **28** and **29** and their reaction with hydrazine hydrate.

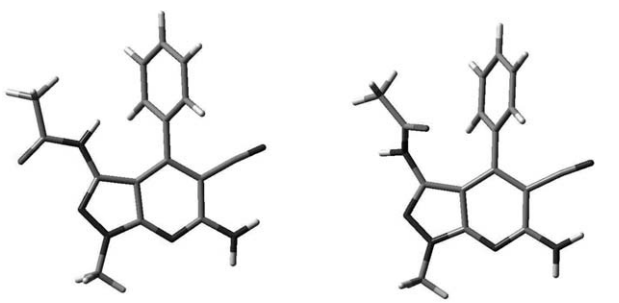



This fact increases the energy of conformer **b** and reduces the energy difference between the two possible conformers. On the other hand, the calculated and the experimental chemical shifts for the methyl groups in NHCOC$H_3$ are in good agreement; the low δ chemical shift observed for this methyl group possibly due to the shielding effect of the aromatic ring at C4.

Finally, we have prepared precursor **6** in good yield in the reaction of 2-amino-6-chloropyridine-3,5-dicarbonitrile (**34**) with *N*-phenylhydrazine (Chart 4). After selective nOe experiments in the $^1$H NMR spectrum of this compound, the resonance at δ 6.97 was assigned to the amino group at C3, while the singlet integrating for two protons at δ 6.48 corresponded to (C6)$NH_2$. This analysis is the reverse that we have observed in the other precursors investigated in this work and must ascribed to the presence of a phenyl ring at N2. In fact, it is well known that the reaction of 2-halogeno-3-cyanopyridines with *N*-arylhydrazines respect to *N*-alkylhydrazines provides 2-aryl-2*H*-pyrazolo[3,4-*b*]pyridines instead of 1-alkyl-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines [16]. The acetylation of compound **6** at reflux for 40 min gave the diacetylated derivative **35** in 21% yield (Chart 4), which showed spectroscopic and analytical data in good agreement with this structure (see Experimental).

**Computational studies.** In view of the results obtained for pyrazolopyridine **3** (Chart 4), we next addressed the reaction mechanisms to explain the observed regioselectivities during the acetylation reactions.

All calculations were carried out with Gaussian03 package [17]. All the minima and transition states involving were fully optimized with the B3LYP hybrid functional [18]. As the key aspect to account for reactivity and regioselectivity concerns atoms bearing lone-pair electrons, we have applied the extended 6-31+G(d,p) basis set to get reliable structures and energy values. Then, to optimize computational resources, we have selected AcCl as acetylated agent instead of $Ac_2O$. Treatment of precursor **1** with both electrophiles has shown similar results (see main text). Zero-point energies and thermal contributions to thermodynamic functions and activation parameters, as well as harmonic frequencies to assess the nature of the stationary points, were computed at the same level of theory on the



**33** (conformer **a**)
Predicted: δ[(NHCOC$H_3$)]= 1.93

**33** (conformer **b**)
Predicted: δ [(NH COC$H_3$)] = 1.43

**Figure 2.** Conformers for compound **33**.

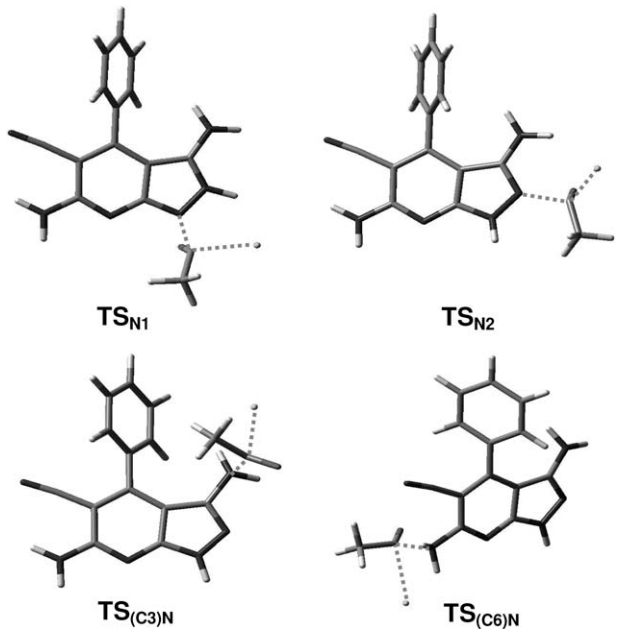



**Figure 3.** Transition structures for the N-acetylation of **3**.

optimized structures. To test the influence of solvation effects, we have calculated solvation free energies in solution $\Delta G_{solv}$ for the ground state and transition structures at the PCM/UAHF/B3LYP/6-31G(d) level [19] using the previously optimized gas-phase structures. Combination of these solvation free energies with gas-phase free energies obtained at B3LYP/6-31+G(d,p) level yields the relative free energy in solution $\Delta G^{\ddagger}_{sol}$ compiled in Table 2 in column 4 and Figure 3. Natural bond orbital (NBO) analyses [20] have been performed by the module NBO v.3.1 implemented in Gaussian 03 to evaluate the NPA charges at the optimization level.

We have initially carried out the study of the tautomeric equilibrium for compound **3**. We have focused on the prototropy tautomerism between the **3**-1*H* and **3**-2*H* forms involving the azole moiety (Scheme 2) as the structure with the hydrogen atom attached to the pyridine nitrogen at the position 7 is energetically unfavorable, as was expected from valence bond resonance considerations and verified by calculations on this [our calculations (B3LYP/6-31+G(d,p) reveal a structure 24.5 kcal mol$^{-1}$ less stable than **3**-1*H*] and related structures [21].

Both structures **3**-1*H* and **3**-2*H* have in common that the amino groups are partially planarized (out-of-plane deviation of (C3)N/(C6)N: 29.4°/10.8° and 28.9°/14.2° in **3**-1*H* and **3**-2*H*, respectively) as the N electron pairs are part of the aromatic system, and that the aromatic ring attached to the C4 position is rotated with respect to the pyridine plane (with dihedral angles of 57.5 and 59.7°, respectively) to avoid steric repulsions with substituents at C3 and C5.

At the B3LYP/6-31+G(d,p) level, the tautomer **3**-2*H* is predicted to be less stable than **3**-1*H* by 9.5 and 4.0 kcal/mol in the gas phase and in DMSO, respectively. According to the Boltzmann distribution, at a temperature of 298 K, this difference in energy corresponds to a **3**-1*H*:**3**-2*H* ratio of >99:<1, with the population of the minor tautomer below the limit of detection for conventional NMR spectroscopy. Thus, according to the calculations, tautomer **3**-2*H* is unlikely to coexist with the other tautomer.

This preference of the 1*H* tautomer in pyrazolopyridines agrees with structural analysis of 4-aryl-5-cyano-pyrazolo[3,4-*b*]pyridines [22], theoretical studies of pyrazolo[3,4-*b*]pyridines bearing a variety of substituents [23], and crystallographic data of protein–ligand complexes [24], which indeed confirm that in this class of compounds, the (N1)H forms key H-bonds with the enzymes (cyclin-dependent kinases).

This picture contrasts with that for the related structures pyrano[2,3-c]pyrazoles (6-amino-5-cyano-3-methyl-4-aryl/heteroaryl-2*H*,4*H*-dihydropyrano[2,3-*c*]pyrazoles) as they exist predominantly in the 2*H* tautomeric form [25]. To confirm the reliability of our calculations in the prediction of tautomeric equilibria, we have performed further computations on the 6-amino-5-cyano-3-methyl-4-phenyl-dihydropyrano[2,3-*c*]pyrazole ring system [25–27]. Our results indicate that the 2*H* tautomer is 3.7 kcal mol$^{-1}$ more stable than the 1*H* form in the gas phase. These data are in agreement with the crystallographic results [25–27], thus supporting our theoretical protocol in the estimation of the tautomeric equilibrium.

The reactivity of the 3,6-diamino-pyrazolo[3,4-b]pyridines against acetylation merits a careful analysis as four nucleophilic positions can undergo acetylation: besides both amino moieties [(C3)N and (C6)N], the piridinic- and pyrrole-type N of the pyrazole (N1, N2). The electron pair of the pyridinic-type N makes this position more nucleophilic than the pyrrole-type N, whose electron pair is part of the aromatic system.

In an attempt to rationalize the regioselectivity, DFT calculations were performed to determine both the atomic charges and the HOMO of **3**. In general, reactions with hard (high-lying LUMOs) electrophiles are charged

**Scheme 2.** Tautomer equilibrium in compound **3**.

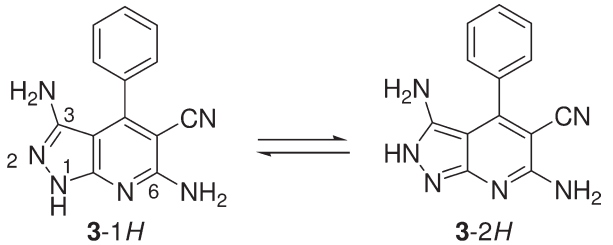


**Table 1**

Calculated NPA charges and HOMO coefficients for the N atoms of **3** prone to undergo attack by the acylating agent.

| | NPA charges | | HOMO coefficients | |
|---|---|---|---|---|
| | **3**-1*H* | **3**-2*H* | **3**-1*H* | **3**-2*H* |
| N1 | −0.397 | −0.327 | 0.47 | 0.73 |
| N2 | −0.340 | −0.380 | 0.64 | 0.34 |
| (C3)N | −0.861 | −0.861 | 0.58 | 0.46 |
| (C6)N | −0.829 | −0.837 | 0.30 | 0.36 |

controlled, whereas reactions with soft (low-lying LUMOs) electrophiles are under frontier molecular orbital (FMO) control. The calculated atomic charges are not consistent with the experimentally determined regioselectivity. Thus, the greatest amount of negative charge is found at the (C3)N position (atomic charge = −0.861, Table 1), while reaction occurs selectively at the azole moiety. On the other hand, the observed selectivity fits well with the computed HOMO coefficients on both tautomers **3**-1*H* and **3**-2*H* (Table 1) as the largest value, and hence providing better overlapping orbital with the electrophile, is situated at the pyridinic-type nitrogen.

Although orbital properties can account only for the electronic factors, the steric effects (if exist) are included in the free energy of activation for the reaction. From a mechanistic point of view, when the reaction is carried out in the absence of a deprotonating agent, it should be expected that the N—H of the azole becomes acidic enough to be deprotonated only when the pyridinic-type N has been attacked by the acylated agent [28]. According to this assumption, we have considered the attack on every N of the neutral structure and have selected acetyl chloride (see Experimental) as electrophile to simulate the acetylation reaction.

The calculated transition structures (Fig. 3) provide free energy differences that suggest a kinetically favored attack on the azole ($\mathbf{TS_{N1}}$ and $\mathbf{TS_{N2}}$) rather than on the amino moieties ($\mathbf{TS_{(C3)N}}$ and $\mathbf{TS_{(C6)N}}$) in the gas phase and in solution (Table 2). In fact, as has been described earlier, these groups are rather planarized as the lone pair is partially delocalized in the aromatic system, thus being less nucleophilic groups than expected. This observation agrees with the experimental selectivity shown earlier (Chart 4). In the azole, the kinetically preferred site for the acetylation, in the gas phase and in solution, is N2 in the **3**-1*H* form (Table 2), which indeed is the proposed predominant tautomer. Also, according to these results, a small amount of the regioisomeric product could be formed by attacking at N1 in the **3**-2*H* form (estimation of the Boltzmann distribution N2:N1 93:7). In summary, these results suggest that **21** should be mostly the N2-substituted structure that results from N-acetylation of the major tautomer of **3** (**3**-1*H*). In view of these theoretical results and to support the position of the acetyl group at N1/N2, we tried to crystallize compound **21** as a free base or as its hydrochloride, but without success; consequently, the location of the acetyl groups at N1 is a tentative hypothesis that still needs to be experimentally confirmed.

Bases on these data, if the azole positions are blocked to undergo reaction, the (C3)N should be the preferred reactive site. This hypothesis agrees with the experimental observations as (C3)N is the acetylation site found in **20**. To further shed light on this result, we have performed calculations for the formation of **20** from the pyrazolopyridine **2**. The HOMO coefficients are parallel to those found for **3**-1*H*: (C3)N = 0.62, (C6)N = 0.27. Likewise, the calculated transition structure for the attacking on the amino group at C3 is 8.3 kcal $mol^{-1}$ more stable than on the amino at C6 (Fig. 4). Accordingly, **20** is acetylated at (C3)N, which is supported by the experimental evidence.

In conclusion, in this work, we have described the acetylation of differently substituted 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile derivatives (**1**–**6**. The structure of the resulting acetamides has been investigated and confirmed by analytical, spectroscopic, and chemical transformations. From these studies, we conclude that, in general, under mild conditions, and using acetic anhydride, when free, the *N*(1)H moiety is the more reactive center respect to the C(3)$N$H$_2$ and C(6)$N$H$_2$ groups. This trend is reversed when no steric hindrance due to presence of a phenyl group at C4 drives the preferred acetylation to C(3)NH$_2$, as it is evident by comparing the observed results from precursor **1** with **3**. When N1 is blocked, the (C3)$N$H$_2$ group undergoes preferential acetylation over the (C6)$N$H$_2$ site, which only has been mono (or diacetylated) at reflux.

On the basis of these data, we have also undertaken a computational analysis to explain the observed selectivities during the acetylation reactions. The calculations of frontier orbital coefficients on the reactants pyrazolopyridines and activation barriers agree with the regiochemistry observed. The regioselectivity on the acetylation of the amino groups can be explained by the availability of

**Table 2**

Thermodynamic data (in kcal $mol^{-1}$) in gas phase and in solution for the potential transition structures for the N-acetylation of **3**.

| Transition structures | $\Delta H^{\ddagger}_{gas}$ | $\Delta G^{\ddagger}_{gas}$ | $\Delta G^{\ddagger}_{sol}$ |
|---|---|---|---|
| $TS_{N1}$ | 1.7 | 1.6 | 1.6 |
| $TS_{N2}$ | 0.0 | 0.0 | 0.0 |
| $TS_{(C3)N}$ | 6.2 | 6.5 | 3.2 |
| $TS_{(C6)N}$ | 11.2 | 11.1 | 7.3 |

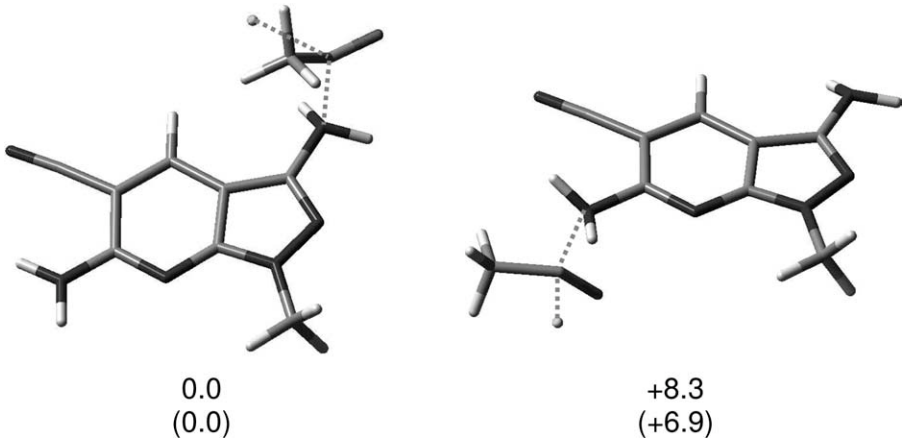



**Figure 4.** Transition structures for the acetylation of **2** at (C3)N (left) and (C6)N (right). Free-energy differences (in kcal $mol^{-1}$) are shown in the gas phase and in solution (in parenthesis).

the N lone pair. A NBO analysis on **2**, **3**-1*H* and the unsubstituted pyrazole[3,4-*b*]pyridine (Chart 5, values in blue) reveals that for the cyano derivatives the lone-pair orbital at (C6)N is less populated, and hence less prone to act as nucleophile, than (C3)N because of a higher delocation on the aromatic system. This induces a higher planarization of the amino group at C6 (Chart 5, values in parenthesis). Conversely, the absence of the electron-withdrawing nitrile substituent allows a more populated lone-pair orbital at (C6)N, in accordance with a decreased *N*-planarization. Therefore, the regioselectivity could be modulated by a careful choice of substituents [29].

## EXPERIMENTAL

Melting points were determined on a microscope type apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded at rt at 300, 400, or 500 MHz and at 75, 100, or 125 MHz. The assignment of chemical shifts is based on standard NMR experiments ($^1$H, $^{13}$C-DEPT, $^1$H,$^1$H-COSY, HSQC, HMBC). In the NMR spectra, values with (*) can be interchanged. Two-dimensional [$^1$H, $^1$H] NMR experiments (NOESY) were carried out with the following parameters: a delay time of 1 s, a spectral width of 3000 Hz in both dimensions, 4096 complex points in t2 and 4 transients for each of 256 time increments, and linear prediction to 512. The data were zero-filled to 4096 × 4096 real points. NOESY experiments were acquired with a mix time of 300 ms. Mass spectra were recorded on a GC/MS spectrometer with an API-ES ionization source. Elemental analyses were performed at CQO (CSIC, Spain). TLC was performed on silica F254 and detection by UV light at 254 nm or by charring with ninhydrin, anisaldehyde, or phosphomolybdic-$H_2SO_4$ dyeing reagents. Where anhydrous solvents were needed, they were purified following the usual procedures. Column chromatography was performed on silica gel 60 (230 mesh).

**Acetylation of 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (1)**

***Method A.*** A solution of compound **1** [8] (100 mg, 0.57 mmol) in $Ac_2O$ (4 mL, 26.52 mmol, 70 equiv) was heated at 144°C for 21 h. The $Ac_2O$ in excess was removed, and the crude submitted to flash chromatography eluting with mixtures of $CH_2Cl_2$/MeOH from 1 to 4% to give *N*,*N*′-(5-cyano-3a,7a-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-3,6-diyl)diacetamide (**17**) (13 mg, 8%) [mp 294–296°C; IR (KBr) ν 3434, 3306, 32470, 2928, 1685, 1673, 1611, 1584, 1517, 1430, 1395, 1246, 1011 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 13.62 (s, 1H, N1H), 10.96 (s, 1H, C3NHAc), 10.79 (s, 1H, C6NHAc), 8.89 (s, 1H, H4), 2.12 (s, 6H, 2xCOCH$_3$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): δ 169.2 (2xN*C*OCH3), 168.4 (C6), 150.8 (C7a), 141.5 (C3),* 141.1 (C4),* 116.9 (CN), 104.7 (C3a), 97.2 (C5), 23.0

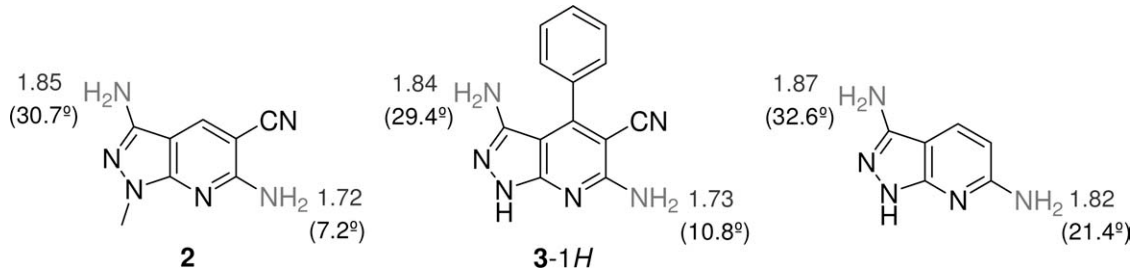



**Chart 5.** NBO analysis on 2,3-1*H* and the unsubstituted pyrazole[3,4-*b*]pyridine.

and 22.8 (2xNCO*C*H3); MS (ES): $[M + 1]^+$ 259.3, $[M + Na]^+$ 281.2, $[2M + Na]^+$ 539.5. Anal. Calcd. for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.54; found C, 51.29; H, 4.05; N, 32.81.

***Method B.*** A solution of compound **1** (100 mg, 0.57 mmol) in $Ac_2O$ (4 mL, 26.52 mmol, 70 equiv) was stirred at rt for 5 days. The $Ac_2O$ in excess was evaporated. The crude was washed with water and ethanol to give a solid (84 mg) that was purified by chromatography eluting with $MeOH/CH_2Cl_2$ mixtures (from 1, 2 to 4%) affording compounds **17** [8 mg, 5% (10%)], **18** [15 mg, 12% (21%)], and unreacted precursor **1** (57 mg). The mother liquors were concentrated and recrystallized from ethanol to give compound **19** [20 mg, 14%, (24%)]. **18**: mp 253–256°C; IR (KBr) ν 3442, 2219, 1686, 1621, 1582, 1406, 1027 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz): δ 12.66 (s, 1H, NH1), 10.69 [s, 1H, C(3)NHCOCH$_3$], 8.55 [s, 1H, 1CH (H4)], 6.95 (s, 2H, $NH_2$), 2.12 (s, 3H, NCOCH$_3$); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): δ 168.2 (NH*C*OCH$_3$), 158.3 (C6), 152.6 (C7a), 141.7 (C4), 141.1 (C3), 117.7 (CN), 100.2 (C3a), 86.4 (C5), 22.8 (NHCO*C*H$_3$); MS (ES): $[M + 1]^+$ 217.1, $[M + Na]^+$ 239.3, $[2M + Na]^+$ 455.1. Anal. Calcd. for $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.87; found C, 49.74; H, 3.54; N, 38.66. **19**: mp 244–246°C; IR (KBr) ν 3471, 3327, 2212, 1671, 1619, 1597, 1426, 1376, 1318, 1141 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 11.08 (s, 1H, NH), 8.63 (s, 1H, H4), 7.54 (s, 2H, $NH_2$), 2.67 [s, 3H, NCOCH$_3$)], 2.11 (s, 3H, NCOCH$_3$); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): δ 169.1 [N(3)H*C*OCH$_3$], 166.9 [N(1)H*C*OCH$_3$], 159.4 (C6)*, 152.8 (C7a)*, 144.0 (C3), 141.9 (C4), 116.7 (CN), 103.3 (C3a), 88.3 (C5), 24.6 [N(1)HCO*C*H$_3$], 23.0 [N(3)HCO*C*H$_3$]; MS (ES): $[M + 1]^+$ 259.3, $[M + Na]^+$ 281.2, $[2M + Na]^+$ 539.5. Anal. Calcd. for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.54; found C, 50.98; H, 3.81; N, 32.38.

**Acetylation of 3,6-diamino-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (2).** A solution of compound **2** (100 mg, 0.53 mmol) in $Ac_2O$ (2.5 mL, 26.52 mmol, 70 equiv) was stirred at rt for 3 h. The mixture was cooled at 0°C, the solid was filtrated, washed with cold ethanol, and recrystallized to give *N*-(6-amino-5-cyano-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)acetamide (**20**) (100 mg, 82%) as a white solid: mp 246–249°C; IR (KBr) ν 3429, 3332, 3222, 3128, 3086, 2217, 1658, 1617, 1586, 1443, 1276 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 10.74 (s, 1H, N*H*COCH$_3$), 8.57 (s, 1H, H4), 7.08 (s, 2H, C6NH$_2$), 3.70 (s, 3H, NCH$_3$), 2.07 (s, 3H, NHCOC*H*$_3$); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 168.1 (CO), 158.3 (C6), 150.7 (C7a), 142.1 (C3), 140.0 (C4), 117.6 (CN), 100.3 (C3a), 86.4 (C5), 32.8 (NCH$_3$), 22.9 (CH$_3$); MS (ES) $[M + 1]^+$ 231.0; $[M + Na]^+$ 253.0. Anal. Calcd. for $C_{10}H_{10}N_6O.1/2H_2O$: C, 50.20; H, 4.63; N, 35.13; found C, 50.49; H, 4.61; N, 34.65.

**3,6-Diamino-4-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (3).** A solution of 2-amino-6-chloro-4-phenylpyridine-3,5-dicarbonitrile [11] (100 mg, 0.39 mmol) and hydrazine hydrate (80 μL, 1,57 mmol, 4.0 equiv) in DMF (4 mL, 5mL/mmol) was warmed at 153°C for 1 h until complete reaction (TLC analysis). The mixture was cooled, the solid formed and filtered, washed with water/ethanol, dried, and purified by column chromatography eluting with $CH_2Cl_2$/MeOH (4%) to give compound **3** (70 mg, 74%): mp 282–283°C; IR (KBr) ν 3498, 3334, 3230, 2931, 1725, 1629, 1571, 1540, 1445, 1269, 1223, 1077 $cm^{-1}$; $^1H$ NMR (DMSO, 300 MHz): δ 11.88 [s, 1H, N(1)H], 7.58–7.50 (m, 5H, aromatic), 6.79 [s, 2H, C(6)NH$_2$], 4.26 [s, 2H, C(3)NH$_2$]; $^{13}C$ NMR (DMSO, 75 MHz): δ 159.9 (C6), 153.1 (C4), 152.1 (C3), 148.9 (C7a), 134.7 (C1′), 130.3 (C4′), 129.4 [2C (C2′,C6′)], 128.9 [2C (C3′,C5′)], 118.0 (CN), 98.5 (C3a), 85.1 (C5); MS (ES): $[M + 1]^+$ 251.3. Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.58; found C, 62.21; H, 4.08; N, 33.58.

**Acetylation of 3,6-diamino-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (3)**

***Method A.*** A solution of compound **3** (100 mg, 0.4 mmol) in $Ac_2O$ (2.5 mL, 28 mmol, 70 equiv) was stirred at 0°C for 20 h. Then, the solid was filtered, washed with water/ethanol, and recrystallized from ethanol to give compound **21** (29 mg, 25%). **21**: mp 221–223°C; IR (KBr) ν 3471, 3316, 3194, 2212, 1720, 1621, 1590, 1575, 1430, 1382, 1291 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ.7.61–7.50 (m, 5H, Ph), 7.40 (s, 2H, $NH_2$), 4.82 (s, 2H, $NH_2$), 2.58 (s, 3H, OCCH$_3$); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 166.5 (N*C*OCH$_3$), 160.3 (C6)*, 152.7 (C7a)*, 151.5 (C4), 150.0 (C3), 132.9, 130.1, 129.0, 128.2 (aromatic, $C_6H_5$), 116.0 (CN), 101.3 (C3a), 87.6 (C5), 24.5 (NCO*C*H$_3$); MS (ES): $[M + 1]^+$ 293.2, $[M + Na]^+$ 315.2, $[2M + Na]^+$ 607.5. Anal. Calcd. for $C_{15}H_{12}N_6O.1/2H_2O$: C, 59.79; H, 4.35; N, 27.89; found C, 59.83; H, 4.50; N, 28.30.

***Method B.*** A solution of compound **3** (75 mg, 0.3 mmol) in $Ac_2O$ (2 mL) was refluxed for 6 h to give after column chromatography [hexane/ethyl acetate (6/4, 5/5, 4/6)] *N*-(6-acetamido-5-cyano-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-*N*-acetylacetamide (**22**) (35 mg, 30%) and *N*,*N*′-(5-cyano-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3,6-diyl)bis(*N*-acetylacetamide) (**23**) (50 mg, 40%). **22**: mp 183–185°C; IR (KBr) ν 3060, 3015, 2222, 1746, 1587, 1368, 1231, 1027 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz): δ 14.46 [s, 1H, N(1)H], 10.98 [s, 1H, C(3)N*H*COCH$_3$)], 7.55–7.34 [m, 5H, aromatic), 2.15 [C(3)NHCOC*H*$_3$)], 1.91 [s, 6H, 2xC(6)NCOCH$_3$]; $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): δ 171.6 [2x(C3)N*C*OCH$_3$], 169.5 [(C(6)N*C*OCH$_3$], 152.3 (C6), 151.2 (C7a)*, 150.9 (C3)*, 140.1 (C4), 132.4 (C1′), 129.9 (C4′), 128.6 [2C (C2′,C6′)], 128.1 [2C (C3′,C5′)], 115.4 (CN), 106.5 (C3a), 100.0 (C5), 25.5 [2xC(6)NCO*C*H$_3$], 23.1 [C(3)NCO*C*H$_3$]; MS (ES): $[M + 1]^+$ 377.2, $[M + Na]^+$ 399.2; $[2M + Na]^+$ 775.7. Anal. Calcd. for $C_{19}H_{16}N_6O_3$: C, 60.63; H, 4.28; N, 22.33; found C, 60.54; H, 4.39; N, 22.08. **23**: mp 137–139°C; IR (KBr) ν 3009, 2929, 2855, 2230, 1730, 1589, 1369, 1229, 1029 $cm^{-1}$; $^1H$ NMR (DMSO, 300 MHz) δ 14.93 [s, 1H, N(1)H], 7.60–7.43 (m, 5H, aromatic), 2.35 (s, 6H, 2xNCOCH$_3$), 1.95 (s, 6H, 2xNCOCH$_3$); MS (ES): $[M + 1]^+$ 419.2; $[M + Na]^+$ 441.2; $[2M + Na]^+$ 859.7. Anal. Calcd. for $C_{21}H_{18}N_6O$: C, 60.28; H, 4.34; N, 20.09; found C, 60.04; H, 4.18; N, 19.95.

**Reaction of 2-chloro-6-methoxy-4-phenylpyridine-3,5-dicarbonitrile (24) hydrazine hydrate.** A solution of compound **24** [12] (269 mg, 1 mmol) and hydrazine hydrate (0.1 mL, 2 mmol, 2 equiv) was refluxed in ethanol (20 mL) for 20 h until complete reaction (TLC analysis). The mixture was cooled at 0°C, water was added, and the solid was filtered, washed with water, and purified by chromatography eluting with $CH_2Cl_2$/MeOH (from 0.5 to 1%) to give compounds 4-phenyl-1,7-dihydrodipyrazolo[3,4-*b*:4′,3′-e]pyridine-3,5-diamine (**25**) (13 mg, 5%) and 3-amino-6-methoxy-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**4**) (95 mg, 58%): mp 248–250°C; IR (KBr) ν 3489, 3391, 3225, 3032, 2938, 2216, 1596, 1313, 1157 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 12.63 [s,

1H, N(1)H], 7.61–7.53 (m, 5H, Ph), 4.49 (s, 2H, $NH_2$), 4.01 (s, 3H, $OCH_3$); $^{13}C$ NMR (DMSO-$d_6$,75 MHz): δ 164.0 (C6), 153.4 (C4), 150.9 (C3)*, 149.3 (C7a)*, 133.8, 130.7, 129.6, 129.1 (aromatic, $C_6H_5$), 116.5 (CN), 100.3 (C3a), 88.2 (C5), 55.3 ($OCH_3$); MS (ES): [M + 1]+ 266.0, [M + Na]+ 288.0, [2M + Na]+ 553.3. Anal. Calcd. for $C_{14}H11N_5O$: C, 63.39; H, 4.18; N, 26.40; found C, 63.15; H, 4.41; N, 26.37. **25**: mp 328–330°C; IR (KBr) ν 3428, 3249, 3037, 2948, 2593, 1597, 1099 $cm^{-1}$; $^1H$ NMR (DMSO, 300 MHz): δ 11.67 (s, 2H, 2 NH), 7.63–7.46 (m, 5H, aromatic), 4.24 (s, 4H, 2 $NH_2$); $^{13}C$ NMR (DMSO, 75 MHz): δ 153.4 (2C, C7a, C8a), 148.1 (2C, C3, C5), 139.3 (C4), 133.4 (C1′), 129.3 (C4′), 129.3 [C, (C2′,C6′)], 128.8 [C, (C3′,C5′)], 101.5 (2C C3a, C4a); MS (ES): $[M + 1]^+$ 266.2. Anal. Calcd. for $C_{13}H_{11}N_7$: C, 58.86; H, 4.18; N, 36.96; found: C, 58.79; H, 4.36; N, 36.72.

**1-Acetyl-3-amino-6-methoxy-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (26).** A solution of **4** (80 mg, 0.3 mmol) in $Ac_2O$ (4 mL, 3.9 mmol, 13 equiv) was stirred at 0°C for 16 h and at rt for 4 h. Alter evaporation of the excess of $Ac_2O$, the crude was purified by column chromatography, eluting with $CH_2Cl_2$/MeOH 1% to afford compound **26** (63 mg, 84%): mp 236–238°C; IR (KBr) ν 3485, 3265, 3181, 2225, 1715, 1624, 1589, 1571, 1393, 1349, 1153 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 7.65–7.57 (m, 5H, Ph), 5.10 (s, 2H, $NH_2$), 4.10 (s, 3H, $OCH_3$), 2.69 (s, 3H, $NCOCH_3$); $^{13}C$ NMR (DMSO-$d_6$,75 MHz): δ 167.8, 164.9, 153.4, 151.0, 150.7, 132.7, 131.2, 129.8, 129.0 (aromatic, $C_6H_5$), 115.4 (CN), 104.8 (C3a), 92.5 (C5), 55.6 ($OCH_3$), 25.3 ($NCOCH_3$); MS (ES): $[M + 1]^+$ 308.3, $[M + Na]^+$ 370.2, $[2M + Na]^+$ 637.5. Anal. Calcd. for $C_{16}H_{13}N_5O.1/2H_2O$: C, 60.75; H, 4.46; N, 22.14; found: C, 60.59; H, 4.21; N, 22.07.

**Reaction of *N*-acetyl-*N*-(3,5-dicyano-6-methoxy-4-phenylpyridin-2-yl)acetamide (29) with hydrazine hydrate.** A solution of compound **29** (50 mg, 0.15 mmol) and hydrazine hydrate (20 μL, 0.22 mmol, 1.5 equiv) in DMF (5 mL) was refluxed (153°C) for 30 min until complete reaction. Then, the excess of DMF was removed, AcOEt was added, and washed with water. The organic phase was dried, filtered, and evaporated to give a solid that was submitted to chromatography eluting with (hexane/EtOAc, from 8/2 to 1/1) to give compounds **27** (23 mg, 61%), **30** [11] (2 mg, 6%), and **3** (10 mg, 27%).

**2,6-Diamino-4-phenylpyridine-3,5-dicarbonitrile (30).** In a 30-mL glass tube equipped with septa was placed a solution of 6-amino-2-chloro-4-phenylpyridine-3,5-dicarbonitrile (**32**) (0.382 g, 1.5 mmol) in 10 mL of DMF. The reaction mixture was stirred for 30 s before the irradiation to homogenize the solution and then exposed to MWI 250W at 180°C during 3 min. After completion showed by TLC (hexane/AcOEt, 3/2), the reaction mixture was diluted with water, and the precipitate was filtered and washed with water. The residue was purified by column chromatography ($CH_2Cl_2$/MeOH, 25/1 to 10/1, v/v) to yield product **30** (155 mg, 44%), which showed spectroscopic data in good accord with those reported in literature [11].

**6-Amino-2-chloro-4-phenylpyridine-3,5-dicarbonitrile (32).** To a solution of trimethylorthobenzoate (**31**) (1.82 g, 0.01 mol) in pyridine (5 mL) was added malononitrile (1.32 g, 0.02 mol, 2 equiv). The mixture was heated at 110°C for 7 h. After cooling, concentrated aqueous hydrochloric acid (10 mL) was added, and the mixture was heated at 100°C for 2.5 h. After cooling to rt, the mixture was diluted with water and filtered to afford compound **32** (1.0 g, 40%), which showed spectroscopic data in agreement with those reported in literature [11].

**3,6-Diamino-1-methyl-4-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5).** A mixture of 6-amino-2-chloro-4-phenylpyridine-3,5-dicarbonitrile (**32**) (254 mg, 1 mmol) and methylhydrazine (0.11 mL, 1.1 mmol, 1.1 equiv) in DMF (10 mL) was warmed at 153°C for 5 min. The mixture was cooled at rt; the solid was filtered and recrystallized from ethanol to give precursor **5** (211 mg, 80%): mp 279–281°C; IR (KBr) ν 3477, 3427, 3379, 3323, 3191, 2201, 1654, 1589, 1573, 1561, 1405, 1204 $cm^{-1}$; $^1H$ NMR (DMSO, 300 MHz): δ 7.58–7.48 (m, 5H, $C_6H_5$), 6.90 [s, 2H, C(6)$NH_2$], 4.36 [s, 2H, C(3)$NH_2$], 3.59 (s, 3H, $NCH_3$); $^{13}C$ NMR (DMSO, 75 MHz): δ 158.2 (C6), 151.7 (C4), 150.5 (C7a), 147.5 (C3), 133.8 (C1′), 129.7 (C4′), 128.8 [2C (C2′,C6′)], 128.2 [2C (C3′,C5′)], 117.3 (CN), 98.0 (C3a), 84.3 (C5), 32.4 ($NCH_3$); MS (ES): $[2M]^+$ 528.7, $[2M - 1]^+$ 527.7. Anal. Calcd. for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80; found C, 63.60; H, 4.65; N, 32.04.

***N*-(6-Amino-5-cyano-1-methyl-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)acetamide (33).** A solution of compound **5** (100 mg, 0.38 mmol) in $Ac_2O$ (2.5 mL, 26.52 mmol, 70 equiv) was stirred at rt for 8 h. The crude was cooled at 0°C, and the precipitate was filtered, washed with EtOH, and submitted to chromatography (AcOEt) to give compound **33** (24 mg, 21%): mp 249–251°C; IR (KBr) ν 3489, 3414, 3330, 3263, 3052, 2218, 1664, 1625, 1590, 1571, 1518, 1444, 1399, 1379, 1259, 1196 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 9.49 (s, 1H, NH), 7.58–7.48 (m, 5H, $C_6H_5$), 7.12 (s, 2H, $NH_2$), 3.78 (s, 3H, $NCH_3$), 1.42 (s, 3H, $COCH_3$); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 169.1 ($NCOCH_3$), 159.8 (C6), 152.7 (C4), 151.7 (C7a), 139.0 (C3), 133.9 (C1′), 129.9 (C4′), 129.3 (2C, C2′,C6′), 128.6 (2C, C3′,C5′), 117.5 (CN), 102.9 (C3a), 88.3 (C5), 33.8 ($NCH_3$), 22.51 ($NCOCH_3$); MS (ES): $[M + 1]^+$ 307.1. Anal. Calcd. for $C_{14}H_{12}N_6$: C, 62.74; H, 4.61; N, 27.44; found C, 62.96; H, 4.68; N, 27.31.

**3,6-Diamino-2-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (6).** A solution of precursor **34** [8] (100 mg, 0.56 mmol) and *N*-phenylhydrazine (82 μL, 0.84 mmol, 1.5 equiv) in DMF (2 mL, 5mL/mmol) was warmed at 153°C for 1 h until complete reaction (TLC analysis). The mixture was cooled at 0°C; the solid was recovered and submitted to chromatography eluting with $CH_2Cl_2$/MeOH (from 0.5 to 2%) to give product **6** (91 mg, 70%): mp 306–308°C; IR (KBr) ν 3467, 3353, 3299, 3154, 2211, 1620, 1596, 1455, 1343 $cm^{-1}$; $^1H$ NMR (DMSO, 300 MHz): δ 8.36 [s, 1H, H4), 7.57–7.37 (m, 5H, aromatic), 6.95 [s, 2H, (C3)$NH_2$], 6.47 [s, 2H, (C6)$NH_2$]; $^{13}C$ NMR (DMSO, 75 MHz): δ 157.9 (C6)*, 156.5 (C7a)*, 143.0 (C3), 140.0 (C4), 138.2 (C1′), 129.3 (C3′,C5′), 127.4 (C4′), 123.9 (C2′,C6′), 118.5 (CN), 96.9 (C3a), 84.6 (C5); MS (CI): *m/z* 251 [$M^+$, 100], 234 [$M^+$-$NH_2$, 8], 92 (14), 77(21). Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.58; found C, 62.10; H,4.32; N, 33.31.

***N*,*N*′-(5-Cyano-2-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine-3,6-diyl)diacetamide (35).** A solution of compound **6** (100 mg, 0.4 mmol) in $Ac_2O$ (2.5 mL, 28 mmol, 70 equiv) was heated at 144°C for 40 min. The mixture was cooled at rt, the solvent was removed under vacuo, and the crude submitted to chromatography ($CH_2Cl_2$/MeOH from 0.1 to 2%) to give product **35** (28 mg, 21%): mp 229–230°C; IR (KBr) ν 3467, 3353, 3299, 3154, 2211, 1619, 1596, 1454, 1343 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ 10.82 (s, 1H, N*H*$COCH_3$), 10.68 (s, 1H, N*H*$COCH_3$), 8.84 (s, 1H, H4), 7.69–7.57 (m, 5 H, aromatic), 2.12 (s, 3H, NHCOC*H*$_3$), 2.08 (s, 3H, NHCOC*H*$_3$); $^{13}C$ NMR

(DMSO-$d_6$, 75 MHz): δ 169.8 (N*C*OCH$_3$), 169.4 (NC*O*CH$_3$), 154.6 (C6)*, 151.4 (C7a), 141.4 (C4), 137.8 (C1′), 131.8 (C3), 129.5 (2C, C3′,5′), 129.4 (C4′), 124.8 (2C, C2′,C6′), 116.7 (CN), 106.0 (C3a), 100.0 (C5), 22.9 (NCO*C*H$_3$), 22.7 (NCO*C*H$_3$); MS (ES): $[M + 1]^+$ 335.2, $[M + Na]^+$ 357.2, $[2M + Na]^+$ 691.5. Anal. Calcd for $C_{17}H_{14}N_6O$: C, 61.07; H, 4.22; N, 25.14; found C, 60.85; H, 4.36; N, 24.98.

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## REFERENCES AND NOTES

[1] Beutner, G. L.; Kuethe, J. T.; Kim, M. M.; Yasuda, N. J Org Chem 2009, 74, 789.

[2] Dai, Y.; Hartandi, K.; Soni, N. B.; Pease, L. J.; Reuter, D. R.; Olson, A. M.; Osterling, D. J.; Doktor, S. Z.; Albert, D. H.; Bouska, J. J.; Glaser, K. B.; Marcotte, P. A.; Stewart, K. D.; Davidsen, S. K.; Michaelides, M. R. Bioorg Med Chem Lett 2008, 18, 386.

[3] Witherington, J.; Bordas, V.; Garland, S. L.; Hickey, D. M. B.; Ife, R. J.; Liddle, J.; Saunders, M.; Smith, D. G.; Ward, R. W. Bioorg Med Chem Lett 2003, 13, 1577.

[4] Chioua, M.; Samadi, A.; Soriano, E.; Lozach, O.; Meijer, L.; Marco-Contelles, J. Bioorg Med Chem Lett 2009, 19, 4566.

[5] Pevarello, P.; Fancelli, D.; Vulpetti, A.; Amici, R.; Villa, M.; Pittalà, V.; Vianello, P.; Cameron, A.; Ciomei, M.; Mercurio, C.; Bischoff, J. R.; Roletto, F.; Varasi, M.; Brasca, M. G. Bioorg Med Chem Lett 2006, 16, 1084.

[6] Pevarello, P.; Brasca, M. G.; Amici, R.; Orsini, P.; Traquandi, G.; Corti, L.; Piutti, C.; Sanssona, P.; Villa, M.; Pierce, B. S.; Pulici, M.; Giordano, P.; Martina, K.; Fritzen, E. L.; Nugent, R. A.; Casale, E.; Cameron, A.; Ciomei, M.; Roletto, F.; Isacchi, A.; Fogliatto, G. P.; Pesenti, E.; Pastori, W.; Marsiglio, A.; Leach, K. L.; Clare, P. M.; Fiorentini, F.; Varasi, M.; Vulpetti, A.; Warpehoski, M. A. J Med Chem 2004, 47, 3367.

[7] Ortega, M. A.; Montoya, M. E.; Zarranz, B.; Jaso, A.; Aldana, I.; Leclerc, S.; Meijer, L.; Monge, A. Bioorg Med Chem 2002, 10, 2177.

[8] Cottis, S. G.; Clarke, P. B.; Tieckelmann, H. J Heterocycl Chem 1965, 2, 192.

[9] Braña, M. F.; Cacho, M.; García, M. L.; Mortal, E. P.; López, B.; de Pascual-Teresa, B.; Ramos, A.; Linares, F.; Muñoz-Mingarro, D.; Lozach, O.; Meijer, L. J Med Chem 2005, 48, 6843.

[10] Londregan, A. T.; Storer, G.; Wooten, C.; Yang, X.; Warmus, J. Tetrahedron Lett 2009, 50, 1986.

[11] Murray, T. J.; Zimmerman, S. C.; Kolotuchin, S. V. Tetrahedron 1995, 51, 635.

[12] Abdelrazek, F. M.; Metwally, N. H.; Sobhy, N. A. Afinidad 2006, 63, 149.

[13] Quintela, J. M.; Soto, J. L. Anal Quim C 1983, 79, 368.

[14] Goswami, S.; Das, N. K. J Heterocycl Chem 2009, 46, 324.

[15] 6-Amino-2-chloro-4-phenylpyridine-3,5-dicarbonitrile (**32**) can also be synthesized from 2-amino-3,5-dicyano-5-hydroxy-4-phenylpyridine: Peinador, C.; Veiga, C. M.; Vilar, J.; Quintela, J. M. Heterocycles 1994, 38, 1299.

[16] Schmidt, P.; Eichenberger, M.; Wilhelm, M.; Druey, J. Helv Chim Acta 1959, 42, 763.

[17] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; González, C.; Pople, J. A. Gaussian 03, Revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.

[18] Lee, C.; Yang, W.; Parr, R. Phys Rev B 1988, 37, 785.

[19] Amovilli, C.; Barone, V.; Cammi, R.; Cances, E.; Cossi, M.; Mennucci, B.; Pomelli, C. S.; Tomasi, J. Adv Quantum Chem 1998, 32, 227.

[20] Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO Version 3.1; University of Wisconsin: Madison, WI, 1998.

[21] Zapotoczny, S.; Danel, A.; Sterzel, M. T.; Pilch, M. J Phys Chem A 2007, 111, 5408.

[22] Quiroga, J.; Cruz, S.; Insuasty, B.; Abonia, R.; Cobo, J.; Sánchez, A.; Nogueras, M.; Low, J. N. J Heterocycl Chem 2001, 38, 53.

[23] Duca, J. S.; Madison, V. S. Biopolymers 2005, 80, 312.

[24] Misra, R. N.; Rawlins, D. B.; Xiao, H. Y.; Shan, W.; Bursuker, I.; Kellar, K. A.; Mulheron, J. G.; Sack, J. S.; Tokarski, J. S.; Kimball, S. D.; Webster, K. R. Bioorg Med Chem Lett 2003, 13, 1133.

[25] Shestopalov, A. M.; Yakubov, A. P.; Tsyganov, D. V.; Emel'yanova, Y. M.; Nesterov, V. N. Chem Heterocycl Compd 2002, 38, 1180.

[26] Gogoi, S.; Zhao, C. G. Tetrahedron Lett 2009, 50, 2252.

[27] Vasuki, G.; Kumaravel, K. Tetrahedron Lett 2008, 49, 5636.

[28] Luo, G.; Chen, L.; Dubowchik, G. J Org Chem 2006, 71, 5392.

[29] The inhibition of a panel of protein kinases by the new compounds synthesized here is being evaluated by Dr. Francisco Wandosell (CBM, CSIC, Madrid, Spain), and will be reported elsewhere.

# An Efficient and Highly Selective Method for the Synthesis of Cryptotackiene Derivatives Catalyzed by Iodine



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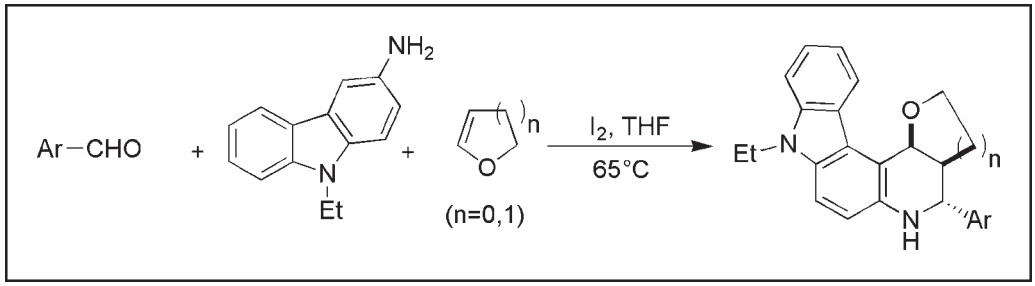


A mild, efficient and highly selective approach to the synthesis of cryptotackiene derivatives via three-component reactions of 3-amino-9-ethylcarbazole and aromatic aldehydes with electron-rich alkenes, such as 2,3-dihydrofuran, or 3,4-dihydro-2*H*-pyran catalyzed by iodine in THF is reported. It is worth to note that only *trans*-products were obtained with high selectivity in good to high yields, which confirmed by X-ray diffraction analysis.

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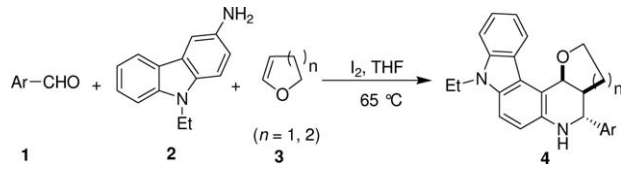
## INTRODUCTION

Cryptotackiene, a linear 5-*N*-methyl-5*H*-indolo[2,3-*b*]quinoline alkaloid isolated from the West African shrub *Cryptolepis sanguinolenta*, has been reported to exhibit strong antiplasmodial activity [1]. A few of cryptotackiene derivatives are found to display strong antimicrobial and cytotoxic activities *in vitro* and significant antitumor properties *in vivo* [2]. In addition, its isomeric moiety, named ellipticine (5,11-dimethyl-6*H*-indolo[2,3-*g*]isoquinoline), also exhibits promising results in the treatment of osteolytic breast cancer metastases, brain tumors, kidney sarcoma, and myeloblastic leukemia [3]. More recent studies have also indicated that they possessed a good activity against HIV [4]. Accordingly, a wide variety of strategies [5–7] have been reported to construct these aforementioned active moieties for their important biological activities.

The imino Diels–Alder [4+2] cyclo-addition reaction presents a powerful synthetic tool to the construction of the polycyclic cryptotackiene ring systems. Of which the imines derived from aromatic amines and aldehyde, act as heterodienes and undergo Diels–Alder reaction with various dienophiles in the presence of acidic catalysts [8–11]. The multicomponent reactions (MCRs) involving 3-amino-9-ethylcarbazole, which reported by Gaddam and Nagarajan, represent an effective synthetic pathway toward cryptotackiene derivatives [12]. However, the known methods suffer from some disadvantages. For instance, these procedures often require harsh reaction conditions, multistep reaction, metal catalysts, expensive reagents or no stereo-selectivity. Especially for the stereo-selectivity, they always give *cis*- and *trans*-isomers using 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran as starting materials.

As an inexpensive, efficient, and environmentally benign catalyst, iodine has been used extensively in organic synthesis. More and more organic transformations [13] promoted by molecular iodine have been documented in recent years. In our previous paper, we have synthesized series of benzo[*f*]quinoline derivatives via three-component reactions of aromatic aldehyde, naphthalen-2-amine, and various ketones [14] induced by iodine. As a continuation of our research devoted to this iodine-catalyzed reaction, 3-amino-9-ethylcarbazole was selected as similar amine to react with aromatic aldehyde, and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran for the challenge of its stereo-selectivity. It was noteworthy that only *trans*-4-aryl-8-ethyl-3,3*a*,4,5,8,12*d*-hexahydro-2*H*-furo[3,2-*c*]indolo[3,2-*f*]quinoline or *trans*-5-aryl- 9-

**Scheme 1.** Reaction of **1**, **2**, and **3**.




ethyl-2,3,4,4*a*,5,6,9,13*d*-hexahydropyrano[3,2-*c*]indolo [3,2-*f*]quinoline derivatives were obtained with high selectivity in good to high yields.

## RESULTS AND DISCUSSION

Treatment of aromatic aldehyde **1**, 3-amino-9-ethylcarbazole **2**, and 2,3-dihydrofuran **3** in THF in the presence of 5 mol % iodine at reflux condition afforded the corresponding *trans*-4-aryl-8-ethyl-3,3*a*,4,5,8,12*d*-hexahydro-2*H*-furo[3,2-*c*]indolo[3,2-*f*]quinoline derivatives **4** in good to high yields with high stereo-selectivity (Scheme 1). Obviously, these results were different from *trans*- to *cis*-isomers catalyzed by $InCl_3$ in ionic liquid [12].

In our initial study, the reaction of 4-nitrobenzaldehyde **1d**, 3-amino-9-ethylcarbazole **2**, and 2,3-dihydrofuran **3** was used as a model reaction to optimize the reaction conditions. The reaction was first carried out in THF in the absence of $I_2$. It was found that no reaction occurred at room temperature or reflux condition (Table 1, entries 1 and 2). Similar reactions were attempted in the presence of 5, 10, and 20 mol % of $I_2$. The results from Table 1 (entries 5-7) show that 5 mol % $I_2$ at reflux in THF is sufficient to initiate the reaction. Higher loading of the catalyst had no significant influence on the reaction yield. To find the optimum reaction temperature, the reaction was carried out with 5 mol % of $I_2$ at room temperature, 50°C and reflux temperature, resulting in the isolation of **4d** in trace amount, 68% and 88% yields (Table 1, entries 3-5), respectively. Thus, 5 mol % of $I_2$ and a reaction temperature at reflux were optimal conditions. In addition, $CH_3CN$, benzene, DMF, and $CHCl_3$ (Table 1, entries 8-11) were also tested as the solvents. In these cases, product **4d** was formed in slightly lower yields (Table 1, entries 8-11).

According to the optimized conditions, various aromatic aldehydes **1** were then subjected to react with 3-amino-9-ethylcarbazole **2** and **3** to generate a library of **4** (Table 2, entries 1 to 8). For aldehyde **1**, the yields of **4** were not sensitive to the electronic properties of the aromatic ring in the presence of electron-withdrawing groups (such as halide and nitro) or electron-donating groups (such as alkoxyl group) (Table 2). The *trans*-structure of **4g** was further confirmed by X-ray diffraction analysis, and the crystal structure was shown in Figure 1. The 2,3-dihydrofuran could be expended to other electron-rich alkenes, such as 3,4-dihydro-2*H*-pyran was also chosen as reactant to react with **1** and **2**, giving corresponding *trans*-5-aryl-9-ethyl-2,3,4,4*a*,5,6,9,13*d*-hexahydropyrano[3,2-*c*]indolo[3,2-*f*]quinoline with good yields and stereo-selectivity (Table 2, entries 9 to 12).

According to the literatures [15], we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was tentatively proposed as shown in Scheme 2. The Schiff base **I** may be formed first by the reaction of aromatic aldehyde and 3-amino-9-ethylcarbazole. Then imino-Diels–Alder reaction between the iodine-activated Schiff base **II** and 2,3-dihydrofuran takes place

**Table 1**

Synthetic results of **4d** under different reaction conditions.[a]

| Entry | Temp. (°C) | Amount (mol %) | Solvent | Time (h) | Yields (%)[b] |
|---|---|---|---|---|---|
| 1 | r.t. | 0 | THF | 24 | 0 |
| 2 | Reflux | 0 | THF | 24 | 0 |
| 3 | r.t. | 5 | THF | 24 | trace |
| 4 | 50 | 5 | THF | 24 | 68 |
| 5 | Reflux | 5 | THF | 19 | 88 |
| 6 | Reflux | 10 | THF | 19 | 88 |
| 7 | Reflux | 20 | THF | 19 | 83 |
| 8 | Reflux | 5 | $CH_3CN$ | 20 | 72 |
| 9 | Reflux | 5 | Benzene | 24 | 82 |
| 10 | 80 | 5 | DMF | 15 | 75 |
| 11 | Reflux | 5 | $CHCl_3$ | 19 | 76 |

[a] Reagents and conditions: 4-Nitrobenzaldehyde **1d** (0.302 g, 2 mmol), **2** (0.420 g, 2 mmol), **3** 2,3-dihydrofuran (0.210 g, 3 mmol), solvent (10 mL).
[b] Isolated yields.

**Table 2**

Synthetic results of **4** catalyzed by iodine in THF.[a]

| Entry | Ar | *n* | Products | Time (h) | Isolated yields (%) |
|---|---|---|---|---|---|
| 1 | 4-$ClC_6H_4$ | 1 | **4a** | 19 | 85 |
| 2 | 4-$BrC_6H_4$ | 1 | **4b** | 18 | 85 |
| 3 | 4-$MeOC_6H_4$ | 1 | **4c** | 12 | 80 |
| 4 | 4-$NO_2C_6H_4$ | 1 | **4d** | 20 | 88 |
| 5 | 3-$ClC_6H_4$ | 1 | **4e** | 20 | 80 |
| 6 | 2,4-$Cl_2C_6H_3$ | 1 | **4f** | 19 | 78 |
| 7 | 3,4-$Cl_2C_6H_3$ | 1 | **4g** | 20 | 70 |
| 8 | 3,5-$(MeO)_2C_6H_3$ | 1 | **4h** | 18 | 82 |
| 9 | 4-$FC_6H_4$ | 2 | **4i** | 20 | 78 |
| 10 | 4-$CH_3C_6H_4$ | 2 | **4j** | 19 | 75 |
| 11 | 3,4-$Cl_2C_6H_3$ | 2 | **4k** | 20 | 82 |
| 12 | 4-$MeOC_6H_4$ | 2 | **4l** | 19 | 80 |

[a] Reagents and conditions: **1** (2 mmol), **2** (0.420 g, 2 mmol), **3** (3 mmol), $I_2$ (0.026 g, 0.1 mmol), THF (10 mL).

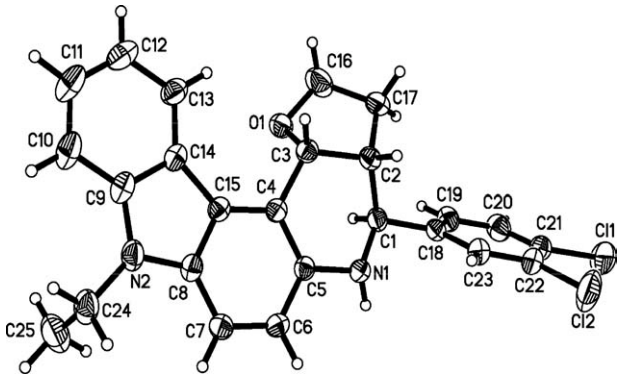



**Figure 1.** Crystal structure of product **4g** indicating the *trans*-structure.

selectively to form intermediate **III** for its stability, followed by isomerization to give the final product **4**.

## CONCLUSIONS

In conclusion, we found a mild and efficient method for the synthesis of *trans*-cryptotackiene derivatives via three-component reactions of aromatic aldehyde, 3-amino-9-ethylcarbazole, and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran catalyzed by iodine. The features of this procedure are mild reaction conditions, good to high yields, operational simplicity, and high stereoselectivity.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. $^1$H NMR spectra were obtained from solution in DMSO-$d_6$ with $Me_4Si$ as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using Bruker-micro TOF-Q-MS analyzer.

**General procedure for the syntheses of *trans*-4-aryl-8-ethyl-3,3*a*,4,5,8,12*d*-hexahydro-2*H*-furo[3,2-*c*]indolo[3,2-*f*]quinoline or *trans*-5-aryl-9-ethyl-2,3,4,4*a*,5,6,9,13*d*-hexahydropyrano[3,2-*c*]indolo[3,2-*f*]quinoline derivatives 4.** A dry 50 mL flask was charged with aromatic aldehyde (2.0 mmol), 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran (3.0 mmol), 3-amino-9-ethylcarbazole (0.420 g, 2.0 mmol), $I_2$ (0.026 g, 0.1 mmol), and THF (10 mL). The reaction mixture was stirred at reflux condition for 12–20 h, and then cooled to room temperature. The generated yellow solid was filtered off. The crude yellow products were washed with ethanol and purified by recrystallization from DMF and water, followed by being dried at 50°C several hours at vacuum to give **4**.

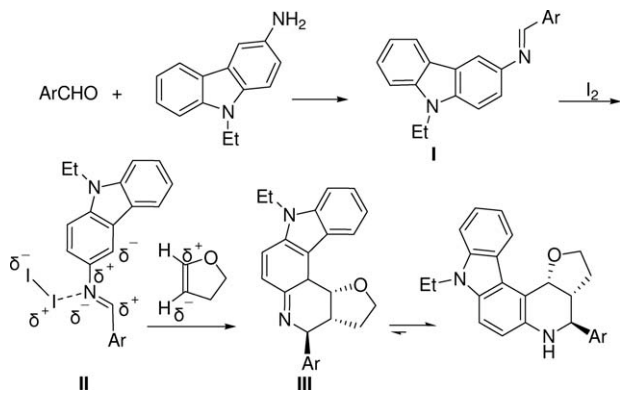
***trans*-4-(4-Chlorophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4a).** This compound was obtained as yellow crystals (0.683 g, 85%), m.p.: 223–225°C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3371, 3047, 2974, 2871, 1593, 1504, 1487, 1455, 1410, 1380, 1327, 1285, 1266, 1209, 1186, 1154, 1090, 1045, 1012, 926, 828, 802, 751. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 1.56–1.62 (m, 1H, CH), 1.98–2.09 (m, 1H, CH), 2.37–2.43 (m, 1H, CH), 3.72 (d, $J$ = 11.2 Hz, 1H, CH), 3.85–3.91 (m, 1H, CH), 4.00 (q, $J$ = 4.0 Hz, 1H, CH), 4.39 (q, $J$ = 7.2 Hz, 2H, $NCH_2$), 5.03 (d, $J$ = 5.2 Hz, 1H, CH), 6.01 (s, 1H, NH), 6.98 (d, $J$ = 8.8 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.37–7.41 (m, 2H, ArH), 7.47 (d, $J$ = 8.4 Hz, 2H, ArH), 7.52 (d, $J$ = 8.4 Hz, 1H, ArH), 7.56 (d, $J$ = 8.4 Hz, 2H, ArH), 8.15 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m*/*z*): Calcd. for $C_{25}H_{23}ClON_2Na$ (M + $Na^+$) 425.1397, found 425.1381.

***trans*-4-(4-Bromophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4b).** This compound was obtained as yellow crystals (0.758 g, 85%), m.p.: 227–230°C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3349, 2972, 2858, 1623, 1590, 1502, 1457,1406, 1382, 1327, 1285, 1266, 1210, 1184, 1152, 1092, 1069, 1041, 1010, 925, 828, 802, 743. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.56–1.63 (m, 1H, CH), 1.99–2.06 (m, 1H, CH), 2.37–2.43 (m, 1H, CH), 3.71 (d, $J$ = 11.2 Hz, 1H, CH), 3.86–4.03 (m, 1H, CH), 4.01 (q, $J$ = 4.0 Hz, 1H, CH), 4.39 (q, $J$ = 14.0 Hz, 2H, $NCH_2$), 5.03 (d, $J$ = 5.2 Hz, 1H, CH), 6.01 (s, 1H, NH), 6.98 (d, $J$ = 8.8 Hz, 1H, ArH), 7.10–7.14 (m, 1H, ArH), 7.37–7.42 (m, 2H, ArH), 7.50–7.53 (m, 3H, ArH), 7.61 (d, $J$ = 8.4 Hz, 2H, ArH), 8.14 (d, $J$ = 7.6 Hz, 1H, ArH). HRMS (ESI, *m*/*z*): Calcd. for $C_{25}H_{23}BrN_2ONa$ (M + $Na^+$) 469.0891, found 469.0888.

***trans*-8-Ethyl-4-(4-methoxyphenyl)-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4c).** This compound was obtained as yellow crystals (0.611 g, 80%), m.p.: 166–167°C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3350, 3042, 2929, 2836, 1604, 1509, 1380, 1351, 1325, 1302, 1285, 1267, 1248, 1171, 1153, 1109, 1093, 1046, 1025, 972, 924, 887, 834, 806, 782, 742. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.26 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 1.59–1.62 (m, 1H, CH), 1.98–2.07 (m, 1H, CH), 2.37–2.42 (m, 1H, CH), 3.78 (d, $J$ = 3.2 Hz 1H, CH), 3.86 (m, 3H, $CH_3O$), 3.98–3.99 (m, 1H, CH), 4.38 (q, 2H, $NCH_2$), 5.02 (d, $J$ = 4.8 Hz, 1H, CH), 5.90 (s, 1H, NH), 6.96–7.00 (m, 3H, ArH), 7.10–7.14 (m, 1H, ArH), 7.36–7.40 (m, 2H, ArH), 7.44 (d, $J$ = 8.4 Hz, 2H, ArH), 7.51 (d, $J$ = 8.4 Hz, 1H, ArH), 8.14 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m*/*z*): Calcd. for $C_{26}H_{27}N_2O_2$ (M + $H^+$) 399.2067, found 399.2073.

***trans*-8-Ethyl-4-(4-nitrophenyl)-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4d).** This compound was obtained as yellow crystals (0.727 g, 88%), m.p.: 253–254°C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3367, 2976, 2932, 2845, 1668, 1624, 1600, 1515, 1459, 1382, 1344, 1287, 1267, 1209, 1185,

**Scheme 2.** Possible mechanism for the formation of products **4**.



1154, 1092, 1047, 1012, 930, 860, 796, 741. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 1.57–1.63 (m, 1H, CH), 2.01–2.06 (m, 1H, CH), 2.43–2.46 (m, 1H, CH), 3.87–3.93 (m, 2H, $CH_2$), 4.04 (q, 1H, CH), 4.40(q, $J$ = 7.2 Hz, 2H, $NCH_2$), 5.06 (d, $J$ = 5.2 Hz, 1H, CH), 6.17 (s, 1H, NH), 6.99 (d, $J$ = 8.8 Hz, 1H, ArH), 7.11–7.15 (m, 1H, ArH), 7.37–7.44 (m, 2H, ArH), 7.53 (d, $J$ = 8.4 Hz, 1H, ArH), 7.84 (d, $J$ = 8.8 Hz, 2H, ArH), 8.15 (d, $J$ = 7.6 Hz, 1H, ArH), 8.27 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{23}BrN_2ONa$ (M + $Na^+$) 436.1637, found 4636.1634.

***trans-4-(3-Chlorophenyl)-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4e).*** This compound was obtained as yellow crystals (0.643 g, 80%), m.p.: 194–196°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3375, 3048, 2968, 2929, 2856, 1597, 1503, 1471, 1381, 1329, 1269, 1206, 1152, 1091, 1041, 890, 798, 742. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 1.60–1.65 (m, 1H, CH), 2.03–2.08 (m, 1H, CH), 2.41–2.47 (m, 1H, CH), 3.74 (d, $J$ = 11.2 Hz, 1H, CH), 3.88–3.90 (m, 1H, CH), 4.02 (q, 1H, CH), 4.39 (q, $J$ = 7.2 Hz, 2H, $NCH_2$), 5.03 (d, $J$ = 5.2 Hz, 1H, CH), 6.08 (s, 1H, NH), 6.98 (d, $J$ = 8.8 Hz, 1H, ArH), 7.10–7.14 (m, 1H, ArH), 7.37–7.47 (m, 5H, ArH), 7.52 (d, $J$ = 8.0 Hz, 2H, ArH), 7.62 (s, 1H, ArH), 8.14 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{24}ClN_2O$ (M + $H^+$) 403.1572, found 403.1582.

***trans-4-(2,4-Dichlorophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4f).*** This compound was obtained as yellow crystals (0.680 g, 78%), m.p.: 213–215°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3053, 2970, 2885, 1588, 1503, 1470, 1452, 1383, 1325, 1285, 1266, 1209, 1152, 1095, 1046, 925, 867, 823, 793, 735. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.55–1.61 (m, 1H, CH), 2.09–2.14 (m, 1H, CH), 3.94–4.00 (m, 2H, $CH_2$), 4.29 (d, $J$ = 11.2 Hz, 1H, CH), 4.39 (q, $J$ = 7.2 Hz, 2H, $NCH_2$), 5.07 (d, $J$ = 8.8 Hz, 1H, CH), 6.06 (s, 1H, NH), 6.96 (d, $J$ = 8.8 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.37–7.44 (m, 2H, ArH), 7.52–7.55 (m, 2H, ArH), 7.70 (d, $J$ = 2.0 Hz, 1H, ArH), 7.76 (d, $J$ = 8.4 Hz, 1H, ArH), 8.15 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{23}Cl_2N_2O$ (M + $H^+$) 437.1182, found 437.1180.

***trans-4-(3,4-Dichlorophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4g).*** This compound was obtained as yellow crystals (0.611 g, 70%), m.p.: 227–229°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3053, 2970, 2885, 1588, 1503, 1470, 1452, 1383, 1325, 1285, 1266, 1209, 1152, 1095, 1046, 925, 867, 823, 793, 735. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 1.59–1.63 (m, 1H, CH), 2.04–2.09 (m, 1H, CH), 2.41–2.47 (m, 1H, CH), 3.75 (d, $J$ = 11.2 Hz, 1H, CH), 3.89–3.92 (m, 1H, CH), 4.01 (q, 1H, CH), 4.39 (q, $J$ = 14.0 Hz, 2H, $NCH_2$), 5.03 (d, $J$ = 4.8 Hz, 1H, CH), 6.09 (s, 1H, NH), 6.96 (d, $J$ = 8.4 Hz, 1H, ArH), 7.12 (t, $J$ = 7.6 Hz, 1H, ArH), 7.37–7.43 (m, 2H, ArH), 7.52–7.57 (m, 2H, ArH), 7.68 (d, $J$ = 8.4 Hz, 1H, ArH), 7.84 (d, $J$ = 2.0 Hz, 1H, ArH), 8.14 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{23}Cl_2N_2O$ (M + $H^+$) 437.1182, found 437.1190.

***trans-4-(3,5-Dimethoxyphenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4h).*** This compound was obtained as yellow crystals (0.702 g, 82%), m.p.: 229–231°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3352, 3056, 2973, 2875, 1592, 1506, 1461, 1402, 1384, 1335, 1269, 1213, 1153, 1095, 1043, 1028, 946, 893, 835, 793, 740. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.27 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.68–1.74 (m, 1H, CH), 2.02–2.11 (m, 1H, CH), 2.41–2.47 (m, 1H, CH), 3.65 (d, $J$ = 11.2 Hz, 1H, CH), 3.78 (s, 6H, $2CH_3O$), 3.88–3.92 (m, 1H, CH), 3.99–4.04 (m, 1H, CH), 4.39 (q, $J$ = 6.8 Hz, 2H, $NCH_2$), 5.02 (d, $J$ = 5.2 Hz, 1H, CH), 5.97 (s, 1H, NH), 6.49 (s, 1H, ArH), 6.72 (d, $J$ = 1.6 Hz, 2H, ArH), 7.00 (d, $J$ = 8.8 Hz, 1H, ArH), 7.10–7.14 (m,1H, ArH), 7.36–7.41 (m, 2H, ArH), 7.52 (d, $J$ = 8.4 Hz, 1H, ArH), 8.14 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{27}H_{29}N_2O_3$ (M + $H^+$) 429.2173, found 429.2175.

***trans-9-Ethyl-5-(4-fulorophenyl)-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4i).*** This compound was obtained as yellow crystals (0.624g, 78%), m.p.: 217–218°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3374, 3049, 2951, 2928, 2894,2851, 2832, 1623, 1601, 1505, 1469, 1454, 1379, 1365, 1348, 1326, 1285, 1274, 1254, 1215, 1153, 1076, 1058,1042, 1011, 903, 849, 801, 748. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.25 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.32 (d, $J$ = 10.8 Hz, 2H, $CH_2$), 1.75–1.87 (m, 2H, $CH_2$), 2.01 (d, $J$ = 11.2 Hz, 1H, CH), 3.87–3.93 (m, 1H, CH), 4.05–4.07 (m, 1H, CH), 4.36 (q, $J$ = 6.8 Hz, 2H, $NCH_2$), 4.64 (d, $J$ = 11.6 Hz, 1H, CH), 5.06 (d, $J$ = 3.2 Hz, 1H, CH), 5.85 (s, 1H, NH), 6.86 (d, $J$ = 8.8 Hz, 1H, ArH), 7.11–7.15 (m, 1H, ArH), 7.21–7.26 (m, 2H, ArH), 7.35–7.40 (m,2H, ArH), 7.50–7.58 (m, 3H, ArH), 7.92 (d, $J$ = 7.6 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{26}FN_2O$ (M + $H^+$) 401.2029, found 401.2035.

***trans-9-Ethyl-5-(4-methylphenyl)-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4j).*** This compound was obtained as yellow crystals (0.594 g, 75%), m.p.: 206–207°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3369, 3044, 3019, 2976, 2956, 2928, 2893, 2829, 2851, 1600, 1503, 1457, 1379, 1365, 1346, 1326, 1284, 1272, 1255, 1213, 1194, 1152, 1077, 1056, 1042, 1020, 902, 830, 800, 749. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.25 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.35 (d, $J$ = 14 Hz, 2H, $CH_2$), 1.74–1.85 (m, 2H, $CH_2$), 2.00–2.03 (m, 1H, CH), 2.34 (s, 3H, $CH_3$), 3.87–3.92 (m, 1H, CH), 4.04–4.07 (m, 1H, CH), 4.35–4.41 (m, 2H, $NCH_2$), 4.58 (d, $J$ = 11.6 Hz, 1H, CH), 5.05 (s, 1H, CH), 5.77 (s, 1H, NH), 6.86 (d, $J$ = 8.8 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.22 (d, $J$ = 7.6 Hz, 2H, ArH), 7.34–7.43 (m,1H, ArH), 7.50 (d, $J$ = 8.0 Hz, 1H, ArH), 7.92 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{27}H_{29}N_2O$ (M + $H^+$) 397.2280, found 397.2287.

***trans-5-(3,4-Dichlorophenyl)-9-ethyl-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4k).*** This compound was obtained as yellow crystals (0.738 g, 82%), m.p.: 216–217°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3344, 3066, 2970, 2932, 2893, 2843, 1592, 1503, 1460, 1404, 1380, 1365, 1328, 1287, 1273, 1252, 1233, 1216, 1195, 1128, 1082, 1057, 1042, 1026, 1011, 894, 835, 794, 740, 634. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.28 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.33–1.35 (m, 2H, $CH_2$), 1.75–1.89 (m, 2H, $CH_2$), 2.04–2.09 (m, 1H, CH), 3.90 (t, $J$ = 11.2 Hz, 1H, CH), 4.04–4.07 (m, 1H, CH), 4.36–4.39 (m, 2H, CH), 4.66 (d, $J$ = 10.8 Hz, 1H, CH), 5.06 (s, 1H, CH), 5.94 (s, 1H, NH), 6.85 (d, $J$ = 8.4 Hz, 1H, ArH), 7.11–7.15 (m,1H, ArH), 7.36–7.40 (m, 2H, ArH), 7.52–7.54 (m, 2H, ArH), 7.67 (d, $J$ = 8.0 Hz, 1H, ArH), 7.80 (s,1H, ArH), 7.92 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{25}Cl_2N_2O$ (M + $H^+$) 451.1344, found 451.1346.

***trans-9-Ethyl-5-(4-methoxyphenyl)-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4l).*** This compound was obtained as yellow crystals (0.659 g, 80%), m.p.: 190–191°C; IR (KBr) $\nu_{max}/cm^{-1}$ 3371, 3044, 2954, 2928, 2899, 2829, 1606, 1587, 1509, 1456, 1364, 1326, 1284, 1239, 1212,

1174, 1152, 1076, 1056, 1036, 1009, 901, 835, 802, 745. $^1$H NMR (DMSO-$d_6$): $\delta_H$ 1.25 (t, $J$ = 6.80 Hz, 3H, $CH_3$), 1.36 (d, $J$ = 16.4 Hz, 2H, $CH_2$), 1.74–1.85 (m, 2H, $CH_2$), 1.98–2.01 (m, 1H, CH), 3.78 (s, 3H, $CH_3O$), 3.87–3.92 (m, 1H, CH), 4.04–4.07 (m, 1H, CH), 4.35–4.39 (m, 2H, $NCH_2$), 4.56–4.59 (m, 1H, CH), 5.05 (s, 1H, CH), 5.75 (s, 1H, NH), 6.86 (d, $J$ = 8.0 Hz, 1H, ArH), 6.97 (d, $J$ = 8.4 Hz, 2H, ArH), 7.12 (t, $J$ = 7.6 Hz, 1H, ArH), 7.34–7.44 (m, 4H, ArH), 7.50 (d, $J$ = 8.0 Hz, 1H, ArH), 7.92 (d, $J$ = 8.0 Hz, 1H, ArH). HRMS (ESI, $m/z$): Calcd. for $C_{27}H_{29}N_2O_2$ ($M + H^+$) 413.2229, found 413.2223.

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## REFERENCES AND NOTES

[1] Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. J Nat Prod 1997, 60, 688.

[2] (a) Peczynska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. J Med Chem 1994, 37, 3503; (b) Kaczmarek, L.; Balicki, R.; Nantka-Namirski, P.; Peczynska-Czoch, W.; Mordarski, M. Arch Pharm 1998, 321, 463.

[3] Stiborová, M.; Bieler, C. A.; Wiessler, M.; Frei, E. Biochem Pharmacol 2001, 62, 1675.

[4] Stiborová, M.; Breuer, A.; Aimová, D.; Stiborová-Rupertová, M.; Wiessler, M.; Frei, E. Int J Cancer 2003, 107, 885.

[5] (a) Reddy, K. R. Chem Rev 2002, 102, 4303; (b) Marsais, F.; Pineau, P.; Nivolliers, F.; Mallat, M.; Turck, A.; Godard, A.; Queguiner, G. J Org Chem 1992, 57, 565; (c) Gribble, G. W. Synlett 1991,289; (d) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. J Org Chem 1984, 49, 4518.

[6] (a) Sainsbury, M. Synthesis 1977, 437; (b) Kansal, V. K.; Potier, P. Tetrahedron 1986, 42, 2389; (c) Hewlins, M. J. E.; Oliveira--Campos, A.-M.; Shannon, P. V. R. Synthesis 1984, 289.

[7] (a) Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. Tetrahedron 2000, 56, 193; (b) Mal, D.; Senapati, B. K.; Pahari, P. Synlett 2005, 994.

[8] (a) Baudelle, R.; Melnyk, P.; Deprez, B.; Tartar, A. Tetrahedron 1998, 54, 4125; (b) Worth, D. F.; Perricone, S. C.; Elsager, E. F. J Heterocycl Chem 1970, 7, 1353.

[9] (a) Povarov, L. S. Russ Chem Rev 1967, 36, 656; (b) Cabral, J.; Laszlo, P. Tetrahedron Lett 1989, 30, 7237; (c) Babu, G.; Perumal, P. T. Tetrahedron Lett 1998, 39, 3225.

[10] (a) Crousse, B.; Begue, J. P.; Delpon, D. B. Tetrahedron Lett 1998, 39, 5765; (b) Ma, Y.; Qian, C.; Xie, M.; Sun, J. J Org Chem 1999, 64, 6462.

[11] Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujwara, Y. Synthesis 1995, 801; (b) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. Synlett 1995, 233; (c) Kobayashi, S.; Ishitani, H.; Nagayama, S. Synthesis 1995, 1195.

[12] Gaddam, V.; Nagarajan, R. Tetrahedron Lett 2009, 50, 1243.

[13] Togo, H.; Iida, S. Synlett 2006, 2159.

[14] (a) Wang, X. S.; Li, Q.; Wu, J. R.; Li, Y. L.; Yao, C. S.; Tu, S. J. Synthesis 2008, 1902; (b) Wang, X. S.; Li, Q.; Yao, C. S.; Tu, S. J. Eur J Org Chem 2008, 3513; (c) Wang, X. S.; Li, Q.; Yao, C. S.; Tu, S. J. J Comb Chem 2009, 11, 433.

[15] (a) Ji, S. J.; Wang, S. Y.; Zhang, Y.; Loh, T. P. Tetrahedron 2004, 60, 2051; (b) Ke, B. W.; Qin, Y.; He, Q. F.; Huang, Z. Y.; Wang, F. P. Tetrahedron Lett 2005, 46, 1751.

# A Simple and Versatile Protocol for the Preparation of 1,3-Functionalized Heterocycles Utilizing Benzoylpyruvates

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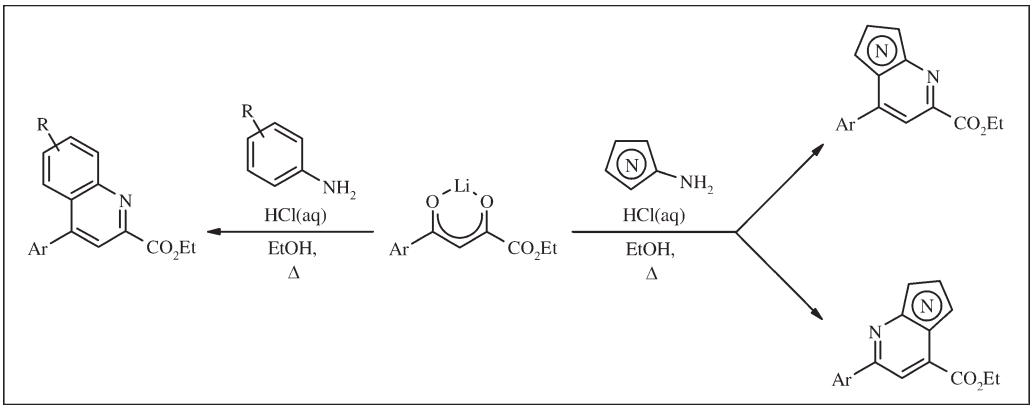


Acid-mediated condensation between benzoylpyruvates and various dinucleophiles in alcoholic solvent furnished the heterocyclic imprint in moderate to good yield. Combining a range of symmetric as well as nonsymmetric nitrogen/nitrogen or nitrogen/carbon centered dinucleophiles resulted in excellent regioselectivity. γ-Difunctionalized fused pyrimidines, pyridazines, and pyridines were produced in this manner. The protocol was designed to obviate chromatographic purification.

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## INTRODUCTION

Addition of ambivalent nitrogenous nucleophiles to β-diketones offers an attractive entry to the preparation of aromatic heterocyclic structures carrying distinct functional motifs. Acting as a template, the structural features of the β-diketone provide the central framework to be resonated in the resulting aza-heterocycle. We have in particular directed our attention towards the application of benzoylpyruvates **1** as the means to prepare pyridine and pyrimidine derivatives incorporating a γ-related aryl ester pattern.

From a pharmaceutical point of view, the spatial arrangement of substituents conferred on heterocycles via benzoylpyruvate chemistry is highly interesting, as it can give rise to pronounced biological activity. For example, pyrazoles, isoxazoles, pyrimidines, and pyridines carrying a γ-aryl carboxy motif are associated with such diverse effects as GPCR antagonism [1–4], ion-channel modulation [5], and kinase inhibition [6,7].

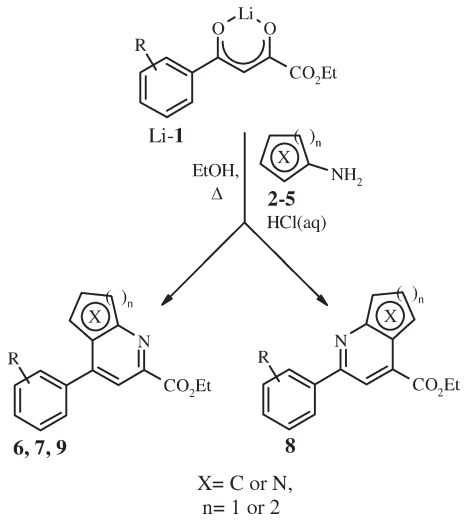
Herein, we want to report a convenient route for the preparation of novel γ-arylated aza-heterocyclic esters by highly chemo- and regioselective condensation of lithio benzoylpyruvate **1** with aromatic amines **2–5** (Scheme 1). Considering the number of different benzoylpyruvates **1** readily available from commercial acetophenones **10**, this protocol can be seen as an alternative to arylation of the parent heterocyle via cross-coupling reactions. Indeed, the preparation of prerequisite substrate for the corresponding cross-coupling may be a nontrivial matter. In contrast, merited by the ease of execution, the delineated condensation strategy is amenable for parallel synthesis.

## RESULTS AND DISCUSSION

As is expected for β-diketones lacking a mirror plane, the ambiphilic nature of benzoylpyruvates poses a potential regiochemical problem. However, in the latter case, the reactivity gets further complicated by the presence of the ester functionality. Although the ester functionality imparts the adjacent carbonyl with an augmented electron deficiency, it might itself undergo nucleophilic attack, thereby giving rise to a potential chemoselective problem as well (Fig. 1) [8].

In general, the stipulated benzoylpyruvate **1** can readily be accessed by reacting the metal enolate of the

**Scheme 1**




corresponding acetophenone **10** with diethyl oxalate **11** [9–11]. In particular, owing to the excellent chelating ability of β-diketones, the *en route* lithium salt of benzoylpyruvate **1** can usually be isolated as a shelf-stabile solid by simple filtration [11]. Thus, sequential treatment of **10** with LDA and diethyl oxalate **11** was the preferred method to prepare the needed starting material (Scheme 2). Initially, we opted for the *p*-Br-substituted benzoylpyruvate Li-**1** as a model compound, expecting it to be conducive in terms of product identification, based on its isotopic fingerprint (LC-MS) and crystallographic properties (X-ray). However, in some cases we found that the parent benzoylpyruvate Li-**1** (R = H) proved superior for crystallographic purposes.

Although the binding of lithium was beneficial with regard to the isolation of **1**, the chelated form proved to have an adverse effect on the cyclodehydration. Without *in situ* quenching of Li-**1**, concomitant retro-aldol reaction was observed on the application of any prospect dinucleophile in refluxing ethanol. Consequently, the initial attempts only returned acetophenone **10** as the breakdown product.

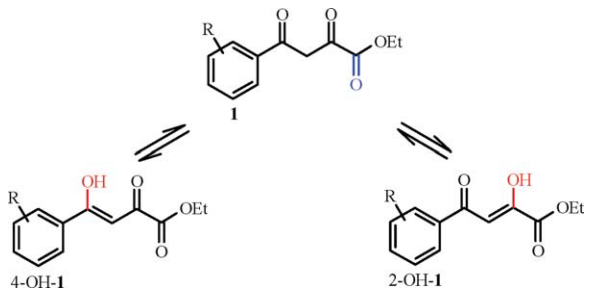
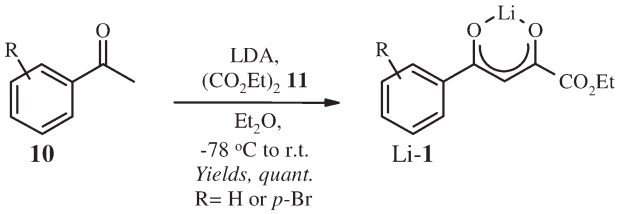



**Figure 1.** Tautomery in benzoylpyruvates. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2**




Gratifyingly, when first having treated Li-**1** with two equivalents of hydrochloric acid, subsequent cyclodehydration could be realized for a range of aromatic amines **2–5** *vide infra*. Furthermore, the reaction displayed a distinct regiochemical preference in each case.

In accordance with the delineated protocol, a selection of five-membered aza-heterocyclic amines **2** was reacted with Li-**1** to furnish the corresponding [*a*]-fused pyrimidines **6** (Scheme 3). However, the influence exerted by the individual N,N-dinucleophiles on the success of cyclodehydration implicated a dependency on the p$K_a$ of the protonated parent heterocyclic system (Table 1). To expand upon the latter point, the p$K_a$-values of pyrazole, 1,3,4-triazole, and tetrazole are 2.5, 2.2, and –3.0, respectively [12,13], whereas the p$K_a$ of imidazole is 7.0 [12]. This may provide an explanation for the failure of imidazole **2b** and benzimidazole **2f** to react under the given conditions.

By the means of single-crystal diffraction technique, it was subsequently possible to make an unambiguous regiochemical assignment of **6b** (Fig. 2), resulting from cyclodehydration with pyrazole **2a**. Curiously, a reversal of regiochemistry takes place when interchanging the ester moiety in Li-**1** for a $CF_3$-group, *i.e.*, turning the system into a conventional β-diketone. Thus, applying a similar protocol as ours, Filyakova *et al.* have reported on the preparation of an analogous 5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine, which was verified by crystallography [14]. The two opposing results indicate the ability of the ester to act as regiochemical handle (*vide infra*).

With respect to regiochemistry, the fused system obtained through condensation of tetrazole **2d** posed the intriguing possibility of valence tautomery [15]. At the outset, it was expected that the initially formed tetrazolo[1,5-*a*]pyrimidines **6f** and **6g** could undergo

**Scheme 3**

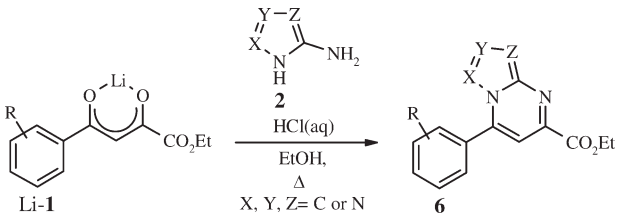


**Table 1**

Synthesis of [*a*]-fused pyrimidines **6**.[a]

| Entry | Product | R | Aryl amine | Time (h)[c] | Yield (%)[d] |
|---|---|---|---|---|---|
| 1 | **6a** | *p*-Br | 1H-Pyrazol-5-yl **2a** | 13 | 75 |
| 2 | **6b** | H | 1H-Pyrazol-5-yl **2a** | 13 | 69 |
| 3 | **6c** | *p*-Br | 1H-Imidazol-5-yl **2b** | 96[e] | n.r. |
| 4 | **6d** | *p*-Br | 1H-1,2,4-Triazol-5-yl **2c** | 48 | 73 |
| 5 | **6e** | H | 1H-1,2,4-Triazol-5-yl **2c** | 48 | 70 |
| 6 | **6f**[b] | *p*-Br | 1H-Tetrazol-5-yl **2d** | 13 | 79 |
| 7 | **6g**[b] | H | 1H-Tetrazol-5-yl **2d** | 13 | 68 |
| 8 | **6h** | *p*-Br | 2H-Indazol-3-yl **2e** | 13 | 85 |
| 9 | **6i** | H | 2H-Indazol-3-yl **2e** | 13 | 87 |
| 10 | **6j** | *p*-Br | 1H-Benzimidazol-2-yl **2f** | 96[e] | n.r. |

[a] The reactions were performed with equimolar proportions of Li-1 and amine 2 in the presence of 2 equiv. of HCl (aq).
[b] Interconverts to the corresponding azide 12.
[c] Time to achieve full conversion according to HPLC and LC-MS.
[d] Isolated yield.
[e] Experiment was terminated at the time indicated as no reaction had occurred.

equilibration to 2-azidopyrimidines **12f, g** (Fig. 3). However, the ''pseudo symmetry'' of **12f, g** would then obliterate the existing regiochemical preference via the erosive interconversion to **13f, g**. Subsequently, it was indeed demonstrated by the application of X-ray crystallography that in the solid state the tentatively assigned structure of fused tetrazole **6f** actually was 2-azidopyrimidine **12f** (Fig. 4).

Having established the feasibility of cyclodehydration on Li-**1** utilizing selected N,N-dinucleophiles, the focus of the protocol was aimed at fusion with other types of five-membered aza-heterocylic amines, *i.e.*, prospective C,N-dinucleophiles. Following this line of reasoning, Li-**1** was allowed to react with N-amino heterocycles **3** to provide [*b*]-fused pyridazines **7** (Scheme 4). In the selected cases, the observed regiochemistry corresponded to the results obtained with aryl amines **2**. Here, however, the degree of aza-functionalization had a dramatic influence on the efficiency, with regard to product formation (Table 2).

Five-membered aza-heterocycles with an encased ethylene amine motif could in principle be rendered operational C,N-dinucleophiles via blocking or replacing the active ring-nitrogen. Hence, it was envisioned that the ''aniline-type'' aryl amines **4** would furnish [*b*]-fused pyridines. Although the primary projection was correct, the regiochemistry was at variance with the preceding examples. Thus, when Li-**1** was reacted with C,N-dinucleo-philes **4**, the resultant cyclodehydration provided the [*b*]-fused pyridine **8** (Scheme 5).

Applied on the product originating from condensation between Li-**1** (R = H) and ''enamine'' **4a**, X-ray crystallography provided the conclusive structural information, showing **8b** to be the resulting regioisomer (Fig. 5).

Though, seemingly contradictory, with regard to benzoylpyruvate **1**, the sequence of addition leading to the different fused systems could well be the same (*vide supra*). Instead, it was surmised that the origin of regiochemical divergence resided on the nature of the applied dinucleophile. Depending on the hard/soft character of the aryl amine, in analogy with enamines, either the interconnected nitrogen or carbon could take precedence in the cyclodehydration. However, it also became clear

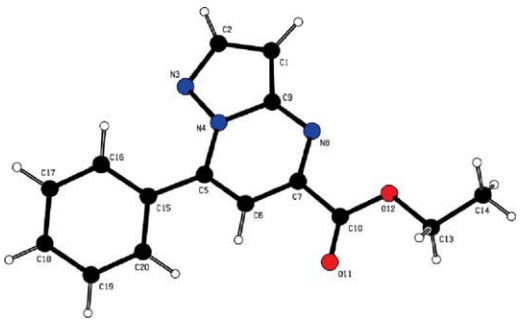



**Figure 2.** Crystal structure of compound **6b** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

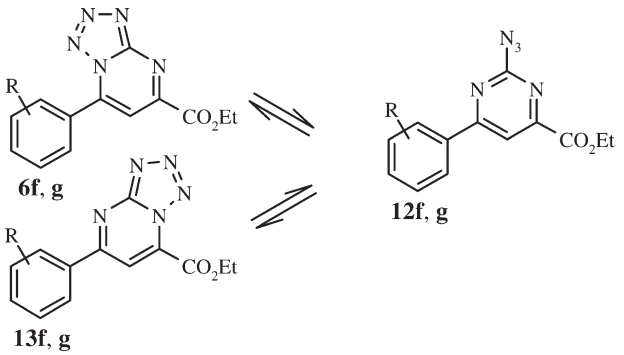



**Figure 3.** Valence tautomery in tetrazolo[1,5-a]pyrimidine **6f** and **6g**.

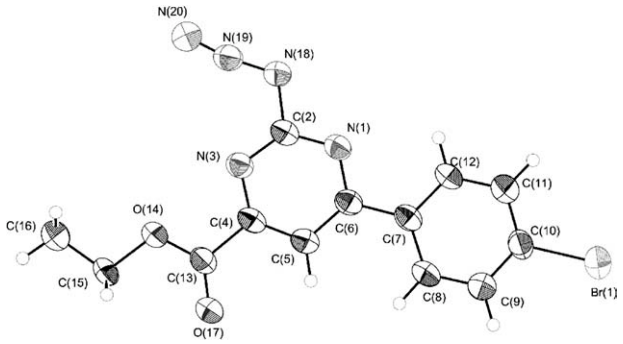



**Figure 4.** ORTEP presentation of compound **12f**.

that the choice of C,N-dinucleophiles **4** was rather limited (Table 3).

By extending the ensemble of C,N-dinucleophiles to six-membered aryl amines **5**, *i.e.*, *bona fide* anilines, it was anticipated that the regiochemistry would realign with the initially observed preference to provide [*b*]-fused pyridines **9** (Scheme 6). However, if the underlying assumption regarding the regiochemical preference of benzoylpyruvate **1** proved correct, the resulting quinolines **9** would have the reversed structure compared with the Skraup–Doebner–von Miller protocol [15].

Upon reacting Li-**1** with anilines **5**, it became evident that cyclodehydration could only be achieved when strongly electron donating substituents were present on the aryl moiety of the prospective C,N-dinucleophile (Table 4). The interplay of electronic properties is however more subtle than what might initially be gleaned from the reaction scheme. Thus, when Li-**1** was treated

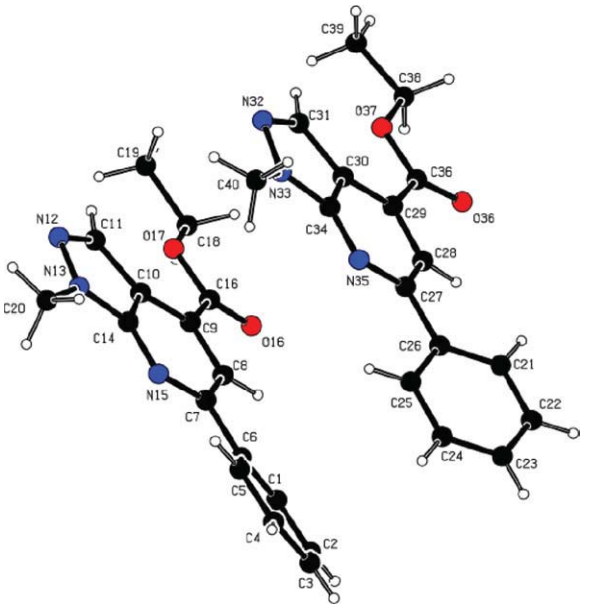
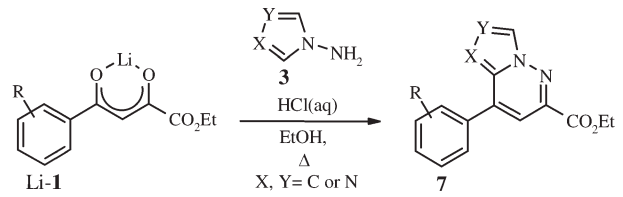



**Figure 5.** Crystal structure of compound **8b** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

with 4-amino-1H-indole **5d**, cyclization proceeded smoothly (entry 8 and 9). While, in contrast, the reaction with 6-amino-1H-indole **5e** was exceedingly sluggish (entry 11). Yet in both instances, the position *ortho* to the aniline functionality is activated by an indole-nitrogen (Fig. 6).

Another aspect of the 4-amino-1H-indole derivatives **9f** and **9g** is the comprehensive prototropic tautomery available to the fused rings. Thus, in the pertinent case, $^1$H NMR indicates that the extended 14 π-electron system

**Scheme 4**




**Scheme 5**

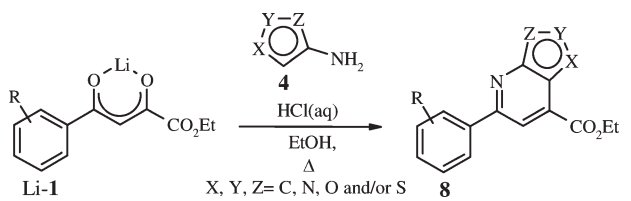



**Table 2**

Synthesis of [*b*]-fused pyridazines **7**.[a]

| Entry | Product | R | Aryl amine | Time (h)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **7a** | *p*-Br | Pyrrol-1-yl **3a** | 0.5 | 85 |
| 2 | **7b** | H | Pyrrol-1-yl **3a** | 0.5 | 79 |
| 3 | **7c** | *p*-Br | 1,2,4-Triazol-4-yl **3b** | 120 | 71 |
| 4 | **7d** | H | 1,2,4-Triazol-4-yl **3b** | 120 | 65 |

[a] The reactions were performed with equimolar proportions of Li-1 and amine 3 in the presence of 2 equiv. of HCl (aq).
[b] Time to achieve full conversion HPLC or LC-MS.
[c] Isolated yield.

**Table 3**

Synthesis of [*b*]-fused pyridines **8**.[a]

| Entry | Product | R | Aryl amine | Time (h)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **8a** | *p*-Br | 2-Methyl-2H-pyrazol-3-yl **4a** | 120 | 70 |
| 2 | **8b** | H | 2-Methyl-2H-pyrazol-3-yl **4a** | 120 | 70 |
| 3 | **8c** | *p*-Br | 5-Methylisox-azole-3-yl **4b** | 120 | n.r. |
| 4 | **8d** | *p*-Br | 3-Methylisothi-azol-5-yl **4c** | 120 | n.r. |

[a] The reactions were performed with equimolar proportions of Li-1 and amine 4 in the presence of 2 equiv. of HCl (aq).
[b] Time to achieve full conversion.
[c] Isolated yield.

**Scheme 6**

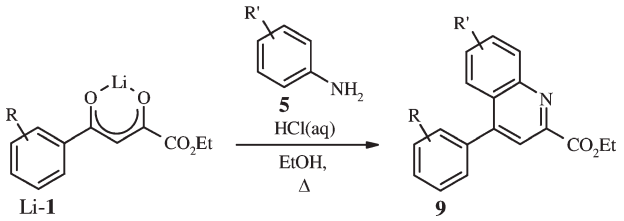



**Table 4**

Synthesis of [*b*]-fused pyridines **9**.[a]

| Entry | Product | R | Aryl amine | Time (h)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **9a** | *p*-Br | 3-Methoxy-phenyl **5a** | 120 | n.r. |
| 2 | **9b** | *p*-Br | 3,5-Dimethoxy-phenyl **5b** | 13 | 82 |
| 3 | **9c** | H | 3,5-Dimethoxy-phenyl **5b** | 13 | 73 |
| 4 | **9d** | *p*-Br | 3-(Dimethylamino)-phenyl **5c** | 13 | 90 |
| 5 | **9e** | H | 3-(Dimethylamino)-phenyl **5c** | 13 | 72 |
| 6 | **9f** | *p*-Br | 1H-Indol-4-yl **5d** | 13 | 25[d] |
| 7 | **9g** | H | 1H-Indol-4-yl **5d** | 13 | 23[d] |
| 8 | **9h** | *p*-Br | 1H-Indol-6-yl **5e** | n.d. | n.d. |
| 9 | **9i** | H | 1H-Indol-6-yl **5e** | 120 | 28[d] |

[a] The reactions were performed with equimolar proportions of Li-1 and amine 5 in the presence of 2 equiv. of HCl (aq).
[b] Time to achieve full conversion or no further reaction occurred by HPLC or LC-MS.
[c] Isolated yield.
[d] Preparative HPLC due to instability.

behaves less aromatic than anticipated. The repositioning of the active proton also involves carbon prototropes and the only specie observed by NMR-spectroscopy was attributed to the 4H-tautomer (Fig. 7). This behavior probably reflects the ''quinone-like'' nature of the compound.

By comparison, the linear isomer **9i** resulting from condensation of Li-**1** (R = H) with 6-amino-1H-indole **5e** behaves more like an aromatic 14 π-electron system and prototropic tautomery is less pronounced. However, in general the quinolines **9** were less stabile than the previous classes of cyclodehydration products **6**, **7**, and **8**.

With regard to the identity of the resulting compounds, we once again resolved to address the issue of regiochemical preference by capitalizing on X-ray crystallography. Applied to the cyclodehydration of Li-**1** (R = Br) with 3-(*N*,*N*-dimethylamino)aniline **5d**, the structure was shown to be **9d** (Fig. 8). Thus, the condensation between benzoylpyruvates **1** and anilines **5** provide verily regioisomeric quinolines not attainable via the classic Skraup–Doebner–von Miller procedure [15].

## CALCULATIONS

In the light of some contrasting findings published by Filyakova *et al*. regarding condensation on selected β-diketones [14], we wanted to make a side-by-side comparison with benzoylpyruvate **1**, applying high-level QM calculations to gain insight into the origin of the observed regio-divergence.

Discounting the reactive nature of the ester moiety, a cursory inspection of benzoylpyruvate **1** might pin down the system as merely a benzoylacetone with an electron withdrawing group append to its terminus. Indeed from

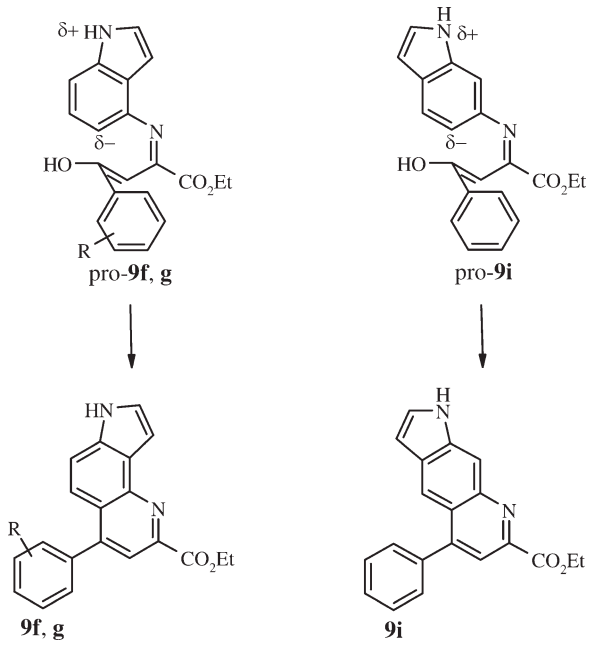



**Figure 6.** Tricycles resulting from condensation with 4-amino-1H-indole **5e** and 6-amino-1H-indole **5f**.

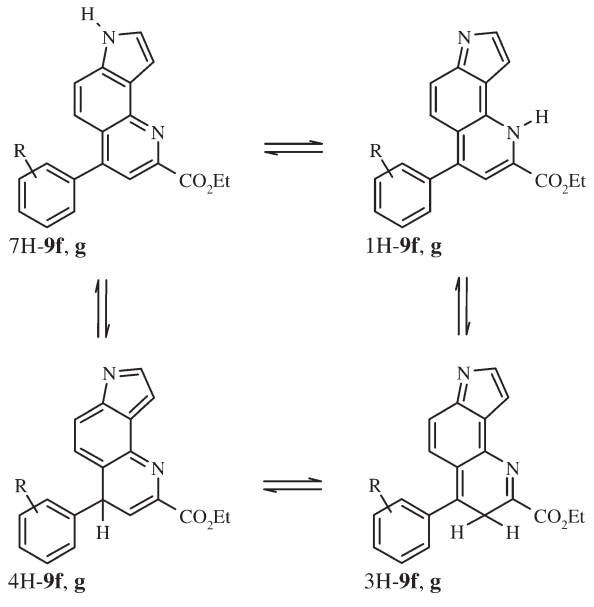
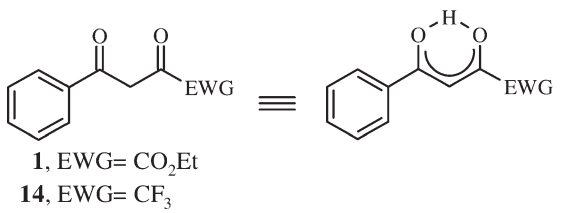



**Figure 7.** Tautomery in pyrrolo[2,3-h]quinolines **9f** and **9g**.

**Figure 8.** Crystal structure of compound **9d** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

this vantage point, benzoylpyruvate **1** compares well with the fluorinated β-diketone **14** used by Filyakova *et al*. [14]. Thus, in both cases, the keto-functionalities might be projected to exhibit ''pseudo-degenerate'' behavior (Fig. 9). As an initial conjecture, one would consequently expect cyclodehydration on benzoylpyruvate **1** and fluorinated β-diketone **14** to give rise to similar regioselectivity. Indeed, our calculations on the relative energies of protonated β-diketone **14** only differ with 0.3 kcal/mol for the two positions. This is within the error margin of the applied method [16].

Taking into account, the participation of the ester moiety in benzoylpyruvate **1** alters the picture dramatically: The ability of the ester function to act as a hydrogen bond acceptor facilitates formation of a five-membered chelate with the adjacent carbonyl. According to the performed calculations, using methyl derivative **15** as a model compound, the individual protonated forms of the β-diketo system alone are energetically comparable. However, when the protonated forms involving a five-membered chelate are introduced, the energy of the system is markedly lower by 2.6 and 3.2 kcal/mol, respectively (Fig. 10) [16,17]. Thus, these calculations lend support to the hypothesis that the ester moiety in benzoylpyruvate **1** may serve as a regiochemical handle.




**1**, EWG= $CO_2Et$
**14**, EWG= $CF_3$

**Figure 9.** Pseudo-degenerate nature of the β-diketo system.

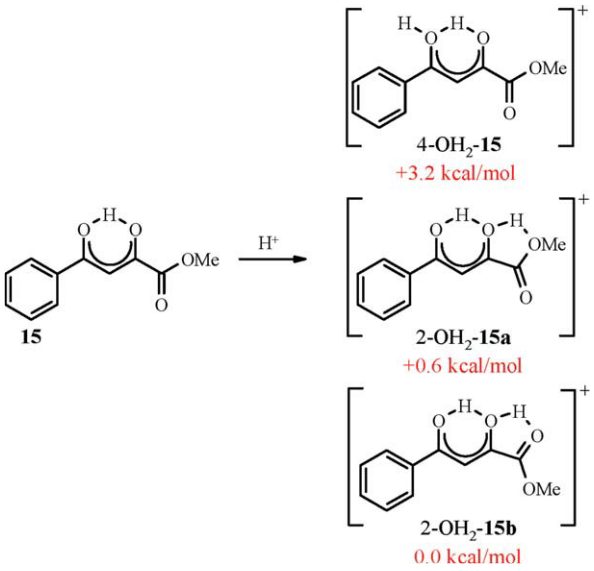



**Figure 10.** Calculated relative energies of protonated model benzoylpyruvate 15 based on B3LYP/6-31G**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

## CRYSTALLOGRAPHY

**Data collection, structure solution, and refinement.** Diffraction data for (**6b**), (**8b**), (**9f**), and (**12a**) were collected at 200(2) K using either a Nonius Kappa-CCD or a Bruker APEX-II CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined with $F^2$ against all reflections. All but one had one molecule in the asymmetric unit, which for **8b** contained two crystallographically unique molecules. Figures 2–5 and 8 show the molecular conformation, with the atom-labeling schemes. Compounds **6b**, **8b**, **9d**, and **12a** do not contain H-bond donor atoms and consequently do not form classical H-bonds [18].

## CONCLUSIONS

This article outlines a simple and versatile approach to furnish fused heterocycles grafted on the benzoylpyruvate backbone. Depending on the nature of the applied dinucleophilic class, an alternation of regiochemistry could be observed. However, in each case the process was highly regioselective. At the basis of the observed selectivity, we postulate the participation of the ester portion in benzoylpyruvates as a decisive factor.

## EXPERIMENTAL

NMR spectra were recorded either on a Bruker DPX400 NMR spectrometer operating at 400 MHz for $^1$H, and 101 MHz for $^{13}$C equipped with a four-nucleus probe-head with Z-gradients, or a Bruker Avance III 500 NMR spectrometer, operating at 500 MHz for $^1$H and 126 MHz for $^{13}$C equipped

with a 5mm TCI cryo probe-head with Z-gradients. Chemical shifts are given in ppm down- and upfield from tetramethylsilane (0.00 ppm). DMSO-$d_6$ $\delta_H$ 2.49; $\delta_C$ 39.51 and $CDCl_3$ $\delta_H$ 7.27; $\delta_C$ 77.00 were used as reference signals. All experiments were performed at a sample temperature of 26°C ± 2°C. LC-MS analyses were performed on a LC-MS system consisting of a Waters Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 75 ELS detector, and a ZQ 2000 single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. The capillary voltage was set to 3.3 kV and the cone voltage to 28 V, respectively. The mass spectrometer was scanned between *m*/*z* 100–700 with a scan time of 0.3 s. The diode array detector scanned from 200–400 nm. The temperature of the ELS detector was adjusted to 40°C and the pressure was set to 1.9 bar. Separation was performed on Gemini C18 3.0 × 50, 3 μm (Phenomenex) run at a flow rate of 1 mL/min. A linear gradient was applied starting at 100% A (A: 10 m*M* ammonium acetate in 5% acetonitrile) ending at 100% B (B: acetonitrile) in 4 min followed by 100% B until 5.5 min. The column oven temperature was set to 40°C. HPLC analyses were performed on an Agilent HP1100 system consisting of a G1322A Micro Vacuum Degasser, a G1311A Quaternary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostated Column Compartment and a G1315A Diode Array Detector. The diode array detector was scanned from 200 to 400 nm, step and peak width were set to 2 nm and 0.01 min, respectively. The column used was Gemini C18, 3.0 × 50 mm, 3.0 μm, 110 Å run at a flow rate of 1.0 mL/min. The column oven temperature was set to 40°C. A linear gradient was applied, starting at 100% A (A: 10 m*M* ammonium acetate in 5% acetonitrile) and ending at 95% B (B: acetonitrile) after 6.5 min then 95% B for 0.5 min. High resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof micro mass spectrometer equipped with a LockSpray source and connected to an Acquity UPLC system with a PDA detector. All analyses were acquired using positive mode electrospray ionisation (ESI+) in full scan and Leucine Enkephalin (Sigma) was used as the lock mass (*m*/*z* 556.2771) at a concentration of 0.9 pmol/μL and a flow rate of 100 μL/min with a 1:10 split, ion source:waste. Cone Voltage was set to 54 to achieve ∼ 200 counts for Leucine Enkephalin. Nitrogen was used as the nebulizing and desolvation gas, with the source operated at 120°C and the desolvation gas at 300°C. Capillary voltage was about 3000 V and cone voltage was about 30 V. Argon was used as the collision gas. Chromatographic separation for HRMS was achieved with a 2.3 min linear gradient from 95% A (A: 10 m*M* ammonium acetate in MilliQ water + 5% acetonitrile) to 95% B (B: acetonitrile) over an ACQUITY UPLC BEH C18 1.7 μm, 2.1 × 50 mm column maintained at 65°C and run at a flow rate of 0.7 mL/min with a 1:5 split, ion source:waste. Analytes were diluted in $H_2O$:ACN (50:50) until suitable concentration for the LC-MS analysis.

**General methods for the condensation of benzoylpyruvates (Li-1, R = H, Br) with dinucleophiles (2–5).** Lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) (0.226 g, 1.00 m*M*) or lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) (0.305 g, 1.00 m*M*) and the appropriate dinucleophile (**2–5**) (1.00 m*M*) were mixed together, suspended in ethanol (5.0 mL) and conc. aqueous hydrochloric acid (166 μL, 12.0*M*, 2.00 m*M*) was added. The resulting homogeneous mixture was heated and refluxed for the times given (*vide supra*). After heating, the reaction mixture was allowed to slowly cool to ambient temperature. In case of precipitation, the deposited material was collected, washed with ethanol, and the mother liquor was evaporated *in vacuo*. Upon evaporation, the remnant was recrystallized from ethanol and further cropped.

If no initial precipitation occurred, the reaction mixture was evaporated *in vacuo*, whereupon the remnant was dissolved in chloroform and washed with dilute aqueous sodium hydroxide. The organic phase was subsequently evaporated *in vacuo* and the remnant was dissolved in hot methanol, ethanol, or extracted with boiling hexane. Subsequently, upon cooling crystallization ensued and the deposited material was cropped.

***Ethyl 4-(4-bromophenyl)-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (6a).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and 3-aminopyrazole (**2a**). Yield: 0.259 g (75%). $^1$H NMR ($CDCl_3$): δ 1.49 (t, 3H, *J* = 7.2 Hz), 4.56 (q, 2H, *J* = 7.1 Hz), 7.05 (d, 1H, *J* = 2.3 Hz), 7.70 (s, 1H), 7.7–7.8 (m, 2H), 8.0–8.1 (m, 2H), 8.28 (d, 1H, *J* = 2.3 Hz). $^{13}$C NMR ($CDCl_3$): δ 14.3, 62.8, 100.0, 106.7, 126.1, 129.4, 130.8, 132.0, 145.98, 146.01, 146.3, 148.9, 164.0. HRMS: Found 346.0198, Calcd. for $C_{15}H_{13}BrN_3O_2$: 346.0191.

***Ethyl 4-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (6b).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 3-aminopyrazole (**2a**). Yield: 0.185 g (69%). $^1$H NMR ($CDCl_3$): δ 1.50 (t, 3H, *J* = 7.1 Hz), 4.57 (q, 2H, *J* = 7.1 Hz), 7.05 (d, 1H, *J* = 2.5 Hz), 7.6–7.7 (m, 3H), 7.71 (s, 1H), 8.1–8.2 (m, 2H), 8.29 (d, 1H, *J* = 2.3 Hz). $^{13}$C NMR ($CDCl_3$): δ 14.3, 62.7, 99.8, 106.9, 128.8, 129.3, 130.6, 131.4, 146.0, 146.4, 147.2, 149.0, 164.1. HRMS: Found 268.1097, Calcd. for $C_{15}H_{14}N_3O_2$: 268.1086.

***Ethyl 7-(4-bromophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5-carboxylate (6d).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and 3-amino-1,2,4-triazole (**2c**). Yield: 0.255 g (73%). $^1$H NMR ($CDCl_3$): δ 1.50. (t, 3H, *J* = 7.2 Hz), 4.57 (q, 2H, *J* = 7.1 Hz), 7.78 (d, 2H, *J* = 8.6 Hz), 8.03 (s, 1H), 8.11 (d, 2H, *J* = 8.60 Hz), 8.70 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.2, 63.2, 108.6, 127.4, 128.0, 130.9, 132.4, 147.8, 151.9, 155.7, 157.6, 163.5. HRMS: Found 347.0151, Calcd. for $C_{14}H_{12}BrN_4O_2$: 347.0144.

***Ethyl 7-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine-5-carboxylate (6e).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 3-amino-1,2,4-triazole (**2c**). Yield: 0.187 g (70%). $^1$H NMR ($CDCl_3$): δ 1.40 (t, 3H, *J* = 7.1 Hz), 4.57 (q, 2H, *J* = 7.1 Hz), 7.6–7.7 (m, 3H), 8.04 (s, 1H), 8.1–8.2 (m, 2H), 8.70 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.2, 63.1, 108.8, 129.1, 129.3, 129.5, 132.4, 149.0, 151.8, 155.7, 157.6, 163.5. HRMS: Found 269.1039, Calcd. for $C_{14}H_{13}N_4O_2$: 269.1039.

***Ethyl 2-azido-6-(4-bromophenyl)pyrimidine-4-carboxylate (12f).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and 5-aminotetrazole (**2d**). Yield: 0.277 g (79%). $^1$H NMR ($CDCl_3$): δ 1.46 (t, 3H, *J* = 7.1 Hz), 4.51 (q, 2H, *J* = 7.2 Hz), 7.6–7.7 (m, 2H), 8.0–8.1 (m, 2H), 8.11 (s, 1H). $^{13}$C

NMR ($CDCl_3$): δ 14.2, 62.9, 111.9, 127.2, 128.9, 132.4, 133.9, 158.2, 163.0, 163.7, 167.0. HRMS: Found 348.0099, Calcd. for $C_{13}H_{11}BrN_5O_2$: 348.0096.

***Ethyl 2-azido-6-phenyl-pyrimidine-4-carboxylate (12g).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 5-aminotetrazole (**2d**). Yield: 0.182 g (68%). $^1$H NMR ($CDCl_3$): δ 1.47 (t, 3H, *J* = 7.1 Hz), 4.51 (q, 2H, *J* = 7.1 Hz), 7.5–7.6 (m, 3H), 8.15 (s, 1H), 8.2 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ 14.1, 62.8, 112.2, 127.5, 129.1, 132.2, 134.5, 157.9, 162.9, 163.8, 168.2. HRMS: Found 270.0993, Calcd. for $C_{13}H_{12}N_5O_2$: 270.0991.

***Ethyl 4-(4-bromophenyl)pyrimido[1,2-b]indazole-2-carboxylate (6h).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and 3-aminoindazole (**2e**). Yield: 0.339 g (85%). $^1$H NMR ($CDCl_3$): δ 1.54 (t, 3H, *J* = 7.1 Hz), 4.60 (q, 2H, *J* = 7.2 Hz), 7.4–7.5 (m, 1H), 7.7–7.8 (m, 1H), 7.8–7.9 (m, 2H), 7.9–8.0 (m, 1H), 8.09 (s, 1H), 8.1–8.2 (m, 2H), 8.5–8.6 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.4, 62.7, 110.9, 114.7, 117.0, 121.6, 122.4, 126.0, 129.7, 130.6, 131.0, 132.2, 141.7, 143.5, 144.4, 151.7, 164.1. HRMS: Found 396.0349, Calcd. for $C_{19}H_{15}BrN_3O_2$: 396.0348.

***Ethyl 4-phenylpyrimido[1,2-b]indazole-2-carboxylate (6i).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 3-aminoindazole (**2e**). Yield: 0.277 g (87%). $^1$H NMR ($CDCl_3$): δ 1.54 (t, 3H, *J* = 7.1 Hz), 4.60 (q, 2H, *J* = 7.1 Hz), 7.4–7.5 (m, 1H), 7.6–7.8 (m, 4H), 7.9–8.0 (m, 1H), 8.11 (s, 1H), 8.2–8.3 (m, 2H), 8.4–8.6 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.4, 62.6, 111.2, 114.7, 117.0, 121.6, 122.2, 128.9, 129.5, 130.4, 131.0, 131.4, 141.8, 144.4, 144.7, 151.8, 164.2. HRMS: Found 318.1250, Calcd. for $C_{19}H_{16}N_3O_2$: 318.1243.

***Ethyl 4-(4-bromophenyl)pyrrolo[2,1-f]pyridazine-2-carboxylate (7a).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and 1-aminopyrrole (**3a**). Yield: 0.292 g (85%). $^1$H NMR ($CDCl_3$): δ 1.48 (t, 3H, *J* = 7.1 Hz), 4.54 (q, 2H, *J* = 7.1 Hz), 6.72 (dd, 1H, *J* = 4.3 Hz, 1.5 Hz), 7.06 (dd, 1H, *J* = 4.4 Hz, 2.9 Hz), 7,28 (s, 1H) 7.6–7.8 (m, 4H), 8.02 (dd, 1H, *J* = 2.8 Hz, 1.5 Hz). $^{13}$C NMR ($CDCl_3$): δ 14.3, 62.3, 100.5, 108.0, 115.7, 119.1, 124.0, 125.4, 129.6, 132.1, 135.0, 139.6, 142.2, 163.9. HRMS: Found 345.0248, Calcd. for $C_{16}H_{14}BrN_2O_2$: 345.0239.

***Ethyl 4-phenylpyrrolo[2,1-f]pyridazine-2-carboxylate (7b).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = H) and 1-aminopyrrole (**3a**). Yield: 0.211 g (79%). $^1$H NMR ($CDCl_3$): δ 1.48 (t, 3H, *J* = 7.2 Hz), 4.54 (q, 2H, *J* = 7.1 Hz), 6.77 (dd, 1H, *J* = 4.4 Hz, 1.4 Hz), 7.05 (dd, 1H, *J* = 4.3 Hz, 2.8 Hz), 7.32 (s, 1H), 7.5–7.6 (m, 3H), 7.7–7.8 (m, 2H), 8.02 (dd, 1H, *J* = 2.8 Hz, 1.3 Hz). $^{13}$C NMR ($CDCl_3$): δ 14.3, 62.3, 100.6, 108.1, 115.6, 118.9, 125.8, 128.1, 128.9, 129.7, 136.1, 140.9, 142.2, 164.1. HRMS: Found 267.1133, Calcd. for $C_{16}H_{15}N_2O_2$: 267.1134.

***Ethyl 8-(4-bromophenyl)-[1,2,4]triazolo[3,4-f]pyridazine-6-carboxylate (7c).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and *N*-4-amino-1,2,4-triazole (**3b**). Yield: 0.248 g (71%). $^1$H NMR ($CDCl_3$): δ 1.52 (t, 3H, *J* = 7.1 Hz), 4.59 (q, 2H, *J* = 7.2 Hz), 7.7–7.8 (m, 2H), 8.03 (s, 1H), 8.3–8.4 (m, 2H), 9.33 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.2, 63.5, 115.3, 126.8, 130.1, 130.7, 132.5, 136.5, 139.9, 142.9 146.3, 162.2. HRMS: Found 347.0151, Calcd. for $C_{14}H_{12}BrN_4O_2$: 347.0144.

***Ethyl 8-phenyl-[1,2,4]triazolo[3,4-f]pyridazine-6-carboxylate (7d).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 4-amino-1,2,4-triazole (**3b**). Yield: 0.174 g (65%). $^1$H NMR ($CDCl_3$): δ 1.51 (t, 3H, *J* = 7.1 Hz), 4.58 (q, 2H, *J* = 7.2 Hz), 7.5–7.6 (m, 3H), 8.03 (s, 1H), 8.3–8.4 (m, 2H), 9.33 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.2, 63.4, 115.5, 129.2, 129.3, 131.4, 131.8, 137.8, 139.8, 143.2 146.3, 162.3. HRMS: Found 269.1043, Calcd. for $C_{14}H_{13}N_4O_2$: 269.1039.

***Ethyl 6-(4-bromophenyl)-1-methyl-pyrazolo[3,4-b]pyridine-4-carboxylate (8a).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) and 3-amino-2-methyl-2*H*-pyrazole (**4a**). Yield: 0.253 g (70%). $^1$H NMR ($CDCl_3$): δ 1.53 (t, 3H, *J* = 7.1 Hz), 4.25 (s, 3H), 4.56 (q, 2H, *J* = 7.1 Hz), 7.6–7.7 (m, 2H), 8.0–8.1 (m, 2H), 8.21 (s, 1H), 8.39 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.3, 34.0, 62.0, 111.9, 114.6, 124.3, 128.9, 131.89, 131.93, 132.5, 137.2, 151.5, 155.3, 165.1. HRMS: Found 360.0342, Calcd. for $C_{16}H_{15}BrN_3O_2$: 360.0348.

***Ethyl 1-methyl-6-phenyl-pyrazolo[3,4-b]pyridine-4-carboxylate (8b).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 3-amino-2-methyl-2*H*-pyrazole (**4a**). Yield: 0.196 g (70%). $^1$H NMR ($CDCl_3$): δ 1.52 (t, 3H, *J* = 7.1 Hz), 4.25 (s, 3H), 4.54 (q, 2H, *J* = 7.1 Hz), 7.5–7.6 (m, 3H), 8.2 (m, 2H), 8.23 (s, 1H), 8.38 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.3, 34.1, 61.9, 111.7, 115.2, 127.5, 128.9, 129.7, 128.9, 131.8, 132.5, 138.5, 151.7, 156.7, 165.3. HRMS: Found 282.1249, Calcd. for $C_{16}H_{16}N_3O_2$: 282.1243.

***Ethyl 4-(4-bromophenyl)-5,7-dimethoxy-quinoline-2-carboxylate (9b).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = H) and 3,5-dimethoxyaniline (**5b**). Yield: 0.342 g (82%). $^1$H NMR ($CDCl_3$): δ 1.46 (t, 3H, *J* = 7.1 Hz), 3.53 (s, 3H), 3.96 (s, 3H), 4.53 (q, 2H, *J* = 7.1 Hz), 6.55 (d, 1H, *J* = 2.3 Hz), 7.1–7.2 (m, 2H), 7.38 (d, 1H, *J* = 2.3 Hz), 7.5–7.6 (m, 2H), 7.76 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.3, 55.3, 55.8, 62.3, 101.2, 101.3, 115.7, 121.0,121.3, 129.8, 130.2, 140.8, 147.2, 148.2, 150.9, 156.6, 161.6, 165.0. HRMS: Found 416.0509, Calcd. for $C_{20}H_{19}BrNO_4$: 416.0497.

***Ethyl 5,7-dimethoxy-4-phenyl-quinoline-2-carboxylate (9c).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 3,5-dimethoxyaniline (**5b**). Yield: 0.248 g (73%). $^1$H NMR ($CDCl_3$): δ 1.47 (t, 3H, *J* = 7.2 Hz), 3.51 (s, 3H), 3.97 (s, 3H), 4.54 (q, 2H, *J* = 7.1 Hz), 6.55 (d, 1H, *J* = 2.3 Hz), 7.3 (m, 2H), 7.35 (d, 1H, *J* = 2.0 Hz), 7.4 (m, 3H), 7.83 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.4, 55.3, 55.8, 62.2, 101.1, 101.5, 116.0, 121.3, 127.0, 127.1, 128.1, 142.0, 147.4, 149.3, 151.1, 156.9, 161.3, 165.3. HRMS: Found 338.1389, Calcd. for $C_{20}H_{20}NO_4$: 338.1392.

***Ethyl 4-(4-bromophenyl)-7-(dimethylamino)quinoline-2-carboxylate (9d).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = H) and 3-(*N*,*N*-dimethylamino)aniline (**5c**). Yield: 0.360 g (90%). $^1$H NMR ($CDCl_3$): δ 1.48 (t, 3H, *J* = 7.1 Hz), 3.13 (s, 6H), 4.54 (q, 2H, *J* = 7.1 Hz), 7.21 (dd,

1H, $J$ = 9.4 Hz, 2.8 Hz), 7.4 (m, 2H), 7.42 (br. s, 1H), 7.6 (m, 2H), 7.72 (d, 1H, $J$ = 9.4 Hz), 7.80 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.4, 40.4, 62.1, 108.0, 117.3, 118.4, 119.8, 122.8, 125.8, 131.1, 131.7, 137.0, 147.8, 150.0, 151.3, 165.7. HRMS: Found 399.0711, Calcd. for $C_{20}H_{20}BrN_2O_2$: 399.0708.

***Ethyl 7-(dimethylamino)-4-phenyl-quinoline-2-carboxylate (9e).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 3-(*N*,*N*-dimethylamino)aniline (**5c**). Yield: 0.231 g (72%). $^1$H NMR ($CDCl_3$): δ 1.49 (t, 3H, $J$ = 7.1 Hz), 3.13 (s, 6H), 4.56 (q, 2H, $J$ = 7.2 Hz), 7.21 (dd, 1H, $J$ = 9.5 Hz, 2.7 Hz), 7.45 (br. s, 1H), 7.5–7.6 (m, 5H), 7.80 (d, 1H, $J$ = 9.4 Hz), 7.85 (s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.4, 40.4, 62.1, 107.8, 117.6, 118.3, 120.3, 126.3, 128.46, 128.53, 129.5, 138.1, 147.6, 149.3, 149.9, 151.3, 165.7. HRMS: Found 321.1612, Calcd. for $C_{20}H_{21}N_2O_2$: 321.1603.

***Ethyl 4-(4-bromophenyl)-7H-pyrrolo[2,3-h]quinoline-2-carboxylate (9f).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = H) and 4-amino-1*H*-indole (**5d**). Yield (based on prep. HPLC of 0.080 g crude material): 0.020 g (25%). $^1$H NMR (DMSO-$d_6$): δ 1.21 (t, 3H, $J$ = 7.1 Hz), 4.11 (q, 2H, $J$ = 7.2 Hz), 5.08 (s, 1H), 6.2–6.3 (m, 1H), 6.3–6.4 (m, 1H), 6.6–6.7 (m, 2H), 7.3–7.5 (m, 2H), 7.5–7.7 (m, 2H) 8.31 (s, 1H), 11.02 (d, 1H, $J$ = 2.0 Hz). $^{13}$C NMR (DMSO-$d_6$): δ 14.0, 61.3, 79.2, 113.2, 116.7, 117.5, 120.6, 122.1, 124.0, 125.2, 127.3, 128.1, 131.8, 138.5, 139.6, 144.5, 152.0, 156.0, 165.3. HRMS: Found 395.0403, Calcd. for $C_{20}H_{16}BrN_2O_2$: 395.0395.

***Ethyl 4-phenyl-7H-pyrrolo[2,3-h]quinoline-2-carboxylate (9g).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 4-amino-1*H*-indole (**5d**). Yield (based on prep. HPLC of 0.080 g crude material): 0.018 g (23%). $^1$H NMR ($CDCl_3$): δ 1.30 (t, 3H, $J$ =7.2 Hz), 4.23 (q, 2H, $J$ = 7.2 Hz), 5.45 (s, 1H), 6.25 (s, 1H), 6.48 (d, 1H, $J$ = 6.8 Hz), 6.6–6.8 (m, 2H), 7.3–7.5 (m, 5H), (br. s, 1H). $^{13}$C NMR ($CDCl_3$): δ 14.0, 62.1, 112.6, 117.9, 119.9, 121.7, 121.8, 125.6, 126.1, 127.7, 128.6, 129.1, 139.3, 139.9, 144.8, 153.3, 156.3,165.9. HRMS: Found 317.1282, Calcd. for $C_{20}H_{17}N_2O_2$: 317.1290.

***Ethyl 5-phenyl-1H-pyrrolo[3,2-g]quinoline-7-carboxylate (9i).*** The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-**1**, R = H) and 6-amino-1*H*-indole (**5e**). Yield (based on prep. HPLC of 0.080 g crude material): 0.022 g (28%). $^1$H NMR ($CDCl_3$): δ 1.50 (t, 3H, $J$ = 7.2 Hz), 4.57 (q, 2H, $J$ = 7.2 Hz), 6.67 (dd, 1H, $J$ = 3.0 Hz, 2.3 Hz), 7.08 (t, 1H, $J$ = 2.9 Hz), 7.5–7.6 (m, 2H), 7.6–7.7 (m, 3H), 7.91 (br. s, 1H), 8.0–8.1 (m, 2H), 8.10 (s,1H). $^{13}$C NMR ($CDCl_3$): δ 14.2, 62.1, 104.0, 117.0, 121.7, 123.7, 124.3, 125.4, 126.4, 128.5, 128.6, 129.3, 129.5, 139.8, 141.4, 144.4, 144.8, 146.5, 165.7. HRMS: Found 317.1299, Calcd. for $C_{20}H_{17}N_2O_2$: 317.1290.

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## REFERENCES AND NOTES

[1] Astles, P. C.; Harper, M. F.; Harris, N. V.; McLay, I.M.; Walsh, R. J. A.; Lewis, R. A.; Smith, C.; Porter, B.; McCarthy, C. PCT Int Appl 1995, WO 95/13262 A1, 191.

[2] Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Rinaldi, M.; Anne-Archard, G. U.S. Pat. Appl 1997, US 5624941 A, 45.

[3] Ghosh, S.; Elder, A. M.; Carson, K. G.; Sprott, K.; Harrison, S. PCT Int Appl 2004, WO 2004/032848 A2, 257.

[4] Goodfellow, V.; Rowbottom, M.; Dyck, B. P.; Tamiya, J.; Zhang, M.; Grey, J.; Vickers, T.; Kiankarimi, M.; Wade, W.; Hudson, S.C. PCT Int Appl 2004, WO 2004/080411 A2, 86.

[5] Makings, L.R.; Grootenhuis, P.; Hurley, D.J.; Tung, R.D.; Termin, A.P. PCT Int Appl 2004, WO 2004/108133 A2, 79.

[6] Lee, J.; Kim, H. J.; Choi, S.; Choi, H. G.; Yoon, S.; Kim, J.-H.; Jo, K.; Kim, S.; Koo, S.-Y.; Kim, M.-H.; Kim, J. I.; Hong, S.-Y.; Kim, M. S.; Ahn, S.; Yoon, H.-S.; Cho, H.-S. PCT Int Appl 2004, WO 2004/080979 A1, 106.

[7] Anderson, D. R.; Stehle, N. W.; Kolodziej, S. A.; Reinhard, E. J. PCT Int Appl 2004, WO 2004/055015 A1, 223.

[8] Nolsöe, J. M. J.; Weigelt, D. J Heterocyclic Chem 2009, 46, 1.

[9] Freri, M. Gazz Chim Ital 1938, 68, 612.

[10] Butenandt, A.; Hallmann, G.; Beckmann, R. Chem Ber 1957, 90, 1120.

[11] Murray, W. V.; Wachter, M. P. J. Heterocyclic Chem 1989, 26, 1389.

[12] Grimmett, M. R. In Comprehensive Organic Chemistry; Barton, D. H. R., Ollis, W. D., Sammes, P. G., Eds.; Pergamon: New York, 1979; Vol. 4, p 357.

[13] Sokololova, M. M.; Ostrovskii, V. A.; Koldobskii, G. I.; Mel'nikov, V. V.; Gidaspov, B. V. Zh Org Khim 1974, 10, 1085.

[14] Filyakova, V. I.; Kuznetsova, O. A.; Ulomskii, E. N.; Rybalova, T. V.; Gatilov, Yu. V.; Kodess, M. I.; Rusinov, V. L.; Pashkevich, K. I. Russ Chem Bull Int Ed 2002, 51, 332.

[15] Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. J Org Chem 2006, 71, 6592 and references therein.

[16] Calculations where performed using the Jaguar program (v7.5) from Schrodinger Inc using the B3LYP functional and the LACVP** basis set. The relative energies includes solvent effects using the PBF approximation.

[17] For structure **15b**, the C-O bond of the carbonyl proximal to the ester moiety is more elongated compared to the benzylic carbonyl (1.33Å vs. 1.31Å) and therefore more electrophilic. This is in line with the observed regiochemical preference in this reaction.

[18] Crystallographic details are available in the supporting information.

# Copper-Catalyzed Alkyne Cycloaddition on Electron Deficient Azides *via* Tetrazolo[1,5-*a*]pyrimidines



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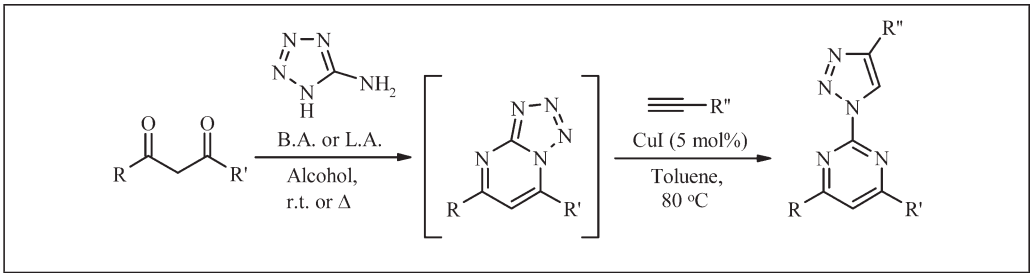


Tetrazolo[1,5-*a*]pyrimidines are capable of serving as masked azides in copper-catalyzed Huisgen cyclization with a variety of terminal alkynes, providing a simple protocol for the generation of novel 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidines.

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## INTRODUCTION

In recent years, the application of transition metals to promote 1,3-dipolar cycloaddition between organic azides and alkynes has effected a revitalization of the field pioneered by Huisgen *et al.* in the 1960s [1]. This surge of attention has been brought about by reports from the research groups of Meldal and Sharpless, independently demonstrating how the catalytic presence of copper(I) facilitates a remarkable enhancement of reactivity and regioselectivity, in the case of terminal alkynes acting as the dipolarophile [2,3].

The intrinsic affinity of organic azides toward terminal alkynes, realized in the established protocol, has prompted Sharpless to coin the term ''Click Chemistry'' [4]. However, despite the many merits publicized to endorse copper-catalyzed azide-alkyne cycloaddition (CuAAC) [5,6], there is a notable absence of examples involving electron deficient 1,3-dipoles.

In the instance of electron deficient hetaryl azides, the authors of this article have only come across a handful of articles entailing CuAAC [7–9]. The obvious reason is the ability of the appended heterocycle to disperse negative charge residing on the azide, thereby disrupting its innate dipolar nature and hampering the concomitant cycloaddition.

The reactivity can be improved through the introduction of electron donating substituents on the heterocyclic moiety, enabling the CuAAC to take place under non-forcing conditions [7,8]. Conversely, the absence of any mitigating functionality may result in a sluggish reaction that demands elevated temperature and auxiliary reagent to bring about conversion [9,10].

Observing the facile reaction between β-diketones **1** and 5-aminotetrazole **2** as an entry to 2-azidopyrimidines **4**, we wanted to explore their ability to undergo alkyne cycloaddition within the context of copper(I) catalysis [11].

## RESULTS AND DISCUSSION

The electron deficient 1,3-dipoles, projected as the investigative starting point for CuAAC, were synthesized by performing cyclodehydration on the appropriate β-diketone **1** with 5-aminotetrazole **2**, capitalizing on the tautomeric equilibrium existing between tetrazolo[1,5-*a*]-pyrimidine **3** and 2-azidopyrimidine **4** (Scheme 1). It was found that the presence of either Brönsted or Lewis acid in refluxing alcoholic solvent advanced cyclodehydration, allowing the prerequisite azides to be isolated in high purity by simple filtration upon cooling of the reaction media (Table 1).

The coexistence of **3** and **4**, through valence tautomery, seems to be an inherent feature of fused tetrazoles. However, the directional preference of the equilibrium is subject to several factors, including phase, solvent, temperature, and pH [12].

**Scheme 1**

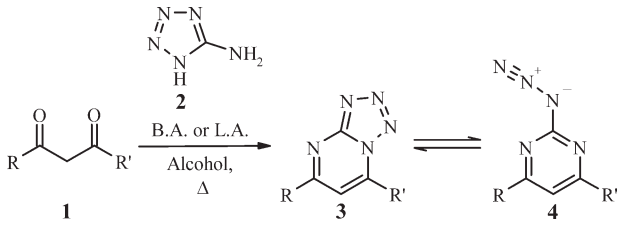


**Table 1**

Synthesis of 2-azidopyrimidines **4**.[a]

| Entry | Compound | R | R′ | Method[c] | Solvent | Time (h) | Yield (%)[d] | DSC: Exotherm (J/g)[e] | DSC: Peak interval (°C) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | Me | H[b] | A | EtOH | n.d. | n.d. | 1457 | 138–224 |
| 2 | **4a** | Me | H[b] | B | EtOH | 3 | 17 | | |
| 3 | **4b** | Me | Me | A | EtOH | 4 | 42 | 1578 | 163–273 |
| 4 | **4b** | Me | Me | B | EtOH | 3 | 98 | | |
| 5 | **4c** | Ph | Me | A | EtOH | 2 | 84 | 1188 | 193–269 |
| 6 | **4c** | Ph | Me | B | EtOH | 72 | 43 | | |
| 7 | **4d** | Ph | Ph | A | MeOH | 48 | 23 | 851 | 169–272 |
| 8 | **4d** | Ph | Ph | B | EtOH | n.d. | 0 | | |
| 9 | **4e** | Ph | $CO_2Me$ | A | EtOH | 48 | 35 | 1145 | 181–298 |
| 10 | **4e** | Ph | $CO_2Me$ | B | EtOH | n.d. | n.d. | | |

[a] The reactions were run with equimolar proportions of diketone **1** and aminotetrazole **2**.
[b] The corresponding dimethyl acetal **1a** was used.
[c] Method A: 10 mol % of conc. HCl (aq) in refluxing solvent. Method B: Preincubated solution of 10 mol % $CuCl_2$ and 10 mol % Vitamin C at ambient temperature.
[d] Isolated yield.
[e] The measured exotherms are >800 J/g, the compounds should thus be treated as potentially explosive. We strongly advise to take safety precautions, as e.g. described in *Bretherick's Handbook of Reactive Chemical Hazards* [14].

When applying single-crystal diffraction technique on a select cyclodehydration product, subsequent X-ray analysis clearly demonstrated that the compound preferred the azido-tautomer in the solid state (Fig. 1) [13].

Considering the generally high nitrogen content manifest in 2-azidopyrimidines **4**, the prepared compounds were submitted to differential scanning calorimetry (DSC) for the purpose of establishing safety margins (Table 1). Based on the relative thermal stability and yield, **4c** was subsequently selected as the candidate dipole to be tested in CuAAC (Scheme 2).

In accordance with the precognized conditions published by Sharpless and coworkers [3], cycloaddition was initially attempted utilizing an *in situ* generated Cu(I)-catalyst and a polar solvent. However, no product formation was observed and the reaction remained unresponsive to alteration of temperature as well as electronic modulation of the dipolarophile **5** (Table 2; entry 1,2).

Surprisingly, when the catalytic constellation was interchanged and Cu(I) instead was added directly, reaction proceeded at elevated temperatures. Furthermore, it became evident that the nature of the alkyne substituent dramatically affected the rate. Thus, with an aryl appendage, cycloaddition occurred only reluctantly, while the ester counterpart participated readily (Table 2; entry 3,4).

To encourage swifter conversion, it was in turn opted to perform the CuAAC in a nonpolar solvent. Seeing the ability to delocalize charge within its interior, the pyrimidine featured in **4c** effectively acts as an electronic

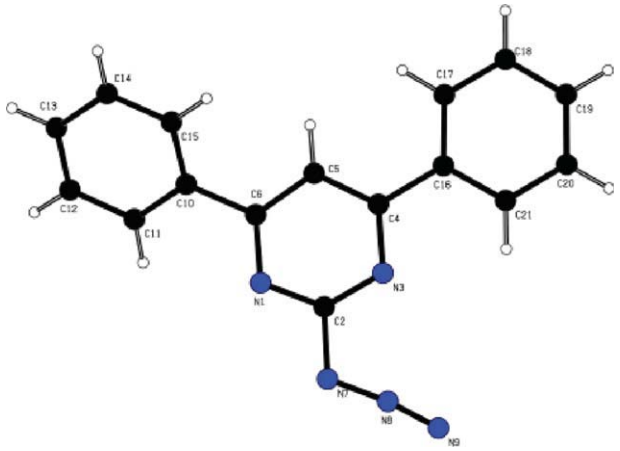


**Figure 1.** Crystal structure of compound **4d** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2**

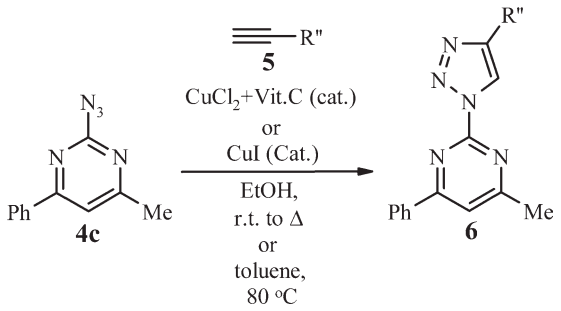


**Table 2**

Synthesis of 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidines **6**.[a]

| Entry | Compound | R′′ | Solvent | Temp.(°C) | Catalyst/Loading (mol%) | Time (h) | Yield[c]/Conversion[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | Ph | EtOH | r.t. to δ | $CuCl_2$+Vit.C/10 | 1 Week | n.d./No |
| 2 | **6b** | $CO_2Et$ | EtOH | r.t. to δ | $CuCl_2$+Vit.C/10 | 1 Week | n.d./No |
| 3 | **6a** | Ph | EtOH | δ | CuI/10 | 1 Week | n.d./Full |
| 4 | **6b** | $CO_2Et$ | EtOH | δ | CuI/10 | 4 | n.d./Full |
| 5 | **6a** | Ph | Toluene | 80 | CuI/5 | 2 | 64/Full |
| 6 | **6b** | $CO_2Et$ | Toluene | 80 | CuI/5 | 2 | 77/Full |
| 7 | **6c** | *o*-Toluyl | Toluene | 80 | CuI/5 | 15[b] | 56/Full |
| 8 | **6d** | *m*-Toluyl | Toluene | 80 | CuI/5 | 15[b] | 70/Full |
| 9 | **6e** | *p*-Toluyl | Toluene | 80 | CuI/5 | 15[b] | 67/Full |
| 10 | **6f** | *o*-Anisyl | Toluene | 80 | CuI/5 | 2 | 58/Full |
| 11 | **6g** | *m*-Anisyl | Toluene | 80 | CuI/5 | 2 | 73/Full |
| 12 | **6h** | *p*-Anisyl | Toluene | 80 | CuI/5 | 2 | 58/Full |
| 13 | **6i** | 4-(Dimethylamino)phenyl | Toluene | 80 | CuI/5 | 24 | 71/Full |
| 14 | **6j** | 6-Methoxynaphth-2-yl | Toluene | 80 | CuI/5 | 7 | 71/Full |
| 15 | **6k** | Benzyl | Toluene | 80 | CuI/5 | 2 | 72/Full |
| 16 | **6l** | Cyclopropyl | Toluene | 80 | CuI/5 | 3 | 91/Full |
| 17 | **6m** | Diethoxymethyl | Toluene | 80 | CuI/5 | 2 | 79/Full |
| 18 | **6n** | $CO_2Me$ | Toluene | 80 | CuI/5 | 3 | 51/Full |

[a] The reactions were performed on an 0.47 mmol scale with equimolar proportions of azide **4c** and alkyne **5**.
[b] The reaction was run overnight.
[c] Isolated yield after recrystallization.
[d] The reactions were monitored by HPLC and LC-MS.

sink, draining the azide of its latent reactivity. Running the CuAAC in a nonpolar solvent would thus *a priori* act as a counter, disfavoring charge separation and ensure a more well-behaved dipole. Gratifyingly, the choice solvent proved efficacious in bringing about the reaction: By changing from ethanol to toluene, rapid reaction was realized with both aryl and ester appended alkyne **5**. Additionally, the catalytic mediation of copper was underpinned on the account that 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidine **6** was the sole cyclized product observed. In contrast to the preceding literature [3], neither additional base nor the exclusion of oxygen was needed, as none of the reported by-products were formed.

Having established workable conditions, the generality of the CuAAC was tested by subjecting 2-azidopyrimi-dine **4c** to an ensemble of terminal alkynes **5**, exploring both electronic and steric effects (Table 2; entry 5–18). In the majority of cases, full conversion was realized smoothly within a couple of hours and at the latest after 24 h. The isolated yield of compound **6** varied between 51 and 91% after recrystallization, which was performed to remove the catalyst.

## CONCLUSIONS

This article outlines a novel protocol for highly selective copper-catalyzed 1,3-dipolar cycloaddition between electron deficient hetaryl azides and a variety of terminal alkynes. Applied on 2-azidopyrimidines, the protocol allows smooth transformation to the corresponding 4′-substituted 2-triazolylpyrimidines in the absence of any auxiliary reagents.

## EXPERIMENTAL

NMR spectra were recorded either on a Bruker DPX400 NMR spectrometer operating at 400 MHz for $^1$H, and 101

MHz for $^{13}C$ equipped with a 4-nucleus probe-head with Z-gradients, or a Bruker Avance III 500 NMR spectrometer, operating at 500 MHz for $^{1}H$ and 126 MHz for $^{13}C$ equipped with a 5 mm TCI cryo probe-head with Z-gradients. Chemical shifts are given in ppm down- and upfield from TMS (0.00 ppm). DMSO-$d_6$ $\delta_H$ 2.49; $\delta_C$ 39.51 and $CDCl_3$ $\delta_H$ 7.27; $\delta_C$ 77.00 were used as reference signals. All experiments were performed at a sample temperature of 26°C ± 2°C. LC-MS analyses were performed on a LC-MS system consisting of a Waters Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 75 ELS detector, and a ZQ 2000 single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. The capillary voltage was set to 3.3 kV and the cone voltage to 28 V, respectively. The mass spectrometer was scanned between *m/z* 100 and 700 with a scan time of 0.3 s. The diode array detector scanned from 200 to 400 nm. The temperature of the ELS detector was adjusted to 40°C, and the pressure was set to 1.9 bar. Separation was performed on an Gemini C18 3.0 × 50, 3 μm (Phenomenex) run at a flow rate of 1 mL/min. A linear gradient was applied starting at 100% A (A: 10 m*M* $NH_4OAc$ in 5% $CH_3CN$) ending at 100% B (B: $CH_3CN$) in 4 min followed by 100% B until 5.5 min. The column oven temperature was set to 40°C. HPLC analyses were performed on an Agilent HP1100 system consisting of a G1322A Micro Vacuum Degasser, a G1311A Quaternary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostated Column Compartment and a G1315A Diode Array Detector. The diode array detector was scanned from 200 to 400 nm, step and peak width were set to 2 nm and 0.01 min, respectively. The column used was an Gemini C18, 3.0 mm × 50 mm, 3.0 μm, 110 Å run at a flow rate of 1.0 mL/min. The column oven temperature was set to 40°C. A linear gradient was applied, starting at 100% A (A: 10 m*M* $NH_4OAc$ in 5% $CH_3CN$) and ending at 95% B (B: $CH_3CN$) after 6.5 min then 95% B for 0.5 min. High resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof micro mass spectrometer equipped with a LockSpray source and connected to an Acquity UPLC system with a PDA detector. All analyses were acquired using positive mode electrospray ionization (ESI+) in full scan, and Leucine Enkephalin (Sigma) was used as the lock mass (m/z 556.2771) at a concentration of 0.9 pmol/μL and a flow rate of 100 μL/min with a 1:10 split, ion source:waste. Cone Voltage was set to 54 to achieve ~200 counts for Leucine Enkephalin. Nitrogen was used as the nebulizing and desolvation gas, with the source operated at 120°C and the desolvation gas at 300°C. Capillary voltage was 3000 V, Cone voltage 30 V. Argon was used as the collision gas. Chromatographic separation for HRMS was achieved with a 2.3 min linear gradient from 95% A (A: 10 m*M* NH4OAc in MilliQ water + 5% MeCN) to 95% B (B: MeCN) over an ACQUITY UPLC BEH C18 1.7 μm, 2.1 mm × 50 mm column maintained at 65°C and run at a flow rate of 0.7 mL/min with a 1:5 split, ion source:waste. Analytes were diluted in H2O:ACN (50:50) until suitable concentration for the LC-MS analysis. DSC was performed in a Mettler Toledo DSC 820 equipped with a high-pressure gold-plated capsule in the temperature range of 30–500°C using a heating rate of 5 K/min.

**2-Azido-4-methylpyrimidine (4a)**

***Method B.*** $CuCl_2$ (10.1 mg, 0.07 mmol) was dissolved in MeOH (2 mL), resulting in a green solution. Ascorbic acid (13.3 mg, 0.07 mmol) was added and the mixture was stirred for 5 min, to give a colorless solution. 4,4-Dimethoxybutan-2-one (**1a**) (100 mg, 0.76 mmol) and 1H-tetrazol-5-amine (**2**) (64.4 mg, 0.76 mmol) were added in sequence and the mixture was stirred at ambient temperature for 3 h. Saturated $NH_4Cl$ (10 mL) was added and the resulting suspension was extracted with EtOAc (5 × 30 mL). The organic layers were dried with $NaSO_4$ and evaporated *in vacuo*. The crude material was washed with hot heptane, yielding the title compound as a pink solid after failed recrystallization with MeOH/$H_2O$. Yield: 19 mg, 17%. $^{1}H$ NMR (400 MHz, DMSO-$d_6$): δ 2.93 (s, 3H), 7.48 (d, $J$ = 4.3 Hz, 1H), 9.02 (d, $J$ = 4.3 Hz, 1H). MS: (ES) *m/z* 136 [M+1].

**2-Azido-4,6-dimethylpyrimidine (4b)**

***Method A.*** Pentane-2,4-dione (**1b**) (0.103 mL, 1.00 mmol) was dissolved in EtOH (2.5 mL) and hydrochloric acid, 37% (0.1 mL) to give a colorless solution. 1H-Tetrazol-5-amine (**2**) (85 mg, 1.00 mmol) was added and the resulting mixture refluxed for 4 h. The formed suspension was evaporated to dryness yielding a white solid, and the solid was redissolved in a minimal amount of hot EtOH. The title compound precipitated on cooling and was collected by suction filtration as a white solid. Yield: 63 mg, 42%.

***Method B.*** $CuCl_2$ (13.4 mg, 0.01 mmol) was dissolved in EtOH (3 mL), resulting in a green solution. Ascorbic acid (17.6 mg, 0.01 mmol) was added and the mixture was stirred for 5 min to give a colorless, homogenous, mixture. Pentane-2,4-dione (**1b**) (0.103 mL, 1.00 mmol) and 1H-tetrazol-5-amine (**2**) (85 mg, 1.00 mmol) were added in sequence, and the resulting mixture was stirred at ambient temperature for 3 h. Saturated $NH_4Cl$ (10 mL) was added and the resulting suspension was extracted with EtOAc (5 × 30 mL). The organic layers were dried with $NaSO_4$ and evaporated *in vacuo*, yielding the title compound as a white solid. Yield: 132 mg, 98%. $^{1}H$ NMR (400 MHz, DMSO-$d_6$): δ 2.61 (m, 3H), 2.86 (s, 3H), 7.39 (s, 1H). MS: (ES): *m/z* 150 [M+1], 148 [M–1].

**2-Azido-4-methyl-6-phenylpyrimidine (4c)**

***Method A.*** 1-Phenylbutane-1,3-dione (**1c**) (100 mg, 0.62 mmol) was dissolved in EtOH (2.5 mL) and hydrochloric acid, 37% (0.06 mL) to give a colorless solution. 1H-Tetrazol-5-amine (**2**) (52.5 mg, 0.62 mmol) was added and the resulting mixture was refluxed for 2 h. The formed suspension was evaporated *in vacuo*, yielding a white solid. The solid was dissolved in hot EtOH and cooled to ambient temperature, followed by storage in the refrigerator overnight. The precipitated material was collected by suction filtration to yield the title compound as colorless, needle-like crystals. Yield: 111 mg, 84%. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 2.97 (s, 3H), 7.6–7.7 (m, 3H), 8.18 (s, 1H), 8.3–8.4 (m, 2H). MS; ES *m/z* 212 [M+1].

***Method B.*** $CuCl_2$ (4.2 mg, 0.03 mmol) was dissolved in EtOH (3 mL), resulting in a green solution. Ascorbic acid (17.6 mg, 0.03 mmol) was added, and the mixture was stirred for 5 min to give a colorless, homogenous mixture. 1-Phenylbutane-1,3-dione (**1c**) (100 mg, 0.62 mmol) and 1H-tetrazol-5-amine (**2**) (52 mg, 0.62 mmol) were added in sequence, and the resulting mixture was stirred at ambient temperature for 72 h. Saturated $NH_4Cl$ (10 mL) was added and the resulting suspension was extracted with EtOAc (5 × 30 mL). The organic layers were dried with $NaSO_4$ and evaporated *in vacuo*. The crude material was recrystallized in MeOH/$H_2O$, yielding the titled compound as colorless, needle-like, crystals. Yield: 56 mg, 43%.

**2-Azido-4,6-diphenylpyrimidine (4d)**

***Method A.*** 1,3-Diphenylpropane-1,3-dione (**1d**) (100 mg, 0.45 mmol) was dissolved in EtOH (2.5 mL) and hydrochloric acid 37% (0.04 mL, 0.48 mmol) to give a colorless solution. 1H-

Tetrazol-5-amine (**2**) (40 mg, 0.45 mmol) was added and the resulting mixture was refluxed for 48 h. The mixture was cooled to ambient temperature, followed by storage in the refrigerator overnight. The precipitated material was collected by suction filtration to yield the title compound as colorless, needle-like crystals. Yield: 27.8 mg, 23%. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.5–7.8 (m, 6H), 8.3–8.5 (m, 5H). MS: (ES) *m*/*z* 274 [M+1].

**Methyl 2-azido-6-phenylpyrimidine-4-carboxylate (4e)**

***Method A.*** Methyl 2,4-dioxo-4-phenylbutanoate (**1e**) (100 mg, 0.48 mmol) was dissolved in EtOH (3 mL) and hydrochloric acid 37% (0.04 mL, 0.48 mmol) to give a colorless mixture. 1H-Tetrazol-5-amine (**2**) (41.3 mg, 0.48 mmol) was added and the resulting mixture was refluxed for 48 h. The solution was cooled to ambient temperature, followed by storage in the refrigerator overnight. The precipitated material was collected by suction filtration to yield the title compound as colorless, needle-like crystals. Yield: 43.4 mg, 35%. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.96 (s, 3H), 7.6–7.7 (m, 3H), 8.2–8.3 (m, 3H). MS: (ES) *m*/*z* 256 [M+1].

**General procedure for the synthesis of 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidines (6).** Copper(I) iodide (9 mg, 0.05 mmol) was suspended in toluene (2 mL), whereupon the alkyne (**5**) (0.47 mmol) was added, followed by 2-azido-4-methyl-6-phenylpyrimidine (**4c**) (100 mg, 0.47 mmol) to yield a heterogeneous mixture. The resulting reaction mixture was heated to 80°C for the time specified (Table 2) and full conversion was observed according to HPLC. The volatiles were evaporated *in vacuo* to afford the crude as a solid. The solid was suspended/dissolved in a minimum of hot EtOH, and water was subsequently added until a turbid liquid phase was observed. Upon refrigeration/cooling precipitation ensued and the product was isolated and dried to give the yield specified.

***4-Methyl-6-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrimidine (6a).*** Starting alkyne: Ethynylbenzene (**5a**). Reaction time: 2 h. Yield: 95 mg, 64%. $^1$H NMR (500 MHz, $CDCl_3$): δ 2.77 (s, 3H), 7.40 (t, $J$ = 7.5 Hz, 2H), 7.65 (s, 1H), 8.01 (d, $J$ = 7.8 Hz, 2H), 7.61–7.54 (m, $J$ = 7.1 Hz, 3H), 7.49 (t, $J$ = 7.5 Hz, 2H), 8.21 (dd, $J$ = 6.8 Hz, 7.8 Hz, 2H), 8.94 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 24.6, 58.5, 115.5, 118.5, 126.1, 127.4, 128.5, 128.9, 129.1, 130.1, 131.8, 135.4, 147.9, 154.5, 166.0, 170.8. MS: (ES) *m*/*z* 314 [M+1]. HPLC: $R_t$= 4.6 min. HRMS: Found 314.1406, calc. for $C_{19}H_{16}N_5$: 314.1400.

***Ethyl 1-(4-methyl-6-phenylpyrimidin-2-yl)-1H-1,2,3-triazole-4-carboxylate (6b).*** Starting alkyne: Ethyl propiolate (**5b**). Reaction time: 2 h. Yield: 112 mg, 90%. $^1$H NMR (500 MHz, $CDCl_3$): δ 1.47 (t, $J$ = 7.4 Hz, 3H), 2.76 (s, 3H), 4.50 (q, $J$ = 7.4 Hz, 2H), 7.5–7.6 (m, 3H), 7.69 (s, 1H), 8.19 (dd, $J$ = 7.2 Hz, 2H), 9.24 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 14.4, 24.6, 61.6, 116.1, 126.9, 127.4, 129.2, 132.0, 135.0, 140.3, 154.1, 160.6, 166.2, 171.1. MS: (ES) *m*/*z* 310 [M+1]. HPLC: $R_t$= 4.9 min. HRMS: Found 310.1305, calc. for $C_{16}H_{16}N_5O_2$: 310.1304.

***4-Methyl-6-phenyl-2-(4-o-tolyl-1H-1,2,3-triazol-1-yl)pyrimidine (6c).*** Starting alkyne: 1-Ethynyl-2-methylbenzene (**5c**). Reaction time: Overnight. Yield: 88 mg, 56%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.78 (s, 3H), 7.3–7.4 (m, 3H), 7.5–7.6 (m, 3H), 7.66 (s, 1H), 7.9 (m, 1H), 8.2–8.3 (m, 2H), 8.80 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.40, 24.6, 115.4, 120.6, 126.1, 127.4, 128.5, 129.1, 129.3, 129.5, 130.9, 131.7, 135.4, 136.0, 147.3, 154.6, 166.0, 170.8. MS: (ES) *m*/*z* 328 [M+1]. HPLC: $R_t$ = 5.8 min. HRMS: Found 328.1570, calc. for $C_{20}H_{18}N_5$: 328.1562.

***4-Methyl-6-phenyl-2-(4-m-tolyl-1H-1,2,3-triazol-1-yl)pyrimidine (6d).*** Starting alkyne: 1-Ethynyl-3-methylbenzene (**5d**). Reaction time: Overnight. Yield: 109 mg, 70%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.76 (s, 3H), 7.37 (t, $J$ = 7.5 Hz 1H), 7.5–7.6 (m, 3H), 7.63 (s, 1H), 7.64 (s, 1H), 7.78 (d, $J$ = 7.5 Hz 1H), 7.86 (s, 1H), 8.2–8.3 (m, 2H), 8.91 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.4, 24.6, 115.4, 118.5, 123.2, 126.7, 127.4, 128.7, 129.1, 129.3, 130.0, 131.7, 135.5, 138.6, 148.0, 154.5, 166.0, 170.8. MS: (ES) *m*/*z* 328 [M+1]. HPLC: $R_t$ = 5.9 min. HRMS: Found 328.1569, calc. for $C_{20}H_{18}N_5$: 328.1562.

***4-Methyl-6-phenyl-2-(4-p-tolyl-1H-1,2,3-triazol-1-yl)pyrimidine (6e).*** Starting alkyne: 1-Ethynyl-4-methylbenzene (**5e**). Reaction time: Overnight. Yield: 105 mg, 67%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.75 (s, 3H), 7.29 (d, $J$ = 8.0 Hz, 3H), 7.5–7.6 (m, 3H), 7.63 (s, 1H), 7.90 (d, $J$ = 8.0 Hz, 2H), 8.2–8.3 (m, 2H), 8.86 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.3, 24.6, 115.4, 118.1, 126.00, 127.3, 127.4, 129.1, 129.5, 131.7, 135.5, 138.4, 148.0, 154.5, 166.0, 170.8. MS: (ES) *m*/*z* 328 [M+1]. HPLC: $R_t$ = 5.9 min. HRMS: Found 328.1568, calc. for $C_{20}H_{18}N_5$: 328.1562.

***2-(4-(2-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6f).*** Starting alkyne: 1-Ethynyl-2-methoxy-benzene (49). Reaction time: 2 h. Yield: 95 mg, 58%. $^1$H NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 3H), 4.03 (s, 3H), 7.04 (d, $J$ = 8.4 Hz, 1H), 7.13 (t, $J$ = 7.6 Hz, 1H), 7.2–7.4 (m, 1H), 7.6 (m, 3H), 7.64 (s, 1H), 8.2–8.3 (m, 2H), 8.5 (m, 1H), 9.10 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 24.5, 55.5, 110.7, 115.3, 118.9, 120.9, 121.7, 127.4, 128.2, 129.0, 129.2, 131.6, 135.5, 143.3, 154.7, 155.9, 165.9, 170.6. MS: (ES) *m*/*z* 344 [M+1]. HPLC: $R_t$ = 5.7 min. HRMS: Found 344.1522, calc. for $C_{20}H_{18}N_5O$: 344.1511.

***2-(4-(3-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6g).*** Starting alkyne: 1-Ethynyl-3-methoxy-benzene (**5g**). Reaction time: 2 h. Yield: 120 mg, 73%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3H), 3.91 (s, 3H), 6.9–7.0 (m, 1H), 7.38 (t, $J$ = 8.1 Hz, 1H), 7.5–7.6 (m, 5H), 7.64 (s, 1H), 8.2–8.3 (m, 2H), 8.91 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 24.6, 55.4, 111.1, 114.6, 115.5, 118.5, 118.7, 127.4, 129.1, 129.9, 131.4, 131.8, 135.4, 147.8, 154.4, 160.0, 166.0, 170.8. MS: (ES) *m*/*z* 344 [M+1]. HPLC: $R_t$= 5.6 min. HRMS: Found 344.1503, calc. for $C_{20}H_{18}N_5O$: 344.1511.

***2-(4-(4-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6h).*** Starting alkyne: 1-Ethynyl-4-methoxy-benzene (**5h**). Reaction time: 2 h. Yield: 95 mg, 58%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3H), 3.87 (s, 3H), 7.01 (d, $J$ = 8.8 Hz, 2H), 7.5–7.6 (m, 3H), 7.64 (s, 1H), 7.93 (d, $J$ = 8.8 Hz, 2H), 8.2–8.3 (m, 2 H), 8.84 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 24.6, 55.3, 114.2, 115.4, 117.6, 122.8, 127.2, 127.4, 128.2, 128.9, 129.1, 129.3, 131.3, 131.7, 132.4, 135.4, 147.8, 154.5, 159.8, 166.0, 170.8. MS: (ES) *m*/*z* 344 [M+1]. HPLC: $R_t$ = 5.5 min. HRMS: Found 344.1504, calc. for $C_{20}H_{18}N_5O$: 344.1511.

***N,N-Dimethyl-4-(1-(4-methyl-6-phenylpyrimidin-2-yl)-1H-1,2,3-triazol-4-yl)aniline (6i).*** Starting alkyne: 4-Ethynyl-*N,N*-dimethylbenzenamine (**5i**). Reaction time: 24 h. Yield: 120 mg, 71%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.75 (s, 3H), 3.02 (s, 6H), 6.82 (d, $J$ = 8.7 Hz, 2H), 7.5–7.6 (m, 3H), 7.62 (s, 1H), 7.87 (d, $J$ = 8.7 Hz, 2H), 8.2–8.3 (m, 2H), 8.78 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 24.6, 40.5, 112.4, 115.2, 116.7, 127.1, 127.4, 129.1, 131.6, 135.6, 118.2, 148.4, 150.6, 154.6,

165.9, 170.7. MS: (ES) *m/z* 357 [M+1]. HPLC: $R_t$ = 5.8 min. HRMS: Found 357.1823, calc. for $C_{21}H_{21}N_6$: 357.1828.

***2-(4-(6-Methoxynaphthalen-2-yl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6j).*** Starting alkyne: 2-ethynyl-6-methoxynaphthalene (**5j**). Reaction time: 7 h. Yield: 133 mg, 71%. $^1$H NMR (400 MHz, $CDCl_3$): δ 3.31 (s, 3H), 3.90 (s, 3H), 7.1–7.3 (m, 3H), 7.3–7.4 (m, 1H), 7.6–7.7 (m, 3H), 7.94 (d, $J$ = 8.9 Hz, 2H), 8.2–8.3 (m, 2H), 8.4–8.5 (m, 2H), 8.59 (bs, 1 H), 9.60 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ 24.6, 55.3, 105.7, 115.5, 118.3, 119.3, 124.6, 124.9, 125.3, 127.36, 127.43, 128.9, 129.1, 129.8, 131.8, 134.5, 135.4, 148.1, 154.5, 158.0, 166.0, 170.8. MS: (ES) *m/z* 394 [M+1]. HPLC: $R_t$ = 6.2 min. HRMS: Found 394.1660, calc. for $C_{24}H_{20}N_5O$: 394.1668.

***2-(4-Benzyl-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6k).*** Starting alkyne: Prop-2-ynylbenzene (**5k**). Reaction time: 2 h. Yield: 112 mg, 72%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.72 (s, 3H), 4.24 (s, 2H), 7.2-7.3 (m, 1H), 7.34 (d, $J$ = 4.6 Hz, 4H), 7.5–7.6 (m, 3H), 7.60 (s, 1H), 8.13 (dd, $J$ = 8.2 Hz, 7.2 Hz, 2H), 8.35 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 24.5, 32.2, 115.4, 120.7, 126.6, 127.4, 128.6, 128.8, 129.0, 131.7, 135.4, 138.7, 148.0, 154.5, 165.9, 170.7. MS: (ES) *m/z* 328 [M+1]. HPLC: $R_t$= 4.6 min. HRMS: Found 328.1552, calc. for $C_{20}H_{18}N_5$: 328.1562.

***2-(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6l).*** Starting alkyne: Ethynylcyclopropane (**5l**). Reaction time: 3 h. Yield: 119 mg, 91%. $^1$H NMR (400 MHz, $CDCl_3$): δ 0.9–1.0 (m, 4H), 2.1–2.2 (m, 1H), 2.73 (s, 1H), 7.5–7.6 (m, 3H), 7.61 (s, 1H), 8.1–8.2 (m, 2H), 8.36 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 6.78, 7.89, 24.6, 115.2, 118.5, 127.4, 129.1, 131.7, 135.5, 154.5, 165.9, 170.7. MS: (ES) *m/z* 277 [M+1]. HPLC: $R_t$= 4.9 min. HRMS: Found 278.1409, calc. for $C_{16}H_{16}N_5$: 278.1406.

***2-(4-Diethoxymethyl-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6m).*** Starting alkyne: 3,3-Diethoxyprop-1-yne (**43**). Reaction time: 2 h. Yield: 127 mg, 79%. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, $J$ = 7.1 Hz, 6H), 2.81 (bs, 3H), 3.6–3.8 (m, 4H), 5.87 (s, 1H), 7.5–7.6 (m, 3H), 7.66 (s, 1H), 8.1–8.2 (m, 2H), 8.76 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 15.2, 24.7, 61.6, 96.5, 115.7, 121.4, 127.4, 129.1, 131.8, 135.3, 147.5, 166.0, 170.8. MS: (ES) *m/z* 278 [M–61]. HPLC: $R_t$ = 4.9 min. HRMS: Found 294.1351, calc. for $C_{16}H_{16}N_5O$: 294.1354 (The parent ion could not be observed. The observed mass corresponds to $[M+H^+ - C_2H_6O]$.)

***Methyl 1-(4-methyl-6-phenylpyrimidin-2-yl)-1H-1,2,3-triazole-4-carboxylate (6n).*** Starting alkyne: Methyl propiolate (**37**). Reaction time: 3 h. Yield: 77 mg, 51%. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3H), 4.03 (s, 3H), 7.69 (s, 1H), 7.5–7.6 (m, 3H), 8.1–8.2 (m, 2H), 9.26 (s, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 24.6, 52.4, 116.1, 127.0, 127.4, 129.2, 132.0, 135.0, 140.1, 154.1, 161.0, 166.2, 171.1. MS: (ES) *m/z* 296 [M+1]. HPLC: $R_t$ = 4.5 min. HRMS: Found 296.1137, calc. for $C_{15}H_{14}N_5O_2$: 296.1147.

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## REFERENCES AND NOTES

[1] Huisgen, R.; Szeimies, G.; Möbius, L. Chem Ber 1967, 100, 2494.

[2] Tornöe, C. W.; Christensen, C.; Meldal, M. J Org Chem 2002, 67, 3057.

[3] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew Chem Int Ed 2002, 41, 2596.

[4] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew Chem Int Ed 2001, 40, 2004.

[5] Kolb, H. C.; Sharpless, K. B. Drug Discov Today 2003, 8, 1128.

[6] Sharpless, K. B.; Manetsch, R. Expert Opin Drug Discov 2006, 1, 525.

[7] Cosyn, L.; Palaniappan, K. K.; Kim, S.-K.; Duong, H. T.; Gao, Z.-G.; Jacobson, K. A.; Van Calenbergh, S. J Med Chem 2006, 49, 7373.

[8] Gupte, A.; Boshoff, H. I.; Wilson, D. J.; Neres, J.; Labello, N. P.; Somu, R. V.; Xing, C.; Barry C. E., III; Aldrich, C. C. J Med Chem 2008, 51, 7495.

[9] Lu, R. J.; Tucker, J. A.; Zinevitch, T.; Kirichenko, O.; Konoplev, V.; Kuznetsova, S.; Sviridov, S.; Pickens, J.; Tandel, S.; Brahmachary, E.; Yang, Y.; Wang, J.; Freel, S.; Fisher, S.; Sullivan, A.; Zhou, J.; Stanfield-Oakley, S.; Greenberg, M.; Bolognesi, D.; Bray, B.; Koszalka; B.; Jeffs, P.; Khasanov, A.; Ma, Y-A.; Jefferies, C.; Liu, C.; Proskurina, T.; Zhu, T.; Chucholowski, A.; Li, R.; Sexton, C. J Med Chem 2007, 50, 6535.

[10] Farmer, J. J.; Bhattacharjee, A.; Chen, Y.; Goldberg, J. A.; Ippolito, J. A.; Kanyo, Z. F.; Lou, R.; Oyelere, A. K.; Sherer, E. C.; Sutcliffe, J. A.; Wang, D.; Wu, Y.; Du, Y. PCT Int Appl WO 2005, 085266 A2, 332 p.

[11] Nolsöe, J. M. J.; Ertan, A.; Svensson, M.; Weigelt, D. J Heterocycl Chem 2010, 47.

[12] Wentrup, C. Tetrahedron 1970, 26, 4969.

[13] Compound **4d**, $C_{16}$ $H_{11}$ $N_5$ ($M_r$ = 273.30), Colorless, Rod, Monoclinic space group $P$ $2_1/c$, $Z$ = 4, $a$ = 11.437(1) Å, $b$ = 16.761(1) Å, $c$ = 7.030(1) Å, α = 90°, β = 94.435(2)°, γ = 90°, $V$ = 1343.6(2) Å$^3$, Mo $K\alpha$ radiation, θ = 1.0–27.5°, 6126 measured reflections, $T$ = 200(2) K on Bruker-Nonius KappaCCD diffractometer. The structure was solved using direct methods SIR97 (Altomare *et al*., 1999). Program used to refine structure: SHELXL97 (Sheldrick, 1997). Molecular graphics: PLATON (Spek, 2003). The final $R[F^2 > 2\sigma(F^2)]$ = 0.0567 and $wR = [w = 1/[\sigma^2(F_o^2) + (0.0730P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$.

[14] Urben, P. G. Bretherick's Handbook of Reactive Chemical Hazards, Vol. 1–2, 7th ed.; Elsevier: Oxford, 2007.

# Double 1,3-Dipolar Cycloaddition of *N*-Methyl Azomethine Ylide to Meta-Dinitrobenzene Annelated with Nitrogen Aromatic Heterocycles



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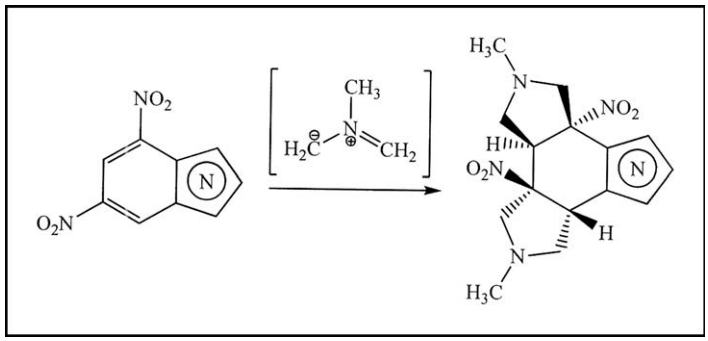


The 1,3-dipolar cycloaddition of unstabilized azomethine ylide **1** with meta-dinitrobenzene fused with nitrogen heterocycles affords the corresponding decahydropyrrolo[3,4-*e*]isoindole cycloadducts in good yields. This is a first example of [3+2]-cycloaddition of azomethine ylides to nitroarenes.

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## INTRODUCTION

The 1,3-dipolar cycloaddition (1,3-DC) reactions play one of the most important roles in modern organic synthesis, being simple and available method for the preparation of different five-membered heterocycles. It is important that 1,3-DC usually proceeds regio- and stereoselectively [1]. A number of dipoles, including azomethine ylides, readily undergo cycloaddition reactions with conjugated nitroalkenes [2]. As a result, pyrrolidine derivatives are formed (Scheme 1); this heterocycle is a part of many natural compounds and pharmaceuticals [3].

## RESULTS AND DISCUSSION

We have found that nitro arenes, e.g. 1,3-dinitrobenzene and 1,3,5-trinitrobenzene, do not form the cycloaddition products with azomethine ylides. We believe that 1,3-DC with nitro arenes requires the reduction of their aromaticity in order to carbon–carbon double bond of C— C—$NO_2$ fragment would approach to that of conjugated nitro alkenes. It is known that isoelectronic process – [4+2]-cycloaddition to unsaturated compounds (Diels-Alder reaction) takes place in case of meta-dinitroarenes, fused with some aromatic nitrogen heterocycles [4]. In this connection, we studied an interaction of *N*-methyl azomethine ylide **1** with meta-dinitrobenzene annelated with number of aromatic nitrogen heterocycles. Azomethine ylide **1** was generated *in situ* from sarcosine and paraformaldehyde refluxing in toluene [2(a)] in the presence of dinitro compounds **2a-e** [5] as dipolarophiles (Scheme 2).

In all cases, the double cycloaddition afforded the previously unknown tetracyclic heterosystems – fused decahydropyrrolo[3,4-*e*]isoindoles **3a-e**.

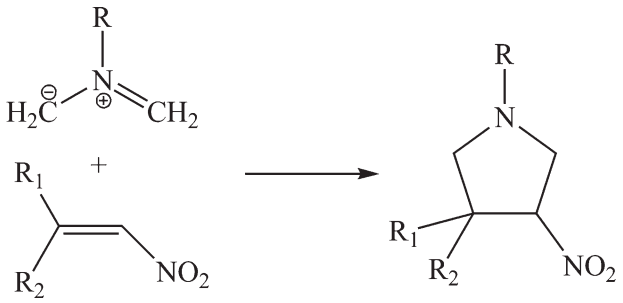
It should be noted that azomethine ylide **1** formed cycloaddition products more readily than dienes: dinitro compounds **2a** and **2d** did not undergo Diels-Alder reactions with dienes though they form cycloaddition adducts with azomethine ylide **1**.

Diels-Alder reactions can be carried out in case of aromatic nitro carbocycles only if they are fused with some strong electron-withdrawing five-membered nitrogen heterocycles – furoxan, furazan, and some of their analogs [4]. This increases the electrophilicity dramatically (by many orders of magnitude), e.g. the ability to add nucleophiles to the benzene ring that indicates the considerable reduction of aromaticity in comparison with 1,3,5-trinitrobenzene [6].

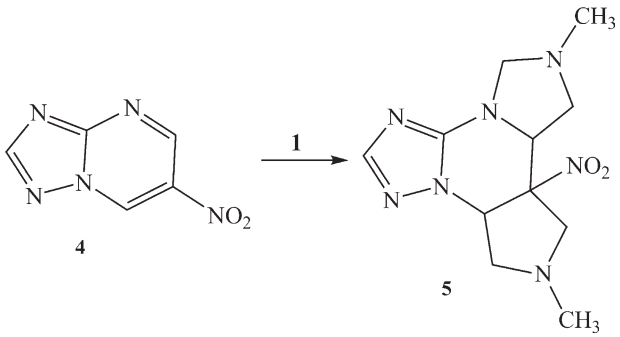
In case of azomethine ylide **1**, the cycloaddition takes place also if less electron-deficient *N*-heterocycle is fused with dinitro arene.

The formation of cycloaddition products **3a-e** seems to be diastereoselective. In case of compound **3a**, the crystal and molecular structure (Fig. 1) confirmed the expected cis-addition of the azomethine ylide [7].

**Scheme 1**



**Scheme 3**



X-ray analysis data shows that the cycloaddition occurred from the opposite sides of the dinitro arene plane.

Interestingly that double cycloaddition of azomethine ylide **1** was possible even in the presence of one nitro group as was illustrated by the reaction with nitrotriazolo[1,5-a]pyrimidine [8] (**4**) (Scheme 3):

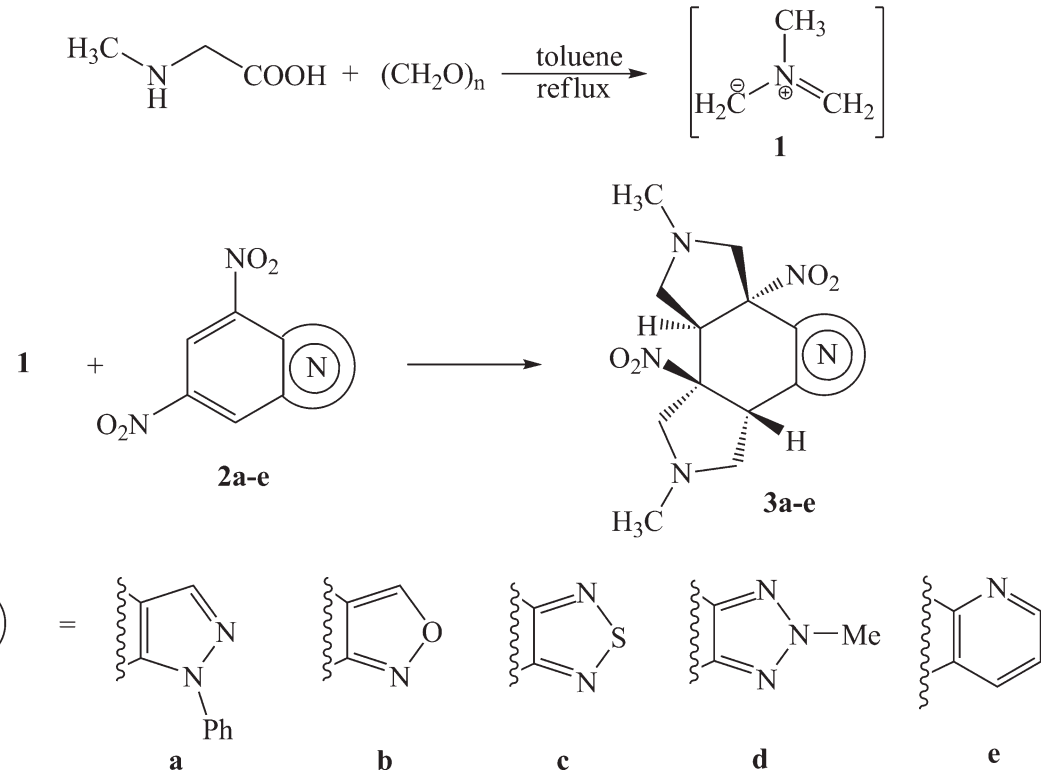
In summary, the 1,3-dipolar cycloaddition of meta-dinitrobenzene fused with nitrogen heterocycles with unstabilized *N*-methylazomethine ylide generated *in situ* from sarcosine and paraformaldehyde in refluxing toluene affords decahydropyrrolo[3,4-*e*]isoindole cycloadducts in good yields.

## EXPERIMENTAL

Melting points were uncorrected and were determined on a Reichert Kofler thermopan apparatus. NMR spectra were measured in $CDCl_3$ using the Bruker DRX 500 spectrometer operating at 500.13 MHz ($^1$H), 125.77 MHz ($^{13}$C). Tetramethylsilane was used as internal standard for $^1$H (δ 0.05). The $^{13}$C NMR spectra were standardized by means of the middle signal of the solvent multiplet (δ 76.9).

**General procedure for the reaction of compounds 2a–e and 4 with sarcosine and paraformaldehyde.** A mixture of compound **2** or **4** (1 mmol), paraformaldehyde (0.18 g, 6 mmol), and *N*-methylglycine (0.44 g, 5 mmol) in dry toluene (15 mL) was refluxed for 2 h until all the starting material disappeared by TLC. Then the reaction mixture was cooled,

**Scheme 2**



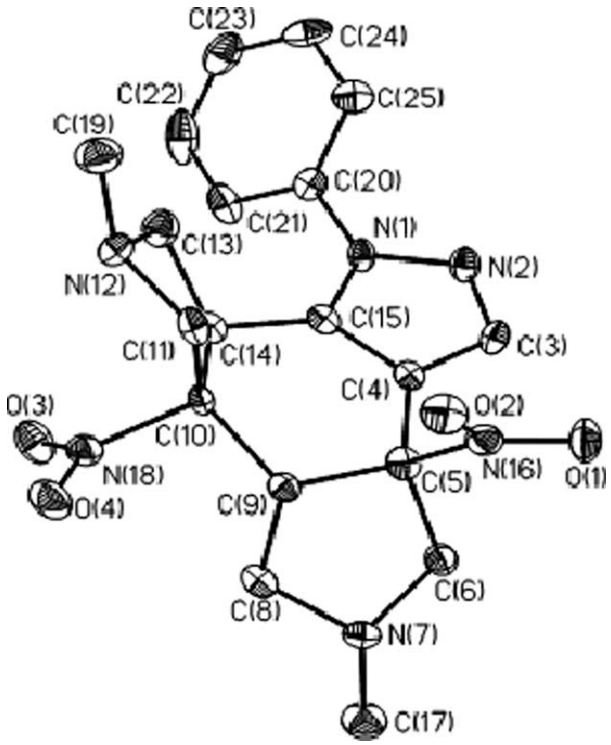



**Figure 1.** General view of **3a**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn with probability 50%.

filtered and the solvent was removed by rotary evaporation. The products were purified by dissolving in minimal volume of THF, following by adding of excess of hexane to this solution with further filtering of the precipitate formed.

***5,8-Dimethyl-3b,6b-dinitro-1-phenyl-3b,4,5,6,6a,6b,7,8,9,9a-decahydro-1H-dipyrrolo[3,4-e:3′,4′-g]indazole (3a).*** This compound was obtained as yellow needles, yield 69%; mp 175–176°C; $^1$H NMR δ 1.89 (dd, 1H, $J$ = 5.1, 4.5 Hz), 2.10 (s, 3H), 2.32 (s, 3H), 2.55–2.60 (m, 2H), 2.88 (t, 1H, $J$ = 8.8 Hz), 3.09 (t, 1H, $J$ = 8.9 Hz), 3.19 (d, 1H, $J$ = 10.0 Hz), 3.61 (d, 1H, $J$ = 11.0 Hz), 3.77 (d, 1H, $J$ = 10.0 Hz), 4.34 (t, 1H, $J$ = 8.8 Hz), 4.77–4.90 (m, 1H), 7.45–7.48 (m, 1H), 7.55 (m, 4H), 7.91 (s, 1H); $^{13}$C NMR δ 36.1, 40.6, 41.5, 45.0, 57.2, 59.5, 63.8, 69.7, 89.6, 98.8, 122.9, 124.2, 128.6, 129.7, 139.0, 139.2, 139.6; Anal. Calcd. for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.09. Found: C, 56.98; H, 5.68; N, 20.92.

***5,8-Dimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydroisoxazolo[3,4-e]pyrrolo[3,4-g]isoindole (3b).*** This compound was obtained as dark brown solid, yield 50%; mp 193–195°C; 1H NMR δ 2.27 (s, 6H), 2.53 (t, 1H, $J$ = 9.1 Hz), 2.71 (d, 1H, $J$ = 11.3 Hz), 2.87–2.91 (m, 2H), 3.08 (d, 1H, $J$ = 9.9 Hz), 3.52 (d, 1H, $J$ = 11.3 Hz), 3.59 (t, 1H, $J$ = 8.1 Hz), 3.67 (d, 1H, $J$ = 9.9 Hz), 4.36–4.45 (m, 2H), 8.77 (s, 1H); $^{13}$C NMR δ 35.6, 41.0, 41.1, 44.3, 56.9, 60.0, 63.4, 70.3, 88.2, 97.6, 112.3, 158.7, 160.5. Anal. Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.38; H, 5.18; N, 21.51.

***5,8-Dimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydropyrrolo[3,4-e][1,2,5]thiadiazolo[3,4-g]isoindole (3c).*** This compound was obtained as brown solid, yield 40%; mp 123–124°C; $^1$H NMR δ 2.26 (s, 3H), 2.27 (s, 3H), 2.51 (t, 1H, $J$ = 8.6 Hz), 2.87–2.90 (m, 2H), 2.94 (t, 1H, $J$ = 9.3 Hz), 3.40 (d, 1H, $J$ = 10.1 Hz), 3.48 (d, 1H, $J$ = 11.2 Hz), 3.60 (dd, 1H, $J$ = 9.5, 7.4 Hz), 3.87 (d, 1H, $J$ = 10.1 Hz), 4.27 (t, 1H, $J$ = 8.6 Hz), 4.62–4.64 (m, 1H); $^1$3C NMR δ 40.9, 41.3, 41.5, 47.6, 57.3, 60.6, 64.2, 67.3, 90.1, 97.2, 151.3, 160.4; Anal. Calcd. for $C_{12}H_{16}N_6O_4S$: C, 42.35; H, 4.74; N, 24.69. Found: C, 42.35; H, 4.87; N, 24.75.

***2,5,8-Trimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydro-2H-pyrrolo[3,4-e][1,2,3]triazolo[4,5-g]isoindole (3d).*** This compound was obtained as brown solid, yield 67%; mp 118–120°C; $^1$H NMR δ 2.25 (s, 3H), 2.27 (s, 3H), 2.46 (t, 1H, $J$ = 9.4 Hz), 2.65 (dd, 1H, $J$ = 9.3 Hz, 3.7 Hz), 2.75 (d, 1H, $J$ = 11.3 Hz), 2.86 (t, 1H, $J$ = 9.0 Hz), 3.25 (d, 1H, $J$ = 10.1), 3.50 (d, 1H, $J$ = 11.2), 3.58 (t, 1H, $J$ = 7.7), 3.79 (d, 1H, $J$ = 10.1 Hz), 4.20–4.23 (m, 1H), 4.25 (s, 3H), 4.46 (dd, 1H, $J$ = 7.6 Hz, 3.4 Hz); $^{13}$C NMR δ 36.1, 41.0, 41.4, 42.6, 47.3, 57.2, 60.3, 63.6, 67.4, 88.3, 97.9, 137.1, 146.1; Anal. Calcd. for $C_{13}H_{19}N_7O_4$: C, 46.29; H, 5.68; N, 29.07. Found: C, 46.56; H, 6.00; N, 28.81.

***6,9-Dimethyl-7a,10a-dinitro-4b,5,6,7,7a,7b,8,9,10,10a-decahydrodipyrrolo[3,4-f:3′,4′-h]quinoline (3e).*** This compound was obtained as yellow-brown solid, yield 24%; mp 159–160°C; $^1$H NMR δ 2.29 (s, 6H), 2.39 (t, 1H, $J$ = 9.4 Hz), 2.59 (dd, 1H, $J$ = 5.5 Hz, 3.5 Hz), 2.97 (m, 2H), 3.24 (d, 1H, $J$ = 11.0 Hz), 3.62, (m, 2H), 4.00 (t, 1H, $J$ = 8.8 Hz), 4.13 (d, 1H, $J$ = 11.0 Hz), 4.55 (t, 1H, $J$ = 6.0 Hz), 7.37 (dd, 1H, $J$ = 7.9 Hz, 4.2 Hz), 7.58 (d, 1H, $J$ = 7.9 Hz), 8.61 (d, 1H, $J$ = 4.2 Hz). $^{13}$C NMR δ 41.1, 41.7, 41.8, 47.6, 58.3, 63.0, 64.6, 67.2, 95.0, 95.5, 124.9, 132.6, 137.0, 147.9, 149.5; Anal. Calcd. for $C_{15}H_{19}N_5O_4$: C, 54.05; H, 5.75; N, 21.01. Found: C, 53.83; H, 5.81; N, 20.37.

***7b-Nitro-7,7a,7b,8,10,10a-hexahydro-5H-imidazo[1,5-c]pyrrolo[3,4-e][1,2,4]triazolo[1,5-a]pyrimidine-6,9-diamine (5).*** This compound was obtained as white needles, yield 42%; mp 147–148°C; $^1$H NMR δ 2.36 (s, 3H), 2.37 (s, 3H), 2.79 (dd, 1H, $J$ = 10.2 Hz, 5.9 Hz),z), 3.07–3.10 (m, 1H), 3.15–3.22 (m, 2H), 3.43 (d, 1H, $J$ = 10.6 Hz), 3.96 (d, 1H, 10.6 Hz), 4.13 (d, 1H, $J$ = 5.1 Hz), 4.18–4.21 (m, 2H), 4.90 (dd, 1H, $J$ = 7.7, 5.8 Hz), 7.61 (s, 1H). $^{13}$C NMR δ 40.1, 41.0, 56.0, 60.2, 60.3, 60.8, 71.1, 88.4, 151.0, 152.1; Anal. Calcd. for $C_{11}H_{17}N_7O_2$: C, 47.30; H, 6.14; N, 35.10. Found: C, 47.36; H, 6.02; N, 35.23.

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## REFERENCES AND NOTES

[1] Padwa, A.; Pearson, W. H. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Wiley: New York, 2002; pp 169–252.

[2] (a) Tsuge, O.; Kanemasa, S. Adv Heterocycl Chem 1989, 45, 231; (b) Baranski, A.; Kelarev, V. I. Chem Heterocycl Compd 1990, 26, 371; (c) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. Chem Lett 1986, 15, 1271; (d) Viranyi, A.; Marth, G.; Dancso, A.; Blasko, G.; Toke, L.; Nyerges, M. Tetrahedron 2006, 62, 8720; (e) Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. Tetrahedron Lett 2008, 49, 6910.

[3] (a) Sardina, F. J.; Rappoport, H. Chem Rev 1996, 96, 1825; (b) Attygalle, A. B.; Morgan, D. E. Chem Soc Rev 1984, 13, 245.

[4] Lakhdar, S.; Goumont, R.; Boubaker, T.; Mokhtaric, M.; Terrier, F. Org Biomol Chem 2006, 4, 1910.

[5] Starting dinitrocompounds 2a–e were synthesized according to the procedures described earlier: compound **2a**: Starosotnikov, A. M.; Lobach, A. V.; Kachala, V. V.; Shevelev, S. A. Russ Chem Bull Int Ed 2004, 53, 584; compound **2b**: Mezhnev, V. V.; Dutov, M. D.; Shevelev, S. A. Russ Chem Bull Int Ed 2009, 58, 476; compound **2c**: Pesin, V.G.; Khaletskii, A. M.; Sergeev, V. A. J Gen Chem USSR (Engl. Transl.) 1963, 33, 1714; compound **2d**: Asadulina, E. M.; Bastrakov, M. A.; Starosotnikov, A. M.; Kachala, V. V.; Shevelev, S. A. Russ Chem Bull Int Ed 2009, 58, 421; compound **2e** was prepared via modified Skraup procedure: Fujiwara, H.; Kitagawa, K. Heterocycles 2000, 53, 409.

[6] Cottyn, B.; Starosotnikov, A.; Vichard, D.; Goumont, R.; Shevelev, S.; Terrier, F. Org Biomol Chem 2009, 7, 1137 (and references cited therein).

[7] Crystallographic data for the structure of **3a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 737503. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223–336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data for **3a**: Intensity data were collected on a Bruker SMART APEX II CCD area detector system equipped with a graphite monochromator and a MoKa fine-focus sealed tube ($\lambda = 0.71073$ Å) at 100(2) K, using the $\phi$- and $\omega$-scan scan technique to a maximum $\theta$ angle of 26°. $C_{19}H_{22}N_6O_4$, M = 398.43, orthorhombic, a = 15.691(4) Å, b = 8.5090(19) Å, c = 27.905(6) Å, V = 3725.8(15) Å$^3$, space group Pbcn, Z = 8, $d_{calcd}$ = 1.421 g/cm$^3$, 22222 reflections measured, 3669 reflections [$I > 2\sigma(I)$] were used in all calculations, R = 0.0566, Rw = 0.1005. Structure solution and refinement were performed by Bruker SHELXTL.

[8] Rusinov, V. L.; Myasnikov, A. V.; Pilicheva, T. L.; Chupakhin, O. N.; Kiprianova, E. A.; Garagulya, A. D. Pharm Chem 1990, 24, 52.

# Synthesis, Crystal Structure, and Fungicidal Activity of Novel 1,5-Diaryl-1*H*-pyrazol-3-oxyacetate Derivatives



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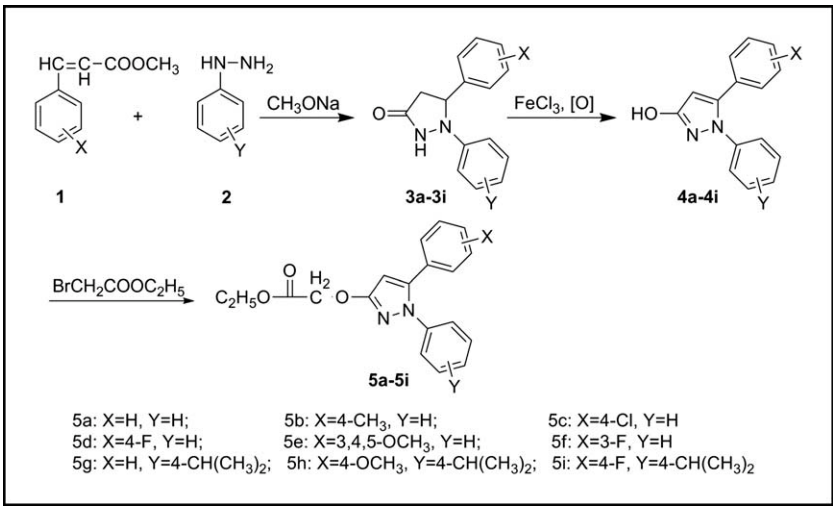



A series of ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetate derivatives (**5a–5i**) have been efficiently synthesized by the reaction of 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) with ethyl 2-bromoacetate. The structures of the newly synthesized compounds were characterized by $^1$H NMR spectra and elemental analysis, and the crystal structure of the compound ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5c**) was determined by single crystal X-ray diffraction analysis. The compound **5c** belongs to triclinic system with space group P(-1), $a = 5.8170(12)$ Å, $b = 11.804(2)$ Å, $c = 12.783(2)$ Å, $\alpha = 83.89(2)^\circ$, $\beta = 89.24(3)^\circ$, $\gamma = 89.73(3)^\circ$, Formula weight: 356.80, Triclinic $V = 872.7(3)$ Å$^3$, $D_c = 1.358$ mg/m$^3$, $Z = 2$, $F$ (000) = 372. Bioassay results indicated that the compound ethyl 2-(5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5d**) exhibited moderate inhibitory activity against *Gibberella zeae* at the dosage of 10 μg/mL.

*J. Heterocyclic Chem.*, **47**, 897 (2010).

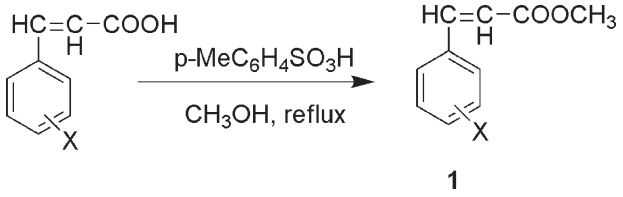
## INTRODUCTION

Biological studies of the pyrazole nucleus have been shown to posses a variety of biological activities such as fungicidal [1], insecticidal [2], herbicidal [3], and plant growth regulatory activities [4]. Furthermore, several biological studies have also pointed out the value of alkyloxyacetate [5] and aryloxyacetate [6] as biologically active groups. These findings primarily focused on incorporating alkyloxyacetate and aryloxyacetate groups with 1*H*-pyrazole derivatives in the hope of obtaining compounds of potential insecticidal, fungicidal, and herbicidal activities.

1,5-Diaryl-1*H*-pyrazol-3-ols, one important kind of 1*H*-pyrazole derivatives, have been developed for their synthesis since the early twentieth century. The first synthesis of 1,5-diaryl-1*H*-pyrazol-3-ol from a pyrazolidone derivative was published by Japp and Maitland [7]. Then the reaction of arylpropiolic acids and their esters with phenylhydrazine became one of the most popular methods for the synthesis of 1,5-diaryl-1*H*-pyrazol-3-ols [8–11]. In recent years, synthesis of 1,5-diaryl-1*H*-pyrazol-3-ols by the reactions of 4-arylidene-1-phenyl-3,5-pyrazolidinediones with oxidizing agents has been achieved [12]. However, very few representatives of biologically active 1,5-diaryl-1*H*-pyrazol-3-oxyacetate derivatives have hitherto been described in the literature.

3-Arylacrylic acids and their esters are convenient and easily available starting materials or intermediates for the synthesis of a wide variety of heterocyclic compounds [13,14]. In our previous studies, we have successfully improved the procedure for the synthesis of 1,5-diaryl-1*H*-pyrazol-3-ols by the reaction of methyl 3-arylacrylates with arylhydrazines in high yields and have reported some crystal structures [15–17]. In continuation of our program directed toward the synthesis of

**Scheme 1**




**1**

biologically active novel 1,5-diaryl-1*H*-pyrazol-3-oxyacetate derivatives, we report herein the synthesis and fungicidal activity of a series of novel ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetates (**5a–5i**), and the single crystal structure of the compound ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5c**). A preliminary *in vitro* bioassay indicated that some of these newly synthesized compounds displayed fungicidal activity.

## RESULTS AND DISCUSSION

Methyl 3-arylacrylates (**1**) (Scheme 1) were prepared by the reaction of 3-arylacrylic acids with methanol, using *p*-toluenesulfonic acid as catalyst. Intermediates arylhydrazines (**2**) (Scheme 2) were prepared according to the reported methods from the substituted anilines through diazotization reactions [18].

A previous report by Gaede and McDermott [19] described that addition of methylhydrazine to a variety of haloalkyl-substituted α,β-unsaturated ethers could give 1,5-disubstituted-3-hydroxypyrazoles. Motivated by this finding, in our procedure, methyl 3-arylacrylates (**1**) were allowed to react with arylhydrazines (**2**) in boiling *n*-butanol in the presence of sodium methoxide to afford 1,5-diarylpyrazolidin-3-ones (**3a–3i**) (Scheme 3) as sole isolable products. No other pyrazoline type compounds could be detected in the crude products. It was found that the desired mode of initial Michael addition to methyl 3-arylacrylates (**1**) could be achieved. The crude solid 1,5-diarylpyrazolidin-3-ones (**3a–3i**) were recrystallized from ethyl acetate.

The conversions from 1,5-diarylpyrazolidin-3-ones (**3a–3i**) to 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) (Scheme 3) were carried out in organic solvents, using oxygen as oxidizing agent and iron (III) chloride as catalyst. To optimize the reaction conditions, different organic solvents, such as ethanol and DMF were tested in the synthesis of 1,5-diphenyl-1*H*-pyrazol-3-ol (**4a**). When the conversion was carried out using iron (III) chloride in refluxing ethanol, the yield was low and the separation of the product from the iron (II) salts was tedious. However, the conversion in DMF gave good results. Moreover, the most satisfactory result was obtained when the reaction was stirred in DMF at 80°C for 2 h, and then at 30°C for another 20 h. The crude solid 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) were recrystallized from ethanol.

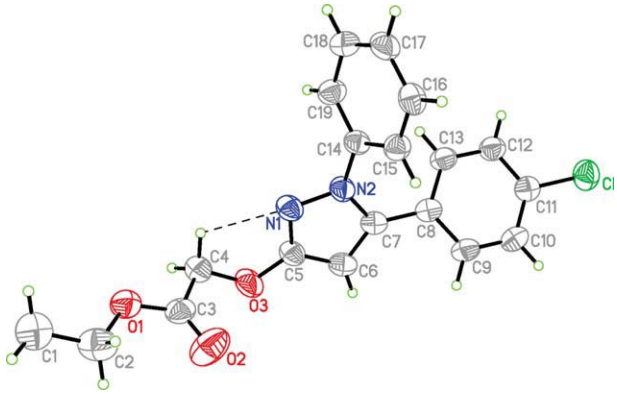
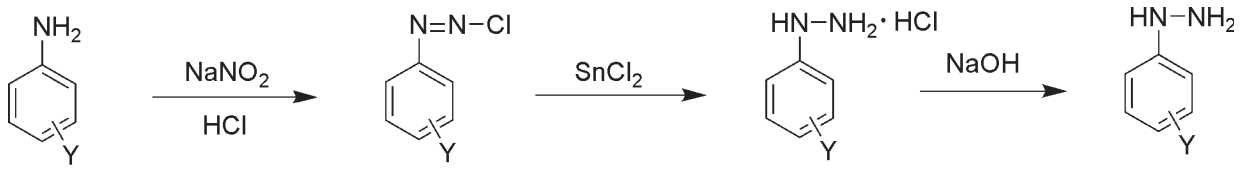



**Figure 1.** The molecular structure of **5c**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The reactions of 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) with ethyl 2-bromoacetate were carried out in a molar ratio 1:1.1 in acetone as solvent, and all the reactions were monitored by thin-layer chromatography (TLC). The most satisfactory results were obtained when the reactions were performed under hot acetone for 3 h. The crude residues were purified *via* flash chromatography to give the pure products ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetates (**5a–5i**) (Scheme 3).

A suitable crystal of ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5c**) was obtained by dissolving the compound in ethyl acetate and evaporating the solvent slowly at room temperature for about 10 days. Its solid-state structure was determined by single crystal X-ray diffraction. Details of the structure determination and refinement are given in the experiment section. The drawing of the molecular structure with the

**Scheme 2**




**2**

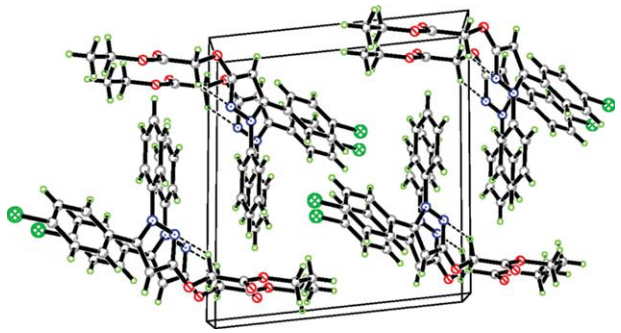


**Figure 2.** A partial packing diagram of **5c**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

atom-numbering scheme and higher occupancy in the three-dimensional packing arrangement is shown in Figures 1 and 2. Hydrogen bond is shown as a dashed line. Atomic coordinates of nonhydrogen atoms ($\times 10^{-4}$) and their thermal parameters are summarized in Table 1. The crystal data and structure refinement of **5c** are listed in Table 2.

The compounds **5a–5i** were screened for activity against two fungi, namely *Gibberella zeae* and *Rhizoctonia cerealis*, at a concentration of 10 μg/mL according to a reported method [20]. As the results in Table 3 show, most of the compounds have weak fungicidal activity. Among these compounds, only compound **5d**, in which X is F group in position 4 of the phenyl ring and Y is H, exhibited moderate inhibitory activity against *G. zeae*. This might imply that the introduction of the F group to the phenyl ring of 1*H*-pyrazoles was important for its fungicidal activity. In terms of X, the substituents with electron-attracting groups on the phenyl rings seem to have somewhat higher fungicidal activity. For example, compounds **5c** and **5d** showed better activity than

**Table 1**

Atomic coordinates of nonhydrogen atoms ($\times 10^{-4}$) and their thermal parameters.

| | *x* | *y* | *z* | U(eq) |
|---|---|---|---|---|
| Cl | 2885(2) | 58,718(10) | 6585(10) | 743(4) |
| O1 | 16,539(5) | −2205(3) | 8826(2) | 689(11) |
| O2 | 12,920(7) | −1840(3) | 9270(3) | 1065(19) |
| O3 | 13,728(5) | 437(3) | 8980(2) | 728(11) |
| N1 | 12,700(6) | 935(3) | 7229(2) | 545(11) |
| N2 | 11,051(5) | 1659(3) | 6779(2) | 509(11) |
| C1 | 18,381(9) | −3992(5) | 8956(4) | 960 |
| C2 | 16,191(10) | −3413(4) | 9100(4) | 870(2) |
| C3 | 14,764(8) | −1527(4) | 8947(3) | 606(16) |
| C4 | 15,430(7) | −319(4) | 8637(3) | 648(17) |
| C5 | 12,367(7) | 979(3) | 8241(3) | 534(12) |
| C6 | 10,561(7) | 1696(3) | 8479(3) | 550(14) |
| C7 | 9752(6) | 2124(3) | 7514(3) | 468(12) |
| C8 | 8028(6) | 3022(3) | 7255(3) | 498(12) |
| C9 | 6091(7) | 3104(3) | 7898(3) | 585(16) |
| C10 | 4502(7) | 3959(3) | 7686(3) | 585(16) |
| C11 | 4829(7) | 4762(3) | 6843(3) | 524(12) |
| C12 | 6739(7) | 4710(3) | 6195(3) | 575(12) |
| C13 | 8317(7) | 3842(3) | 6398(3) | 554(12) |
| C14 | 10,695(6) | 1660(3) | 5682(3) | 465(12) |
| C15 | 8648(6) | 1285(3) | 5333(3) | 516(12) |
| C16 | 8322(7) | 1245(3) | 4273(3) | 573(14) |
| C17 | 10,066(8) | 1601(4) | 3566(3) | 642(16) |
| C18 | 12,104(8) | 1983(4) | 3911(3) | 662(17) |
| C19 | 12,425(7) | 2025(3) | 4976(3) | 579(16) |

**Table 2**

Crystal data and structure refinement for **5c**.

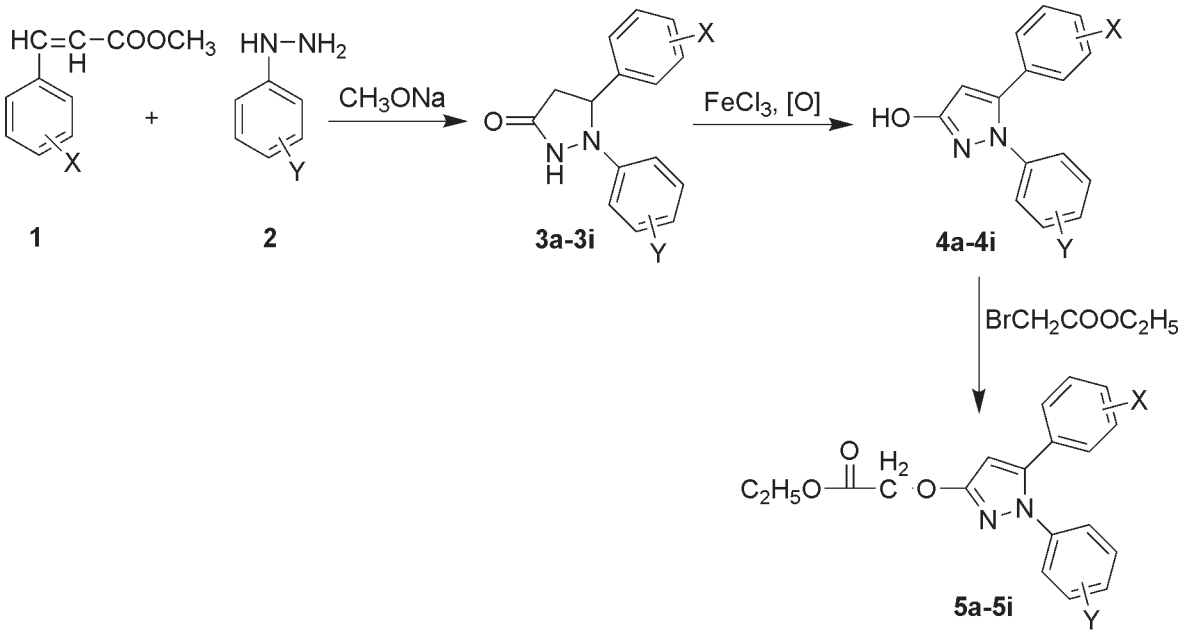
| | |
|---|---|
| Empirical formula | $C_{19}H_{17}ClN_2O_3$ |
| Formula weight | 356.80 |
| Temperature (K) | 293 |
| Wavelength | 0.71073 Å |
| Crystal system | Triclinic |
| Space group | P-1 |
| *a* (Å) | 5.8170(12) |
| *b* (Å) | 11.804(2) |
| *c* (Å) | 12.783(2) |
| α (°) | 83.89(2) |
| β (°) | 89.24(3) |
| γ (°) | 89.73(3) |
| *V* (Å$^3$) | 872.7(3) |
| *Z* | 2 |
| $D_{calc}$ (mg/m$^3$) | 1.358 |
| Absorption coefficient (mm$^{-1}$) | 0.239 |
| *F* (000) | 372 |
| Crystal size (mm) | 0.10 × 0.10 × 0.20 |
| θ range, deg | 1.6–25.3 |
| Reflections collected | 3480 |
| Independent reflections | 3140($R_{int}$ = 0.084) |
| Date/restraints/parameters | 3140/0/220 |
| Goodness-of-fit on $F^2$ | 1.009 |
| Final *R* indices [$I > 2s(I)$] | |
| R1 | 0.0671 |
| wR2 | 0.1483 |
| Final *R* indices (all date) | |
| R1 | 0.1104 |
| wR2 | 0.1778 |
| Extinction correction | none |

**Table 3**

Antifungal activity of newly synthesized compounds (% inhibition).

| | | | 10 μg/mL | |
|---|---|---|---|---|
| Compounds | X | Y | *G. zeae* | *R. cerealis* |
| **5a** | H | H | 21.29 | 18.44 |
| **5b** | 4-$CH_3$ | H | 0.00 | 7.79 |
| **5c** | 4-Cl | H | 39.20 | 15.53 |
| **5d** | 4-F | H | 53.09 | 24.27 |
| **5e** | 3,4,5-$OCH_3$H3 | H | 20.06 | 9.06 |
| **5f** | 3-F | H | 30.25 | 17.15 |
| **5g** | H | 4-$CH(CH_3)_2$ | 13.89 | 0.97 |
| **5h** | 4-$OCH_3$ | 4-$CH(CH_3)_2$ | 14.20 | 0.97 |
| **5i** | 4-F | 4-$CH(CH_3)_2$ | 13.89 | 1.62 |

**Scheme 3**




5a: X=H, Y=H; 5b: X=4-$CH_3$, Y=H; 5c: X=4-Cl, Y=H
5d: X=4-F, Y=H; 5e: X=3,4,5-$OCH_3$, Y=H; 5f: X=3-F, Y=H
5g: X=H, Y=4-$CH(CH_3)_2$; 5h: X=4-$OCH_3$, Y=4-$CH(CH_3)_2$; 5i: X=4-F, Y=4-$CH(CH_3)_2$

compounds **5a** and **5b**. Switching the substituent Y from H to isopropyl has no effective impact on the inhibition rates. Furthermore, compound **5d** with the F group in position 4 of the phenyl ring showed better activity than **5f**.

## EXPERIMENTAL

All reagents were of analytical reagent grade or were chemically pure. All solvents were dried by standard methods and distilled before use. Reactions were monitored by TLC. Analytical TLC was performed on silica gel GF254. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure. *G. zeae* and *R. cerealis* were obtained from Jiangsu Research and Development Center for Pesticides, China.

The melting points were measured on an X-4 microscope electrothermal apparatus (Taike, China) and were uncorrected. Elemental analyses were determined on a Vario EL III elemental analyzer. The $^1$H NMR (solvent $CDCl_3$ or DMSO-$d_6$) spectra was obtained on a Bruker AV 500 or AV 300 spectrometer at room temperature using tetramethylsilane as an internal standard. Chemical shift values (δ) are given in parts per million. X-ray intensity data were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite monochromated Mo Kα radiation (λ = 0.71073) Å.

**The synthesis of 1,5-diarylpyrazolidin-3-ones (3a–3i).** A mixture of *n*-butanol (40 mL) and ethanolamine (60 mmol) was added to a solution of sodium (36 mmol) in anhydrous methanol (9 mL). Then, methanol was removed by distillation, and methyl 3-arylacrylate **1** (30 mmol) was added. The mixture was refluxed for 40 min, after which arylhydrazine **2** (33 mmol) was added. The mixture was refluxed for another 8 h and then left to cool to room temperature. It was then acidified with acetic acid (36%), allowed to stand and filtered. The solid was recrystallized from ethyl acetate to give the compounds **3a–3i**.

**1,5-Diphenylpyrazolidin-3-one (3a).** White crystal; mp 159–161°C; yield, 85%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.52 (q, $J$ = 3.33, 16.8 Hz, 1H, CH), 3.28 (q, $J$ = 9.18, 16.8 Hz, 1H, CH), 4.93 (q, $J$ = 3.36, 9.17 Hz, 1H, CH), 7.02–7.43 (m, 10H, Ar-H); Anal. Calcd for $C_{15}H_{14}N_2O$: C 75.61, H 5.92, N 11.76; found C 75.69, H 5.89, N 11.72.

**1-Phenyl-5-p-tolylpyrazolidin-3-one (3b).** White crystal; mp 145–146°C; yield, 82%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.38 (s, 3H, $CH_3$), 2.50 (q, $J$ = 3.45, 16.82 Hz, 1H, CH), 3.26 (q, $J$ = 9.12, 16.77 Hz, 1H, CH), 4.89 (q, $J$ = 3.48, 9.08 Hz, 1H, CH), 7.01–7.38 (m, 9H, Ar-H), 8.49 (s, 1H, NH); Anal. Calcd for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.10; found C 76.25, H 6.37, N 11.15.

**5-(4-Chlorophenyl)-1-phenylpyrazolidin-3-one (3c).** White crystal; mp 160–162°C; yield, 80%. $^1$H NMR (DMSO-$d_6$, 300 MHz, ppm): δ 2.25 (q, $J$ = 2.79, 16.71 Hz, 1H, CH), 3.18 (q, $J$ = 9.03,16.71 Hz, 1H, CH), 5.07 (q, $J$ = 2.67, 9.03 Hz, 1H, CH), 6.94–7.58 (m, 9H, Ar-H), 10.45 (s, 1H, NH); Anal. Calcd for $C_{15}H_{13}ClN_2O$: C 66.06, H 4.80, N 10.27; found C 66.15, H 4.79, N 10.23.

**5-(4-Fluorophenyl)-1-phenylpyrazolidin-3-one (3d).** Yellow crystal; mp 158–159°C; yield, 78%. $^1$HNMR ($CDCl_3$, 300 MHz, ppm): δ 2.50 (q, $J$ = 2.82, 16.77 Hz, 1H, CH), 3.31 (q, $J$ = 9.06, 16.71 Hz, 1H, CH), 4.95 (q, $J$ = 2.82, 9 Hz, 1H,

CH), 7.04–7.44 (m, 9H, Ar-H); Anal. Calcd for $C_{15}H_{13}FN_2O$: C 70.30, H 5.11, N 10.93; found C 70.22, H 5.10, N 10.98.

**1-Phenyl-5-(3,4,5-trimethoxyphenyl)pyrazolidin-3-one (3e).** White crystal; mp 157–159°C; yield, 78%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.54 (q, $J$ = 3.88, 16.82 Hz, 1H, CH), 3.28 (q, $J$ = 9.26, 16.82 Hz, 1H, CH), 3.86 (s, 9H, $OCH_3$), 4.85 (q, $J$ = 3.76, 9.21 Hz, 1H, CH), 6.70–7.32 (m, 7H, Ar-H), 8.45 (s, 1H, NH); Anal. Calcd for $C_{18}H_{20}N_2O_4$: C 65.84, H 6.14, N 8.53; found C 65.76, H 6.12, N 8.58.

**5-(3-Fluorophenyl)-1-phenylpyrazolidin-3-one (3f).** Yellow crystal; mp 165–167°C; yield, 75%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.50 (d, 1H, CH), 3.30 (q, $J$ = 9.15, 16.85 Hz, 1H, CH), 4.98 (d, 1H, CH), 7.03–7.40 (m, 9H, Ar-H), 8.41 (s, 1H, NH); Anal. Calcd for $C_{15}H_{13}FN_2O$: C 70.30, H 5.11, N 10.93; found C 70.23, H 5.10, N 10.96.

**1-(4-Isopropylphenyl)-5-phenylpyrazolidin-3-one (3g).** Yellow crystal; mp 136–137°C; yield, 78%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, $J$ = 6.85 Hz, 6H, $CH_3$), 2.50 (q, $J$ = 3.35, 16.75 Hz, 1H, CH), 2.86 (m, 1H, CH), 3.26 (q, $J$ = 9.15,16.75 Hz, 1H, CH), 4.87 (q, $J$ = 3.35, 8.98 Hz, 1H, CH), 6.99–7.48 (m, 9H, Ar-H); Anal. Calcd for $C_{18}H_{20}N_2O$: C 77.11, H 7.19, N 9.99; found C 77.05, H 7.21, N 9.94.

**1-(4-Isopropylphenyl)-5-(4-methoxyphenyl)pyrazolidin-3-one (3h).** Yellow crystal; mp 143–145°C; yield, 81%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, $J$ = 6.90 Hz, 6H, $CH_3$), 2.55 (m, 1H, CH), 2.87 (m, 1H, CH), 3.21 (m, 1H, CH), 3.83 (s, 3H, $OCH_3$), 4.82 (m, 1H, CH), 6.92–7.39 (m, 8H, Ar-H); Anal. Calcd for $C_{19}H_{22}N_2O_2$: C 73.52, H 7.14, N 9.03; found C 73.46, H 7.16, N 8.99.

**5-(4-Fluorophenyl)-1-(4-isopropylphenyl)pyrazolidin-3-one (3i).** Yellow crystal; mp 126–127°C; yield, 79%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.25 (d, $J$ = 6.87 Hz, 6H, $CH_3$), 2.52 (q, $J$ = 3.78, 16.82 Hz, 1H, CH), 2.89 (m, 1H, CH), 3.33 (q, $J$ = 9.12, 16.8 Hz, 1H, CH), 4.87 (q, $J$ = 3.69, 9.14 Hz, 1H, CH), 6.94–7.19 (m, 8H, Ar-H); Anal. Calcd for $C_{18}H_{19}FN_2O$: C 72.46, H 6.42, N 9.39; found C 72.42, H 6.44, N 9.35.

**1,5-Diaryl-1H-pyrazol-3-ols (4a–4i).** Using oxygen as oxidizing agent, compound **3a–3i** (10 mmol) was dissolved in DMF (40 mL) and mixed with $FeCl_3$ (0.162 g, 1 mmol). The mixture was heated to 80°C and maintained at that temperature for 2 h, and then stirred at 30°C for another 20 h. The reaction mixture was then poured into water (500 mL) with good stirring. The precipitate which formed was filtered off, washed with water and dried under reduced pressure. The crude product was then recrystallized from ethanol to give the compounds **4a–4i**.

**1,5-Diphenyl-1H-pyrazol-3-ol (4a).** White crystal; mp 258–259°C; yield, 81%. $^1$H NMR (DMSO-$d_6$, 300 MHz, ppm): δ 5.92 (s, 1H, CH), 7.14–7.33 (m, 10H, Ar-H), 10.36 (s, 1H, OH); Anal. Calcd for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found C 75.32, H 5.09, N 11.82.

**1-Phenyl-5-p-tolyl-1H-pyrazol-3-ol (4b).** White crystal; mp 254–255°C; yield, 84%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.33 (s, 3H, $CH_3$), 5.89 (s, 1H, CH), 7.09–7.36 (m, 9H, Ar-H); Anal. Calcd for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19; found C 76.69, H 5.63, N 11.25.

**5-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-ol (4c).** White crystal; mp 285–286°C; yield, 82%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 5.92 (s, 1H, CH), 7.13–7.46 (m, 9H, Ar-H); Anal. Calcd for $C_{15}H_{11}ClN_2O$: C 66.55, H 4.10, N 10.35; found C 66.46, H 4.08, N 10.38.

**5-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-3-ol (4d).** White crystal; mp 266–267°C; yield, 81%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 5.90 (s, 1H, CH), 6.98–7.33 (m, 9H, Ar-H), 11.35 (s, 1H, OH); Anal. Calcd for $C_{15}H_{11}FN_2O$: C 70.86, H 4.36, N 11.02; found C 70.78, H 4.34, N 11.06.

**1-Phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazol-3-ol (4e).** Brown crystal; mp 203–205°C; yield, 85%. $^1$H NMR (DMSO-$d_6$, 500 MHz, ppm): δ 3.62 (s, 9H, $OCH_3$), 5.97 (s, 1H, CH), 6.46 (s, 2H, Ar-H), 7.21–7.39 (m, 5H, Ar-H), 10.09 (s, 1H, OH); Anal. Calcd for $C_{18}H_{18}N_2O_4$: C 66.25, H 5.56, N 8.58; found C 66.29, H 5.55, N 8.53.

**5-(3-Fluorophenyl)-1-phenyl-1H-pyrazol-3-ol (4f).** White crystal; mp 274–275°C; yield, 78%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 6.45 (s, 1H, CH), 6.90–7.35 (m, 9H, Ar-H); Anal. Calcd for $C_{15}H_{11}FN_2O$: C 70.86, H 4.36, N 11.02; found C 70.78, H 4.35, N 11.06.

**1-(4-Isopropylphenyl)-5-phenyl-1H-pyrazol-3-ol (4g).** Yellow crystal; mp 203–205°C; yield, 76%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.24 (d, $J$ = 6.75 Hz, 6H, $CH_3$), 2.90 (m, 1H, CH), 5.90 (s, 1H, CH), 7.14–7.28 (m, 9H, Ar-H); Anal. Calcd for $C_{18}H_{18}N_2O$: C 77.67, H 6.52, N 10.06; found C 77.60, H 6.49, N 10.09.

**1-(4-Isopropylphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-ol (4h).** Yellow crystal; mp 193–194°C; yield, 72%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.25 (d, $J$ = 7.00 Hz, 6H, $CH_3$), 2.90 (m, 1H, CH), 3.80 (s, 3H, $OCH_3$), 5.86 (s, 1H, CH), 6.80–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found C 73.94, H 6.53, N 9.12.

**5-(4-Fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-3-ol (4i).** Yellow crystal; mp 225–227°C; yield, 78%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.21 (d, $J$ = 6.96 Hz, 6H, $CH_3$), 2.85 (m, 1H, CH), 6.34 (s, 1H, CH), 6.90–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{18}H_{17}FN_2O$: C 72.95, H 5.78, N 9.45; found C 72.88, H 5.76, N 9.42.

**Ethyl 2-(1,5-diaryl-1H-pyrazol-3-yloxy)acetates (5a–5i).** To a solution of **4a–4i** (10 mmol) in acetone (30 mL) was added potassium carbonate (2.07 g, 15 mmol). Then, the mixture was refluxed and ethyl 2-bromoacetate (1.84 g, 11 mmol) was added slowly. The mixture was refluxed and monitored by TLC for about 3 h. The potassium carbonate was filtered off and the solvent was evaporated under reduced pressure. After the removal of the solvent, the residue was chromatographed over silica gel (500 g) eluting with a mixture of ethyl acetate and petroleum ether to gain the target compounds **5a–5i**.

**Ethyl 2-(1,5-diphenyl-1H-pyrazol-3-yloxy)acetate (5a).** White crystal; mp 79–80°C; yield, 89%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.31 (t, $J$ = 7.17, 14.25 Hz, 3H, $CH_3$), 4.28 (q, $J$ = 7.17, 14.28 Hz, 2H, $CH_2$), 4.88 (s, 2H, $CH_2$), 6.04 (s, 1H, CH), 7.20–7.27 (m, 10H, Ar-H); Anal. Calcd for $C_{19}H_{18}N_2O_3$: C 70.79, H 5.63, N 8.69; found C 70.72, H 5.62, N 8.73.

**Ethyl 2-(1-phenyl-5-p-tolyl-1H-pyrazol-3-yloxy)acetate (5b).** White crystal; mp 106–107°C; yield, 85%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.30 (t, $J$ = 7.15, 14.25 Hz, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 4.28 (q, $J$ = 7.15, 14.28 Hz, 2H, $CH_2$), 4.86 (s, 2H, $CH_2$), 6.00 (s, 1H, CH), 7.09–7.29 (m, 9H, Ar-H); Anal. Calcd for $C_{20}H_{20}N_2O_3$: C 71.41, H 5.99, N 8.33; found C 71.34, H 5.97, N 8.28.

**Ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetate (5c).** Yellow crystal; mp 51–52°C; yield, 88%. $^1$H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.30 (t, $J$ = 7.20, 14.28 Hz, 3H, $CH_3$), 4.28 (q, $J$ = 7.20, 14.19 Hz, 2H, $CH_2$), 4.86 (s, 2H,

$CH_2$), 6.03 (s, 1H, CH), 7.13–7.38 (m, 9H, Ar-H); Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C 63.96, H 4.80, N 7.85; found C 63.88, H 4.82, N 7.82.

**Ethyl 2-(5-(4-fluorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetate (5d).** White crystal; mp 76–77°C; yield, 81%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.33 (t, $J$ = 7.15, 14.3 Hz, 3H, $CH_3$), 4.31 (q, $J$ = 7.15, 14.2 Hz, 2H, $CH_2$), 4.90 (s, 2H, $CH_2$), 6.08 (s, 1H, CH), 7.01–7.28 (m, 9H, Ar-H); Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C 67.05, H 5.03, N 8.23; found C 67.14, H 5.04, N 8.19.

**Ethyl 2-(1-phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazol-3-yloxy)acetate (5e).** Yellow crystal; mp 75–76°C; yield, 84%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.21 (t, $J$ = 7, 14.2 Hz, 3H, $CH_3$), 3.58 (s, 6H, $OCH_3$), 3.65 (s, 3H, $OCH_3$), 4.17 (q, $J$ = 7.2, 14.2 Hz, 2H, $CH_2$), 4.83 (s, 2H, $CH_2$), 6.26 (s, 1H, CH), 6.49 (s, 2H, Ar-H), 7.22–7.39 (m, 5H, Ar-H); Anal. Calcd for $C_{22}H_{24}N_2O_6$: C 64.07, H 5.87, N 6.79; found C 63.98, H 5.85, N 6.75.

**Ethyl 2-(5-(3-fluorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetate (5f).** White crystal; mp 67–68°C; yield, 81%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.30 (t, $J$ = 7.2, 14.25 Hz, 3H, $CH_3$), 4.28 (q, $J$ = 7, 14.35 Hz, 2H, $CH_2$), 4.87 (s, 2H, $CH_2$), 6.05 (s, 1H, CH), 6.91–7.27 (m, 9H, Ar-H); Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C 67.05, H 5.03, N 8.23; found C 67.14, H 5.04, N 8.20.

**Ethyl 2-(1-(4-isopropylphenyl)-5-phenyl-1H-pyrazol-3-yloxy)acetate (5g).** Yellow crystal; mp 133–134°C; yield, 88%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, $J$ = 6.85 Hz, 6H, $CH_3$), 1.30 (t, $J$ = 7.15, 14.3 Hz, 3H, $CH_3$), 2.87 (q, $J$ = 7, 13.8 Hz, 1H, CH), 4.28 (q, $J$ = 7.15, 14.15 Hz, 2H, $CH_2$), 4.87 (s, 2H, $CH_2$), 6.02 (s, 1H, CH), 7.12–7.29 (m, 9H, Ar-H); Anal. Calcd for $C_{22}H_{24}N_2O_3$: C 72.50, H 6.64, N 7.69; found C 72.43, H 6.66, N 7.66.

**Ethyl 2-(1-(4-isopropylphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yloxy)-acetate (5h).** Yellow crystal; mp 127–128°C; yield, 83%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, $J$ = 6.8 Hz, 6H, $CH_3$), 1.30 (t, $J$ = 7.15, 14.25 Hz, 3H, $CH_3$), 2.88 (t, $J$ = 6.8, 13.75 Hz, 1H, CH), 3.80 (s, 3H, $OCH_3$), 4.28 (q, $J$ = 7.15, 14.25 Hz, 2H, $CH_2$), 4.86 (s, 2H, $CH_2$), 5.96 (s, 1H, CH), 6.81–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{23}H_{26}N_2O_4$: C 70.03, H 6.64, N 7.10; found C 70.12, H 6.67, N 7.08.

**Ethyl 2-(5-(4-fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-3-yloxy)-acetate (5i).** Yellow crystal; mp 81–82°C; yield, 89%. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, $J$ = 6.75 Hz, 6H, $CH_3$), 1.30 (t, $J$ = 7.2, 14.2 Hz, 3H, $CH_3$), 2.88 (q, $J$ = 6.85, 13.8 Hz, 1H, CH), 4.15 (q, $J$ = 7.15, 14.18 Hz, 2H, $CH_2$), 4.83 (s, 2H, $CH_2$), 6.19 (s, 1H, CH), 7.07–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{22}H_{23}FN_2O_3$: C 69.09, H 6.06, N 7.33; found C 69.15, H 6.11, N 7.31.

## REFERENCES AND NOTES

[1] Vicentini, C. B.; Romagnoli, C.; Andreotti, E.; Mares, D. J Agric Food Chem 2007, 55, 10331.

[2] Meegalla, S. K.; Doller, D.; Sha, D.; Soll, R.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. Bioorg Med Chem Lett 2004, 14, 4949.

[3] Morimoto, K.; Makino, K.; Yamamoto, S.; Sakata, G. J Heterocycl Chem 1990, 27, 807.

[4] Sohn, E.; Handte, R.; Mildenberger, H.; Buerstell, H.; Bauer, K.; Bieringer, H. Ger. Pat.3,633,840 (1988); Chem Abstr 1989, 110, 8202.

[5] Tohyama, Y.; Sanemitsu, Y. Eur. Pat.1,122,244 (2001); Chem Abstr 2001, 135, 152820.

[6] Ono, R.; Nagaoka, M.; Yamada, O.; Tokumura, J. Jpn. Pat.2,008,120,736 (2008); Chem Abstr 2008, 149, 10016.

[7] Japp, F. R.; Maitland, W. J Chem Soc Trans 1904, 85, 1490.

[8] Al-Jallo, H. N. A. Tetrahedron Lett 1970, 11, 875.

[9] Al-Jallo, H.; Shandala, M.; Al-Hajjar, F.; Al-Jabour, N. J Heterocycl Chem 1976, 13, 455.

[10] Baddar, F. G.; El-Newaihy, M. F.; Salem, M. R. J Chem Soc 1969, 5, 836.

[11] Selwood, D. L.; Brummell, D. G.; Budworth, J.; Burtin, G. E.; Campbell, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.; Hobbs, A. J.; Kling, M. R.; Liu, Q.; Madge, D. J.; Millerais, S.; Powell, K. L.; Reynolds, K.; Spacey, G. D.; Stables, J. N.; Tatlock, M. A.; Wheeler, K. A.; Wishart, G.; Woo, C.-K. J Med Chem 2001, 44, 78.

[12] Metwally, S. A. M.; Mohamed, T. A.; Moustafa, O. S.; El-Ossaily, Y. A. Chem Heterocycl Compd 2007, 43, 1131.

[13] Baumgartner, C.; Brandli, L.; Diederich, F. Heterocycles 2008, 76, 401.

[14] Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Foces-Foces, C.; Llamas-Saiz, A. L.; Jagerovic, N.; Elguero, J. Tetrahedron 1999, 55, 10187.

[15] Liu, Y.-Y.; Wu, Z.-Y.; Shi, H.; Chu, Q.-Y.; Zhu, H.-J. Acta Crystallogr Sect E 2008, 64, o2101.

[16] Liu, Y.-Y.; Shi, H.; Chu, Q.-Y.; Zhu, H.-J. Acta Crystallogr Sect E 2008, 64, o1886.

[17] Sun, Y.-F.; Jia, H.-S.; Liu, S.; Zhu, H.-J. Acta Crystallogr Sect E 2007, 63, o3397.

[18] Czeskis, B. A.; Wheeler, W. J. J Labelled Comp Radiopharm 2005, 48, 407.

[19] Gaede, B. J.; McDermott, L. L. J Heterocycl Chem 1993, 30, 49.

[20] Ren, Q.-Y.; Cui, Z.-P.; He, H.-W.; Gu, Y.-C. J Fluor Chem 2007, 128, 1369.

# Synthesis and Biological Evaluation of Novel 2-(4-*o*-β-D-Glucosidoxyphenyl)-4,5-disubstituted Imidazoles



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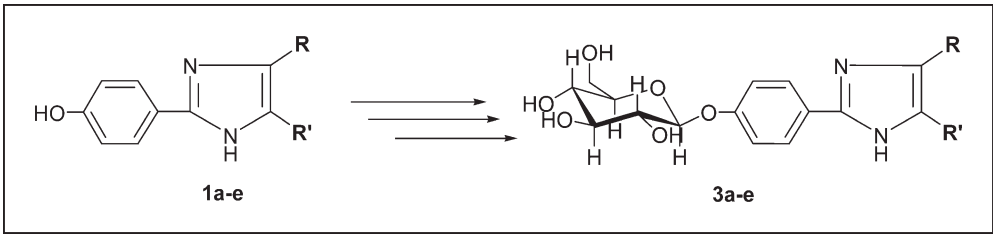


A series of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles (**1a–e**) prepared from α-diketones, ammonium acetate, and *p*-hydroxybenzaldehyde, which were glucosylated by using α-acetobromoglucose to form 2-(4-*o*-β-D-2,3,4,6-tetra-*o*-acetyl-glucosidoxyphenyl)-4,5-disubstituted imidazoles (**2a–e**) which on catalytic deacetylation with $CH_3ONa$ in methanol afforded the title compound 2-(4-*o*-β-D-glucosidoxyphenyl)-4,5-disubstituted imidazoles (**3a–e**). Compounds were characterized by elemental analysis and by instrumental technique, similarly the title compounds were investigated for antimicrobial and antifungal activity.

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## INTRODUCTION

In continuation of our work [1] with imidazole ring which were very important in living systems like vitamin $B_{12}$. Imidazole also forms a part of some important compounds such as purine, adenine, xanthine, guanine, co-enzyme-a. It is also distributed in essential amino acid, e.g., 1-histidine. Imidazoles possess, various biological activities, *viz*., antibacterial [2,3], antifungal [4], anti-inflammatory [5], antihistaminic [6], and hypertensive [7]. Glucoconjugate and the carbohydrate containing structure [8,9] exhibit a variety of biological and therapeutic properties [10]. As a result, the formation of glucosidic linkage continues to be a dominant theme in carbohydrate chemistry [11,12]. The attached sugar molecules increase water solubility and tissue penetration. In addition to acting as a modifier, carbohydrate can induce biological activity. In view of various biological activities of imidazoles and the importance of glucose moiety in the metabolism, several compounds containing imidazole and glucose moiety have been synthesized. Herein, we reported the synthesis of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles and 2-(4-*o*-β-D-glucosidoxyphenyl)-4, 5-disubstituted imidazoles.

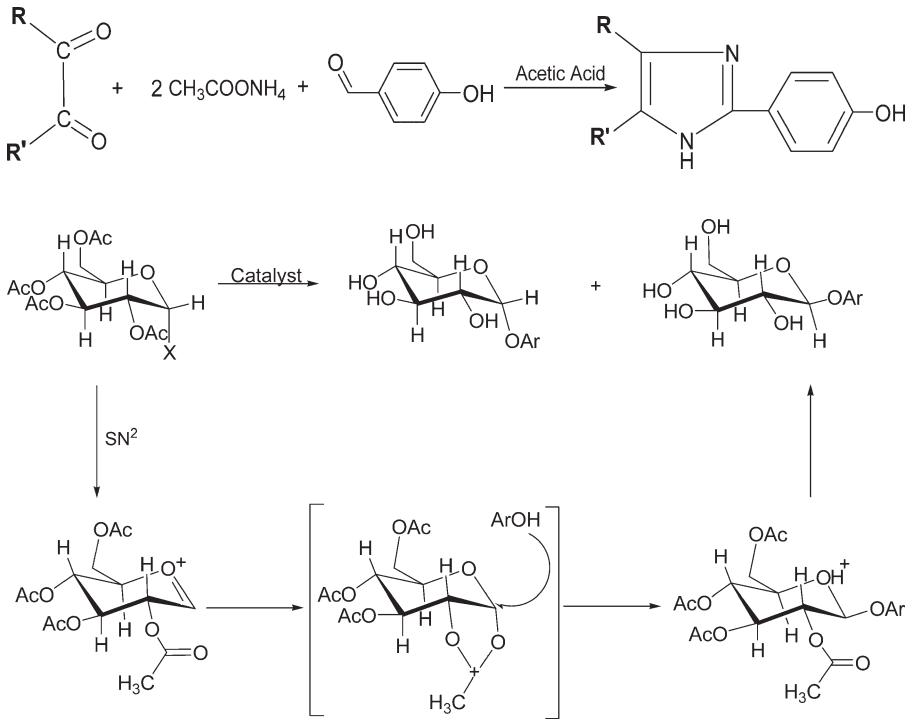
## RESULTS AND DISCUSSION

Our general synthetic route starts with the aglycon synthesis **1** it was prepared by condensation between α-diketones, *p*-hydroxybenzaldehyde, and ammonium acetate in the acetic acid medium [13]. The series of these aglycon prepared by changing substitutions at 4,5 positions (**1a–e**). The glucosylation is carried out by using modified Koenigs-Knorr method [14] (Scheme 1).

The mechanism of *o*-glucosylation reaction gained immense importance due to its stereo-and regeoselective nature. Glucosylation of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazole with α-acetobromoglucose (ACBG) followed by deacetylation leads to the desired *o*-glucoside with distereoselectivity in favors of β-anomer. *o*-Glucosylation takes place *via* $S_N1$ and $S_N2$ mechanism. In the absence of heavy metal salts or Lewis acid catalyst mostly follows $S_N2$ mechanism which mainly leads to β-anomer as the preferred product. In contrast, the presence of Lewis acid catalyst follows $S_N1$ mechanism and is less distereoselective and regioselective.

This leads to the formation of α- and β-anomers. An ester protecting group on the 2-hydroxyl group of the donor will lead to the neighboring group participation during *o*-glucosylation reaction and only the 1,2-trans-diaxial glucoside (β-anomer) is the preferred product.

**Scheme 1**




Glucosylation of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles with acetobromoglucose (ACBG) followed by deacetylation leads the desired *o*-glucoside FT-IR data of the *o*-glucoside are in agreement with the assigned structure. Anomeric configuration confirmed by $^1$H NMR since the coupling constant of the compound 8.5 Hz was observed between H-1 and H-2 proton. $^{13}$C NMR spectrum, C-1 resonated downfield of the other glucosyl carbon at δ 100.26 consistent with the formation of *o*-β-glucosides. $S_N2$ mechanism for 1,2-trans glucoside formation 1,2-dioxyacylcarbonium ion (Scheme 2).

## BIOLOGICAL ASSAY

**Antibacterial activity.** The compounds (**3a–e**) were screened for their antibacterial activities against various pathogenic bacteria *Escherichia coli*, *Klebisilla aerogens*, *Staphyllococcus aureus*, and *Bacillus substilis* by the cup plate diffusion of 100 μg/mL by using standard ciprofloxacin and sulphacetamide (100 μg/mL) for bacteria. The zone of inhibition after 24 h of incubation at 37°C was compared with standard drugs (Table 1).

**Antifungal activity.** The compounds (**3a–e**) were screened for antifungal activity tasted at 100 μg/mL concentration in methanol against *Aspergillus niger and Candida albicans* by adopting cup plate diffusion method. The zone of inhibition after 7 days at 37°C was compared with standard drugs gentamycin and clotrimazole (100 μg/mL).

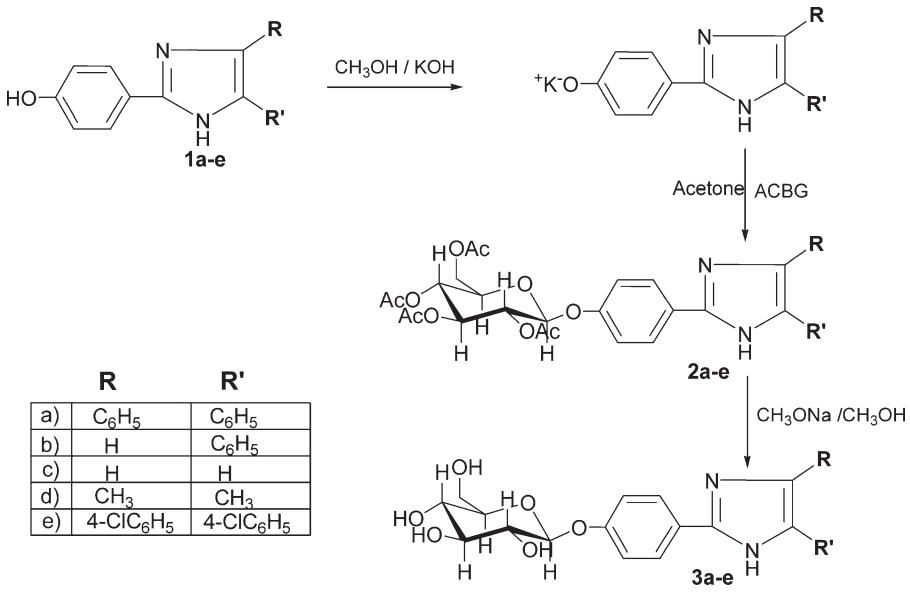
## EXPERIMENTAL

The melting points (mp) are taken by using open capillary method and are uncorrected. The FT-IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr disc. The $^1$H NMR spectra are recorded on Bruker DRX-300 (300 MHz FT-NMR) instrument using DMSO-d6 as a solvent and TMS as internal standard, and the chemical shift are expressed in δ ppm values. EI-MS were recorded by direct insertion technique with a Hitachi Perkin Elmer RMU 6D mass Spectrophotometer. Elemental analysis was determined by the FLASH EA 1112 CHN analyzer, Thermo Finigin, Italy.

**General procedure for 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles (1a–e).** A mixture of 4-hydroxy benzaldehyde (5 mmol), α-diketones (5 mmol), ammonium acetate (10 mmol), and glacial acetic acid (50 mL) was refluxed for 2 h. It was poured on to cold water (200 mL) and neutralized with $NH_4OH$. The solid obtained was filtered, washed with water, and crystallized from alcohol.

**2-(4-Hydroxyphenyl)-4,5-diphenyl imidazole (1a).** Yield 1.4 g (75%), mp 260°C, $R_f$ = 0.78, FT-IR spectrum showed the 3569.4 (—OH, broad) due to the presence of free phenolic hydroxyl group and 1608 (C=N, str.), 3165.3–2793.3 cm$^{-1}$

**Scheme 2**




| | R | R' |
|---|---|---|
| a) | $C_6H_5$ | $C_6H_5$ |
| b) | H | $C_6H_5$ |
| c) | H | H |
| d) | $CH_3$ | $CH_3$ |
| e) | 4-$ClC_6H_5$ | 4-$ClC_6H_5$ |

(aromatic ring, str.), 1235.6 (C—O bend), 3466.6 (—NH); $^1$H NMR: δ 7.2–7.5 (m, 14H, Ar—H), 6.8 (s, 1H, OH), 7.9 (1H, —NH, $D_2O$ exchangeable) Anal. Calcd. for $C_{21}H_{26}N_2O$ (312): C, 80.75; H, 5.16; N, 8.97; Found: C, 80.65; H, 5.11; N, 8.85.

**2-(4-Hydroxyphenyl)-5-phenyl imidazole (1b).** Yield 54%; mp 175°C (ethanol); $R_f$ = 0.70, FT-IR: 3510 (—OH, broad), 3345.5 (—NH), 1612 (C=N, str.), 1218 (C—O bend), 3165.3–2790.3 cm$^{-1}$ (aromatic ring, str.).$^1$H NMR: δ = 6.8 (s, 1H, OH), 10.2 (1H, —NH, exchangeable with $D_2O$), 6.5–7.3 (m, 9H, aromatic). Anal. Calcd. for $C_{15}H_{12}N_2O$ (236): C, 76.25; H, 5.12; N, 11.86; Found: C, 76.18; H, 5.20; N, 11.82.

**2-(4-Hydroxyphenyl)-imidazole (1c).** Yield 72%; mp 190°C (ethanol); $R_f$ = 0.68, FT-IR: 3585 (—OH, broad), 3358.0 (—NH), 1618 (C=N, str.), 1220 (C—O bend), 3105.5–2788.0 cm$^{-1}$ (aromatic ring, str.).$^1$H NMR: δ = 5.6 (s, 1H, OH), 9.5 (1H, —NH, exchangeable with $D_2O$), 6.2—7.4 (m, 4H, aromatic). Anal. Calcd. for $C_9H_8N_2O$ (160): C, 67.49; H, 5.03; N, 17.49; Found: C, 67.56; H, 5.10; N, 17.45.

**2-(4-Hydroxyphenyl)-4,5-dimethyl imidazole (1d).** Yield 62%; mp 135°C (ethanol); $R_f$ = 0.54, FT-IR: 3424 (—OH, broad), 3269.0 (—NH), 1614 (C=N, str.), 1224 (C—O bend), 3015.5–2712. cm$^{-1}$ (aromatic ring, str.). $^1$H NMR: δ = 5.5 (s, 1H, OH), 9.4 (1H, —NH, exchangeable with $D_2O$), 6.2–7.8 (m, 4H, aromatic). Anal. Calcd. for $C_{11}H_{12}N_2O$ (188): C, 70.19; H, 6.43; N, 14.88; Found: C, 70.25; H, 6.40; N, 14.90.

**2-(4-Hydroxyphenyl)-4,5-bis-(4-chlorophenyl)-imidazole (1e).** Yield 60%; mp 245°C (ethanol); $R_f$ = 0.73, FT-IR: 3520 (—OH, broad), 3370.0 (—NH), 1624(C=N, str.), 1222 (C—O bend), 3085–2712 cm$^{-1}$ (aromatic ring, str.).$^1$H NMR δ = 5.8 (s, 1H, OH), 8.5 (1H, —NH, exchangeable with $D_2O$), 6.1–7.5

**Table 1**

Antimicrobial activity 4,5-diaryl-2-(4-*o*-β-D-glucosidoxyphenyl) imidazoles (**3a-e**).

| | Zone of inhibition[a] (mm) (activity index)[std] | | | | | |
|---|---|---|---|---|---|---|
| | Antibacterial activity | | | | | |
| | Gram-positive | | Gram-negative | | Antifungal activity | |
| Compd. No.[b] | *S. aureus* | *B. substilis* | *E. coli* | *K. aerogens* | *C. albicans* | *A. niger* |
| **3a** | 19(0.55)[c] (0.61)[d] | 25(0.86)[c] (0.96)[d] | 18(0.51)[c] (0.62)[d] | 19(0.83)[c] (0.90)[d] | 21(1.00)[c] (0.91)[d] | 23(0.92)[c] (1.00)[d] |
| **3b** | 25(0.73)[c] (0.80)[d] | 17(0.58)[c] (0.65)[d] | 26(0.74)[c] (0.89)[d] | 16(0.72)[c] (0.76)[d] | 25(1.19)[c] (1.09)[d] | 17(0.68)[c] (0.71)[d] |
| **3c** | 30(0.88)[c] (0.96)[d] | 19(0.65)[c] (0.73)[d] | 22(0.62)[c] (0.75)[d] | 20(0.90)[c] (0.95)[d] | 17(0.80)[c] (0.73)[d] | 19(0.76)[c] (0.79)[d] |
| **3d** | 22(0.64)[c] (0.70)[d] | 14(0.48)[c] (0.53)[d] | 16(0.45)[c] (0.55)[d] | 14(0.63)[c] (0.66)[d] | 18(0.85)[c] (0.78)[d] | 20(0.80)[c] (0.83)[d] |
| **3e** | 16(0.47)[c] (0.51)[d] | 20(0.68)[c] (0.76)[d] | 19(0.54)[c] (0.65)[d] | 18(0.81)[c] (0. 85)[d] | 20(0.95)[c] (0.86)[d] | 14(0.56)[c] (0.58)[d] |
| Std. 1 | 34 | 29 | 35 | 22 | 21 | 25 |
| Std. 2 | 31 | 26 | 29 | 21 | 23 | 24 |

[a] Average zone of inhibition in mm.
[b] Concentration of test compounds and standard 100 μg/mL. (Activity index) = Inhibition zone of the sample/inhibition zone of the standard.
[c] Activity index against std. 1.
[d] Activity index against std. 2.For antibacterial activity: Std. 1 = Ciprofloxacin and Std. 2 = Sulphacetamide, for antifungal activity: Std. 1 = Gentamycin and Std. 2 = Clotrimazole.

(m, 12H, aromatic). Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O$ (380): C, 66.16; H, 3.70; N, 7.35; Found: C, 66.32; H, 3.76; N, 7.32.

**General procedure for 2-(4-*o*-β-D-2,3,4,6-tetra-*o*-acetyl-glucosidoxyphenyl)-4,5-disubstituted imidazoles (2a–e).** A solution of 3 g potassium salt of 4,5-disubstituted-2-(4-hydroxyphenyl)-imidazole in 10 mL of 5% methanolic KOH was added drop wise to a solution of 5 g of a acetobromoglucose in 20 mL of dry acetone. The resulting mixture was stirred at 0°C for 2 h. The reaction was allowed to proceed for an additional 24 h and the solvent remove under reduced pressure. The reaction was monitored by TLC, A brown syrupy mass of 4,5-disubstituted-2-(4-*o*-β-D-2,3,4,6-tetra-*o*-acetyl glucosidoxyphenyl)imidazoles were obtained.

**2-(4-*o*-β-D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-4,5-diphenyl imidazole (2a).** Yield 3.57 g (65%). $R_f = 0.28$. The compound was found to be optically active and the specific rotation $[\alpha]_D^{30}$ in DMSO was found to be −8.12. FT-IR spectrum of the compound showed following characteristic bands at $\nu_{max}$ 3424 (—NH), 1607 (C=N), and 1074 (C—O) $cm^{-1}$. The characteristic band due to phenolic hydroxyl group (3300–3500 $cm^{-1}$) was absent and the band due to C—O—C which appear at 1231 $cm^{-1}$ confirms the formation of *o*-glucoside.$^1$H NMR: 2.02, 1.95,1.97, 2.01 (s, 3H) ($COCH_3$), 4.8 (d, 1H, anomeric proton), 6.4–7.1 (m, 14H, Ar—H), 10.5 (s, 1H, —NH). Anal. Calcd. for $C_{35}H_{34}N_2O_{10}$ (642): C, 65.41; H, 5.33; N, 4.36; Found: C, 65.35; H, 5.30; N, 4.38.

**2-(4-*o*-β-D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-5-phenyl imidazole (2b).** Yield 72%; $[\alpha]_D^{30} = -12.56$ (c, 0.1, DMSO); brown syrup; $R_f = 0.12$; FT-IR: 3420 (—NH), 2855 (glucosidic CH), 2420 (Ar—CH), 1610 (C=N), 1089 (C—O), and 1225 $cm^{-1}$ (C—O—C). $^1$H NMR: 2.02, 1.94, 1.97, 2.01 (s, 3H) ($COCH_3$), 5.1 (d, 1H, anomeric proton), 6.2 −7.0 (m, 9H, Ar—H), 9.6 (s, 1H, —NH). Anal. Calcd. for $C_{29}H_{30}N_2O_{10}$ (566): C, 61.48; H, 5.34; N, 4.94; Found: C, 61.42; H, 5.30; N, 4.93.

**2-(4-*o*-β-D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl) imidazole (2c).** Yield 82%; $[\alpha]_D^{30} = -2.24$ (c, 0.1, DMSO); brown syrup; $R_f = 0.22$; FT-IR: 3428 (—NH), 2828 (glucosidic CH), 2610 (Ar—CH), 1618 (C=N), 1085 (C—O), and 1210 $cm^{-1}$ (C—O—C). $^1$H NMR: 2.02, 1.90, 1.96, 2.01 (s, 3H) ($COCH_3$), 5.4 (d, 1H, anomeric proton), 6.0–7.3 (m, 4H, Ar—H), 9.8 (s, 1H, —NH). Anal. Calcd. for $C_{23}H_{26}N_2O_{10}$ (490): C, 56.32; H, 5.34; N, 5.71; Found: C, 56.38; H, 5.32; N, 5.76.

**2-(4-*o*-β-D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-4,5-dimethyl imidazole (2d).** Yield 78%; $[\alpha]_D^{30} = -8.16$ (c, 0.1, DMSO); brown syrup; $R_f = 0.21$; FT-IR (KBr): 3430 (—NH), 2832(glucosidic CH), 2612(Ar—CH), 1625 (C=N), 1087 (C—O), and 1218 $cm^{-1}$ (C—O—C). $^1$H NMR: 2.00, 1.92, 1.98, 2.01 (s, 3H) ($COCH_3$), 5.1 (d, 1H, anomeric proton), 6.2–6.9 (m, 4H, Ar—H), 10.2 (s, 1H, —NH). Anal. Calcd. for $C_{25}H_{30}N_2O_{10}$ (518): C, 57.91; H, 5.83; N, 5.40; Found: C, 57.95; H, 5.84; N, 5.42.

**2-(4-*o*-β-D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)- 4,5-bis-(4-chlorophenyl) imidazole (2e).** Yield 75%; $[\alpha]_D^{30} = -4.10$ (c, 0.1, DMSO); brown syrup; $R_f = 0.28$; FT-IR (KBr): 3440 (—NH), 2795 (glucosidic CH), 2610 (Ar—CH), 1620 (C=N), 1090 (C—O), and 1215 $cm^{-1}$ (C—O—C). $^1$H NMR: 2.00, 1.94, 1.96, 2.02 (s, 3H) ($COCH_3$), 5.5 (d, 1H, anomeric proton), 6.2–6.8 (m, 12H, Ar—H), 11.4 (s, 1H, —NH). Anal. Calcd. for $C_{35}H_{32}Cl_2N_2O_{10}$ (710): C, 59.08; H, 4.53; N, 3.94; Found: C, 59.05; H, 4.56; N, 3.96.

**General procedure for 2-(4-*o*-β-D-glucosidoxyphenyl)-4,5-disubstituted imidazoles (3a–e).** A solution of 4,5-disubstituted-2-(4-*o*-β-D-2,3,4,6-tetra-*o*-acetyl glucosidoxyphenyl) imidazole (2 g) in 25 mL of dry methanol was added 1.5 mL of 5% $CH_3ONa$ solution .The reaction mixture was kept at room temperature for additional 24 h. It was neutralized with ion-exchange resin (Amberlite IR 120, s.d. fine, $H^+$ form) filtered and concentrated in vacuum to afford viscous, strongly hygroscopic brown colored syrupy.

**2-(4-*o*-β-D-Glucosidoxyphenyl)-4,5-diphenyl imidazole (3a).** Yield 65%; $[\alpha]_D^{30} = -9.88$ (c, 0.1, DMSO); brown syrup; $R_f = 0.12$; FT-IR: 3200–3391.7 (—OH, broad, stretching). 2361.9 (aromatic str.), 1073.7 (C—O—C), 1609.9 $cm^{-1}$ (C=N). $^1$H NMR: 6.8–7.7 Hz (H, Ar—H), 10.5 (s, —NH), 4.8 (d, 1H, $J_{1,2} = 8.5$ Hz, 1′H) anomeric proton, 3.9 (1H, 2′H), 3.4 (dd, 1H, 3′H), 3.7 (1H, 4′H), 3.2 (1H, 5′H). $^{13}$C NMR: δ115–128 (Ar—C), sugar moiety: δ 100.26 (s, C-1′) anomeric carbon, 81 (s, C-6′), 77 (s, C-5′), 72 (s, C-4′), 70.5 (s, C-3′), 62 (s, C-2′). EI-MS the molecular ion peak were observed at 474 (M + 1) (46%) base peak observed at 312 (100 %), 118 (10 %), 77 (08 %). Anal.Calcd. for $C_{27}H_{26}N_2O_6$ (474): C, 68.34; H, 5.52; N, 5.90; Found: C, 68.37; H, 5.50; N, 5.86.

**2-(4-*o*-β-D-Glucosidoxyphenyl)-5-phenyl imidazole (3b).** Yield 58%; $[\alpha]_D^{30} = -15.20$ (c, 0.1, DMSO); brown syrup; $R_f = 0.8$; FT-IR: 3300 (—OH, broad), 2718.1 $cm^{-1}$ (aromatic str.), 1079.2 (C—O—C), 1620.6 $cm^{-1}$ (C=N). $^1$H NMR: 6.8–7.8 (m, 9H, Ar—H), 10.4 (s, 1H, —NH), 3.3 (1H,5′H), 3.5 (1H,4′H), 3.4 (1H,3′H), 3.8 (1H,2′H), 5.0 (dd, 1H, $J_{1,2} = 8.8$ Hz, 1′H).$^{13}$C NMR: δ115–128 (Ar—C), sugar moiety: δ108 (s, C-1′) anomeric carbon, 80 (s, C-6′), 76 (s, C-5′), 71.5 (s, C-4′), 70.5 (s, C-3′), 60 (s, C-2′). EI-MS: 398 (M) (20%), 220 (58%) 116 (100%) base peak, 105 (10%), 78(4%). Anal.Calcd. for $C_{21}H_{22}N_2O_6$ (398): C, 63.31; H, 5.57; N, 7.03; Found: C, 63.34; H, 5.50; N, 7.06.

**2-(4-*o*-β-D-Glucosidoxyphenyl) imidazole (3c).** Yield 60%; $[\alpha]_D^{30} = -5.22$ (c, 0.1, DMSO); brown syrup; $R_f = 0.15$; FT-IR: 3400 (—OH, broad), 2818.1 (aromatic str.), 1088.2 (C—O—C) glucosidic linkage, 1624 $cm^{-1}$ (C=N). $^1$H NMR: 6.5–7.9 (m, Ar—H), 11.4 (s, 1H,—NH), 3.2 (1H, 5′H), 3.4 (1H, 4′H), 3.5 (1H, 3′H), 3.9 (1H, 2′H), 5.5 (dd, 1H, $J_{1,2} = 10.2$ Hz, 1′H) anomeric proton. $^{13}$C NMR: δ116–130 (Ar—C), sugar moiety: δ110 (s, C-1′) anomeric carbon, 82 (s, C-6′), 77 (s, C-5′), 72.5 (s, C-4′), 71.5 (s, C-3′), 63 (s, C-2′). EI-MS: 322 (M) (28 %), 160 (100 %) base peak 146 (15 %), 77 (4 %). Anal.-Calcd. for $C_{15}H_{18}N_2O_6$ (322): C, 55.90; H, 5.63; N, 8.69; Found: C, 55.88; H, 5.60; N, 8.65.

**2-(4-*o*-β-D-Glucosidoxyphenyl)-4,5-dimethyl imidazole (3d).** Yield 68%; $[\alpha]_D^{30} = -11.10$ (c, 0.1, DMSO); brown syrup; $R_f = 0.16$; FT-IR: 3380 (—OH, broad), 2910 (aromatic str.), 1085.0 (C—O—C) glucosidic linkage, 1630 $cm^{-1}$ (C=N). $^1$H NMR: 6.0–7.4 (m, Ar—H), 10.2 (s,1H,—NH), 3.0 (1H,5′H), 3.2 (1H,4′H), 3.5 (1H,3′H), 3.7 (1H,2′H), 5.6 (dd, 1H, $J_{1,2} = 9.8$ Hz, 1′H) anomeric proton.$^{13}$C NMR: δ120–136 (Ar—C), sugar moiety: δ115 (s, C-1′) anomeric carbon, 88 (s, C-6′), 86 (s, C-5′), 76 (s, C-4′), 70. (s, C-3′), 65 (s, C-2′). EI-MS: 350 (M) (25 %), 170 (100 %) base peak 118 (12 %), 78 (8 %). Anal.Calcd. for $C_{17}H_{22}N_2O_6$ (350): C, 58.28; H, 6.33; N, 8.00; Found: C, 58.32; H, 6.36; N, 8.05.

**2-(4-*o*-β-D-Glucosidoxyphenyl)-4,5-bis-(4-chlorophenyl) imidazole (3e).** Yield 62%; $[\alpha]_D^{30} = -6.80$ (c, 0.1, DMSO); brown syrup; $R_f = 0.20$; FT-IR: 3420 (—OH, broad), 3015 (aromatic str.), 1088.0 (C—O—C) glucosidic linkage, 1630 $cm^{-1}$ (C=N).

$^1$H NMR: 6.0–7.3 (m, Ar—H), 10.5 (s, 1H,—NH), 3.0 (1H, 5′H), 3.4 (1H, 4′H), 3.5 (1H, 3′H), 3.8 (1H, 2′H), 5.2(dd, 1H, $J_{1,2}$ = 9.0 Hz, 1′H) anomeric proton. $^{13}$C NMR: δ114–136 (Ar—C), sugar moiety: δ103 (s, C-1′) anomeric carbon, 78 (s, C-6′), 77 (s, C-5′), 75 (s, C-4′), 73 (s, C-3′), 67 (s, C-2′). EI-MS: 542 (M) (32 %), 380 (10 %) 246 (100 %) base peak, 163 (24 %), 137 (12 %), 77 (32 %). Anal.Calcd. for $C_{27}H_{24}Cl_2N_2O_6$ (542): C, 59.68; H, 4.45; N, 5.16; Found: C, 59.72; H, 4.48; N, 5.15.

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## REFERENCES AND NOTES

[1] Ingle, V. N.; Hatzade, K. M.; Taile, V. S.; Gaidhane, P. K.; Kharche, S. T. J Carbohydr Chem 2007, 26, 107.

[2] Kondo, H.; Taguchi, M.; Inoue, Y.; Sakamoto, F.; Tssukamoto, G. J Med Chem 1990, 33, 2012.

[3] Dickens, J. P.; Ellames, G. J.; Hare, N. J.; Lawson, K. R.; McKay, W. R.; Mutters, A. P.; Myers, P. L.; Pope, A. M. S.; Upton, R. M. J Med Chem 1991, 34, 2356.

[4] Ogata, M.; Matsumoto, H.; Hamada, Y.; Takehara, M.; Tawara, K. J Med Chem 1983, 26, 768.

[5] Bhatia, M.; Naithani, P. K.; Bhalla, T. N.; Saxena, A. K. J Indian Chem Soc 1992, 60, 594.

[6] Rama Sarma, G. V. S.; Reddy, V. M. Indian J Heterocycl Chem 1993, 3, 111.

[7] Carini, D. J.; Dunica, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S. E.; Pieter, B. M.; Timmermans, W. M. J Med Chem 1991, 34, 2525.

[8] Dwek, R. A. Chem Rev 1996, 96, 683.

[9] Davis, B. G. J Chem Soc Perkin Trans 1 1999, 3215.

[10] McAuliffe, J. C.; Hundsgaul, O. Chem Ind 1997, 170.

[11] Gupta, A.; Sharma, R.; Prakash, L. J Indian Chem Soc 1994, 71, 635.

[12] Huryn, D. M.; Okabe, M. Chem Rev 1992, 92, 1745.

[13] Steck, E. A.; Day, A. R. J Am Chem Soc 1943, 65, 452.

[14] Koenig, W.; Knorr, E. Chem Ber 1901, 34, 957.

# 2-Substituted 4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thiones: Synthesis, Crystal Structure, and Antifungal Activity



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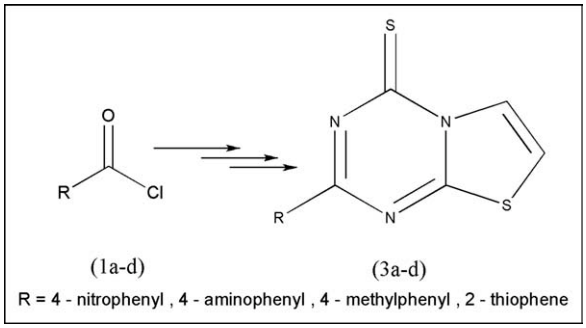


2-(4-Substituted aryl)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thiones (**3a-3b**) and 2-(2-thiophene)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thione (**3d**) were synthesized by the reaction of arylisothiocyanates/thiophene-2-isothiocyanate with 2-aminothiazole in the presence of tetrabutylammonium bromide as phase transfer catalyst. Compound **3c** was synthesized by the catalytic reduction (10% Pd-C) of **3a**. Compounds **3a–d** were characterized by IR, $^{1}$H NMR, $^{13}$C NMR, and elemental analysis. All the compounds were tested *in vitro* against *Fusarium solani, A.fumigatus,* and *Aspergillus flavus* using standard drugs. The crystal structure of **3a** was determined from single crystal X-ray diffraction data.

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## INTRODUCTION

Heterocyclic compounds containing nitrogen and sulphur possess potential pharmacological activities [1–4]. Recent years have seen a dramatic increase in fungal infections, mostly caused by *Candida albicans*; these infections are often spread through the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs [5]. The main problem in the treatment of fungal infections is the increasing prevalence of drug resistance, especially in patient's chronically subjected to antimycotic therapy such as persons infected with HIV [6]. For these reasons, serious attention has recently been directed toward the discovery and development of new antifungal drugs.

Fused heterocyclic 1,3,5-triazines possess a wide array of biological activities such as herbicidal and fungicidal activity [7], antitumor activity [8], and inhibitory activity against the enzymes phosphodiesterase (PED) [9,10], which is expected to be the target for the treatment of diseases such as asthma, diabetes mellitus, and thrombosis. They are also able to block dihydrofolate reductase, the inhibition of which leads to cell death [11]. The title compounds are examples of such fused heterocyclic 1,3,5-triazines.

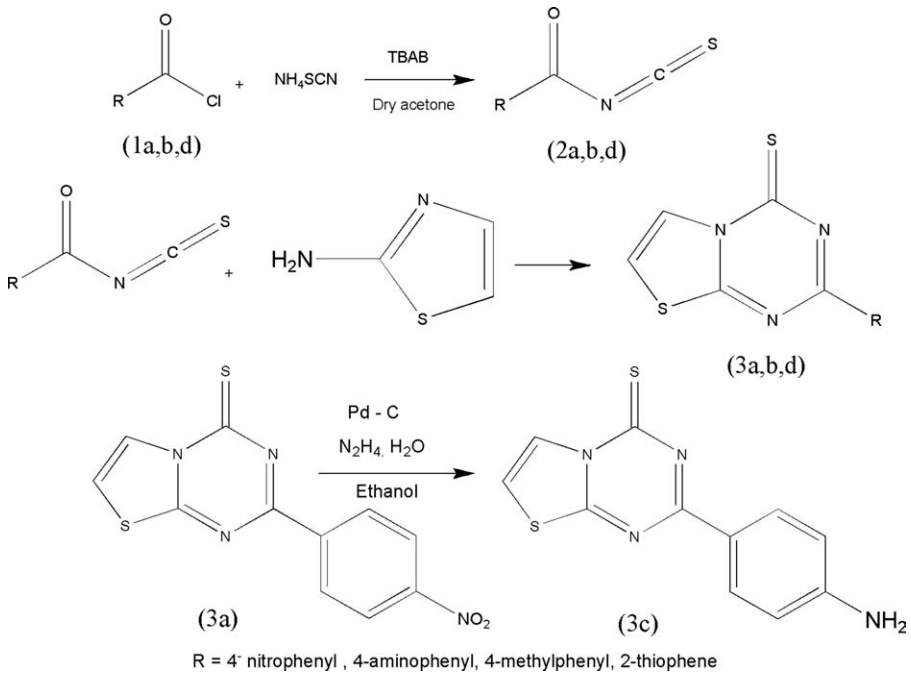
We became interested in the synthesis of fused heterocyclic 1,3,5-triazine compounds containing aryl and thiophene moieties and in the systematic study of their biological activity. All the structures of these novel target compounds were characterized by spectroscopic techniques. We have also confirmed the structure of one representative by X-ray crystallography.

## RESULTS AND DISCUSSION

A series of new fused heterocyclic 1,3,5-triazines **3a–d** with thiophene and aroyl substituents (Scheme 1) were prepared by slight modification of published procedures [12,13]. The use of phase transfer catalysts (PTCs) as a method of agitating a heterogeneous reaction system is gaining recognition [14,15]. In search of improved methods to prepare the target fused heterocyclic 1,3,5-triazines by reacting isothiocyanates with nucleophiles, we have found the use of tetrabutylammonium bromide (TBAB) as PTC, which can afford thiophenoyl and aroyl isothiocyanates in good yield, as reported here.

All the structures of newly synthesized compounds were assigned on the basis of their elemental analysis and spectroscopic data, IR, and $^{1}$H NMR. All the

**Scheme 1.** Preparation of compounds (**3a–d**).




compounds were soluble in DMF, DMSO, ethanol, and ethyl acetate.

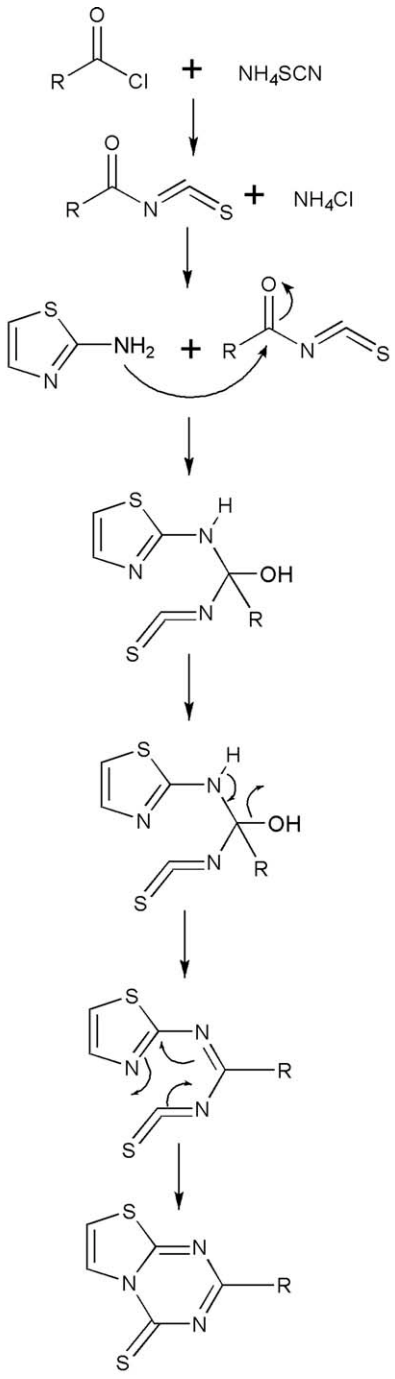
Surprisingly, to the best of our knowledge, 2-(4-substituted phenyl)-4H-[1,3]thiazolo [3,2-a][1,3,5]triazine-4-thiones (**3a–c**) and 2-(2-thiophene)-4H-[1,3]thiazolo [3,2-a][1,3,5]triazine-4-thione (**3d**) have never been described in the literature. The formation of **3a–d** would be explained through the formation of an unstable intermediate form containing thiazole, alcoholic, and isothiocyanate functional groups as shown in Scheme 2. The yield of the target products was very sensitive to the reaction conditions. Two types of products were obtained during the reaction of arylisothiocyanate with 2-aminothiazole. The major product, using a molar ratio of 1:1 between arylisothiocyanate and 2-aminothiazole, was a fused heterocyclic 1,3,5-triazine with about 75% yield and the minor product was a thiourea derivative with about 20% yield. Initially, the experiments were performed three times and these yields remained. However, the yield of fused heterocyclic 1,3,5-triazine products increased to above 90% when the molar concentration of 2-aminothiazole was doubled and refluxed time increased to 4.5 h.

The cyclization of **2a–d** to fused heterocyclic 1,3,5-triazines **3a–d** was monitored by the IR spectra, where the carbonyl chloride peak disappeared on the expense of the appearance of thioamide (C=S) peak in the region of 1445–1440 $cm^{-1}$. The thioamide group was also confirmed by $^{13}C$ NMR, with signals at δ 182–179 ppm.

Single crystals of **3a** suitable for X-ray diffraction studies were obtained by evaporation from dichloromethane/ethanol. The molecular structure is shown in Figure 1. Molecular dimensions may be regarded as normal. The bicyclic thiazolotriazine system is planar (mean deviation 0.01 Å) and subtends an interplanar angle of 11.9° to the phenyl ring. The molecular packing (Fig. 2) displays two contacts, H16···O2 2.36 Å and S1···O1 3.01 Å, which combine to form ribbons parallel to the vector [100] and to the plane (012). These ribbons are connected by N1···O2 3.03 Å (not shown).

Primary bioassay screening provides the first indication of bioactivities and helps in the selection of lead compounds for secondary screening for detailed pharmacological evaluation. The synthesized fused heterocyclic 1,3,5-triazines **3a–d** were checked for their antifungal activity against three fungal strains: *Fusarium solani, A.fumigatus,* and *Aspergillus flavus*. The antifungal activity was carried out in DMSO using the agar tube dilution method [16]. Growth in the media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control. No significant activity against yeast was detected. All the compounds in the series showed weak antimicrobial activity against *Fusarium solani, A.fumigatus,* and *Aspergillus flavus* with 30–40% inhibition, which shows low activity. However, the compound 2-(2-thiophene)-4H-[1,3]thiazolo [3,2-a][1,3,5]triazine-4-thione (**3d**) showed 40% inhibition.

**Scheme 2.** Proposed reaction mechanism.




## EXPERIMENTAL

Melting points were recorded on Electrothermal IA9000 series digital melting point apparatus. The proton NMR and $^{13}C$ spectra were recorded in DMSO-$d_6$ solvent on Bruker 300 MHz spectrophotometer using tetramethylsilane as an internal reference, respectively. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), and m (multiplet). Infrared measurements were recorded in the range 400–4000 $cm^{-1}$ on spectrum 2000 by Perkin Elmer. Elemental analysis was carried out using Perkin Elmer CHNS/O 2400. Obtained results were within 0.4% of the theoretical values. Thin layer chromatography (TLC) analysis were carried out on 5 × 20 cm plate coated with silica gel $GF_{254}$ type 60 (25–250 mesh) using an ethyl acetate-petroleum ether mixture (1:2) as solvent.

**2-(4-Nitrophenyl)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thione (3a).** A solution of 4-nitrobenzoyl chloride (1.85 g, 0.01 mol) in anhydrous acetone (80 mL) and 3% TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.76 g, 0.01 mol) in acetone (50 mL), and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of 2-aminothiazole (1.0 g, 0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 4.5 h. The reaction mixture was poured into five times its volume of cold water, to precipitate the product, which was recrystallized from ethanol: dichloromethane (1:2) as intensely yellow crystals. Yield: 1.50 g (93%), m.p. 196°C; IR (KBr pellet) in $cm^{-1}$: 1529 (benzene ring), 1512 ($NO_2$), 1401 (C—N stretching), 1140 (C=S); $^1H$ NMR (300 MHz, DMSO-$d_6$) in δ (ppm) and $J$ (Hz): 8.10(2H, d, $J$ = 8.41), 7.34 (2H, d, $J$ = 8.7 Hz); $^{13}C$ NMR (300 MHz, DMSO-$d_6$) in δ (ppm): 179.2 (C=S), 165.5 (C), 162.0 (C), 150.4 (C), 145.6 (C), 141.3 (C), 135.1 (C), 128.4 (C) .*Anal*.Calcd. for $C_{11}H_6N_4O_2S_2$ (290.32): C, 45.51; H, 2.08; N, 19.30; S, 22.09. Found: C, 45.50; H, 2.09; N, 19.30; S, 22.07.

**2-(4-Methylphenyl)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thione (3b).** A solution of 4-methylbenzoyl chloride (1.54 g, 0.01 mol) in anhydrous acetone (80 mL) and 3% TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.76 g, 0.01 mol) in acetone (50 mL), and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of 2-aminothiazole (1.0 g, 0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 4.5 h. The reaction mixture was poured into five times its volume of cold water to precipitate the product, which was recrystallized from ethanol as a pale yellow power. Yield: 1.50 g (90%), m.p. 175°C; IR (KBr pellet) in $cm^{-1}$: 1531 (benzene ring), 1403 (C—N stretching), 1143 (C=S); $^1H$ NMR (300 MHz, DMSO-$d_6$) in δ (ppm) and $J$ (Hz): 8.04(2H, d, $J$ = 8.33), 7.24 (2H, d, $J$ = 8.5 Hz), 2.46 (3H,s, —$CH_3$); $^{13}C$ NMR (300 MHz, DMSO-$d_6$) in δ (ppm) : 180.1 (C=S), 165.0 (C), 162.7 (C), 150.4(C), 145.5 (C), 140.7 (C), 135.3 (C), 127.8(C), 25.0 (C). *Anal*.Calcd. for $C_{12}H_9N_3S_2$ (259.35): C, 55.57; H, 3.50; N, 16.20; S, 24.73.Found: C, 55.59; H, 3.52; N, 16.18; S, 24.72.

**2-(4-Aminophenyl)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thione (3c).** Compound **3a** (2.60 g, 0.01 mol), 5 mL hydrazine monohydrate, 70 mL ethanol and 0.03 gm of 10% Pd—C was transferred into 250-mL two-necked round-bottom flask and refluxed for 18 h. The reaction was monitored by TLC. After completion, the reaction mixture was allowed to stand for 1 day and then filtered. The solvent was removed by rotary evaporation. The crude product was recrystallized from ethyl acetate. Yield: 1.50 g (85%), m.p. 165°C; IR (KBr pellet) in $cm^{-1}$: 1529 (benzene ring), 1405 (C—N stretching), 1140 (C=S); $^1H$ NMR (300 MHz, DMSO-$d_6$) in δ (ppm) and $J$ (Hz): 8.10(2H, d, $J$ = 8.41), 7.34 (2H, d, $J$ = 8.7 Hz), 4.01(2H, br s, $NH_2$); $^{13}C$ NMR (300 MHz, DMSO-$d_6$) in

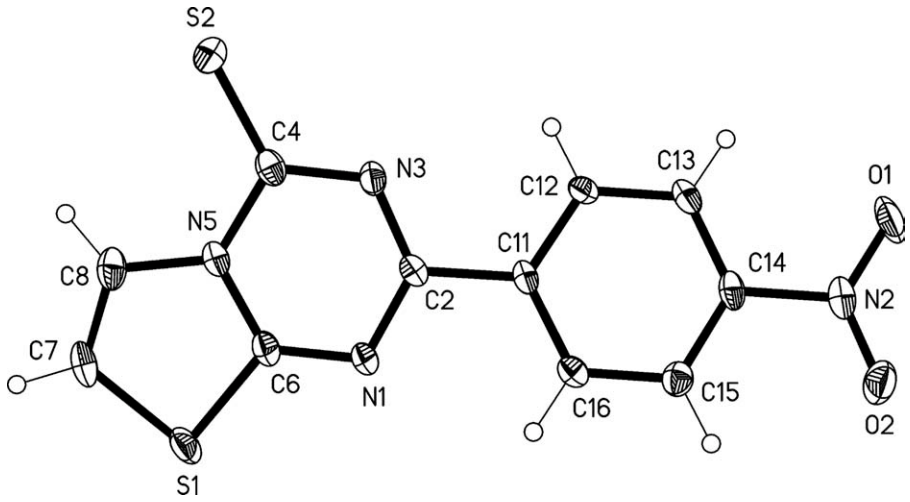



**Figure 1.** The structure of 2-(4-nitrophenyl)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thione (**3a**) with displacement ellipsoids plotted at 50% probability level.

δ (ppm): 180.2 (C=S), 163.3 (C), 162.1 (C), 150.8 (C), 144.6 (C), 140.3 (C), 134.9 (C), 128.7 (C). *Anal*. Calcd. for $C_{11}H_8N_4S_2$ (260.34): C, 50.75; H, 3.10; N, 21.52; S, 24.63. Found: C, 50.78; H, 3.12; N, 21.52; S, 24.64.

**2-(2-Thiophene)-4H-[1,3]thiazolo[3,2-a][1,3,5]triazine-4-thione (3d).** A solution of thiophene-2-carbonyl chloride (1.46 g, 0.01 mol) in anhydrous acetone (80 mL) and 3% TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.76 g, 0.01 mol) in acetone (50 mL), and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of 2-aminothiazole (1.0 g, 0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 5 h. The reaction mixture was poured into five times its volume of cold water to precipitate the product, which was recrystallized from ethanol as an intense yellow powder. Yield: 1.50 g (93%), m.p. 184°C; IR (KBr pellet) in $cm^{-1}$: 1402 (C—N stretching), 1144 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$) in δ (ppm) and *J* (Hz): 8.10 (1H, d, $J = 7.2$ Hz, Thiophene CH), 7.91 (1H, dd, $J_1 = 7.5$ Hz, $J_2 = 8.2$ Hz, Thiophene CH), 7.80 (1H, d, $J = 6.7$ Hz, Thiophene CH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) in δ (ppm): 179.2 (C=S), 165.5 (C), 162.0 (C), 150.4 (C) , 145.6 (C), 141.3 (C), 135.1 (C), 128.4 (C) . *Anal*. Calcd. for $C_9H_5N_3S_3$ (251.35): C, 43.01; H, 2.01; N, 16.72; S, 38.27. Found: C, 43.01; H, 2.01; N, 16.72; S, 38.27.

**Single crystal X-ray diffraction analysis of 3a.** Crystal data: $C_{11}H_6N_4O_2S_2$, orthorhombic, space group *Pbca*, $a = 12.4958(6)$, $b = 8.9836(5)$, $c = 20.5812(12)$ Å, $V = 2310.4(2)$ Å$^3$, $T = 100$ K, $Z = 8$, $F$ (000) = 1184, $D_x = 1.669$ g cm$^{-3}$, $\mu = 4.236$ mm$^{-1}$. Single crystals suitable for X-ray diffraction studies were obtained by evaporation from dichloromethane/ethanol. A yellow plate 0.08 × 0.04 × 0.015 mm$^3$ was mounted on a glass fiber in inert oil. Measurements were performed at 100 K on an Oxford Diffraction Xcalibur Nova diffractometer with mirror-focused Cu-Kα radiation to $2\theta_{max}$ 152° (99.4% complete to 145°). The data were corrected for absorption using the multiscan method. Of 26,206 intensities, 2367 were independent ($R_{int}$ 0.071). The structure was refined anisotropically using SHELXL-97 [17]. Hydrogen atoms were

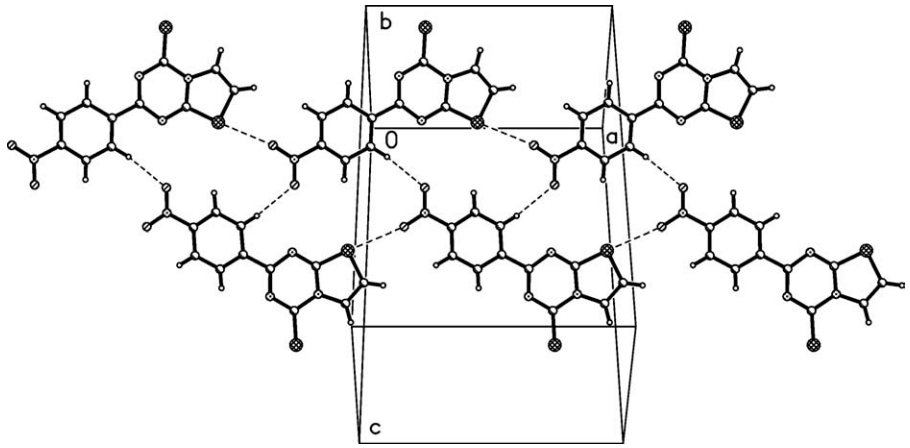



**Figure 2.** Packing diagram of compound **3a**.

included using a riding model. The final *wR*2 was 0.124, with a conventional *R*1 of 0.046, for 172 parameters; $S = 0.94$; max. $\Delta\rho$ 0.39 e $Å^{-3}$.

CCDC 754654 contains the supplementary crystallographic data for this article. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ IEZ, UK. Facsimile (44) 01223 336 033, E-mail: deposit@ccdc.cam.ac.uk or http//www.ccdc.com.ac.uk/deposit.

## ANTIFUNGAL SCREENING

The antifungal activity was carried out in DMSO using the agar tube dilution method. Sabouraud dextrose agar (Merck) was prepared by dissolving 6.5 g/mL in distilled water and the pH was adjusted to 5.6. The contents were dissolved and dispensed in 4-mL aliquots into screw-capped tubes and were autoclaved at 121°C for 21 min. The tubes were allowed to cool to 50°C and nonsolidified SDA was loaded with 66.6 μL of compound by pipette from stock solution, giving a final concentration of 200 μg/mL. The tubes were then allowed to solidify in a leaning position at room temperature. Tubes were prepared in triplicate for each fungus species. The tubes containing solidified media and test compound were inoculated with 4-mm diameter pieces of inocula, taken from a 7-day-old culture of fungus. Other media supplemented with DMSO and nystatin were used as negative and positive control, respectively. The tubes were incubated at 27°C for 7 days. Cultures were examined twice weekly during the incubation. Growth in media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control.

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## REFERENCES AND NOTES

[1] Katrizky, A. R. Advances in Hetrocyclic Chemistry; Academic Press: London, 1985, p 135.

[2] Proto, G.; Thomson, R. H.Endeavour1976, 35, 32.

[3] Faria, C.; Pinza, M.; Gabma, A.; Piffen, G. Eur J Med Chem Chim Ther 1979, 14, 27.

[4] Roberts, J. J.; Warwhich, G. P. Biochem Pharmacol 1963, 12, 135.

[5] Weinberg, E. D. Burger's Medicinal Chemistry and Drug Discovery; Wiley: New York, 1996, p 637.

[6] Wildfeuer, A.; Seidl, H. P.; Haberreiter, A. Mycoses 1998, 41, 306.

[7] Vicentini, C. B.; Mares, D.; Tartari, A.; Manfrini, M.; Forlani, G. J. Agric Food Chem 2004, 52, 1898.

[8] Lakomska, I.; Golankiewicz, B.; Wietryzk, J.; Pelczynska, M.; Nasulewicz, A.; OPolski, A.; Sitkowski, J.; Kozerski, L.; Szlyk, E. Inorg Chim Acta 2005, 358, 1911.

[9] Senga, K.; O'Brien, D. E., Scholten, M. B.; Novinson, T.; Miller, J. P. J Med Chem 1982, 25, 243.

[10] Leroux, F.; Van Keulen, B. J.; Daliers, J.; Pommery, N.; Henichart, J. P. Bioorg Med Chem 1999, 7, 509.

[11] Lee, H. K.; Chui, W. K. Bioorg Med Chem 1999, 7, 509.

[12] Yunus, U.; Tahir, M. K.; Bhatti, M. H.; Ali, S.; Helliwell, M. Acta Crystallogr 2007, E63, o3690

[13] Yunus, U.; Tahir, M. K.; Bhatti, M. H.; Wong, W.-Y. Acta Crystallogr 2008, E64, o722

[14] Wei, T. B.; Chen, J. C.; Wang, X. C. Synth Commun 1996, 26, 1147.

[15] Illi, V. O. Tetrahedron Lett 1979, 20, 2431.

[16] Reiner, R. Antibiotics: An Introduction; Thieme Verlag: Stuttgart, 1980.

[17] Sheldrick, G. M. Acta Cryst 2008, A64, 112.

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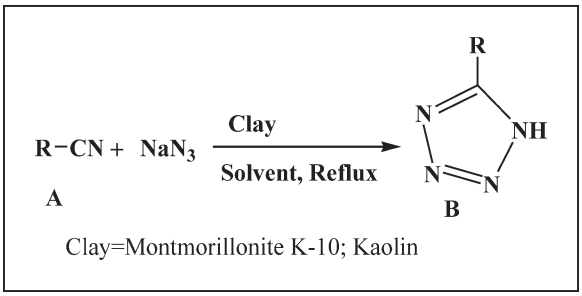


In this study, the possibility of 5-substituted 1-*H*-tetrazoles synthesis using clays as catalyst was investigated. The reaction of a series of aromatic nitriles with sodium azide was catalyzed by montmorillonite K-10 or kaolin clays in water or DMF as solvent. Conventional heating or ultrasonic irradiation was used to promote reaction. The amount of nitrile to sodium azide mole ratio, amount of catalyst, reaction time, and solvent type were optimized. The versatility of this method was checked by using various nitriles, which showed reasonable yields of tetrazole formation. It was found that using nitriles with electron-withdrawing groups result in both higher yields and lower reaction times. The catalysts could be reused several times without significant loss of their catalytic activity. Compared to conventional heating, ultrasonic irradiation reduced reaction times and increased catalyst activity. The present procedure is green and offers advantages, such as shorter reaction time, simple workup, and recovery and reusability of catalyst.

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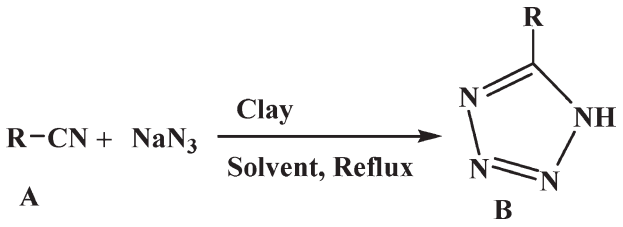
## INTRODUCTION

Tetrazoles are important heterocyclic compounds in medicinal chemistry [1–3]. Among them 5-substituted 1-*H*-tetrazoles are often used as metabolically stable surrogates for carboxyl group and for cis-amide bond [4,5]. Also, an enormous number of biologically active compounds are known, which contain tetrazole [6–8]. The [2+3] cycloaddition of nitriles and azides is a common method for the synthesis of tetrazole derivatives. Because of biological importance of tetrazoles, various synthetic methodologies have been developed for their synthesis. In most of these methods, highly toxic and explosive hydrazoic acid generates through activation of the azide by using strong Lewis acids [9,10], expensive and toxic metals [11–13], or amine salts [14]. The ''click'' chemistry approach using zinc catalysis in aqueous solution is a magnificent improvement over previous methods [15,16], but still requires the tedious and time-consuming steps such as removal of zinc salts from the acidic products. Clay-catalyzed organic transformations have been recently developed and obtained great interest as green methods. This has been attributed to their inexpensive nature and special catalytic activity under heterogeneous reaction conditions [17–22]. Acidic clays are suitable replacement of various homogeneous acid catalysts. They have been used in the synthesis of 1,5-benzodiazepines [23], acetonide protection [24], alkylation of benzene [25], Diels-Alder reaction [26], dihydrofuran synthesis [27], and bromination and chlorination of aromatic compounds [28]. In continuing with our research in tetrazole chemistry [29–31] and application of clays in organic transformations [32,33], herein we report a new process for synthesis of 1-*H*-5-substituted tetrazoles using clays as safe, environmentally benign, and inexpensive catalysts.

## RESULTS AND DISCUSSION

**Synthesis of tetrazoles derivatives under reflux condition.** In the reaction between benzonitrile **1a** and sodium azide (Scheme 1), effect of the catalyst amount was investigated. The different catalyst amounts (20, 50, and 100 mg) were used, and it was found that the maximum reaction yield obtained using 50 mg of catalyst. The results show that for K-10 when the catalyst amount

**Scheme 1.** Clay-catalyzed synthesis of 5-substituted 1-*H*-tetrazoles.




Clay=Montmorillonite K-10; Kaolin

increased to 20 and 50 mg, the conversion increased to 45 and 94% and 56 and 95% in water and DMF as solvent, respectively. However for kaolin, increase of catalyst amount from 20 to 50 mg increased the conversion from 27 to 95% and 43 to 94% in water and DMF, respectively. Also, it is obvious that the catalyst amount more than 50 mg has no significant effect on the conversion of benzonitrile to corresponding tetrazole. Any attempts to carry out the reactions in the absence of montmorillonite K-10 and kaolin were failed, and no products were found despite prolonged reaction times, which emphasis the clay catalytic role. To see whether the action of clays is truly catalytic, we reduced the amount of clays in the reaction between sodium azide and benzonitrile from 20 to 10 mg.

Upon our results, it is evident that a low loading of K-10 and kaolin is still effective, although the reactivity was decreased consequently (see Table 1, entries 13, 14). Even 10 mg of K-10 and kaolin afforded the desired product after 24 h in 29 and 40% yields in water and 38 and 17% yields in DMF, respectively. Although the activity of K-10 in DMF was slightly higher than kaolin, but there is no significant difference between specific activities of these two catalysts in both solvents. One important advantage of clays as catalyst is the easy workup of the reaction. After completion of the reaction, simple filtration of the reaction mixture followed by acidification of filtrate result in precipitating the product as a white powder. Another advantage of this method is its large-scale applicability. For this, we examine a run with 30 mmol of benzonitrile in DMF as the solvent, and the results were comparable to those obtained in the small-scale experiments. The effect of solvent was examined using water and DMF. The results showed that DMF because of its higher boiling point is more efficient. However, the use of water as a clean, inexpensive, and universal solvent combines features of both economic and environmental advantages. A close look at Figure 1 reveals that conversion rate of benzonitrile to phenyl tetrazole for both K-10 and kaolin in the DMF is faster. For example, with using montmorillonite K-10 as catalyst after 6 h, benzonitrile conversion was 72 and 53% in DMF and water, respectively. At the same condition, the conversion values for kaolin were 66 and 54% in DMF and water, respectively (see Fig. 1). The variation of the reaction conversion with the amount of sodium azide was studied, and the experimental results are tabulated in Table 1. It is apparent that the reaction conversion increased as the mole ratio of benzonitrile to sodium azide increased from 1:1 to 1:3 (from 50 to 94% and 69 to 95% for K-10 and from 20 to 95% and 27 to 94% for kaolin in DMF and water, respectively).

**Table 1**

Initial screening of reaction parameters for the formation of tetrazole derivatives.[a]

| Entry | Solvent | Benzonitrile/Sodium azide | Catalyst amount (mg) | % Conversion[b] | |
|---|---|---|---|---|---|
| 1 | $H_2O$ | 1:1 | 50 | 50 | 20 |
| 2 | DMF | 1:1 | 50 | 69 | 27 |
| 3 | $H_2O$ | 1:3 | 50 | 94 | 95 |
| 4 | DMF | 1:3 | 50 | 95 | 94 |
| 5 | $H_2O$ | 1:3 | 100 | 43 | 13 |
| 6 | DMF | 1:3 | 100 | 94 | 24 |
| 7 | $H_2O$ | 1:3 | 20 | 45 | 27 |
| 8 | DMF | 1:3 | 20 | 56 | 43 |
| 9 | H2O | 1:1 | 20 | 30 | 7 |
| 10 | DMF | 1:1 | 20 | 21 | 12 |
| 11 | $H_2O$ | 1:5 | 50 | 74 | 81 |
| 12 | DMF | 1:5 | 50 | 75 | 78 |
| 13 | $H_2O$ | 1:3 | 10 | 29 | 38 |
| 14 | DMF | 1:3 | 10 | 40 | 17 |
| 15 | $H_2O$ | 1:3 | 0 | 0 | 0 |
| 16 | DMF | 1:3 | 0 | 0 | 0 |

[a] Reaction time (24 h).
[b] Conversion was calculated using HPLC. Left (K-10) and right (kaolin).

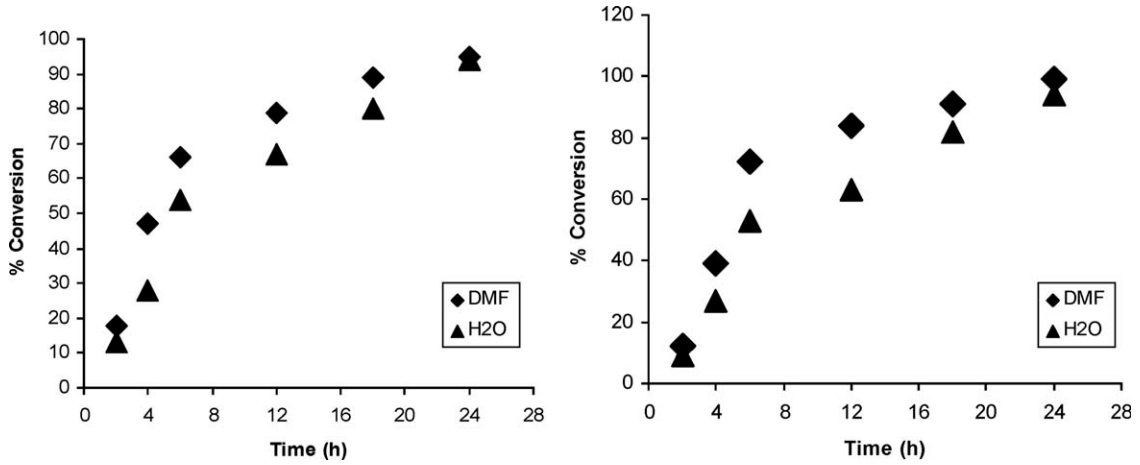



**Figure 1.** Effect of time on conversion of benzonitrile to phenyl tetrazole in DMF and water under reflux condition using montmorillonite K-10 and kaolin. Condition: 2 mmol benzonitrile and 6 mmol sodium azide.

Further increase in mole ratio to 1:5, the benzonitrile conversion decreased slightly to 74 and 75% for K-10 and 81 and 78% for kaolin in the DMF and water, respectively (Table 1, entries 11, 12). This observation suggesting that the excess values of sodium azide may block active sites of catalysts.

The catalytic role of clays in the synthesis of tetrazoles was investigated by two reaction without use of catalysts. The results indicate that no progress was observed. (Table 1, entries 15 and 16).

The effect of time on the product yield using montmorillonite K-10 and kaolin is shown in Figure 1. The conversion increases from 12 to 91% and 9 to 82% as the time increased from 2 to 18 h. With further increase in reaction time to 24 h, formation of phenyl tetrazole marginally increases and reaches to 94 and 95% for K-10 in the water and DMF, respectively. Moreover for kaolin, as the time increased from 2 to 24 h conversion increases from 18 and 13% to 95 and 94% in the water and DMF, respectively.

One of the most important advantages of heterogeneous catalysis over the homogeneous counterpart is the possibility of reusing the catalyst by simple filtration, without loss of activity. The recovery and reusability of the catalyst was investigated in the tetrazole formation with benzonitrile. After completion of the reaction, the catalyst was separated by filtration, washed three times with 5 mL acetone, then with doubly distilled water several times, and dried at 110°C. Then, the recovered catalyst was used in the next run. The results of three consecutive runs showed that the catalyst can be reused several times without significant loss of its activity (see Fig. 2).

Several substituted nitriles reacted with sodium azide to give the corresponding tetrazoles in good yields. Heteroaromatic nitriles such as 2, 3, and 4-pyridinecarbonitriles give the corresponding tetrazoles with excellent yields (Table 2, entries 3–5). Interestingly, phthalonitriles afford the monoaddition product (Table 2, entries 7–9). The nature of the substituents on the nitriles has a significant effect on the tetrazole yield (Table 2). The highest conversions were observed for nitriles with electron-withdrawing substituents (Table 2, entries 1–11).

However, electron-donating groups (*e.g.*, OH and $NH_2$) were the least reactive ones. With acetylation of 4-hydroxy benazonitrile, the reaction yield was improved, but for acetylated 4-amino benzonitrile even with long reaction times no product was formed (Table 2, entries 14–16). A probable mechanistic pathway for synthesis of tetrazoles from nitriles has been shown in Figure 3. Based on this mechanism, the nitrile activated

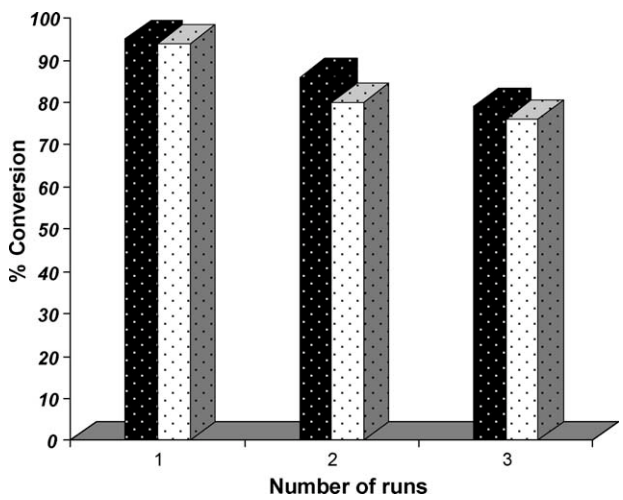
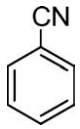
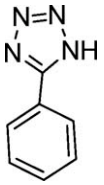
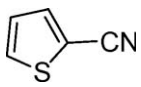
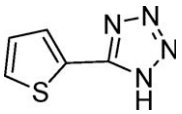
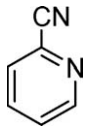
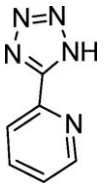
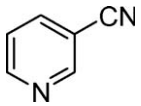
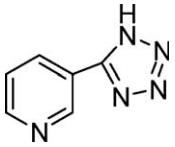
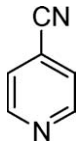
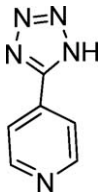
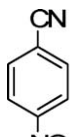
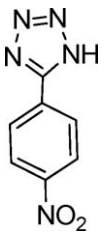
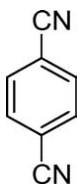
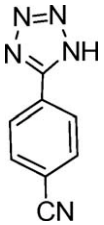



**Figure 2.** The results obtained from catalyst reuse montmorillonite K10 (black bars) and kaolin (white bars) in the tetrazole formation.

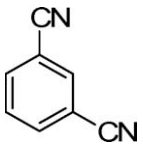
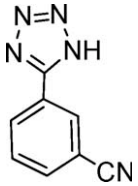
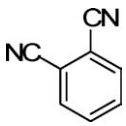
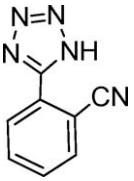
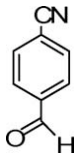
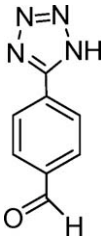
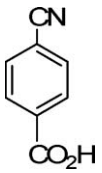
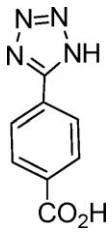
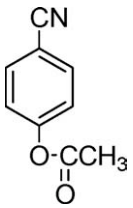
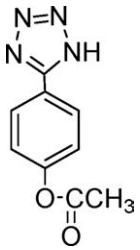
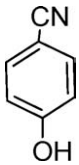
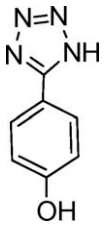
**Table 2**

Synthesis of 5-substituted 1-*H*-tetrazoles catalyzed by clay.[a,b]

| | | | Yields[c] | | | |
|---|---|---|---|---|---|---|
| | | | Montmorillonite K-10 | | Kaolin | |
| Entry | Nitrile | Tetrazole | $H_2O$ | DMF | $H_2O$ | DMF |
| 1 |  |  | 80 | 90 | 82 | 90 |
| 2 |  |  | 88 | 96 | 80 | 90 |
| 3 |  |  | 72 | 86 | 74 | 91 |
| 4 |  |  | 88 | 98 | 74 | 96 |
| 5 |  |  | 90 | 95 | 80 | 90 |
| 6 |  |  | 76 | 95 | 91 | 98 |
| 7 |  |  | 88 | 90 | 82 | 95 |

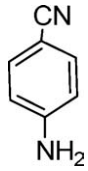
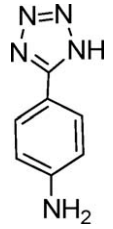
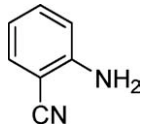
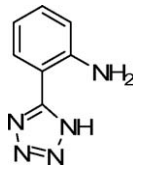
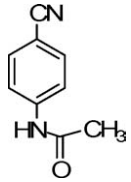
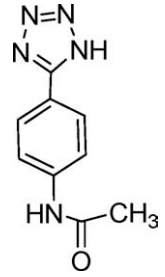
(*Continued*)

**Table 2**
(*Continued*)

| Entry | Nitrile | Tetrazole | Yields[c] Montmorillonite K-10 $H_2O$ | Montmorillonite K-10 DMF | Kaolin $H_2O$ | Kaolin DMF |
|---|---|---|---|---|---|---|
| 8 |  |  | 83 | 95 | 53 | 95 |
| 9 |  |  | 43 | 91 | 53 | 95 |
| 10 |  |  | 55 | 96 | 53 | 56 |
| 11 |  |  | 45 | 64 | 57 | 64 |
| 12 |  |  | 37 | 81 | 30 | 57 |
| 13 |  |  | >10[d] | 30 | 6 | 37 |

(*Continued*)

**Table 2**
(*Continued*)

| | | | Yields[c] | | | |
|---|---|---|---|---|---|---|
| | | | Montmorillonite K-10 | | Kaolin | |
| Entry | Nitrile | Tetrazole | $H_2O$ | DMF | $H_2O$ | DMF |
| 14 |  |  | Trace[d] | Trace | Trace | Trace |
| 15 |  |  | Trace[d] | Trace | Trace | Trace |
| 16 |  |  | <10[d] | <10 | Trace | Trace |

[a] The products were characterized by IR, $^1$H NMR, $^{13}$C NMR, and mass spectroscopy.
[b] Reaction time (24 h).
[c] Isolated yields after recrystallization.
[d] The product was not isolated.

by clay in the first stage and this activated fragment attacked by azide ion to produce the imidoyl azide. The imidoyl azide then converted to tetrazole derivative.

**Synthesis of tetrazole derivatives under ultrasonic irradiation.** Ultrasound has been used recently to accelerate a number of synthetically useful reactions [34,35]. The ultrasound effects observed on organic reactions are due to cavitation, a physical process that create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid. Impulsion of the cavitational bubbles, extreme temperatures, and pressures is generated at the center of the collapsed bubble [36–38]. These effects may enhance liquid–solid mass transfer and cause physicochemical change in the processed medium considerably [39,40]. Advantages and attractive features of sonochemistry led us to explore the effect of ultrasonic waves on this catalytic system. For this reason, reactions were exposed to ultrasonic irradiation using two clay catalysts in the water as the solvent.

The obtained results within reaction conditions are summarized in Table 3. The effect of catalyst amount on reaction times tested, and it was found that with increasing of catalyst amount all reaction times reduced. For example, for phenyl tetrazole with increase of catalyst amounts from 50 to 100 mg, the reaction times reduced from 90 to 40 and 120 to 50 min for montmorillonite and kaolin, respectively (Table 3 entry 1). Again a close look at Table 3 reveals that there is no significant difference between montmorillonite K-10 and kaolin, although the activity of K-10 in water under ultrasound irradiation is slightly higher than kaolin. A comparison of results obtained with nonultrasound reactions (Tables 1 and 2) shows that with ultrasound irradiation the reaction times reduced.

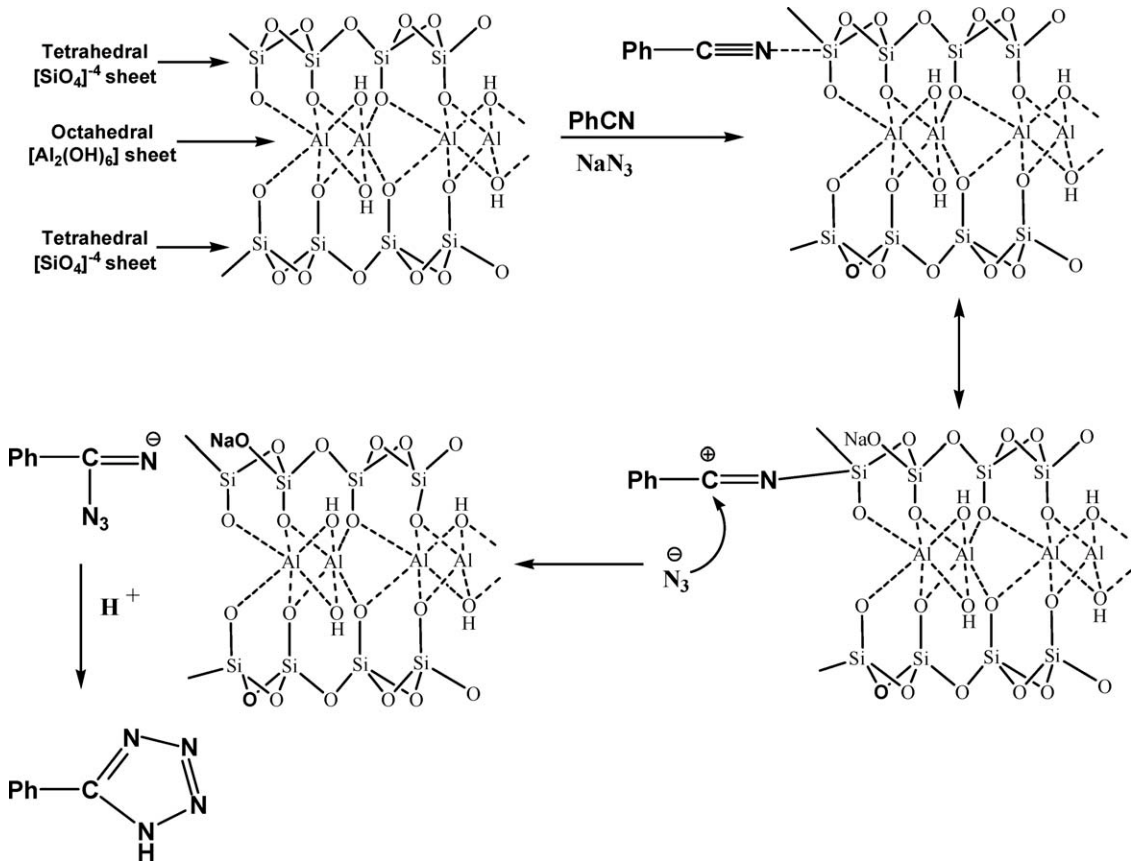



**Figure 3.** Proposed mechanism for conversion of nitriles to tetrazoles over K-10 clay.

## CONCLUSION

In conclusion, we developed a simple, environmentally benign, and efficient method for the preparation of 5-substituted 1-*H*-tetrazoles using clay catalysts. Various nitriles reacted with $NaN_3$ at 100–130°C to yield the corresponding 5-substituted 1-*H*-tetrazoles with moderate to good yields. This methodology may find widespread use in organic synthesis for the preparation of tetrazoles. The advantages of this catalytic system are as follows: mild reaction condition, high product yields, easy preparation of the catalysts, nontoxicity of the catalysts, and simple and clean workup of the desired products.

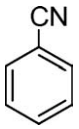
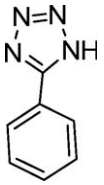
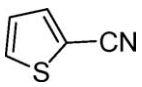
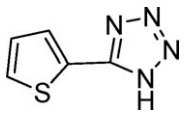
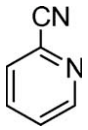
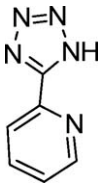
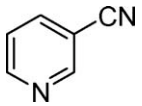
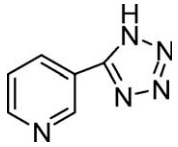
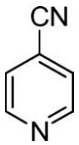
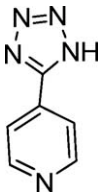
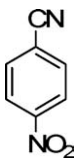
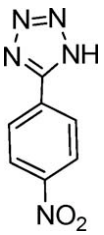
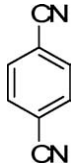
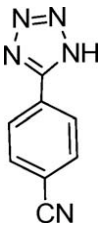
## EXPERIMENTAL

**Materials and instruments.** Montmorillonite K-10, kaolin, sodium azide, and nitriles all were procured from Aldrich and Merck. A JASCO FT/IR-680 PLUS spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded on a Bruker 400 Ultrasheild NMR, and DMSO-$d_6$ was used as a solvent. Melting points reported were determined by open capillary method using a Galen Kamp melting point apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu gas chromatograph mass spectrometer GCMS-QP5050A/Q P5000 apparatus. HPLC analysis was performed using a series 1100 Agilent instrument equipped with Zorbax eclips $C_{18}$ as column, detection at 254 nm, and 30% methanol in water as mobile phase. Reactions under ultrasonic irradiation were performed in an ultrasonic bath with heating system (Tecno-GAZ SPA Ultra Sonic System) at 40 kHz of frequency and 500 W of power. Catalysts were activated before the reaction runs with HCl (2*M*) in the solid to liquid ratio of 1:4 (40 mL, 2*M* HCl for 10 g clay) for a period of 45 min and then filtered. To remove chloride ions, catalysts were washed thoroughly with doubly distilled water and dried in an air oven at 100°C for 6 h.

**General procedure for preparation of tetrazoles under reflux condition.** The procedure for the synthesis of the tetrazole **2a** (Scheme 1) is representative. In a round bottom flask, benzonitrile (0.2 g, 2 mmol), sodium azide (0.4 g, 6mmol), montmorillonite K-10 (50 mg), and DMF or water (20 mL) were charged. Then, the reaction mixture was refluxed for 24 h. The progress of reaction (after 2, 4, 6, 12, 18, and 24 h) was followed by HPLC and TLC (75:25 ethyl acetate/*n*-hexane). After that the reaction was cooled to room temperature, and insoluble material was filtered and washed with doubly distilled water and acetone to separate the catalyst. The solution was acidified with HCl (5 mL, 12*M*). The precipitate was collected, dried, and recrystallized from water/ethanol to afford pure 5-phenyl-1*H*-tetrazole (**1b**) as a white powder weight, mp = 212–214°C; 0.26 g (90% yield). $^1$H NMR (DMSO-$d_6$, 400

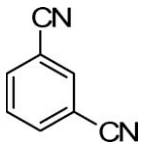
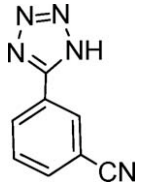
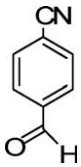
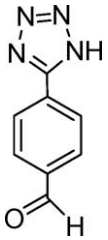
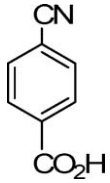
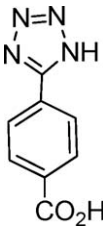
**Table 3**

Preparation of tetrazole derivatives under ultrasound irradiation using clays as catalyst.

| | | | Reaction times | | | |
|---|---|---|---|---|---|---|
| | | | K-10 amount | | Kaolin amount | |
| Entry | Nitrile | Tetrazole | 50 mg | 100 mg | 50 mg | 100 mg |
| 1 |  |  | 90 | 40 | 120 | 50 |
| 2 |  |  | 130 | 110 | 150 | 120 |
| 3 |  |  | 240 | 160 | 220 | 160 |
| 4 |  |  | 240 | 180 | 240 | 210 |
| 5 |  |  | 200 | 180 | 220 | 200 |
| 6 |  |  | 300 | 200 | 320 | 210 |
| 7 |  |  | 320 | 180 | 300 | 220 |

(*Continued*)

**Table 3**
(*Continued*)

| Entry | Nitrile | Tetrazole | Reaction times | | | |
|---|---|---|---|---|---|---|
| | | | K-10 amount | | Kaolin amount | |
| | | | 50 mg | 100 mg | 50 mg | 100 mg |
| 8 |  |  | 300 | 200 | 280 | 220 |
| 9 |  |  | 180 | 150 | 180 | 160 |
| 10 |  |  | 180 | 150 | 180 | 170 |

Reaction progress followed by TLC.
Temperature: 70°C.
Reaction times in min.
Solvent $H_2O$ with 5–6 drops of DMF.
Nitrile/Sodium azide ratio 1:3.

MHz): 7.6–8.1 ppm (m, 5H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 124.5, 127.4, 129.9, 131.7, 155.8; MS (70 eV) *m/z*: 146, 118, 103, 91, 77, 63, 39; IR (KBr) υ: 3054, 2981, 2914, 2837, 2794, 2701, 2610, 1608, 726 cm$^{-1}$; HPLC retention time $R_t$ = 14.7 min.

**5-(Thiophen-2yl)-1*H*-tetrazole (2b).** White solid; mp = 201–203°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7.1 (t, $J$ = 4 Hz, 1H), 7.6 (d, $J$ = 4 Hz, 1H), 7.7 (d, $J$ = 4 Hz, 1H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 149, 134, 130, 125 ppm; MS (70 eV) *m/z*: 154, 152, 124, 109, 97, 69, 45; IR (KBr) υ: 3108, 3093, 3076, 2952, 2890, 2789, 2685, 1505, 1434, 964 cm$^{-1}$; $R_t$ = 9.62 min.

***2-(1-H-tetrazole-5-yl) pyridine (3b).*** White solid; mp = 208–210°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7.4 (t, $J$ = 6.4 Hz, 1H), 7.8 (t, $J$ = 6.4 Hz, 1H), 8.0 (t, $J$ = 8.0 Hz, 1H), 8.5 (d, $J$ = 3.2 Hz, 1H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 167, 158, 149, 137, 124, 121 ppm; MS (70 eV) *m/z*: 147, 119, 105, 91, 78, 51; IR (KBr) υ: 3278, 3181, 2929, 1662, 1578, 1390, 923 cm$^{-1}$; $R_t$ = 9.78 min.

***3-(1-H-tetrazole-5-yl) pyridine (4b).*** White solid; mp = 238–240°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 9.1 (s, 1H), 8.8 (d, $J$ = 3.8 Hz, 1H), 8.3 (d, $J$ = 3.8 Hz, 1H), 7.6 (1H, m); $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 165, 153, 150, 136, 126, 123; IR (KBr) υ: 3080, 2950, 2890, 2850, 2761, 1480, 1200 cm$^{-1}$; $R_t$ = 9.50 min.

***4-(1-H-tetrazole-5-yl) pyridine (5b).*** White solid; mp = 254–258°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 8.0 (d, $J$ = 7.8 Hz, 2H), 8.8 (d, $J$ = 7.8 Hz, 2H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 165, 149, 134, 121 ppm; MS (70 eV) *m/z*: 147, 119, 92, 78, 62, 50; IR (KBr) υ: 3080, 3060, 3028, 2955, 2917, 2832, 2751, 2689, 1608, 1581, 1492, 1065, 784 cm$^{-1}$; $R_t$ = 8.16 min.

***5-(4-Nitrophenyl)-1H-tetrazole (6b).*** White solid; mp = 218–220°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 8.1 (d, $J$ = 8 Hz, 2H), 8.2 (d, $J$ = 8 Hz, 2H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 156, 130, 128, 124 ppm; MS (70 eV) *m/z*: 191, 163, 149, 134, 90, 63; IR (KBr) υ: 3103, 2914, 2853, 2752, 2621, 1605, 1526, 1487, 861 cm$^{-1}$; $R_t$ = 11 min.

***4-(1H-tetrazole-5-yl)benzonitrile (7b).*** White solid; mp = 258–260°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 8.0 (d, $J$ = 7.8 Hz, 2H), 8.2 (d, $J$ = 7.8 Hz, 2H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 160, 135, 132, 130, 126, 114 ppm; MS (70 eV) *m/z*: 171, 143, 129, 103, 62; IR (KBr) υ: 3100, 2848, 2750, 2250, 1480, 781 cm$^{-1}$; $R_t$ = 7.47 min.

***3-(1H-tetrazole-5-yl)benzonitrile (8b).*** White solid; mp = 214–216°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7.7–8.1 (5H, m); $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 164, 134, 133, 132, 131, 129, 115 ppm; MS (70 eV) *m/z*: 171, 143, 102, 62; IR (KBr) υ: 3113, 2981, 2780, 2442, 2237, 1476, 870, 780 cm$^{-1}$; $R_t$ = 8.0 min.

***2-(1H-tetrazole-5-yl)benzonitrile (9b).*** White solid; mp = 208–210°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7.6 (t, $J$ = 6.8 Hz, 1H), 7.7 (t, $J$ = 6.8 Hz, 1H), 7.8 (m, 2H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 166, 140, 136, 133, 132, 128, 126, 118, ppm; MS (70 eV) *m/z*: 171, 143, 129, 115, 88, 76, 62, 57; IR (KBr) υ: 3096, 2531, 2110, 2023, 1632, 1436, 845 cm$^{-1}$; $R_t$ = 12 min.

***4-(1H-tetrazole-5-yl)benzaldehyde (10b).*** White solid; mp = 180–182°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7.9 (d, $J$ = 7.2 Hz, 2H), 8.0 (d, $J$ = 7.2 Hz, 2H), 9.1 (s, 1H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 188, 156, 138, 131, 129, 128 ppm; MS (70 eV) *m/z*: 174, 146, 130, 116, 102, 90, 57, 43; IR (KBr) υ: 3015, 2924, 2854, 2713, 2612, 1667, 1440, 776 cm$^{-1}$; $R_t$ = 6.4 min.

***4-(1H-tetrazole-5-yl) benzoic acid (11b).*** White solid; mp = 248–250°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7–8 (m, 4H) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 188, 166, 138, 131, 129, 128 ppm; MS (70 eV) *m/z*: 190, 174, 146, 130, 116, 102, 90, 75, 57; (KBr) υ: 3600–3000 (br), 2500, 1760, 1500, 1480, 780 cm$^{-1}$; $R_t$ = 6.9 min.

***4-(1H-tetrazole-5-yl)phenyl acetate (12b).*** White solid; mp = 212–214°C; $^1$H NMR (DMSO-$d_6$, 400 MHz): 7.9 (d, $J$ = 7.4 Hz, 2H), 7.7 (d, $J$ = 7.4 Hz, 2H), 2.59 (s, 3H); ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz); 170, 164, 152, 131, 128, 124, 22 ppm; MS (70 eV) *m/z*: 204, 189, 173, 160, 145, 130, 102, 90; (KBr) υ: 3097, 2925, 2865, 2700, 2625, 1678, 1580, 1269, 843 cm$^{-1}$; $R_t$ = 12.84 min.

**General procedure for preparation of tetrazoles under ultrasonic irradiation.** In a round bottom flask, benzonitrile (0.2 g, 2 mmol,), sodium azide (0.4 g, 6mmol), and DMF or water (20 mL) were charged. The flask was suspended into the ultrasonic bath at the reaction temperature (333 K). Then, 50 mg of catalyst (montmorillonite K-10 or kaolin) was added and the reaction time measured. The flask was suspended at the center of the bath. The progress of the reaction was monitored by TLC. After that the reaction was cooled to room temperature, and product was recovered as mentioned.

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## REFERENCES AND NOTES

[1] Meier, H. R.; Heimgartner, H. In Methoden der Organischen Chemie (Houben-Weyl); Schumann, E., Ed.; Georg Thieme: Stuttgart, 1994; Vol. E8d, p 664.

[2] Herr, R. J. Bioorg Med Chem 2002, 10, 3379.

[3] Butler, R. N. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, 1996; Vol. 4, p 621.

[4] Yu, K. L.; Johnson, R. L. J Org Chem 1987, 52, 2051.

[5] Zabrocki, J.; Smith, D.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. J Am Chem Soc 1988, 110, 5875.

[6] Davis, B.; Brandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. Tetrahedron Lett 1995, 36, 7507.

[7] Burg, D.; Hameetman, L.; Filippov, D. V.; van der Marel, G. A.; Mulder, G. J. Bioorg Med Chem Lett 2002, 12, 1579.

[8] Hayashi, R.; Jin, X.; Cook, G. R. Bioorg Med Chem Lett 2007, 17, 6864.

[9] Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. J Org Chem 1991, 56, 2395.

[10] Kumar, A.; Narayanan, R.; Shechter, H. J Org Chem 1996, 61, 4462.

[11] Curran, D. P.; Hadida, S.; Kim, S.-Y. Tetrahedron 1999, 55, 8997.

[12] Hajra, S.; Sinha, D.; Bhowmick, M. J Org Chem 2007, 72, 1852.

[13] Kantam, M. L.; Balasubrahmanyam, V.; Shiva Kumar, K. B. Synth Commun 2006, 36, 1809.

[14] Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccoro, L. J Org Chem 2004, 69, 2896.

[15] Demko, Z. P.; Sharpless, K. B. J Org Chem 2001, 66, 7945.

[16] Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. J Am Chem Soc 2002, 124, 12210.

[17] Balogh, M.; Laszlo, P. Organic Chemistry Using Clays; Springer: Berlin, 1993.

[18] Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. J Am Chem Soc 2005, 127, 9674.

[19] Choudary, B. M.; Bhaskar, V.; Kantam, M. L.; Rao, K. K.; Raghavan, K. V. Green Chem 2000, 2, 67.

[20] Ballini, R.; Bosica, G.; Maggi, R.; Ricciutelli, M.; Righi, P.; Sartori, G.; Sartorio, R. Green Chem 2001, 3, 178.

[21] Jankovic, L.; Komadel, P. J Catal 2003, 218, 227.

[22] Laszlo, P. Pure Appl Chem 1990, 62, 2027.

[23] Heravi, M. M.; Derikvand, F.; Ranjbar, L. A.; Oskooie, H. A. Heteroatom Chem 2008, 19, 215.

[24] Shaikh, N. S.; Bhor, S. S.; Gajare, A. S.; Deshpande, V. H.; Wakharkar, R. D. Tetrahedron Lett 2004, 45, 5395.

[25] (a) Yadav, J. S.; Subba Reddy, B. V.; Satheesh, G. Tetrahedron Lett 2004, 45, 3673; (b) Sabu, K. R.; Sukumar, R.; Lalithambika, M. Bull Chem Soc Jpn 1993, 66, 3535.

[26] Dintzner, M. R.; Little, A. J.; Pacilli, M.; Pileggi, D. J.; Osner, Z. R.; Lyons, T. W. Tetrahedron Lett 2007, 48, 1577.

[27] Leite, L.; Stonkus, V.; Edolfa, K.; Ilieva, L.; Plyasova, L.; Zaikovskii, V. Appl Catal A 2006, 311, 86.

[28] Hirano, M.; Monobe, H.; Yakabe, S.; Morimoto, T. J Chem Res (S) 1998, 662.

[29] Dabbagh, H. A.; Chermahini, A. N.; Banibairami, S. Tetrahedron Lett 2006, 47, 3929.

[30] Dabbagh, H. A.; Chermahini, A. N.; Teimouri, A. Heteroatom Chem 2006, 17, 416.

[31] Chermahini, A. N.; Esfahani, M. N.; Dalirnasab, Z.; Dabbagh, H. A.; Teimouri, A. J Mol Struct (Theochem) 2007, 820, 7.

[32] Dabbagh, H. A.; Chermahini, A. N.; Teimouri, A. Dyes Pigments 2007, 73, 239.

[33] Dabbagh, H. A.; Chermahini, A. N.; Teimouri, A. Appl Catal B 2007, 76, 24.

[34] Fillion, H.; Luche, J.-L. In Synthetic Organic Sonochemistry; Luche, J.-L., Ed.; Plenum Press: New York, 1998; pp 63–100.

[35] Gedanken, A. Ultrason Sonochem 2004, 11, 47.

[36] Margulis, M. A. High Energy Chem 2004, 38, 135.

[37] Capelo, J. L.; Maduro, C.; Vilhena, C. Ultrason Sonochem 2005, 12, 225.

[38] Run, M.; Wu, S.; Wu, G. Microporous Mesoporous Mater 2004, 74, 37.

[39] Miller-Ihli, N. J.; Fresenius, J. Anal Chem 1993, 345, 482.

[40] Margulis, M. A. In Advances in Sonochemistry; Mason, T. J., Ed.; JAI Press: London, 1990; Vol.1, pp 231–287.

# Synthesis and Antimicrobial Activity of Novel 1,3,4-Oxadiazolyl-quinazolin-4(3*H*)ones



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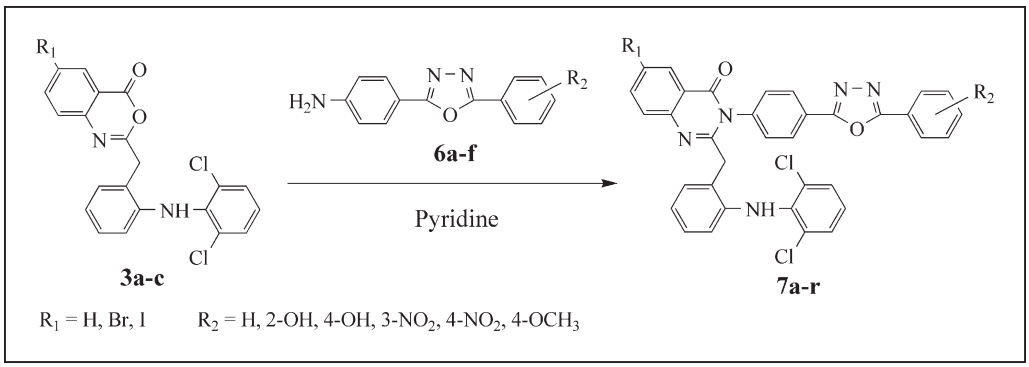


A series of 1,3,4-oxadiazolyl-quinazolin-4(3*H*)ones have been synthesized using known methods. All the compounds have been established on basis of elemental analysis, IR and NMR spectral data. The *in vitro* antimicrobial screening of the synthesized compounds were carried out against two gram-positive bacteria (*S. aureus*, *S. pyogenes*), two gram-negative bacteria (*E. coli*, *P. aeruginosa*), and three fungal species (*C. albicans*, *A. niger*, *A. clavatus*) using the broth microdilution method. The compounds **7d**, **7g**, **7l**, **7o**, **7p**, and **7r** possessed pronounced antibacterial activity whereas compound **7p** exhibited promising antifungal activity.

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## INTRODUCTION

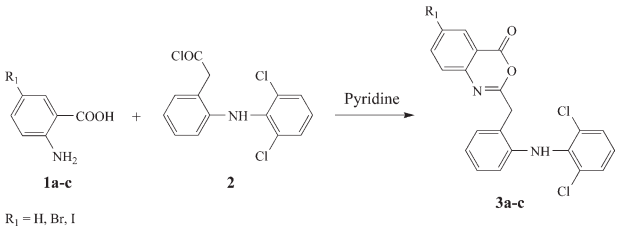
Heterocyclic skeleton contained nitrogen atom is the basic of many pharmaceuticals, to be an active compound. 1,3,4-Oxadiazoles are five member nitrogen atom contained heterocycles, represent broad spectrum of biological activity in both agrochemicals and pharmaceuticals such as insecticidal [1], herbicidal [2], antibacterial [3], antifungal [4], analgesic [5], anti-inflammatory [6], antimalarial [7], antiviral [8], anti-HBV [9], antianexiety [10], anticancer [11], anti-HIV [12], antitubercular [13], and anticonvulsant [14]. Quinazolin-4(3*H*)one derivatives are six member fused heterocycles, possess potent pharmacological activities like antibacterial [15], antifungal [16], analgesic [17], anti-inflammatory [18], anthelminthic [19], antitumor [20], anticonvulsant [21], antihistaminic [22], anti HIV [23], antiproliferative [24], antitubercular [25], antiviral [26], CNS depressant [27], cytotoxicity [28], diuretic [29], and hypolipidemic [30].

The 1,3,4-oxadiazole and quinazolin-4(3*H*)one containing various heterocycle exhibited good pharmacological activities. The aim of this work was to attach 1,3,4-oxadiazole to quinazolin-4(3*H*)one in order to find new biologically active molecule. Thus, synthesis of novel 1,3,4-oxadiazolyl-quinazolin-4(3*H*)one derivatives has been achieved.

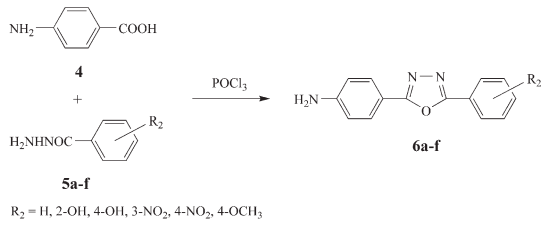
## RESULT AND DISCUSSION

2-[2-(2,6-Dichlorophenyl)amino]benzyl-3,1-benzoxazin-4(*H*)ones **3a-c** were synthesized from substituted anthranilic acids and acid chloride according to the reported process (Scheme 1) [31,32]. The required 2-[(2,6-dichlorophenyl)amino]phenyl acetyl chloride **2**, which is moisture sensitive and easily hydrolysable compound, was synthesized by reported method [33] and used directly in the next step. The cyclization reaction of acid chloride and substituted anthranilic acid in highly basic medium of pyridine at 0–5°C afforded 2-[2-(2,6-dichlorophenyl)-amino]benzyl-3,1-benzoxazin-4(*H*)ones **3a-c**. The structural determinations of these compounds have been

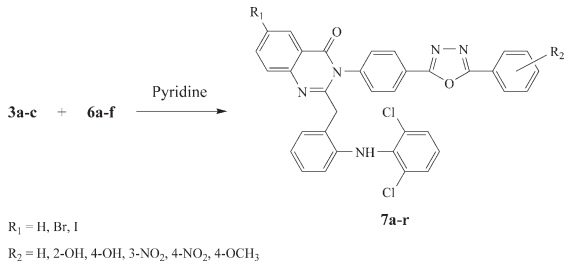
**Scheme 1**



**Scheme 2**




**Scheme 3**




carried out using IR and NMR spectral data. IR spectra showed strong C=O and C=N stretching at around 1740 and 1620 $cm^{-1}$ while $^{13}$C-NMR spectra showed C=O and C=N signal at around δ 159 ppm and δ 165 ppm respectively. 2-(4-Aminophenyl)-5-substitutedphenyl-1,3,4-oxadiazoles **6a-f** were synthesized according to reported method (Scheme 2) [34]. All amino substituted 1,3,4-oxadiazole derivatives showed satisfactory IR and NMR spectral results. Finally the condensation reaction of 4-benzoxazinones **3a-c** with amino substituted 1,3,4-oxadiazoles **6a-f** in pyridine afforded the desired compounds **7a-r** (Scheme 3) [35]. IR spectra showed strong C=O and C=N stretching of quinazolin-4(3*H*)ones at around 1680 and 1610 $cm^{-1}$, respectively. $^{13}$C-NMR spectra showed C=O and C=N signal of quinazolin-4(3*H*)ones near δ 161 ppm and δ 163 ppm respectively. All the synthesized compounds showed satisfactory $^{1}$H-NMR spectral results and for all compounds satisfactory elemental analyses were obtained.

The *in vitro* antibacterial activities of the synthesized compounds are shown in Table 1. The antibacterial activities are expressed in terms of Minimal Bactericidal Concentrations (MBCs μg/mL). The synthesized compounds were screened against two gram positive bacteria (*S. aureus* MTCC 96, *S. pyogenes* MTCC 443) and two

**Table 1**

Antibacterial activity of compounds **6a-f** and **7a-r**.

| | | | Minimal bactericidal concentration (MBC) (μg/mL) | | | |
|---|---|---|---|---|---|---|
| | | | Gram positive bacteria | | Gram negative bacteria | |
| Compound | $R_1$ | $R_2$ | *S. aureus* MTCC-96 | *S. pyogenes* MTCC-443 | *E. coli* MTCC-442 | *P. aeruginosa* MTCC-441 |
| **6a** | – | H | 250 | 250 | 250 | 200 |
| **6b** | – | 2-OH | 500 | 500 | 500 | 250 |
| **6c** | – | 4-OH | 250 | 500 | 500 | 500 |
| **6d** | – | 3-$NO_2$ | 250 | 250 | 250 | 500 |
| **6e** | – | 4-$NO_2$ | 500 | 500 | 500 | 1000 |
| **6f** | – | 4-$OCH_3$ | 250 | 250 | 500 | 500 |
| **7a** | H | H | 500 | 1000 | 250 | 200 |
| **7b** | H | 2-OH | 500 | 250 | 150 | 100 |
| **7c** | H | 4-OH | 500 | 1000 | 250 | 200 |
| **7d** | H | 3-$NO_2$ | 200 | 250 | 250 | 250 |
| **7e** | H | 4-$NO_2$ | 250 | 250 | 500 | 500 |
| **7f** | H | 4-$OCH_3$ | 500 | 250 | 200 | 100 |
| **7g** | Br | H | 200 | 250 | 100 | 250 |
| **7h** | Br | 2-OH | 500 | 500 | 150 | 200 |
| **7i** | Br | 4-OH | 500 | 500 | 250 | 250 |
| **7j** | Br | 3-$NO_2$ | 500 | 500 | 250 | 500 |
| **7k** | Br | 4-$NO_2$ | 500 | 500 | 500 | 1000 |
| **7l** | Br | 4-$OCH_3$ | 200 | 250 | 100 | 250 |
| **7m** | I | H | 500 | 500 | 250 | 200 |
| **7n** | I | 2-OH | 250 | 500 | 100 | 150 |
| **7o** | I | 4-OH | 250 | 250 | 125 | 150 |
| **7p** | I | 3-$NO_2$ | 200 | 200 | 150 | 250 |
| **7q** | I | 4-$NO_2$ | 150 | 250 | 500 | 200 |
| **7r** | I | 4-$OCH_3$ | 200 | 150 | 100 | 250 |
| Ampicillin | – | – | 250 | 100 | 100 | 100 |

**Table 2**

Antifungal activity of compounds **6a-f** and **7a-r**.

| | | | Minimal Fungicidal Concentration (MFC) (μg/mL) | | |
|---|---|---|---|---|---|
| | | | Fungal species | | |
| Compound | $R_1$ | $R_2$ | *C. albicans* MTCC-227 | *A. niger* MTCC-282 | *A. clavatus* MTCC-323 |
| **6a** | – | H | 500 | > 1000 | >1000 |
| **6b** | – | 2-OH | 250 | 500 | >1000 |
| **6c** | – | 4-OH | 500 | 1000 | >1000 |
| **6d** | – | 3-$NO_2$ | 250 | >1000 | >1000 |
| **6e** | – | 4-$NO_2$ | 500 | >1000 | >1000 |
| **6f** | – | 4-$OCH_3$ | >1000 | >1000 | >1000 |
| **7a** | H | H | 500 | 500 | 500 |
| **7b** | H | 2-OH | 500 | 500 | 200 |
| **7c** | H | 4-OH | >1000 | 500 | 250 |
| **7d** | H | 3-$NO_2$ | 250 | 500 | 500 |
| **7e** | H | 4-$NO_2$ | 200 | >1000 | >1000 |
| **7f** | H | 4-$OCH_3$ | 500 | 1000 | >1000 |
| **7g** | Br | H | 200 | >1000 | >1000 |
| **7h** | Br | 2-OH | 500 | 500 | 500 |
| **7i** | Br | 4-OH | 500 | 500 | 1000 |
| **7j** | Br | 3-$NO_2$ | 200 | 500 | 500 |
| **7k** | Br | 4-$NO_2$ | 250 | 500 | 500 |
| **7l** | Br | 4-$OCH_3$ | 200 | >1000 | >1000 |
| **7m** | I | H | 250 | >1000 | >1000 |
| **7n** | I | 2-OH | 1000 | >1000 | >1000 |
| **7o** | I | 4-OH | 500 | 500 | 1000 |
| **7p** | I | 3-$NO_2$ | 200 | 250 | 250 |
| **7q** | I | 4-$NO_2$ | 250 | 500 | 500 |
| **7r** | I | 4-$OCH_3$ | 1000 | 1000 | >1000 |
| Greseofulvin | – | – | 500 | 100 | 100 |

gram negative bacteria (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441). Ampicillin was used as a standard drug. The results show that some of the amino substituted 1,3,4-oxadiazoles possessed good activity against *S. aureus* while moderate activity against *S. pyogenes*, *E. coli* and *P. aeruginosa* compared to ampicillin but its 4-quinazolinonyl derivative displayed very good activity in some cases. Compounds **7d**, **7e**, **7g**, **7l**, **7n**, **7o**, **7p**, **7q**, and **7r** showed very good activity (150–250 μg/mL) against *S. aureus*. Compounds **7b**, **7d**, **7e**, **7f**, **7g**, **7l**, **7o**, **7p**, **7q**, and **7r** exhibited moderate activity (150–250 μg/mL) against *S. pyogenes*. Compounds **7g**, **7l**, **7n**, **7o,** and **7r** possessed good activity (100–125 μg/mL) while **7a**, **7b**, **7c**, **7d**, **7f**, **7h**, **7i**, **7j**, **7m**, and **7p** showed moderate activity (150–250 μg/mL) against *E. coli*. Compounds **7b** and **7f** exhibited good activity (100 μg/mL) while **7a**, **7c**, **7d**, **7g**, **7h**, **7i**, **7l**, **7m**, **7n**, **7o**, **7p**, **7q**, and **7r** possessed moderate activity (150–250 μg/mL) against *P. aeruginosa*.

*In vitro* antifungal activity results are shown in Table 2. Antifungal activities are shown in minimal fungicidal concentrations (MFCs μg/mL). The synthesized compounds were screened against three fungal species *C. albicans*, *A. niger* and *A. clavatus*. Greseofulvin was used as a standard drug. Results show that amino substituted 1,3,4-oxadiazoles possessed good activity while its 4-quinazolinonyl derivative showed increased activity against *C. albicans*. Compounds **7d**, **7e**, **7g**, **7j**, **7k**, **7l**, **7m**, **7p**, and **7q** showed pronounced activity (200–250 μg/mL) against *C. albicans*. Amino substituted 1,3,4-oxadiazoles possessed poor activity against *A. niger* and *A. clavatus* while some of its 4-quinazolinonyl derivative exhibited moderate activity. Compound **7p** was found active against *A. niger* (MFC = 250 μg/mL) whereas compounds **7b**, **7c**, and **7p** were found active against *A. clavatus* (MFC = 200–250 μg/mL) among the whole series.

## CONCLUSION

The *in vitro* antimicrobial screening results were found satisfactory. Amino substituted 1,3,4-oxadiazoles possessed good antibacterial activity but its 4-quinazolinonyl derivative showed increased activity in most of cases. All the compounds displayed very good antifungal activity

against *C. albicans* while poor activity was observed against *A. niger* and *A. clavatus*, except **7p**, **7b**, and **7c** (**7p** was found active against *A. niger* and *A. clavatus* while **7b** and **7c** were found active against *A. clavatus*).

## EXPERIMENTAL

All chemical were of analytical grade and used directly. Melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of compound was confirmed by TLC using Merck silica gel 60 F254. Infrared spectra were recorded on a Perkin-Elmer RX 1 FTIR spectrophotometer, using potassium bromide (KBr) pellets, the frequencies are expressed in $cm^{-1}$. The nuclear magnetic resonance spectra were recorded with a Bruker Avance II 400 NMR spectrometer, using tetramethylsilane (TMS) as the internal reference, with dimethylsulphoxide (DMSO-$d_6$) as solvent. The chemical shifts are reported in parts per million (δ ppm). Elemental analyses were performed on a Heraeus Carlo Erba 1180 CHN analyzer.

**General procedure for the synthesis of 2-[2-(2,6-dichlorophenyl)amino]benzyl-3,1-benzoxazin-4(*H*)ones (3a-c).** The mixture of 3.05 g (0.01 mole) of acid chloride (2) and 1.37 g (0.01 mole) of anthranilic acid (1a) in 20 mL of dry pyridine were stirred at 0–5 °C for 1 h, further stirred for 1 h at room temperature. Progress of reaction was check by TLC using toluene:ethylacetate (80:20) as mobile phase. After completion of reaction, a pasty mass obtained, was washed thoroughly with sodium bicarbonate (5% w/v) to remove unreacted acid. A solid separated was filtered, dried and recrystallized from methanol. Other benzoxazinone derivatives **3b, c** were synthesized by the same method.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3,1-benzoxazin-4(H)one (3a).*** This compound was obtained as reddish solid, yield 53%, mp 183–186°C; IR (KBr): NH 3449, $CH_2$ 2925, 2851, CO 1742, CN 1620, CN 1316, CO 1151, CCl 745 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.52 (s, 2H, $CH_2$), 6.39 (d, 1H, 14-H, J = 7.96 Hz), 6.88 (t, 1H, 16-H, J = 7.4 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.54 Hz), 7.42 (d, 2H, 21- and 23-H, J = 8.08 Hz), 7.51 (d, 1H, 8-H, J = 8.12 Hz), 7.84 (t, 1H, 7-H, J = 7.8 Hz), 8.06 (t, 1H, 6-H, J = 7.64 Hz), 8.12 (d, 1H, 5-H, J = 7.72 Hz), 9.12 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.47 ($CH_2$), 116.27 (16-C), 116.54 (10-C), 120.54 (14-C), 122.35 (8-C), 124.15 (22-C), 126.61 (15-C), 127.12 (12-C), 127.32 (21- and 23-C), 127.54 (6-C), 129.34 (20- and 24-C), 131.23 (17-C), 131.52 (5-C), 135.43 (7-C), 137.23 (19-C), 141.76 (13-C), 149.53 (9-C), 159.36 (4-C), 164.51 ppm (2-C). Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O_2$ (397.25): C, 63.49; H, 3.55; N, 7.05. Found: C, 63.45; H, 3.56; N, 7.03.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-6-bromo-3,1-benzoxazin-4(H)one (3b).*** This compound was obtained as orange solid, yield 55%, mp 194–198°C; IR (KBr): NH 3446, $CH_2$ 2926, 2850, CO 1740, CN 1618, CO 1153, CCl 743, CBr 565 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.40 (d, 1H, 14-H, J = 8 Hz), 6.88 (t, 1H, 16-H, J = 7.44 Hz), 7.03–7.08 (m, 2H, 15- and 22-H), 7.22 (d, 1H, 17-H, J = 7.58 Hz), 7.41 (d, 2H, 21- and 23-H, J = 8.16 Hz), 7.65 (d, 1H, 8-H, J = 8.32 Hz), 8.12 (d, 1H, 7-H, J = 8.32 Hz), 8.16 (s, 1H, 5-H), 9.10 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.43 ($CH_2$), 116.31 (16-C), 118.64 (10-C), 120.62 (14-C), 121.67 (6-C), 124.31 (22-C), 124.57 (8-C), 126.54 (15-C), 127.17 (12-C), 127.43 (21- and 23-C), 129.41 (20- and 24-C), 131.12 (17-C), 135.22 (5-C), 137.29 (19-C), 138.23 (7-C), 141.78 (13-C), 148.73 (9-C), 159.23 (4-C), 164.33 ppm (2-C). *Anal*. Calcd. for $C_{21}H_{13}BrCl_2N_2O_2$ (476.15): C, 52.97; H, 2.75; N, 5.88. Found: C, 52.94; H, 2.74; N, 5.90.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-6-iodo-3,1-benzoxazin-4(H)one (3c).*** This compound was obtained as brown solid, yield 58%, mp 189–193°C; IR (KBr): NH 3450, $CH_2$ 2923, 2848, CO 1745, CN 1617, CO 1148, CCl 747, CI 620 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.41 (d, 1H, 14-H, J = 7.92 Hz), 6.89 (t, 1H, 16-H, J = 7.36 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.22 (d, 1H, 17-H, J = 7.54 Hz), 7.25 (d, 1H, 8-H, J = 8.28 Hz), 7.42 (d, 2H, 21- and 23-H, J = 8.12 Hz), 8.05 (d, 1H, 7-H, J = 8.28 Hz), 8.48 (s, 1H, 5-H), 9.10 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.53 ($CH_2$), 93.14 (6-C), 116.25 (16-C), 118.23 (10-C), 120.57 (14-C), 123.74 (8-C), 124.19 (22-C), 126.58 (15-C), 127.05 (12-C), 127.33 (21- and 23-C), 129.39 (20- and 24-C), 131.14 (17-C), 137.42 (19-C), 138.87 (5-C), 141.81 (13-C), 144.27 (7-C), 148.62 (9-C), 159.53 (4-C), 164.47 ppm (2-C). *Anal*. Calcd. for $C_{21}H_{13}Cl_2IN_2O_2$ (523.15): C, 48.21; H, 2.50; N, 5.35. Found: C, 48.25; H, 2.49; N, 5.33.

**General procedure for the synthesis of 2-(4-aminophenyl)-5-substitutedphenyl-1,3,4-oxadiazoles (6a-f).** A mixture of 0.69 g (0.005 mole) of 4-amino benzoic acid and substituted benzoic acid hydrazides (0.005 mole) in 5 mL of phosphorus oxychloride was refluxed on water bath for 7–10 h. The progress of the reaction was monitored by TLC using toluene:ethylacetate:methanol (70:20:10) as mobile phase. After the completion of reaction, it was cooled and poured onto crushed ice with continuous stirring. The solid mass separated was neutralized with sodium bicarbonate solution (10% w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and crystallized from absolute ethanol.

***2-(4-Aminophenyl)-5-phenyl-1,3,4-oxadiazole (6a).*** This compound was obtained as white solid, yield 72%, mp 196–200°C; IR (KBr): $NH_2$ 3495, 3405, CN 1655, COC 1277, 1035 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 5.44 (s, 2H, $NH_2$), 6.81 (d, 2H, 8- and 10-H, J = 8.4 Hz), 7.30 (d, 2H, 7- and 11-H, J = 8.4 Hz), 7.41 (t, 3H, 14-, 15- and 16-H, J = 6.24 Hz), 7.80 ppm (dd, 2H, 13- and 17-H, J = 6.48 Hz, 1.96 Hz); $^{13}$C-NMR (DMSO-$d_6$): δ 107.47 (6-C), 114.53 (8- and 10-C), 124.34 (12-C), 124.87 (13- and 17-C), 128.53 (15-C), 128.74 (7- and 11-C), 129.82 (14- and 16-C), 148.56 (9-C), 163.15 ppm (2- and 5-C). *Anal*. Calcd. for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; H, 4.67; N, 17.71. Found: C, 70.78; H, 4.65; N, 17.77.

***2-(4-Aminophenyl)-5-(2-hydroxyphenyl)-1,3,4-oxadiazole (6b).*** This compound was obtained as white solid, yield 74%, mp 167–171°C; IR (KBr): $NH_2$ 3502, 3408, OH 3135, CN 1661, COC 1265, 1058 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 5.46 (s, 2H, $NH_2$), 6.78 (d, 2H, 8- and 10-H, J = 8.36 Hz), 6.92 (t, 1H, 16-H, J = 7.56 Hz), 6.97 (d, 1H, 14-H, J = 8.12 Hz), 7.24 (t, 1H, 15-H, J = 7.76 Hz), 7.29 (d, 2H, 7- and 11-H, J = 8.36 Hz), 7.45 (dd, 1H, 17-H, J = 7.72 Hz), 10.05 ppm (br s, 1H, OH); $^{13}$C-NMR (DMSO-$d_6$): δ 107.52 (6-C), 109.15 (12-C), 114.48 (8- and 10-C), 116.58 (14-C), 119.57 (16-C), 125.42 (17-C), 128.82 (7- and 11-C), 131.63 (15-C), 148.65 (9-C), 155.67 (13-C), 162.74 ppm (2- and 5-C). *Anal*. Calcd.

for $C_{14}H_{11}N_3O_2$ (253.26): C, 66.40; H, 4.38; N, 16.59. Found: C, 66.34; H, 4.41; N, 16.64.

***2-(4-Aminophenyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazole (6c).*** This compound was obtained as white solid, yield 78%, mp 190–195°C; IR (KBr): $NH_2$ 3475, 3415, OH 3152, CN 1653, COC 1285, 1023 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 5.45 (s, 2H, $NH_2$), 5.61 (br s, 1H, OH), 6.80 (d, 2H, 8- and 10-H, J = 8.36), 6.93 (d, 2H, 14- and 16-H, J = 8.46 Hz), 7.32 (d, 2H, 7- and 11-H, J = 8.36 Hz), 7.69 ppm (d, 2H, 13- and 17-H, J = 8.46 Hz); $^{13}$C-NMR (DMSO-$d_6$): δ 107.37 (6-C), 114.42 (8- and 10-C), 116.63 (14- and 16-C), 118.22 (12-C), 128.34 (13- and 17-C), 128.66 (7- and 11-C), 148.46 (9-C), 160.18 (15-C), 163.57 ppm (2- and 5-C). *Anal*. Calcd. for $C_{14}H_{11}N_3O_2$ (253.26): C, 66.40; H, 4.38; N, 16.59. Found: C, 66.43; H, 4.35; N, 16.57.

***2-(4-Aminophenyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole (6d).*** This compound was obtained as pale yellow solid, yield 80%, mp 210–214°C; ir (KBr): $NH_2$ 3489, 3407, CN 1658, $NO_2$ 1531, 1352, COC 1280, 1024 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 5.47 (s, 2H, $NH_2$), 6.78 (d, 2H, 8- and 10-H, J = 8.4 Hz), 7.31 (d, 2H, 7- and 11-H, J = 8.4 Hz), 7.82 (t, 1H, 16-H, J = 7.84 Hz), 8.23 (d, 1H, 17-H, J = 7.12 Hz), 8.34 (d, 1H, 15-H, J = 7.72 Hz), 8.45 ppm (s, 1H, 13-H); $^{13}$C-NMR (DMSO-$d_6$): δ 107.59 (6-C), 114.68 (8- and 10-C), 120.17 (13-C), 124.37 (15-C), 125.68 (12-C), 128.64 (7- and 11-C), 130.74 (16-C), 133.43 (17-C), 148.42 (14-C), 148.55 (9-C), 163.95 ppm (2- and 5-C). *Anal*. Calcd. for $C_{14}H_{10}N_4O_3$ (282.25): C, 59.57; H, 3.57; N, 19.85. Found: C, 59.51; H, 3.54; N, 19.80.

***2-(4-Aminophenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (6e).*** This compound was obtained as light yellow solid, yield 85%, mp 201–205°C; ir (KBr): $NH_2$ 3498, 3410, CN 1655, $NO_2$ 1535, 1354, COC 1283, 1027 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 5.45 (s, 2H, $NH_2$), 6.81 (d, 2H, 8- and 10-H, J = 8.36 Hz), 7.32 (d, 2H, 7- and 11-H, J = 8.36 Hz), 8.07 (d, 2H, 13- and 17-H, J = 8.76 Hz), 8.32 ppm (d, 2H, 14- and 16-H, J = 8.76 Hz); $^{13}$C-NMR (DMSO-$d_6$): δ 107.56 (6-C), 114.57 (8- and 10-C), 124.55 (14- and 16-C), 127.18 (13- and 17-C), 128.75 (7- and 11-C), 131.23 (12-C), 148.18 (15-C), 148.67 (9-C), 164.28 ppm (2- and 5-C). *Anal*. Calcd. for $C_{14}H_{10}N_4O_3$ (282.25): C, 59.57; H, 3.57; N, 19.85. Found: C, 59.54; H, 3.59; N, 19.83.

***2-(4-Aminophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (6f).*** This compound was obtained as white solid, yield 75%, mp 203–207°C; ir (KBr): $NH_2$ 3505, 3415, CN 1660, COC 1257, 1025 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.59 (s, 3H, $OCH_3$), 5.43 (s, 2H, $NH_2$), 6.77 (d, 2H, 8- and 10-H, J = 8.4 Hz), 6.80 (d, 2H, 14- and 16-H, J = 8.72 Hz), 7.26 (d, 2H, 7- and 11-H, J = 8.4 Hz), 7.46 ppm (d, 2H, 13- and 17-H, J = 8.72 Hz); $^{13}$C-NMR (DMSO-$d_6$): δ 55.19 ($OCH_3$), 107.43 (6-C), 114.28 (14- and 16-C), 114.45 (8- and 10-C), 116.85 (12-C), 126.57 (13- and 17-C), 128.62 (7- and 11-C), 148.51 (9-C), 160.61 (15-C), 163.77 ppm (2- and 5-C). *Anal*. Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.48; H, 4.86; N, 15.75.

**General procedure for the synthesis of 2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[5-(substituted phenyl)-1,3,4-oxadiazol-2-yl]phenyl}quinazolin-4(3*H*)ones (7a-r).** A mixture of 4-benzoxazinone (0.0025 mole) and 2-(4-aminophenyl)-5-substitutedphenyl-1,3,4-oxadiazole (0.0025 mole) in 10 mL of pyridine was refluxed on an oil bath for 6–8 h. After completion of the reaction, the oily mass was slowly poured onto crushed ice cold water contained HCl (5 mL) with continues stirring. For TLC monitoring toluene:ethylacetate:methanol (70:20:10) was used as mobile phase. The product obtained was filtered and washed several times with cold water, dried and recrystallized from ethanol.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl] quinazolin-4(3H)one (7a).*** This compound was obtained as white solid, yield 57%, mp 240–244°C; IR (KBr): NH 3445, $CH_2$ 2927, 2852, CO 1681, CN 1649, 1611, COC 1273, 1057, CCl 748 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.52 (s, 2H, $CH_2$), 6.39 (d, 1H, 14-H, J = 7.96 Hz), 6.89 (t, 1H, 16-H, J = 7.4 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.56 Hz), 7.38–7.45 (m, 7H, 21-, 23-, 26-, 30-, 38-, 39- and 40-H), 7.49–7.55 (m, 3H, 6-, 27- and 29-H), 7.59 (d, 1H, 8-H, J = 8.12 Hz), 7.75 (t, 1H, 7-H, J = 7.8 Hz), 7.83 (dd, 2H, 37- and 41-H, J = 6.44 Hz, 1.92 Hz), 8.11 (d, 1H, 5-H, J = 7.68 Hz), 9.12 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.47 (11-C), 116.18 (16-C), 120.41 (14-C), 120.82 (10-C), 121.46 (28-C), 121.84 (26- and 30-C), 122.57 (8-C), 124.28 (22-C), 124.36 (36-C), 124.85 (37- and 41-C), 126.79 (15-C), 127.25 (12-C), 127.48 (21- and 23-C), 127.63 (6-C), 127.73 (27- and 29-C), 128.55 (39-C), 128.81 (5-C), 129.42 (20- and 24-C), 129.84 (38- and 40-C), 131.16 (17-C), 132.69 (25-C), 133.72 (7-C), 137.22 (19-C), 141.75 (13-C), 147.21 (9-C), 160.67 (4-C), 162.65 (2-C), 163.07 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{23}Cl_2N_5O_2$ (616.5): C, 68.19; H, 3.76; N, 11.36. Found: C, 68.12; H, 3.71; N, 11.41.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}quinazolin-4(3H)one (7b).*** This compound was obtained as off white solid, yield 61%, mp 228–232°C; IR (KBr): NH 3451, OH 3130, $CH_2$ 2924, 2850, CO 1678, CN 1661, 1610, COC 1263, 1060, CCl 745 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.54 (s, 2H, $CH_2$), 6.41 (d, 1H, 14-H, J = 8 Hz), 6.88 (t, 1H, 16-H, J = 7.44 Hz), 6.93 (t, 1H, 40-H, J = 7.52 Hz), 6.98 (d, 1H, 38-H, J = 8.12 Hz), 7.03–7.08 (m, 2H, 15- and 22-H), 7.21–7.26 (m, 2H, 17- and 39-H), 7.41 (d, 2H, 21- and 23-H, J = 8.12 Hz), 7.45 (d, 2H, 26- and 30-H, J = 8.32 Hz), 7.47–7.54 (m, 4H, 6-, 27-, -29 and 41-H), 7.58 (d, 1H, 8-H, J = 8.16 Hz), 7.77 (t, 1H, 7-H, J = 7.84 Hz), 8.09 (d, 1H, 5-H, J = 7.72 Hz), 9.08 (br s, 1H, NH), 10.04 ppm (br s, 1H, OH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.54 (11-C), 109.22 (36-C), 116.14 (16-C), 116.61 (38-C), 119.63 (40-C), 120.51 (14-C), 120.84 (10-C), 121.48 (28-C), 121.76 (26- and 30-C), 122.53 (8-C), 124.32 (22-C), 125.42 (41-C), 126.73 (15-C), 127.28 (12-C), 127.44 (21- and 23-C), 127.62 (6-C), 127.85 (27- and 29-C), 128.75 (5-C), 129.36 (20- and 24-C), 131.11 (17-C), 131.64 (39-C), 132.52 (25-C), 133.68 (7-C), 137.23 (19-C), 141.83 (13-C), 147.25 (9-C), 155.75 (37-C), 160.58 (4-C), 162.55 (2-C), 162.68 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{23}Cl_2N_5O_3$ (632.49): C, 66.46; H, 3.67; N, 11.07. Found: C, 66.53; H, 3.63; N, 11.03.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}quinazolin-4(3H)one (7c).*** This compound was obtained as white solid, yield 65%, mp 251–255°C; IR (KBr): NH 3453, OH 3151, $CH_2$ 2928, 2855, CO 1677, CN 1650, 1607, COC 1278, 1022, CCl 741 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.51 (s, 2H, $CH_2$), 5.59 (br s, 1H, OH), 6.40 (d, 1H, 14-H, J = 7.96 Hz), 6.90–6.95 (m, 3H, 16-, 38- and 40-H), 7.04–7.10 (m, 2H, 15- and 22-H), 7.23 (d, 1H, 17-H, J = 7.52 Hz), 7.39 (d, 2H, 21- and 23-H, J = 8.08 Hz), 7.44 (d, 2H, 26- and 30-H, J = 8.36 Hz), 7.50 (t, 1H, 6-H, J = 7.56 Hz), 7.55 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.61 (d, 1H, 8-H, J = 8.12 Hz), 7.70 (d, 2H, 37- and 41-H, J

= 8.44 Hz), 7.78 (t, 1H, 7-H, J = 7.76 Hz), 8.12 (d, 1H, 5-H, J = 7.64 Hz), 9.13 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.51 (11-C), 116.12 (16-C), 116.68 (38- and 40-C), 118.31 (36-C), 120.54 (14-C), 120.78 (10-C), 121.53 (28-C), 121.87 (26- and 30-C), 122.46 (8-C), 124.32 (22-C), 126.84 (15-C), 127.31 (12-C), 127.37 (21- and 23-C), 127.64 (6-C), 127.77 (27- and 29-C), 128.29 (37- and 41-C), 128.82 (5-C), 129.44 (20- and 24-C), 131.19 (17-C), 132.63 (25-C), 133.74 (7-C), 137.22 (19-C), 141.76 (13-C), 147.23 (9-C), 160.22 (39-C), 160.64 (4-C), 162.74 (2-C), 163.52 ppm (32- and 35-C); *Anal*. Calcd. for $C_{35}H_{23}Cl_2N_5O_3$ (632.49): C, 66.46; H, 3.67; N, 11.07. Found: C, 66.42; H, 3.72; N, 11.01.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}quinazolin-4(3H)one (7d).*** This compound was obtained as light orange solid, yield 58%, mp 280–285°C; IR (KBr): NH 3443, $CH_2$ 2918, 2847, CO 1675, CN 1653, 1610, $NO_2$ 1533, 1351, COC 1275, 1024, CCl 744 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.55 (s, 2H, $CH_2$), 6.42 (d, 1H, 14-H, J = 7.96 Hz), 6.91 (t, 1H, 16-H, J = 7.44 Hz), 7.03–7.09 (m, 2H, 15- and 22-H), 7.23 (d, 1H, 17-H, J = 7.6 Hz), 7.42 (d, 2H, 21- and 23-H, J = 8.16 Hz), 7.47 (d, 2H, 26- and 30-H, J = 8.28 Hz), 7.52 (t, 1H, 6-H, J = 7.6 Hz), 7.57 (d, 2H, 27- and 29-H, J = 8.28 Hz), 7.62 (d, 1H, 8-H, J = 8.12 Hz), 7.74 (t, 1H, 7-H, J = 7.8 Hz), 7.84 (t, 1H, 40-H, J = 7.8 Hz), 8.11 (d, 1H, 5-H, J = 7.68 Hz), 8.26 (d, 1H, 41-H, J = 7.12 Hz), 8.36 (d, 1H, 39-H, J = 7.68 Hz), 8.46 (s, 1H, 37-H), 9.11 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.46 (11-C), 116.23 (16-C), 120.22 (37-C), 120.53 (14-C), 120.64 (10-C), 121.47 (28-C), 121.75 (26- and 30-C), 122.45 (8-C), 124.34 (22-C), 124.46 (39-C), 125.73 (36-C), 126.73 (15-C), 127.21 (12-C), 127.47 (21- and 23-C), 127.58 (6-C), 127.65 (27- and 29-C), 128.85 (5-C), 129.52 (20- and 24-C), 130.78 (40-C), 131.21 (17-C), 132.54 (25-C), 133.45 (41-C), 133.62 (7-C), 137.19 (19-C), 141.68 (13-C), 147.07 (9-C), 148.51 (38-C), 160.53 (4-C), 162.77 (2-C), 163.89 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{22}Cl_2N_6O_4$ (661.49): C, 63.55; H, 3.35; N, 12.70. Found: C, 63.48; H, 3.39; N, 12.75.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}quinazolin-4(3H)one (7e).*** This compound was obtained as pale yellow solid, yield 74%, mp 245–249°C; IR (KBr): NH 3448, $CH_2$ 2927, 2852, CO 1676, CN 1652, 1612, $NO_2$ 1537, 1356, COC 1282, 1028, CCl 747 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.39 (d, 1H, 14-H, J = 7.92 Hz), 6.89 (t, 1H, 16-H, J = 7.36 Hz), 7.04–7.10 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.52 Hz), 7.39 (d, 2H, 21- and 23-H, J = 8.04 Hz), 7.45 (d, 2H, 26- and 30-H, J = 8.36 Hz), 7.48 (t, 1H, 6-H, J = 7.64 Hz), 7.55 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.61 (d, 1H, 8-H, J = 8.16 Hz), 7.76 (t, 1H, 7-H, J = 7.84 Hz), 8.05 (d, 2H, 37- and 41-H, J = 8.72 Hz), 8.10 (d, 1H, 5-H, J = 7.72 Hz), 8.34 (d, 2H, 38- and 40-H, J = 8.72 Hz), 9.13 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.61 (11-C), 116.27 (16-C), 120.63 (14-C), 120.73 (10-C), 121.54 (28-C), 121.82 (26- and 30-C), 122.58 (8-C), 124.26 (22-C), 124.47 (38- and 40-C), 126.62 (15-C), 127.12 (37- and 41-C), 127.33 (12-C), 127.55 (21- and 23-C), 127.63 (6-C), 127.74 (27- and 29-C), 128.76 (5-C), 129.44 (20- and 24-C), 131.18 (36-C), 131.27 (17-C), 132.63 (25-C), 133.56 (7-C), 137.29 (19-C), 141.77 (13-C), 147.15 (9-C), 148.13 (39-C), 160.65 (4-C), 162.63 (2-C), 164.25 ppm (32- and 35-C). *Anal*. Calcd. for (661.49): C, 63.55; H, 3.35; N, 12.70. Found: C, 63.46; H, 3.41; N, 12.74.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}quinazolin-4(3H)one (7f).*** This compound was obtained as off white, yield 67%, mp 265-268°C; ir (KBr): NH 3453, $CH_2$ 2924, 2850, CO 1672, CN 1654, 1608, COC 1257, 1023, CCl 743 cm$^{-1}$; $^1$H nmr (DMSO-$d_6$): δ; 3.51 (s, 2H, $CH_2$), 3.60 (s, 3H, $OCH_3$), 6.38 (d, 1H, 14-H, J = 7.96 Hz), 6.79 (d, 2H, 38- and 40-H, J = 8.68 Hz), 6.88 (t, 1H, 16-H, J = 7.36 Hz), 7.03–7.08 (m, 2H, 15- and 22-H), 7.19 (d, 1H, 17-H, J = 7.52 Hz), 7.39–7.56 (m, 9H, 6-, 21-, 23-, 26-, 27-, 29-, 30-, 37- and 41-H), 7.62 (d, 1H, 8-H, J = 8.16 Hz), 7.75 (t, 1H, 7-H, J = 7.84 Hz), 8.12 (d, 1H, 5-H, J = 7.68 Hz), 9.15 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.53 (11-C), 55.23 ($OCH_3$), 114.32 (38- and 40-C), 116.14 (16-C), 116.79 (36-C), 120.47 (14-C), 120.74 (10-C), 121.54 (28-C), 121.83 (26- and 30-C), 122.56 (8-C), 124.27 (22-C), 126.62 (37- and 41-C), 126.74 (15-C), 127.22 (12-C), 127.42 (21- and 23-C), 127.51 (6-C), 127.75 (27- and 29-C), 128.76 (5-C), 129.43 (20- and 24-C), 131.13 (17-C), 132.70 (25-C), 133.66 (7-C), 137.23 (19-C), 141.72 (13-C), 147.16 (9-C), 160.56 (39-C), 160.73 (4-C), 162.78 (2-C), 163.75 ppm (32- and 35-C). *Anal*. Calcd. for $C_{36}H_{25}Cl_2N_5O_3$ (646.52): C, 66.88; H, 3.90; N, 10.83. Found: C, 66.97; H, 3.88; N, 10.78.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl]-6-bromo-quinazolin-4(3H)one (7g).*** This compound was obtained as light reddish, yield 63%, mp 261–264°C; IR (KBr): NH 3452, $CH_2$ 2929, 2855, CO 1682, CN 1651, 1614, COC 1272, 1053, CCl 742, CBr 574 cm$^{-1}$; $^1$H nmr (DMSO-$d_6$): δ 3.54 (s, 2H, $CH_2$), 6.41 (d, 1H, 14-H, J = 8 Hz), 6.89 (t, 1H, 16-H, J = 7.48 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.22 (d, 1H, 17-H, J = 7.6 Hz), 7.39–7.44 (m, 5H, 21-, 23-, 38-, 39- and 40-H), 7.46 (d, 2H, 26- and 30-H, J = 8.32 Hz), 7.55 (d, 2H, 27- and 29-H, J = 8.32 Hz), 7.65 (d, 1H, 8-H, J = 8.36 Hz), 7.81 (dd, 2H, 37- and 41-H, J = 6.48 Hz, 1.96 Hz), 8.06 (d, 1H, 7-H, J = 8.36 Hz), 8.15 (s, 1H, 5-H), 9.11 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.55 (11-C), 116.16 (16-C), 120.57 (14-C), 121.41 (28-C), 121.54 (6-C), 121.74 (26- and 30-C), 123.18 (10-C), 124.26 (22-C), 124.35 (36-C), 124.58 (8-C), 124.84 (37- and 41-C), 126.85 (15-C), 127.24 (12-C), 127.47 (21- and 23-C), 127.62 (27- and 29-C), 128.54 (39-C), 129.46 (20- and 24-C), 129.80 (38- and 40-C), 131.15 (17-C), 132.26 (5-C), 132.53 (25-C), 136.41 (7-C), 137.31 (19-C), 141.82 (13-C), 146.23 (9-C), 160.71 (4-C), 162.74 (2-C), 163.11 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{22}BrCl_2N_5O_2$ (695.39): C, 60.45; H, 3.19; N, 10.07. Found: C, 60.54; H, 3.12; N, 10.11.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-bromo-quinazolin-4(3H)one (7h).*** This compound was obtained as white solid, yield 55%, mp 246–250°C; IR (KBr): NH 3448, OH 3128, $CH_2$ 2928, 2850, CO 1679, CN 1658, 1607, COC 1260, 1055, CCl 745, C-Br 566 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.39 (d, 1H, 14-H, J = 7.96 Hz), 6.88–6.93 (m, 2H, 16- and 40-H), 6.96 (d, 1H, 38-H, J = 8.12 Hz), 7.04–7.10 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.56 Hz), 7.26 (t, 1H, 39-H, J = 7.76 Hz), 7.40–7.46 (m, 5H, 21-, 23-, 26-, 30- and 41-H), 7.54 (d, 2H, 27- and 29-H, J = 8.28 Hz), 7.67 (d, 1H, 8-H, J = 8.32 Hz), 8.08 (d, 1H, 7-H, J = 8.32 Hz), 8.16 (s, 1H, 5-H), 9.08 (br s, 1H, NH), 10.06 ppm (br s, 1H, OH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.48 (11-C), 109.18 (36-C), 116.12

(16-C), 116.59 (38-C), 119.54 (40-C), 120.53 (14-C), 121.46 (6-C), 121.57 (28-C), 121.86 (26- and 30-C), 123.14 (10-C), 124.33 (22-C), 124.66 (8-C), 125.38 (41-C), 126.75 (15-C), 127.15 (12-C), 127.36 (21- and 23-C), 127.79 (27- and 29-C), 129.34 (20- and 24-C), 131.10 (17-C), 131.57 (39-C), 132.17 (5-C), 132.74 (25-C), 136.39 (7-C), 137.22 (19-C), 141.76 (13-C), 146.34 (9-C), 155.66 (37-C), 160.67 (4-C), 162.58 (2-C), 162.74 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{22}BrCl_2N_5O_3$ (711.39): C, 59.09; H, 3.12; N, 9.84. Found: C, 58.95; H, 3.17; N, 9.89.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-bromo-quinazolin-4(3H)one (7i).*** This compound was obtained as off white solid, yield 66%, mp 232–236°C; IR (KBr): NH 3450, OH 3143, $CH_2$ 2924, 2849, CO 1672, CN 1656, 1610, COC 1274, 1022, CCl 739, CBr 571 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.55 (s, 2H, $CH_2$), 5.62 (br s, 1H, OH), 6.43 (d, 1H, 14-H, J = 8 Hz), 6.90–6.96 (m, 3H, 16-, 38-, and 40-H), 7.04–7.09 (m, 2H, 15- and 22-H), 7.23 (d, 1H, 17-H, J = 7.6 Hz), 7.41 (d, 2H, 21- and 23-H, J = 8.12 Hz), 7.47 (d, 2H, 26- and 30-H, J = 8.32 Hz), 7.56 (d, 2H, 27- and 29-H, J = 8.32 Hz), 7.64 (d, 1H, 8-H, J = 8.36 Hz), 7.71 (d, 2H, 37- and 41-H, J = 8.48 Hz), 8.05 (d, 1H, 7-H, J = 8.36 Hz), 8.12 (s, 1H, 5-H), 9.14 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.55 (11-C), 116.18 (16-C), 116.65 (38- and 40-C), 118.26 (36-C), 120.52 (14-C), 121.53 (6-C), 121.64 (28-C), 121.89 (26- and 30-C), 123.24 (10-C), 124.37 (22-C), 124.45 (8-C), 126.85 (15-C), 127.21 (12-C), 127.53 (21- and 23-C), 127.72 (27- and 29-C), 128.32 (37- and 41-C), 129.44 (20- and 24-C), 131.22 (17-C), 132.26 (5-C), 132.71 (25-C), 136.47 (7-C), 137.18 (19-C), 141.75 (13-C), 146.21 (9-C), 160.15 (39-C), 160.62 (4-C), 162.72 (2-C), 163.64 ppm (32- and 35-C); *Anal*. Calcd. for $C_{35}H_{22}BrCl_2N_5O_3$ (711.39): C, 59.09; H, 3.12; N, 9.84. Found: C, 58.98; H, 3.08; N, 9.86.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-bromo-quinazolin-4(3H)one (7j).*** This compound was obtained as yellow solid, yield 62%, mp 274–277°C; ir (KBr): NH 3444, $CH_2$ 2920, 2846, CO 1682, CN 1647, 1612, $NO_2$ 1528, 1345, COC 1280, 1025, CCl 748, CBr 569 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.41 (d, 1H, 14-H, J = 7.96 Hz), 6.89 (t, 1H, 16-H, J = 7.36 Hz), 7.03–7.08 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.52 Hz), 7.39 (d, 2H, 21- and 23-H, J = 8.12 Hz), 7.44 (d, 2H, 26- and 30-H, J = 8.36 Hz), 7.53 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.66 (d, 1H, 8-H, J = 8.4 Hz), 7.81 (t, 1H, 40-H, J = 7.88 Hz), 8.06 (d, 1H, 7-H, J = 8.4 Hz), 8.14 (s, 1H, 5-H), 8.25 (d, 1H, 41-H, J = 7.16 Hz), 8.36 (d, 1H, 39-H, J = 7.76 Hz), 8.44 (s, 1H, 37-H), 9.11 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.47 (11-C), 116.22 (16-C), 120.12 (37-C), 120.48 (14-C), 121.57 (6-C), 121.68 (28-C), 121.91 (26- and 30-C), 123.15 (10-C), 124.26 (22-C), 124.35 (39-C), 124.49 (8-C), 125.64 (36-C), 126.82 (15-C), 127.21 (12-C), 127.42 (21- and 23-C), 127.82 (27- and 29-C), 129.52 (20- and 24-C), 130.69 (40-C), 131.17 (17-C), 132.25 (5-C), 132.65 (25-C), 133.37 (41-C), 136.46 (7-C), 137.22 (19-C), 141.79 (13-C), 146.32 (9-C), 148.41 (38-C), 160.56 (4-C), 162.78 (2-C), 163.93 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{21}BrCl_2N_6O_4$ (740.39): C, 56.78; H, 2.86; N, 11.35. Found: C, 56.87; H, 2.82; N, 11.29.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-bromo-quinazolin-4(3H)one (7k).*** This compound was obtained as yellow solid, yield 65%, mp 258–262°C; IR (KBr): NH 3440, $CH_2$ 2918, 2844, CO 1673, CN 1647, 1605, $NO_2$ 1536, 1356, COC 1267, 1023, CCl 741, CBr 561 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.52 (s, 2H, $CH_2$), 6.43 (d, 1H, 14-H, J = 7.92 Hz), 6.91 (t, 1H, 16-H, J = 7.36 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.20 (d, 1H, 17-H, J = 7.52 Hz), 7.41 (d, 2H, 21- and 23-H, J = 8.08 Hz), 7.46 (d, 2H, 26- and 30-H, J = 8.36 Hz), 7.57 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.65 (d, 1H, 8-H, J = 8.36 Hz), 8.05 (d, 1H, 7-H, J = 8.36 Hz), 8.08 (d, 2H, 37- and 41-H, J = 8.68 Hz), 8.15 (s, 1H, 5-H), 8.31 (d, 2H, 38- and 40-H, J = 8.68 Hz), 9.13 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.55 (11-C), 116.27 (16-C), 120.56 (14-C), 121.54 (6-C), 121.63 (28-C), 121.85 (26- and 30-C), 123.05 (10-C), 124.36 (22-C), 124.42 (8-C), 124.64 (38- and 40-C), 126.94 (15-C), 127.15 (37- and 41-C), 127.26 (12-C), 127.54 (21- and 23-C), 127.77 (27- and 29-C), 129.43 (20- and 24-C), 131.17 (36-C), 131.24 (17-C), 132.19 (5-C), 132.59 (25-C), 136.54 (7-C), 137.20 (19-C), 141.91 (13-C), 146.24 (9-C), 148.15 (39-C), 160.72 (4-C), 162.81 (2-C), 164.33 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{21}BrCl_2N_6O_4$ (740.39): C, 56.78; H, 2.86; N, 11.35. Found: C, 56.68; H, 2.89; N, 11.31.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-bromo-quinazolin-4(3H)one (7l).*** This compound was obtained as orange solid, yield 70%, mp 289–292°C; ir (KBr): NH 3443, $CH_2$ 2918, 2844, CO 1683, CN 1659, 1610, COC 1255, 1023, CCl 743, CBr 565 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 3.61 (s, 3H, $OCH_3$), 6.39 (d, 1H, 14-H, J = 8 Hz), 6.77 (d, 2H, 38- and 40-H, J = 8.72 Hz), 6.89 (t, 1H, 16-H, J = 7.44 Hz), 7.04–7.10 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.56 Hz), 7.39 (d, 2H, 21- and 23-H, J = 8.12 Hz), 7.43 (d, 2H, 26- and 30-H, J = 8.32 Hz), 7.48 (d, 2H, 37- and 41-H, J = 8.72 Hz), 7.55 (d, 2H, 27- and 29-H, J = 8.32 Hz), 7.67 (d, 1H, 8-H, J = 8.4 Hz), 8.08 (d, 1H, 7-H, J = 8.4 Hz), 8.16 (s, 1H, 5-H), 9.10 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.63 (11-C), 55.15 ($OCH_3$), 114.25 (38- and 40-C), 116.27 (16-C), 116.83 (36-C), 120.47 (14-C), 121.57 (6-C), 121.68 (28-C), 121.88 (26- and 30-C), 123.13 (10-C), 124.34 (22-C), 124.46 (8-C), 126.55 (37- and 41-C), 126.91 (15-C), 127.17 (12-C), 127.56 (21- and 23-C), 127.82 (27- and 29-C), 129.38 (20- and 24-C), 131.25 (17-C), 132.19 (5-C), 132.73 (25-C), 136.52 (7-C), 137.23 (19-C), 141.94 (13-C), 146.12 (9-C), 160.56 (39-C), 160.68 (4-C), 162.65 (2-C), 163.80 ppm (32- and 35-C). *Anal*. Calcd. for $C_{36}H_{24}BrCl_2N_5O_3$ (725.42): C, 59.61; H, 3.33; N, 9.65. Found: C, 59.69; H, 3.37; N, 9.58.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl]-6-iodo-quinazolin-4(3H)one (7m).*** This compound was obtained as light brownish solid, yield 63%, mp 256–258°C; IR (KBr): NH 3452, $CH_2$ 2926, 2852, CO 1680, CN 1648, 1613, COC 1270, 1052, CCl 749, CI 618 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.52 (s, 2H, $CH_2$), 6.42 (d, 1H, 14-H, J = 8 Hz), 6.92 (t, 1H, 16-H, J = 7.48 Hz), 7.03–7.09 (m, 2H, 15- and 22-H), 7.23 (d, 1H, 17-H, J = 7.64 Hz), 7.29 (d, 1H, 8-H, J = 8.4 Hz), 7.38–7.43 (m, 5H, 21-, 23-, 38-, 39- and 40-H), 7.45 (d, 2H, 26- and 30-H, J = 8.28 Hz), 7.56 (d, 2H, 27- and 29-H, J = 8.28 Hz), 7.78 (dd, 2H, 37- and 41-H, J = 6.44 Hz, 1.92 Hz), 7.97 (d, 1H, 7-H, J = 8.4 Hz), 8.30 (s, 1H, 5-H), 9.13 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.46 (11-C), 93.17 (6-C), 116.22 (16-C), 120.45 (14-C), 121.53 (28-C), 121.84 (26- and 30-C), 122.43 (10-C), 124.18 (8-C), 124.25 (22-C), 124.37 (36-C), 124.86 (37- and 41-C),

126.76 (15-C), 127.33 (12-C), 127.44 (21- and 23-C), 127.78 (27- and 29-C), 128.55 (39-C), 129.34 (20- and 24-C), 129.77 (38- and 40-C), 131.27 (17-C), 132.75 (25-C), 136.24 (5-C), 137.18 (19-C), 141.86 (13-C), 142.38 (7-C), 146.05 (9-C), 160.62 (4-C), 162.82 (2-C), 163.21 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{22}Cl_2IN_5O_2$ (742.39): C, 56.62; H, 2.99; N, 9.43. Found: C, 56.73; H, 2.91; N, 9.36.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-iodo-quinazolin-4(3H)one (7n).*** This compound was obtained as light reddish solid, yield 67%, mp 266–270°C; IR (KBr): NH 3446, OH 3135, $CH_2$ 2921, 2846, CO 1673, CN 1656, 1611, COC 1255, 1048, CCl 743, CI 620 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.40 (d, 1H, 14-H, J = 7.96 Hz), 6.87–6.95 (m, 2H, 16- and 40-H), 6.98 (d, 1H, 38-H, J = 8.12 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.52 Hz), 7.23–7.28 (m, 2H, 8- and 39-H), 7.40 (d, 2H, 21- and 23-H, J = 8.12 Hz), 7.44–7.47 (m, 3H, 26-, 30- and 41-H), 7.57 (d, 2H, 27- and 29-H, J = 8.28 Hz), 7.95 (d, 1H, 7-H, J = 8.36 Hz), 8.28 (s, 1H, 5-H), 9.11 (br s, 1H, NH), 10.06 ppm (br s, 1H, OH); $^{13}$C NMR (DMSO-$d_6$): δ 32.62 (11-C), 93.33 (6-C), 109.28 (36-C), 116.19 (16-C), 116.67 (38-C), 119.68 (40-C), 120.46 (14-C), 121.48 (28-C), 121.80 (26- and 30-C), 122.53 (10-C), 124.16 (8-C), 124.25 (22-C), 125.51 (41-C), 126.85 (15-C), 127.31 (12-C), 127.45 (21- and 23-C), 127.68 (27- and 29-C), 129.44 (20- and 24-C), 131.18 (17-C), 131.72 (39-C), 132.64 (25-C), 136.30 (5-C), 137.21 (19-C), 141.82 (13-C), 142.47 (7-C), 146.22 (9-C), 155.61 (37-C), 160.73 (4-C), 162.52 (2-C), 162.69 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{22}Cl_2IN_5O_3$ (758.39): C, 55.43; H, 2.92; N, 9.23. Found: C, 55.40; H, 2.95; N, 9.29.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-iodo-quinazolin-4(3H)one (7o).*** This compound was obtained as off white solid, yield 65%, mp 269–273°C; IR (KBr): NH 3453, OH 3145, $CH_2$ 2927, 2854, CO 1681, CN 1657, 1614, COC 1273, 1024, CCl 740, CI 619 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.51 (s, 2H, $CH_2$), 5.63 (br s, 1H, OH), 6.38 (d, 1H, 14-H, J = 7.96 Hz), 6.88 (t, 1H, 16-H, J = 7.4 Hz), 6.94 (d, 2H, 38- and 40-H, J = 8.44 Hz), 7.03–7.08 (m, 2H, 15- and 22-H), 7.19 (d, 1H, 17-H, J = 7.56 Hz), 7.26 (d, 1H, 8-H, J = 8.4 Hz), 7.38 (d, 2H, 21- and 23-H, J = 8.08 Hz), 7.43 (d, 2H, 26- and 30-H, J = 8.36 Hz), 7.54 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.70 (d, 2H, 37- and 41-H, J = 8.44 Hz), 7.94 (d, 1H, 7-H, J = 8.4 Hz), 8.27 (s, 1H, 5-H), 9.09 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.45 (11-C), 93.21 (6-C), 116.13 (16-C), 116.71 (38- and 40-C), 118.32 (36-C), 120.48 (14-C), 121.46 (28-C), 121.76 (26- and 30-C), 122.42 (10-C), 124.16 (8-C), 124.25 (22-C), 126.76 (15-C), 127.20 (12-C), 127.49 (21- and 23-C), 127.67 (27- and 29-C), 128.39 (37- and 41-C), 129.52 (20- and 24-C), 131.11 (17-C), 132.56 (25-C), 136.35 (5-C), 137.26 (19-C), 141.81 (13-C), 142.36 (7-C), 146.14 (9-C), 160.22 (39-C), 160.74 (4-C), 162.83 (2-C), 163.60 ppm (32- and 35-C); *Anal*. Calcd. for $C_{35}H_{22}Cl_2IN_5O_3$ (758.39): C, 55.43; H, 2.92; N, 9.23. Found: C, 55.48; H, 2.98; N, 9.18.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-iodo-quinazolin-4(3H)one (7p).*** This compound was obtained as brown solid, yield 61%, mp 286–290°C; IR (KBr): NH 3444, $CH_2$ 2926, 2853, CO 1675, CN 1653, 1610, $NO_2$ 1530, 1346, COC 1276, 1028, CCl 742, CI 613 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.53 (s, 2H, $CH_2$), 6.40 (d, 1H, 14-H, J = 7.96 Hz), 6.91 (t, 1H, 16-H, J = 7.36 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.21 (d, 1H, 17-H, J = 7.52 Hz), 7.28 (d, 1H, 8-H, J = 8.44 Hz), 7.39 (d, 2H, 21- and 23-H, J = 8.08 Hz), 7.44 (d, 2H, 26- and 30-H, J = 8.32 Hz), 7.55 (d, 2H, 27- and 29-H, J = 8.32 Hz), 7.80 (t, 1H, 40-H, J = 7.84 Hz), 7.96 (d, 1H, 7-H, J = 8.44 Hz), 8.22 (d, 1H, 41-H, J = 7.12 Hz), 8.29 (s, 1H, 5-H), 8.35 (d, 1H, 39-H, J = 7.72 Hz), 8.45 (s, 1H, 37-H), 9.10 ppm (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 32.61 (11-C), 93.17 (6-C), 116.22 (16-C), 120.23 (37-C), 120.52 (14-C), 121.52 (28-C), 121.83 (26- and 30-C), 122.57 (10-C), 124.10 (8-C), 124.30 (22-C), 124.35 (39-C), 125.72 (36-C), 126.84 (15-C), 127.32 (12-C), 127.53 (21- and 23-C), 127.74 (27- and 29-C), 129.47 (20- and 24-C), 130.76 (40-C), 131.22 (17-C), 132.64 (25-C), 133.44 (41-C), 136.46 (5-C), 137.34 (19-C), 141.92 (13-C), 142.46 (7-C), 146.21 (9-C), 148.38 (38-C), 160.62 (4-C), 162.77 (2-C), 164.05 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{21}Cl_2IN_6O_4$ (787.39): C, 53.39; H, 2.69; N, 10.67. Found: C, 53.47; H, 2.63; N, 10.61.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-iodo-quinazolin-4(3H)one (7q).*** This compound was obtained as light brownish solid, yield 70%, mp 254–257°C; IR (KBr): NH 3440, $CH_2$ 2918, 2846, CO 1684, CN 1656, 1613, $NO_2$ 1535, 1348, COC 1278, 1025, CCl 750, CI 618 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ 3.54 (s, 2H, $CH_2$), 6.42 (d, 1H, 14-H, J = 8 Hz), 6.89 (t, 1H, 16-H, J = 7.44 Hz), 7.04–7.10 (m, 2H, 15- and 22-H), 7.22 (d, 1H, 17-H, J = 7.6 Hz), 7.29 (d, 1H, 8-H, J = 8.36 Hz), 7.41 (d, 2H, 21- and 23-H, J = 8.12 Hz), 7.47 (d, 2H, 26- and 30-H, J = 8.36 Hz), 7.56 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.95 (d, 1H, 7-H, J = 8.36 Hz), 8.06 (d, 2H, 37- and 41-H, J = 8.72 Hz), 8.31 (s, 1H, 5-H), 8.35 (d, 2H, 38- and 40-H, J = 8.72 Hz), 9.12 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.51 (11-C), 93.25 (6-C), 116.15 (16-C), 120.47 (14-C), 121.60 (28-C), 121.87 (26- and 30-C), 122.50 (10-C), 124.16 (8-C), 124.22 (22-C), 124.61 (38- and 40-C), 126.78 (15-C), 127.23 (37- and 41-C), 127.26 (12-C), 127.45 (21- and 23-C), 127.82 (27- and 29-C), 129.42 (20- and 24-C), 131.12 (17-C), 131.28 (36-C), 132.68 (25-C), 136.34 (5-C), 137.25 (19-C), 141.84 (13-C), 142.39 (7-C), 146.15 (9-C), 148.24 (39-C), 160.72 (4-C), 162.85 (2-C), 164.30 ppm (32- and 35-C). *Anal*. Calcd. for $C_{35}H_{21}Cl_2IN_6O_4$ (787.39): C, 53.39; H, 2.69; N, 10.67. Found: C, 53.52; H, 2.61; N, 10.63.

***2-[2-(2,6-Dichlorophenyl)amino]benzyl-3-{4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] phenyl}-6-iodo-quinazolin-4(3H)one (7r).*** This compound was obtained as light orange solid, yield 68%, mp 276–278°C; IR (KBr): NH 3453, $CH_2$ 2925, 2850, CO 1676, CN 1651, 1609, COC 1258, 1074, CCl 746, CI 618 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 3.52 (s, 2H, $CH_2$), 3.58 (s, 3H, $OCH_3$), 6.39 (d, 1H, 14-H, J = 7.96 Hz), 6.78 (d, 2H, 38- and 40-H, J = 8.68 Hz), 6.88 (t, 1H, 16-H, J = 7.36 Hz), 7.04–7.09 (m, 2H, 15- and 22-H), 7.20 (d, 1H, 17-H, J = 7.52 Hz), 7.26 (d, 1H, 8-H, J = 8.4 Hz), 7.39 (d, 2H, 21- and 23-H, J = 8.08 Hz), 7.44–7.49 (m, 4H, 26-, 30-, 37- and 41-H), 7.54 (d, 2H, 27- and 29-H, J = 8.36 Hz), 7.97 (d, 1H, 7-H, J = 8.4 Hz), 8.28 (s, 1H, 5-H), 9.10 ppm (br s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): δ 32.43 (11-C), 55.22 ($OCH_3$), 93.21 (6-C), 114.32 (38- and 40-C), 116.13 (16-C), 116.92 (36-C), 120.42 (14-C), 121.58 (28-C), 121.87 (26- and 30-C), 122.56 (10-C), 124.17 (8-C), 124.33 (22-C), 126.63 (37- and 41-C), 126.82 (15-C), 127.21 (12-C), 127.48 (21- and 23-C), 127.69 (27- and 29-C), 129.42 (20- and 24-C), 131.14 (17-C), 132.57 (25-C), 136.39

(5-C), 137.28 (19-C), 141.83 (13-C), 142.44 (7-C), 146.12 (9-C), 160.54 (39-C), 160.67 (4-C), 162.74 (2-C), 163.77 ppm (32- and 35-C). *Anal*. Calcd. for $C_{36}H_{24}Cl_2IN_5O_3$ (772.42): C, 55.98; H, 3.13; N, 9.07. Found: C, 55.89; H, 3.07; N, 9.14.

**General procedure for *in vitro* antimicrobial screening.** The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan [36]. Antibacterial activity was screened against two gram-positive bacteria (*S. aureus* MTCC 96, *S. pyogenes* MTCC 443) and two gram-negative bacteria (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441). Ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323. Greseofulvin was used as a standard antifungal agent.

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjust to $10^8$ CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was sub cultured and incubated overnight at 37°C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 μg/mL concentration, as a stock solution. In primary screening 500, 250, and 125 μg/mL concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125, and 1.5625 μg/mL concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC.

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## REFERENCES AND NOTES

[1] Zheng, X.; Li, Z.; Wang, Y.; Chen, W.; Huang, Q.; Liu, C.; Song, G. J Fluorine Chem 2003, 123, 163.

[2] Chavan, V. P.; Sonawane, S. A.; Shingare, M. S.; Karale, B. K. Chem Heterocycl Compd 2006, 42, 625.

[3] Khiati, Z; Othman, A. A.; Guessas, B. South African J Chem 2007, 60, 20.

[4] George, S.; Parameswaran, M. K.; Chakraborty, A. R.; Ravi, T. K. Acta Pharm 2008, 58, 119.

[5] Narayana, B.; Raj, K. K. V.; Ashalatha, B. V.; Kumari, N. S. Arch Pharm 2005, 338, 373.

[6] Sharma, S.; Srivastava, V. K.; Kumar A. Eur J Med Chem 2002, 37, 689.

[7] Zareef, M.; Iqbal, R.; Dominguez, N. G.; Rodrigues, J.; Zaidi, J. H.; Arfan, M.; Supuran, C. T. J Enz Inhib Med Chem 2007, 22, 301.

[8] Hashem, A. I.; Youssef, A. S. A.; Kandeel, K. A.; Abou-Elmagd, W. S. I. Eur J Med Chem 2007, 42, 934.

[9] El-Essawy, F. A.; Khattab, A. F.; Abdel-Rahman, A. A. H. Monatsh Chem 2007, 138, 777.

[10] Amr, A. E. E.; Mohamed, S. F.; Abdel-Hafez, N. A.; Abdalla, M. M. Monatsh Chem 2008, 139, 1491.

[11] Wagner, E.; Al-Kadasi, K.; Zimecki, M.; Dobrowolska, W. S. Eur J Med Chem 2008, 43, 2498.

[12] Zareef, M.; Iqbal, R.; Al-Masoudi, N. A.; Zaidi, J. H.; Arfan, M.; Shahzad, S. A. Phosphorus Sulfur Silicon 2007, 182, 281.

[13] Yar, M. S.; Siddiqui, A. A.; Ali, M. A. J Chin Chem Soc 2007, 54, 5.

[14] Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. Bioorg Med Chem Lett 2004, 14, 6057.

[15] El-Sayed, R.; Wasfy, A. F. J Chin Chem Soc 2005, 52, 129.

[16] Habib, N. S.; Khali, M. A. J Pharm Sci 1984, 73, 982.

[17] Alafeefy, A. M.; Kadi, A. A.; El-Azab, A. S.; Abdel-Hamide, S. G.; Daba, M. Y. Arch Pharm 2008, 341, 377.

[18] Fathalla, O. A. M.; Kassem, E. M. M.; Ibrahem, N. M.; Kamel, M. M. Acta Pol Pharm 2008, 65, 11.

[19] Shukla, J. S.; Agarwal, K.; Rastogi, R. Arch Pharm 1983, 316, 525.

[20] Cao, S.; Feng, Y.; Jiang, Y.; Liu, S.; Ding, G.; Li, R. Bioorg Med Chem Lett 2005, 15, 1915.

[21] Archana; Srivastava, V. K.; Kumar, A. Eur J Med Chem 2002, 37, 873.

[22] Alagarsamy, V.; Prabakaran, L.; Murugan, R. D.; Gurumurth, G.; Bindu, P.; Arunkumar, M.; Bothiraja, C. Acta Pharm Turcica 2000, XLII, 33.

[23] Alagarsamy, V.; Murugesan, S.; Dhanabal, K.; Murugan, M.; Clercq, E. Indian J Pharm Sci 2007, 69, 304.

[24] Raffa, D.; Daidone, G.; Maggio, B.; Schillaci, D.; Plescia, F. Arch Pharm 1999, 332, 317.

[25] Raghavendra, N. M.; Thampi, P.; Gurubasavarajaswamy, P. M.; Sriram, D. Arch Pharm 2007, 340, 635.

[26] Selvam, P.; Babu, K.; Padamraj, R.; Persoons, L.; Clercq, E. African J Pharm Pharmacol 2008, 2, 110.

[27] Jatav, V.; Mishra, P.; Kashaw, S.; Stables, J. P. Eur J Med Chem 2008, 43, 135.

[28] Gursoy, A.; Karali, N. Eur J Med Chem 2003, 38, 633.

[29] Maarouf, A. R.; El-Bendary, E. R.; Goda, F. E. Arch Pharm 2004, 337, 527.

[30] Kurogi, Y.; Inoue, Y.; Tsutsumi, K.; Nakamura, S.; Nagao, K.; Yoshitsugu, H.; Tsuda, Y. J Med Chem 1996, 39, 1433.

[31] Gao, X.; Cai, X.; Yan, K.; Song, B.; Gao, L.; Chen, Z. Molecules 2007, 12, 2621.

[32] Ameta, U.; Ojha, S.; Bhambi, D.; Talesara, G. L. Arkivoc 2006, xiii, 83.

[33] Furniss B. S.; Hannaford A. J.; Smith, P. W. G.; Tatchell, A. R. In Vogel's Textbook of Practical Organic Chemistry; 5th ed.; John Wiley & Sons: New York, 1989; p 692.

[34] Frank, P. V.; Girish, K. S.; Kalluraya, B. J Chem Sci 2007, 119, 41.

[35] Laddha, S. S.; Wadodkar, S. G.; Meghal, S. K. Arkivoc 2006, xi, 1.

[36] Rattan, A. In Antimicrobials in Laboratory Medicine; Churchill B.I.; Livingstone: New Delhi, 2000; p 85.

# Preparation of 2,4,5-Triarylimidazol-4-ols and Their Stereoselective Rearrangement by 1,5-Phenyl Migration



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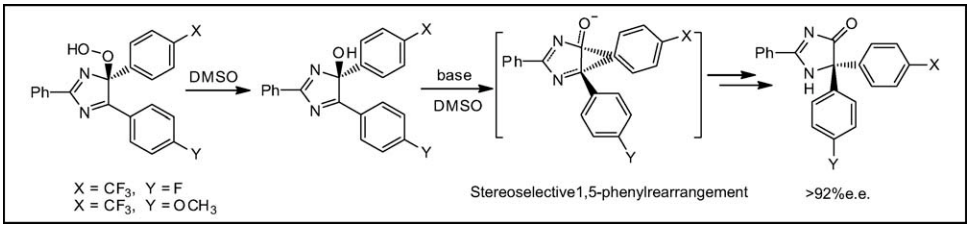


Lophine hydroperoxides underwent base-triggered 1,5-phenyl migration in DMSO to afford imidazolones in high yields, instead of amidines with chemiluminescence (CL). The corresponding imidazolols were believed to intermediates and they were successfully obtained by treating the peroxides with DMSO without the base. The diminished CL was because of the reduction of the hydroperoxides with DMSO. The imidazolols subsequently underwent smooth base-mediated rearrangement to afford imidazolones. Furthermore, the chiral imidazolols provided stereoselective imidazolones in high enantiomeric excess (>92%), which supported the mechanism of an intramolecular ring for the migration.

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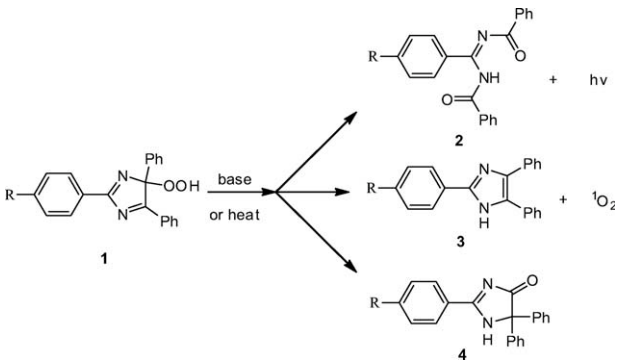
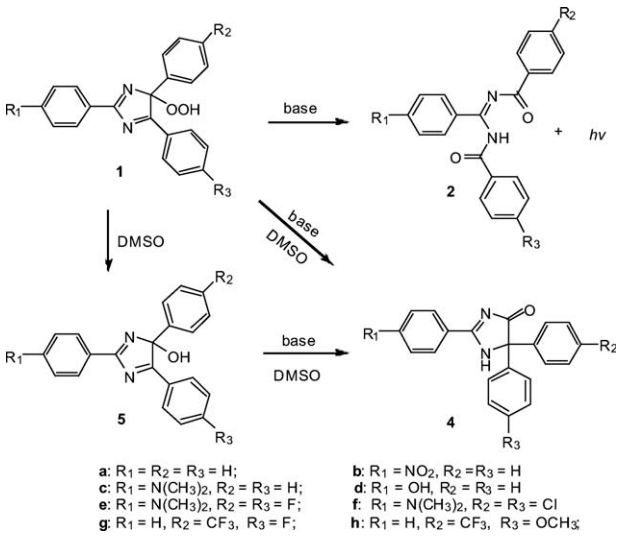
## INTRODUCTION

The chemiluminescent reactions of lophine hydroperoxides (**1**) have attracted considerable attention for many decades [1,2]. Many studies have been reported [3] and these studies mainly focused on the chemiluminescence (CL) efficiency. The other reactions occurring in this chemiluminescent process are still not clear. Recently, we reported that **1** underwent three different but simultaneous reactions upon treatment with a base to yield the corresponding amidines (**2**) accompanied with CL, imidazoles (**3**) with singlet oxygen, and a trace of imidazolones (**4**) (Scheme 1) [4]. However, the CL of peroxides **1** can be observed by base-triggered reactions in typical solvents, but not in DMSO. It is well known that a CL system like dioxetane can provide the most efficient CL in DMSO [5]. We first believed that a polar aprotic solvent like DMSO should enhance the CL efficiency of lophine peroxides. However, the CL efficiency of hydroperoxides **1** in was so low that it could not be detected. The results were quite unexpected, and therefore, they attracted our attention. The subsequent investigation showed that hydroperoxides **1** underwent an exclusive 1,5-phenyl migration in DMSO to afford imidazolones **4** in high yields via imidazolols (**5**) as intermediates (Scheme 2) [6]. Further investigation showed that these imidazolols **5** could be easily obtained under milder conditions, when treated with DMSO without the trigger base [6b]. In addition, these imidazolols **5** subsequently underwent base-mediated rearrangement to afford imidazolones in high yields.

**Scheme 1**



**Scheme 2**




Although imidazolol has been long proposed as one of the intermediate byproducts in the CL reaction of lophine, it has not been obtained thus far because it is unstable under basic reaction conditions [1b]. The present research provides an easy method to obtain these intermediates, and this should help in completely understanding the reactions occurring in the CL reaction of lophine peroxides. In addition, the sigmatropic migration of an aryl group is known for 1,2,3,4,5-pentaphenylcyclo-pentadienol [7], which is a π-conjugated analogue of **5**; however, its stereochemistry has not yet been investigated. In a previous investigation, [6a] the 1,5-phenyl rearrangement of silyl-protected hydroperoxides was reported. However, the stereospecificities were low under thermal conditions and the enantiomeric excesses (EEs) were less than 60%; these factors made it difficult to understand the stereochemistry. In the previous study, we first believed that the low stereospecificities resulted from the racemization of imidazolones through a ring opening/closing sequence, and therefore, a control experiment was carried out with imidazolone; however, it was found that it did not racemize. Therefore, we believed that the alkoxide racemized through a ring opening/closing sequence under strong thermal conditions that lowered the stereochemical specificities. In this study, the absence of strong thermal activation prevents ring opening from occurring, as a result of which imidazolols can serve as a good system for the study of 1,5-phenyl migration.

Furthermore, it should be noted that many natural compounds include imidazolol and/or imidazolone moieties [8]. In this article, we report the preparation and the stereoselective 1,5-phenyl rearrangement of imidazolols. We expect that imidazolols will find numerous applications in the synthesis of natural compounds.

## RESULTS AND DISCUSSION

The reaction of the peroxides **1** proceeded smoothly proceeded to afford imidazolols in good yields in DMSO at room temperature (entries 1–8, Table 1). The reaction completed within 4–6 h. Aromatic substituents containing electron-donating as well as electron-withdrawing groups underwent the elimination of oxygen facilely. In the case of unstable **1c**, which is difficult to isolate, [2] **5c** was consequently prepared by treating the mixture by the photooxidation of the corresponding imidazole with DMSO. In the cases of **1g**, **h**, the mixtures with their isomers (**1′g**, **h**) were used to afford mixtures of **5g**, **h** with their isomers (**5′g**, **h**), as shown in Scheme 3.

On treatment with the base, the imidazolols **5** were smoothly converted into the imidazolones **4** via phenyl migration from C4 to C5 within 3 h in good yields in DMSO at room temperature (Table 1). From the Woodward–Hoffmann rules, the phenyl migration is recognized as a thermally allowed 1,5-sigmatropic migration.

To elucidate the stereochemistry of the migration, imidazolols **5g**, **h** were successfully isolated from their mixtures with their isomers **5′g**, **h** by crystallization from 2-propanol, respectively. The chiral imidazolols (**5g** and **h**) were isolated using a chiral HPLC column. To determine the absolute configurations, the circular dichroism (CD) spectra were recorded, and the calculated CD spectra were processed using Gaussian 03w software package [6a,9]. The absolute configurations were assigned by comparing the experimental CD spectra with the calculated ones (for details, see Experimental section). When the chiral imidazolols (**5g** and **h**)

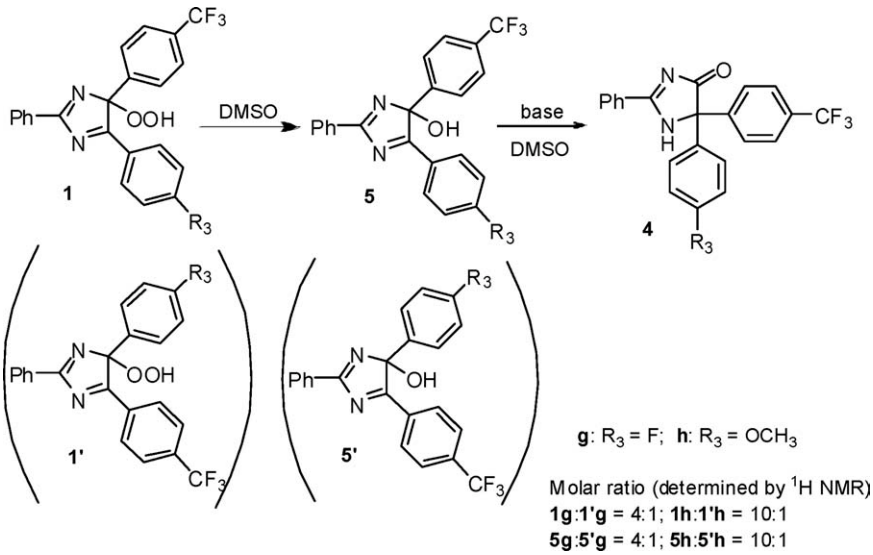
**Table 1**

Preparation of imidazolols and imidazolones.

| Entry | Reactants | Product[a] | Yield (%)[b] |
|---|---|---|---|
| 1 | **1a** | **5a** | 77 |
| 2 | **1b** | **5b** | 87 |
| 3 | **1c** | **5c** | 64 |
| 4 | **1d** | **5d** | 76 |
| 5 | **1e** | **5e** | 70 |
| 6 | **1f** | **5f** | 72 |
| 7 | **1g**[c] | **5g**[c] | 78 |
| 8 | **1h**[c] | **5h**[c] | 82 |
| 9 | **5a** | **4a** | 78 |
| 10 | **5b** | **4b** | 85 |
| 11 | **5c** | **4c** | 68 |
| 12 | **5d** | **4d** | 73 |
| 13 | **5e** | **4e** | 70 |
| 14 | **5f** | **4f** | 76 |
| 15 | **5g**[c] | **4g** | 79 |
| 16 | **5h**[c] | **4h** | 74 |

[a] The structure of products were determined from spectral data ($^1$H NMR, MS, and E.A.).
[b] Isolated yields after column chromatography.
[c] Mixture with its isomer.

**Scheme 3**




were subjected to phenyl migration under the action of the base (Scheme 4), the corresponding imidazolones **4g** and **h** were exclusively obtained in >92% EE in DMSO (Table 2). When compared with the previous study in which silyl-protected peroxides under thermal condition were used, the stereoselectivities were largely increased. The reaction mechanism was confirmed to be stereoselective 1,5-phenyl migration via an intramolecular ring (Scheme 5).

In conclusion, we have demonstrated that an imidazolol derivative can easily be prepared in good yield from the corresponding peroxide. The imidazolol can be smoothly converted to an imidazolone via a stereoselective phenyl migration from C4 to C5 under the action of a base.

## EXPERIMENTAL

**General procedure.** All melting points were measured using a Yanagimoto micro melting point apparatus. The IR spectra were recorded by a JASCO FT/IR-5000 spectrophotometer. The UV-vis spectra were measured by a JASCO V-530 spectro-photometer. The $^{1}H$ and $^{13}C$ NMR spectra were recorded using a Varian MERCURY (FT, 300 MHz) spectrometer or a Varian VXR-500 (FT, 500 MHz) spectrometer. Elemental analyses were performed by a Perkin Elmer CHNS/O

**Scheme 4**

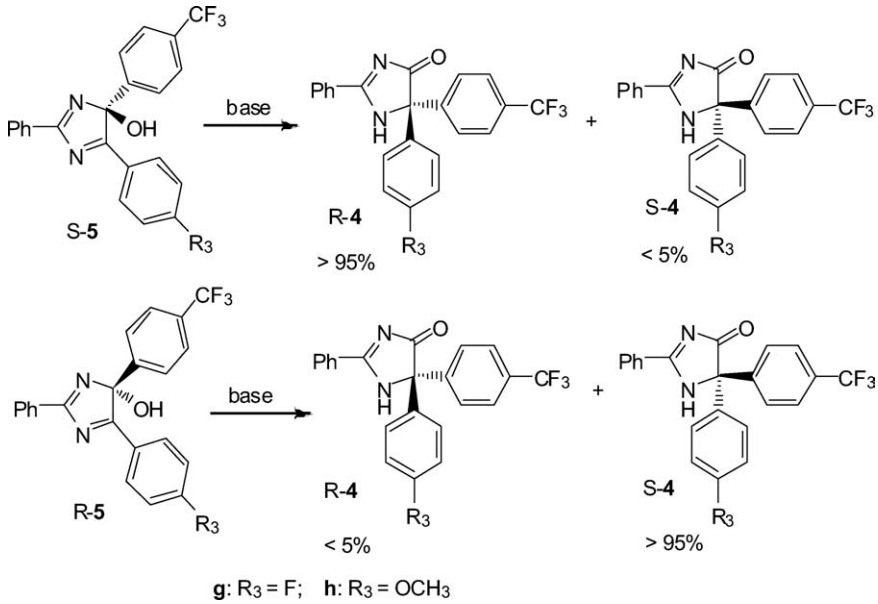


**Table 2**

The analyses of the enantiomeric excess.

| Entry | Imidazolols | Products[a,b] | | |
|---|---|---|---|---|
| | | R-4 | S-4 | EE (%) |
| 1 | **R-5g** | 2 | 98 | 96 |
| 2 | **S-5g** | 97 | 3 | 94 |
| 3 | **R-5h** | 3 | 97 | 94 |
| 4 | **S-5h** | 96 | 4 | 92 |

[a] Yields calculated on the base of HPLC integral quantity.
[b] The conversion was estimated to be 100% because of no other peak appearing on the $^1$H NMR spectra.

Analyzer 2400. The fast atom bombardment (FAB) mass spectra were recorded by a Micromass 70-SE. 2,4,5-Triarylphenyl-1*H*-imidazoles were prepared by the method of Davidson *et al*. [6,8a]. 4-Hydroperoxy-2,4,5-triphenyl-4*H*-imidazoles were prepared by the method of White and Harding [2]. HPLC analyses were performed on a Hitachi 655 liquid chromatography and recorded on a Hitachi 561 recorder; Column for EE and optical resolution was Daicel Chiralpak AD-H: 4.6 mm × 250 mm. CD spectra were recorded on a JASCO J-820 spectropolarimeter.

**Preparation of imidazolols.** A solution of hydroperoxides **1** (0.2 mmol) in DMSO (5 mL) was stirred for 4–6 h at room temperature. After the reaction, the solution was poured into water, and the crude product **5** was obtained by filtration. The crude product was purified by chromatography (silica, hexane:AcOEt = 10 ∼ 8:1).

***2,4,5-Triphenyl-4-hydroxy-4H-isoimidazole (5a).*** mp 128–130°C; IR (KBr) 1613 (C=N) cm$^{-1}$, $^1$H NMR (500 MHz, $CDCl_3$) δ 7.16–7.22 (m, 3H), 7.34 (dd, *J* = 7.5, 5.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 8.16 (d, *J* = 7.5 Hz, 2H), 8.41 (d, *J* = 7.5 Hz, 2H), 6.49 (br s, 1H); $^{13}$C NMR (300 MHz, $CDCl_3$) δ 107.66 (s), 124.9 (d), 128.3 (d), 128.6 (d), 128.7 (d), 128.8 (d), 129.8 (d), 130.2 (d), 130.6 (d), 130.9 (s), 132.5 (d), 133.0 (d), 137.6 (s), 172.5 (s), 194.3 (s); UV-vis $\lambda_{max}$ (EtOH) 281 (log ε 4.31) nm; MS (FAB) *m*/*z* 313 ($M^+$+1); E.A. Calcd for $C_{21}H_{16}N_2O$: C, C, 80.75; H, 5.16; N, 8.97. Found: C, 80.70; H, 5.14; N, 8.96.

***2-(p-Nitrophenyl)-4-hydroxy-4,5-diphenyl-4H-isoimidazole (5b.)*** Pale yellow powder, mp 168–169°C; IR (KBr) 1633 (C=N), 1524 ($NO_2$), 1350 ($NO_2$) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33–7.38 (m, 3H), 7,43 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.56 (t, *J* = 8.1 Hz, 2H), 7.66 (t, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 2H), 8.19 (d, *J* = 9.2 Hz, 2H), 8.36 (d, *J* = 8.1 Hz, 2H), 6.94 (s, 1H); MS (FAB) *m*/*z* 358 ($M^+$+1); E.A. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.53; H, 4.30; N, 11.73%.

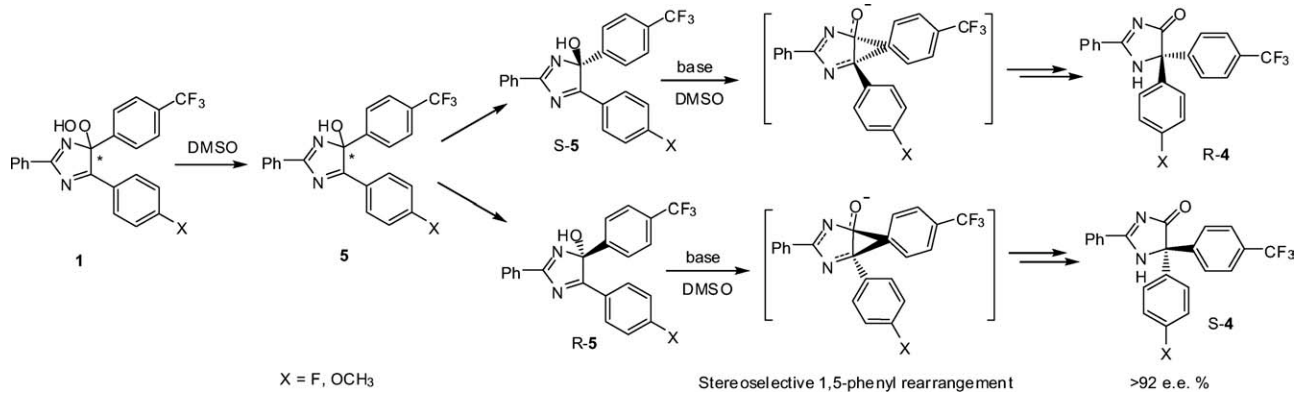
***2-(p-Dimethylaminophenyl)-4-hydroxy-4,5-diphenyl-4H-isoimidazole (5c).*** Orange powder, mp 126–128°C; IR (KBr) 1603 (C=N) cm$^{-1}$; $^1$H NMR (500 MHz $CDCl_3$) δ 3.00 (s, 6H), 6.44 (d, *J* = 7.5 Hz, 2H), 7.26–7.31 (m, 3H), 7.47 (dd, *J* = 7.0, 7.53 Hz, 2H), 7.48–7.51 (m, 2H), 7.53 (d, *J* = 7.53 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 8.35 (d, *J* = 7.0 Hz, 2H), 6.32 (br s, 1H); MS (FAB) *m*/*z* 356 ($M^+$+1); E.A. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.77; H, 5.98; N, 11.81.

***2-(p-Hydroxyphenyl)-4-hydroxy-4,5-diphenyl-4H-isoimidazole (5d).*** Yellow powder; mp 103–105°C (dec.); IR (KBr) 3326 (O—H), 1607 (C=N) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.00–7.03 (m, 2H), 7.30–7.34 (m, 5H), 7.41–7.51 (m, 3H), 7.59 (d, *J* = 7.5 Hz,2H), 8.29 (d, *J* = 7.5 Hz, 2H). MS (FAB) *m*/*z* 329 ($M+H^+$). E.A. Calcd for $C_{21}H_{16}N_2O_2 \cdot 1/2H_2O$: C, 74.76; H, 5.08; N, 8.30. Found: C, 74.69; H, 5.02; N, 8.81.

***2-(p-Dimethylaminophenyl)-4-hydroxy-4,5-bis(p-fluorophenyl)4H-isoimidazole (5e).*** Orange powder; mp 138–140°C (dec.); IR (KBr) 1603 (C=N) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 3.04 (s, 6H), 6.64 (d, *J* = 8.9 Hz, 2H), 6.97 (t, *J* = 8.8 Hz, 2H), 7.15 (t, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.8, 2H), 7.98 (d, *J* = 8.9 Hz, 2H), 8.35 (d, *J* = 9.0 Hz, 2H), 6.52 (br s, 1H); E.A. Calcd for $C_{23}H_{19}F_2N_3O$: C, 67.81; H, 4.70; N, 10.31. Found: C, 67.78; H, 4.76; N, 10.31.

***2-(p-Dimethylaminophenyl)-4-hydroxy-4,5-bis(p-chlorophenyl)4H-isoimidazole (5f).*** Orange powder; mp 142–144°C (dec.); IR (KBr) 1601 (C=N) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 3.02 (s, 6H), 6.65 (d, *J* = 8.9 Hz, 2H), 6.90 (t, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 8.8, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 8.25 (d, *J* = 9.0 Hz, 2H), 6.49 (br s,

**Scheme 5**



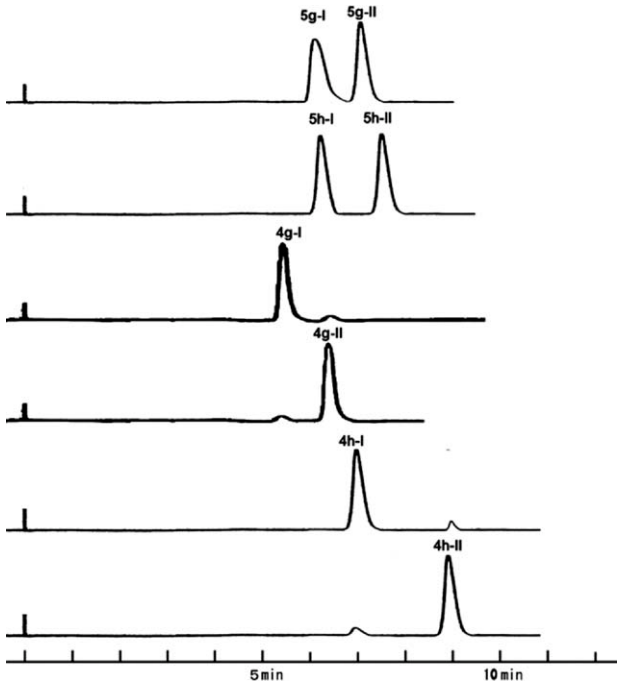



**Figure 1.** HPLC charts for the resolution.

1H); E.A. Calcd for $C_{23}H_{19}F_2N_3O$: C, 67.81; H, 4.70; N, 10.31. Found: C, 67.35; H, 4.66; N, 10.12.

***Mixture of 2-phenyl-4-hydroxy-4-(p-trifluoromethyl-phenyl)-5-(p-fluorophenyl)-4H-isoimidazole (5g) and 2-phenyl-4-hydroxy-4-(p-fluorophenyl)-5-(p-trifluoromethyl-phenyl)-4H-isoimidazole (5′g).*** Molar ratio = 4:1, determined by $^1$H NMR. Colorless powder; mp 136–139°C; IR (KBr) 1603 (C=N), 1325 ($CF_3$), 1272 (C—F) $cm^{-1}$; UV-vis $\lambda_{max}$ ($CH_2Cl_2$) 281 (4.28) nm. MS (FAB) *m/z* 399 ($M^+$+1); E.A. Calcd for $C_{22}H_{14}F_4N_2O{\cdot}1/2H_2O$: C, 64.87; H, 3.71; N, 6.88;. Found: C, 64.83; H, 3.75; N, 6.88%. **5g:** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.18–7.28 (m, 4H), 7.38–7.44 (m, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 7.5 Hz, 2H), 8.33 (dd, *J* = 8.5, 5.5 Hz, 2H); **5′g**: $^1$H NMR (500 MHz, $CDCl_3$) 7.03 (t, *J* = 8.5 Hz, 2H), 7.18–7.27 (m, 2H), 7.37–7.44 (m, 3H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 7.5 Hz, 2H), 8.46 (d, *J* = 8.2 Hz, 2H).

***Mixture of 2-phenyl-4-hydroxy-4-(p-trifluoromethyl-phenyl)-5-(p-methoxyphenyl)-4H-isoimidazole (5h) and 2-phenyl-4-hydroxy-4-(p-methoxyphenyl)-5-(p-trifluoro-methylphenyl)-4H-isoimidazole (5′h).*** Molar ratio = 10:1, determined by $^1$H NMR. Pale yellow powder; mp 123–125°C; IR (KBr) 1607 (C=N), 1328 ($CF_3$), 1263, 1069 (C—O—C) $cm^{-1}$; UV-vis $\lambda_{max}$ ($CH_2Cl_2$) 308 (log ε 4.27), 318 (4.16), 347 (4.12) nm; MS (FAB) *m/z* 427 ($M^+$+1); E.A. Calcd for $C_{23}H_{17}F_3N_2O_2$: C, 67.31; H, 4.18; N, 6.83; Found: C, 67.33; H, 4.15; N, 6.85%. **5h:** $^1$H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 1H), 7.58 (d, *J* = 9.2 Hz, 2H), 7.62 (d, *J* = 9.2 Hz, 2H), 8.01 (d, *J* = 7.0 Hz, 2H), 8.28 (d, *J* = 9.0 Hz, 2H).

**Preparation of imidazolones..** 0.5 ml of TBAF/THF (1.0 N) was added to a solution of **5** (0.1 mmol) in DMSO, and the mixed solution was stirred for 3 h. Then the reaction mixture was poured into water and the product **4** was precipitated. The crude product was purified by chromatography (silica, hexane:AcOEt = 8:1).

***2,5,5-Triphenyl-1H-imidazol-4(5H)-one (4a).*** mp 222–224°C (lit.[3] 220–222°C); IR (KBr) 1721 (C=O), 1628 (C=N), 698 (Phenyl) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 4H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 4H), 7.97 (d, *J* = 7.5 Hz, 2H), 9.11 (br s, 1H); UV-vis $\lambda_{max}$ (EtOH) 255 (log ε 4.07) nm; MS (FAB) *m/z* 313 ($M^+$+1); E.A. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.47; H, 5.06; N, 8.94%.

***2-(p-Nitrophenyl)-5,5-diphenyl-1H-imidazol-4(5H)-one (4b.)*** Pale yellow powder; mp 205–206°C; IR (KBr) 1524 ($NO_2$), 1350 ($NO_2$) $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.32 (t, 2H), 7,43 (m, 4H), 7.65 (t, 4H), 8.08 (d, *J* = 9.2 Hz, 2H), 8.18 (d, *J* = 9.2 Hz, 2H), 9.40 (br s, 1H); MS (FAB) *m/z* 358 ($M^+$+1); E.A. Calcd for $C_{21}H_{15}N_3O_3$: C, 66.75; H, 4.13; N, 11.12. Found: C, 66.73; H, 4.00; N, 11.13%.

***2-(p-Dimethylaminophenyl)-5,5-diphenyl-1H-imidazol-4(5H)-one (4c).*** Orange powder, mp 86–88°C; IR (KBr) 1604 (C=N) $cm^{-1}$; $^1$H NMR (500 MHz $CDCl_3$) δ 3.04 (s, 6H), 6.45 (d, *J* = 7.5 Hz, 2H), 7.26–7.31 (m, 6H), 7.47–7.51 (m, 4H), 7.93 (d, *J* = 7.5 Hz, 2H), 9.02 (br s, 1H); MS (FAB) *m/z* 356 ($M^+$+1); E.A. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.70; H, 6.01; N, 11.80.

***2-(p-Hydroxyphenyl)-4,5-diphenyl-4H-imidazol-4(5H)-one (4d).*** Yellow powder; mp 112–114°C (dec.); IR (KBr) 3323 (O—H), 1605 (C=N) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.6 Hz, 2H), 7.25–7.31 (m, 6H), 7.45–7.50 (m, 4H), 7.98 (d, *J* = 7.6 Hz, 2H), 9.02 (br s, 1H). MS (FAB) *m/z* 329 ($M+H^+$). E.A. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.79; H, 4.92; N, 8.51.

***2-(p-Dimethylaminophenyl)-5,5-bis(p-fluorophenyl)-1H-imidazol-4(5H)-one (4e).*** Orange powder; mp 118–120°C (dec.); IR (KBr) 1605 (C=N) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 3.06 (s, 6H), 6.67 (d, *J* = 8.9 Hz, 2H), 6.97–7.15 (t, *J* = 8.8, 4H), 7.57–7.71 (t, *J* = 8.8, 4H), 7.92 (d, *J* = 8.9 Hz, 2H), 9.12 (br s, 1H); MS (FAB) *m/z* 392 ($M^+$+1); E.A. Calcd for $C_{23}H_{19}Cl_2N_3O$: C, 65.10; H, 4.51; N, 9.90. Found: C, 65.12; H, 4.46; N, 9.92.

**Table 3**

The conditions of HPLC analysis.

| | Effluent | Detector wavelength (nm) | Retention time/min I | Retention time/min II |
|---|---|---|---|---|
| **5g** | Hexane:2-PrOH 80:20 (V/V)[a] | 281 | 6.1 | 7.1 |
| **5h** | Hexane:EtOH 90:10 (V/V)[a] | 308 | 6.3 | 7.8 |
| **4g** | EtOH 100%[b] | 261 | 5.4 | 6.4 |
| **4h** | EtOH 100%[b] | 259 | 7.0 | 9.0 |

[a] Flow rate 1.0 mL/min.
[b] Flow rate 0.7 mL/min.

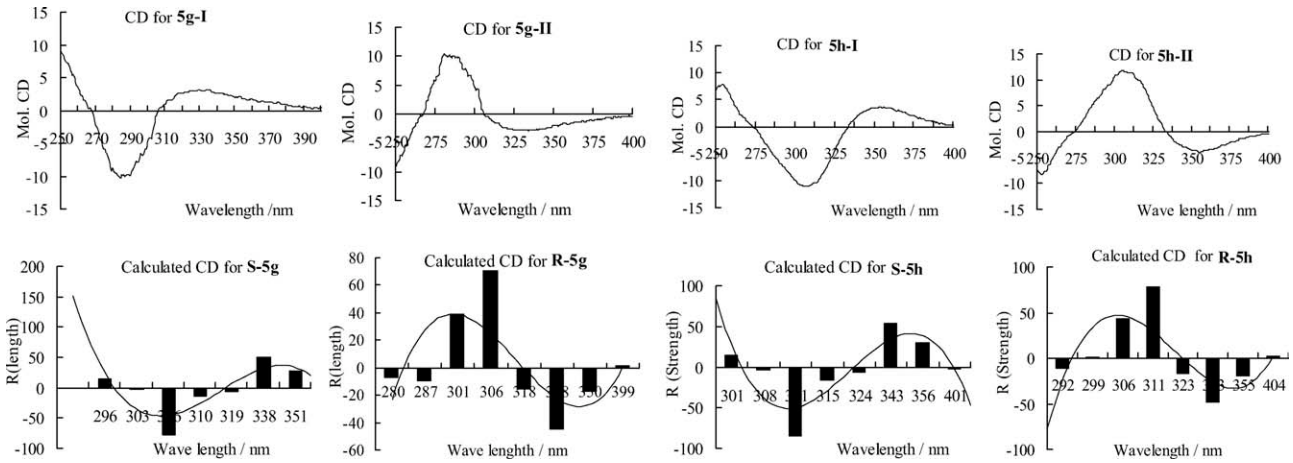



**Figure 2.** The CD spectra (above) of **5g**, **h** recorded in EtOH and the calculated CD spectra (below) of **5g**, **h** using the TDDFT-B3LYP method. Rotational strengths (*R*) are given in cgs ($10^{-40}$ erg esu cm/Gauss).

***2-(p-Dimethylaminophenyl)-5,5-bis(p-chlorophenyl)-1H-imidazol-4(5H)-one (4f).*** Orange powder; mp 122–124°C (dec.); IR (KBr) 1603 (C=N) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.03 (s, 6H), 6.65 (d, $J$ = 8.2 Hz, 2H), 6.90–7.12 (t, $J$ = 8.6 Hz, 4H), 7.61–7.86 (t, $J$ = 8.6, 4H), 7.98 (d, $J$ = 8.2 Hz, 2H), 6.09 (br s, 1H); MS (FAB) *m/z* 425 ($M^+$+1); E.A. Calcd for $C_{23}H_{19}F_2N_3O$: C, 67.81; H, 4.70; N, 10.31. Found: C, 67.35; H, 4.66; N, 10.12.

***2-Phenyl-5-(p-fluorophenyl)-5-(p-trifluoromethylphenyl)-1H-imidazol-4(5H)-one (4g).*** Colorless crystals; mp 82–88°C; IR (KBr) 1734 (C=O), 1618 (C=N), 1328 ($CF_3$) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.04 (t, $J$ = 8.8 Hz, 2H), 7.55 (t, $J$ = 7.5 Hz, 2H), 7.57–7.64 (m, 5H), 7.75 (d, $J$ = 8.0 Hz, 2H), 7.98 (d, $J$ = 7.5 Hz, 2H), 9.19 (br s, 1H);UV-vis $\lambda_{max}$ (EtOH) 214 (log ε 4.30), 231 (4.33), 259 (4.02) nm; MS (FAB) *m/z* 399 ($M^+$+1); E.A. Calcd for $C_{22}H_{14}F_4N_2O$: C, 66.33; H, 3.54; N, 7.03. Found: C, 66.40; H, 3.56; N, 6.98%.

***2-Phenyl-5-(p-methoxyphenyl)-5-(p-trifluoromethyl-phenyl)-1H-imidazol-4(5H)-one (4h).*** Colorless crystals; mp 86–90°C; IR (KBr) 1727 (C=O), 1618 (C=N), 1328 ($CF_3$), 1253, 1071 (C—O—C) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.86 (d, $J$ = 9.0 Hz, 2H), 7.48 (d, $J$ = 9.0 Hz, 2H), 7.53 (t, $J$ = 7.0 Hz, 2H), 7.58 (d, $J$ = 8.3 Hz, 2H), 7.60 (t, $J$ = 7.0 Hz, 1H), 7.75 (d, $J$ = 8.3 Hz, 2H), 8.02 (d, $J$ = 7.0 Hz, 2H); UV-vis $\lambda_{max}$ (EtOH) 214 (log ε 4.33), 232 (4.41) 259 4.08) nm; MS (FAB) *m/z* 411 ($M^+$+1); E.A. Calcd for $C_{23}H_{17}F_3N_2O_2$: C, 67.31; H, 4.18; N, 6.83; Found: C, 67.40; H, 4.16; N, 6.88%

**HPLC analysis.** The resolution of the racemic imidazolols **5** and the analysis of the EE were carried out using a chiral HPLC column and a HITACHI 561 recorder, as shown in Figure 1. The conditions are summarized in Table 3.

**Assignment of absolute configuration by comparison of experimental and calculated CD spectra.** To determine the absolute configuration, the CD spectra were recorded and calculated using the Gaussian 03w software package, [9] as shown in Figures 2 and 3. A geometry optimization was performed using the B3LYP functional with 6-31G* basis sets. The absolute configurations of **5-I** and **5-II** in the HPLC spectra were assigned as **S-5** and **R-5**, respectively, as shown in

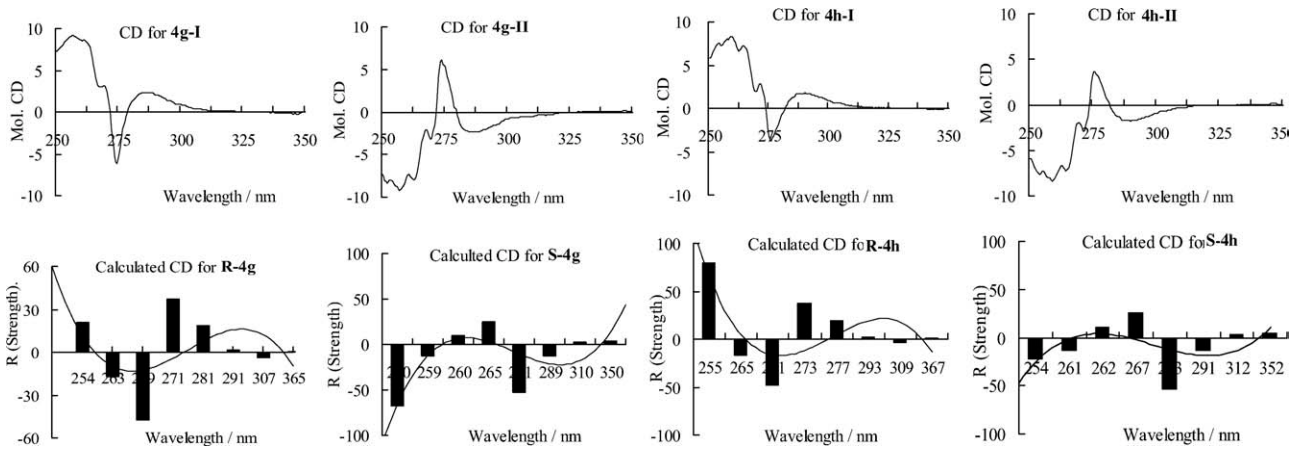



**Figure 3.** The CD spectra (above) of **4g**, **h** recorded in EtOH and the calculated CD spectra (below) of **4g**, **h** using the TDDFT-B3LYP method. Rotational strengths (*R*) are given in cgs ($10^{-40}$ erg esu cm/Gauss).

Figure 2. In the same manner, the absolute configurations of products **4-I** (HPLC: first fraction) and **4-II** (HPLC: second fraction) were also assigned to **R-4** and **S-4**, respectively, as shown in Figure 3.

## REFERENCES AND NOTES

[1] (a) Radziszewski, B. Chem Ber 1877, 10, 70; (b) Dufraisse, C.; Etienne, A.; Martel, J. Comp Rend 1957, 244, 970.

[2] (a) White, E. H.; Harding, M. J. C. J Am Chem Soc 1964, 86, 5686; (b) White, E. H.; Harding, M. J. C. Photochem Photobiol 1965, 4, 1129.

[3] (a) Kimura, M.; Nishikawa, H.; Kura, H.; Lim, H.; White, E. H. Chem Lett 1993, 505; (b) Kimura, M.; Morioka, M.; Tsunenaga, M.; Hu, Z. Z. ITE Lett 2000, 1, 418; (c) Hu, Z. Z.; Takami, S.; Kimura, M.; Tachi, Y.; Naruta, Y. Acta Cryst 2000, C56, e465.

[4] Kimura, M.; Lu, G. H.; Nishigawa, H.; Zhang, Z. Q.; Hu, Z. Z. Luminescence 2007, 22, 72.

[5] (a) Schaap, A. P.; Chen, T. S.; Handley, R. S.; DeSilva, R.; Giri, B. P. Tetrahedron Lett 1987, 28, 1155; (b) McCapra, F. J. Photochem Photobiol A: Chem. 1990, 15, 21; (c) Watanabe, N.; Nagashima, Y.; Yamazaki, T.; Matsumoto, M. Tetrahedron 2003, 59, 4811; (d) Matsumoto, M.; Sakuma, T.; Watanabe, N. Tetrahedron Lett 2002, 43, 8955.

[6] (a) Kimura, M.; Lu, G. H.; Iga, H.; Tsunenaga, M.; Zhang, Z. Q.; Hu, Z. Z. Tetrahedron Lett 2007, 48, 3109; (b) Kimura, M.; Lu, G. H.; Tsunenaga, M. ITE Lett Batter New Technol Med 2007, 8, 57.

[7] (a) Allen, C. F. H.; VanAllan, J. A. J Am Chem Soc 1943, 65, 1384; (b) Breslow, R.; Chang, H. W.; J Am Chem Soc 1961, 83, 3727; (c) Youssef, A. F.; Ogliaruso, M. J Org Chem 1972, 37, 2601.

[8] (a) Davidson, D.; Weiss, M.; Jelling, M. J Org Chem 1937, 2, 319; (b) Lee, S. H.; Yoshida, K.; Matsushita, H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. J Org Chem 2004, 69, 8829; (c) Anthony, P.; Adam, D.; Luc, V. H. J Org Chem 2006, 71, 5303; (d) Lovely, C. J.; Du, H.; He, Y.; Dias. R. Org Lett 2004, 6, 735.

[9] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision B.01; Gaussian, Inc.: Pittsburgh PA, 2003.

# One-Pot Synthesis of 2,3-Dihydro-2-thioxoquinazolin-4(1*H*)-ones from Nitro-Compounds with the Aid of Tin(II) Chloride



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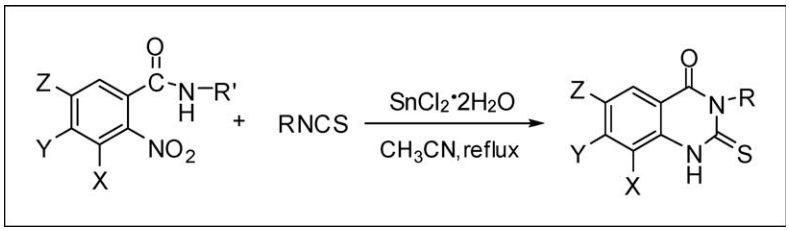


A facile synthetic method using $SnCl_2 \cdot 2H_2O$ system to promote the novel reductive cyclization of 2-nitrobenzamides and isothiocyanates is described. Sequentially, a series of 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones were synthesized in good yields.

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## INTRODUCTION

It has been reported that quinazolineones are responsible for a variety of biological responses, including applications for hypertension [1], diabetes [2], cancer [3], inflammation [4], and immunosuppression [4]. The quinazolindione moiety, in particular, is widely found in natural purine bases [5], alkaloids, intermediates in organic synthesis [6], and many biologically active compounds. For example, 6,7-dimethoxy-1*H*-quinazoline-2,4-dione is a key intermediate for the production of the following medicines (Prazosin (Minipress) [7], Bunazosin (Detantol) [8], and Doxazosin (Cardenalin [9]). 7-Chloro-1*H*-quinazoline-2,4-diones is also a key intermediate for the production of the medicines such as FK366 [10] and KF31327 [11].

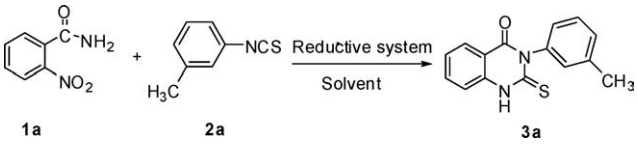
The conventional syntheses of quinazolinedione ring system are carried out by anthranilic acid with urea [12a,b], anthranilamide with phosgene [13], and anthranilic acid with potassium cyanate [14] or chlorosulfonyl isocyanate [15]. Recently, several methods have been developed for synthesizing this heterocyclic system, for example, Mizuno and Iahino have reported the simple solvent-free synthesis of 1*H*-quinazoline-2,4-diones using supercritical carbon dioxide and catalytic amount of base [16]. Buckman and Mohan have reported the solid-phase synthesis of quinazoline-2,4-diones [17–20]. Li *et al*. reported the synthesis of 2,4(1*H*,3*H*)-quinazolinediones and 2-thioxoquinazolines [21]. Alagarsamy *et al*. reported the synthesis of 3-phenyl-2-substituted-3*H*-quinazolin-4-ones by reaction of the amino group of 2-hydrazino-3-phenyl-3*H*-quinazolin-4-one with different aldehydes and ketones [22]. Our group also have reported the synthesis of quinazolinones [23], quinazoline-2,4-diones [24], imidazo[1,2-*c*]quinazolinones [24], and 2-thioxo- quinazolinones [25,26] by the reaction of nitro-compounds with orthoformates, triphosgene, ketones, and isothiocyanates, respectively, induced by low-valent titanium reagent. However, these methods suffer from some disadvantages such as drastic conditions, unsatisfactory yields, long-reaction time, higher temperature, complex manipulation, and inaccessible starting materials. Therefore, the development of more efficient methods for preparing this kind of compounds with milder reaction conditions is highly desired.

In recent years, our interest has been focused on the usage of $SnCl_2$ reagent. We have previously reported the synthesis of 2-aryl-2*H*-indazoles [27], 1-hydroxy quinazolinones [28], imidazo[1,2-*c*]quinazoline-5(6*H*)-thione, and imidazo[1,2-*c*]quinazolin-5(6*H*)-one [29], respectively, mediated by $SnCl_2$ reagent. As our earlier works goes, herein, we will describe a new approach to synthesizing 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones by treating 2-nitrobenzamides with isothiocyanates mediated by $SnCl_2$ reagent.

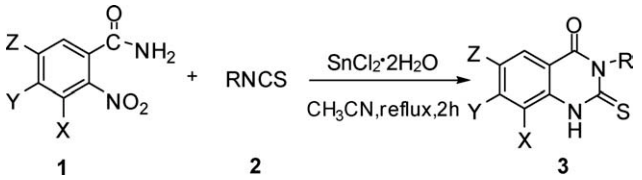
## RESULTS AND DISCUSSION

On the basis of our previous experience, we selected 2-nitrobenzamide **1a** and the 3-methylphenyl isothiocyanate **2a** as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

**Scheme 1**




**Scheme 2**




As shown in Table 1, we firstly examined the effect of different reductive systems (entries 1–4), and concluded that $SnCl_2{\cdot}2H_2O$ was the best. Then, we also briefly examined the effect of different temperatures, different solvents, and ratio of **1a**:$SnCl_2{\cdot}2H_2O$. The results showed that at refluxing temperature the reaction preceded smoothly in high yield. To further evaluate the influence of the ratio of **1a**:$SnCl_2{\cdot}2H_2O$, the reaction was carried out in acetonitrile using a 1:1 to 1:5 ratio of **1a**:$SnCl_2{\cdot}2H_2O$ (Table 1, entries 8, 9, 10, 1, 11), leading to **3a** in 26%, 33%, 60%, 75%, and 72% yields, respectively. We concluded the best ratio of **1a**:$SnCl_2{\cdot}2H_2O$ was 1:4. Moreover, different organic solvents were further investigated as shown in Table 1; we concluded that acetonitrile was the best solvent for this reaction.

With the optimized conditions in hand, we then performed the reaction of a variety of 2-nitrobenzamides **1** and isothiocyanates **2** *via* tin(II) chloride systerm (Scheme 2, Table 2).

As shown in Table 2, it can be seen that this protocol can be applied not only to the aryl isothiocyanates with electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups) but also to aliphatic isothiocyanates under the same conditions, which highlighted the wide scope of this reaction. Furthermore, it was particularly noteworthy that the effects of substituted *o*-nitrobenzamides were also investigated. 3-Methyl and 4-chloro substitution can also give moderate to good yields.

Moreover, we also studied the reaction of a variety of *N*-substitued-*o*-nitrobenzamides **4** and isothiocyanates **2** under optimized conditions. The desired products **3** were obtained in good yields (Scheme 3, Table 3).

Similarly, *N*-substitued-o-nitrobenzamides containing electron-donating and electron-withdrawing substituents were reacted well with aryl isothiocyanates and aliphatic isothiocyanates; therefore, we can conclude that the electronic nature of the substituents has no significant effect on this reaction. Meanwhile, it was found that *o*-nitrobenzamides showed better reactivity trends than *N*-substituted-*o*-nitrobenzamides.

A plausible mechanistic pathway to products **3** is illustrated in Scheme 4, although the details are still unclear. In the initial step, **1** or **4** are reduced by tin (II) chloride to **A**. The amine compounds **A** then reacted with isothiocyanates to give intermediate **B**. Intermediate **C** was formed by attack of the amino group onto the the central carbon atom of the carbonyl. Finally, products **3** were obtained by eliminating of an amine molecule.

For the investigation of the reaction mechanism, the intermediate of **3j** (2-amino-*N*-(4-methoxy- phenyl)benzamide) was isolated and characterized by spectroscopic methods. When the intermediate and 1-isothiocyanato-4-

**Table 1**

Optimization for the reductive cyclization reaction.

| Entry | Reductive system | Temperature (°C) | Ratio[a] | Solvent | Yield (%) |
|---|---|---|---|---|---|
| 1 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:4 | $CH_3CN$ | 75 |
| 2 | Fe/HCl | reflux | 1:4 | $CH_3CN$ | 47 |
| 3 | Zn/HOAc | reflux | 1:4 | $CH_3CN$ | 38 |
| 4 | Mg/HCl | reflux | 1:4 | $CH_3CN$ | 0 |
| 5 | $SnCl_2{\cdot}2H_2O$ | r.t | 1:4 | $CH_3CN$ | 0 |
| 6 | $SnCl_2{\cdot}2H_2O$ | 40 | 1:4 | $CH_3CN$ | 20 |
| 7 | $SnCl_2{\cdot}2H_2O$ | 60 | 1:4 | $CH_3CN$ | 45 |
| 8 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:1 | $CH_3CN$ | 26 |
| 9 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:2 | $CH_3CN$ | 33 |
| 10 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:3 | $CH_3CN$ | 60 |
| 11 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:5 | $CH_3CN$ | 72 |
| 12 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:4 | $CH_3CH_2OH$ | 0 |
| 13 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:4 | $CHCl_3$ | 56 |
| 14 | $SnCl_2{\cdot}2H_2O$ | reflux | 1:4 | DMF | 30 |

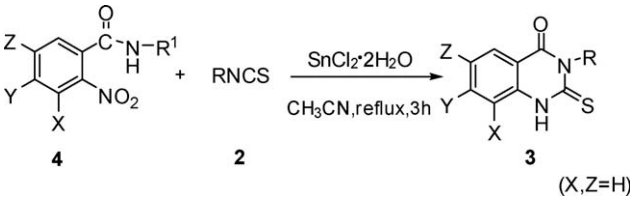
[a] Ratio of **1** and reductive agent.

**Table 2**

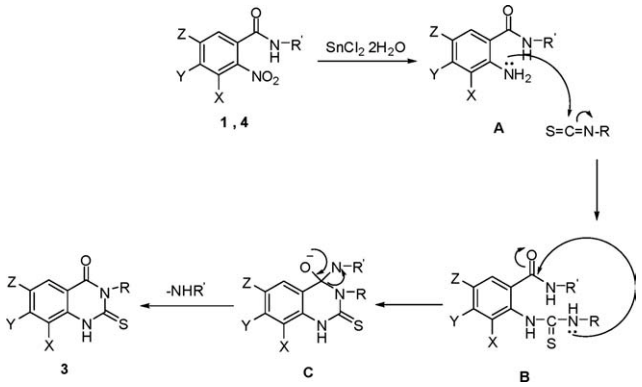
Synthesis of compounds **3** from *o*-nitrobenzamides **1** and isothiocyanates **2**.

| | X | Y | Z | R | Yield (%) |
|---|---|---|---|---|---|
| **3a** | H | H | H | 3-$CH_3C_6H_4$ | 75 |
| **3b** | H | H | H | $C_6H_5CH_2$ | 83 |
| **3c** | H | H | H | *n*-Butyl | 91 |
| **3d** | $CH_3$ | H | H | 4-$ClC_6H_4$ | 81 |
| **3e** | H | Cl | H | *n*-Butyl | 91 |
| **3f** | H | Cl | H | 4-$ClC_6H_4$ | 76 |
| **3g** | H | H | Cl | $C_6H_5$ | 87 |
| **3h** | H | H | Cl | 3-$CH_3C_6H_4$ | 83 |
| **3i** | H | H | Cl | *n*-Butyl | 80 |

**Scheme 3**




**Scheme 4**




methylbenzene **2j** were reacted under the same reaction conditions, the product **3j** was obtained in 82% yield.

The structures of products **3** were confirmed by IR and $^1$H NMR.

In summary, a series of 2,3-dihydro-2-thioxo-quinazolin-4(1*H*)-ones were synthesized *via* $SnCl_2{\cdot}2H_2O$ induced reductive cyclization of isothiocyanates with 2-nitrobenzamides. A variety of substrates can participate in the process with good yields. The new method has advantages such as easily accessible starting materials, handy manipulation (only one pot), moderate to high yields, and isolation of products *via* simple recrystallization to give higher purities.

## EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm$^{-1}$. $^1$H NMR was determined on Varian-400 MHz spectrometer in DMSO-$d_6$ or $CDCl_3$-$d_6$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS.

**General procedure for synthesis of 2,3-dihydro-2-thioxo-quinazolin-4(1*H*)-ones 3.** A solution of **1** or **4** (1 mmol), isothiocyanates **2** (1 mmol), and $SnCl_2{\cdot}2H_2O$ (4 mmol) in $CH_3CN$ (5 mL) was stirred at reflux for 2–3 h. After this period, the TLC analysis of the mixture showed the reaction to be completed. The mixture was quenched with 3% HCl (10 mL) and filtered, and the crude product was purified by recrystallization from 95% ethanol and DMF.

***2-Thioxo-3-m-tolyl-2,3-dihydroquinazolin-4(1H)-one (3a).*** This compound was obtained as solid with mp 280–281°C (ref. 21; 286–288°C); IR (KBr) ν: 3248, 3134, 3028, 1664, 1621, 1529, 1488, 1402, 1340, 1271, 1203, 913, 798, 692, 651 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 2.34 (s, 3H, $CH_3$), 7.07 (d, $J$ = 8.8 Hz, 2H, ArH), 7.22 (d, $J$ = 7.6 Hz, 1H, ArH), 7.33–7.38 (m, 2H, ArH), 7.45 (d, $J$ = 8.4 Hz, 1H, ArH), 7.78 (t, $J$ = 7.2 Hz, 1H, ArH), 7.95 (d, $J$ = 8.0 Hz, 1H, ArH), 13.02 (s, 1H, NH).

**Table 3**

Synthesis of compounds **3** from *N*-substitued-*o*-nitrobenzamides **4** and isothiocyanates **2**.

| | Y | $R^1$ | R | Yield (%) |
|---|---|---|---|---|
| **3j** | H | 4-$CH_3OC_6H_4$ | 4-$CH_3C_6H_4$ | 75 |
| **3k** | H | 4-$BrC_6H_4$ | 4-$ClC_6H_4$ | 81 |
| **3l** | H | $CH_3(CH_2)_7$ | $C_6H_5$ | 93 |
| **3m** | Cl | 4-$ClC_6H_4CH_2$ | 3-$CH_3C_6H_4$ | 83 |
| **3n** | Cl | $C_5H_{11}$ | $C_6H_5CH_2$ | 85 |

***3-Benzyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3b).*** This compound was obtained as solid with mp 238–240°C (ref. 25; 235–236°C); IR (KBr) ν: 3201, 3129, 3073, 1688, 1623, 1542, 1489, 1436, 1340, 1291, 1181, 959, 760, 705, 686 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 5.67 (s, 2H, $CH_2$), 7.21–7.24 (m, 1H, ArH), 7.27–7.37 (m, 5H, ArH), 7.43 (d, $J$ = 8.0 Hz, 1H, ArH), 7.77 (t, $J$ = 7.2 Hz, 1H, ArH), 7.96 (d, $J$ = 8.0 Hz, 1H, ArH), 13.07 (s, 1H, NH).

***3-Butyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3c).*** This compound was obtained as solid with mp 164–166°C (ref. 25; 166–167°C); IR (KBr) ν: 3250, 3144, 2955, 2935, 1652, 1626, 1538, 1490, 1340, 1272, 1184, 1128, 990, 798, 758, 690 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 0.93 (t, $J$ = 7.6 Hz, 3H, $CH_3$), 1.30–1.40 (m, 2H, $CH_2$), 1.63–1.70 (m, 2H, $CH_2$), 4.40 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 7.32–7.40 (m, 2H, ArH), 7.74 (t, $J$ = 8.8 Hz, 1H, ArH), 7.96 (d, $J$ = 8.0 Hz, 1H, ArH), 12.92 (s, 1H, NH).

***3-(4-Chlorophenyl)-8-methyl-2-thioxo-2,3-dihydro-quinazolin-4(1H)-one (3d).*** This compound was obtained as solid with mp 186–188°C (ref. 26; 182–184°C); IR (KBr) ν: 3275, 3144, 2974, 2873, 1704, 1699, 1616, 1524, 1492, 1410, 1213, 1090, 988, 795, 758, 736 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 3.36 (s, 3H, $CH_3$), 7.27 (t, $J$ = 7.6 Hz, 1H, ArH), 7.33 (d, $J$ = 8.8 Hz, 2H, ArH), 7.55 (d, $J$ = 8.8 Hz, 2H, ArH), 7.63 (d, $J$ = 7.2 Hz, 1H, ArH), 7.83 (d, $J$ = 7.6 Hz, 1H, ArH), 11.89 (s, 1H, NH).

***3-Butyl-7-chloro-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3e).*** This compound was obtained as solid with mp 232–233°C (ref. 25; 225–226°C); IR (KBr) ν: 3182, 3119, 2957, 2870, 1652, 1619, 1533, 1484, 1436, 1390, 1338, 1197, 1122, 946, 863, 765, 739 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 0.93 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 1.30–1.40 (m, 2H, $CH_2$), 1.62–1.70 (m, 2H, $CH_2$), 4.37 (t, $J$ = 8.0 Hz, 2H, $CH_2$), 7.36–7.40 (m, 2H, ArH), 7.96 (d, $J$ = 8.4 Hz, 1H, ArH), 12.96 (s, 1H, NH).

***7-Chloro-3-(4-chlorophenyl)-2-thioxo-2,3–dihydro-quinazolin-4(1H)-one (3f).*** This compound was obtained as solid with mp 296–298°C; IR (KBr) ν: 3197, 3078, 3041, 2938, 1658, 1617, 1530, 1492, 1387, 1280, 1220, 1194, 1091, 925, 857, 815, 758 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): 7.34 (d, $J$ = 8.4 Hz,

2H, ArH), 7.39 (dd, $J_1$= 2.0 Hz, $J_2$= 8.4 Hz, 1H, ArH), 7.46 (s, 1H, ArH), 7.55 (d, $J$ = 8.4 Hz, 2H, ArH), 7.95 (d, $J$ = 8.8 Hz, 1H, ArH), 13.13 (s, 1H, NH).

***6-Chloro-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3g).*** This compound was obtained as solid with mp 293–294°C; IR (KBr) ν: 3241, 3113, 3037, 2942, 1691, 1666, 1616, 1525, 1481, 1390, 1269, 1194, 1100, 993, 815, 772 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 7.28 (d, $J$ = 7.2 Hz, 2H, ArH), 7.42–7.51 (m, 4H, ArH), 7.83–7.89 (m, 2H, ArH), 13.15 (s, 1H, NH).

***6-Chloro-2-thioxo-3-m-tolyl-2,3-dihydroquinazolin-4(1H)-one (3h).*** This compound was obtained as solid with mp 268–270°C; IR (KBr) ν: 3243, 3037, 2890, 1663, 1617, 1524, 1482, 1387, 1270, 1222, 1200, 1100, 834, 771, 708 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.35 (s, 3H, $CH_3$), 7.07 (d, $J$ = 8.8 Hz, 2H, ArH), 7.23 (d, $J$ = 7.6 Hz, 1H, ArH), 7.37 (t, $J$ = 7.6 Hz, 1H, ArH), 7.46 (d, $J$ = 8.8 Hz, 1H, ArH), 7.83–7.88 (m, 2H, ArH), 13.14 (s, 1H, NH).

***3-Butyl-6-chloro-2-thioxo-2,3-dihydroquinazolin 4(1H)-one (3i).*** This compound was obtained as solid with mp 236–237°C; IR (KBr) ν: 3249, 3040, 2965, 1650, 1621, 1528, 1483, 1373, 1345, 1274, 1183, 1141, 1103, 828, 759 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 0.93 (t, $J$ = 7.6 Hz, 3H, $CH_3$), 1.30–1.39 (m, 2H, $CH_2$), 1.62–1.69 (m, 2H, $CH_2$), 4.37 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 7.39 (d, $J$ = 8.8 Hz, 1H, ArH), 7.79 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H, ArH), 7.88 (d, $J$ = 2.0 Hz, 1H, ArH), 13.03 (s, 1H, NH).

***2-Thioxo-3-p-tolyl-2,3-dihydroquinazolin-4(1H)-one (3j).*** This compound was obtained as solid with mp 296–298°C (ref. 25; 294–296°C); IR (KBr) ν: 3245, 3132, 3029, 2980, 1664, 1621, 1533, 1489, 1408, 1270, 1232, 1200, 990, 807, 759, 710 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.38 (s, 3H, $CH_3$), 7.14 (d, $J$ = 8.0 Hz, 2H, ArH), 7.28 (d, $J$ = 7.6 Hz, 2H, ArH), 7.35 (t, $J$ = 7.6 Hz, 1H, ArH), 7.45 (d, $J$ = 8.0 Hz, 1H, ArH), 7.79 (t, $J$ = 8.4 Hz, 1H, ArH), 7.95 (d, $J$ = 8.0 Hz, 1H, ArH), 13.02 (s, 1H, NH).

***3-(4-Chlorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3k).*** This compound was obtained as solid with mp >300°C (ref. 25; >300°C); IR (KBr) ν: 3246, 3138, 3038, 1664, 1621, 1532, 1489, 1407, 1268, 1234, 1201, 1094, 990, 812, 760, 737 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 7.33–7.38 (m, 3H, ArH), 7.46 (d, $J$ = 8.8 Hz, 1H, ArH), 7.55 (d, $J$ = 8.4 Hz, 2H, ArH), 7.80 (t, $J$ = 7.6 Hz, 1H, ArH), 7.96 (d, $J$ = 7.6 Hz, 1H, ArH), 13.09 (s, 1H, NH).

***3-Phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3l).*** This compound was obtained as solid with mp 294–296°C (ref. 25; >300°C); IR (KBr) ν: 3246, 3137, 3029, 1662, 1623, 1533, 1489, 1406, 1267, 1227, 1197, 988, 843, 799, 760 $cm^{-1}$. $^1H$ NMR (DMSO-*d*6): 7.26–7.28 (m, 2H, ArH), 7.34–7.50 (m, 5H, ArH), 7.71–7.76 (m, 1H, ArH), 8.05 (d, $J$ = 8.0 Hz, 1H, ArH), 13.09 (s, 1H, NH).

***7-Chloro-2-thioxo-3-m-tolyl-2,3-dihydroquinazolin-4(1H)-one (3m).*** This compound was obtained as solid with mp 228–230°C (ref. 25; 230–232°C); IR (KBr) ν: 3190, 3074, 3021, 1660, 1616, 1526, 1479, 1417, 1385, 1258, 1193, 1073, 927, 857, 803, 781, 757 $cm^{-1}$. $^1H$ NMR (DMSO-*d*6): 2.35 (s, 3H, CH3), 7.08–7.10 (m, 2H, ArH), 7.25–7.27 (m, 1H, ArH), 7.33–7.35 (m, 2H, ArH), 7.45 (d, $J$ = 1.6 Hz, 1H, ArH), 7.95 (d, $J$ = 8.4 Hz, 1H, ArH), 13.01 (s, 1H, NH).

***3-Benzyl-7-chloro-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3n).*** This compound was obtained as solid with mp 260–262°C (ref. 25; 255–257°C); IR (KBr) ν: 3204, 3127, 3041, 1648, 1617, 1529, 1482, 1387, 1335, 1290, 1164, 1150, 1075, 948, 862, 762, 726 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 5.64 (s, 2H, $CH_2$), 7.22–7.25 (m, 1H, ArH), 7.28–7.34 (m, 4H, ArH), 7.39 (d, $J$ = 8.4 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.96 (d, $J$ = 8.4 Hz, 1H, ArH), 13.11 (s, 1H, NH).

***2-amino-N-(4-methoxyphenyl)benzamide.*** This compound was obtained as solid with mp 116–118°C (ref. [30] 117–118°C); IR (KBr) ν: 3400, 3330, 3250, 1640, 1604, 1535, 1507, 1429, 1220, 1160, 987, 752 $cm^{-1}$. $^1H$ NMR ($CDCl_3$-$d_6$): 3.35 (s, 3H, $OCH_3$), 5.02 (s, 2H, NH), 6.24 (t, $J$ = 8.0 Hz, 2H, ArH), 6.44 (d, $J$ = 8.8 Hz, 2H, ArH), 6.78 (t, $J$ = 8.4 Hz, 1H, ArH), 6.99 (d, $J$ = 8.8 Hz, 3H, ArH), 7.26 (s, 1H, NH).

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## REFERENCES AND NOTES

[1] Ismail, M. A. H.; Barker, S.; El Ella, D. A. A.; Abouzid, K. A. M.; Toubar, R. A.; Todd, M. H. J Med Chem 2006, 49, 1526.

[2] Tsuboi, H.; Kagara, K. Chem Exp 1993, 8, 761.

[3] Choo, H.-Y. P.; Kim, M.; Lee, S. K.; Kim, S. W.; Chung, I. K. Bioorg Med Chem 2002, 10, 517.

[4] Buckley, G. M.; Davies, N.; Dyke, H. J.; Gilbert, P. J.; Hannah, D. R.; Haughan, A. F.; Hunt, C. A.; Pitt, W. R.; Profit, R. H.; Ray, N. C.; Richard, M. D.; Sharpe, A.; Taylor, A. J.; Whitworth, J. M.; Williams, S. C. Bioorg Med Chem Lett 2005, 15, 751.

[5] Dreyer, D. L.; Brenner, R. C. Phytochemistry 1980, 19, 935.

[6] Alagarsamy, V.; Solomon, V. R.; Dhanabal, K. Bioorg Med Chem 2007, 15, 235.

[7] Merck. Merck Index, Vol. 12; Merck: Whitehouse Station, NJ, 1996; p 7897.

[8] Merck. Merck Index, Vol. 12; Merck: Whitehouse Station, NJ, 1996; p 1512.

[9] Merck. Merck Index, Vol. 12; Merck: Whitehouse Station, NJ, 1996; p 3489.

[10] (a) Goto, S.; Tsuboi, H.; Kagara, K. Chem Express 1993, 8, 761; (b) Kagara, K.; Goto, S.; Tsuboi, H. Jpn. Pat. 25,767,1989; Chem Abstr 1989, 111, 97274.

[11] Mohri, S. J Synth Org Chem Jpn 2001, 59, 514.

[12] (a) Pastor, G.; Blanchard, C.; Montginoul, C.; Torreilles, E.; Giral, L.; Texier, A. Bull Soc Chim Fr 1975, 1331; (b) Khalifa, M.; Osman, A. N.; Ibrahim, M. G.; Ossman, A. R. E.; Ismail, M. A. Pharmazie 1982, 37, 115.

[13] Michman, M.; Patai, S.; Wiesel, Y. Org Prep Proced Int 1978, 10, 13.

[14] Lange, N. A.; Sheibley, F. E. Org Synth 1943, 2, 79.

[15] Vorbrueggen, H.; Krolikiewicz, K. Tetrahedron 1994, 50, 6549.

[16] (a) Mizuno, T.; Iahino, Y. Tetrahedron 2002, 58, 3155; (b) Mizuno, T.; Iwai, T.; Ishino, Y. Tetrahedron Lett 2004, 45, 7073.

[17] Buckman, B. O.; Mohan, R. Tetrahedron Lett 1996, 37, 4439.

[18] Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. Tetrahedron Lett 1997, 38, 1729.

[19] Smith, A. L.; Thomson, C. G.; Leeson, P. D. Bioorg Med Chem Lett 1996, 6, 1483.

[20] Choo, H. P.; Kim, M.; Lee, S. K.; Kim, S. W.; Chung, I. K. Bioorg Med Chem Lett 2002, 10, 517.

[21] Li, Z. G.; Huang, H.; Sun, H. B.; Jiang, H. L.; Liu, H. J. Comb Chem 2008, 10, 484.

[22] Alagarsamy, V.; Solomon, V. R.; Dhanabal, K. Bioorg Med Chem 2007, 15, 235.

[23] Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. Tetrahedron Lett 2003, 44, 3199.

[24] Shi, D. Q.; Dou, G. L.; Li, Z. Y.; Ni, S. N.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Tetrahedron 2007, 63, 9764.

[25] Dou, G. L.; Wang, M. M.; Shi, D. Q. J Comb Chem 2009, 11, 151.

[26] Dou, G. L.; Wang, M. M.; Huang, Z. B.; Shi, D. Q. J Heterocycl Chem 2009, 46, 645.

[27] Shi, D. Q.; Dou, G. L.; Ni, S. N.; Shi, J. W.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Synlett 2007, 16, 2509.

[28] Shi, D. Q.; Dou, G. L.; Zhou, Y. Synthesis 2008, 13, 2000.

[29] Wang, M. M.; Dou, G. L.; Shi, D. Q. J Heterocycl Chem 2009, 46, 1364.

[30] Coyne, W. E.; Cusic, J. W. J Med Chem 1968, 11, 1208.

# The First Synthesis of 3-Hydroxy-2-(polyfluoroalkyl)chromones and Their Ammonium Salts. 3-Hydroxychromone in the Mannich Reaction

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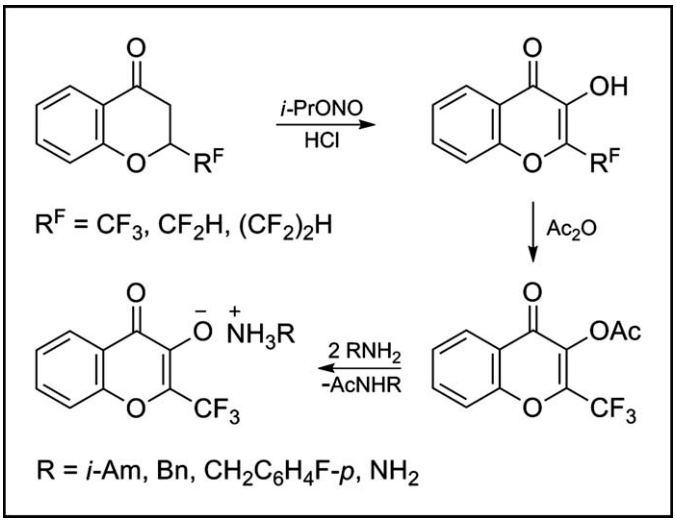


3-Hydroxy-2-(polyfluoroalkyl)chromones were obtained in good yields via the nitrozation reaction of 2-(polyfluoroalkyl)chroman-4-ones with isopropyl nitrite in the presence of hydrochloric acid. Treatment of 3-acetoxy-2-(trifluoromethyl)chromone with primary amines and hydrazine gave the corresponding ammonium salts. Reaction of 3-hydroxychromone, prepared by this method, with formaldehyde and α-aminoacids has been studied.

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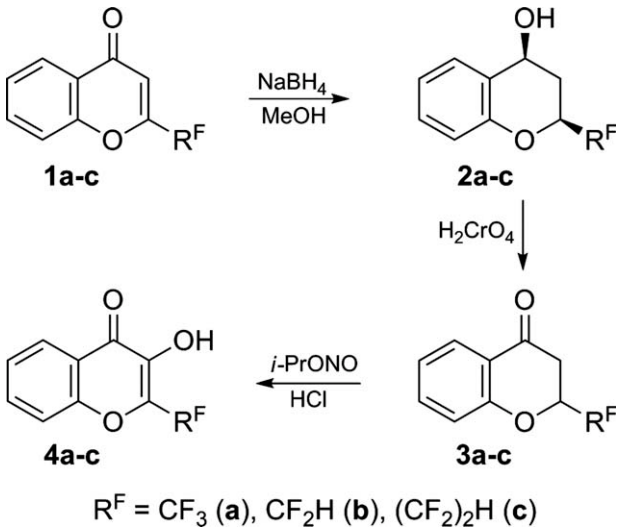
## INTRODUCTION

The chromone ring is an integral part of many natural and biologically active substances. The biological potency of chromone derivatives and, in particular, halogen-containing chromones, has been widely documented [1,2]. Therefore, considerable efforts have been paid to explore new synthetic route to halogenated derivatives of chromone and to study their chemical properties. Polyfluoroalkyl groups, especially the $CF_3$ group, are highly important substituents in the field of organic chemistry. The introduction of these groups into organic molecules can bring about some remarkable changes in the physical properties, chemical reactivity, and biological activity of the derived fluorinated compounds [3]. Thus, it is well known that the insertion of polyfluoroalkyl substituents into the 2-position of chromones activates molecules of these compounds and reveals significant differences in the reactivity of 2-alkyl- and 2-(polyfluoroalkyl)chromones with respect to nucleophilic reagents [4]. The variety of the reactions of 2-$R^F$-chromones makes this class of compounds very useful for synthesis of $R^F$-containing heterocycles with potential biological activity [2].

However, to the best of our knowledge, very little is known about the synthesis and properties of 3-substituted 2-$R^F$-chromones. There have been only some papers on the preparation of 3-chloro- [5], 3-bromo- [6], 3-cyano- [7], 3-carbamoyl- [7], and 3-carbethoxychromones [8] with a $R^F$ group at the 2-position. 2-(Polyfluoroalkyl)chromones containing electron-donating substituents at the 3-position had not been described yet. In view of the unique biological properties displayed by chromones [1,2] on one hand and by many fluorine-containing heterocycles [9] on the other hand, it was of interest to obtain 2-$R^F$-chromones with an electron-donating hydroxy group at the C-3 atom and their derivatives. It is worth to note that 3-hydroxyflavone is the most simple model of aglucones of polyhydroxyflavones

**Scheme 1**




which, linked by glucoside bond at the C-3 atom, are very widely spread heterocycles in the nature.

Recently [10], we have reported that reduction of readily available 2-(polyfluoroalkyl)chromones **1** with sodium borohydride provides a simple preparative procedure to *cis*-2-(polyfluoroalkyl)chroman-4-ols **2**, the oxidation of which to 2-(polyfluoroalkyl)chroman-4-ones **3** was performed with chromic acid in ethyl ether. We regarded these compounds as desirable targets because of their relationship to naturally occurring benzopyran derivatives and usefulness as $R^F$-containing building blocks for the preparation of more complex partially fluorinated heterocycles and other highly functionalized biologically and medicinally important products.

## RESULTS AND DISCUSSION

Now we wish to report the successful nitrozation reaction of 2-$R^F$-chroman-4-ones **3** for the synthesis of previously unknown 3-hydroxy-2-(polyfluoroalkyl)chromones **4**. We found that treatment of an alcoholic solution of **3a–c** with an excess of isopropyl nitrite (3.0 equiv) and concentrated hydrochloric acid at 0–80°C for 3 h gave chromones **4a–c** in 42–68% yields as colorless crystals (Scheme 1). In the $^1$H NMR spectra of these products in DMSO-$d_6$, a singlet at δ 10.4–10.7 ppm for the OH proton appeared in place of the disappearance of signals at δ 2.9–3.0 and 4.8–4.9 ppm associated with the C-3 methylene and C-2 methine protons of the starting 2-$R^F$-chroman-4-ones **3**. It was also observed that all protons of the benzene ring shifted to lower field and, hence, formation of the pyrone ring took place under the action of isopropyl nitrite.

To demonstrate the ability of compounds **4** to undergo alkylation and acylation reactions, chromone **4a** as a representative example was allowed to react with MeI and $Ac_2O$. Our results showed that **4a** smoothly reacts with an excess of MeI (refluxing acetone, $K_2CO_3$, 8 h) and $Ac_2O$ (pyridine, ~20°C, 2 days) to produce the expected 3-methoxy- and 3-acetoxy-2-(trifluoromethyl)-chromones **5** and **6** in 87% and 77% yields, respectively (Scheme 2). The most notable feature in the $^1$H NMR spectra of **5** and **6** is the absence of a signal of the hydroxy group and the appearance of singlets at δ 4.04 and 2.41 ppm due to the MeO and MeCO groups. Previously, their non-fluorinated analogs, 3-methoxy-, 3-acetoxy-, and 3-hydroxy-2-methylchromones, were obtained by reaction of ω-bromo-2-hydroxyacetophenone with acetic acid anhydride and sodium acetate [11]. The synthesis of 3-hydroxy-2-methylchromone has been also achieved by oxidation of 2-methylchroman-4-one with isoamyl nitrite [12].

It is known that reactions of 2-$R^F$-chromones **1** with amines and hydrazines proceed at the C-2 atom with pyrone ring opening to form β-aminovinylketones [13] and pyrazoles [14]. However, the acetylated derivative **6** did not show any analogous behavior to **1** and reacted with isoamyl-, benzyl-, and *p*-fluorobenzylamines in ethanol at room temperature immediately to give the corresponding salts **7a–c** as the sole isolated products in 47–85% yields. Similarly, reaction with hydrazine hydrate leads to hydrazinium 4-oxo-2-(trifluoromethyl)-4*H*-chromen-3-olate **7d** in 69% yield (Scheme 2). These salts are stable compounds and can be stored at room

**Scheme 2**

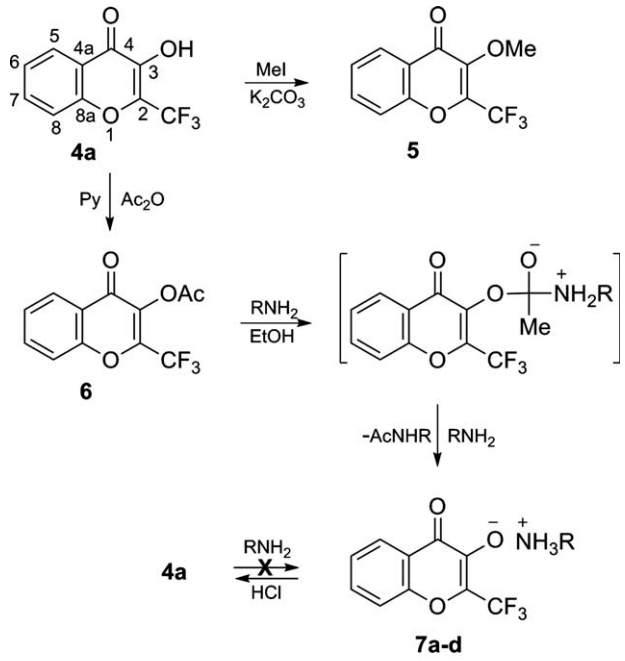


**Table 1**

Selected $^{13}C$ NMR data of chromones **1a** [16], **6**, **4a**, **7a**, and **8** [17a].

| Chromone | Chemical shifts, δ (ppm) | | |
|---|---|---|---|
| | C-2 | C-3 | C-4 |
| **1a**[a] | 152.2 | 110.4 | 176.8 |
| **6**[a] | 144.8 | 135.2 | 171.7 |
| **4a**[b] | 133.7 | 141.3 | 173.6 |
| **7a**[b] | 131.8 | 152.3 | 180.4 |
| **8**[a] | 139.9 | 142.1 | 174.0 |

[a] In $CDCl_3$.
[b] In DMSO-$d_6$.

temperature within several months. Thus, the salts formation was achieved without destruction of the chromone ring system. However, when an ethanolic solution of **4a** or **6** with benzylamine or hydrazine was heated, the reaction did not occur and only resinification was observed. Also, we were unable to obtain the corresponding salts from **6** and *tert*-butylamine, cyclohexylamine, and ethylenediamine. It should be noted that 3-hydroxychromone reacts with hydrazine hydrate in methanol to give 4-hydroxy-3-(2-hydroxyphenyl)-1*H*-pyrazole [15].

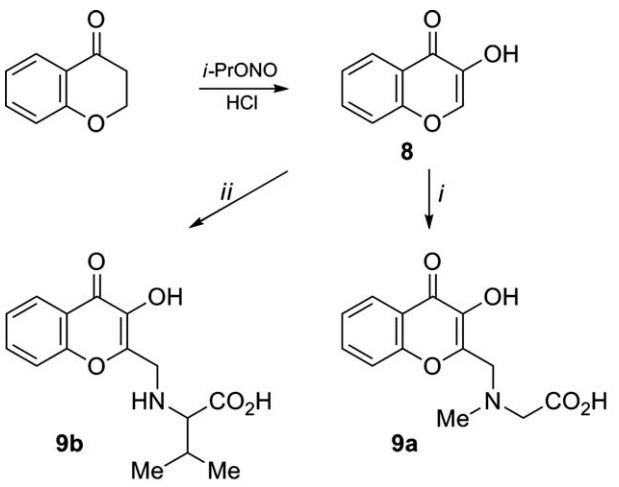
Reaction of the chromone derivative **6** with amines and hydrazine under mild conditions represents an easy access to the ammonium salts of 3-hydroxy-2-(trifluoromethyl)chromone **7a–d**, which could not be directly prepared from chromone **4a** and amines. The salts produced by this addition-elimination sequence gave the starting compound **4a** when treated by an ethanolic solution of hydrochloric acid at −30°C. The lack of chromone reactivity towards amines and hydrazine can be caused by the conjugation effect of the electron releasing OH and OAc groups, which decrease the electrophilic character of the C-2 atom, which is usually attacked first in the reaction of a chromone system with nucleophiles [2].

The IR spectra of **7a–d** display two distinct absorption bands at approximately 1630 and 1610 $cm^{-1}$ assigned to the C=O and C=C functions, respectively, as in the case of the protonated form **4a**. In the $^1H$ NMR spectra of these compounds, the ammonium protons appeared as broad singlets within the range δ 3.0–7.2 ppm ($CDCl_3$). The $^{13}C$ spectra of compounds **7a,d** are much more informative and display low field signals at ca. δ 180.3, 154.2, and 152.1 ppm, which are assigned to C-4, C-8a, and C-3, respectively. The aromatic carbons fall within the range δ 118–133 ppm; the C-2 atom, adjacent to the $CF_3$ group, appeared as a quartet at δ 131.8–132.0 ppm ($^2J_{C,F}$ = 32.0 Hz), shifted upfield compared with C-2 of chromones **1**, **4**, and **6**. The $^1H$-coupled $^{13}C$ NMR spectrum of **7a** was used to assign signals for the quaternary carbon atoms. The chemical shifts of the pyrone carbon atoms are presented in Table 1 to demonstrate the deshielding and shielding effects of the oxygen substituent at the 3-position on the C-3 and C-2 atoms compared with H-3 of chromone **1a**. As can been seen from Table 1, the appearance of the 3-OH group leads to considerable shielding of the C-2 atom, which is related to the lack of usual chromone reactivity.

Next, taking into account the above results and that the 3-hydroxychromone ring is an important structural fragment of many natural and biologically active substances [18], we decided to investigate the possibility of preparing 3-hydroxychromone **8** through nitrozation reaction of chroman-4-one under our reaction conditions. Previously, this compound was prepared by oxidation of chromone and 3-formylchromone using different reagents in two steps [17]. We found that the reaction between commercially available chroman-4-one and isopropyl nitrite is a useful method for the preparation of **8** because it requires only one step, cheap common reagents, and short reaction times (2–3 h in this case), albeit in only 35% yield (Scheme 3).

The replacement of a H-3 atom in 2- and 3-unsubstituted chromones by an alkyl- or dialkylaminomethyl group in the Mannich reaction is well known [19]. Very recently [20], it has been shown that 3-formylchromones react with α-aminoacids in the presence of excess formaldehyde to produce *N*-(chromone-3-ylmethyl)-α-aminoacids by a deformylative Mannich type reaction. It was also observed that α-aminoacids can be used as the amine component in a Mannich reaction with kojic acid [21]. However, the use of 3-hydroxychromones in this reaction has not been reported in the literature. Our preliminary results showed that 3-hydroxychromone **8** smoothly reacted with such α-aminoacids as sarcosine

**Scheme 3**




*Reaction conditions: i*, $CH_2O$, sarcosine; *ii*, $CH_2O$, valine

and valine in the presence of 37% formalin in refluxing ethanol for 5 h to give the corresponding chromone derivatives **9a,b** in high yields (70–80%). The resulting products represent an important class of chromone derivatives, in which two different fragments with remarkably interesting biological and pharmaceutical activities are linked at the same carbon atom.

In conclusion, we have shown that the reaction of 2-(polyfluoroalkyl)chroman-4-ones with isopropyl nitrite is a simple and practical method for the preparation of 3-hydroxy-2-(polyfluoroalkyl)chromones and 3-hydroxychromone. Treatment of 3-acetoxy-2-(trifluoromethyl)chromone with primary amines and hydrazine gave the corresponding ammonium salts. 3-Hydroxychromone reacts with formaldehyde and α-aminoacids to form previously unknown *N*-(3-hydroxychromone-2-ylmethyl)-α-aminoacids.

## EXPERIMENTAL

$^1$H (400 MHz), $^{19}$F (376 MHz), and $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-$d_6$ and $CDCl_3$ with TMS and $CFCl_3$ as the internal standards. IR spectra were recorded on Perkin-Elmer Spectrum BX-II and Bruker Alpha instruments as KBr discs and ATR (ZnSe), respectively. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting 2-(polyfluoroalkyl)chroman-4-ones **3a–c** were prepared according to described procedure [10].

**General procedure for the synthesis of 3-hydroxy-2-(polyfluoroalkyl)chromones (4a–c).** Concentrated hydrochloric acid (3.4 mL) was added dropwise over 1 h to a cold stirred solution of chroman-4-one **3** (2.0 mmol) and isopropyl nitrite (6.0 mmol) in ethanol (5 mL) and methanol (2 mL). On completion of the addition, the reaction mixture was allowed to warm to room temperature (1 h) and was then heated to 80°C for 2–3 h. After cooling, the precipitated product was isolated by filtration and washed with water to give colorless crystals.

***3-Hydroxy-2-(trifluoromethyl)chromone (4a).*** Yield 290 mg (68%), mp 166–167°C; IR (ATR) 3275, 1634, 1612, 1576 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.53 (ddd, 1H, H-6, $J$ = 8.0, 7.1, 1.0 Hz), 7.73 (dd, 1H, H-8, $J$ = 8.6, 1.0 Hz), 7.88 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.14 (dd, 1H, H-5, $J$ = 8.0, 1.7 Hz), 10.71 (s, 1H, OH); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ −64.90 (s, $CF_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 118.48 (C8), 120.33 (q, $CF_3$, $^1J_{C,F}$ = 273.4 Hz), 121.48 (C4a), 125.16 (C5/6), 125.39 (C6/5), 133.71 (q, C2, $^2J_{C,F}$ = 36.5 Hz), 135.04 (C7), 141.29 (C3), 154.07 (C8a), 173.59 (C=O). Anal. Calcd. for $C_{10}H_5F_3O_3$: C, 52.19; H, 2.19. Found: C, 52.15; H, 2.39.

***3-Hydroxy-2-(difluoromethyl)chromone (4b).*** Yield 180 mg (42%), mp 184–185°C; IR (KBr) 3265, 1633, 1609 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.33 (t, 1H, $CF_2H$, $^2J_{H,F}$ = 51.8 Hz), 7.51 (ddd, 1H, H-6, $J$ = 8.0, 7.1, 1.0 Hz), 7.73 (dd, 1H, H-8, $J$ = 8.6, 1.0 Hz), 7.86 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.13 (dd, 1H, H-5, $J$ = 8.0, 1.7 Hz), 10.38 (s, 1H, OH); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ −122.80 (d, $CF_2H$, $^2J_{F,H}$ = 51.8 Hz). Anal. Calcd. for $C_{10}H_6F_2O_3$: C, 56.61; H, 2.85. Found: C, 56.72; H, 2.86.

***3-Hydroxy-2-(1,1,2,2-tetrafluoroethyl)chromone (4c).*** Yield 470 mg (66%), mp 134–135°C; IR (KBr) 3238, 1628, 1611, 1575 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.96 (tt, 1H, $CF_2CF_2H$, $^2J_{H,F}$ = 51.9 Hz, $^3J_{H,F}$ = 5.5 Hz), 7.54 (ddd, 1H, H-6, $J$ = 8.0, 7.1, 1.0 Hz), 7.71 (dd, 1H, H-8, $J$ = 8.6, 1.0 Hz), 7.88 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.14 (dd, 1H, H-5, $J$ = 8.0, 1.7 Hz), 10.70 (s, 1H, OH). Anal. Calcd. for $C_{11}H_6F_4O_3$: C, 50.40; H, 2.31. Found: C, 50.66; H, 2.46.

**3-Methoxy-2-(trifluoromethyl)chromone (5).** To a solution of chromone **4a** (400 mg, 1.74 mmol) and MeI (740 mg, 5.22 mmol) in acetone (10 mL) was added $K_2CO_3$ (600 mg, 4.35 mmol) and the mixture was reflux for 8 h. After cooling, the inorganic salts were filtered off and washed with acetone (10 mL). Evaporation of the filtrate at heating gave a solid, which was recrystallized from hexane to give colorless crystals. Yield 370 mg (87%), mp 57°C; IR (ATR) 1614 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H, MeO), 7.46 (ddd, 1H, H-6, $J$ = 8.1, 7.1, 1.0 Hz), 7.55 (dd, 1H, H-8, $J$ = 8.6, 1.0 Hz), 7.75 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.24 (dd, 1H, H-5, $J$ = 8.1, 1.7 Hz). Anal. Calcd. for $C_{11}H_7F_3O_3$: C, 54.11; H, 2.89. Found: C, 54.03; H, 3.14.

**3-Acetoxy-2-(trifluoromethyl)chromone (6).** A solution of **6** (330 mg, 1.43 mmol) and acetic anhydride (300 mg, 2.87 mmol) in pyridine (5 mL) was kept at room temperature for 2 days. Then the reaction mixture was poured into diluted hydrochloric acid (1:10) and allowed to stand for 1 day at room temperature. The resulting colorless solid was filtered and washed with water. Yield 300 mg (77%), mp 110°C; IR (ATR) 1790, 1664, 1611 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 2.41 (s, 3H, Me), 7.64 (ddd, 1H, H-6, $J$ = 8.0, 7.1, 1.0 Hz), 7.85 (ddd, 1H, H-8, $J$ = 8.6, 1.0, 0.4 Hz), 7.98 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.13 (ddd, 1H, H-5, $J$ = 8.0, 1.7, 0.4 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ −67.87 (s, $CF_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 20.00 (Me), 118.44 (C8), 118.75 (q, $CF_3$, $^1J_{C,F}$ = 275.8 Hz), 123.56 (C4a), 126.27 (C5/6), 126.29 (C6/5), 135.18 (C7/3), 135.26 (C3/7), 144.80 (q, C2, $^2J_{C,F}$ = 37.7 Hz), 154.73 (C8a), 167.17 (OC=O), 171.73 (C=O). Anal. Calcd. for $C_{12}H_7F_3O_4$: C, 52.95; H, 2.59. Found: C, 52.99; H, 2.79.

**General procedure for the synthesis of ammonium salts of 3-hydroxy-2-(trifluoromethyl)chromone (7a–d).** To a solution of **6** (270 mg, 1.0 mmol) in absolute ethanol (5 mL) was added the corresponding amine (4.0 mmol). The resulting colorless solid was filtered, washed with cooled ethanol, and dried at 60–70°C.

***Isoamylammonium 2-(trifluoromethyl)chromone-3-olate (7a).*** Yield 150 mg (47%), mp 132–133°C; IR (ATR) 3035, 2958, 2874, 1633, 1609, 1584, 1557 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.70 (d, 6H, 2Me, $J$ = 6.6 Hz), 1.29–1.36 (m, 2H, $CH_2$), 1.48 (sept, 1H, CH, $J$ = 6.6 Hz), 2.85–2.90 (m, 2H, $NCH_2$), 6.70 (br s, 3H, $NH_3^+$), 7.31 (ddd, 1H, H-6, $J$ = 8.1, 7.0, 1.0 Hz), 7.46 (d, 1H, H-8, $J$ = 8.6 Hz), 7.63 (ddd, 1H, H-7, $J$ = 8.6, 7.0, 1.7 Hz), 8.17 (dd, 1H, H-5, $J$ = 8.1, 1.7 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 22.60 (qm, 2 Me, $J_{C,H}$ = 125.0 Hz), 25.50 (dm, CH, $J_{C,H}$ = 127.0 Hz), 36.70 (tm, $CH_2$, $J_{C,H}$ = 127.0 Hz), 37.77 (tm, $CH_2$, $J_{C,H}$ = 140.0 Hz), 118.60 (dd, C8, $J_{C,H}$ = 165.4, 7.0 Hz), 121.99 (dd, C4a, $J_{C,H}$ = 7.7, 4.0 Hz), 123.40 (dd, C5/6, $J_{C,H}$ = 163.6, 7.3 Hz), 123.84 (q, $CF_3$, $^1J_{C,F}$ = 270.7 Hz), 125.75 (dd, C6/5, $J_{C,H}$ = 164.3, 8.0 Hz), 131.75 (q, C2, $^2J_{C,F}$ = 31.5 Hz), 133.10 (dd, C7, $J_{C,H}$ = 164.3, 8.8 Hz), 152.27 (br s, C3), 154.20 (t, C8a, $J_{C,H}$ = 8.8 Hz), 180.38

(s, C=O). Anal. Calcd. for $C_{15}H_{18}F_3NO_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.34; H, 5.38; N, 4.18.

***Benzylammonium 2-(trifluoromethyl)chromone-3-olate (7b).*** Yield 250 mg (74%), mp 167–168°C; IR (ATR) 3167, 1597, 1547 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.93 (s, 2H, $CH_2$), 4.72 (br s, 3H, $NH_3^+$), 7.11 (tt, 1H, H-4', $J$ = 7.3, 1.3 Hz), 7.18–7.22 (m, 2H, H-3', H-5'), 7.25–7.29 (m, 2H, H-2', H-6'), 7.40 (ddd, 1H, H-6, $J$ = 8.1, 7.1, 1.0 Hz), 7.51 (ddd, 1H, H-8, $J$ = 8.6, 1.0, 0.4 Hz), 7.72 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.18 (ddd, 1H, H-5, $J$ = 8.1, 1.7, 0.4 Hz). Anal. Calcd. for $C_{17}H_{14}F_3NO_3$: C, 60.54; H, 4.18; N, 4.15. Found: C, 60.47; H, 4.21; N, 4.23.

***(4-Fluorobenzyl)ammonium 2-(trifluoromethyl)chromone-3-olate (7c).*** Yield 300 mg (85%), mp 156–157°C; IR (ATR) 2895, 1633, 1608, 1585, 1546, 1512 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.96 (br s, 3H, $NH_3^+$), 3.87 (s, 2H, $CH_2$), 6.96–7.02 (m, 2H, arom.), 7.26–7.30 (m, 2H, arom.), 7.47 (ddd, 1H, H-6, $J$ = 8.1, 7.1, 1.0 Hz), 7.57 (dd, 1H, H-8, $J$ = 8.6, 1.0 Hz), 7.78 (ddd, 1H, H-7, $J$ = 8.6, 7.1, 1.7 Hz), 8.23 (dd, 1H, H-5, $J$ = 8.1, 1.7 Hz); $^{19}F$ NMR (376 MHz, $CDCl_3$) δ −65.14 (s, $CF_3$), −115.23 (br s, F). Anal. Calcd. for $C_{17}H_{13}F_4NO_3$: C, 57.47; H, 3.69; N, 3.94. Found: C, 57.85; H, 3.49; N, 3.92.

***Hydrazinium 2-(trifluoromethyl)chromone-3-olate (7d).*** Yield 180 mg (69%), mp 118–119°C; IR (ATR) 3320, 3243, 1630, 1610, 1594, 1550 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.20 (br s, 5H, $NH_2NH_3^+$), 7.34 (ddd, 1H, H-6, $J$ = 8.0, 7.0, 1.0 Hz), 7.54 (d, 1H, H-8, $J$ = 8.6 Hz), 7.69 (ddd, 1H, H-7, $J$ = 8.6, 7.0, 1.7 Hz), 8.04 (dd, 1H, H-5, $J$ = 8.0, 1.7 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 118.63 (C8), 121.94 (C4a), 123.58 (C5/6), 123.64 (q, $CF_3$, $^1J_{C,F}$ = 270.7 Hz), 125.74 (C6/5), 131.98 (q, C2, $^2J_{C,F}$ = 32.3 Hz), 133.28 (C7), 151.90 (br s, C3), 154.19 (C8a), 180.29 (C=O). Anal. Calcd. for $C_{10}H_9F_3N_2O_3 \cdot 0.5H_2O$: C, 44.29; H, 3.72; N, 10.33. Found: C, 44.63; H, 3.50; N, 10.20.

***3-Hydroxychromone (8).*** This compound was prepared from chroman-4-one analogously to **4**. Yield 290 mg (35%), mp 178–180°C (lit. [17a] mp 179–180°C); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7.46 (ddd, 1H, H-6, $J$ = 8.0, 7.0, 1.0 Hz), 7.63 (dd, 1H, H-8, $J$ = 8.5, 1.0 Hz), 7.77 (ddd, 1H, H-7, $J$ = 8.5, 7.0, 1.7 Hz), 8.12 (dd, 1H, H-5, $J$ = 8.0, 1.7 Hz), 8.24 (s, 1H, H-2), 9.15 (s, 1H, OH).

***N-(3-hydroxychromone-2-ylmethyl)-N-methylglycine (9a).*** A solution of **8** (200 mg, 1.23 mmol), sarcosine (110 mg, 1.23 mmol) and formaldehyde as 37% formalin (500 mg, 6.15 mmol) in ethanol (5 mL) was refluxed for 5 h. The reaction mixture was refrigerated until a crystalline precipitate appeared. The colorless solid was filtered off and washed with ethanol. Yield 260 mg (80%), mp 274–275°C; IR (ATR): 3018, 1630, 1608, 1574 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 2.39 (s, 3H, Me), 3.34 (s, 2H, $CH_2$), 3.89 (s, 2H, $CH_2$), 7.44 (br t, 1H, H-6, $J$ = 7.5 Hz), 7.61 (d, 1H, H-8, $J$ = 8.5 Hz), 7.76 (ddd, 1H, H-7, $J$ = 8.5, 7.2, 1.5 Hz), 8.09 (br d, 1H, H-5, $J$ = 8.0 Hz), 8.5–12.0 (br s, 2H, 2OH). Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.41; H, 4.93; N, 5.02.

***N-(3-hydroxychromone-2-ylmethyl)valine (9b).*** This compound was prepared from **8** and valine analogously to **9a**. Yield 200 mg (70%), mp 126–127°C; IR (ATR): 3295, 1613 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 0.85 (d, 3H, Me, $J$ = 6.8 Hz), 0.89 (d, 3H, Me, $J$ = 6.8 Hz), 1.85–1.95 (m, 1H, CH), 3.00 (d, 1H, NCH, $J$ = 5.1 Hz), 3.85 (AB-system, 2H, $CH_2$, $J$ = 14.6 Hz), 7.44 (ddd, 1H, H-6, $J$ = 8.0, 7.1, 1.0 Hz), 7.60 (d, 1H, H-8, $J$ = 8.5 Hz), 7.75 (ddd, 1H, H-7, $J$ = 8.5, 7.1, 1.7 Hz), 8.08 (dd, 1H, H-5, $J$ = 8.0, 1.7 Hz), OH non observed. Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 62.05; H, 5.74; N, 4.92.

## REFERENCES AND NOTES


[1] Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893.

[2] Sosnovskikh, V. Ya. Russ Chem Rev 2003, 72, 489.

[3] (a) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds. Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications; Elsevier: Amsterdam, 1993; (b) Welch, J. T.; Eswarakrishnan, S. Fluorine in Bioorganic Chemistry; Wiley: New York, NY, 1991; (c) Hiyama, T. Organofluorine Compounds. Chemistry and Application; Springer: Berlin, 2000.

[4] (a) Sosnovskikh, V. Ya.; Usachev, B. I.; Sizov, A. Yu.; Barabanov, M. A. Synthesis 2004, 942; (b) Sosnovskikh, V. Ya.; Usachev, B. I.; Sizov, A. Yu. Synlett 2004, 1765; (c) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Röschenthaler, G.-V. Tetrahedron 2003, 59, 2625; (d) Sosnovskikh, V. Ya.; Barabanov, M. A.; Usachev, B. I. Org Lett 2003, 5, 2501; (e) Sosnovskikh, V. Ya.; Usachev, B. I.; Sizov, A. Yu.; Vorontsov, I. I.; Shklyaev, Yu. V. Org Lett 2003, 5, 3123.

[5] (a) Sosnovskikh, V. Ya.; Usachev, B. I.; Sizov, A. Yu. Russ Chem Bull Int Ed 2003, 52, 508; (b) Sosnovskikh, V. Ya.; Usachev, B. I.; Sizov, A. Yu. Russ Chem Bull Int Ed 2003, 52, 984.

[6] Usachev, B. I.; Shafeev, M. A.; Sosnovskikh, V. Ya. Russ Chem Bull Int Ed 2004, 53, 2285.

[7] Sosnovskikh, V. Ya.; Moshkin, V. S.; Kodess, M. I. Tetrahedron 2008, 64, 7877.

[8] (a) Coppola, G. M.; Dodsworth, R. W. Synthesis 1981, 523; (b) Coppola, G. M.; Dodsworth, R. W. U.S. Pat. 6,077,850 (2000); Chem Abstr 2000, 133, 43440a.

[9] (a) Dolbier, W. R., Jr. J Fluor Chem 2005, 126, 157; (b) Bégué, J.-P.; Bonnet-Delpon, D. J Fluor Chem 2006, 127, 992.

[10] Sosnovskikh, V. Ya.; Irgashev, R. A.; Levchenko, A. A. ARKIVOC 2009, iv, 125.

[11] Jerzmanowska, Z.; Zielińska, L. Pol J Chem 1983, 57, 49.

[12] Geissman, T. A.; Armen, A. J Am Chem Soc 1955, 77, 1623.

[13] Sosnovskikh, V. Ya.; Kutsenko, V. A.; Yachevskii, D. S. Mendeleev Commun 1999, 204.

[14] Sosnovskikh, V. Ya.; Barabanov, M. A.; Sizov, A. Yu. Russ Chem Bull Int Ed 2002, 51, 1280.

[15] Eiden, F.; Dölcher, D. Arch Pharm 1975, 308, 385.

[16] Sosnovskikh, V. Ya.; Usachev, B. I.; Kodess, M. I. Russ Chem Bull Int Ed 2002, 51, 1817.

[17] (a) Constantino, M. G.; Júnior, V. L.; da Silva, G. V. J. J Heterocycl Chem 2003, 40, 369; (b) Pace, P.; Nizi, E.; Pacini, B.; Pesci, S.; Matassa, V.; De Francesco, R.; Altamura, S.; Summa, V. Bioorg Med Chem Lett 2004, 14, 3257.

[18] (a) Ahmad-Junan, S. A.; Whiting, D. A. J Chem Soc Perkin Trans 1 1990, 418; (b) Ahmad-Junan, S. A.; Whiting, D. A. J Chem Soc Perkin Trans 1 1992, 675; (c) Nath, A.; Mal, J.; Venkateswaran, R. V. J Org Chem 1996, 61, 4391.

[19] (a) Wiley, P. F. J Am Chem Soc 1952, 74, 4326; (b) Sacquet, M.-C.; Fargeau-Bellassoued, M.-C.; Graffe, B. J Heterocycl Chem 1991, 28, 667.

[20] Panja, S. K.; Maiti, S.; Drew, M. G. B.; Bandyopadhyay, C. Tetrahedron 2009, 65, 1276.

[21] O'Brien, G.; Patterson, J. M.; Meadow, J. R. J Org Chem 1962, 27, 1711.

# One-Pot Synthesis of New Spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones from 3-Phenacylideneoxindoles



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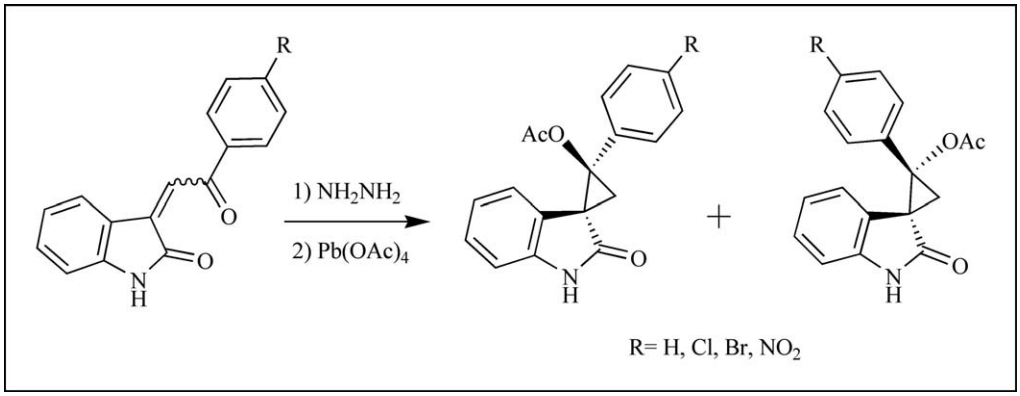


In a one-pot procedure, the 3-phenacylideneoxindoles **1a–d** were reacted with hydrazine and then *in situ* with lead(IV) acetate and new diastereoisomers of spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones were prepared. Compounds **1a–d** underwent a highly diastereoselective cyclopropanation leading to diastereoisomers **2a–d**. These new compounds containing both 2-oxindole and cyclopropane moieties may be valuable in medicinal chemistry.

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## INTRODUCTION

Isatin or 1*H*-indole-2,3-dione is an indole derivative. This compound was found in many plants. Isatin is an endogenous compound identified in humans that possesses wide range of biological activities. It has anxiogenic, anticonvulsant activity, and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro* [1]. Isatin Mannich or Schiff bases had antibacterial, antifungal, antiviral, anti HIV, antiprotozoal, anticancer, muscle relaxant, and antiallergic activity [2–5].

The cyclopropane ring is a main structural part in many synthetic and natural compounds that exhibits a wide range of biological activities from enzyme inhibition to antibiotic, herbicidal, antitumor, and antiviral properties [6–18]. Some derivatives of cyclopropane have shown potent HIV antiviral activities as non-nucleoside reverse transcriptase inhibitors [19]. Because of diversity of cyclopropane-containing compounds with biological activity, chemists have tried to find novel and facile methods for synthesis of these compounds [20–24].

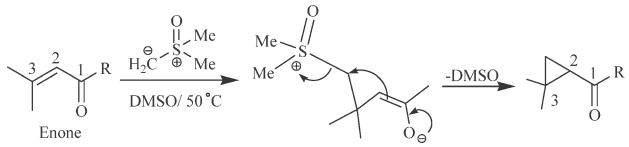
In this study along our pervious works on the synthesis of spiro derivatives of isatins and other biologically active compounds [25,26], we report a simple one-pot procedure for the synthesis of some spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones **2a–d** and **3a–d**, which directly prepared from various 3-phenacylideneoxindoles **1a–d** derivatives of isatin. These new compounds containing both active 2-oxindole and cyclopropane moieties may be of value in pharmaceutical and medicinal chemistry.

## RESULTS AND DISCUSSION

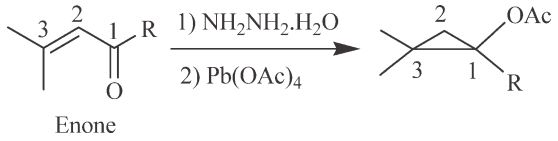
Among the synthetic procedures for preparation of cyclopropane rings, the Michael initiated ring closure reaction [6,14,21,23,24] of α,β-unsaturated carbonyl compounds such as α,β-enones with dimethylsulfoxonium methylides or Corey–Chaykovsky reaction [27,28] is the well-known method. In this reaction, the cyclopropane ring forms between carbon atoms of positions 2 and 3 of enones by addition of a new methylene group (Scheme 1).

The Kishner cyclopropanation reaction is another procedure [29–31]. In the Kishner's method, the cyclopropane derivatives were prepared by thermal decomposition of 2-pyrazolines. The Kishner reaction needs higher

**Scheme 1**




**Scheme 3**




temperatures for removing the nitrogen from 2-pyrazoline to afford cyclopropane (Scheme 2).

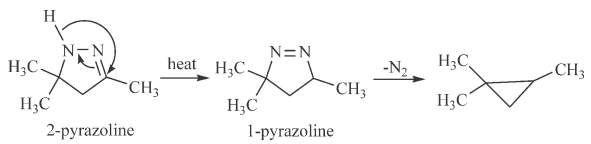
In this work, we report a novel one-pot procedure to synthesis the cyclopropane derivatives with connecting the C-1 and C-3 positions of α,β-enones (Scheme 3). This is a direct and useful method toward preparation of cyclopropanes through the 2-pyrazoline intermediate. Using the lead(IV) acetate renders decomposition of 2-pyrazolines easy [32] and formation of highly substituted cyclopropanes will be possible [33].

For the synthesis of new spiro molecules in this study, we needed the various 3-phenacylideneoxindoles **1a–d**. They have been prepared in our pervious work by the reaction of isatin with acetophenones in a solvent free condition catalyzed first by dimethylamine and then with glacial acetic acid and hydrochloric acid (Scheme 4) [26].

The **1a–d** were reacted with hydrazine hydrate in toluene and then *in situ* with lead(IV) acetate to afford a series of new spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-one derivatives **2a–d** and **3a–d** (Scheme 5).

The reaction intermediate was a spiro[[3*H*]indole-3,3′-[3*H*]pyrazol]-2(1*H*)-one **4** which is the product of hydrazine addition to 3-phenacylideneoxindoles. This reaction is the main method used for preparation of 2-pyrazolines in last century [34–36]. The intermediate **4** was not separated and reacted *in situ* with lead(IV) acetate to form new diastereoisomers **2a–d** and **3a–d**. The reaction of 2-pyrazolines with lead(IV) acetate was performed by Freeman [32] and Kennedy *et al*. [33]. The reaction intermediate is a 1-pyrazoline similar to compound **5**. Particularly, Kennedy's method is a general approach for synthesis of highly substituted cyclopropanes. Bonding of oxidant atom lead(IV) to the nitrogen atom of intermediate **4** increases the polarity of imino group of 2-pyrazoline ring and will facilitate the attack of the acetate anion to the carbon of imino double bond. Therefore, the unstable intermediate **5** forms and readily decomposes to the products by loss of nitrogen. The mechanism of the reaction may be as the Scheme 6.

**Scheme 2**




In comparison with the Kishner reaction, the lead(IV) acetate used here catalyzed the reaction and reacted with intermediate **4** and caused rapid nitrogen extrusion and then the reaction carried out in lower temperatures, whereas the Kishner reaction needs higher temperatures [29–31] for nitrogen loss. This is an advantage of this work. Furthermore, the starting material in the Kishner's method was a 2-pyrazoline derivative, but we used α,β-enones (3-phenacylideneoxindoles) as the starting compounds and then the separation and purification steps for intermediate **4** were omitted. Therefore, the overall yield of the reaction increased.

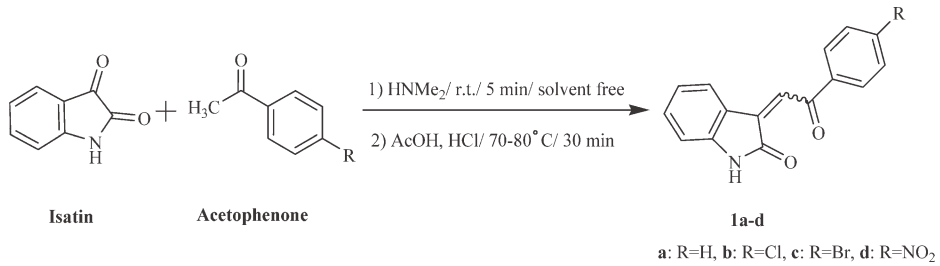
The reaction gave diastereoisomers **2a–d** as major products together with their isomers **3a–d** as minor products. In this case, a high diastereoselectivity was obtained. For instance, the diastereomeric ratios were determined by integration of separated signals in the $^1$H NMR spectra of the mixture of compounds **2c** and **3c** in the reaction product (Fig. 1). The resulted diastereomeric ratios for products were **2a:3a** = 2.70:1, **2b:3b** = 4.26:1, **2c:3c** = 1.78:1, **2d:3d** = 1.94:1.

All compounds **2a–d** and **3a–d** are new derivatives of spiro[cycloprapane-1,3′-[3*H*]indol]-2′(1′*H*)-ones and have not reported in literature. Their structures were deduced from their IR, $^1$H, and $^{13}$C NMR spectra. Their purity was tested by CHN elemental analysis. The experimentally obtained CHN data have shown good agreements (about ±0.2%) with calculated values.

For example, the $^1$H NMR spectrum of **2b** indicated two doublets at δ 2.18 and 2.69 ppm ($J$ = 7 Hz), which belong to diastereotopic methylene protons at position 3 of cyclopropane ring and a singlet at δ 2.04 ppm for methyl protons of acetate group. The multiplets at δ 6.85–7.95 ppm showed the aromatic protons. A singlet at δ 8.91 ppm indicates the secondary amino proton. The $^1$H decoupled $^{13}$C NMR spectrum of **2b** exhibited spiro carbon at δ 37.97, C-2 carbon atom of cyclopropane ring at δ 70.84, methyl carbon at δ 21.25, methylene carbon at δ 27.05, carbonyl carbon of acetate group at δ 169.76, and amido carbon of 2-oxindole moiety at δ 175.42 ppm.

In the $^1$H NMR spectrum of compound **3a**, a doublet was appeared at δ 5.65 ppm ($J$ = 0.02 × 400 = 8 Hz) for the H-4′ hydrogen of 2-oxindole part. This proton

**Scheme 4**




was shielded by the magnetic anisotropy effect of phenyl ring attached to the position 2 of cyclopropane ring (Fig. 2, the structure was not optimized). Similar doublets were appeared for other synthesized compounds **3b–d**.

## CONCLUSION

In summary, some novel spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones were synthesized from 3-phenacylideneoxindoles in a one-pot simple and rapid procedure, and the products were obtained in good yields. These compounds may be active biological substances and worthy of attention for the medicinal and pharmaceutical chemists.

## EXPERIMENTAL

All chemicals used in this study were purchased from Merck and Fluka companies. Melting points were measured on a Qallenkamp melting point apparatus in open capillary tubes. The melting point measurement showed that the synthesized compounds decompose before they melt because they have highly crowded structure at cyclopropane ring. The IR spectra were taken from a Bruker Vector 22 FTIR spectrometer, and samples were used as a potassium bromide pellet. $^1$H NMR was recorded on a Bruker DRX-400 Avance instrument, and $^{13}$C NMR (125 MHz) was run on a Bruker DRX-500 Avance instrument using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. The purity of prepared spiro compounds was tested by the elemental analysis of C, H, and N elements using a Heraus CHN rapid analyzer. All prepared compounds were filtered and fractionally crystallized from ethanol/water solution.

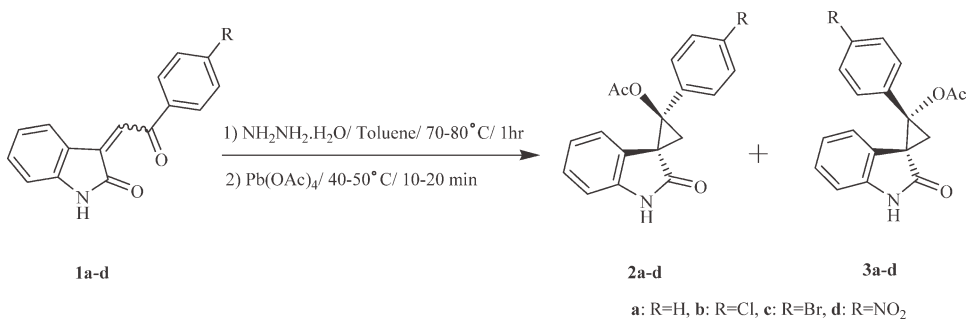
The starting materials, 3-phenacylideneoxindoles **1a–d**, were prepared in this laboratory according to the procedure reported in literature [26].

**General procedure for preparation of spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones 2a–d and 3a–d.** The **1a–d** (10 mmoles) were dissolved in toluene (20 mL) and then hydrazine hydrate (11 mmoles) was added to this solution and the mixture was stirred and refluxed at 70–80°C for 1 h. Then, 11 mmoles of solid lead(IV) acetate was added to the reaction mixture at 40–50°C and nitrogen extrusion began. The reaction was continued for about 10–20 min, and the spiro compounds **2a–d** and **3a–d** were prepared (Scheme 5). The products were filtered and fractionally crystallized from ethanol-water.

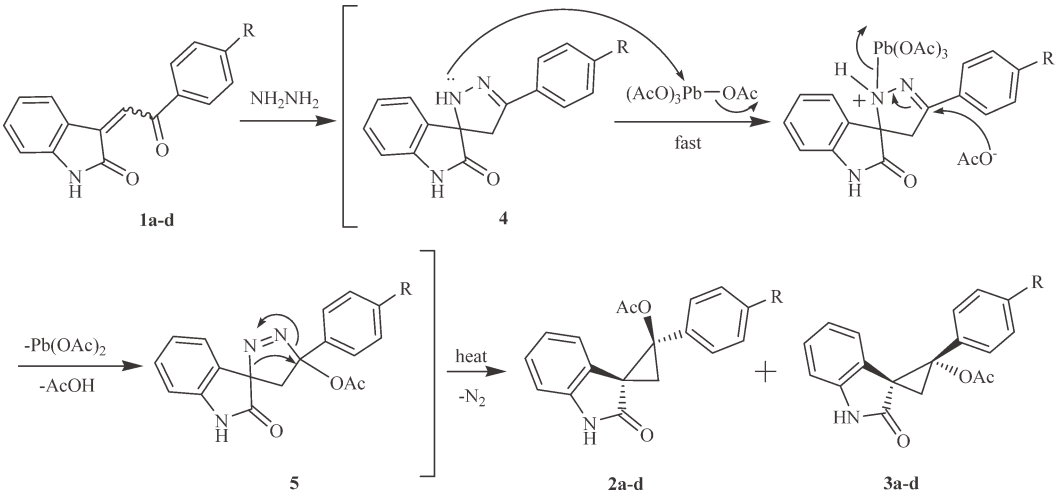
***rel-(1R,2R)-2-Acetyloxy-2-phenylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (2a).*** Light yellow solid (1.96 g), yield 67%, decomp.>98°C; IR (potassium bromide): 3419 (N—H), 3058, 3027, 2928, 2884, 1762 (C=O of acetate), 1709 (C=O of oxindole), 1621, 1597 cm$^{-1}$; $^1$H NMR: δ 2.04 (s, 3H, $CH_3$), 2.19 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.77 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 6.93–8.06 (m, 9H, ArH), 8.40 (s, 1H, NH); $^{13}$C NMR: δ 21.30 ($CH_3$), 27.05 ($CH_2$), 37.98 (spiro carbon), 71.70 (Ph—**C**—OAc), 110.52, 122.17, 122.46, 128.36, 128.70, 129.21, 129.75, 130.47, 134.27, 141.86, 169.77 (—**C**OO—), 175.57 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.67; H, 5.14; N, 4.75%.

***rel-(1R,2S)-2-Acetyloxy-2-phenylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3a).*** Light yellow solid (0.64 g), yield 22%, decomp.>98°C; IR (potassium bromide): 3419 (N—H), 3056, 3025, 2928, 2884, 1760 (C=O of acetate), 1709 (C=O of oxindole), 1620, 1597 cm$^{-1}$; $^1$H NMR: δ 2.03 (s, 3H, $CH_3$), 2.26 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.52 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 5.65 (d, 1H, $J$ = 8 Hz, H-4′ of oxindole), 6.63–7.84 (m, 8H, ArH), 8.45 (s, 1H, NH); $^{13}$C NMR: δ 21.47 ($CH_3$), 27.94 ($CH_2$),

**Scheme 5**



**Scheme 6**




37.47 (spiro carbon), 71.08 (Ph—**C**—OAc), 110.02, 121.69, 122.77, 127.93, 128.65, 129.16, 129.80, 131.90, 134.20, 141.35, 170.85 (—**C**OO—), 175.96 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.58; H, 5.05; N, 4.61%.

***rel-(1R,2R)-2-Acetyloxy-2-(4-chlorophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (2b).*** Light yellow solid (2.41 g), yield 74%, decomp.>101°C; IR (potassium bromide): 3417 (N—H), 3059, 3027, 2927, 2886, 1751 (C=O of acetate), 1703 (C=O of oxindole), 1622, 1597 $cm^{-1}$; $^1H$ NMR: δ 2.04 (s, 3H, $CH_3$), 2.18 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.69 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 6.85–7.95 (m, 8H, ArH), 8.91 (s, 1H, NH); $^{13}C$ NMR: δ 21.25 ($CH_3$), 27.05 ($CH_2$), 37.97 (spiro carbon), 70.84 ($ClC_6H_4$—**C**—OAc), 110.61, 122.31, 122.46, 127.13, 128.65, 128.99, 129.41, 131.89, 135.09, 141.80, 169.76 (—**C**OO—), 175.42 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.89; H, 4.31; N, 4.25%.

***rel-(1R,2S)-2-Acetyloxy-2-(4-chlorophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3b).*** Light yellow solid (0.58 g), yield 18%, decomp.>101°C; IR (potassium bromide): 3417 (N—H), 3057, 3026, 2927, 2884, 1751 (C=O of acetate), 1705 (C=O of oxindole), 1621, 1597 $cm^{-1}$; $^1H$ NMR: δ 2.02 (s, 3H, $CH_3$), 2.21 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.50 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 5.69 (d, 1H, $J$ = 8 Hz, H-4′ of oxindole), 6.66–7.79 (m, 7H, ArH), 8.83 (s, 1H, NH); $^{13}C$ NMR: δ 21.39 ($CH_3$), 27.79 ($CH_2$), 37.40 (spiro carbon), 70.10 ($ClC_6H_4$—**C**—OAc), 110.14, 121.89, 122.81, 127.80, 128.14, 128.58, 129.46, 133.42, 135.77, 141.33, 170.88 (—**C**OO—), 175.8 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.81; H, 4.26; N, 4.19%.

***rel-(1R,2R)-2-Acetyloxy-2-(4-bromophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (2c).*** Light yellow solid (2.22 g), yield 60%, decomp.>110°C; IR (potassium bromide): 3419 (N—H), 3058, 3029, 2926, 2893, 1715 (broad, C=O of

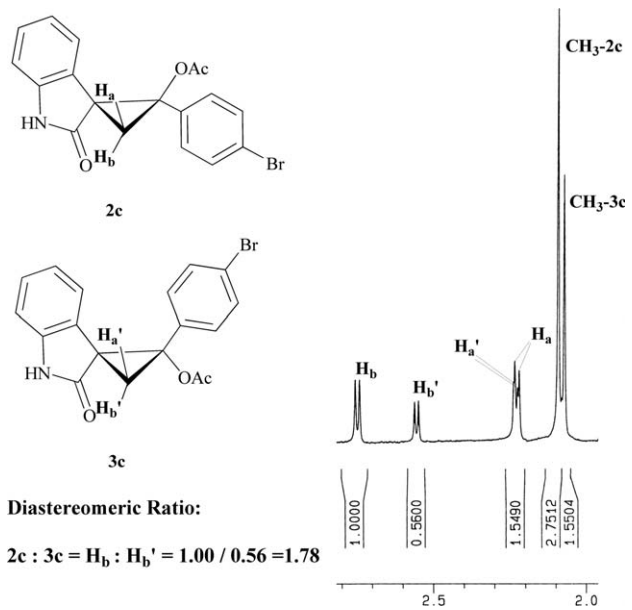



**Figure 1.** $^1H$ NMR signal integrations used for determination of diastereomeric ratio.

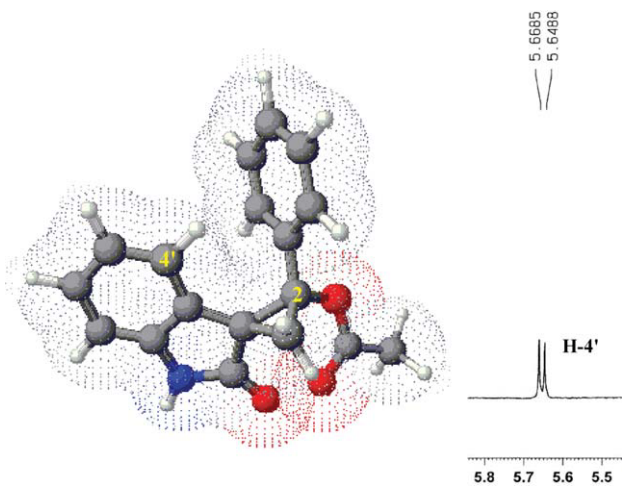



**Figure 2.** Shielding of H-4′ proton by anisotropic effect of phenyl ring. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

acetate and C=O of oxindole overlapped), 1621, 1597 $cm^{-1}$; $^1H$ NMR: δ 2.09 (s, 3H, $CH_3$), 2.21 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.74 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 6.99–7.98 (m, 8H, ArH), 8.48 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.98; H, 3.73; N, 3.75%.

***rel-(1R,2S)-2-Acetyloxy-2-(4-bromophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3c).*** Light yellow solid (1.15 g), yield 31%, decomp.>110°C; IR (potassium bromide): 3419 (N—H), 3056, 3028, 2926, 2892, 1715 (broad, C=O of acetate and C=O of oxindole overlapped), 1620, 1597 $cm^{-1}$; $^1H$ NMR: δ 2.07 (s, 3H, $CH_3$), 2.22 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.55 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 5.76 (d, 1H, $J$ = 8 Hz, H-4′ of oxindole), 6.73–7.87 (m, 7H, ArH), 8.39 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.93; H, 3.65; N, 3.69%.

***rel-(1R,2R)-2-Acetyloxy-2-(4-nitrophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′)-one (2d).*** Light yellow solid (2.09 g), yield 62%, decomp.>154°C; IR (potassium bromide): 3420 (N—H), 3080, 3031, 2925, 2890, 1719 (broad, C=O of acetate and C=O of oxindole overlapped), 1624, 1597 $cm^{-1}$; $^1H$ NMR: δ 2.09 (s, 3H, $CH_3$), 2.24 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.80 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 6.96–8.35 (m, 8H, ArH), 9.59 (s, 1H, NH); $^{13}C$ NMR: δ 21.13 ($CH_3$), 26.87 ($CH_2$), 38.23 (spiro carbon), 70.9 ($NO_2C_6H_4$—**C**—OAc), 110.58, 122.56, 122.72, 123.60, 123.95, 126.52, 128.48, 131.23, 141.27, 141.70, 169.82 (—**C**OO—), 175.54 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.91; H, 4.11; N, 8.26%.

***rel-(1R,2S)-2-Acetyloxy-2-(4-nitrophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3d).*** Light yellow solid (0.94 g), yield 28%, decomp.>154°C; IR (potassium bromide): 3420 (N—H), 3082, 3031, 2924, 2890, 1719 (C=O of acetate and C=O of oxindole overlapped), 1622, 1597 $cm^{-1}$; $^1H$ NMR: δ 2.04 (s, 3H, $CH_3$), 2.26 (d, 1H, $J$ = 7 Hz, C**H**$_{2a}$), 2.59 (d, 1H, $J$ = 7 Hz, C**H**$_{2b}$), 5.8 (d, 1H, $J$ = 8 Hz, H-4′ of oxindole), 6.66–8.65 (m, 7H, ArH), 9.49 (s, 1H, NH); $^{13}C$ NMR: δ 21.39 ($CH_3$), 27.15 ($CH_2$), 38.59 (spiro carbon), 71.11 ($NO_2C_6H_4$—**C**—OAc), 110.22, 122.15, 122.76, 122.90, 123.77, 126.89, 128.25, 131.08, 141.16, 141.60, 170.87 (—**C**OO—), 175.94 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.78; H, 4.09; N, 8.20%.

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## REFERENCES AND NOTES

[1] Pajouhesh, H.; Parson, R.; Popp, F. D. J Pharm Sci 1983, 72, 318.

[2] Jarrahpour, A. A.; Khalili, D. Molbank 2005, 4, M437.

[3] Sarangapani, M.; Reddy, V. M. Indian J Pharm Sci 1997, 59, 105.

[4] Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. Eur J Med Chem 2000, 35, 249.

[5] Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. Pharm Acta Helv 1999, 74, 11.

[6] Donaldson, W. A. Tetrahedron 2001, 57, 8589.

[7] Wessjohann, L. A.; Brandt, W.; Thiemann, T. Chem Rev 2003, 103, 1625.

[8] Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. J Org Chem 2001, 66, 81.

[9] Boger, D. L.; Hughes, T. V.; Hedrick, M. P. J Org Chem 2001, 66, 2207.

[10] Graham, D. W.; Ashton, W. T.; Barash, L.; Brown, J. E.; Brown, R. D.; Canning, L. F.; Chen, A.; Springer, J. P.; Rogers, E. F. J Med Chem 1987, 30, 1074.

[11] Salaun, J.; Baird, M. S. Curr Med Chem 1995, 2, 511.

[12] Yoshida, S.; Rosen, T. C.; Meyer, O. G. J.; Sloan, M. J.; Ye, S.; Haufe, G.; Kirk, K. L. Bioorg Med Chem 2004, 12, 2645.

[13] Faust, R. Angew Chem Int Ed 2001, 40, 2251.

[14] Yanovskaya, L. A.; Dombrovsky, V. A.; Khusid, A. Kh. Tsiklopropanis funktsionalnimi gruppami. Sintez i primenenie; (Cyclopropanes with Functional Groups, Synthesis and Application), Nauka: Moscow, 1980.

[15] Tsuji, T.; Nishida, S. The Chemistry of the Cyclopropyl Group; Wiley: New York, NY, 1987.

[16] Boche, G.; Walbirsky, H. M. Cyclopropane Derived Intermediates; John Wiley: New York, NY, 1990.

[17] Rappoport, Z. The Chemistry of the Cyclopropyl Group; Wiley: New York, NY, 1996.

[18] Salaün, J. Topics In Current Chemistry; Small Ring Compounds in Organic Synthesis VI: Cyclopropane Derivatives and their Diverse Biological Activities, Vol. 207; Springer Berlin: Heidelberg, 2000; pp 1–67.

[19] Ellis, D.; Kuhen, K. L.; Anaclerio, B.; Wu, B.; Wolff, K.; Yin, H.; Bursulaya, B.; Caldwell, J.; Karanewsky, D.; He, Y. Bioorg Med Chem Lett 2006, 16, 4246.

[20] Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. Tetrahedron 2007, 63, 1191.

[21] Ziyat, H.; Ait Itto, M. Y.; Ait Ali, M.; Riahi, A.; Karim, A.; Daran, J.-C. Arkivoc 2006, xii, 152.

[22] Cruz, D. C.; Yuste, F.; Díaz, E.; Ortiz, B.; Sanchez-Obregón, R.; Walls, F.; Ruano, J. L. G. Arkivoc 2005, vi, 211.

[23] Elinson, M. N.; Feducovich, S. K.; Vereshchagin, A. N.; Gorbunov, S. V.; Belyakov, P. A.; Nikishin, G. I. Tetrahedron Lett 2006, 47, 9129.

[24] Elinson, M. N.; Feducovich, S. K.; Stepanov, N. O.; Vereshchagin, A. N.; Nikishin, G. I. Tetrahedron 2008, 64, 708.

[25] Azarifar, D.; Shaabanzadeh, M. Molecules 2002, 7, 885.

[26] Azizian, J.; Shaabanzadeh, M.; Hatamjafari, F.; Mohammadizadeh, M. R. Arkivoc 2006, xi, 47.

[27] Corey, E. J.; Chaykovsky, M. J Am Chem Soc 1965, 87, 1353.

[28] Paxton, R. J.; Taylor, R. J. K. Synlett 2007, 4, 633.

[29] Kishner, N. M.; Zavadovskii, A. J Russ Phys Chem Soc 1911, 43, 1132.

[30] Tomilov, Y. V.; Shulishov, E. V.; Yarygin, S. A.; Nefedov, O. M. Russ Chem Bull 1995, 44, 2109.

[31] Bergman, R.G.; In Free Radicals, Kochi, J., Ed.; Wiley: New York, 1973; vol. 1, p 191.

[32] Freeman, J. P. J Org Chem 1964, 29, 1379.

[33] Kennedy, G. D.; Baumstark, A. L.; Dotrong, M.; Thomas, T.; Narayanan, N. J. J Heterocycl Chem 1991, 28, 1773.

[34] Fischer, E.; Knoevenagel, O. Ann Chem 1887, 239, 194.

[35] Lévai, A. Monatsh Chem 1995, 126, 1245.

[36] Lévai, A. J Heterocycl Chem 2002, 39, 1.

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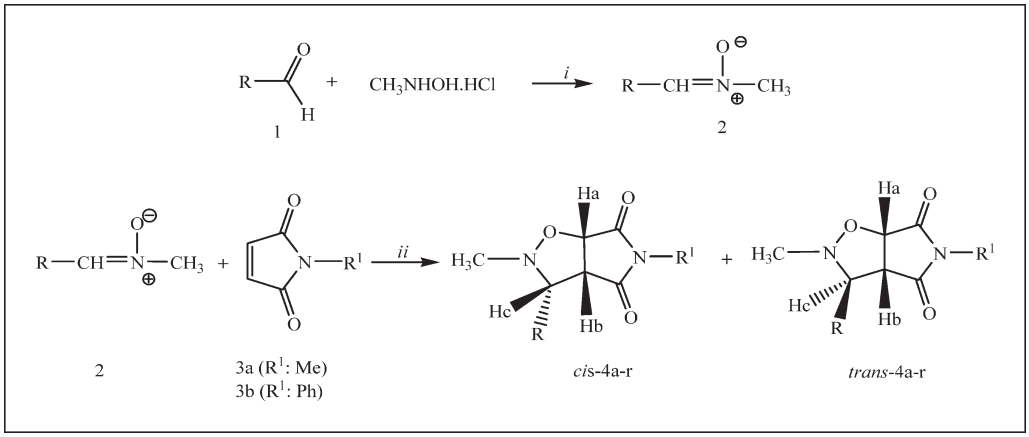


A series of isoxazolidine derivates (isomeric 2,3,5-trisubstitutedperhydropyrrolo[3,4-d]isoxazole-4,6-diones) used as anti-inflammatory, immunosuppressive, antibacterial agent, and inhibitor for some enzymes were synthesized. These compounds were prepared by 1,3-dipolar cycloaddition of *N*-methyl maleimide and *N*-phenyl maleimide with nitrones. Diastereomeric products obtained in this reaction were separated by column chromatography and recrystallized. All compounds synthesized were characterized by elemental analysis and spectroscopic methods ($^1$H NMR, $^{13}$C NMR, and FTIR).

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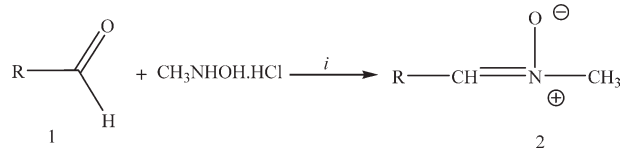
## INTRODUCTION

1,3-Dipolar cycloaddition reactions have been used for the synthesis of heterocyclic compounds [1]. High stereospecificity/stereoselectivity associated with these reactions make them synthetically important [2–5]. It has been found that 1,3-dipolar cycloaddition reactions proceed through a concerted mechanism [6]. The nitrone-olefin 1,3-dipolar cycloaddition reaction is interesting, as it can create as many as three new contiguous stereogenic centers in a single step [7,8]. Both inter and intramolecular nitrone–alkene cycloaddition reactions have received attention because they are useful methods for the formation of heterocycles of biological interest [9–12].

Isoxazolidines, the products of 1,3-dipolar cycloaddition reactions [13–20] between nitrones and alkenes, are saturated, five membered heterocycles containing adjacent nitrogen and oxygen atoms. As a result of the labile nature of the N—O bond under mildly reducing conditions, isoxazolidines have long been regarded as important synthetic intermediates and have been extensively utilized as 1,3-amino alcohol in a similar way to a wide variety of natural products and related molecules, particularly alkaloids [20] amino acids and amino sugars. Among a plethora of functional groups, the nitrone functionality has etched a place of distinction in organic synthesis. Remarkable regio-, stereo-, face-, and chemoselectivity along with efficient incorporation of multiple stereocenters have made nitrone cycloaddition reactions an attractive and efficient key step in the synthesis of a great many natural products of biological interest. In recent years, focus has been shifted toward asymmetric nitrone cycloaddition reactions; enantioselective [21], catalytic enantioselective [22], and diastereoselective [23] synthetic methodologies, as well as metal-assisted stereocontrol [24] have been reported. Isoxazolidines have been found to exhibit antimicrobial activity [25–28] and have been used as enzyme inhibitors [29–31]. Isoxazolidine nucleoside analogues, in which a furanose ring has been replaced by an N,O-heterocyclic system, are a particularly interesting group of compounds due to their potential antiviral activity [32–36]. Isoxazolidines have also been used as useful building blocks in the synthesis of various natural and unnatural compounds, including alkaloids, biologically active β-aminoacids, β-lactams, amino sugars, and simple 1,3-aminoalcohols owing to the facile cleavage of the N—O bond [37–39].

**Scheme 1.** ***i:*** $K_2CO_3$, $CH_2Cl_2$, $MgSO_4$, reflux. **2a:** R = 2-thiophenyl; **2b:** R = 5-methyl-2-thiophenyl; **2c***:* R = 3-methyl-2-thiophenyl; **2d:** R = 4-phenyl-2-thiophenyl; **2e:** 5-phenyl-2-thiophenyl; **2f:** R = 4-methylsulfanylbenzyl; **2g:** R = 2-furanyl; **2h:** R = 5-methyl-2-furanyl; **2i:** 1H-pyrrole-2-yl; **2j:** R = 1-methyl-1-H-indole-3-yl.




A review of the literature revealed that no more reports have been published on the synthesis of sulphur containing isomeric 2,3,5-trisubstitutedperhydropyrrolo[3,4-d] isoxazole-4,6-diones. The aim of this work is to synthesis a new type of isoxazolidine derivatives and characterizes their structures by using spectroscopic techniques such as $^1$H NMR, $^{13}$C NMR.

## RESULTS AND DISCUSSION

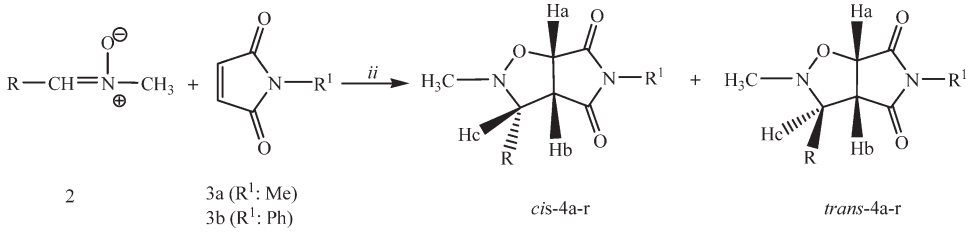
The 1,3-dipolar cycloaddition reactions between nitrones and an alkene is an extremely powerful synthetic method for the creation of complex heterocyclic structures. Best regarded as a concerted but asynchronous [4π + 2 π] suprafacial process, the reaction allows up to three contiguous carbon stereocentres to be created in a single step. In a manner analogous to the famous [4π + 2π] cycloaddition reactions first noted by Diels and Alder [40], nitrone–alkene cycloadditions can occur with the nitrone and alkene approaching each other. The reaction results in two possible products an endo- or exo- fashion; the two possible transition states giving rise to two diastereomeric products [41].

The 1,3-dipolar cycloaddition of nitrones to alkenes has been the most efficient approach used for the construction of isoxazolidines because the stereochemistry of the reaction is predictable, and the mechanism has been established. A wide range of acyclic and cyclic nitrones has been reacted with substituted alkenes leading to the formation of structurally diverse and highly functionalized nitrogen-containing compounds. Studies on both inter- and intramolecular nitrone to alkene dipolar cycloadditions have received much interest from a stereochemical point of view, as up to three new stereogenic centers can be created in the isoxazolidines depending on the structural features of the starting materials. Despite the known existence of acyclic nitrones as mixtures of (*E*)- and (*Z*)-isomers, or as single isomer in the case of cyclic analogues, the diastereoselectivity of cycloaddition depends also on the structures of the alkene dipolarophiles. In most cases, cycloadducts were formed in a predictable stereocontrolled manner due to steric and electronic effects [42].

In this study, a diastereomeric couple of two isoxazolidines was produced by 1,3 dipolar cycloaddition reaction of nitrons to alkenes, and the 1,3 dipolar cycloaddition reactions of substituted-*N*-methyl nitrons with *N*-methyl and *N*-phenyl maleimide were investigated (Schemes 1 and 2).

The evaluation of $^1$H NMR spectra of *cis*-isomers of isoxazolidines exhibited that Ha protons have chemical shifting between 4 and 5 ppm giving doublet peak with a coupling constant ($J \sim 7$ Hz); chemical shift value of Hb protons 3–4 ppm and doublet's doublet peak $J$ = 8/7 Hz; Hc chemical shifting 3–4 ppm and doublet peak with $J$ = 8.5 Hz.*Cis*-isomers of isoxazolidines have greater coupling constant of Hb-Hc protons ($J$ = 6–8 Hz) than *trans*-isomers ($J$ = 2–5 Hz). Hc proton gives a double peak approximately at 3.8–4.0 ppm for cis- isomers but a broad singlet peak at 4.3–4.5 ppm for *trans* isomers. It was observed that *cis*-isomers were obtained in higher yield than *trans*-isomers in the reaction of *N*-methyl-C-substituted nitrons with *N*-methyl maleimide.The peak multiplicity due to the spin spin coupling of Ha and Hb protons are clearly seen from $^1$H NMR spectra of the *trans* addition products. On the other hand, the spin spin coupling between Hb and Hc protons could not be seen. The peak belonging to Hc proton, appeared as a wide singlet. This situation is well

**Scheme 2.** ***ii:*** Benzene, reflux, **4a**: R = 2-thiophenyl, $R^1$ = Me; **4b**: R = 5-methyl-2-thiophenyl, $R^1$ = Me; **4c**: R = 3-methyl-2-thiophenyl, $R^1$ = Me; **4d**: R = 4-phenyl-2-thiophenyl, $R^1$ = Me; **4e**: R = 5-phenyl-2-thiophenyl, $R^1$ = Me; **4f**: R = 4-methylsulfanylphenyl, $R^1$ = Me; **4g**: R = 2-furanyl, $R^1$ = Me; **4h**: R = 5-methyl-2-furanyl, $R^1$ = Me; **4i**: R = 1H-pyrrole-2-yl, $R^1$ = Me; **4j**: R = 1-methyl-1-H-indole-3-yl, $R^1$ = Me; **4k**: R = 2-thiophenyl, $R^1$ = Ph; **4l**: R = 5-methyl-2-thiophenyl, $R^1$ = Ph; **4m**: R = 3-methyl-2-thiophenyl, $R^1$ = Ph; **4n**: R = 4-phenyl-2-thiophenyl, $R^1$ = Ph; **4o**: R = 5-phenyl-2-thiophenyl, $R^1$ = Ph; **4p**: R = 4-methylsulfanylphenyl, $R^1$ = Ph; **4q**: R = 2-furanyl, $R^1$ = Ph; **4r**: R = 5-methyl-2-furanyl, $R^1$ = Ph.



adjusted with the literatures. Because of the free rotation of N—C single bond, the proton in the methyl group and the Hc proton are sterically push each other. The electronic circle of Hc proton is consistently changed. Therefore, the peak due to Hc proton and methyl protons bonded to N atom on the isoxazolidine ring caused to occur a wide peak. The Ortep diagrams obtained from X-Ray analyzes of isoxazolidines (for example, *cis*-4c compound [43] and *cis*-4e compound [44]) it exhibited that Ha, Hb, and Hc protons are at the same side of the plane.The $^{13}C$ NMR spectra of the *trans* addition products showed that some singlet's carbons did not appear. However, the other data (such as X-Ray analyses of these compounds) confirm the proposed structures.

## EXPERIMENTAL

All melting points were determined by an Electrothermal 9100 apparatus and are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker 400 (400 MHz) NMR spectrometer. Samples were prepared in $CDCl_3$ and DMSO-$d_6$ with TMS as internal standard. Chemical shifts are given in ppm and coupling constant are given in Hz. Microanalyses were performed on a LECO-932 CHNS-O element analyzer. FTIR spectra were recorded on a Mattson 1000 spectrometer as KBr pellets. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use. *N*-Methylhydroxylamine hydrochloride, *N*-methylmaleimide, *N*-phenylmaleimide and substituted aldehydes, and other chemicals were obtained from Sigma–Aldrich.

**General procedure for the synthesis of substituted nitrones (2a–j).** Substituted aldehydes (10 mmol) were added to a solution of *N*-methylhydroxylamine hydrochloride (1.65 g, 20 mmol) in $CH_2Cl_2$ (50 mL). $K_2CO_3$ (3.03 g, 22 mmol) and $MgSO_4$ (0.60 g, 5 mmol) were added and the mixture refluxed for 12 h, and the reaction was monitored by TLC. The reaction mixture was filtered and solvent was evaporated. Then, column chromatography of the residue (*n*-hexane/ethyl acetate 1:1) gave nitrone (compound 2). The crude product was recrystallized from $CH_2Cl_2$/*n*-hexane [45].

**General procedure for the synthesis of substituted 2,5-dimethy tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, (exemplified by cis-4a, trans-4a).** A mixture of *N*-methyl-*C*-(thiophene-2-yl) nitrone **2a** (3 mmol, 0,429 g) and *N*-methylmaleimide **3a** (3.3 mmol, 0.370 g) was dissolved in 50 mL benzene. The reacting mixture was refluxed for 6–12 h. During this time, the reaction was monitored by TLC. Then, the solvent was evaporated. The products were separated by column chromatography [46]. The mixture of ethylacetate and petroleum ether was used as an eluent. The *cis*- and *trans*-isomers were recrystallized separately from $CHCl_3$/*n*-hexane mixture. Spectroscopic and analytical data of new compounds are given below.

***2,5-Dimethyl-3-(thiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4a, trans-4a.*** *Cis-4a.* Yield: 63%, mp 149–150°C. IR ($cm^{-1}$): 1714 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.8 (dd, 1H, Hb, $J \approx 8.4/7.5$ Hz), 4.2 (d, 1H, Hc, $J \approx 8.8$ Hz), 5.0 (d, 1H, Ha, $J \approx 7.2$ Hz), 7.0–7.4 (m, 3H, Ar—H), $^{13}C$ NMR (in *CDCl*$_3$, δ, ppm): 25, 43, 54, 71.35, 77, 127.0–127.9 (3C), 136, 173, 176. Anal. Calcd. For $C_{11}H_{12}N_2O_3S$: C 52.37; H, 4.79; N, 11.10; S, 12.71. Found: C, 51.93; H, 4.73; N, 10.96; S, 12.58.

*Trans-4a.* Yield: 35%, mp 168–169°C. IR ($cm^{-1}$): 1700 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.8 (d,1H, Hb, $J \approx 7.2$ Hz), 4.8 (very broad, 1H, Hc), 5.0 (d, 1H, Ha, $J \approx 7$ Hz), 7.0–7.4 (m, 3H, Ar—H); $^{13}C$ NMR (in *CDCl*$_3$, δ, ppm): 24, 41, 56, 72, 76, 127.0–128.2 (3C), 135, 174, 175. Anal. Calcd. For $C_{11}H_{12}N_2O_3S$: C 52,37; H, 4,79; N, 11,10; S, 12,71. Found: C, 52,06; H, 4,72; N, 11,04; S, 12,30.

***2,5-Dimethyl-3-(5-methyl-thiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione cis-4b.*** *Cis-4b.* Yield: 64%, mp 121–122°C. IR ($cm^{-1}$): 1707 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.4 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 3.0 (s, 3H, $CH_3$), 3.7 (dd, 1H, Hb, $J \approx 8.3/7.7$ Hz), 4.1 (d, 1H, Hc, $J \approx 8.8$ Hz), 4.9 (d, 1H, Ha, $J \approx 7.3$ Hz), 6.6–6.9 (dd, 2H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 15, 25, 42, 54, 71.35, 77, 126–142 (4C), 174, 176. Anal. Calcd. For $C_{12}H_{14}N_2O_3S$: C 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.90; H, 5.33; N, 10.04; S, 11.64.

***2,5-Dimethyl-3-(3-methyl-thiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4c, trans-4c.*** *Cis-4c.* Yield: 61%, mp 130–132°C IR ($cm^{-1}$): 1704 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.3 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 3.0 (s, 3H, $CH_3$), 3.6–3.8 (dd, 1H, Hb, $J \approx 8.7/7.5$ Hz), 4.2 (t, 1H, Hc, $J \approx 8.8$ Hz), 4.9–5.0 (d, 1H, Ha, $J \approx 7.3$ Hz), 6.8–7.2 (dd, 2H, Ar—H, $J \approx 5.05$); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 14, 25, 43, 53, 70, 77, 126–137 (4C), 174, 176. Anal. Calcd. For $C_{12}H_{14}N_2O_3S$: C 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 53.71; H, 5.21; N, 10.39; S, 12.03.

*Trans-4c.* Yield: 30%, mp 137–138°C IR ($cm^{-1}$): 1714 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.3 (s, 3H, $CH_3$), 2.4 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.6–3.8 (dd,1H, Hb $J \approx 7.2$ Hz), 4.5–4.8 (very broad, 1H, Hc), 4.8–5.0 (d, 1H, Ha, $J \approx 6$ Hz),, 6.5–6.9(dd, 2H, Ar—H, $J \approx 5.05$ ); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 15, 25, 39, 57, 67, 72, 75, 125–142 (4C), 173, 176. Anal. Calcd. For $C_{12}H_{14}N_2O_3S$: C 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 53.81; H, 5.38; N, 10.78; S, 12.02.

***2,5-Dimethyl-3-(4-phenyl-thiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4d, trans-4d.*** *Cis-4d.* Yield: 65%, mp 146–148°C IR ($cm^{-1}$): 1716 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.7 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7–3.8 (dd, 1H, Hb, $J \approx 8.4/7.7$ Hz), 4.2 (d, 1H, Hc, $J \approx 8.8$ Hz), 4.9–5.0 (d, 1H, Ha, $J \approx 7.3$ Hz), 7.3–7.6 (m, 7H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 43, 54, 71, 77, 122–143 (8C), 173, 176.15. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.75; H, 4.88; N, 8.24; S, 10.01.

*Trans-4d.* Yield: 32%, mp 158–160°C IR ($cm^{-1}$): 1700 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7–3.8 (d, 1H, Hb, $J \approx 7.2$ Hz), 4.8 (very broad, 1H, Hc ), 4.9–5.0 (d, 1H, Ha, $J \approx 7.1$ Hz), 7.3–7.7 (m, 7H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 39, 57, 67, 75, 119–142 (8C), 175, 176. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 39.17; H, 3.05; N, 5.32; S, 5.68.

***2,5-Dimethyl-3-(5-phenyl-thiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4e, trans-4e.*** *Cis-*

*4e*. Yield: 60%, mp 180–181°C IR ($cm^{-1}$): 1704 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.8 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7–3.8 (dd, 1H, Hb, $J \approx 8.4/7.7$ Hz), 4.1– 4.2 (d, 1H, Hc, $J \approx 8.8$ Hz), 4.9–5.0 (d, 1H, Ha, $J \approx 7.3$ Hz), 7.2–7.6 (m, 7H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 43, 54, 71, 77, 123–128 (4C),134–135 (3C), 172, 175. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 60.94; H, 5.22; N, 8.59; S, 9.17.

*Trans-4e*. Yield: 33%, mp 126–128°C IR ($cm^{-1}$): 1700 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.8 (d, 1H, Hb, $J \approx 7.2$ Hz), 4.6–4.8 (very broad, 1H, Hc ), 4.9.5.0 (d, 1H, Ha, $J \approx 7.2$ Hz), 6.8–7.7 (m, 7H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 75, 122–133 (5C). Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.52; H, 5.06; N, 8.56; S, 9.55.

***2,5-Dimethyl-3-(4-methylsulfanyl-phenyl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4f, trans-4f.*** *Cis-4f*. Yield: 62%, mp 140–141°C IR ($cm^{-1}$): 1718 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7–3.8 (dd, 1H, Hb, $J \approx 8.4/7.4$ Hz), 3.8 (d, 1H, Hc, $J \approx 8.6$ Hz), 4.9 (d, 1H, Ha, $J \approx 7.2$ Hz), 7.1–7.3 (dd, 4H, Ar—H, $J \approx 8$ Hz); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 15, 25, 42.8, 54.6, 75, 76.75, 127–128 (2C), 134–135 (3C), 174, 176. Anal. Calcd. For $C_{14}H_{16}N_2O_3S$: C 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 60.79; H, 7.26; N, 8.15; S, 9.29.

*Trans-4f*. Yield: 32%, mp 148–150°C IR ($cm^{-1}$): 1696 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.4–2.8 (6H, $2CH_3$), 3.1 (s, 3H, $CH_3$), 3.6–3.8 (d, 1H, Hb, $J \approx 7.2$ Hz), 4.6–4.8 (very broad, 1H, Hc ), 4.9.5.0 (d, 1H, Ha, $J \approx 7.2$ Hz), 7.2–7.7.4 (m, 4H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 17, 26, 43, 54, 71, 77, 122–143 (5C), 161, 176. Anal. Calcd. For $C_{14}H_{16}N_2O_3S$: C 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 57.91; H, 6.63; N, 9.43; S, 10.73

***2,5-Dimethyl-3-(furan-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4g, trans-4g.*** *Cis-4g*. Yield: 52%, mp 143–144°C IR ($cm^{-1}$): 1717 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.7 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7–3.8 (dd, 1H, Hb, $J \approx 8.1/7.8$ Hz), 3.9 (d, 1H, Hc, $J \approx 8.5$ Hz), 4.9 (d, 1H, Ha, $J \approx 7.3$ Hz), 6.2–7.5 (m, 3H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 40, 44, 50, 69, 76, 110–147 (4C), 174, 176. Anal. Calcd. For $C_{11}H_{12}N_2O_4$: C 55.93; H, 5.12; N, 11.86. Found: C, 58.02; H, 5.47; N, 12.03.

*Trans-4g*. Yield: 40%, mp 150–152°C IR ($cm^{-1}$): 1704 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.4 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7 (d, 1H, Hb, $J \approx 7.3$ Hz), 4.6 (very broad, 1H, Hc ), 4.9 (d, 1H, Ha, $J \approx 7.4$ Hz), 6.3–7.5 (m, 3H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 40, 54, 71, 77, 135–150 (4C), 173, 176. Anal. Calcd. For $C_{11}H_{12}N_2O_4$: C 55.93; H, 5.12; N, 11.86. Found: C, 55.77; H, 4.75; N, 11.65.

***2,5-Dimethyl-3-(5-methylfuran-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4h, trans-3h.*** *Cis-4h*. Yield: 64%, mp 150–151°C IR ($cm^{-1}$): 1702 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.3 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7–3.8 (dd, 1H, Hb, $J \approx 8.2/7.7$ Hz), 3.9 (d, 1H, Hc, $J \approx 8.6$ Hz), 4.9 (d, 1H, Ha, $J \approx 7.3$ Hz), 5.9–6.2 (dd, 2H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 13, 25, 39, 54, 69, 76, 110–153 (4C), 175, 176. Anal. Calcd. For $C_{12}H_{14}N_2O_4$: C 57.59; H, 5.64; N, 11.19. Found: C, 57.37; H, 5.59; N, 11.25.

*Trans-4h*. Yield: 33%, mp 154–155°C IR ($cm^{-1}$): 1701 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.3 (s, 3H, $CH_3$), 2.4 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.8 (d, 1H, Hb, $J \approx 7$ Hz), 4.5 (very broad, 1H, Hc ), 4.9–5.0 (d, 1H, Ha, $J \approx 7.4$ Hz), 5.98–6.25 (m, 2H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 13, 25, 53, 75, 106, 111. Anal. Calcd. For $C_{12}H_{14}N_2O_4$: C 57.59; H, 5.64; N, 11.19. Found: C, 58.08; H, 5.46; N, 11.21.

***2,5-Dimethyl-3-(1-methyl-1H-pyrrol-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4i, trans-4i.*** *Cis-4i*. Yield: 62%, mp 179–180°C IR ($cm^{-1}$): 1703 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.7 (s, 3H, $CH_3$), 2.9–3.0 (s, 3H, $CH_3$), 3.7 (s, 3H, $CH_3$), 3.7–3.8 (dd, 1H, Hb, $J \approx 7.8$ Hz), 3.9 (d, 1H, Hc, $J \approx 8.6$ Hz), 4.9 (d, 1H, Ha, $J \approx 7.3$ Hz), 6.2–7.5 (m, 3H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 34, 43, 53, 69, 76, 110–125 (4C), 174, 176. Anal. Calcd. For $C_{12}H_{15}N_3O_3$: C 57.82; H, 6.07; N, 16.86. Found: C, 58.28; H, 5.96; N, 17.01.

*Trans-4i*. Yield: 29%, mp 145–146°C IR ($cm^{-1}$): 1705 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.7 (s, 3H, $CH_3$), 3.7–3.8 (d, 1H, Hb, $J \approx 7$ Hz), 4.6 (very broad, 1H, Hc ), 4.9–5.0 (d, 1H, Ha, $J \approx 7.5$ Hz), 6.0–6.7 (m, 3H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 37 43, 54, 71, 77, 135–150 (4C), 175, 176. Anal. Calcd. For $C_{12}H_{15}N_3O_3$: C 57.82; H, 6.07; N, 16.86. Found: C, 57.72; H, 6.09; N, 17.09.

***2,5-Dimethyl-3-(1-methyl-1H-indol-3-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4j, trans-4j.*** *Cis-4j*. Yield: 60%, mp 198–200°C IR ($cm^{-1}$): 1703 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.7 (s, 3H, $CH_3$), 3.0 (s, 3H, $CH_3$), 3.8 (s, 3H, $CH_3$), 3.6–3.7 (dd, 1H, Hb, $J \approx 8.0/7.7$ Hz), 4.1–4.2 (d, 1H, Hc, $J \approx$ 8.6 Hz), 4.9–5.0 (d, 1H, Ha, $J \approx 7.3$ Hz), 6.9–7.0 (s,1H), 7.1–7.6 (m, 4H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 25, 33, 43, 54, 70, 76, 106, 109–127 (6C), 173, 176. Anal. Calcd. For $C_{16}H_{17}N_3O_3$: C 64.20; H, 5.72; N, 14.04. Found: C, 63.67; H, 5.79; N, 14.17.

*Trans-4j*. Yield: 32%, mp 131–133°C IR ($cm^{-1}$): 1704 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 3.1 (s, 3H, $CH_3$), 3.9 (s, 3H, $CH_3$), 3.7–3.8 (d, 1H, Hb, $J \approx 7$ Hz), 4.8 (very broad, 1H, Hc ), 4.9–5.0 (d, 1H, Ha, $J \approx 7.1$ Hz), 6.9–7.0 (s,1H), 7.1–7.8 (m, 4H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 24, 25, 30, 32, 56, 76, 108, 109–128 (6C). Anal. Calcd. For $C_{16}H_{17}N_3O_3$: C 64.20; H, 5.72; N, 14.04. Found: C, 65.21; H, 5.34; N, 14.50.

***2-Methyl-5-phenyl-3-(thiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4k.*** *Cis-4k*. Yield: 43%, mp 154–156°C IR ($cm^{-1}$): 1711 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.8 (s, 3H, $CH_3$), 3.8–3.9 (dd, 1H, Hb, $J \approx 8.3/8.0$ Hz), 4.4 (d, 1H, Hc, $J \approx 8.8$ Hz), 5.0–5.1 (d, 1H, Ha, $J \approx 7.5$ Hz), 7.0–7.5 (m, 8H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 43, 55, 72, 77, 112–136 (8C), 173, 176. Anal. Calcd. For $C_{16}H_{14}N_2O_3S$: C 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 62.42; H, 4.49; N, 8.92; S, 10.17.

***2-Methyl-5-phenyl-3-(5-methylthiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4l, trans-4l.*** *Cis-4l*. Yield: 41%, mp 139–141°C IR ($cm^{-1}$): 1722 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$) 3.7–3.8 (dd, 1H, Hb, $J \approx 8.5/7.7$ Hz), 4.2 (d, 1H, Hc, $J \approx 8.8$ Hz), 5.0–5.1 (d, 1H, Ha, $J \approx 7.5$ Hz), 6.6–7.5 (m, 7H, Ar—H); $^{13}C$ NMR (in $CDCl_3$, δ, ppm): 16, 43, 54, 72, 77, 126–142 (8C), 173, 176. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.96; H, 4.86; N, 8.72; S, 9.55.

*Trans-4l*. Yield: 47%, mp 152–155°C IR ($cm^{-1}$): 1718 s (C=O); $^1H$ NMR: (in $CDCl_3$, δ, ppm): 2.4 (s, 3H, $CH_3$), 2.6 (s, 3H, $CH_3$), 3.8–3.9 (d, 1H, Hb, $J \approx 7,2$ Hz), 4.8–4.9 (very broad, 1H, Hc), 5.0–5.1 (d, 1H, Ha, J ≈ 7.1 Hz), 6.6–7.6 (m,

8H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 15, 39, 53, 71, 77, 125–142 (8C), 175.0, 175.46. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.91; H, 4.90; N, 8.41; S, 10.16.

***2-Methyl-5-phenyl-3-(3-methylthiophen-2-yl)-tetrahydro-pyrrolo [3,4-d]isoxazole-4,6-dione, cis-4m, trans-4m.*** *Cis-4m.* Yield: 40%, mp 108–109°C IR ($cm^{-1}$): 1722 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 2.8 (s, 3H, $CH_3$) 3.8–3.9 (dd, 1H, Hb, $J \approx 8.5/7.9$ Hz), 4.2–4.4 (d, 1H, Hc, $J \approx 8.9$ Hz), 5.0–5.1 (d, 1H, Ha, $J \approx 7.5$ Hz), 6.8–7.6 (m, 7H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 14, 43, 53, 70, 77, 125–137 (8C), 171, 175. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.63; H, 5.15; N, 8.65; S, 9.46.

*Trans-4m.* Yield: 46%, mp 144–145°C IR ($cm^{-1}$): 1718 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.4 (s, 3H, $CH_3$), 2.6 (s, 3H, $CH_3$), 3.8–3.9 (d, 1H, Hb $J \approx 7$ Hz), 5.0–5.1 (very broad, 1H, Hc), 5.1–5.2 (d, 1H, Ha, J ≈ 7.1 Hz), 6.8–7.6 (m, 7H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 14, 44, 54, 67, 77, 126–144 (8C), 175, 177. Anal. Calcd. For $C_{17}H_{16}N_2O_3S$: C 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.91; H, 4.90; N, 8.41; S, 10.16

***2-Methyl-5-phenyl-3-(4-phenylthiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4n, trans-4n.*** *Cis-4n.* Yield: 41%, mp 145–146°C IR ($cm^{-1}$): 1723 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.8–2.9 (s, 3H, $CH_3$) 3.7–3.8 (dd, 1H, Hb, $J \approx 8.7/7.7$ Hz), 4.3 (d, 1H, Hc, $J \approx 8.8$ Hz), 5.0–5.1 (d, 1H, Ha, $J \approx 7.5$ Hz), 7.2–7.6 (m, 12H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 43, 55, 72, 77, 122–143 (12C), 173, 176. Anal. Calcd. For $C_{22}H_{18}N_2O_3S$: C 67.67; H, 4.65; N, 7.17; S, 8.21. Found: C, 67.83; H, 4.68; N, 7.11; S, 7.92.

*Trans-4n.* Yield: 44%, mp 134–138°C IR ($cm^{-1}$): 1710 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.6 (s, 3H, $CH_3$), 3.8–3.9 (d, 1H, Hb $J \approx 7.3$ Hz), 4.9–5.0 (very broad, 1H, Hc), 5.1–5.2 (d, 1H, Ha, J ≈ 7.1 Hz), 6.8–7.6 (m, 7H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 49, 76, 120–142 (11C), 175. Anal. Calcd. For $C_{22}H_{18}N_2O_3S$: C 67.67; H, 4.65; N, 7.17; S, 8.21. Found: C, 67.23; H, 4.67; N, 6.99; S, 7.36.

***2-Methyl-5-phenyl-3-(5-phenylthiophen-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4o, trans-4o.*** *Cis-4o.* Yield: 43%, mp 166–167°C IR ($cm^{-1}$): 1717 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.9 (s, 3H, $CH_3$), 3.9 (dd, 1H, Hb, $J \approx 8.5/7.8$ Hz), 4.3 (d, 1H, Hc, $J \approx 8.8$ Hz), 5.1–5.2 (d, 1H, Ha, $J \approx 7.5$ Hz), 7.2–7.6 (m, 12H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm):. 43, 55, 72, 77, 122–135 (12C), 173, 175. Anal. Calcd. For $C_{22}H_{18}N_2O_3S$: C 67.67; H, 4.65; N, 7.17; S, 8.21. Found: C, 67.64; H, 4.59; N, 7.27; S, 8.08.

*Trans-4o.* Yield: 48%, mp 175–176°C IR ($cm^{-1}$): 1718 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.7 (s, 3H, $CH_3$), 3.9 (d, 1H, Hb $J \approx 7.3$ Hz), 4.3 (very broad, 1H, Hc), 5.1–5.2 (d, 1H, Ha, J ≈ 7.3 Hz), 7.0–7.7 (m, 12H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 122–135 (9C). Anal. Calcd. For $C_{22}H_{18}N_2O_3S$: C 67.67; H, 4.65; N, 7.17; S, 8.21. Found: C, 67.82; H, 4.64; N, 7.11; S, 8.00.

***2-Methyl-5-phenyl-3-(4-methylsulfanyl-phenyl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4p, trans-4p.*** *Cis-4p.* Yield: 40%, mp 172–174°C IR ($cm^{-1}$): 1714 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.5 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 3.8–3.9 (dd, 1H, Hb, $J \approx 7.3/7.4$ Hz), 3.9–4.0 (d, 1H, Hc, $J \approx 8.7$ Hz), 5.0–5.1 (d, 1H, Ha, $J \approx 7.3$ Hz), 7.2–7.5 (m, 9H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 16, 43, 55, 76, 77, 127–140 (8C), 174, 176. Anal. Calcd. For $C_{19}H_{18}N_2O_3S$: C 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.43; H, 5.14; N, 7.75; S, 8.87.

*Trans-4p.* Yield: 42%, mp 184–185°C IR ($cm^{-1}$): 1718 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.0–3.0 (6H, $2CH_3$), 3.8–3.9 (d, 1H, Hb, $J \approx 7.5$ Hz), 4.8 (broad, 1H, Hc), 5.0–5.1 (d, 1H, Ha, $J \approx 7.4$ Hz), 7.2–7.6 (m, 9H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 15, 75, 126–139 (6C). Anal. Calcd. For $C_{19}H_{18}N_2O_3S$: C 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.43; H, 5.50; N, 8.07; S, 7.67.

***2-Methyl-5-phenyl-3-(furan-2-yl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione, cis-4q.*** *Cis-4q.* Yield: 40%, mp 101–103°C IR ($cm^{-1}$): 1710 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.7 (s, 3H, $CH_3$), 3.8–3.9 (dd, 1H, Hb, $J \approx 8.5/7.7$ Hz), 4.0–4.1 (d, 1H, Hc, $J \approx 8.7$ Hz), 5.0–5.1 (d, 1H, Ha, $J \approx 7.5$ Hz), 6.3–7.6 (m, 8H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 43, 53, 71, 77, 110–147 (7C), 172, 175. Anal. Calcd. For $C_{16}H_{14}N_2O_4$: C 64.42; H, 4.73; N, 9.39 Found: C, 56.33; H, 5.02; N, 12.10.

***2-Methyl-5-phenyl-3-(5-methylfuran-2-yl)-tetrahydro-pyrrolo [3,4-d]isoxazole-4,6-dione, cis-4r.*** *Cis-4r.* Yield: 42%, mp 137–140°C IR ($cm^{-1}$): 1701 s (C=O); $^1$H NMR: (in $CDCl_3$, δ, ppm): 2.4 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 3.8–3.9 (dd, 1H, Hb, $J \approx 8.5/7.7$ Hz), 3.9–4.0 (d, 1H, Hc, $J \approx 8.7$ Hz), 5.1–5.2 (d, 1H, Ha, $J \approx 7.5$ Hz), 6.3–7.6 (m, 7H, Ar—H); $^{13}$C NMR (in $CDCl_3$, δ, ppm): 14, 43, 50, 53, 77, 111–147 (8C), 155, 176. Anal. Calcd. For $C_{17}H_{16}N_2O_4$: C 65.38; H, 5.16; N, 8.97. Found: C, 68.07; H, 5.19; N, 9.14.

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## REFERENCES AND NOTES

[1] Padwa, A. 1,3-Dipolar Cycloaddition Chemistry; Wiley-Interscience: New York, 1984; pp 83–87.

[2] Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D.; Phalgune, U. D. J Org Chem 1999, 64, 4990.

[3] Werner, K. M.; de los Santos, J. M.; Weinreb, S. M. J Org Chem 1999, 64, 4865.

[4] Young, D. G.; Gomez-Bengoa, E.; Hoveyda, A. H. J Org Chem 1999, 64, 692.

[5] Snider, B. B.; Lin, H. J Am Chem Soc 1999, 121, 7778.

[6] Huisgen, R. In 1,3-Dipolar-Cycloaddition Chemistry; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; pp 1–167.

[7] Dondas, H. A.; Cummins, J. E.; Grigg, R.; Thornton-Pett, M. Tetrahedron 2001, 57, 7951.

[8] Alibes, R.; Blanco, P.; de March, P.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. Tetrahedron Lett 2003, 44, 523.

[9] Kumar, K. R. R.; Mallesha, H.; Rangappa, K. S. Eur J Med Chem 2003, 38, 613.

[10] Gothelf, K. V.; Jorgenson, K. A. Chem Rev 1998, 98, 863.

[11] Broggini, G.; Zecchi, G. Synthesis 1999, 6, 905.

[12] Mulzer, J. Organic Synthesis Highlights; Verlag Chemie: Weinheim, 1991, 77.

[13] Tufariello, J. J. In 1,3-Dipolar Cycloaddition Chemistry; Padwa, A. Ed.; John Wiley: New York, 1984; pp 83–87.

[14] Torsell, K. B. G. Nitrile oxides, Nitrones and Nitronates in Organic Synthesis; VCH: New York, 1988.

[15] Confalone, P. N.; Huie, E. M. Org React 1988, 36, 1.

[16] Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. Gazz Chim Ital 1989, 119, 253.

[17] Padwa, A. In Comprehensive Organic Synthesis 4; Trost, B.M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; pp 1069–1109.

[18] Wade, P. A. In Comprehensive Organic Synthesis 4; Trost, B.M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; pp 1113–1124.

[19] (a) Breuer, E. In Nitrones, Nitronates and Nitroxides, Breuer, E., Aurich, H. G., Nielsen, A., Eds.; John Wiley: Chichester, 1989; (b) Breuer, E. In Nitrones, Nitronates and Nitroxides; Breuer, E., Aurich, H. G., Nielsen, A., Eds.; John Wiley: Chichester, 1989; pp 248–312.

[20] Tufariello, J. J. Acc Chem Res 1979, 12, 396.

[21] (a) Ding, S.; Tangiguchi, K.; Ukaji, Y.; Inomata, K. Chem Lett 2001,468; (b) Jen, W. S.; Weiner, J. J. M.; McMillan, D. W. C. J Am Chem Soc 2000, 122, 9874.

[22] Goethelf, K. V.; Jorgensen, K. A. Chem Commun 2000,1449.

[23] Karlsson, S.; Högberg, H. Org Prep Proced Int 2001, 33, 103.

[24] Kanemasa, S. Synlett 2002,1371.

[25] Sadashiva, M. P.; Mallesha, H.; Hitesh, N. A.; Rangappa, K. S. Bioorg Med Chem 2004, 12, 6389.

[26] Ravi Kumar, K. R.; Mallesha, H.; Rangappa, K. S. Synth Commun 2003, 33, 1545.

[27] Vishu Kumar, B. K.; Dhananjaya, K.; Rangappa, K. S. Synth Commun 2002, 32, 1887.

[28] Vallance, P.; Bush, H. D.; Mok, B. J.; Hurtado-Guerrero, R.; Gill, H.; Rossiter, S.; Wilden, J. D.; Caddick, S. Chem Commun 2005,5563.

[29] Ding, P.; Miller, M. J.; Chen, Y.; Helquist, P.; Oliver, A. J.; Wiest, O. Org Lett 2004, 6, 1805.

[30] Rescifina, A.; Chiacchio, M. A.; Corsaro, A.; De Clercq, E.; Iannazzo, D.; Mastino, A.; Piperno, A.; Romeo, G.; Romeo, R.; Valveri, V. J Med Chem 2006, 49, 709.

[31] Procopio, A.; Alcaro, S.; De Nino, A.; Maiuolo, L.; Ortuso, F.; Sindona, G. Bioorg Med Chem Lett 2005, 15, 545.

[32] Chiacchio, U.; Genovese, F.; Iannazzo, D.; Piperno, A.; Quadrelli, P.; Antonino, C.; Romeo, R.; Valveri, V.; Mastino, A. Bioorg Med Chem 2004, 12, 3903.

[33] Merino, P.; Tejero, T.; Unzurrunzaga, F. J.; Franco, S.; Chiacchio, U.; Saita, M. G.; Iannazzo, D.; Piperno, A.; Romeo, G. Tetrahedron Asymmetry 2005, 16, 3865.

[34] Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. Tetrahedron 2003, 59, 5231.

[35] Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. J Org Chem 2000, 65, 5575.

[36] Chiacchio, U.; Saita, M. G.; Crispino, L.; Gumina, G.; Mangiafico, S.; Pistara, V.; Romeo, G.; Piperno, A.; De Clercq, E. Tetrahedron 2006, 62, 1171.

[37] Padwa, A.; Pearson, W. H. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Wiley: New York, NY, 2003; pp 1–81.

[38] Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. J Chem Soc Perkin Trans 1 2002, **22**, 2419.

[39] Kobayashi, S.; Jorgensen, K. A. Cycloaddition Reactions in Organic Synthesis; Wiley-VCH: Weinheim, 2001; pp 3737–3740.

[40] Diels, O.; Alder, K. Liebigs Ann Chem 1928, 460, 98.

[41] Frederickson, M. Tetrahedron 1997, 53, 403.

[42] Piotrowska, D. G. Tetrahedron 2006, 62, 12306.

[43] Odabasoglu, M.; Ozkan, H.; Yildirir, Y.; Buyukgungor, O. Acta Cryst 2008, E64, 1102.

[44] Odabasoglu, M.; Ozkan, H.; Yildirir, Y.; Buyukgungor, O. Acta Cryst 2008, E64, 1423.

[45] Heaney, F.; Rooney, O.; Cunningham, D. J Chem Soc Perkin Trans 2, 2001, 3, 373.

[46] Fisera, L.; Altimari, U. A. R.; Ertl, P.; Pronayova, N. Monatsh Chem 1993, 124, 1019.

# Synthesis and Biological Evaluation of New Naphthoquinone-Containing Pyrrolo-Thiazoles as Anticancer Agents

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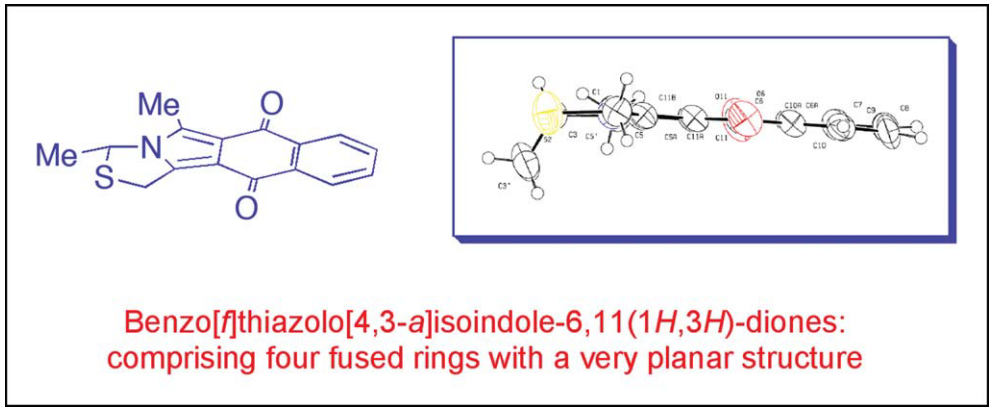


Naphthoquinones undergo 1,3-dipolar cycloaddition with bicyclic münchnones generated from thiazolidines affording new pyrrolo-thiazoles with a fused quinone nucleus. The products were obtained as single enantiomers in good yields. These benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-diones are comprised of four fused rings and present a very planar structure. The evaluation of their anticancer activity against melanoma A375 and colorectal adenocarcinoma WiDr human cell lines showed only moderate activity but gave insight into the modeling of new structures. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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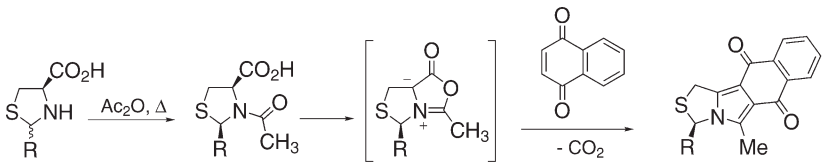
## INTRODUCTION

Quinone-containing drugs such as adriamycin, daunorubicin, and mitoxantrone have been established as one of the most effective classes of antitumor agents in clinical use. However, the drawbacks are the risk of dose-related cardiotoxicity and the development of resistance toward these compounds. To overcome these problems, there is a demand for the search of new lead compounds retaining the ''core quinone'' chromophore [1–4]. Hence, there is particular interest in combining the nucleus of a quinone with heterocyclic rings to achieve molecules with anticancer activity [5,6]. On the other hand, the thiazolidine ring is known to be involved in biologically active compounds with anti-inflammatory [7], anti-HIV [8], antimicrobial [9,10], or anticancer properties [11,12]. Particularly relevant is the anticancer activity of 2-arylthiazolidine carboxylic acid derivatives that are effective against the melanoma [13,14].

Our goal was to prepare structures combining the ''core quinone'' chromophore with a thiazolidine ring via the construction of the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles ring system. One important mechanism of action of quinone-containing drugs is thought to be related to intercalation processes with DNA in which planarity of the active nucleus is important.[6] Thus, a naphthoquinone ring system fused to a pyrrolo[1,2-*c*]thiazole should allow the system to attain the required planarity. On the other hand, pyrrolo[1,2-*c*]thiazoles are a class of compounds some of which showing biological activity namely antitumoral activity [15,16].

We have been interested in exploring a straightforward approach to new chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives via 1,3-dipolar cycloaddition of bicyclic münchnones [17–19]. Therefore, we used this synthetic strategy to prepare a range of new chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles retaining the ''core quinone''

**Scheme 1**




1 2 3

| Compound | R | Yield (%) |
|---|---|---|
| **4a** | H | 60 |
| **4b** | Me | 71 |
| **4c** | Ph | 76 |
| **4d** | $C_6H_4$-F-*p* | 74 |
| **4e** | $C_6H_4$-Cl-*p* | 73 |

chromophore using 1,4-naphthoquinones as dipolarophiles. The new heterocycles were tested against two cancer cell lines namely A375 melanoma and WiDr colorectal adenocarcinoma.

## RESULTS AND DISCUSSION

**Chemistry.** (*R*)-2-Substituted-thiazolidine-4-carboxylic acids **1** was obtained as mixture of the (*2S*,*4R*) and (*2R*,*4R*)-diastereoisomers from the reaction of an aldehyde and L-cysteine [20]. The synthesis of the corresponding 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **4** was carried out by heating a solution of the appropriate thiazolidine in acetic anhydride in the presence of 1,4-naphthoquinone. In this process, the thiazolidine undergoes *in situ* acylation followed by cyclodehydration to give a bicyclic münchnone **3**, which reacts further with 1,4-naphthoquinone to afford the corresponding 1,3-dipolar cycloadduct. The benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-diones **4** was obtained in yields ranging from 60 to 76%. It is worth to emphasize that derivatives **4b**–**4e** were isolated as single enantiomers with *R* configuration (Scheme 1).

The structure of compound **4b** was established by X-ray crystallography (Fig. 1) determining the absolute configuration of chiral 1*H*,3H-pyrrolo[1,2-*c*]thiazole derivatives **4b** as being *R*. The compound **4b** crystallizes in the chiral space group $P3_2$, with three symmetry related molecules in the unit cell. The molecules are comprised of four fused rings that are essentially planar. Only the carbon atom C3′ deviates significantly from the molecular plane, the C1-S2-C3-C3′ torsion angle is 124.1(2)°. In the solid state, due to the lack of conventional donors, only weak C—H. . .O and C—H. . .π intermolecular interactions join the molecules in a three-dimensional network.

The selectivity observed can be explained considering that 2-substituted-1,3-thiazolidine-4-carboxylic acids can undergo selective inversion at C-2 through a mechanism involving the opening of the ring with the formation of the corresponding Schiff base. However, the N-acylation of the 2-substituted-1,3-thiazolidine-4-carboxylic acids prevents this epimerization and allows the isolation of pure diastereoisomers [22–26]. Therefore, starting with (*2S*,*4R*) and (*2R*,*4R*)-2-substituted-1,3-thiazolidine-4-carboxylic acids mixture **1**, diastereoisomerically pure *N*-acetyl-2-substituted-1,3-thiazolidine-4-carboxylic acids **2** was generated allowing the synthesis of chiral cycloadducts. The chirality of the thiazolidine at C-4 is lost, and the chirality at C-2 is retained.

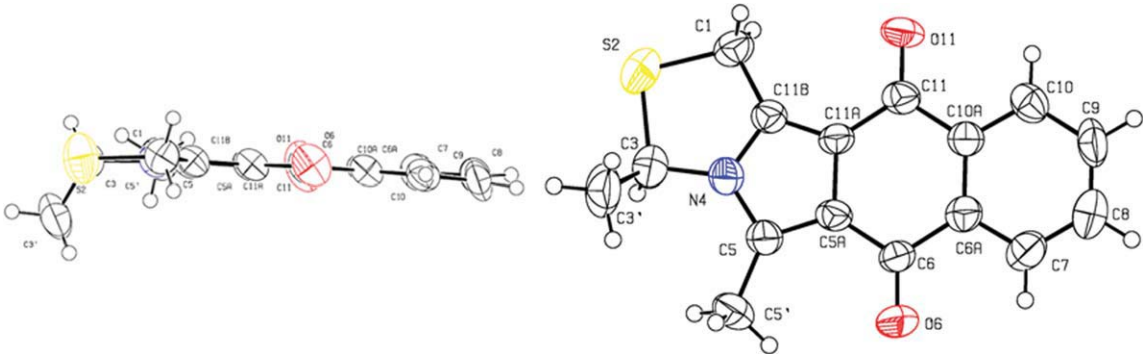
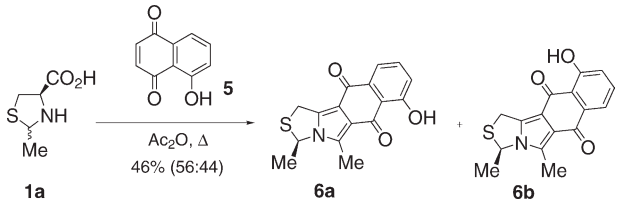



**Figure 1.** Ortep diagrams [21] for (*R*)-3,5-dimethylbenzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-dione **4b**. The displacement ellipsoids are drawn at the 50% probability level. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Scheme 2**




Juglone (5-hydroxy-1,4-naphthoquinone) **5** can also be used as dipolarophile in the 1,3-dipolar cycloaddition of the bicyclic münchnone generated from thiazolidine **1a**. However, a mixture of the two possible regioisomers **6a** and **6b** was obtained in 46% overall yield (Scheme 2).

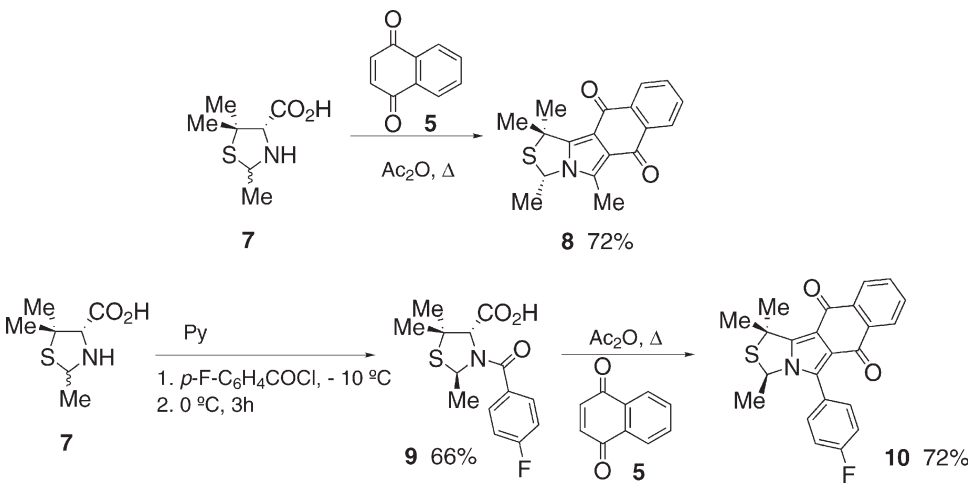
Similar chemistry can be carried to prepare the chiral benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-dione **8**. In this case, D-penicilamine, an α-amino acid with *S* configuration, was condensed with acetaldehyde leading to (*4S*)-2,5,5-trimethyl-1,3-thiazolidine-4-carboxylic acid (**7**) [27]. Therefore, the 1,3-dipolar cycloaddition of the bicyclic münchnone generated from thiazolidine **7** with 1,4-naphthoquinone afforded heterocycle **8** with *S* configuration (Scheme 3).

The synthetic strategy to prepare the chiral benzo[*f*]-thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-dione **10** required the synthesis of (2*R*,4*S*)-3-(4-fluorophenylcarbonyl)-2,5,5-trimethylthiazolidine-4-carboxylic acid (**9**) in diastereoisomeric pure form. Thus, the *N*-acylation of the starting thiazolidine **7** was carried out with the 4-fluorobenzoyl chloride following a general procedure previously reported [28,29]. Heating a solution of the heterocycle **9** in acetic anhydride in the presence of 1,4-naphthoquinone afforded the corresponding cycloadduct **10** with *R* configuration (Scheme 3).

**Anticancer activity.** Studies of the anticancer activity of the new benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-diones (except compound **4a** due to low solubility) have been carried out against WiDR colorectal adenocarcinoma and A375 melanoma human cancer cell lines. The results of the cell viability using different concentrations of the compounds in cultures of WiDr and A375 cells are presented in Figures 2 and 3. Cells were incubated during 48 h with DMSO solution of the selected compounds, washed, and then cell viability was evaluated by MTT test and compared with control experiments, where the incubation was carried out with only DMSO solution.

Values of cell viability show that the pyrrolo-thiazoles do not show considerable anticancer activity against the two cell lines tested. Nevertheless, the compounds are more active against melanoma cells than against colon adenocarcinoma cells. The comparison of the activity is clearer when the corresponding $IC_{50}$ values (Table 1) calculated from the dose-response curves (Figs. 2 and 3) are analysed. In the case of WiDr cells, with the exception of compound **4b** ($IC_{50} = 86$ μ*M*), using concentrations of up to 100 μ*M*, the $IC_{50}$ was not reached. For melanoma cells, with exception of compounds **8** and **6**, the values for $IC_{50}$ allow a comparison of the activity of the different structures. In this case, the anticancer activity order is **4c** > **10**,**4b**,**4e** > **4d** > **8**,**6**. Looking at the results of the two cell lines, it seems that compound **4b** with a methyl groups at positions 3 and 5 is the most active. Curiously, the similar structure **6** with only an additional hydroxyl substituent at the naphthoquinone moiety showed a much lower activity. Relatively to A375 melanoma cells, the pyrrolo-thiazole compounds synthesized are less active than 2-arylthiazolidine compounds described [14]. Also the activities of the pyrrolo-thiazoles are lower than those observed for 4-thiazolidinones for human colon carcinoma, albeit refering to different cell line [12]. The only exception to our results is

**Scheme 3**



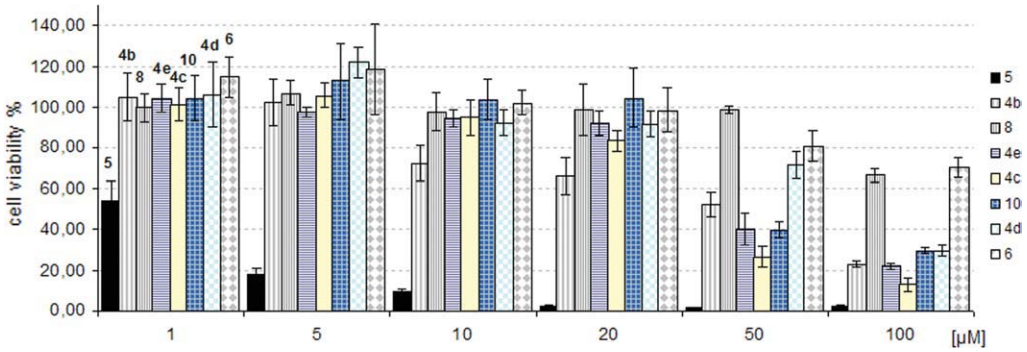



**Figure 2.** Values of cell viability of tested compounds against A375 melanoma cells. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the parent quinone, juglone (**5**), which shows potent cytotoxicity against the two cell lines, particularly in the case of the melanoma cells with lower $IC_{50}$, 1.23 μ*M* for A375 cells and 8.8 μ*M* for WiDr cells.

It is evident from the results that the incorporation of a thiazolidine ring to the quinone structure drastically reduce the anticancer activity as can be seen by the observed activity of juglone (**5**) and that of the corresponding 1,3-dipolar cycloadducts **6**. This can be explained by the fact that one important mechanism of action of quinones is related to the oxidation–reduction properties [30], which are probably altered by the introduction of the extra ring in compound **6**. Another plausible explanation for the observed low activity is related to the fact that juglone or quinone derivatives are good Michael acceptors that can react with the thiol group of proteins causing their deactivation as described for Pin 1 isomerase [31]. Our pyrrolo-thiazole compounds without the α,β-unsaturated carbonyl system lost this ability. Nevertheless, the low cytotoxycity of the pyrrolo-thiazole compounds was somewhat unexpected considering the geometry of the molecule (see Fig. 1). Molecular shape of thiazolidinones, characterized by the preferencial ''butterfly-like'' conformation, is particularly important regarding the activity as HIV [8]. However, in the case of quinones others suggest that planarity is an important factor to achieve biological activity because DNA intercalation is another possible mechanism of action [6]. For anthracene-9,10-diones which interfere with topoisomerase II, the derivatives need to be planar and also need another structural feature, like alkyl amino side chains, to interact with protein as observed for mixoxantrone [32]. In our case, the very planar structure of the benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-diones caused by the extended conjugation is not sufficient to allow a high anticancer activity possible because of the lack of this type of side chains. Studies are underway to construct new structures via our synthetic methodology aiming to obtain higher activities.

## CONCLUSIONS

Herein, we describe the successful synthesis of new naphthoquinone-containing heterocyclic compounds. Two kinds of chiral benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-diones, one derived from 1,4-naphthoquinone and the other from juglone, were prepared in good yield and high stereoselectivity. The new heterocylic systems are comprised of four fused rings that are

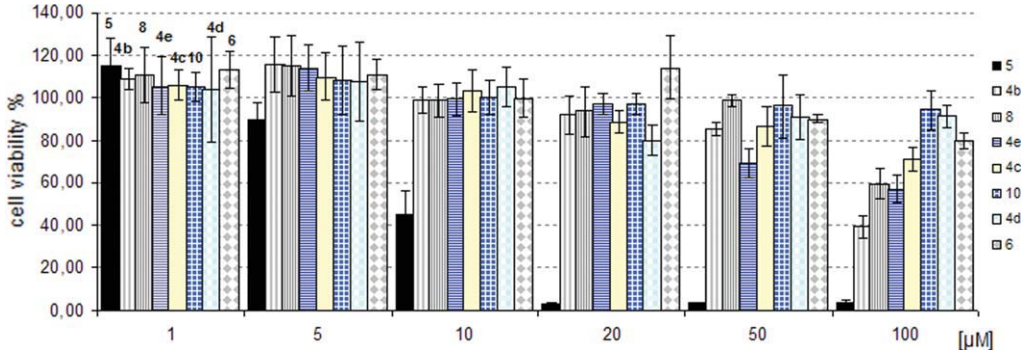
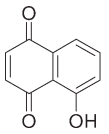
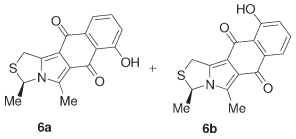
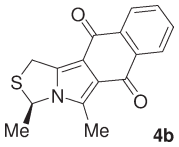
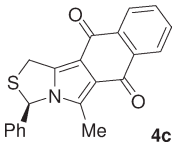
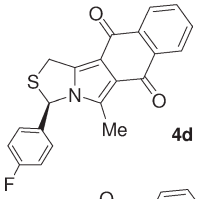
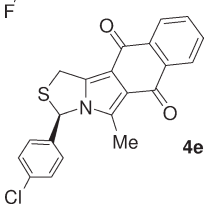
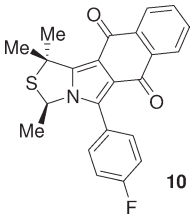
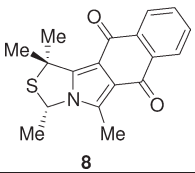



**Figure 3.** Values of cell viability of tested compounds against WiDr colon adenocarcinoma cells. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Table 1**

$IC_{50}$ values of the tested compounds.

| Compound | $IC_{50}$ ($\mu M$)[a] WiDr | A375 |
|---|---|---|
|  **5** | 8.8 ± 1.14 | 1.23 ± 0,22 |
|  **6a** **6b** | >100 | >100 |
|  **4b** | 86.0 ± 6.0 | 46.2 ± 2.8 |
|  **4c** | >100 | 36.2 ±1.8 |
|  **4d** | >100 | 65.7 ± 4.6 |
|  **4e** | >100 | 47.8 ± 3.8 |
|  **10** | >100 | 46.0 ± 6.4 |
|  **8** | >100 | >100 |

[a] Concentration needed to inhibit cell growth by 50% as determined from dose-response curves by exponential decay fitting ($r^2 > 0.9$).

essentially planar, only the substituent at C-3 deviates significantly from the molecular plane.

Anticancer activity of the synthesized compounds against WiDR colorectal adenocarcinoma and A375 melanoma cancer cells lines was determined. These heterocyclic compounds bearing a range of different functionalities showed low anticancer activity.

## EXPERIMENTAL

Reagents were commercial grade and were used as supplied. Chromatographic separations were performed using 70–230 mesh silica gel. Juglone (**5**) was prepared by a known procedure [33]. $^1$H NMR spectra were recorded on an instrument operating at 300 MHz or at 400 MHz. $^{13}$C NMR spectra were recorded on an instrument operating at 75.5 MHz or at 100 MHz. The solvent is deuteriochloroform except where indicated otherwise; chemical shifts are expressed in parts per million related to internal TMS, and coupling constants ($J$) are in hertz. Microanalyses were performed using an EA 1108-HNS-O Fisons instrument. Mass spectra were recorded under electron impact (EI) at 70 eV. HRMS spectra were obtained on a VG Autospect M spectrometer (TOF MS EI$^+$).

**General procedure for the synthesis of benzo[*f*]thiazolo[4,3-*a*]isoindole-6,11(1*H*,3*H*)-diones 4, 6, and 8.** The appropriate 1,3-thiazolidine-4-carboxylic acid (5 mmol), 1,4-naphthoquinone or juglone (7.5 mmol), and acetic anhydride (20 mL) were heated at 110–120°C for 2 h. The crude product was purified by flash chromatography [hexane/ethyl acetate].

***5-Methylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (4a).*** Yellow solid; mp > 250°C; IR (KBr): 721, 1255, 1553, 1650, 1659 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 400 MHz): δ 2.60 (s, 3H), 4.35 (s, 2H), 5.19 (s, 2H), 7.79–7.82 (m, 2H, Ar*H*), 8.07–8.12 (m, 2H, Ar*H*); $^{13}$C NMR (DMSO-d$_6$, 100MHz): δ 11.8, 25.3, 58.4, 117.4, 118.8, 122.0, 123.2, 123.5, 132.1, 135.3, 135.5, 138.7, 185.5, 186.0; HRMS (EI) Calcd. for (M$^+$)$C_{15}H_{11}NO_2S$ 269.0511. Found: 269.0519.

***(R)-3,5-Dimethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (4b).*** Yellow solid; mp 227–229°C (ethyl acetate/hexane); IR (KBr): 721, 1257, 1546, 1650, 1659 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz): δ 1,81 (d, $J$ = 6.3 Hz, 3H), 2.69 (s, 3H), 4.35 (d, $J$ = 15.7 Hz, 1H), 4.49 (dd, $J_1$ = 1.6 Hz and $J_2$ = 15.6 Hz, 1H), 5.47 (m, 1H), 7.67–7.70 (m, 2H, Ar*H*), 8.18–8.25 (m, 2H, Ar*H*); $^{13}$C NMR ($CDCl_3$,100MHz): δ 11.8, 25.3, 28.4, 58.2, 113.9, 122.1, 126.5, 126.8, 131.4, 132.8, 132.9, 135.2, 136.1, 138.2, 180.1, 181.2; MS (EI) $m/z$ 283 (M$^+$, 100%), 268 (82), 250 (21), 224 (74), 196 (9), 126 (10); HRMS (EI) Calcd. for (M$^+$)$C_{16}H_{13}NO_2S$ 283.0667. Found: 283.0671: $[\alpha]_{20}^{D} = +140$ ($c$ 0.5, $CH_2Cl_2$).

***(R)-5-Methyl-3-phenylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (4c).*** Yellow solid; mp 196–198°C (ethyl acetate/hexane); IR (KBr): 721, 1254, 1546, 1660 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz,): δ 2.31 (s, 3H), 4.48 (d, $J$ = 15.6 Hz, 1H), 4.64 (dd, $J_1$ = 1.7 Hz and $J_2$ = 15.7 Hz, 1H), 6.37 (d, $J$ = 1.7 Hz, 1H), 7.12–7.16 (m, 2H, Ar*H*), 7.35–7.40 (m, 3H, Ar*H*), 7.70–7.73 (m, 2H, Ar*H*), 8.22–8.26 (m, 2H, m, Ar*H*); $^{13}$C NMR ($CDCl_3$, 100MHz): δ 11.8, 29.4, 64.5, 113.9, 122.4, 125.8, 126.6, 126.9, 129.3, 129.4, 132.6, 132.9, 133.1, 135.6, 136.2, 139.1, 139.3, 180.3, 181.3; MS (EI) $m/z$ 334 ([M-Me]$^+$, 80%), 207 (12), 187 (100), 118

(32); HRMS (EI) Calcd. for ($M^+$)$C_{16}H_{13}NO_2S$ 283.0667. Found: 283.0671. HRMS (EI) Calcd. for ($M^+$)$C_{21}H_{15}NO_2S$ 345.0824. Found: 345.0838; $[\alpha]_{20}^{D} = +230$ (*c* 0.5, $CH_2Cl_2$).

***(R)-3-(4-Fluorophenyl)-5-methylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (4d).*** Yellow solid; mp 221–224°C (ethyl acetate/hexane); IR (KBr): 722, 1253, 1547, 1579, 1659 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.30 (s, 3H), 4.46 (d, *J* = 15.7 Hz, 1H), 4.62 (dd, $J_1$ = 1.6 Hz and $J_2$ = 15.6 Hz, 1H), 6.36 (s, 1H), 7.05–7.18 (m, 4H, Ar*H*), 7.69–7.72 (m, 2H, Ar*H*), 8.22–8.25 (m, 2H, Ar*H*); $^{13}C$ NMR ($CDCl_3$, 100MHz): δ 11.8, 29.4, 63.9, 114.0, 116.4, 116.6, 122.6, 126.6, 126.9, 127.8, 127.9, 132.3, 132.9, 133.1, 135.2, 136.2, 138.9, 163.0 (d, J = 248 Hz), 180.3, 181.2; MS (EI) *m/z* 345 ([M-F]$^+$, 100%), 312 (22), 224 (21), 121 (54); Anal. Calcd for $C_{21}H_{14}FNO_2S$: C, 69.41; H, 3.88; N, 3.85. Found: C,69.33; H, 3.82; N, 3.65; $[\alpha]_{20}^{D} = +210$ (*c* 0.5, $CH_2Cl_2$).

***(R)-3-(4-Chlorophenyl)-5-methylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (4e).*** Yellow solid; mp 213–215°C (ethyl acetate/hexane); IR (KBr): 720, 1255, 1547, 1573, 1647, 1659 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H), 4.47 (d, *J* = 15.6 Hz, 1H), 4.62 (dd, $J_1$ = 1.7 Hz and $J_2$ = 15.7 Hz, 1H), 6.36 (d, *J* = 1.7 Hz, 1H), 7.07–7.10 (m, 2H, Ar*H*), 7.34–7.38 (m, 2H, Ar*H*), 7.69–7.73 (m, 2H, Ar*H*), 8.22–8.25 (m, 2H, Ar*H*); $^{13}C$ NMR ($CDCl_3$, 100MHz): δ 11.8, 29.4, 63.9, 114.1, 122.6, 126.6, 126.9, 127.9, 129.7, 132.3, 132.9, 133.3, 135.2, 135.3, 136.2, 137.9, 138.9, 180.3, 181.2; MS (EI) *m/z* 363 ([M-Me]$^+$, 100%), 330 (16), 224 (31), 139 (61); Anal. Calcd for $C_{21}H_{14}ClNO_2S$: C, 66.40; H, 3.71; N, 3.69. Found:; C, 66.19; H, 3.71; N, 3.42; $[\alpha]_{20}^{D} = +280$ (*c* 0.5, $CH_2Cl_2$).

***(R)-7-Hydroxy-3,5-dimethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (6a) and (R)-10-hydroxy-3,5-dimethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (6b).*** (R)-7-Hydroxy-3,5-dimethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (6a) and (R)-10-hydroxy-3,5-dimethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (6b) was obtained as a mixture of regioisomers with a 56:44 distribution; mp 196.2–198.9°C (ethyl acetate/hexane); IR (KBr): 1159, 1249, 1551, 1575, 1624, 1654 $cm^{-1}$.

*Major component.* $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.82 (d, *J* = 6.3 Hz, 3H), 2.69 (s, 3H), 4.34 (d, *J* = 15.8 Hz, 1H), 4.45–4.51 (m, 1H), 5.45–5.51 (m, 1H), 7.16–7.20 (m, 1H, Ar*H*), 7.55–7.59 (m, 1H, Ar*H*), 7.70–7.75 (m, 1H, Ar*H*), 12.94 (s, 1H, OH).

*Minor Component.* $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.82 (d, *J* = 6.3 Hz, 3H), 2.69 (s, 3H), 4.34 (d, *J* = 15.8 Hz, 1H), 4.45–4.51 (m, 1H), 5.45–5.51 (m, 1H), 7.16–7.20 (m, 1H, Ar*H*), 7.55–7.59 (m, 1H, Ar*H*), 7.70–7.75 (m, 1H, Ar*H*), 13.18 (s, 1H, OH); $^{13}C$ NMR ($CDCl_3$, 100MHz): δ 11.8, 25.3, 28.4, 58.3, 58.4, 117.4, 118.6, 118.8, 122.0, 123.2, 123.6, 132.1, 135.3, 135.5, 136.4, 138.7, 162.6, 162.8, 186.0; MS (EI) *m/z* 299 ($M^+$, 100%), 284 (79), 266 (24), 240 (61), 212 (12); Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.04; H, 4.25; N, 4.64; $[\alpha]_{20}^{D} = +130$ (*c* 0.5, $CH_2Cl_2$).

***(S)-1,1,3,5-Tetramethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (8).*** Yellow solid; mp 185.4–188.2°C (ethyl acetate/hexane); IR (KBr): 732, 1262, 1418, 1541, 1589, 1655 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1,85 (d, *J* = 6.3 Hz, 3H), 1.98 (s, 3H), 2.03 (s, 3H), 2.69 (s, 3H), 5.55 (q, *J* = 6.3 Hz, 1H), 7.67–7.72 (m, 2H, Ar*H*), 8.19–8.24 (m, 2H, Ar*H*); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 11.8, 26.6, 28.8, 31.7, 52.2, 58.7, 112.3, 122.7, 126.6, 126.7, 130.6, 132.8, 132.9, 135.5, 135.6, 147.4, 179.7, 181.6; MS (EI) *m/z* 311 ($M^+$, 45%), 296 (100), 281 (7), 250 (14), 236 (30); Anal.Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C,69.65; H, 5.30; N, 4.52; $[\alpha]_{20}^{D} = +40$ (*c* 0.5, $CH_2Cl_2$).

***Synthesis of (R)-5-(4-fluorophenyl)-1,1,3-trimethylbenzo[f]-thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (10).*** The (2*R*,4*S*)-3-(4-fluorophenylcarbonyl)-2,5,5-trimethylthiazolidine-4-carboxylic acid (**9**) [7] (1.49 g, 5 mmol), 1,4-naphthoquinone (0.79 g, 7.5 mmol), and acetic anhydride (20 mL) were heated at 110–120°C for 2 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [hexane/ethyl acetate]. Compound **10** was obtained as a yellow solid; mp 183.4–185.0°C (ethyl acetate/hexane); IR (KBr): 735, 1268, 1498, 1542, 1594, 1609, 1656 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): δ 1.37 (d, *J* = 6.3 Hz, 3H), 2.04 (s, 3H), 2.08 (s, 3H), 5.72 (q, *J* = 6.3 Hz, 1H), 7.19–7.26 (m, 2H, Ar*H*), 7.56–7.71 (m, 4H, Ar*H*), 8.13–8.25 (m, 2H, Ar*H*); $^{13}C$ NMR ($CDCl_3$, 100MHz): δ 26.1, 29.0, 31.4, 52.2, 59.6, 112.8, 115.8, 116.1, 123.2, 125.4, 125.43, 126.7, 130.9, 131.6, 131.7, 133.0, 133.1, 135.3, 135.5, 148.6, 163.3 (d, *J* = 249 Hz), 179.8, 180.5; MS (EI) *m/z* 391 ($M^+$, 65%), 376 (100), 331 (50), 316 (52); Anal. Calcd for $C_{23}H_{18}FNO_2S$: C, 70.57; H, 4.63; N, 3.58. Found: C, 70.58; H, 4.58; N, 3.61; $[\alpha]_{20}^{D} = +50$ (*c* 0.5, $CH_2Cl_2$).

***Crystal data for (R)-3,5-dimethylbenzo[f]thiazolo[4,3-a]isoindole-6,11(1H,3H)-dione (4b).*** $C_{16}H_{13}N_1O_2S_1$, M = 283.33, hexagonal, *a* = 16.1968(3) Å, *c* = 4.44350(10) Å, *V* = 1009.52(3) Å$^3$, *T* = 293(2) K, space group $P3_2$, *Z* = 3, $m(MoK\alpha) = 0.240$ $mm^{-1}$, 3340 reflections measured, of which 1677 unique, used for direct methods structure determination [34] and full matrix least-squares refinement. The H atoms were placed at calculated idealized positions and refined as riding atoms. The final *R* ($F^2$) was 0.053 (for $I > 2\sigma(I)$) and $R_W(F^2)$ was 0.150 (for all reflections). The crystal used in data collection was twinned. Twin ratios refined to nearly 0.80:0.20. The Flack parameter refined to 0.0(2) [35].

***Measurement of cell viability.*** The *in vitro* cytotoxic effect of the molecules was evaluated in human colorectal adenocarcinoma (WiDR) and human melanoma (A375) cell lines both purchased from American Type Culture Collection. The cells were cultured in Dulbecco's Modified Eagle Medium supplemented with 10% heat-inactivated fetal bovine serum and 100 μ*M* sodium piruvate at 37°C, in a humidified incubator 95% air and 5% $CO_2$. For each experiment, cells were plated in 48-well plates, in a concentration of 40,000 cells/mL and kept overnight in the incubator, allow the attachment of the cells. The molecules tested were reconstituted on dimethylsulfoxide (DMSO) to achieve solutions with a concentration of 4 mg/mL. Several concentrations (1, 5, 10, 20, 50, and 100 μ*M*) of the molecules were tested by addition to the cell media. Final concentration of DMSO varied from 0.17 to 0.99%. For each experiment, two controls were performed: untreated cell cultures and cells treated with 1% DMSO, the vehicle of administration of the molecules. Cell-plates were incubated for 48 h. To analyze the proliferation inhibition, the MTT assay was performed. The ratio of absorbance of treated cultures to that of DMSO control cultures was obtained for all concentrations of every drug. From the dose-response curve obtained, a 50% inhibitory concentration ($IC_{50}$) was determined. Each experiment was performed in triplicate and repeated in two different sets of tests.

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## REFERENCES AND NOTES

[1] Hadden, M. K.; Hill, S. A.; Davenport, J.; Matts, R. L.; Blagg, B. S. J. Bioorg Med Chem 2009, 17, 634.

[2] Tandon, V. K.; Maurya, H. K.; Tripathi, A.; ShivaKeshava, G. B.; Shukla, P. K.; Srivastava, P.; Panda, D. Eur J Med Chem 2009, 44, 1086.

[3] Valderrama, J. A.; Leiva, H.; Rodríguez, J. A.; Theoduloz, C.; Schmeda-Hirshmann, G. Bioorg Med Chem 2008, 16, 3687.

[4] Pérez-Sacau, E.; Díaz-Penate, R. G.; Estévez-Braun, A.; Ravelo, A. G.; García-Castellano, J. M.; Pardo, L.; Campillo, M. J Med Chem 2007, 50, 696.

[5] Krapcho, A. P.; Menta, E.; Oliva, A.; Di Domenico, R.; Fiocchi, L.; Maresch, M. E.; Gallagher, C. E.; Hacker, M. P.; Beggiolin, G.; Giuliani, F. C.; Pezón, G.; Spinelli, S. J Med Chem 1998, 41, 5429.

[6] Gomez-Monterrey, I.; Santelli, G.; Campiglia, P.; Califano, D.; Falasconi, F.; Pisano, C.; Vesci, L.; Lama, T.; Grieco, P.; Novellino, E. J Med Chem 2005, 48, 1152.

[7] Zarghi, A.; Najafnia, L.; Daraee, B.; Dadrass, O. G.; Hedayati, M. Bioorg Med Chem Lett 2007, 17, 5634.

[8] Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Holtje, H. D.; Holtje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappalà, M. J Med Chem 2002, 45, 5410.

[9] Gouveia, F. L.; Oliveira, R. M. B.; Oliveira, T. B.; Silva, I. M.; Nascimento, S. C.; Sena, K. X. F. R.; Albuquerque, J. F. C. Eur J Med Chem 2009, 44, 2038.

[10] Bozdag-Dundar, O.; Ozgen, O.; Mentese, A.; Altanlar, N.; Atli, O.; Kendi, E.; Ertan, R. Bioorg Med Chem 2007, 15, 6012.

[11] Gududuru, V.; Hurh, E.; Dalton, J. T.; Miller, D. D. J Med Chem 2005, 48, 2584.

[12] Ottanà, R.; Carotti, S.; Maccari, R.; Landini, I.; Chiricosta, G.; Caciagli, B.; Vigorita, M. G.; Mini, E. Bioorg Med Chem Lett 2005, 15, 3930.

[13] Li, W.; Lu, Y.; Wang, Z.; Dalton, J. T.; Miller, D. D. Bioorg Med Chem Lett 2007, 17, 4113.

[14] Chen, J.; Wang, Z.; Lu, Y.; Dalton, J. T.; Miller, D. D.; Li, W. Bioorg Med Chem Lett 2008, 18, 3183.

[15] Anderson, W. K.; Mach, R. H. J Med Chem 1987, 30, 2109.

[16] Dureé, D.; Lancelot, J.; Robba, M.; Chenu, E.; Mathé, G. J Med Chem 1989, 32, 456.

[17] Pinho e Melo, T. M. V. D.; Barbosa, D. M.; Ramos, P. J. R. S.; Rocha Gonsalves, A. M. d'A.; Gilchrist, T. L.; Beja, A. M.; Paixão, J. A.; Silva, M. R.; Alte da Veiga, L. J Chem Soc Perkin Trans I 1999, 1219.

[18] Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Barbosa, Dália M.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Ramos Silva, M.; Alte da Veiga, L. Tetrahedron 2000, 56, 3419.

[19] Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Barbosa, D. M.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Ramos Silva, M.; Alte da Veiga, L.; Costa Pessoa, J. J Org Chem 2002, 67, 4045.

[20] Gilchrist, T. L.; Rocha Gonsalves, A. M. d'A.; Pinho e Melo, T. M. V. D. Tetrahedron 1994, 50, 13709.

[21] Johnson, C. K. ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA, 1976.

[22] Szilágyi, L.; Györgydeák, Z. J Am Chem Soc 1979, 101, 427.

[23] Györgydeák, Z.; Kajtár-Peredy, M.; Kajtár, J.; Kajtár, M. Liebigs Ann Chem 1987, 927.

[24] Benedini, F.; Ferrario, F.; Sala, A.; Sala, L.; Soresinetti, P. A. J Heterocycl Chem 1994, 31, 1343.

[25] Lázár, L.; Fülöp, F. Eur J Org Chem 2003, 3025.

[26] Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Barbosa, D. M.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Ramos Silva, M.; Alte da Veiga, L. Tetrahedron 2000, 56, 3419.

[27] Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Nunes, C. M. Tetrahedron 2007, 63, 1833.

[28] Pinho e Melo, T. M. V. D.; Gomes, C. S. B.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Ramos Silva, M.; Alte da Veiga, L. Tetrahedron 2002, 58, 5093.

[29] Soares, M. I. L.; Lopes, S. M. M.; Cruz, P. F.; Brito, R. M. M.; Pinho e Melo, T. M. V. D. Tetrahedron 2008, 64, 9745.

[30] Hodnett, E. M.; Wongwiechintana, C.; Dunn, W. J., III; Marrs, P. J Med Chem 1983, 26, 570.

[31] (a) Hennig, L.; Christner, C.; Kipping, M.; Schelbert, B.; Rücknagel, K. P.; Grabley, S.; Küllertz, G.;Fischer G. Biochemistry 1998, 37, 5953; (b) Fila, C.; Metz, C.; Van der Sluijs, P. J Biol Chem 2008, 283, 21714.

[32] Krapcho, A. P.; Petry, M. E.; Getahun, Z.; Landi, J. J.; Stallman, J.; Polsenberg, J. F.; Gallagher, C. E.; Maresch, M. J.; Hacker, M. P.; Giuliani, F. C.; Beggiolin, G.; Pezzoni, G.; Menta, E.; Manzotti, C.; Oliva, A.; Spinelli, S.; Tognella, S. J Med Chem 1994, 37, 828.

[33] Ribeiro, S. M.; Serra, A. C.; Rocha Gonsalves, A. M. d'A. Tetrahedron 2007, 63 7885.

[34] Sheldrick, G. M. SHELXS97 & SHELXL97; University of Göttingen: Germany, 1997.

[35] Flack, H. D. Acta Cryst 1983, A39, 876.

# One-Pot and Three-Component Synthesis of Spiro[chromeno[2,3-*d*] pyrimidine-5,3′-indoline]-diones and Spiro[chromeno[2,3-*c*] pyrazole-4,3′-indoline]-diones

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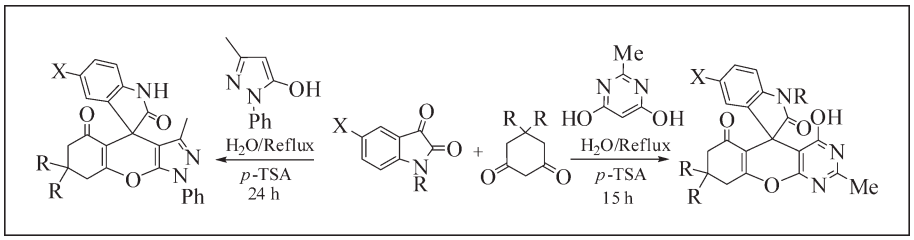


A novel, clean, one-pot and three-component synthesis of new spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones and spiro[chromeno[2,3-*c*]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones via cyclocondensation reaction of isatins, 1,3-cyclohexadiones, and 2-methylpyrimidine-4,6-diol or 3-methyl-1-phenyl-1*H*-pyrazol-5-ol, in aqueous media is reported.

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## INTRODUCTION

Multi-step reactions usually produce significant amount of waste, principally due to a series of isolation procedures which often involves toxic, hazardous, and expensive solvents after each step. Thus, multi-component reactions (MCRs) constitute an efficient synthetic strategy for the rapid and effective libratory organic transformations. Because, products are prepared in a one-pot and the diversity can be obtained directly by changing the reacting components [1,2]. On the other hand, polyfunctionalized heterocycles play considerable roles in the drug discovery process, and analysis of drugs shows that most of them are polyfunctionalized heterocycles [3]. Therefore, research on the multi-component synthesis of polyfunctionalized heterocyclic compounds is an interesting challenge.

Pyrimidine and its derivatives are important heterocyclic compounds with wide applications in medicinal chemistry, as antibacterial, antiviral, and antitumor agents [4]. A number of heterocycles fused with pyrimidines are known for their varied biological activities [5–8]. Similarly, chromene derivatives are an important group of compounds, widely exist in plants, including edible vegetables and fruits [9]. Synthetic analogues were developed over the years, some of them displaying remarkable effects as pharmaceuticals [10–13], including antifungal [12,14] and antimicrobial activity [15–17].

The indole skeleton is common in many natural products and medicinal agents [18]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindolines can highly enhance biological activity [19–21]. The spirooxindole nucleus occurs in several natural alkaloids and pharmacologically active substances displaying a broad range of biological activity [22–25]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [26–30].

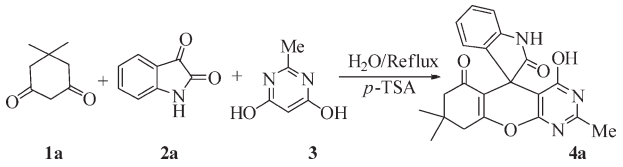
In continuation of our previous works for the synthesis of heterocyclic compounds [31–43], we performed the preparation of some new spirooxindole containing chromene ring fragments via three-component condensation reaction employing water as the reaction medium. Organic transformations in water without using toxic organic solvents are one of the current focuses today especially in our environmentally conscious society.

## RESULTS AND DISCUSSION

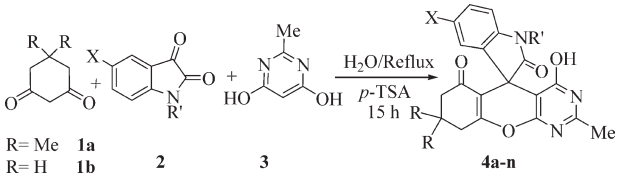
First, we carried out the three-component reaction of dimedone 1a, isatin **2a**, and 2-methylpyrimidine-4,6-diol **3** as a model reaction in different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive catalyst (Scheme 1). It was found that refluxing water was a best condition for the reaction and the desired product obtained in good yield after 15 h (Table 1).

Encouraged by this result, we extended the reaction of cyclic 1,3-dicarbonyls 1a,b and 2-methylpyrimidine-4,6-diol 3 with a range of isatins 2 under similar

**Scheme 1**




**Scheme 2**




conditions (Water/*p*-TSA) for 15 h, furnishing the respective 4-hydroxy-2-methyl-8,9-dihydrospiro[chromeno [2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones **4a–n** in good yields (Scheme 2, Table 2).

The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA the yields of products were very low (<30%) even after 48 h.

To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of 8,9-dihydrospiro [chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones.

Compounds **4a–n** are stable solids whose structures were established by IR, $^1$H NMR, and $^{13}$C NMR spectroscopy and elemental analysis. We have not established an exact mechanism for the formation of spiro [chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-dione 4, however, a reasonable possibility is shown in Scheme 3.

To further explore the potential of this protocol for spiro-heterocyclic synthesis, we investigated reaction of malononitrile 5 instead of 1,3-cyclohexadione 1 and obtained spiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitriles 6a–d selectively, in good yields for 24 h (Scheme 4, Table 3).

To further expand the scope of the reaction, we replaced 2-methylpyrimidine-4,6-diol **3** with 3-methyl-1-phenyl-1*H*-pyrazol-5-ol **7** and desired spiro[chromeno[2,3-*c*]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones **8** was selectively synthesized in good yields for 24 h (Scheme 5, Table 4).

Finally, when we extended this reaction to acenaphthylene-1,2-dione **9**, product of 3′,7′,7′-trimethyl-1′-phenyl-7′,8′-dihydro-1′*H*,2*H*-spiro[acenaphthylene-1,4′-chromeno[2,3-*c*]pyrazole]-2,5′(6′*H*)-dione **10** was generated in 70% yield after 24 h (Scheme 6).

**Table 1**

Conditions effect on the reaction.[a]

| Entry | Conditions | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | Water (80°C) | 24 | 63 |
| 2 | Water (reflux) | 15 | 85 |
| 3 | $CH_3CN$ (reflux) | 24 | 60 |
| 4 | EtOH (reflux) | 24 | 67 |
| 5 | DMF (100°C) | 24 | 60 |

[a] Dimedone (1 mmol), 2-methylpyrimidine-4,6-diol (1 mmol), isatin (1 mmol), and *p*-TSA (0.05 g).

## EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. $^1$H NMR and $^{13}$C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using a Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

**Typical procedure for the preparation of 4-hydroxy-2-methyl-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones (4a–n).** A mixture of dimedone or 1,3-cyclohexadione (1 mmol), 2-methylpyrimidine-4,6-diol (1 mmol), isatins (1 mmol), and *p*-TSA (0.05 g) in refluxing water (5 mL) was stirred for 15 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with water (10 mL) and recrystallized by EtOH to afford the pure product **4**.

***4-Hydroxy-2,8,8-trimethyl-8,9-dihydrospiro[chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4a).*** Light Brown powder (85%); m.p 205°C (dec). IR (KBr): 3450, 2952, 1718, 1670, 1622, 1596 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.97 (3H, s, $CH_3$), 1.03 (3H, s, $CH_3$), 2.05, 2.21 (2H, ABq, $J$ = 15.9 Hz, $CH_2$), 2.25 (3H, s $CH_3$), 2.57, 2.67 (2H, ABq, $J$ = 18.4 Hz, $CH_2$), 6.70–6.78 (2H, m, ArH), 6.85–6.87 (1H, m, ArH), 7.05–7.10 (1H, m, ArH), 10.37 (1H, s, NH), 12.49 (1H, s, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.2, 27.1, 28.3, 32.2, 46.6, 50.9, 100.6, 108.9, 112.8, 121.2, 123.2, 128.3, 133.9, 144.3, 159.8, 160.5, 161.1, 164.9, 178.1, 195.4. MS, *m*/

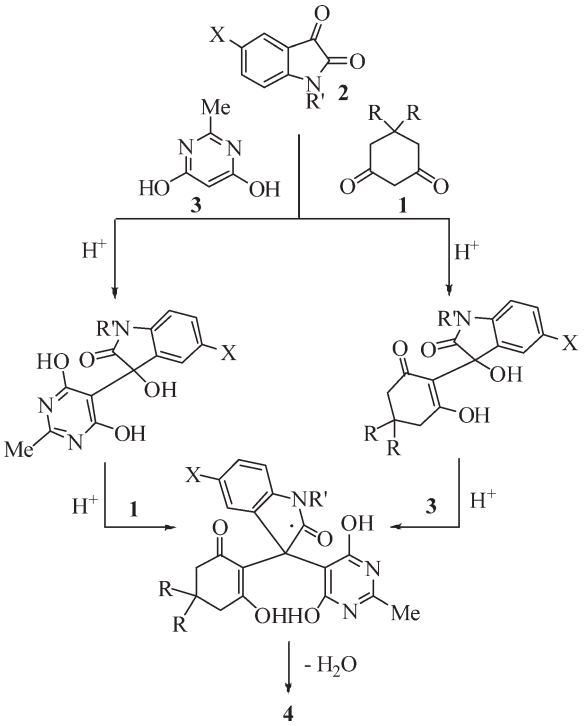
**Table 2**

Synthesis of spirochromenopyrimidine-indolines **4a–n**.

| Product **4** | R | R' | X | Yield (%)[a] |
|---|---|---|---|---|
| a | Me | H | H | 85 |
| b | Me | H | $NO_2$ | 89 |
| c | Me | $PhCH_2$ | H | 75 |
| d | Me | Me | H | 80 |
| e | Me | Me | $NO_2$ | 84 |
| f | Me | Me | Br | 80 |
| g | Me | Et | $NO_2$ | 82 |
| h | H | H | Br | 76 |
| i | H | H | $NO_2$ | 80 |
| j | H | Me | H | 77 |
| k | H | Et | H | 75 |
| l | H | $PhCH_2$ | H | 74 |
| m | H | Me | Br | 75 |
| n | H | Et | $NO_2$ | 77 |

[a] Isolated yields.

**Scheme 3**



$z$: 377 ($M^+$). Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.88; H, 5.01; N, 11.06.

***4-Hydroxy-2,8,8-trimethyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4b).*** Light Brown powder (89%); m.p 245°C (dec). IR (KBr): 3445, 2957, 1737, 1680, 1627, 1600 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.00 (3H, s, $CH_3$), 1.03 (3H, s, $CH_3$), 2.07–2.22 (2H, m, $CH_2$), 2.26 (3H, s, $CH_3$), 2.60–2.73 (2H, m, $CH_2$), 6.62–6.96 (1H, m, ArH), 7.87 (1H, m ArH), 8.11 (1H, d, $J$ = 8.5 Hz, ArH), 11.17 (1H, s, NH), 12.60 (1H,s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 21.3, 27.5, 27.7, 32.3, 46.6, 50.6, 99.5, 108.8, 111.8, 119.0, 126.1, 134.8, 142.2, 151.0, 160.4, 160.7, 161.3, 165.0, 166.1, 178.8, 196.0. MS, $m/z$: 422 ($M^+$). Anal. Calcd. for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.26. Found: C, 59.65; H, 4.35; N, 13.19.

Due to very low solubility of the product **4c**, we can not report the $^{13}C$ NMR data for this product.

***1′-Bnzoyl-4-hydroxy-2,8,8-trimethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4c).*** Light Brown powder (74%); mp 125–135°C (dec). IR (KBr): 3452, 2957, 1730, 1673, 1608 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1. 21 (3H, t, $J$ = 6.7 Hz, $CH_3$), 0.99 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.09, 2.25 (2H, ABq, $J$ = 16.0 Hz, $CH_2$), 2.27 (3H, s, $CH_2$), 2.61, 2.71 (2H, ABq, $J$ = 17.0 Hz, $CH_2$), 4.84, 4.94 (2H, ABq, $J$ = 16.0 Hz, $NCH_2$), 6.53 (1H, d, $J$ = 8.8 Hz, ArH), 6.82–6.87 (1H, m, ArH), 6.98 (1H, d, $J$ = 8.4 Hz, ArH), 7.03–7.08 (1H, m, ArH), 7.25–7.34 (3H, m, ArH), 7.63–7.66 (2H, m, ArH), 12.64 (1H, s, OH). MS, $m/z$: 467 ($M^+$). Anal. Calcd. for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.88; H, 5.44; N, 8.91.

***4-Hydroxy-1′,2,8,8-tetramethyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4d).*** Light Brown powder (80%); m.p 218°C (dec). IR (KBr): 3527, 2952, 1694, 1671, 1596 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 0. 98 (3H, s, $CH_3$), 1.03 (3H, s, $CH_3$), 2.04, 2.18 (2H, ABq, $J$ = 16.0 Hz, $CH_2$), 2.26 (3H, s, $CH_3$), 2.59, 2.67 (2H, ABq, $J$ = 17.1 Hz, $CH_2$), 3.13 (3H, s, $NCH_3$), 6.82–6.94 (3H, m, ArH), 7.16–7.21 (1H, m,ArH), 12.44 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 21.3, 26.9, 27.2, 28.3, 32.2, 46.1, 50.8, 100.4, 107.8, 112.6, 122.0, 123.0, 128.6, 133.0, 145.7, 159.9, 160.5, 160.9, 165.1, 176.8, 195.4, 195.6. MS, $m/z$: 391 ($M^+$). Anal. Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.47; H, 5.36; N, 10.69.

***4-Hydroxy-1′,2,8,8-tetramethyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4e).*** Light Brown powder (84%); m.p 207°C (dec). IR (KBr): 3548, 2967, 1740, 1686, 1609 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 0. 99 (3H, s, $CH_3$), 1.02 (3H, s, $CH_3$), 2.12–2.15 (2H, m, $CH_2$), 2.27 (3H, s, $CH_3$), 2.63–2.69 (2H, m, $CH_2$), 3.24 (3H, s, $NCH_3$), 7.19 (1H, d, $J$ = 8.7 Hz, ArH), 7.92 (1H, s, ArH), 8.19 (1H, d, $J$ = 8.7 Hz, ArH), 12.57 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 21.4, 27.3, 27.7, 27.8, 32.2, 32.3, 46.0, 50.5, 99.3, 107.9, 111.7, 118.6, 126.2, 133.9, 142.7, 151.8, 160.6, 160.8, 161.2, 166.3, 177.7, 196.0. MS, $m/z$: 436 ($M^+$). Anal. Calcd. for $C_{22}H_{20}N_4O_6$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.61; H, 4.66; N, 12.89.

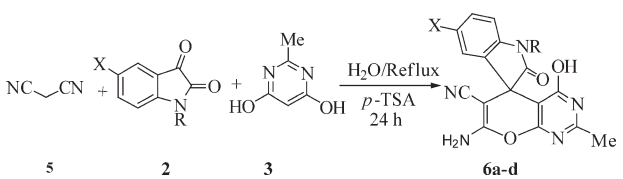
***5′-Bromo-4-hydroxy-1′,2,8,8-tetramethyl-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4f).*** Light Brown powder (80%); m.p 230°C (dec). IR (KBr): 3517, 2952, 1703, 1677, 1653, 1607 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 0. 99 (3H, s, $CH_3$), 1.02 (3H, s, $CH_3$), 2.05–2.10 (2H, m, $CH_2$), 2.26 (3H, s, $CH_3$), 2.63 (2H, brs, $CH_2$), 3.12 (3H, s, $NCH_3$), 6.90 (1H,d, $J$ = 8.4 Hz, ArH), 7.16 (1H, s, ArH), 7.37 (1H, d, $J$ = 8.6 Hz, ArH), 12.50 (1H, s, OH). $^{13}C$

**Table 3**

Synthesis of spiro[indoline-pyranopyrimidine]-carbonitriles **6a–d**.

| Product **6** | R | X | Yield (%) |
|---|---|---|---|
| a | H | H | 80 |
| b | H | $NO_2$ | 82 |
| c | Me | $NO_2$ | 65 |
| d | Et | $NO_2$ | 63 |

**Scheme 4**



**Scheme 5**

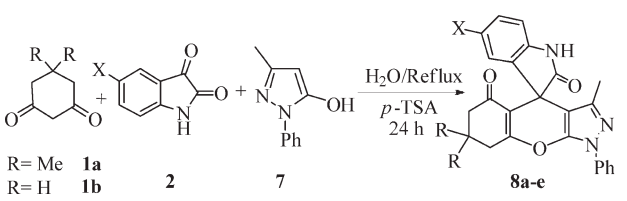


**Table 4**

Synthesis of spiro[chromenopyazole-indoline]-diones **8a–e**.

| Product **8** | R | R' | X | Yield (%) |
|---|---|---|---|---|
| a | Me | H | H | 80 |
| b | Me | H | $NO_2$ | 75 |
| c | Me | H | Br | 81 |
| d | H | H | H | 73 |
| e | H | H | $NO_2$ | 70 |

NMR (75 MHz, DMSO-$d_6$): δ = 21.3, 27.0, 27.7, 27.8, 32.2, 46.2, 50.7, 99.8, 109.7, 112.1, 113.7, 126.0, 131.2, 135.3, 145.2, 160.2, 160.6, 161.3, 165.7, 176.5, 195.7, 195.8. MS, *m*/*z*: 471 ($M^+$), 469 ($M^+$). Anal. Calcd. for $C_{22}H_{20}BrN_3O_4$: C, 56.18; H, 4.29; N, 8.93. Found: C, 56.23; H, 4.23; N, 8.85.

***1′-Ethyl-4-hydroxy-2,8,8-trimethyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4g).*** Light Brown powder (82%); m.p 240°C (dec). IR (KBr): 3530, 2952, 1735, 1680, 1608 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 0. 99 (3H, s, $CH_3$), 1.02 (3H, s, $CH_3$), 1.22 (3H, t, *J* = 6.9 Hz, $CH_3$), 2.09–2.15 (2H, m, $CH_2$), 2.60–2.74 (2H, m, $CH_2$), 3.80–3.82 (2H, m, $NCH_2$), 7.21 (1H, d, *J* = 8.7 Hz, ArH), 7.91 (1H, s, ArH), 8.18 (1H, d, *J* = 8.4 Hz, ArH), 12.57 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 12.1, 21.4, 27.7, 32.2, 32.3, 35.3, 50.5, 50.6, 99.4, 107.8, 111.7, 118.7, 126.2, 134.1, 142.5, 151.0, 160.5, 160.8, 161.2, 165.2, 166.2, 177.1, 195.9. MS, *m*/*z*: 450 ($M^+$). Anal. Calcd. for $C_{23}H_{22}N_4O_6$: C, 61.33; H, 4.92; N, 12.44. Found: C, 61.39; H, 4.97; N, 12.38.

***5′-Bromo-4-hydroxy-2-methyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4h).*** Light Brown powder (74%); m.p 240°C (dec). IR (KBr): 3404, 2957, 1748, 1704, 1647, 1615 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1. 92 (2H, brs, $CH_2$), 2.25 (5H, brs, $CH_2$, and $CH_3$), 2.71 (2H, brs, $CH_2$), 6.68 (1H, d, *J* = 8.1 Hz, ArH), 7.11 (1H, s, ArH), 7.25 (1H, d, *J* = 8.1 Hz, ArH), 10.55 (1H, s, NH), 12.53 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 20.1, 21.3, 27.6, 37.2, 46.9, 100.1, 110.7, 112.9, 113.3, 125.9, 126.2, 131.0, 136.4, 143.7, 160.4, 160.1, 167.3, 177.9, 195.8. MS, *m*/*z*: 427 ($M^+$). Anal. Calcd. for $C_{19}H_{14}BrN_3O_4$: C, 53.29; H, 3.30; N, 9.81. Found: C, 53.23; H, 3.36; N, 9.88.

***4-Hydroxy-2-methyl-5′-nitro-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4i).*** Light Brown powder n(80%); m.p 250°C (dec). IR (KBr): 2450, 3203, 1717, 1682, 1627 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.93 (2H, brs, $CH_2$), 2.27 (5H, brs, $CH_2$, and $CH_3$), 2.50 (2H, brs, $CH_2$), 6.93 (1H,d, *J* = 8.7 Hz, ArH), 7.89 (1H, s, ArH), 8.10 (1H,d, *J* = 8.6 Hz, ArH), 11.18 (1H, s, NH), 12.58 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 20.1, 21.3, 27.6, 37.0, 46.7, 99.6, 108.8, 112.8, 119.2, 126.1, 134.9, 142.2, 150.9, 160.4, 160.6, 161.2, 168.0, 178.9, 196.1. MS, *m*/*z*: 394 ($M^+$). Anal. Calcd. for $C_{19}H_{14}N_4O_6$: C, 57.87; H, 3.58; N, 14.21. Found: C, 57.92; H, 3.53; N, 14.15.

***4-Hydroxy-1′,2-dimethyl-8,9-dihydrospiro[chromeno[2,3-d] pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4j).*** Light Brown powder (76%); m.p 246°C (dec). IR (KBr): 3450, 2936, 1693, 1647, 1607 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1. 91 (2H, brs, $CH_2$), 2.19–2.25 (5H, m, $CH_2$, and $CH_3$), 2.72 (2H, brs, $CH_2$), 3.13 (3H, s, $NCH_3$), 6.82–6.95 (3H, m, ArH), 7.15–7.20 (1H, m, ArH), 12.43 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 20.2, 21.3, 26.8, 27.5, 37.2, 46.1, 100.4, 107.7, 113.7, 122.0, 123.1, 128.5, 133.1, 145.6, 159.8, 160.3, 160.9, 167.0, 176.9, 195.6. MS, *m*/*z*: 363 ($M^+$). Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 66.17; H, 4.68; N, 11.62.

***1′-Ethyl-4-hydroxy-2-methyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4k).*** Light Brown powder (72%); m.p 235°C (dec). IR (KBr): 3435, 2931, 1683, 1599 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1. 21 (3H, t, *J* = 6.7 Hz, $CH_3$), 1.89–1.90 (2H, m, $CH_2$), 2.18–2.25 (5H, m, $CH_2$, and $CH_3$), 2.70–2.71 (2H, m, $CH_2$), 3.67–3.71 (2H, m, $NCH_2$), 6.80–6.85 (1H, m, ArH), 6.90–6.92 (2H, m, ArH), 7.14–7.19 (1H, m, ArH), 12.43 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 12.1, 20.2, 21.3, 27.5, 34.7, 37.2, 46.3, 100.5, 107.6, 113.8, 121.7, 123.3, 128.5, 133.3, 144.7, 159.8, 160.3, 160.9, 166.9, 176.1, 195.5. MS, *m*/*z*: 377 ($M^+$). Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.77; H, 5.00; N, 11.07.

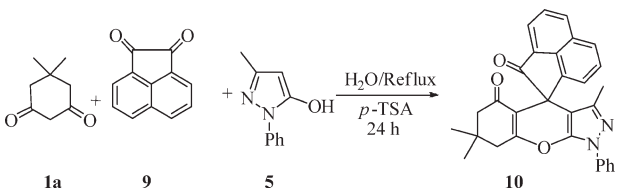
Due to very low solubility of the product **4l**, we can not report the $^{13}C$ NMR data for this product.

***1′-Benzoyl-4-hydroxy-2-methyl-8,9-dihydrospiro [chromeno [2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4l).*** Light Brown powder (75%); m.p 129°C (dec). IR (KBr): 3440, 2921, 1734, 1671, 1609 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.93 (2H, brs, $CH_2$), 2.27 (5H, brs, $CH_3$ and $CH_2$), 2.75 (2H, brs, $CH_2$), 4.87–4.96 (2H, m, $NCH_2$), 6.52 (1H, d, *J* = 7.1 Hz, ArH), 6.83 (1H, m, H—Ar), 6.97 (1H, m, ArH), 7.03–7.10 (1H, m, Ar H), 7.31–7.33 (3H, m, ArH ), 7.56–7.64 (2H, m, ArH ), 12.62 (1H, s, OH). MS, *m*/*z*: 439 ($M^+$). Anal. Calcd. for $C_{26}H_{19}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 71.00; H, 4.87; N, 9.48.

***5′-Bromo-4-hydroxy-1′,2-dimethyl-8,9-dihydro spiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4m).*** Light Brown powder (75%); m.p 232°C (dec). IR (KBr): 3471, 2926,1702, 1688, 1599 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.91–1.93 (2H, m, $CH_2$), 2.26 (3H, s, $CH_3$), 2.50 (2H, brs, $CH_2$), 3.12 (3H, s, $NCH_3$), 3.38 (2H, brs, $CH_2$), 6.89 (1H, d, *J* = 7.5 Hz, ArH), 7.20 (1H, s, ArH), 7.36 (1H, d, *J* = 8.4 Hz, ArH), 12.48 (1H, s, OH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 20.1, 21.4, 26.9, 27.6, 46.3, 100.0, 109.6, 113.1, 113.7, 126.1, 131.1,m 135.4, 145.1, 160.2, 160.4, 161.0, 167.6, 176.5, 195.8. MS, *m*/*z*: 441 ($M^+$). Anal. Calcd. for $C_{20}H_{16}BrN_3O_4$: C, 54.31; H, 3.65; N, 9.50. Found: C, 54.26; H, 3.61; N, 9.56.

***1′-Ethyl-4-hydroxy-2-methyl-5′-nitro-8,9-dihydrospiro [chromeno[2,3-d]pyrimidine-5,3′-indoline]-2′,6(7H)-dione (4n).*** Light Brown powder (77%); m.p 228°C (dec). IR (KBr): 3527, 2936, 1704, 1683, 1605 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 0.97 (3H, s, $CH_3$), 1.22 (3H, t, *J* = 6.6 Hz, $CH_3$), 1.93 (2H, brs, $CH_2$), 2.23–2.26 (5H, m, $CH_2$, and $CH_3$), 2.75 (2H, brs, $CH_2$), 3.79–3.82 (2H, m, $NCH_2$), 7.20 (1H, d, *J* = 8.7 Hz, ArH), 7.95 (1H, s, ArH), 8.18 (1H, d, *J* = 8.7 Hz,

**Scheme 6**




**1a** **9** **5** **10**

ArH), 12.56 (1H, s, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.1, 20.1, 21.4, 27.6, 35.3, 36.9, 46.2, 99.4, 107.7, 112.7, 119.0, 126.1, 134.2, 142.5, 151.0, 160.5, 161.2, 168.2, 177.1, 196.1. MS, *m*/*z*: 422 ($M^+$). Anal. Calcd. for $C_{21}H_{18}N_4O_6$: C, 59.71; H, 4.30; N, 13.26. Found: C, 59.77; H, 4.36; N, 13.20.

***7′-Amino-4′-hydroxy-2′-methyl-2-oxospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6a).*** Cream powder (80%); m.p 287°C (dec). IR (KBr): 3378, 3306, 3142, 2207, 1716, 1676 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.27 (3H, s, $CH_3$), 6.78–7.18 (4H, m, ArH), 7.31 (2H, s, $NH_2$), 10.49 (1H, s, NH), 12.61 (1H, s, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 21.4, 47.9, 57.1, 98.3, 109.7, 117.9, 122.2, 124.0, 128.8, 134.0, 142.6, 160.0, 160.3, 160.8, 161.0, 177.9. MS, *m*/*z*: 321 ($M^+$). Anal. Calcd. for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.76; H, 3.41; N, 21.86.

***7′-Amino-4′-hydroxy-2′-methyl-5-nitro-2-oxospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6b).*** Cream powder (82%); m.p 270°C (dec). IR (KBr): 3471, 3363, 3193, 2202, 1704, 1658 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.28 (3H, s, $CH_3$), 7.02 (1H, d, *J* = 8.8 Hz, ArH), 7.50 (2H, s, $NH_2$), 8.04 (1H, s, ArH), 8.16 (1H, d, *J* = 8.6 Hz, ArH), 11.24 (1H, s, NH), 12.68 (1H, s, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 21.5, 48.1, 55.4, 97.2, 109.9, 117.7, 120.0, 126.4, 134.9, 142.9, 149.1, 160.4, 160.8, 161.1, 161.2, 178.7. MS, *m*/*z*: 366 ($M^+$). Anal. Calcd. for $C_{16}H_{10}N_6O_5$: C, 52.46; H, 2.75; N, 22.94. Found: C, 52.50; H, 2.80; N, 22.88.

***7′-Amino-4′-hydroxy-1,2′-dimethyl-5-nitro-2-oxospiro [indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6c).*** powder (65%); m.p 180°C (dec). IR (KBr): 3429, 3322, 2202, 1730, 1667 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.29 (3H, s, $CH_3$), 3.25 (3H, s, $CH_3$), 7.30 (1H, d, *J* = 9.0 Hz, ArH), 7.57 (2H, s, $NH_2$), 8.11 (1H, s, ArH), 8.27 (1H, d, *J* = 8.9 Hz, ArH), 12.66 (1H, s, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 21.5, 27.3, 47.7, 55.1, 97.1, 108.9, 117.6, 119.6, 126.4, 134.2, 143.4, 150.1, 160.6, 160.9, 161.0, 161.1, 177.3. MS, *m*/*z*: 380 ($M^+$). Anal. Calcd. for $C_{17}H_{12}N_6O_5$: C, 53.69; H, 3.18; N, 22.10. Found: C, 53.64; H, 3.22; N, 22.18.

***7′-Amino-1-ethyl-4′-hydroxy-2′-methyl-5-nitro-2-oxospiro [indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (6d).*** Cream powder (63%); m.p 233°C (dec). IR (KBr): 3481, 3325, 2197, 1755, 1668, 1647 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.17 (3H, t, *J* = 8.4 Hz, $CH_3$), 2.22 (3H, s, $CH_3$), 3.74 (2H, m, $CH_2$), 7.10 (1H, d, *J* = 8.9 Hz, ArH), 8.14 (1H, d, *J* = 8.9 Hz, ArH), 8.14 (1H, s, ArH), 12.16 (3H, bs, $NH_2$ and OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 11.9, 18.0, 34.9, 39.07, 48.5, 95.3, 107.5, 118.4, 125.3, 135.3, 141.8, 150.6, 158.2, 161.4, 171.8, 178.6. MS, *m*/*z*: 394 ($M^+$). Anal. Calcd. for $C_{18}H_{14}N_6O_5$: C, 54.82; H, 3.58; N, 21.31. Found: C, 54.86; H, 3.63; N, 21.36.

***3,7,7-Trimethyl-1-phenyl-7,8-dihydro-1H-spiro [chromeno [2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8a).*** Cream powder (80%); m.p 243°C (dec). IR (KBr): 3142, 2880, 1703, 1591 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.04 (6H, s, $2CH_3$), 1.61 (3H, s, $CH_3$), 2.19 (2H, bs, $CH_2$), 2.78 (2H, bs, $CH_2$), 6.87–7.73 (9H, m, ArH), 10.64 (1H, s, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.2, 27.5, 27.9, 32.5, 41.1, 47.2, 50.8, 99.1, 109.6, 112.3, 120.8, 122.3, 123.7, 127.1, 128.6, 129.9, 134.6, 137.7, 142.5, 144.9, 145.2, 166.4, 178.1, 196.1. MS, m/z : 397 ($M^+$). Anal. Calcd. for $C_{26}H_{23}N_3O_3$: C, 73.39; H, 5.45; N, 9.88. Found: C, 73.35; H, 5.40; N, 9.82.

Due to very low solubility of the product **8b**, we can not report the $^{13}$C NMR data for this product.

***3,7,7-Trimethyl-5′-nitro-1-phenyl-7,8-dihydro-1H-spiro [chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8b).*** Cream powder (75%); m.p 315°C (dec). IR (KBr): 3424, 2957, 1749, 1649 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.04 (6H, s, $2CH_3$), 1.61 (3H, s, $CH_3$), 2.21 (2H, bs, $CH_2$), 2.78 (2H, bs, $CH_2$), 7.08–8.15 (8H, m, ArH), 11.38 (1H, s, NH). MS, *m*/*z*: 470 ($M^+$). Anal. Calcd. for $C_{26}H_{22}N_4O_5$: C, 66.37; H, 4.71; N, 11.91. Found: C, 66.42; H, 4.75; N, 11.97.

***3,7,7-Trimethyl-5′-bromo-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8c).*** Cream powder (81%); m.p 244°C (dec). IR (KBr): 3441, 2955, 1734, 1646 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.05 (6H, s, $2CH_3$), 1.64 (3H, s, $CH_3$), 2.22 (2H, bs, $CH_2$), 2.77 (2H, bs, $CH_2$), 6.84–7.53 (8H, m, ArH), 10.79 (1H, s, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.2, 27.6, 27.8, 32.6, 41.2, 47.3, 50.6, 99.4, 109.5, 113.9, 120.9, 122.3, 123.6, 127.2, 128.5, 129.9, 131.4, 137.6, 141.9, 144.7, 145.3, 166.4, 178.3, 196.3. MS, *m*/*z*: 505 ($M^+$+2), 503 ($M^+$). Anal. Calcd. for $C_{26}H_{22}BrN_3O_3$: C, 61.91; H, 4.40; N, 8.33. Found: C, 61.95; H, 4.35; N, 8.40.

***3-Methyl-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8d).*** Light brown powder (73%); m.p 312°C (dec). IR (KBr): 3193, 3085, 1730, 1634 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.60 (3H, s, $CH_3$), 1.97 (2H, bs, $CH_2$), 2.29 (2H, bs, $CH_2$), 2.85 (2H, bs, $CH_2$), 6.86–7.74 (9H, m, ArH), 10.64 (1H, s, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.2, 20.5, 28.0, 37.2, 47.3, 99.1, 109.5, 113.3, 120.9, 122.2, 123.8, 127.1, 128.6, 129.9, 134.8, 137.7, 142.5, 144.9, 145.0, 168.3, 178.2, 196.2. MS, *m*/*z*: 397 ($M^+$). Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.49; H, 4.85; N, 10.62.

Due to very low solubility of the products **8e** and **10**, we can not report the $^{13}$C NMR data for these products.

***3-Methyl-5′-nitro-1-phenyl-7,8-dihydro-1H-spiro [chromeno [2,3-c]pyrazole-4,3′-indoline]-2′,5(6H)-dione (8e).*** Cream powder (70%); m.p 310°C (dec). IR (KBr): 3290, 2952, 1750, 1640 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.63 (3H, s, $CH_3$), 2.14 (2H, m, $CH_2$), 2.46 (2H, m, $CH_2$), 2.91 (2H, m, $CH_2$), 7.02–8.54 (8H, m, ArH), 10.73 (1H, s, NH). MS, *m*/*z*: 442 ($M^+$). Anal. Calcd. for $C_{24}H_{18}N_4O_5$: C, 65.15; H, 4.10; N, 12.66. Found: C, 65.19; H, 4.06; N, 12.60.

***3′,7′,7′-Trimethyl-1′-phenyl-7′,8′-dihydro-1′H,2H-spiro [acenaphthylene-1,4′-chromeno[2,3-c]pyrazole]-2,5′(6′H)-dione (10).*** Cream powder (70%); m.p 188°C (dec). IR (KBr): 3162, 3055, 1704, 1643 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.02 (6H, s, $2CH_3$), 1.22 (3H, s, $CH_3$), 2.10 (2H, bs, $CH_2$), 2.80 (2H, bs, $CH_2$), 7.31–8.26 (1H, m, ArH). MS, m/z: 460 ($M^+$). Anal. Calcd. for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 78.19; H, 5.29; N, 6.15.

## REFERENCES AND NOTES

[1] Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[2] Ugi, I.; Domling, A. Endeavour 1994, 18, 115.

[3] Dömling, A. Chem Rev 2006, 106, 17.

[4] Fellahi, Y.; Dubois, P.; Agafonov, V.; Moussa, F.; Ombetta-Goka, J. E.; Guenzet, J.; Frangin, Y. Bull Soc Chim Fr 1996, 133, 869.

[5] Sharma, P.; Rane, N.; Gurram, V. K. Bioorg Med Chem Lett 2004, 14, 4185.

[6] Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. F. Adv Heterocycl Chem 1984, 41, 319.

[7] Suzuki, N. Chem Pharm Bull 1980, 28, 761.

[8] Parakash, L.; Shaihla, M.; Mital, R. L. Pharmazie 1989, 44, 490.

[9] Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. Curr Med Chem 2006, 13, 199.

[10] Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K. H. Med Res Rev 2003, 23, 322.

[11] Khan, K. M.; Saify, Z. S.; Khan, M. Z.; Choudhary, M. I.; Perveen, S.; Chohan, Z. H.; Supuran, C. T.; Atta-Ur-Rahman, Z. U. J Enzyme Inhib Med Chem 2004, 19, 373.

[12] Abd El-Aziz, A. S.; El-Agrody, A. M.; Bedair, A. H.; Corkery, T. C.; Ata, A. Heterocycles 2004, 63, 1793.

[13] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[14] Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. Tetrahedron Lett 2006, 43, 3067.

[15] Kitamura, R. O. S.; Romoff, P.; Young, M. C. M.; Kato, M. J.; Lago, J. H. G. Phytochemistry 2006, 67, 2398.

[16] Iqbal, M. C. M.; Jayasinghe, U. L. B.; Herath, H. M. T. B.; Wijesekara, K. B.; Fujimoto, Y. Phytoparasitica 2004, 32, 119.

[17] Kraus, G. A.; Kim, I. J Org Chem 2003, 68, 4517.

[18] Sundberg, R. J. The Chemistry of Indoles; Academic Press: New York, 1996.

[19] Joshi, K. C.; Chand, P. Pharmazie 1982, 37, 1.

[20] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[21] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, S. M. Bioorg Med Chem 2006, 12, 2488.

[22] Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39.

[23] Ma, J.; Hecht, S. M. Chem Commun 2004, 1190.

[24] Usui, T.; Kondoh, M.; Cui, C. B.; Mayumi, T.; Osada, H. Biochem J 1998, 333, 543.

[25] Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. Farmaco 2002, 57, 715.

[26] Zhu, S. L.; Jia, S. J.; Zhang, Y. Tetrahedron 2007, 63, 9365.

[27] Kumar, R. S.; Perumal, S. Tetrahedron Lett 2007, 48, 7164.

[28] Redkin, R. G.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. Tetrahedron 2007, 63, 11444.

[29] Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghazanfarpour-Darjani, M. Tetrahedron 2007, 63, 9423.

[30] Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. Tetrahedron 2007, 63, 2057.

[31] Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. Tetrahedron Lett 2007, 48, 8790.

[32] Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 2375.

[33] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. J Heterocycl Chem 2007, 44, 1009.

[34] Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. Heterocycles 2008, 75, 87.

[35] Dabiri, M.; Delbari, A. S.; Bazgir, A. Synlett 2007, 821.

[36] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2007, 63, 1770.

[37] Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543.

[38] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. Terahedron Lett 2008, 49, 5165.

[39] Ghahremanzadeh, R.; Imani Shakibaei, G.; Bazgir, A. Synlett 2008, 1129.

[40] Dabiri, M.; Azimi, S. C.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 7307.

[41] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. J Comb Chem 2009, 11, 341.

[42] Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. J Comb Chem 2009, 11, 393.

[43] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. Tetrahedron 2009, 65, 2005.

# A One-Pot Synthesis of the 1-Benzopyrano[2,3-*b*]pyridine Moiety from 2-(Alkyl/arylamino)-4-oxo-4*H*-1-Benzopyran-3-Carbaldehyde



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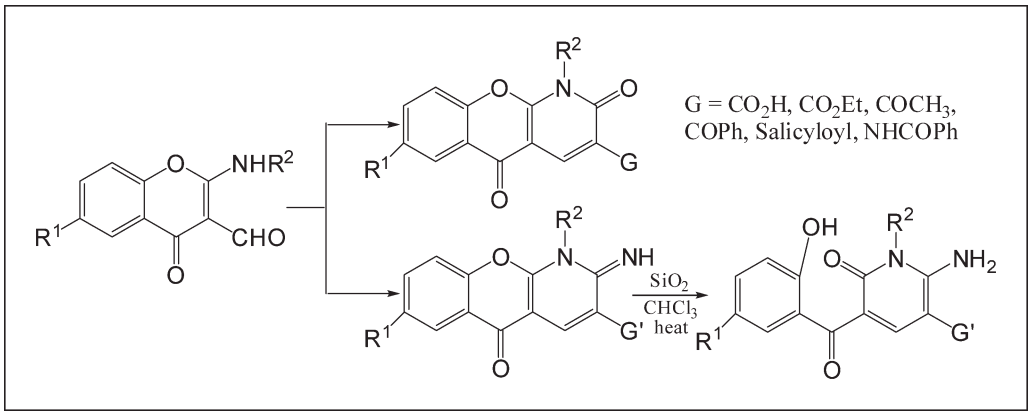


2-(Alkyl/arylamino)chromone-3-carbaldehyde reacts with Meldrum's acid, hippuric acid, 4-hydroxycoumarin, diethyl malonate, ethyl acetoacetate, or ethyl benzoylacetate to produce 1-benzopyrano[2,3-*b*]pyridine-2,5-dione moiety, but ethyl cyanoacetate and malononitrile react differently.

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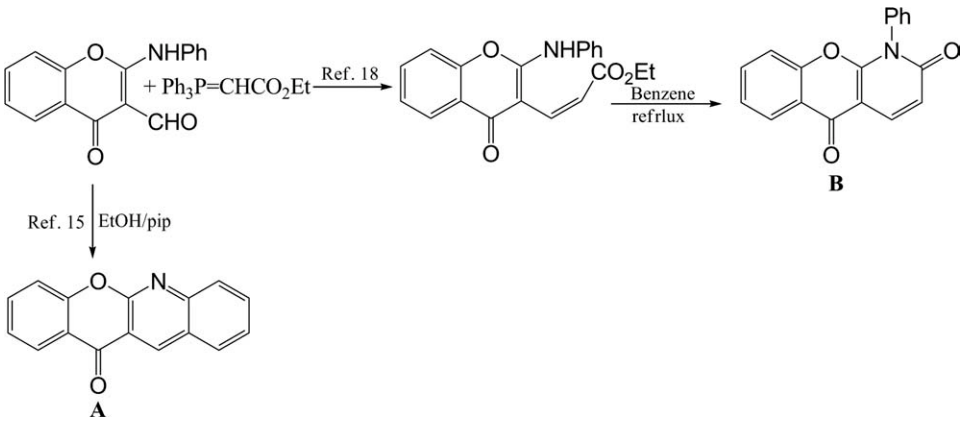
## INTRODUCTION

1-Benzopyranopyridine derivatives have found diverse application in the field of medicinal chemistry. 1-Benzopyrano[3,4-*c*]pyridine-5-ones act as human dopamine $D_4$ receptor antagonists and serve as potential antipsychotic agents [1]. Some nonsteroidal human androgen receptor agonists were synthesized based on 4-(trifluoromethyl)-2*H*-pyrano[3,2-*g*]-2-quinolone [2]. 1-Benzopyrano[2,3-*b*]pyridine-2,5-dione **1** ($R^2$ = H, G = $COCH_2COCH_3$) functions as a polyketide, which are involved in the biosynthesis of natural products [3]. Some chromenopyridines are designed and synthesized as an analogue of tetracycline [4]. 5-Salicyloyl-2-oxopyridine-3-carbonitriles play comparable roles as the nonglycosidic cardiotonic agents milrinone or amrinone [5]. Compounds **1**($R^2$ = H, G = CN, $CO_2R$, $CO_2H$) exhibit antiallergic properties and are used in the preparation of bronchodialators [6]. 1-Benzopyrano[2,3-*b*]pyridine-4,5-dione having a $CO_2H$ group at 3-position provides 100% inhibition in the passive cutaneous anaphylaxis screen when applied in a dose of 0.9 mg/kg [7]. Recently, some chromenopyridines are proved to be effective sensitizers for europium and terbium luminescence [8].

Synthesis of the 1-Benzopyrano[2,3-*b*]pyridine motif have been accomplished (a) from chromone-3-carbonitrile by reaction either with acetylacetone in the presence of piperidine [9] or with 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene in the presence of $Me_3SiOTf$ [10], (b) from chromone-3-carbaldehyde by the reaction of 2-aminochromone [11] or with aniline in the presence of TMSCl in DMF [12]. 2-Aminochromone-3-carbaldehyde **3** ($R^2$ = H) has also been used for the synthesis of **1**($R^2$ = H) [13].

Although the reactions of 2-aminochromone-3-carbaldehyde **3** ($R^2$ = H) and 2-(*N*,*N*-dialkylamino)chromone-3-carbaldehyde **3** ($NR_2$ in place of $NHR^2$) have been studied in detail [13], the chemistry of 2-(mono substituted amino)chromone-3-carbaldehyde **3** has only been little explored. Most of its reactions were carried out by converting it into *N*,*N*-disubstituted analogue [14a,b]. Reaction of **3** with primary amine produces corresponding Schiff base [14], but with aliphatic secondary amines like diethylamine or piperidine compound **3** ($R^2$ = aryl) produces 1-benzopyranoquinolones (**A**) (Scheme 1) [15]. Recently, diethyl 1-benzopyrano[2,3-*b*]pyridine-2,3-dicarboxylate has been synthesized from **3** and diethyl acetylenedicarboxylate in the presence of $Ph_3P$ [16]. Synthesis of 2-pyridone moiety having ester or carbamoyl functionality at its 3-positions from β-formyl-β-nitroenamine has recently been reported [17].

**Scheme 1**




A literature survey revealed that functionlization at the 3-position of 1-benzopyrano [2,3-*b*]pyridine-2,5-dione made this system medicinally efficacius [6]. 1-Benzopyrano[2,3-*b*]pyridine-2,5-dione (**B**) having no functionality at its 3-position had been synthesized by the reaction of **3** ($R^2$ = Ph) with ethyl (triphenylphosphoranylidene)acetate followed by heating in benzene (Scheme 1) [18].

Our objective was to synthesize **1** with varying substituents at its 3-position utilizing the C3N1 building block of the β-amino-α, β-unsaturated aldehyde moiety of **3.** We report herein a few new one-pot syntheses of compound **1** from **3** by condensation with 2,2-dimethyl-1,3-dioxan-4,6-dione (Meldrum's acid), *N*-benzoylglycine (hippuric acid), 4-hydroxycoumarin, and other active methylene compounds under suitable reaction conditions. Compound **3** can readily be obtained from *N*-alkyl/aryl-*C*-(4-oxo-4*H*-1-benzopyran-3-yl)nitrones **2** [19] or directly from chromone-3-carbaldehyde [20].

## RESULTS AND DISCUSSION

Meldrum's acid (**4**), an active methylene compound having strong electrophillic centres, has made its position in the synthesis of many organic compounds having use in the fields of drugs and pharmaceuticals [21]. Very recently, its chemical bonding and structure-reactivity relation have been studied both experimentally and theoretically [22]. Its chemical versatility has also been discussed in several review articles [23]. We have used Meldrum's acid in the synthesis of 1-benzopyrano[2,3-*b*]pyridine-2,5-dione moiety from **3**.

An equimolar mixture of **3** and **4** was heated under reflux in ethanol in the presence of catalytic amount of pyridine for 2–4 h. White solids (**1a–e**) were found to precipitate under this reaction condition in moderate to good yields (Table 1, entries 1–5). Compound **3** undergoes Knoevenagel condensation with Meldrum's acid to form **5**, which cyclizes to **1a–e** under the reaction condition (Scheme 2, path-a). The structures of the

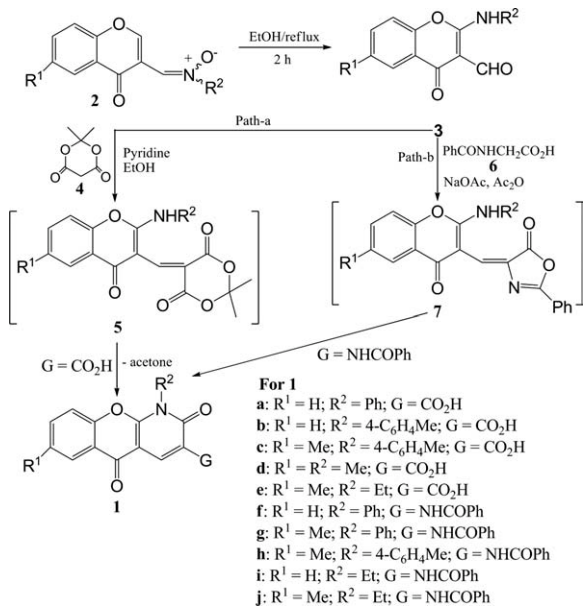
**Table 1**

Results of the reactions of **3** with **4** or **6** or **8** under different conditions.

| Entry | $R^1$ | $R^2$ | Reagent | Reaction condition | Time (h) | Product | Yield (%) | Mps (°C) |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Ph | **4** | A | 3 | **1a** | 70 | >320 |
| 2 | H | Ar | **4** | A | 4 | **1b** | 68 | >320 |
| 3 | Me | Ar | **4** | A | 3 | **1c** | 70 | 298–300 |
| 4 | Me | Me | **4** | A | 2 | **1d** | 52 | 296–298 |
| 5 | Me | Et | **4** | A | 2.5 | **1e** | 50 | 276–278 |
| 6 | H | Ph | **6** | B | 7 | **1f** | 41 | >320 |
| 7 | Me | Ph | **6** | B | 6 | **1g** | 40 | >320 |
| 8 | Me | Ar | **6** | B | 7 | **1h** | 45 | >320 |
| 9 | H | Et | **6** | B | 6.5 | **1i** | 32 | 258–260 |
| 10 | Me | Et | **6** | B | 6 | **1j** | 30 | 286–288 |
| 11 | Me | Ph | **8** | A | 5 | **10a** | 85 | 284–286 |
| 12 | H | Ph | **8** | A | 6 | **10b** | 79 | 268–270 |
| 13 | H | Et | **8** | A | 5.5 | **10c** | 79 | 238–240 |

A, Heated in EtOH under reflux containing catalytic amount of pyridine.
B, Heated a mixture of **3**, **6** and fused NaOAc in $Ac_2O$ on a water bath.
Ar stands for 4-$C_6H_4Me$.

**Scheme 2**




compounds were established on the basis of IR, $^1$H NMR, and mass spectral analysis. It is to be mentioned here that the carboxylic acid protons for compounds **1a** and **1b** were not observed in their $^1$H NMR spectra. The presence of carboxylic acid group in **1a** and **1b** was confirmed from their mass spectral analyses and the singlet appearance of $C_4$-H in the $^1$H NMR spectra of **1a,b**.

In connection to our earlier studies [24] on the reactions of different nitrogenous nucleophiles on 4-[(4-oxo-4*H*-1-benzopyran-3-yl)methylene]-2-phenyl-5-oxazolone **7** ($R^1$ = $NHR^2$ = H)(Scheme 2), derived from 3-formylchromone, it has been observed that nitrogenous nucleophiles are prone to interact on the carbonyl function of oxazolone moiety. Compound **3** can be considered as 3-formylchromone moiety having an inbuilt amino function in appropriate position. To utilize this special structural feature of **3**, an equimolar mixture of **3** ($R^2$ = aryl) and hippuric acid (**6**) was heated in the presence of excess amount of fused sodium acetate in acetic anhydride on water bath for 6–7 h and after usual work-up, compounds **1f–h** were obtained as white solids in moderate yields (Table 1, entries 6–8). On similar treatment of **3** ($R^2$ = alkyl), the reaction mixture yielded **1i** and **1j** (entries 9, 10) after chromatographic separation on silica gel using 10% ethyl acetate in benzene as eluent. Formation of **1f–j** from **3** may be rationalized by the initial formation of azlactone **7**, followed by intramolecular attack of the amino function to the carbonyl carbon of oxazolone moiety (Scheme 2, path-b).

This reaction was further extended by using 4-hydroxycoumarin (**8**). On heating an equimolar mixture of **3** and **8** in ethanol under reflux for 5–6 h in the presence of catalytic amount of pyridine, the reaction mixture produced compound **10** in good yields *via* the Knoevenagel condensate **9** (Scheme 3) (Table 1, entries 11–13). Suitably placed $NHR^2$ group in **9** reacted intramolecularly on the carbonyl function with a lesser decrease in entropy compared to the Michael addition of second molecule of **8**, which is the common feature for the reaction of an aldehyde with **8** [25].

With an endeavor to synthesize **1**(G = $CO_2$Et), compound **3** ($R^2$ = aryl) was stirred at room temperature with diethyl malonate in pyridine, but no change in **3** was observed (Table 2, entry 1). Ethyl acetoacetate also failed to cause any change in **3** on stirring at room temperature in pyridine (entry 2), even on heating **3** with ethyl acetoacetate in ethanol for 25 h in the presence of pyridine showed no considerable change (entry 3). On stirring an ethanolic solution of **3** ($R^2$ = aryl) with diethyl malonate at room temperature in the presence of piperidine for 40 h resulted in the formation of 1-benzopyrano[2,3-*b*]-12-quinolone (**A**) [15,18,19] (Scheme 1) (Table 2, entry 4). No pure compound could be isolated from the reaction mixture obtained by heating a mixture of **3**, diethyl malonate, fused NaOAc in $Ac_2O$ on a water bath for 5 h (entry 5). Surprisingly, compound **3** reacted with diethyl malonate in $CHCl_3$ under reflux in the presence of piperidine to produce **1k,l** (entries 6, 7) (Scheme 4). It was observed that more than stoichiometric amounts of diethyl malonate (1.5 equiv) and piperidine (1.5 equiv) were required for complete consumption of **3**. This methodology was then applied for the synthesis of **1** having various substituents at its 3-position. On heating **3** ($R^2$ = aryl) with ethyl acetoacetate and piperidine in equimolar amounts in $CHCl_3$ for 4 h produced **1o** (entry 8). Similarly, ethyl benzoylacetate reacted stoichiometrically with **3** ($R^2$ = aryl) within 2 h to produce **1q,r** (entries 9, 10).

**Scheme 3**

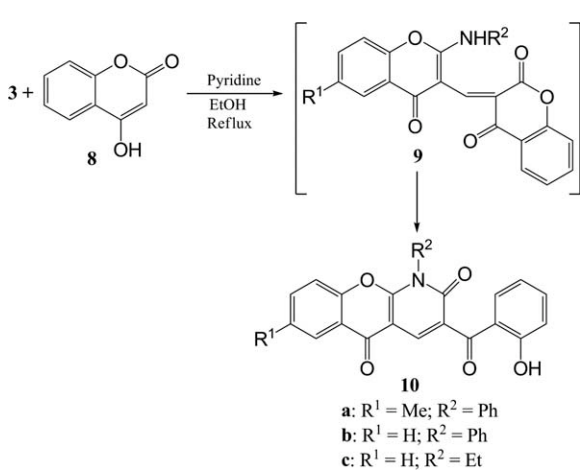


**Table 2**

Results of the reactions of **3** with active methylene compounds ($EtO_2C$-$CH_2$-G) under different conditions.

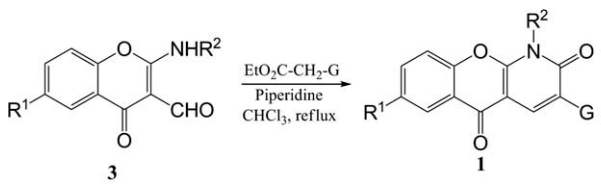
| Entry | $R^1$ | $R^2$ | G | Reaction condition | Time (h) | Product | Yield (%) | Mps (°C) |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Ph | $CO_2Et$ | Py/RT | 40 | N. R. | – | – |
| 2 | Me | Ph | $COCH_3$ | Py/RT | 20 | N. R. | – | – |
| 3 | Me | Ph | $COCH_3$ | Py/EtOH/Reflux | 25 | N. R.[a] | – | – |
| 4 | H | Ph | $CO_2Et$ | Pip/EtOH/RT | 40 | **A** | 70 | 236–238 |
| 5 | H | Ph | $CO_2Et$ | $NaOAc/Ac_2O$/heat | 5 | Not isolated | – | – |
| 6 | H | Ph | $CO_2Et$ | Pip/$CHCl_3$/reflux | 18 | **1k** | 55 | 278–280 |
| 7 | Me | Ph | $CO_2Et$ | Pip/$CHCl_3$/reflux | 12 | **1l** | 74 | 208–210 |
| 8 | Me | Ph | $COCH_3$ | Pip/$CHCl_3$/reflux | 4 | **1o** | 68 | 278–280 |
| 9 | H | Ph | COPh | Pip/$CHCl_3$/reflux | 2 | **1q** | 72 | 264–266 |
| 10 | Me | Ph | COPh | Pip/$CHCl_3$/reflux | 2 | **1r** | 74 | 278–280 |
| 11 | H | Me | COPh | Pip/$CHCl_3$/reflux | 2 | **1s** | 60 | 256–258 |
| 12 | H | Et | COPh | Pip/$CHCl_3$/reflux | 2 | **1t** | 62 | 224–226 |
| 13 | H | Et | $COCH_3$ | Pip/$CHCl_3$/reflux | 4 | **1p** | 43 | 218–220 |
| 14 | H | Et | $CO_2Et$ | Pip/$CHCl_3$/reflux | 28 | **1m** | 42 | 178–180 |
| 15 | Me | Et | $CO_2Et$ | Pip/$CHCl_3$/reflux | 25 | **1n** | 40 | 192–194 |
| 16 | H | Et | COPh | Pip/EtOH/reflux | 6 | **1t** | 70 | 224–226 |
| 17 | Me | Ph | $COCH_3$ | Pip/EtOH/reflux | 2 | **1o** | 20[b] | 278–280 |
| 18 | H | Et | $COCH_3$ | Pip/EtOH/reflux | 7 | **1p** | 62 | 218–220 |
| 19 | H | Ph | COPh | Morpholine/ $CHCl_3$/reflux | 5 | **1q** | 60 | 264–266 |
| 20 | H | Ph | COPh | $Et_2NH/CHCl_3$/ reflux | 13 | **1q** | 56 | 264–266 |

''Py'' stands for Pyridine; ''Pip'' stands for piperidine; ''RT'' stands for room temperature.
''N. R.'' stands for No Reaction.
[a] 80% **3** was recovered.
[b] 40% of compound **A** was isolated.

The reaction was extended with **3** ($R^2$ = alkyl). Ethyl benzoylacetate (entries 11,12), ethyl acetoacetate (entry 13), and diethyl malonate (entries 14, 15) produced corresponding **1** but in lower yields. On changing the solvent from $CHCl_3$ to ethanol, the yield of **1** ($R^2$ = alkyl) was found to improve, but a little longer reaction time was required (entries 12,16 and 13, 18). Similar reaction with **3** ($R^2$ = aryl) in ethanol always produced some 1-benzopyrano quinolone (**A**) along with **1** (entry 17). Use of triethylamine or pyridine as a base in the reaction between **3** and $PhCOCH_2CO_2Et$ either in $CHCl_3$ or in EtOH failed to show the formation of **1** even after heating under reflux for 30 h. Piperidine was found to be a better reagent than morpholine or diethylamine for this transformation (entries 9, 19, 20).

Compound **3** reacted differently when ethyl cyanoacetate or malononitrile were used as active methylene component. On stirring an equimolar mixture of **3** and ethyl cyanoacetate in ethanol in the presence of piperidine at room temperature, followed by usual work-up [*vide* experimental Section ''General procedure for the reaction of ethyl cyanoacetate on 2-alkyl/arylaminochromone-3-carbaldehyde (3)''] and chromatographic purification produced **11** (G' = $CO_2Et$) (Scheme 5, path a). But malononitrile yielded **12** when reacted with **3** under similar reaction condition (Scheme 5, path b). In an attempt to purify compound **12** (G' = CN) by column chromatography, a partial change in **12** was observed and finally the new compound was assigned to be **11** (G′ = CN). This observation led us to check the silica-induced conversion of **12** (G′ = CN) to **11** (G′ = CN). A chloroform solution of **12** (G′ = CN) containing some silica gel was heated under reflux for 5 h with stirring. Indeed, complete conversion of **12** (G′ = CN) to **11** (G′ = CN) was observed. Use of benzene in place of chloroform also accomplished this transformation under identical condition. However, on heating under reflux in ordinary $CHCl_3$ or benzene in the absence of silica gel, compound **12** failed to show any change. In an earlier report [17], β–allylamino-2-nitroacrolein was made to react with malononitrile and was supposed to

**Scheme 4**

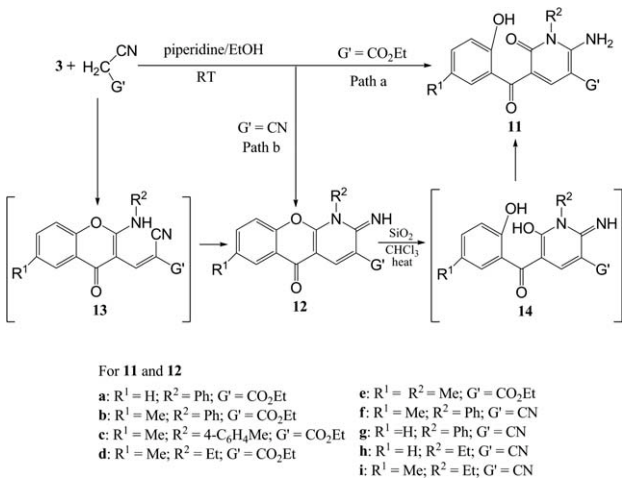



**3** **1**

For **1**

**k**: $R^1$ = H; $R^2$ = Ph; G = $CO_2Et$
**l**: $R^1$ = Me; $R^2$ = Ph; G = $CO_2Et$
**m**: $R^1$ = H; $R^2$ = Et; G = $CO_2Et$
**n**: $R^1$ = Me; $R^2$ = Et; G = $CO_2Et$
**o**: $R^1$ = Me; $R^2$ = Ph; G = $COCH_3$
**p**: $R^1$ = H; $R^2$ = Et; G = $COCH_3$
**q**: $R^1$ = H; $R^2$ = Ph; G = COPh
**r**: $R^1$ = Me; $R^2$ = Ph; G = COPh
**s**: $R^1$ = H; $R^2$ = Me; G = COPh
**t**: $R^1$ = H; $R^2$ = Et; G = COPh

**Scheme 5**




For **11** and **12**

**a**: $R^1$ = H; $R^2$ = Ph; G' = $CO_2Et$
**b**: $R^1$ = Me; $R^2$ = Ph; G' = $CO_2Et$
**c**: $R^1$ = Me; $R^2$ = 4-$C_6H_4$Me; G' = $CO_2Et$
**d**: $R^1$ = Me; $R^2$ = Et; G' = $CO_2Et$
**e**: $R^1$ = $R^2$ = Me; G' = $CO_2Et$
**f**: $R^1$ = Me; $R^2$ = Ph; G' = CN
**g**: $R^1$ =H; $R^2$ = Ph; G' = CN
**h**: $R^1$ = H; $R^2$ = Et; G' = CN
**i**: $R^1$ = Me; $R^2$ = Et; G' = CN

pass through an amidine like intermediate as in **12**, but the intermediate could not be isolated. Isolation of **12** (G′ = CN) gave us an impetus to take an attempt for the isolation of **12** (G′ = $CO_2Et$). But careful investigation of the solid [*vide* experimental Section ''General procedure for the reaction of ethyl cyanoacetate on 2-alkyl/arylaminochromone-3-carbaldehyde (3)''] obtained from the reaction mixture of **3** ($R^1$ = H, $R^2$ = Ph) and ethyl cyanoacetate revealed that there was more than one product (TLC). However, chromatographic separation yielded only **11a** in moderate yield. The other components were separated by preparative TLC and the bands corresponding to two different spots were extracted separately with $CHCl_3$. Unfortunately, the isolated compounds were same in both cases and the compound was **11a**. Compound **12** ($R^2$ = aryl, G′ = $CO_2Et$) could not be isolated even after using neutral $Al_2O_3$ as adsorbent in the column chromatography. The only such compound **12d** was obtained by stirring a pyridine solution of **3** ($R^1$ = Me, $R^2$ = Et) and ethyl cyanoacetate at room temperature. Compound **12d** was readily converted to **11d** within 1 h when heated in ordinary $CHCl_3$ in the presence of silica gel. Formation of **12** can be rationalized *via* the Knoevenagel condensate **13** (Scheme 5). It was presumed that the conversion of **12** to **11** took place by silica-induced hydration. The source of water was supposed to be from silica adsorbent or solvent or atmosphere. Water molecule attacks **12** and opens the pyran ring to form **14** and subsequently tautomerizes to **11**. To justify this presumption, compound **12** was heated in dry $CHCl_3$ in the presence of dry silica gel and under argon atmosphere and indeed compound **12** failed to show any change.

## CONCLUSION

We have reported a few new efficient one-pot methods for the synthesis of 1-benzopyrano [2,3-*b*]pyridine-2,5-dione moiety bearing various functionalities at its 3-position. The differential behavior of the active methylene compounds bearing cyano group toward **3** has also been reported.

## EXPERIMENTAL

**General.** The recorded mps are uncorrected. IR spectra were recorded in KBr on a Beckman IR 20a, $^1$H NMR/$^{13}$C NMR spectra on a bruker 300 MHz/75 MHz spectrometer, mass spectra on a Qtof micro YA 263 instrument and elemental analysis on a Perkin Elmer 240c elemental analyzer. Light petroleum refers to the fraction with 60–80°C. All chemicals used were of commercial grade and were used as such.

**General procedure for the synthesis of 1-alkyl/aryl-2*H*,5*H*-1-benzopyrano[2,3-*b*]pyridine-3-carboxylic acids (1a–e).** An ethanolic solution (10 mL) of a mixture of **3** (1 mmol), **4** (144 mg, 1 mmol), and catalytic amount of pyridine (2 drops) was heated under reflux for 2–4 h. The white solid separated out during the reaction was filtered off and crystallized from benzene to obtain **1a–e** as white crystalline solids.

***1-Phenyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylic acid (1a).*** This compound was obtained in 70% yield as white crystalline solid, mp > 320°C; IR: 3493, 3064, 2784, 1754, 1646, 1533, 1427 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 7.23 (br d, 1H, 9-H, *J* = 8.1 Hz), 7.56–7.64(m, 6H, ArH), 7.75–7.80 (m, 1H, 8-H), 8.17 (br d, 1H, 6-H, *J* = 7.5 Hz), 8.86 (s, 1H, 4-H); ms: m/z 356 ($M^+$ +Na). *Anal*. Calcd for $C_{19}H_{11}NO_5$: C, 68.47; H, 3.33; N, 4.20. Found: C, 68.67; H, 3.37; N, 4.12.

***1-p-Tolyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylic acid (1b).*** This compound was obtained in 68% yield as white crystalline solid, mp > 320°C; IR: 3453, 2976, 2755, 1767, 1652, 1540, 1453 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), 7.27 (br d, 1H, 9-H, *J* = 8.4 Hz), 7.38–7.50 (m, 4H, ArH), 7.57 (br t, 1H, 7-H, *J* = 7.5 Hz), 7.75–7.80 (m, 1H, 8-H), 8.17 (br d, 1H, 6-H, *J* = 7.5 Hz), 8.86 (s, 1H, 4-H); ms: m/z 370 ($M^+$ +Na). *Anal*. Calcd for $C_{20}H_{13}NO_5$: C, 69.16; H, 3.77; N, 4.03. Found: C, 68.98; H, 3.72; N, 3.95.

***7-Methyl-1-p-tolyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylic acid (1c).*** This compound was obtained in 70% yield as white crystalline solid, mp 298–300°C; IR: 3460, 3015, 2812, 1743, 1647, 1553, 1437 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.46 (s, 3H, $ArCH_3$), 2.53 (s, 3H, $ArCH_3$), 7.12–7.47 (m, 6H, ArH), 8.03 (br s, 1H, 6-H), 9.32 (s, 1H, 4-H), 12.94 (s, 1H, COOH, deuterium oxide exchangeable)). *Anal*. Calcd for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 70.01; H, 4.11; N, 3.79.

***1,7-Dimethyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylic acid (1d).*** This compound was obtained in 52% yield as white crystalline solid, mp 296–298°C; IR: 3456, 3045, 2934, 1741, 1634, 1542, 1475 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.51 (s, 3H, $ArCH_3$), 3.89 (s, 3H, $NCH_3$), 7.47 (d, 1H, 9-H, *J* = 8.4 Hz), 7.62 (br d, 1H, 8-H, *J* = 8.4 Hz), 8.11 (br s, 1H, 6-H), 9.35 (s, 1H, 4-H), 13.20 (s, 1H, COOH, deuterium oxide exchangeable)). *Anal*. Calcd for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 62.98; H, 3.82; N, 4.83.

***1-Ethyl-7-methyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylic acid (1e).*** This compound was obtained in 50% yield as white crystalline solid, mp 276–278°C; IR: 3420,

3050, 2945, 1750, 1634, 1530, 1466 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.51 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz ), 2.51 (s, 3H, $ArCH_3$), 4.52 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 7.47 (d, 1H, 9-H, $J$ = 8.1 Hz), 7.62 (br d, 1H, 8-H, $J$ = 8.1 Hz), 8.10 (br s, 1H, 6-H), 9.32 (s, 1H, 4-H), 13.27 (s, 1H, COOH, deuterium oxide exchangeable)). *Anal*. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.32; H, 4.43; N, 4.59.

**General procedure for the synthesis of 3-benzoylamino-1-alkyl/aryl-2H,5H-1-benzopyrano[2,3-*b*]pyridine-2,5-diones (1f–j).** A mixture of **3** (1 mmol), **6** (180 mg, 1 mmol), NaOAc (250 mg, 3 mmol), and acetic anhydride (5 mL) was heated on water bath for 6–7 h. Crushed ice (50 g) was then added to the cold reaction mixture. A solid mass was separated when the reaction was carried out with **3** ($R^2$ = aryl). The solid was filtered off, washed with water, dried in air, and recrystallized from $CHCl_3$ to afford **1f–h**. But the reaction mixture obtained from **3** ($R^2$ = alkyl) afforded a semisolid mass when ice-water was added. The semisolid mass was extracted with $CHCl_3$. The organic layer was washed with water, dried over $Na_2SO_4$, and chromatographed over silica gel (100–200) using 10% EtOAc in benzene as eluent to get **1i–j** as white crystalline solid.

***3-Benzoylamino-1-phenyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1f).*** This compound was obtained in 41% yield as white crystalline solid, mp > 320°C; IR: 3379, 3050, 1655, 1520, 1459 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.13 (br d, 1H, 9-H, $J$ = 8.1 Hz), 7.36–7.66 (m, 10H, ArH), 7.93 (dd, 2H, ArH, $J$ = 8.1, 1.2 Hz), 8.32 (dd, 1H, 6-H, $J$ = 7.8, 1.5 Hz), 8.99 (br s, 1H, NH, deuterium oxide exchangeable), 9.35 (s, 1 H, 4-H); ms: m/z 409 ($M^+$ + H), 431 ($M^+$ +Na). *Anal*. Calcd for $C_{25}H_{16}N_2O_4$: C, 73.52; H, 3.95; N, 6.86. Found: C, 73.67; H, 3.86; N, 6.75.

***3-Benzoylamino-7-methyl-1-phenyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1g).*** This compound was obtained in 40% yield as white crystalline solid, mp > 320°C; IR: 3360, 3120, 1640, 1545, 1422 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.44 (s, 3H, $ArCH_3$), 7.03 (d, 1H, 9-H, $J$ = 8.1 Hz), 7.40-7.63 (m, 9H, ArH), 7.92 (dd, 2H, ArH, $J$ = 8.0, 1.2 Hz), 8.10 (brs, 1H, 6-H), 8.97 (br s, 1H, NH, deuterium oxide exchangeable), 9.34 (s, 1H, 4-H). *Anal*. Calcd for $C_{26}H_{18}N_2O_4$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.80; H, 4.26; N, 6.58.

***3-Benzoylamino-7-methyl-1-p-tolyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1h).*** This compound was obtained in 45% yield as white crystalline solid, mp > 320°C; IR: 3350, 3074, 1635, 1533, 1428 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.45 (s, 3H, $ArCH_3$), 2.51 (s, 3H, $ArCH_3$), 6.90 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.39–7.56 (m, 8H, ArH), 7.93 (br d, 2H, ArH, $J$ = 7.2 Hz), 8.11 (brs, 1H, 6-H), 8.99 (br s, 1H, NH, deuterium oxide exchangeable), 9.34 (s, 1H, 4-H). *Anal*. Calcd for $C_{27}H_{20}N_2O_4$: C, 74.30; H, 4.62; N, 6.42. Found: C, 74.15; H, 4.55; N, 6.34.

***3-Benzoylamino-1-ethyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1i).*** This compound was obtained in 32% yield as white crystalline solid, mp 256–258°C; IR: 3385, 3096, 1680, 1651, 1628, 1518, 1482 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.50 (t, 3H, $CH_2CH_3$, $J$ = 6.5 Hz), 4.52 (q, 2H, $CH_2CH_3$, $J$ = 6.5 Hz), 7.49–7.53 (m, 5H, ArH), 7.68–7.70 (m, 1H, 8-H), 7.93 (br d, 2H, ArH, $J$ = 7.2 Hz), 8.31 (br d, 1H, 6-H, $J$ = 7.2 Hz), 8.97 (br s, 1H, NH, deuterium oxide exchangeable), 9.21 (s, 1H, 4-H). *Anal*. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 70.18; H, 4.43; N, 7.84.

***3-Benzoylamino-1-ethyl-7-methyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1j).*** This compound was obtained in 30% yield as white crystalline solid, mp 286–288°C; IR: 3390, 3100, 2968, 1670, 1651, 1626, 1500, 1468 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.48 (t, 3H, $CH_2CH_3$, $J$ = 6.6 Hz), 2.46 (s, 3H, $ArCH_3$), 4.50 (q, 2H, $CH_2CH_3$, $J$ = 6.6 Hz), 7.39 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.47–7.56 (m, 4H, ArH), 7.93 (brd, 2H, ArH, $J$ = 7.2 Hz), 8.07 (br s, 1H, 6-H ), 8.96 (br s, 1 H, NH, deuterium oxide exchangeable), 9.19 (s, 1H, 4-H). *Anal*. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.41; H, 4.78; N, 7.39.

**General procedure for the synthesis of 1-alkyl/aryl-3-salicyloyl-2H,5H-1-benzopyrano[2,3-*b*]pyridine-2,5-diones (10a–c).** An ethanolic solution of a mixture of **3** (1 mmol), **8** (162 mg, 1 mmol), and pyridine (2 drops) was heated under reflux for 5–6 h. A white solid, separated out during the reaction, was filtered off and crystallized from benzene-light petroleum (80:20) to obtain **10a–c** as white crystalline solid.

***7-Methyl-1-phenyl-3-salicyloyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (10a).*** This compound was obtained in 85% yield as white crystalline solid, mp 284–286°C; IR: 3448, 2925, 1681, 1648, 1623, 1544 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.46 (s, 3H, $ArCH_3$), 6.87 (br t, 1H, ArH, $J$ = 7.8 Hz), 7.05 (br t, 2H, ArH, $J$ = 7.8 Hz), 7.36–7.59 (m, 8H, ArH), 8.06 (br s, 1H, 6-H), 8.52 (s, 1H, 4-H), 11.90 (s, 1H, OH, deuterium oxide exchangeable); $^{13}C$ NMR ($CDCl_3$): δ 20.8, 101.7, 117.4, 118.4, 118.9, 119.5, 121.6, 126.1, 126.2, 128.2, 128.3, 129.7, 132.7, 133.3, 135.6, 136.6, 136.9, 137.8, 151.9, 156.9, 159.1, 163.2, 173.4, 197.2; ms: m/z 424 ($M^+$+H), 446 ($M^+$+Na). *Anal*. Calcd for $C_{26}H_{17}NO_5$: C, 73.75; H, 4.05; N, 3.31. Found: C, 73.61; H, 4.12; N, 3.22.

***1-Phenyl-3-salicyloyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (10b).*** This compound was obtained in 79% yield as white crystalline solid, mp 268–270°C; IR: 3400, 2940, 1692, 1660, 1630, 1524 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.87 (br t, 1H, ArH, $J$ = 7.5 Hz), 7.03 (br d, 1H, 9-H, $J$ = 8.4 Hz), 7.16 (br d, 1H, ArH, $J$ = 8.4 Hz), 7.36–7.41 (m, 3H, ArH), 7.44–7.52 (m, 2H, ArH), 7.58–7.67 (m, 4H, ArH), 8.27 (br d, 1H, 6-H, $J$ = 7.5 Hz), 8.51 (s, 1H, 4-H), 11.88 (s, 1 H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{25}H_{15}NO_5$: C, 73.35; H, 3.69; N, 3.42. Found: C, 73.52; H, 3.63; N, 3.35.

***1-Ethyl-3-salicyloyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (10c).*** This compound was obtained in 79% yield as white crystalline solid, mp 238–240°C; IR: 3425, 2920, 1690, 1640, 1620, 1500 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.48 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.47 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 6.86 (br t, 1H, ArH, $J$ = 7.5 Hz), 7.04 (br d, 1H, 9-H, $J$ = 8.4 Hz), 7.48–7.59 (m, 4H, ArH), 7.79 (br t, 1H, 8-H, $J$ = 8.4 Hz), 8.30 (br d, 1H, 6-H, $J$ = 7.8 Hz), 8.39 (s, 1H, 4-H), 11.92 (s, 1 H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.62; H, 4.12; N, 3.95.

**General procedure for the synthesis of ethyl 1-alkyl/aryl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-*b*]pyridine-3-carboxylates (1k-n) and 3-acetyl/benzoyl-1-alkyl/aryl-2H,5H-1-benzopyrano[2,3-*b*]pyridine-2,5-diones (1o-t).** A mixture of **3** (1 mmol), diethyl malonate (240 mg, 1.5 mmol) and piperidine (130 mg, 1.5 mmol) or **3** (1 mmol), ethyl acetoacetate (130 mg, 1 mmol) and piperidine (85 mg, 1 mmol) or **3** (1 mmol), ethyl benzoylacetate (190 mg, 1 mmol) and piperidine (85 mg, 1 mmol) in $CHCl_3$ (10 mL) was heated under reflux

for several hours (Table 2) till the completion of reaction (TLC). Solvent was removed from the reaction mixture under reduced pressure and resulted residue was stirred with water (10 mL) for 10 min. The separated solid was filtered off, dried, and purified by column chromatography over silica gel (100–200) using 10% EtOAc in benzene as eluent to obtain **1k–t**.

***Ethyl 1-phenyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylate (1k).*** This compound was obtained in 55% yield as white crystalline solid, mp 278–280°C; IR: 2927, 1752, 1717, 1657, 1542 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.40 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 4.39 (q, 2H, $CH_2CH_3$, $J$ = 7.2 Hz), 7.13 (br d, 1H, 9-H, $J$ = 8.4 Hz), 7.34 (br d, 2H, ArH, $J$ = 7.5 Hz), 7.46 (br t, 1H, ArH, $J$ = 7.2 Hz), 7.59–7.66 (m, 4H, ArH), 8.28 (br d, 1H, 6-H, $J$ = 7.2 Hz), 9.08 (s, 1H, 4-H); $^{13}C$ NMR ($CDCl_3$): δ 14.2, 61.4, 101.4, 117.6, 117.8, 121.7, 126.3, 126.5, 128.1, 129.6, 129.7, 133.2, 134.5, 141.7, 153.4, 157.5, 158.4, 163.5, 173.3; ms: m/z 362 ($M^+$+H), 384 ($M^+$+Na). *Anal.* Calcd for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.67; H, 4.09; N, 3.81.

***Ethyl 7-methyl-1-phenyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylate (1l).*** This compound was obtained in 74% yield as white crystalline solid, mp 208–210°C; IR: 2940, 1740, 1710, 1648, 1535 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.39 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 2.44 (s, 3H, $ArCH_3$), 4.39 (q, 2H, $CH_2CH_3$, $J$ = 7.2 Hz), 7.01 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.41 (br d, 1H, 8-H, $J$ = 8.4 Hz), 7.40–7.43 (m, 2H, ArH,), 7.50–7.58 (m, 3H, ArH), 8.10 (br s, 1H, 6-H), 9.06 (s, 1H, 4-H). *Anal.* Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.56; N, 3.73. Found: C, 70.25; H, 4.52; N, 3.68.

***Ethyl 1-ethyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylate (1m).*** This compound was obtained in 42% yield as white crystalline solid, mp 178–180°C; IR: 2939, 1728, 1685, 1610, 1537 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.41 (t, 3H, $NCH_2CH_3$, $J$ = 7.2 Hz), 1.46 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 4.38 (q, 2H, $NCH_2CH_3$, $J$ = 7.2 Hz), 4.46 (q, 2H, $OCH_2CH_3$, $J$ = 7.2 Hz), 7.49–7.56 (m, 2H, ArH), 7.78 (br t, 1H, 8-H, $J$ = 7.2 Hz), 8.29 (br d, 1H, 6-H, $J$ = 7.8 Hz), 8.95 (s, 1H, 4-H). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.95; H, 4.78; N, 4.49.

***Ethyl 1-ethyl-7-methyl-2H,5H-2,5-dioxo-1-benzopyrano[2,3-b]pyridine-3-carboxylate (1n).*** This compound was obtained in 40% yield as white crystalline solid, mp 192–194°C; IR: 2956, 1712, 1690, 1618, 1540 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.41 (t, 3H, $NCH_2CH_3$, $J$ = 7.2 Hz), 1.44 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.50 (s, 3H, $ArCH_3$), 4.38 (q, 2H, $NCH_2CH_3$, $J$ = 7.2 Hz), 4.44 (q, 2H, $OCH_2CH_3$, $J$ = 7.2 Hz), 7.43 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.56 (br d, 1H, 8-H, $J$ = 8.4 Hz), 8.08 (br s, 1H, 6-H,), 8.96 (s, 1H, 4-H). *Anal.* Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.90; H, 5.17; N, 4.21.

***3-Acetyl-7-methyl-1-phenyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1o).*** This compound was obtained in 68% yield as white crystalline solid, mp 278–280°C; IR: 2940, 1696, 1654, 1527, 1478 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.45 (s, 3H, $ArCH_3$), 2.68 (s, 3H, $COCH_3$), 7.03 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.36–7.38 (m, 2H, ArH), 7.43 (br d, 1H, 8-H, $J$ = 8.4 Hz), 7.63–7.65 (m, 3H, ArH), 8.05 (br s, 1H, 6-H), 9.08 (s, 1H, 4-H); $^{13}C$ NMR ($CDCl_3$): δ 20.8, 30.8, 102.0, 117.4, 121.3, 124.1, 126.0, 128.0, 129.7, 129.8, 133.4, 135.6, 136.5, 141.0, 151.7, 157.7, 160.5, 173.5, 195.4; ms: m/z 346 ($M^+$+ H), 368 ($M^+$+Na). *Anal.* Calcd for $C_{21}H_{15}NO_4$: C, 73.04; H, 4.38; N, 4.06. Found: C, 72.90; H, 4.34; N, 3.99.

***3-Acetyl-1-ethyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1p).*** This compound was obtained in 43% yield as white crystalline solid, mp 218–220°C; IR: 2940, 1700, 1660, 1540, 1480 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.47 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 2.70 (s, 3H, $COCH_3$), 4.45 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 7.49–7.56 (m, 2H, ArH), 7.75–7.80 (m, 1H, 8-H), 8.27 (br d, 1H, 6-H, $J$ = 7.8 Hz), 8.92 (s, 1H, 4-H). *Anal.* Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.70; H, 4.56; N, 4.87.

***3-Benzoyl-1-phenyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1q).*** This compound was obtained in 72% yield as white crystalline solid, mp 264–266°C; IR: 2930, 1671, 1643, 1540, 1458 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.16 (br d, 1H, 9-H, $J$ = 8.4 Hz), 7.37–7.40 (m, 2H, ArH), 7.43–7.48 (m, 3H, ArH), 7.55–7.67 (m, 5H, ArH), 7.87 (br d, 2H, ArH, $J$ = 7.8 Hz), 8.28 (br d, 1H, 6-H, $J$ = 7.8Hz), 8.64 (s, 1H, 4-H); $^{13}C$ NMR ($CDCl_3$): δ 101.8, 117.7, 121.8, 126.3, 126.4, 126.6, 128.1, 128.4, 129.4, 129.7, 129.8, 133.1, 133.2, 134.5, 137.0, 139.0, 153.5, 157.0, 159.4, 173.4, 192.3; ms: m/z 394 ($M^+$+H), 416 ($M^+$+Na). *Anal.* Calcd for $C_{25}H_{15}NO_4$: C, 76.33; H, 3.84; N, 3.56. Found: C, 76.20; H, 3.80; N, 3.49.

***3-Benzoyl-7-methyl-1-phenyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1r).*** This compound was obtained in 74% yield as white crystalline solid, mp 278–280°C; IR: 2936, 1680, 1650, 1550, 1480 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.46 (s, 3H, $ArCH_3$), 7.05 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.36–7.60 (m, 9H, ArH), 7.86 (br d, 2H, ArH, $J$ = 7.5 Hz), 8.06 (br s, 1H, 6-H), 8.64 (s, 1H, 4-H). *Anal.* Calcd for $C_{26}H_{17}NO_4$: C, 76.65; H, 4.21; N, 3.44. Found: C, 76.50; H, 4.16; N, 3.47.

***3-Benzoyl-1-methyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1s).*** This compound was obtained in 60% yield as white crystalline solid, mp 256–258°C; IR: 3010, 1675, 1660, 1540, 1470 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 3.80 (s, 3H, $CH_3$), 7.44–7.62 (m, 5H, ArH), 7.79 (br t, 1H, ArH, $J$ = 8.1 Hz), 7.84 (br d, 2H, ArH, $J$ = 8.1 Hz), 8.30 (br d, 1H, 6-H, $J$ = 8.1 Hz), 8.52 (s, 1H, 4-H). *Anal.* Calcd for $C_{20}H_{13}NO_4$: C, 72.50; H, 3.95; N, 4.23. Found: C, 72.40; H, 3.88; N, 4.19.

***3-Benzoyl-1-ethyl-2H,5H-1-benzopyrano[2,3-b]pyridine-2,5-dione (1t).*** This compound was obtained in 62% yield as white crystalline solid, mp 224–226°C; IR: 2958, 1690, 1662, 1548, 1474 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.47 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.45 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 7.44–7.61 (m, 5H, ArH), 7.76–7.79 (m, 1H, ArH), 7.84 (br d, 2H, ArH, $J$ = 7.5 Hz), 8.30 (br d, 1H, 6-H, $J$ = 7.5 Hz), 8.51 (s, 1H, 4-H). *Anal.* Calcd for $C_{21}H_{15}NO_4$: C, 73.04; H, 4.38; N, 4.06. Found: C, 72.91; H, 4.32; N, 3.98.

**General procedure for the reaction of ethyl cyanoacetate on 2-alkyl/arylaminochromone-3-carbaldehyde (3).** An ethanolic solution (30 mL) of a mixture of **3** (1 mmol), ethyl cyanoacetate (115 mg, 1 mmol), and piperidine (85 mg, 1 mmol) was stirred at room temperature for 3.5 h to afford a solid. The solid was filtered off, washed with ethanol, and purified by column chromatography over silica gel (100–200) using 10% EtOAc in benzene as eluent to afford **11a–e** in moderate yields.

***Ethyl 2-amino-1,6-dihydro-5-(salicyloyl)-6-oxo-1-phenylpyridine-3-carboxylate (11a).*** This compound was obtained in 60% yield as yellow crystalline solid, mp 166–168°C; IR: 3351, 3253, 2983, 1694, 1654, 1574 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.36 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.30 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.93 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 6.83–6.85 (br t, 1H, 5'-H, $J$ = 7.2 Hz), 6.97 (br d, 1H, 3'-H, $J$ = 8.1 Hz),

7.29–7.31 (m, 2H, ArH), 7.36–7.44 (m, 1H, ArH), 7.54–7.62 (m, 4H, ArH), 8.41 (s, 1H, 4-H), 9.18 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 12.03 (s, 1 H, OH, deuterium oxide exchangeable); $^{13}C$ NMR ($CDCl_3$): δ 14.3, 60.8, 89.6, 114.9, 117.8, 118.4, 119.7, 128.4, 130.2, 130.7, 132.8, 133.5, 135.8, 145.2, 156.6, 159.5, 162.4, 166.6, 197.7; ms: m/z 379 ($M^+$ +H), 401 ($M^+$ +Na). *Anal*. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.80; H, 4.85; N, 7.45.

***Ethyl 2-amino-1,6-dihydro-5-(5-methylsalicyloyl)-6-oxo-1-phenylpyridine-3-carboxylate (11b).*** This compound was obtained in 57% yield as yellow crystalline solid, mp 116–118°C; IR 3400, 3156, 2985, 1691, 1650, 1554 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.35 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 2.25 (s, 3H, $ArCH_3$), 4.30 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.94 (br s, 1H, $NH_2$, deuterium oxide exchangeable ), 6.88 (d, 1H, 3'-H, $J$ = 8.4Hz), 7.23–7.31 (m, 3H, ArH), 7.36–7.39 (m, 1H, ArH), 7.54–7.63 (m, 3H, ArH), 8.36 (s, 1H, 4-H), 9.15 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 11.81 (s, 1H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.55; H, 5.08; N, 7.08.

***Ethyl 2-amino-1,6-dihydro-5-(5-methylsalicyloyl)-6-oxo-1-p-tolylpyridine-3-carboxylate (11c).*** This compound was obtained in 52% yield as yellow crystalline solid, mp 202–204°C; IR 3320, 3148, 2976, 1685, 1663, 1562 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.34 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 2.24 (s, 3H, $ArCH_3$), 2.42 (s, 3H, $ArCH_3$), 4.30 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 5.02 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 6.87 (d, 1H, 3'-H, $J$ = 8.4 Hz), 7.16 (d, 2H, ArH, $J$ = 7.8 Hz), 7.23 (br d, 1H, 4'-H, $J$ = 8.4 Hz), 7.36–7.40 (m, 3H, ArH), 8.35 (s, 1H, 4-H), 9.12 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 11.82 (s, 1H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.80; H, 5.41; N, 6.82.

***Ethyl 2-amino-1,6-dihydro-1-ethyl-5-(5-methylsalicyloyl)-6-oxo-pyridine-3-carboxylate (11d).*** This compound was obtained in 40% yield as yellow crystalline solid, mp 160–162°C; IR 3359, 3204, 2977, 1689, 1604, 1542 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.33 (t, 6H, $2\times CH_2CH_3$, $J$ = 6.9 Hz), 2.25 (s, 3H, $ArCH_3$), 4.12 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.29 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 5.11 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 6.91 (d, 1H, 3′-H, $J$ = 8.4 Hz), 7.25 (br d, 1H, 4′-H, $J$ = 8.4 Hz), 7.32 (br s, 1H, 6′-H), 8.24 (s, 1H, 4-H), 8.99 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 11.87 (s, 1H, OH, deuterium oxide exchangeable); ms: m/z 345 ($M^+$+H), 367 ($M^+$+Na). *Anal*. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.62, H, 5.80; N, 8.10.

***Ethyl 2-amino-1,6-dihydro-1-methyl-5-(5-methylsalicyloyl)-6-oxo-pyridine-3-carboxylate (11e).*** This compound was obtained in 45% yield as yellow crystalline solid, mp 208–210°C; IR 3333, 3194, 2970, 1684, 1635, 1574 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.33 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 2.25 (s, 3H, $ArCH_3$), 3.50 (s, 3H, $NCH_3$), 4.29 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 5.12 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 6.91 (d, 1H, 3′-H, $J$ = 8.4 Hz), 7.26 (br d, 1H, 4′-H, $J$ = 8.4 Hz), 7.32 (br s, 1H, 6′-H), 8.23 (s, 1H, 4-H), 8.98 (br s, 1H, $NH_2$, deuterium oxide exchangeable), 11.86 (s, 1H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.74; H, 5.45; N, 8.42.

**General procedure for the reaction of malononitrile on 2-alkyl/arylaminochromone-3-carbaldehyde (3).** A mixture of **3** (1 mmol), malononitrile (66 mg, 1 mmol), and piperidine (85 mg, 1 mmol) in ethanol (30 mL) was stirred at room temperature for 1 h. The deposited solid was filtered off, washed with ethanol, and recrystallized from benzene to afford **12f–i**.

***7-Methyl-1-phenyl-2H,5H-2-imino-5-oxo-1-benzopyrano[2,3-b]pyridine-3-carbonitrile (12f).*** This compound was obtained in 80% yield as faint yellow crystalline solid, mp 286–288°C; IR 3316, 2210, 1637, 1533, 1475 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.44 (s, 3H, $ArCH_3$), 6.95 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.27–7.39 (m, 5H, ArH), 7.60–7.67 [m, 2H (1 H, deuterium oxide exchangeable), NH+ArH)], 7.98 (br s, 1H, 6-H), 8.23 (s, 1H, 4-H); ms: m/z 328 ($M^+$+H), 350 ($M^+$+Na). *Anal*. Calcd for $C_{20}H_{13}N_3O_2$: C, 73.39; H, 4.00; N, 12.84. Found: C, 73.25; H, 3.92; N, 12.78.

***1-Phenyl-2H,5H-2-imino-5-oxo-1-benzopyrano[2,3-b]pyridine-3-carbonitrile (12g).*** This compound was obtained in 83% yield as faint yellow crystalline solid, mp > 320°C; IR 3330, 2230, 1648, 1520, 1460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.05 (br d, 1H, 9-H, $J$ = 8.1 Hz ), 7.44 (br t, 1H, 7-H, $J$ = 7.2 Hz), 7.58–7.63 (m, 1H, 8-H), 7.64–7.67 (m, 6H, NH+ArH), 8.22 (br d, 1H, 6-H, $J$ = 7.2 Hz), 8.30 (s, 1H, 4-H). *Anal*. Calcd for $C_{19}H_{11}N_3O_2$: C, 72.84; H, 3.54; N, 13.41. Found: C, 72.72; H, 3.48; N, 13.48.

***1-Ethyl-2H,5H-2-imino-5-oxo-1-benzopyrano[2,3-b]pyridine-3-carbonitrile (12h).*** This compound was obtained in 86% yield as faint yellow crystalline solid, mp 266–268°C; IR 3298, 3022, 2222, 1626, 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.45 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.49 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 7.48–7.52 (m, 2H, ArH), 7.62 (br s, 1H, NH, deuterium oxide exchangeable), 7.75 (ddd, 1H, 8-H, $J$ = 8.4, 7.9, 1.8 Hz), 8.19 (s, 1H, 4-H), 8.24 (dd, 1H, 6-H, $J$ = 7.8, 1.8 Hz). *Anal*. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.10; H, 4.23; N, 15.76.

***1-Ethyl-7-methyl-2H,5H-2-imino-5-oxo-1-benzopyrano[2,3-b]pyridine-3-carbonitrile (12i).*** This compound was obtained in 64% yield as faint yellow crystalline solid, mp 256–258°C; IR 3300, 2983, 2254, 1645, 1615 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.44 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 2.48 (s, 3H, $ArCH_3$), 4.46 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 7.39 (br d, 1H, 9-H, $J$ = 8.4 Hz), 7.54 (br d, 1H, 8-H, $J$ = 8.4 Hz), 7.58 (br s, 1H, NH, deuterium oxide exchangeable), 8.01 (br s, 1H, 6-H), 8.17 (s, 1H, 4-H). *Anal*. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.70; H, 4.62; N, 14.96.

**Silica-induced hydrolysis of 12 to 1-alkyl/aryl-2-amino-1,6-dihydro-5-(salicyloyl)-6-oxo-pyridine-3-carbonitrile (11f).** Compound **12** (1 mmol) was dissolved in $CHCl_3$ (25 mL). Silica gel (1 g) was added to the $CHCl_3$ solution and the resultant mixture was heated under reflux with stirring for 5 h. Silica gel was filtered off and it was eluted with 20% ethyl acetate in benzene. Filtrate ($CHCl_3$ solution) and eluents were mixed together and was concentrated under reduced pressure. The residue was crystallized from benzene to afford **11f–i**.

***2-Amino-1,6-dihydro-1-phenyl-5-(5-methylsalicyloyl)-6-oxo-pyridine-3-carbonitrile (11f).*** This compound was obtained in 70% yield as yellow crystalline solid, mp 194–196°C; IR 3400, 3388, 3220, 2981, 2255, 1690, 1647, 1540 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.26 (s, 3H, $ArCH_3$), 5.50 (br s, 2H, $NH_2$, deuterium oxide exchangeable), 6.89 (d, 1H, 3'-H, $J$ = 8.7 Hz), 7.29–7.31 (m, 4H, ArH), 7.57–7.65 (m, 3H, ArH), 7.74 (s, 1H, 4-H), 11.61 (s, 1H, OH, deuterium oxide exchangeable); $^{13}C$ NMR ($CDCl_3$): δ 20.6, 72.0, 116.2, 117.1, 118.0, 119.1, 127.7, 128.1, 128.3, 130.8, 131.0, 132.1, 133.2, 137.6, 144.2, 156.5, 160.7, 196.4; ms: m/z 346 ($M^+$+H), 368

($M^+$+Na). *Anal*. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.38; H, 4.40; N, 12.12.

***2-Amino-1,6-dihydro-1-phenyl-5-salicyloyl-6-oxo-pyridine-3-carbonitrile (11g).*** This compound was obtained in 72% yield as yellow crystalline solid, mp 228–230°C; IR 3410, 3398, 3213, 2922, 2216, 1681, 1638, 1526 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.41 (br s, 2H, $NH_2$, deuterium oxide exchangeable), 6.85 (ddd, 1H, 5'-H, $J$ = 7.5, 7.2, 0.6 Hz), 6.98 (dd, 1H, 3'-H, $J$ = 8.1, 0.6 Hz), 7.28–7.31 (m, 2H, ArH), 7.42–7.48 (m, 1H, ArH), 7.55–7.65 (m, 4H, ArH), 7.81 (s, 1H, 4-H), 11.81 (s, 1H, OH, deuterium oxide exchangeable); *Anal*. Calcd for $C_{19}H_{13}N_3O_3$: C, 68.88; H, 3.95; N, 12.68. Found: C, 68.75; H, 3.92; N, 12.63.

***2-Amino-1-ethyl-1,6-dihydro-5-salicyloyl-6-oxo-pyridine-3-carbonitrile (11h).*** This compound was obtained in 69% yield as yellow crystalline solid, mp 252–254°C; IR 3344, 3314, 3227, 2941, 2212, 1631, 1581 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.09 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 4.0 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 6.81–6.88 (m, 2H, ArH), 7.34–7.36 (m, 2H, ArH), 7.78 (s, 1H, 4-H), 8.14 (br s, 2H, $NH_2$, deuterium oxide exchangeable), 10.61 (s, 1H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.45; H, 4.56; N, 14.74.

***2-Amino-1-ethyl-1,6-dihydro-5-(5-methylsalicyloyl)-6-oxo-pyridine-3-carbonitrile (11i).*** This compound was obtained in 67% yield as yellow crystalline solid, mp 248–250°C; IR 3340, 3324, 3220, 2955, 2220, 1640, 1578 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.10 (t, 3H, $CH_2CH_3$, $J$ = 6.9 Hz), 2.20 (s, 3H, $ArCH_3$), 4.00 (q, 2H, $CH_2CH_3$, $J$ = 6.9 Hz), 6.77 (d, 1H, 3'-H, $J$ = 7.5 Hz), 7.16–7.18 (m, 2H, ArH), 7.75 (s, 1H, 4-H), 8.12 (br s, 2H, $NH_2$, deuterium oxide exchangeable), 10.42 (s, 1H, OH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.03; N, 14.13. Found: C, 64.74; H, 5.06; N, 14.19.

**Synthesis of Ethyl 1-ethyl-7-methyl-2H,5H-2-imino-5-oxo-1-benzopyrano[2,3-b]pyridine-3-carboxylate (12d) from 3 ($R^1$ = Me, $R^2$ = Et).** A mixture of **3** ($R^1$ = Me, $R^2$ = Et) (230 mg, 1 mmol), ethyl cyanoacetate (115 mg, 1 mmol) in pyridine (5 mL) was stirred at room temperature for 2 h when a solid was found to separate. It was filtered off, washed with water, dried in air, and crystallized from benzene-light petrol (80:20) to produce **12d**.

***Ethyl 1-ethyl-7-methyl-2H,5H-2-imino-5-oxo-1-benzopyrano[2,3-b]pyridine-3-carboxylate (12d).*** This compound was obtained in 40% yield as faint yellow crystalline solid, mp 256–258°C; IR 3303, 2985, 1702, 1625, 1537, 1478 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.37–1.44 (m, 6H, 2×$CH_2CH_3$), 2.47 (s, 3H, $ArCH_3$), 4.34 (q, 2H, $NCH_2CH_3$, $J$ = 6.9 Hz), 4.47 (q, 2H, $OCH_2CH_3$, $J$ = 6.6 Hz), 7.36 (d, 1H, 9-H, $J$ = 8.4 Hz), 7.48 (br d, 1H, 8-H, $J$ = 8.4 Hz), 8.01 (br s, 1H, 6-H), 8.63 (s, 1H, 4-H), 9.57 (br s, 1H, NH, deuterium oxide exchangeable). *Anal*. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.40; H, 5.49, N, 8.52.

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## REFERENCES AND NOTES

[1] Unangst, P. C.; Capiris, T.; Connor, D. T.; Heffner, T. G.; Mackenzie, R. G.; Miller, S. R.; Pugsley, T. A.; Wise, L. D. J Med Chem 1997, 40, 2688.

[2] Edwards, J. D.; Higuchi, R. I.; Winn, D. T.; Pooley, C. F.; Caferro, T. R.; Hamann, L. G.; Zhi, L.; Marschke, K. B.; Goldman, M. E.; Jones, T. K. Bioorg Med Chem Lett 1999, 9, 1003.

[3] Siddique, Z. N.; Khuwaja, G.; Asad, M. Indian J Chem 2006, 45B, 2341.

[4] Weng, L. L.; Ln, G.; Zheng, H. Chin Chem Lett 2002, 13, 13.

[5] Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. Synlett 2004, 2287.

[6] (a) Nohara, A.; Sugihara, H.; Ukawa, K. Ger. Pat. 2,809,720; (b) Nohara, A.; Ishiguro, T.; Ukawa, K. Ger. Pat. 2,841,644; (c) Nohara, A.; Sugihara, H.; Ukawa, K. Jpn. Pat. 7,988,298; (d) Nohara, A.; Sugihara, H.; Ukawa, K. U.S. Pat. 4,255,576;

[7] Connor, D. T.; Strandtmann, V. U.S. Pat. 4,117,134;

[8] Atkinson, P.; Findlay, K. S.; Kielar, F.; Pal, R.; Parker, D.; Poole, R. A.; Puschmann, H.; Richardson, S. L.; Stenson, P. A.; Thompson, A. L.; Yu, J. Org Biomol Chem 2006, 4, 1707.

[9] Ghosh, C. K.; Sinha Roy, D. K.; Mukhopadhyay, K. K. J Chem Soc Perkin Trans1 1979,1964.

[10] (a) Langer, P.; Appel, B. Tetrahedron Lett 2003, 44, 5133; (b) Rashid, M. A.; Rasool, N.; Appel, B.; Adeel, M.; Karapetyan, V.; Mkrtchyan, S.; Reinke, H.; Fischer, C.; Langer, P. Tetrahedron 2008, 64, 5416.

[11] Ghosh, T.; Bandyopadhyay, C. J Heterocycl Chem 2006, 43, 1431.

[12] Plaskon, A. S.; Ryabukhin, S. V.; Volochnyuk, D. M.; Gavrilenko, K. S.; Shivanyuk, A. N.; Tolmachev, A. A. J Org Chem 2008, 73, 6010.

[13] Ghosh, C. K.; Bandyopadhyay, C.; Maiti, J. Heterocycles 1987, 26, 1623.

[14] (a) Sottofattori, E.; Anzaldi, M.; Balbi, A.; Artali, R.; Bombieri, G. Helv Chim Acta 2002, 85, 1698; (b) Singh, G.; Singh, L.; Ishar, M. P. S. Tetrahedron 2002, 58, 7883; (c) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. Indian J Chem 2009, 48B, 1447.

[15] Maiti, S.; Panja, S. K.; Bandyopadhyay, C. Tetrahedron Lett 2009, 50, 3966.

[16] Esmaeili, A. A.; Gharenghani, O. Helv Chim Acta 2007, 90, 1712.

[17] Nakaike, Y.; Hayashi, D.; Nishiwaki, N.; Tobe, Y.; Ariga, M. Org Biomol Chem 2009, 7, 325.

[18] Singh, G; Singh, G.; Ishar, M. P. S. Helv Chim Acta 2003, 86, 169.

[19] (a) Ishar, M. P. S.; Kumar, K.; Singh, R. Tetrahedron Lett 1998, 39, 6547; (b) Ghosh, T.; Bandyopadhyay, C. Tetrahedron Lett 2004, 45, 6169.

[20] (a) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Banerjee, S. J Chem Res (S) 2003,459; (b) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Banerjee, S. J Chem Res (M) 2003, 847.

[21] (a) Song, A.; Wang, X.; Lam, K. S. Tetrahedron Lett 2003, 44, 1755; (b) Gao, S.; Tsai, C. H.; Yao, C.-F. Synlett 2009, 949.

[22] Chopra, D.; Zhurov, V. V.; Zhurova, E. A.; Pinkerton, A. A. J Org Chem 2009, 74, 2389.

[23] (a) Mc Nab, H. Chem Soc Rev 1978, 7, 345; (b) Ivanor, A. S. Chem Soc Rev 2008, 37, 789.

[24] Ghosh, C. K.; Bandyopadhyay, C. Indian J Chem 1984, 23B, 1048.

[25] (a) Trivedi, K. N.; Madhava Rao, S. S.; Mistry, S. V.; Desai, S. M. J Indian Chem Soc 2001, 78, 579; (b) Mitra, A. K.; De, A.; Karchaudhuri, N.; Misra, S. K.; Mukhopadhyay, A. K. J Indian Chem Soc 1998, 75, 666.

# Synthesis and X-ray Crystal Structures of Chiral, Nonracemic 5,6-Dihydro-4*H*-1,3,4-oxadiazines

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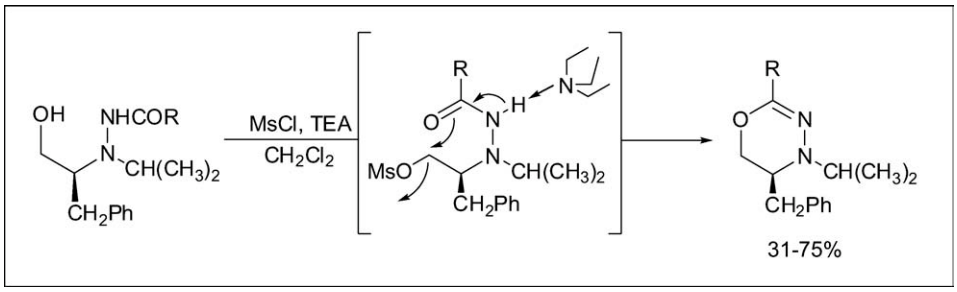


A series of chiral, nonracemic oxadiazines have been prepared from (1*R*,2*S*)-ephedrine, (1*R*,2*S*)-norephedrine, and L-phenylalaninol. The synthesis of the *Ephedra*-based oxadiazines was accomplished by a process of *N*-nitrosation, reduction, acylation, and acid-catalyzed cyclization. The *trans*- and *cis*-diastereomeric oxadiazines derived from (1*R*,2*S*)-ephedrine were analyzed by $^1$H NMR spectroscopy and by single crystal X-ray crystallographic analysis. The stereochemistry of the (1*R*,2*S*)-norephedrine–derived oxadiazines was assigned based on $^1$H NMR spectroscopy and by analogy with the X-ray crystal structure of the (1*R*,2*S*)-ephedrine–based oxadiazines. In addition, L-phenylalaninol was used as a template to prepare a series of oxadiazines substituted at the $N_4$-nitrogen with an isopropyl group. This was accomplished by a reductive alkylation of L-phenylalaninol with acetone and subsequent hydrazide formation. These hydrazides were reacted with methanesulfonyl chloride to yield the corresponding oxadiazines by a base-mediated cyclization.

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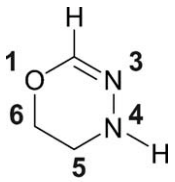
## INTRODUCTION

Many heterocyclic systems such as oxazolidinones [1] and oxazolines [2] have been well-developed in terms of their synthetic [3,4] and medicinal applications [5,6]. In contrast, the heterocycles known as 5,6-dihydro-4*H*-1,3,4-oxadiazines (oxadiazines, **1**) have not been the subject of much interest (Fig. 1). The first report concerning this ring system was described by Ishidate *et al.* and the oxadiazine that was formed only considered to be a contaminant [7]. Research that was directly focused on oxadiazines, as synthetic targets of medicinal worth was launched by the Pitman-Moore division of Dow chemical in the early 1960s [8a]. Consequently, chiral, nonracemic oxadiazines derived from *Ephedra* alkaloids were first prepared by Dow chemists Trepanier *et al.* [8a–f]. The synthetic pathway that was developed involved the preparation of β-hydrazido-alcohols, which were converted into their corresponding oxadiazines by acid-catalyzed cyclization (Scheme 1) [8a–f]. Specifically, ephedrine was converted to *N*-aminoephedrine by *N*-nitrosation and $LiAlH_4$ reduction. The resultant β-hydrazido-alcohol was treated with two equivalents of benzoyl chloride to generate the bis(benzoylated) derivative **4**. Hydrolysis of the ester yielded the required β-hydrazido-alcohol **5**. Trepanier *et al.* used this sequence of steps because of the competitive nucleophilicity between the hydrazine and alcohol. The β-hydrazido-alcohol **5** was then treated with acid [8a–e] to induce cyclization to afford a diasteroemeric mixture of oxadiazines **6** and **7**. The dominant oxadiazine was dependent on the acid that was used. Oxadiazine **6** was the dominant diastereomer [8a–c] when sulfuric acid was used, and oxadiazine **7** was dominant when an acetic acid/HBr mixture was used [8d]. On the basis of seminal efforts of Trepanier *et al.* [8] and the later research efforts of others [9–11] who have investigated the preparation of oxadiazines, we became interested in the synthesis of these compounds as potential tools for conducting asymmetric syntheses via intramolecular chiral relay [12–14,15a].

## RESULTS AND DISCUSSION

The first course of action that was taken involved the preparation of the (1*R*,2*S*)-ephedrine–derived oxadiazines **6** and **7** for the sake of evaluating the literature




**1**

**Figure 1.** 5,6-Dihydro-4*H*-1,3,4-oxadiazine.

method for preparing these compounds. The (1*R*,2*S*)-ephedrine hydrazine was prepared in the same manner as in Trepanier's work using an experimental procedure (*N*-nitrosation/reduction) developed in the our laboratories (Scheme 2) [15]. In contrast to the earlier work involving the use of excess benzoyl chloride (Scheme 1), the hydrazine was treated with one equivalent of benzoic anhydride via dropwise addition at 0°C to afford the corresponding hydrazide **5** in 66% yield without the need for the bis(acylation).

The $H_2SO_4$-catalyzed cyclization of **5** gave a 7:1 ratio of the *trans*-oxadiazine **6** to the *cis*-oxadiazine **7**. This mixture of diastereomers, which presumably arose from stereochemical inversion/retention at the benzylic position, was purified by multiple recrystallizations to afford the diastereomerically enriched **6** in 22%. The low yield was attributed to the competitive process of hydrolysis of the hydrazide to hydrazine **3**. Despite numerous attempts, we were not able to reproduce the yields for this compound that Trepanier *et al*. obtained in his early work perhaps due to the purification [8a].

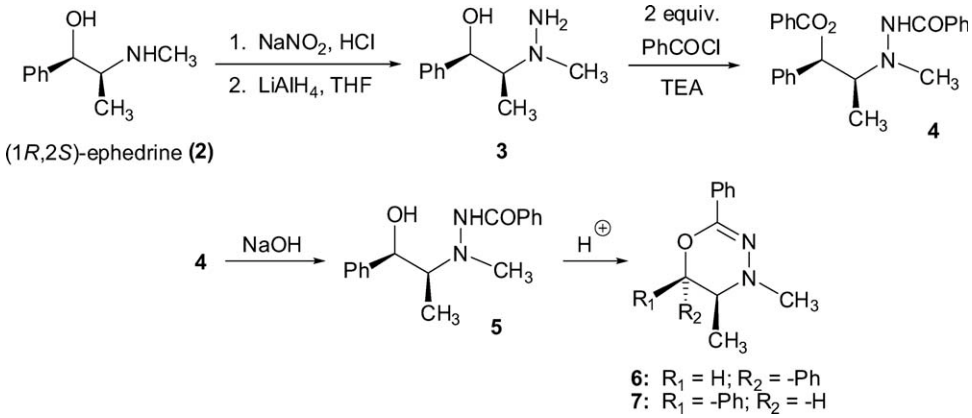
Nonetheless, we were also interested in conducting the hydrobromic acid/propanoic acid cyclization pathway. Under these conditions, treatment of **5** afforded a 6:1 diastereomeric mixture of oxadiazines favoring the *cis*-isomer **7**. Purification by flash chromatography yielded the diastereomerically enriched **7** in 36% isolated yield.

Base-induced cyclization was of interest as there was the possibility that such a pathway might afford improved diastereoselectivities in the oxadiazine products. Trepanier had demonstrated that the base-mediated cyclization (Scheme 1) was limited due to the failure of the intramolecular nucleophilic substitution. The cyclization pathway was investigated through a different synthetic route involving the generation of the mesylate of hydrazide **5**. To pursue this idea, **5** was reacted with methanesulfonyl chloride in the presence of excess triethylamine (TEA) to generate benzylic mesylate intermediate **10**, which presumably underwent further cyclization to **6** (Scheme 2). This process yielded oxadiazine **6** in only 9% yield after flash chromatography from a complex mixture, suggesting that the base-mediated cyclization for the *Ephedra* series was not viable.

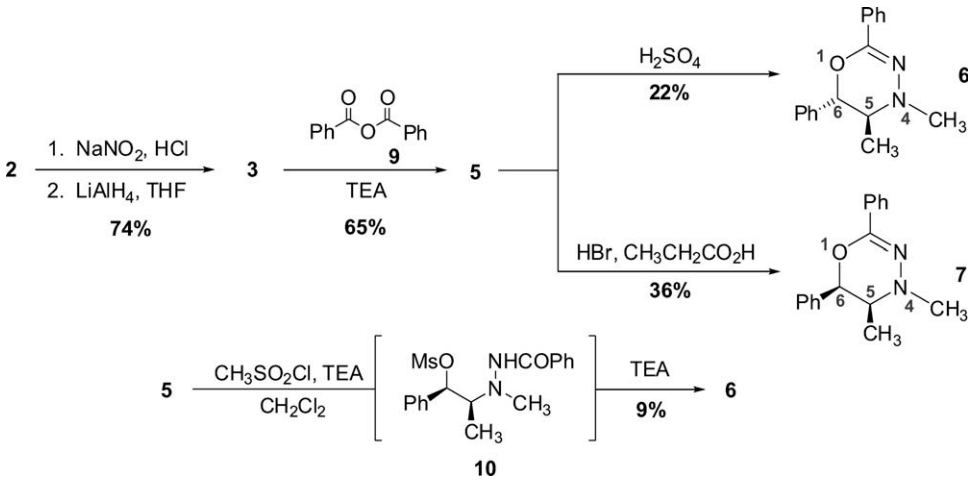
Trepanier originally assigned the configurations of the *trans*- and *cis*-oxadiazines based on the observed coupling constants for the $C_5$ and $C_6$ methine protons (Scheme 2). The $J_{H5–H6}$ coupling constant of the proposed *trans*-isomer **6** was calculated to be 7.4 Hz, whereas the $J_{H5–H6}$ coupling constant of the *cis*-isomer was determined to be 2.9 Hz. The calculated coupling constants were in agreement with the expected values based on the Karplus relation [16], but we were still interested in determining the relative and absolute stereochemistry of these compounds beyond the $^1$H NMR analysis. Thus, the stereochemical structures of **6** and **7** were unambiguously determined by single crystal X-ray crystallography (Figs. 2 and 3) [17].

The oxadiazines **6** and **7** were determined to have relatively planar structures as compared with the twist boat conformations that the related oxadiazinanones possess [18]. In addition to this observation, it was determined that there was a difference in terms of conformational

**Scheme 1.** Trepanier's synthesis of oxadiazines **6** and **7**.



**Scheme 2.** Synthesis of oxadiazines **6** and **7**.




behavior of the $N_4$-nitrogen with regard to the *cis*-oxadiazine **7** as compared with the related oxadiazinanones. Oxadiazine **7** possesses an equatorial $N_4$-methyl group, whereas the corresponding oxadiazinanone possesses an axial $N_4$-methyl group.

Once the stereochemistry of the oxadiazines was unambiguously determined, the synthesis of related oxadiazines derived from (1*R*,2*S*)-norephedrine was pursued (Scheme 3). The (1*R*,2*S*)-ephedrine hydrazine **3** was treated with either 1-naphthoyl chloride or propanoic anhydride to afford the corresponding hydrazides **12** (68%) and **13** (71%), respectively. Hydrazide **12** was reacted with either $H_2SO_4$ or HBr in propanoic acid to afford *trans*-oxadiazine **15** (28%) and *cis*-oxadiazine **16** (21%), respectively. The relative stereochemistry for the oxadiazines **15** and **16** were assigned based on the coupling constants [$J_{H5–H6}$(*trans*) = 7.4 Hz and $J_{H5–H6}$(*cis*) = 3.0 Hz] and correlation with the collected X-ray crystallographic data for **6** and **7**. Interestingly, cyclization of the propanoyl hydrazide **13** with sulfuric acid gave *trans*-oxadiazine **17** in 64% after flash chromatography. With regard to the higher yield of oxadiazine **17**, it is proposed that the 1-naphthoyl group of hydrazide **12** undergoes acid-catalyzed hydrolysis at a rate that is competitive with the cyclization; whereas the propanoyl group of hydrazide **13** does not.

The modifications that were made to prepare oxadiazines **15–17** varied the $C_2$-position. The $N_4$-position was also of interest as this position has been proposed to be the primary means of asymmetric induction in the related oxadiazinanone family of chiral auxiliaries [19]. To examine the impact of altering the $N_4$-position of the oxadiazine core, hydrazine **11** [19] was benzoylated by reaction with benzoic anhydride to yield hydrazide **14** in 31% after chromatography. The lower yield for the acylation process was attributed to the competitive nucleophilicity between the amino group of the hydrazine and the β-hydroxy group due to the presence of the *N*-

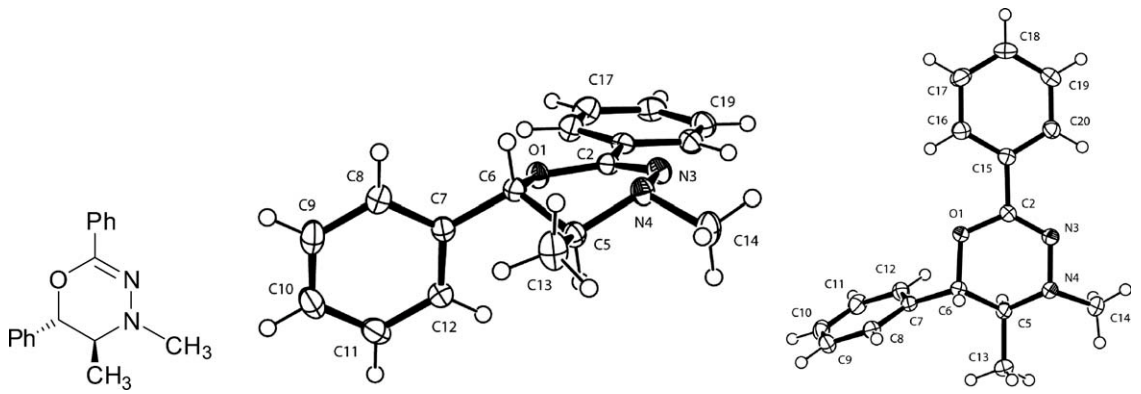



**Figure 2.** ORTEP-3 diagram of **6** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity. ORTEP of *trans*-oxadiazine **6**.

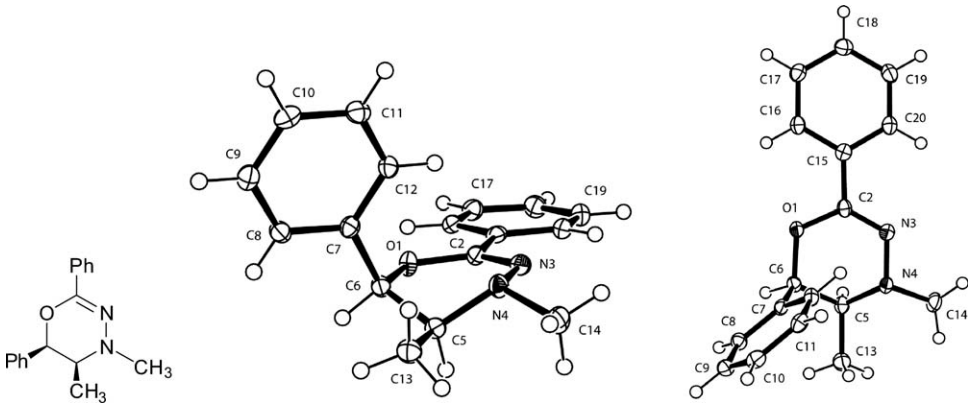



**Figure 3.** ORTEP-3 diagram of **7** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity.

isopropyl group. The hydrazide **14** was cyclized with $H_2SO_4$ to yield the *trans*-oxadiazine **18** in 40% yield.

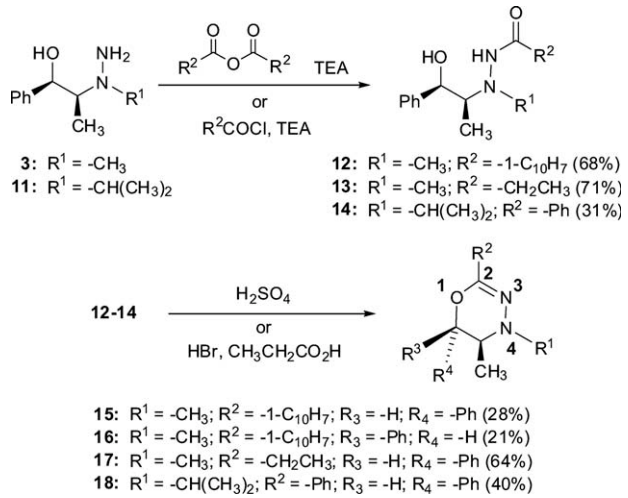
We became interested in determining if it would be possible to prepare chiral oxadiazines from a variety of α-amino acids. We had previously prepared hydrazine **19** from L-phenylalaninol [20] and sought to use this material to prepare a series of oxadiazines (Scheme 4). Thus, hydrazine **19** was acylated at nitrogen using either propanoyl chloride, benzoyl chloride, or 1-naphthoyl chloride to afford the corresponding hydrazides **20a–c**, respectively. The use of acyl chlorides proved to be as effective as the use of anhydrides when the reactions were conducted in 0.1*M* solutions of dichloromethane. The hydrazide **20c** was not directly isolated due to difficulties associated with the crystallinity of the hydrazide and the byproduct naphthoic acid.

The use of an acid-catalyzed process to induce the cyclization of these hydrazides was not pursued as these systems contained primary alcohols that might be susceptible to degradation. Ultimately, a base-mediated process for the cyclization of compounds **20a–c** was used. Thus, the hydrazides were treated with methanesulfonyl chloride and an excess of TEA to afford the desired oxadiazines **22a–c** through putative intermediates **21a–c**. The isolated yields for the oxadiazines were significantly better than the acid-catalyzed pathway perhaps due to the circumvention of the hydrolysis of the hydrazide.

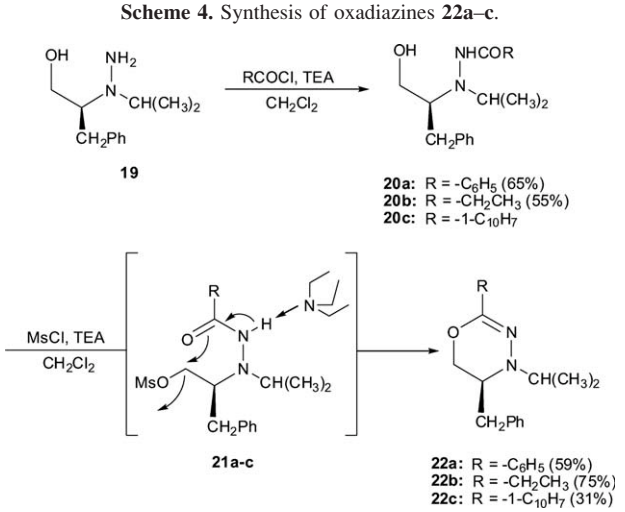
## CONCLUSIONS

We have synthesized a series of *Ephedra*-based oxadiazines using a modified method based on the earlier works of Trepanier *et al*. The stereochemistry of the *Ephedra*-based oxadiazines were evaluated by $^1$H NMR spectroscopy and by X-ray crystallography. The preparation of the oxadiazines from L-phenylaninol was accomplished using a hydrazide pathway with formation on a labile mesylate intermediate.

**Scheme 3.** Synthesis of oxadiazines **15–18**.




**Scheme 4.** Synthesis of oxadiazines **22a–c**.



## EXPERIMENTAL

**General remarks.** Methylene chloride ($CH_2Cl_2$) was purchased as an anhydrous reagent. Unless otherwise stated, all reactions were run under anhydrous conditions and a nitrogen atmosphere. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ operating at 400 and 100 MHz, respectively, or at 300 and 75 MHz as specified. Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed in hertz (Hz). Infrared spectra are reported in reciprocal centimeters ($cm^{-1}$) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Mass spectral analyses were conducted using a quadrupole time of flight mass spectrometer hybrid with MS/MS capability. Optical activities were measured at 589 nm using a digital polarimeter purchased with NSF grant.

**(5*S*,6*R*)-*N*′-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*′-methyl) benzoic acid hydrazide (5).** To a flame dried, nitrogen purged round bottom, the (1*R*,2*S*)-ephedrine–derived hydrazine **4** (2.50 g, 13.9 mmol), dichloromethane (70 mL), and TEA (2.13 mL, 15.3 mmol) was added. The reaction mixture was then cooled to 0°C. The reaction stirred for 5 min and benzoic anhydride (3.30 g, 14.6 mmol) was added by means of a dropping funnel. After 24 h, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (100 mL) and diluted with $CHCl_3$ (100 mL). The organic layer was washed with brine (100 mL) and then dried ($MgSO_4$). The solvent was removed via rotary evaporation to afford the title compound: white solid (66%), Mp = 163–165°C, $[\alpha]_D^{24} = -61.9$ (*c* 0.59, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.6 Hz, 3H), 2.83 (s, 3H), 2.99 (qd, *J* = 6.6, 2.2 Hz, 1H), 5.16 (d, *J* = 2.2 Hz, 1H), 7.20–7.52 (m, 8H), 7.76 (d, *J* = 7.4 Hz, 2H), 8.01 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 9.9, 42.3, 65.8, 71.5, 125.6, 126.3, 127.2, 127.7, 128.3, 131.3, 133.4, 142.7, and 165.7 ppm. IR (nujol mull): 3205 and 1641 $cm^{-1}$. ESI-HRMS calcd. for $C_{17}H_{21}N_2O_2$ ($M + H^+$): 285.1603. Found: 285.1604.

***trans*-(5*S*,6*S*)-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (6).** Hydrazide **5** (1.00 g, 3.40 mmol) and concentrated sulfuric acid (18*M*, 10 mL) were combined and stirred at room temperature. After 2 h, the solution was diluted with water (100 mL) and treated with a saturated solution of sodium bicarbonate until the solution was neutralized as determined by the use of pH paper. The organic layer was extracted with EtOAc (100 mL), treated with $NaHCO_3$ (50 mL), and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation to afford the title compound as a 7:1 mixture of the *trans*- and *cis*-isomers of the oxadiazine. The title compound was recrystallized thrice with hexanes and ethyl acetate to afford the isomerically pure *trans*-isomer as a white solid (22%). Mp = 139–141°C, $[\alpha]_D^{24} = +160.8$ (*c* 0.91, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.6 Hz, 3H), 2.69 (dq, *J* = 7.4, 6.6 Hz, 1H), 2.88 (s, 3H), 5.05 (d, *J* = 7.4 Hz, 1H), 7.30–7.40 (m, 8H), 7.82–7.85 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 14.3, 43.6, 57.5, 82.3, 125.3, 127.4, 128.0, 128.5, 128.6, 128.9, 132.5, 138.1, and 146.0 ppm. IR (nujol mull): 1622 and 1448 $cm^{-1}$. ESI-HRMS calcd. for $C_{17}H_{19}N_2O$ $(M + H)^+$: 267.1497. Found: 267.1487.

***cis*-(5*S*,6*R*)-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (7).** Hydrazide **5** (1.00 g, 3.40 mmol) and HBr in propanoic acid (15 mL, 30% by weight) were combined in 100 mL flask and stirred for 24 h. The solution was diluted with $H_2O$ (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), and dried with $MgSO_4$. Solvents were removed via rotary evaporator. The title product was isolated by flash column chromatography (hexanes:EtOAc, 98:2). White solid (36%), Mp = 94–97°C. $[\alpha]_D^{24} = -176.2$ (*c* 1.00, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ: 0.81 (d, *J* = 6.5 Hz, 3H), 2.88 (s, 3H), 3.35 (dq, *J* = 6.5, 2.9 Hz, 1H), 5.52 (d, *J* = 2.9 Hz, 1H), 7.24–7.91 (m, 10H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 7.9, 42.9, 54.8, 79.1, 125.2, 126.2, 127.9, 128.0, 128.3, 128.8, 132.5, 138.2, and 144.3. IR (diamond): 1621, 1003, 772, and 647 $cm^{-1}$. ESI-HRMS calcd. for $C_{17}H_{19}N_2O$ ($M + H^+$): 267.1497. Found: 267.1496.

***N*′-[(1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl]-*N*′-methyl naphthoic hydrazide (12).** In a 250-mL nitrogen purged round-bottom flask was placed hydrazine **3** (3.00 g, 16.6 mmol), dichloromethane (208 mL), TEA (4.60 mL, 33.3 mmol), and 1-naphthoyl chloride (2.50 mL, 16.6 mmol). After 24 h, the reaction was diluted by the addition of $CH_2Cl_2$ (100 mL) and $NH_4Cl$ (100 mL). The organic layer was washed with brine (100 mL) and then dried with $MgSO_4$. The solvents were removed via rotary evaporation. The title product was isolated by flash column chromatography (hexanes:EtOAc, 60:40). Yellow solid (68%), Mp = 75–77°C. $[\alpha]_D^{25} = -23.5$ (*c* 1.01, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (d, *J* = 6.1 Hz, 3H), 2.79 (s, 3H), 2.89 (dq, *J* = 6.1, 3.7, 1H), 4.33 (s, 1H), 5.13 (s, 1H), 7.20–7.63 (m, 8H), 7.80–7.86 (m, 3H), 8.19–8.22 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 10.2, 43.5, 66.7, 72.4, 124.5, 125.1, 125.2, 125.7, 126.5, 126.8, 127.3, 128.0, 128.1, 128.2, 130.3, 130.9, 132.3, 133.5, and 168.5. IR (nujol): 3291, 1658, 1511, 735, and 701 $cm^{-1}$. ESI-HRMS calcd. for $C_{21}H_{23}N_2O_2$ ($M + H^+$): 335.1760. Found: 335.1761.

***N*′-[(1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl]-*N*′-methyl propanoic hydrazide (13).** In a 250-mL nitrogen purged round-bottom flask was placed hydrazine **3** (2.00 g, 11.1 mmol), dichloromethane (35 mL), and TEA (1.70 mL, 12.2 mmol). The solution was cooled to 0°C and propanoic acid anhydride (1.50 mL, 11.7 mmol) dissolved in dichloromethane (20 mL) was added slowly via a dropping funnel. After 24 h, the reaction was diluted by the addition of $CH_2Cl_2$ (100 mL) and $NH_4Cl$ (100 mL). The organic layer was washed with brine (100 mL) and then dried with $MgSO_4$. The solvents were removed via rotary evaporation. The title compound was isolated as a 7:1 mixture of diasteromers after recrystallization with hexanes:EtOAc and only the major rotomeric diasteromers have been characterized. White solid (71%), Mp = 81–83°C. $[\alpha]_D^{24} = -32.3$ (*c* .04, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 0.85 (d, *J* = 6.6 Hz, 3H), 1.15 (t, *J* = 7.6 Hz, 3H), 2.17 (q, *J* = 7.6 Hz, 2H), 2.69 (s, 3H), 2.86 (dq, *J* = 6.6, 2.3 Hz, 1H), 5.01 (d, *J* = 2.3 Hz, 1H), 7.20–7.54 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ: 10.1, 27.8, 43.2, 66.5, 72.2, 125.7, 126.7, 128.0, 141.4, 173.5, and 178.4 ppm. IR (diamond): 3256, 1655, and 1451 $cm^{-1}$. ESI-HRMS calcd. for $C_{13}H_{21}N_2O_2$ ($M + H^+$): 237.1603. Found: 237.1598.

***N*′-[(1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl]-*N*′-isopropyl benzoic hydrazide (14).** In a 250-mL nitrogen purged round-bottom flask was placed hydrazine **11** (2.00 g, 9.60 mmol), dichloromethane (30 mL), and TEA (1.50 mL, 10.6 mmol). The solution was cooled to 0°C and benzoic anhydride (2.28 g, 10.1 mmol) dissolved in dichloromethane (18 mL) was slowly added via a dropping funnel. After 24 h, the reaction was diluted by the addition of $CH_2Cl_2$ (100 mL) and $NH_4Cl$ (100 mL). The

title compound was isolated by recrystallization (EtOAc:hexanes). White solid (31%), Mp = 119–120°C. $[\alpha]_D^{24} = -58.6$ (*c* 0.58, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ: 0.86 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 3.09–3.11 (m, 1H), 3.43–3.50 (m, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 7.19–7.78 (m, 10H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 9.9, 17.0, 18.9, 52.3, 63.3, 73.2125.7, 127.7, 127.1, 128.0, 128.7, 131.9, 133.2, 141.3, and 168.9. IR (diamond): 3264, 1653, 748, and 680 $cm^{-1}$. ESI-HRMS calcd. for $C_{19}H_{25}N_2O_2$ ($M + H^+$): 313.1916. Found: 313.1913.

***trans*-(5*S*,6*S*)-4,5-Dimethyl-2-(1-naphthyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (15).** Hydrazide **12** (0.50 g, 1.50 mmol) was combined with $H_2SO_4$ (5 mL, 12*M*) was stirred for 2 h. The solution was diluted with $H_2O$ (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), and dried ($MgSO_4$). The title compound was isolated by trituration with pentane. This process afforded the title compound as a ~7:1 mixture of the *trans*- and *cis*-isomers of the title oxadiazine. Yellow solid (28%), Mp = 140–142°C. $[\alpha]_D^{25} = +56.9$ (*c* 0.70, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, *J* = 6.4 Hz, 3H), 2.88 (dq, *J* = 7.4, 6.4 Hz, 1H), 2.95 (s, 3H), 5.19 (d, *J* = 7.4 Hz, 1H), 7.36–7.85 (m, 8H), 7.81–7.84 (m, 3H), 8.79 (d, *J* = 8.5 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 14.4, 43.7, 57.4, 82.8, 124.9, 125.7, 126.1, 126.8, 127.5, 128.3, 128.6, 128.7, 129.7, 130.7, 133.9, 137.9, and 147.1. IR (nujol): 1614, 1020, 759, and 706 $cm^{-1}$. ESI-HRMS calcd. for $C_{21}H_{21}N_2O$ ($M + H^+$): 317.1654. Found: 317.1643.

***cis*-(5*S*,6*S*)-4,5-Dimethyl-2-(1-naphthyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (16).** Hydrazide **13** (1.00 g, 3.40 mmol) and a 30% solution of HBr in propanoic acid (15 mL) were combined in a 100-mL round-bottom flask and this reaction mixture stirred. After 24 h, the reaction was diluted with $H_2O$ (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), dried with $MgSO_4$, and the solvents were removed via rotary evaporation. The title compound was isolated by flash chromatography (95:5, hexanes:EtOAc). Yellow solid (21%), Mp = 125–128°C. $[\alpha]_D^{23} = -86.4$ (*c* 0.53, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94, (d, *J* = 6.6 Hz, 3H), 2.95 (s, 3H), 3.46 (dq, *J* = 6.6, 3.0 Hz, 1H), 5.65 (d, *J* = 3.0 Hz, 1H), 7.39–7.53 (m, 8H), 7.84–7.89 (m, 3H), 8.74 (d, *J* = 8.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 8.2, 43.0, 54.8, 79.6, 124.9, 125.7, 126.1, 126.3, 126.5, 126.8, 127.9, 128.3, 129.7, 130.0, 130.8, 133.9, 138.1, and 145.5. IR (nujol): 1613, 995, 746, and 709 $cm^{-1}$. ESI-HRMS calcd. for $C_{21}H_{21}N_2O$ ($M + H^+$): 317.1654. Found: 317.1642.

***trans*-(5*S*,6*S*)-2-Ethyl-4,4-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (17).** Hydrazide **13** (0.25 g, 1.06 mmol) and $H_2SO_4$ (3 mL, 12*M*) were combined in 100-mL round-bottom flask and stirred for 24 h. The solution was diluted with $H_2O$ (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), dried with $MgSO_4$, and the solvents were removed via rotary evaporation. The title product was isolated by flash column chromatography (hexanes:EtOAc, 9:1). Yellow oil (64%). $[\alpha]_D^{23} = +288.8$ (*c* 0.10, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.3 Hz, 3H), 1.1 (t, *J* = 7.5 Hz, 3H), 2.17 (q, *J* = 7.5 Hz, 2H), 2.37–2.43 (m, 6.3 Hz, 1H), 2.63, (s, 3H), 4.79 (d, *J* = 7.8 Hz, 1H), 7.19–7.30 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.1, 14.3, 26.6, 43.5, 57.8, 82.3, 127.4, 128.5, 128.6, 138.0, and 151.9. IR (neat): 1656, 1066, 756, and 700 $cm^{-1}$. ESI-HRMS calcd. for $C_{13}H_{19}N_2O$ ($M + H^+$): 219.1497. Found: 219.1489.

**(5*S*,6*S*)-4-Isopropyl-5-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (18).** Hydrazide **14** (0.50 g, 1.60 mmol) was combined with $H_2SO_4$ (5 mL, 12*M*) and stirred for 2 h. The solution was diluted with $H_2O$ (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), dried with $MgSO_4$, and the solvents were removed via rotary evaporation. The title product was isolated by flash column chromatography (hexanes:-TEA, 97.5:2.5). White solid (40%), Mp = 160–162°C. $[\alpha]_D^{24} = +175.0$ (*c* 0.25, $CHCl_3$). IR (diamond): 1625, 1027, 756, and 686 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (d, *J* = 6.2 Hz, 3H), 1.04 (d, *J* = 6.2 Hz, 3H), 1.40 (d, *J* = 6.6 Hz, 3H), 2.92 (dq, *J* = 12.9, 6.6 Hz, 1H), 3.52 (septet, *J* = 6.6 Hz, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 7.25–7.86 (m, 10H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9, 15.6, 21.4, 50.2, 53.4, 82.4, 125.1, 127.6, 127.9, 128.5, 128.6, 133.2, 138.6, and 145.3. ESI-HRMS calcd. for $C_{19}H_{23}N_2O$ ($M + H^+$): 295.1810. Found: 295.1798.

**General procedure for the formation of hydrazides 20a and 20b.** Hydrazine **19** (0.700 g, 3.36 mmol) was combined with dichloromethane (17 mL) and TEA (0.515 g, 3.70 mmol) and this mixture was cooled to 0°C. The anhydride (0.798 g, 3.53 mmol) was then added. After 24 h, the reaction was diluted by the addition of a saturated solution of ammonium chloride (100 mL) and diluted with $CH_2Cl_2$ (100 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation.

***N′*-(1-Benzyl-2-hydroxyethyl)-*N′*-isopropyl benzoic acid hydrazide (20a)** The use of benzoic acid afforded the title compound as a yellow solid (55%) contaminated with <5% of benzoic acid: Mp = 126–128°C, $[\alpha]_D^{22} = +27.4$ (*c* 1.24, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.6 Hz, 3H) 1.22 (d, *J* = 6.6 Hz, 3H), 2.53 (m, 1H), 2.91 (d, *J* = 13.3, 3.9 Hz, 1H), 3.23–3.33 (m, 1H), 3.44–3.50 (m, 1H), 7.05 (s, 1H), 7.13–7.74 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 20.6, 32.4, 53.5, 61.3, 63.3, 126.3, 127.1, 128.6, 128.6, 128.9, 131.7, 138.5, and 168.9 ppm. IR (nujol mull): 3203 and 1648 $cm^{-1}$. ESI-HRMS calcd. for $C_{19}H_{25}N_2O_2$ ($M + H^+$): 313.1916. Found: 313.1909.

***N′*-(1-Benzyl-2-hydroxyethyl)-*N′*-isopropyl propanoic acid hydrazide (20b)** The use of propanoic anhydride afforded a white solid (65%). Mp = 118–120°C, $[\alpha]_D^{24} = -7.28$ (*c* 0.82, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H), 2.20 (q, *J* = 7.4 Hz, 2H), 2.38–2.50 (m, 1H), 2.83 (d, *J* = 13.2, 4.1 Hz, 1H), 3.11–3.23 (m, 2H), 3.33–3.45 (m, 2H), 4.52 (broad singlet, 1H) 6.26 (s), 7.12–7.32 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 10.1, 20.5, 27.3, 31.7, 52.7, 61.1, 62.8, 126.1, 128.4, 128.7, 138.5, and 175.5 ppm. IR (nujol mull): 3225 and 1666 $cm^{-1}$. ESI-HRMS calcd. for $C_{15}H_{25}N_2O_2$ ($M + H^+$): 265.1916. Found: 265.1921.

***N′*-(1-Benzyl-2-hydroxyethyl)-*N′*-isopropyl 1-naphthoic acid hydrazide (20c)** Hydrazine **19** (1.00 g, 4.80 mmol) was combined with dichloromethane (24 mL) and TEA (0.736 mL, 5.28 mmol) and the solution was cooled to 0°C. The reaction was stirred for 5 min and 1-naphthoyl chloride (0.76 mL, 5.0 mmol) was added by syringe. After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and diluted with $CH_2Cl_2$ (100 mL). The aqueous layer was drawn off and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and the solvent was

removed by rotary evaporation to afford hydrazide **20c**. This product proved to be difficult to handle due to its poor solubility and was directly converted to oxadiazine **21c**.

**General procedure for the formation of oxadiazines 21a and 21b.** Hydrazide **20a** (0.500 g, 1.60 mmol) was combined with dichloromethane (5 mL), TEA (0.22 mL, 1.6 mmol), and methanesulfonyl chloride (0.130 mL, 1.68 mmol). After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and diluted with dichloromethane (50 mL). The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The crude product was then purified by column chromatography using hexanes and ethyl acetate (98:2).

***(S)-5-Benzyl-4-5,6-dihydro-isopropyl-2-phenyl-4H-1,3,4-oxadiazine (21a)*** The title compound was obtained as yellow oil (75%). $[\alpha]_D^{21} = +197.9$ (*c* 1.45, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, $J = 6.3$ Hz, 3H), 1.37 (d, $J = 6.3$ Hz, 3H), 2.69 (dd, $J = 13.5$, 9.9 Hz, 1H), 3.03 (dd, $J = 13.5$, 4.7 Hz, 1H), 3.32–3.53 (m, 2H), 3.98 (dd, $J = 10.3$, 2.8 Hz, 1H), 4.14 (dd, $J = 10.3$, 4.4 Hz, 1H), 7.20–7.36 (m, 8H), 7.78–7.83 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 17.9, 20.6, 34.5, 52.3, 53.5, 65.7, 124.8, 126.4, 127.8, 128.2, 128.4, 129.2, 133.0, 137.7, and 143.4 ppm. IR: 1628, 1176, 766, and 694 cm$^{-1}$. ESI-HRMS calcd. for $C_{19}H_{23}N_2O$ $(M + H^+)$: 295.1810. Found: 295.1809.

***(S)-5-Benzyl-2-ethyl-5,6-dihydro-4-isopropyl-4H-1,3,4-oxadiazine (21b)*** Hydrazide **12b** was used in the cyclization process to yield **21b**. The product was purified by column chromatography using hexanes and ethyl acetate (97:3) and was obtained as yellow oil (59%). $[\alpha]_D^{24} = +6.12$ (*c* 0.76, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, $J = 6.3$ Hz, 3H), 1.11 (t, $J = 7.4$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H), 2.18 (q, $J = 7.4$ Hz, 2H), 2.57 (dd, $J = 13.5$, 9.9 Hz, 1H), 2.97 (dd, $J = 13.5$, 4.4 Hz, 1H), 3.18–3.3.26 (m, 1H), 3.33 (septet, $J = 6.3$ Hz, 1H), 3.91–3.93 (m, 1H), 7.16–7.33 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 10.7, 17.0, 20.7, 26.4, 33.1, 51.0, 52.6, 66.5, 126.3, 128.5, 129.1, 138.0, and 149.5 ppm. IR: 1662, 1176, 741, and 701 cm$^{-1}$. ESI-HRMS calcd. for $C_{15}H_{23}N_2O$ $(M + H^+)$: 247.1810. Found: 247.1822.

***(S)-5-Benzyl-5,6-dihydro-4-isopropyl-2-naphthyl-4H-1,3,4-oxadiazine (21c)*** The hydrazine **20c** (1.00 g, 4.80 mmol) was combined with dichloromethane (24 mL) and TEA (0.736 mL, 5.28 mmol) and the solution was cooled to 0°C. The reaction was stirred for 5 min and 1-naphthoyl chloride (0.760 mL, 5.04 mmol) was added. After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and diluted with $CH_2Cl_2$ (100 mL). The aqueous layer was drawn off and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation to afford hydrazide **20c**. This product proved to be difficult to handle due to its solubility and was directly converted to oxadiazine **21c**. The hydrazide was combined with dichloromethane (15 mL), TEA (1.34 mL, 9.60 mmol), and methanesulfonyl chloride (0.39 mL, 5.04 mmol) and stirred. After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and dichloromethane (50 mL). The layers were separated and the organic layer was washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The resultant oxadiazine **21c** was purified by column chromatography with hexanes. This process afforded a yellow oil (31%). $[\alpha]_D^{24} = +158.2$ (*c* 1.64, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, $J = 6.3$ Hz, 3H), 1.56 (d, $J = 6.3$ Hz, 3H), 2.91 (dd, $J = 13.3$, 9.8 Hz, 1H), 3.21 (dd, $J = 13.3$, 5.1 Hz, 1H), 3.64 (septet, $J = 6.3$ Hz, 1H), 4.23 (dd, $J = 10.2$, 2.7 Hz, 1H), 4.35 (dd, $J = 10.2$, 4.3 Hz, 1H), 7.38 (t, $J = 5.9$ Hz, 2H), 7.44–7.46 (m, 2H), 7.56–7.62 (m, 3H), 7.69 (m, 1H), 7.95 (t, $J = 6.6$ Hz, 2H), 8.01–8.03 (m, 1H), 9.09 (d, $J = 8.6$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 18.1, 20.9, 34.6, 52.5, 53.6, 66.0, 124.8, 125.5, 126.1, 126.2, 126.4, 126.5, 128.2, 128.5, 129.3, 130.0, 130.5, 133.9, 137.8, and 144.5 ppm. IR: 2970, 1627, 1131, 740, and 700 cm$^{-1}$. ESI-HRMS calcd. for $C_{23}H_{25}N_2O$ $(M + H)^+$: 345.1967. Found: 345.1958.

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## REFERENCES AND NOTES

[1] (a) Zappia, G.; Cancelliere, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. Curr Org Synth 2007, 4, 238; (b) Ager, D. J.; Prakash, I.; Schaad, D. R. Aldrichimica Acta 1997, 30, 3; (c) Bertau, M.; Bürli, M.; Hungerbühler, E.; Wagner, P. Tetrahedron: Asymmetry 2001, 12, 2103; (d) Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. J Org Chem 1998, 63, 2742.

[2] (a) Meyers, A. I. J Org Chem 2005, 70, 6137; (b) McManus, H. A.; Guiry, P. J. Chem Rev 2004, 104, 4151; (c) Gant, T. G.; Meyers, A. I. Tetrahedron 1994, 50, 2297; (d) Meyers, A. I. Acc Chem Res 1978, 11, 375.

[3] (a) Hashimoto, K.; Morita, A.; Kuwahara, S. J Org Chem 2008, 73, 6913; (b) Son, J. B.; Hwang, M.-H.; Lee, W.; Lee, D.-H. Org Lett 2007, 9, 3897; (c) Kaliappan, K. P.; Ravikumar, V. J Org Chem 2007, 72, 6116; (d) Brailsford, J. A.; Zhu, L.; Loo, M.; Shea, K. J. J Org Chem 2007, 72, 9402.

[4] (a) Uchida, K.; Fukuda, T.; Iwao, M. Tetrahedron 2007, 63, 7178; (b) Lee, Y.-S.; Shin, Y.-H.; Kim, Y.-H.; Lee, K.-Y.; Oh, C.-Y.; Pyun, S.-J.; Park, H.-J.; Jeong, J.-H.; Ham, W.-H. Tetrahedron: Asymmetry 2003, 14, 87; (c) Stavenger, R. A.; Schreiber, S. L. Angew Chem Int Ed Engl 2001, 40, 3417.

[5] (a) Barbachyn, M. R.; Ford, C. W. Angew Chem Int Ed Engl 2003, 42, 2010; (b) Gravestock, M. B. Curr Opin Drug Discov Dev 2005, 8, 469; (c) Hutchinson, D. K. Curr Top Med Chem 2003, 3, 1021.

[6] (a) Rathna, G. V. N. J Mater Sci: Mater Med 2008, 19, 2351; (b) Henderson, G. L.; Harkey, M. R.; Chueh, Y.-T. J Anal Toxicol 1995, 19, 563; (c) Matoga, M.; Forfar, I.; Chaimbault, C.; Guillon, J.; Pehourcq, F.; Bosc, J.-J.; Rettori, M.-C.; Jarry, C. J Enzyme Inhib Med Chem 2002, 17, 375.

[7] Ishidate, M.; Sakurai, Y.; Kuwada, Y. Chem Pharm Bull 1960, 8, 543.

[8] (a) Trepanier, D. L.; Sprancmanis, V.; Wiggs, K. G. J Org Chem 1964, 29, 668; (b) Trepanier, D. L.; Sprancmanis, V. J Org Chem 1964, 29, 673; (c) Trepanier, D. L.; Sprancmanis, V. J Org Chem 1964, 29, 2151; (d) Trepanier, D. L.; Spracmanis, V.; Tharpe, D. S.; Krieger, P. E. J Heterocycl Chem 1965, 2, 403; (e) Trepanier, D. L.; Krieger, P. E.; Eble, J. N. J Med Chem 1965, 8, 802; (f) Trepanier, D. L.; Sprancmanis, V.; Eble, J. N. J Med Chem 1966, 9, 753.

[9] (a) Rosling, A.; Klika, K.; Fulop, F.; Sillanpaa, R.; Mattinen, J. Heterocycles 1999, 51, 2575; (b) Rosling, A.; Hotokka, M.; Klika, K. D.; Fulop, F.; Sillanpaa, R.; Mattinen, J. Acta Chem Scand 1999, 53, 213; (c) Rosling, A.; Fulop, F.; Sillanpaa, R.; Mattinen, J. Heterocycles 1997, 45, 95.

[10] Yamazaki, N.; Kibayashi, C. Tetrahedron Lett 1997, 38, 4623.

[11] Forchiassin, M.; Risaliti, A.; Russo, C. Tetrahedron 1981, 37, 2921.

[12] Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, P.; Jasperse, C. P.; Sibi, M. P. Chem Eur J 2003, 9, 28.

[13] Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. J Am Chem Soc 2001, 123, 8444.

[14] Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. Pure Appl Chem 1998, 70, 1501.

[15] (a) Casper, D. M.; Burgeson, J. R.; Esken, J. M.; Ferrence, G. M; Hitchcock, S. R. Org Lett 2002, 4, 3739; (b) Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrence, G. M.; Szczepura, L. F.; Standard, J. M. Tetrahedron 2001, 57, 9789.

[16] Pretsch, E. Bühlmann, P. Affolter, C. Structure Determination of Organic Compounds: Tables of Spectral Data; Springer: Berlin, 2000.

[17] Crystallographic data (excluding structure factors) for **6** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 717022. In addition, crystallographic data (excluding structure factors) for **7** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 717023. Copies of this data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44 (0)12233 336033 or e-mail: deposit@ccdc.cam.ac.uk].

[18] (a) Burgeson, J. R.; Dore, D. D.; Standard, J. M.; Hitchcock, S. R. Tetrahedron 2005, 61, 10965; (b) Casper, D. M.; Blackburn, J. R.; Maroules, C. D.; Brady, T.; Esken, J. M.; Ferrence, G. M.; Standard, J. M.; Hitchcock, S. R. J Org Chem 2002, 67, 8871.

[19] (a) Vaughn, J. F.; Hitchcock, S. R. Tetrahedron: Asymmetry 2004, 15, 3449; (b) Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M.; Esken, J. M. J Org Chem 2004, 69, 714.

[20] Dore, D. D.; Burgeson, J. R.; Davis, R. A.; Hitchcock, S. R. Tetrahedron: Asymmetry 2006, 17, 2386.

# Synthesis of Novel Tricyclic 4-Chloro-7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-ones

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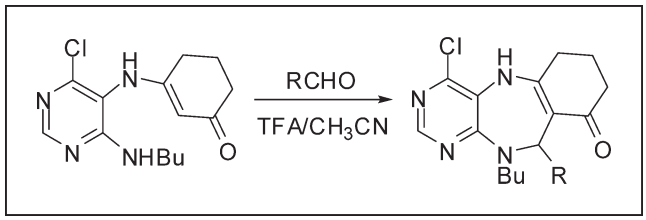


A series of tricyclic 7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-ones were prepared in moderate to high yields using TFA-promoted iminium-cyclization reactions of 3-(6-(butylamino)-4-chloropyrimidin-5-ylamino)cyclohex-2-enones and various aldehydes.

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## INTRODUCTION

Benzodiazepines have long been associated with interesting biological activities. For example, clozapine is used to treat schizophrenia; pirenzepine acts selectively as a muscarinic receptor (M1) antagonist; and apafant acts as the platelet activating factor inhibitors [1]. Consequently, syntheses of benzodiazepine derivatives or diazepine-containing heterocycles are of interest to organic and medicinal chemists. Thus, dibenzo[b,e][1,4]-diazepines and other tricyclic systems with a 1,4-diazepine moiety are well documented in the literature [2–9].

As part of our program to prepare heterocyclic libraries, we developed a series of methodologies to rapidly access various heterocyclic scaffolds with benzodiazepine as the core [10–15]. These methodologies entail Bischler–Napieralski cyclization reactions and iminium cyclization reactions as the key transformation steps. To expand the scope of the iminium-cyclization reaction, we envisioned that enaminones **1** could be reacted with various aldehydes to prepare 7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-ones [16], as depicted in Scheme 1. Although syntheses of dibenzo [b,e][1,4]diazepines are frequently reported, there is few report of aminopyrimidines as substrates for such cyclization reactions [16]. Given the large structural differences between a pyrimidine and benzene, optimization of the cyclization reaction was investigated. Herein, we reported the development of this method to prepare 7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-ones.

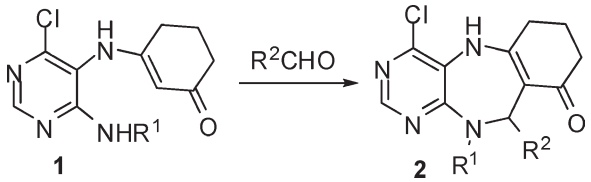
## RESULTS AND DISCUSSION

The desired enaminones **1** were readily prepared *via* condensation of **3** [17] with 1,3-cyclohexandione in acetic acid in 78% yields, as depicted in Scheme 2.

To identify the optimal reaction conditions, the formation of the pyrimido-benzodiazepine nucleus was initially studied using benzaldehyde as the substrate, and results are summarized in Table 1.

The standard conditions of AcOH-EtOH are often reported for similar type of cyclization reactions of anilines leading to dibenzo[b,e][1,4]diazepines [2,4]. Therefore, these conditions were studied initially. No desired product was detected at room temperature (entry 1, Table 1) and only trace amount was isolated after prolonged heating (entry 2, Table 1). The lower reactivity of pyrimidines **1** compared to standard anilines is likely because of the large structural differences between pyrimidine and benzene. It is possible that the pyrimidine ring nitrogens are protonated under the acidic reaction conditions, which decreased the propensity of the n-butylamino group toward imine formation. It was reasoned that a stronger acid, such as TFA might help to promote the key imine formation step. Thus, switching the acid from acetic acid to stronger acids, such as TFA and sulfuric acid led to low yields of desired product **2**, entries 3–5, Table 1. The conditions of TFA-acetonitrile proved to be productive in other iminium cyclization reactions, therefore they were investigated next. Treatment of pyrimidine **1** and benzaldehyde in the presence of TFA at room temperature led to product **2** in 22% yield (entry 6, Table 1). On the hand, moderate heating at 60°C produced the desired product **2** in 56% yield. The reaction temperature to reflux shortened the reaction time to 18 h, producing compound **2** in 59% yield (entry 8, Table 1). To test the solvent effect of acetonitrile, the reaction was repeated using AcOH with $CH_3CN$ (entry 9), and after reflux for 18 h only 11% of the desired product was obtained. Another

**Scheme 1**




condition investigated was $Py/SOCl_2$-$CH_2Cl_2$ [18], which was reported for aniline cyclization reactions. Reflux for 78 h, the desired product was isolated in 40% yield (entry 10). Thus, the TFA-acetonitrile conditions (entry 8, Table 1) were identified as optimal, which were applied to other aldehydes and results are summarized in Table 2.

As disclosed in Table 2, both aliphatic and aromatic aldehydes are compatible for the current reactions, producing the expected 7,8,10,11-tetrahydro-5*H*-benzo[*e*]-pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-ones **2** in moderate to good yields. The reactions with aliphatic aldehydes (entries 1–3) proceeded at room temperature to generate the desired products in moderate yields. Various functional groups ranging from electron-donating (methyl or methoxy; entries 4–6) to electron-withdrawing groups (halo, cyano, or nitro; entries 8–14) were tolerated under the reaction conditions. The Results presented in Table 2 seem to suggest that both electronic and steric effects may affect the yields when benzaldehydes were used. For example, electron-withdrawing groups tend to give higher yields (entries 11–14) compared to electron-donating groups (entries, 4–6). The presence of an ortho substituent (entries 3 and 8) led to lower yields compared to the corresponding meta- and para-substituted analogs (entries 4 and 9), which suggests steric hindrance may lead to lower yields.

In summary, a novel heterocyclic scaffold entailing 7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-one was prepared efficiently from *N*-substituted pyrimidinediamine and aldehydes. The standard AcOH-EtOH conditions commonly used to prepare dibenzo[b,e][1,4]diazepines proved to unsuitable for aminopyrimidines. Thus, a new TFA-acetonitrile condition was successfully developed to produce the desired 4-chloro-7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-ones in moderate to excellent yields.

**Scheme 2**

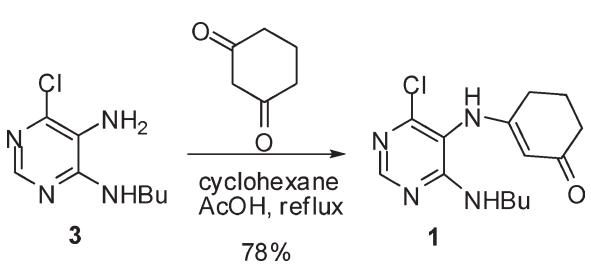
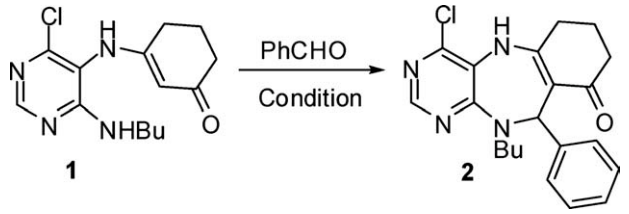



**Table 1**




| Entry | Solvent | Acid | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | EtOH | AcOH | 24 | 24 | NR[b] |
| 2 | EtOH | AcOH | reflux | 43 | 5[c] |
| 3 | EtOH | TFA | 24 | 24 | 2[c] |
| 4 | EtOH | TFA | reflux | 43 | 10 |
| 5 | EtOH | $H_2SO_4$ | reflux | 95 | 8 |
| 6 | $CH_3CN$ | TFA | 24 | 24 | 22[c] |
| 7 | $CH_3CN$ | TFA | 60 | 52 | 56 |
| **8** | **$CH_3CN$** | **TFA** | **reflux** | **18** | **59** |
| 9 | $CH_3CN$ | AcOH | reflux | 18 | 11[c] |
| 10 | DCM | $Py/SOCl_2$ | reflux | 78 | 40 |

[a] Yields are isolated products and the reaction was monitored by LC-MS.
[b] NR denotes no reaction, all starting materials remained.
[c] Some starting material **1** was recovered.

## EXPERIMENTAL

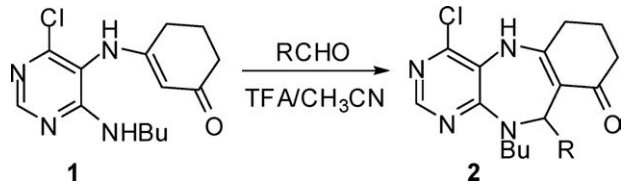
Acetonitrile ($CH_3CN$) was dried with $CaH_2$ and distilled. All other commercial reagents were used as received without purification. Melting points were uncorrected. Mass spectra and HPLC data were recorded on a LC/MS system with ELSD detection. The $^1H$ and $^{13}C$ NMR data were obtained on a Varian 300 (300 and 75 MHz, respectively) spectrometer with TMS as the internal standard and $CDCl_3$ as the solvent unless otherwise stated. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) are quoted in Hertz.

**3-(6-(Butylamino)-4-chloropyrimidin-5-ylamino)cyclohex-2-enone (1).** A solution of 5-amino-4-chloro-6-(butylamino)-pyrimidine **3** (1.5 g, 7.5 mmol), 1,3-cyclohexandione (0.84 g, 7.5 mmol), and a catalytic amount of acetic acid (30 μL, 0.52 mmol) in cyclohexane (40 mL) was heated in an azeotropic distillation apparatus for 2 days. The solvent was removed *in vacuo* to give the crude product, which was recrystallized from acetone to give 1.71 g (78%) of **1**, mp 190–192°C.$^1H$ NMR: 8.29 (s, 1H), 5.74 (s, 1H), 5.32 (s, 1H), 4.93 (s, 1H), 3.47 (q, 2H, $J = 6.9$ Hz), 2.51 (t, 2H, $J = 5.4$ Hz), 2.35 (t, 2H, $J = 6.3$ Hz), 2.10–2.02 (m, 2H), 1.61–1.29 (m, 2H), 1.41–1.29 (m, 2H), 0.92 (t, 3H, $J = 7.2$ Hz). MS (ESI): *m*/*z* 295.3 [M+H$^+$].

**General procedure for the synthesis of 4-chloro-7,8,10,11-tetrahydro-5*H*-benzo[*e*]pyrimido[4,5-*b*][1,4]diazepin-9(6*H*)-one (2).** To a solution of 3-(6-(butylamino)-4-chloropyrimidin-5-ylamino)cyclohex-2-enone **1** (150 mg, 0.51 mmol) and an aldehyde (0.612 mmol) in 4 mL acetonitrile was added TFA (20 μL, 0.27 mmol). The mixture was stirred for corresponding time at ambient temperature or 80°C. After cooling to

**Table 2**

Synthesis of 4-chloro-7,8,10,11-tetrahydro-SH-benzo[e]pyrimido[4,5-6][1,4]diazepin 9(6H)-ones.[a]




**1** **2**

| Entry | R | Compd. | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $CH_3CH_2CH_2$ | **2.1** | 7h | 34 |
| 2 | $CH_3CH_2CH_2$ | **2.1** | 3d[b] | 51 |
| 3 | $CH_3CH_2$ | **2.2** | 3d[b] | 62 |
| 4 | *o*-$MeOC_6H_4$ | **2.3** | 9h | 13 |
| 5 | *p*-$MeOC_6H_4$ | **2.4** | 20h | 22 |
| 6 | *p*-$MeC_6H_4$ | **2.5** | 20h | 57 |
| 7 | Ph | **2.6** | 18h | 59 |
| 8 | *o*-$ClC_6H_4$ | **2.7** | 20h | 41 |
| 9 | 2′,4′-di-$ClC_6H_3$ | **2.8** | 20 | 45 |
| 10 | 3′,4′-di-$ClC_6H_3$ | **2.9** | 22h | 65 |
| 11 | *p*-$FC_6H_4$ | **2.10** | 22h | 68 |
| 12 | *p*-$CNC_6H_4$ | **2.11** | 18h | 80 |
| 13 | *m*-$NO_2C_6H_4$ | **2.12** | 17h | 87 |
| 14 | *p*-$NO_2C_6H_4$ | **2.13** | 18h | 87 |

[a] All reactions were conducted at 80°C unless noted, yields are based on isolated products.
[b] Reaction was carried out at 25°C.

room temperature, the solvent was removed *in vacuo* to give the crude product. Purification by flash chromatography (Petroleum ether/EtOAc = 5:1 or 2:1) afforded the desired products.

***11-Butyl-4-chloro-10-propyl-7,8,10,11-tetrahydro-5H-benzo[e]-pyrimido[4,5-b] [1,4]diazepin-9(6H)-one (2.1).*** 51%. mp: 83–85°C. $^1$H NMR: 8.05 (s, 1H), 6.45 (s, 1H), 4.87 (t, 1H, $J$ = 8.1 Hz), 4.32–4.22 (m, 1H), 3.10–3.01 (m, 1H), 2.72–2.59 (m, 1H), 2.56–2.42 (m, 3H), 2.12–1.91 (m, 2H), 1.65–1.45 (m, 4H), 1.33–1.15 (m, 4H). 0.92–0.83 (m, 6H). $^{13}$C NMR: 194.4, 155.5, 154.4, 149.5, 144.3, 119.1, 116.7, 55.2, 51.7, 36.3, 35.5, 31.6, 29.8, 20.9, 19.93, 19.86, 13.8, 13.7. MS (ESI): *m*/*z* 349.1 [M+H$^+$].

***11-Butyl-4-chloro-10-ethyl-7,8,10,11-tetrahydro-5H-benzo[e]-pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.2).*** 62%. oil. $^1$H NMR: 8.03 (s, 1H), 7.29 (s, 1H), 4.78 (t, 1H, $J$ = 8.1 Hz), 4.34–4.25 (m, 1H), 3.09–2.97 (m, 1H), 2.68–2.59 (m, 1H), 2.52 (t, 1H, $J$ = 5.1 Hz), 2.48–2.41 (m, 2H), 2.10–1.94 (m, 2H), 1.74–1.48 (m, 4H), 1.30–1.23 (m, 2H), 0.91–0.80 (m, 6H). $^{13}$C NMR: 193.9, 154.8, 154.2, 149.6, 144.8, 119.2, 116.5, 56.7, 51.8, 35.8, 31.6, 29.8, 27.1, 21.0, 19.9, 13.7, 11.1. MS (ESI): *m*/*z* 335.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(2-methoxyphenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.3).*** 13%. mp: 168–169°C. $^1$H NMR: 7.97 (s, 1H), 7.18–7.13 (m, 1H), 6.99 (d, 1H, $J$ = 6.3 Hz), 6.82–6.73 (m, 2H), 6.25 (s, 1H), 6.23 (s, 1H), 4.36–4.26 (m, 1H), 3.78 (s, 3H), 3.33–3.24 (m, 1H), 2.70–2.61 (m, 1H), 2.57–2.42 (m, 3H), 2.12–1.91 (m, 2H), 1.68–1.50 (m, 2H). 1.37–1.24 (m, 2H), 0.90 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR: 193.4, 157.1, 155.7, 155.6, 149.8, 145.1, 128.6, 128.1, 126.8, 120.2, 119.8, 116.7, 111.0, 55.14, 55.11, 51.8, 35.9, 31.6, 30.2, 20.8, 20.1, 13.8. MS (ESI): *m*/*z* 413.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(4-methoxyphenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.4).*** 22%. mp: 167–169°C. $^1$H NMR: 8.04 (s, 1H), 7.09 (d, 2H, $J$ = 8.7 Hz), 6.73 (d, 2H, $J$ = 8.7 Hz), 6.30 (s, 1H), 6.09 (s, 1H), 4.50–4.41 (m, 1H), 3.74 (s, 3H), 3.23–3.14 (m, 1H), 2.73–2.59 (m, 1H), 2.55–2.43 (m, 3H), 2.16–1.95 (m, 2H), 1.73–1.53 (m, 2H). 1.38–1.26 (m, 2H), 0.91 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR: 194.0, 158.4, 156.2, 155.3, 149.8, 145.2, 133.0, 127.2, 119.4, 118.3, 113.9, 57.8, 55.1, 52.4, 35.8, 31.7, 30.1, 20.9, 20.0, 13.8. MS (ESI): *m*/*z* 413.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(4-methylphenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.5).*** 57%. mp: 144–146°C. $^1$H NMR: 8.04 (s, 1H), 7.00 (d, 2H, $J$ = 8.1 Hz), 6.86 (d, 2H, $J$ = 7.8 Hz), 6.29 (s, 1H), 6.11 (s, 1H), 4.50–4.41 (m, 1H), 3.23–3.13 (m, 1H), 2.72–2.56 (m, 1H), 2.54–2.41 (m, 3H), 2.26 (s, 3H), 2.16–1.94 (m, 2H), 1.71–1.50 (m, 2H). 1.38–1.26 (m, 2H), 0.91 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR: 193.9, 156.3, 155.2, 149.6, 145.1, 137.8, 136.4, 129.1, 125.7, 119.2, 118.3, 57.8, 52.3, 35.7, 31.5, 30.0, 20.70, 20.68, 19.9, 13.7. MS (ESI): *m*/*z* 397.2 [M+H$^+$].

***11-Butyl-4-chloro-10-phenyl-7,8,10,11-tetrahydro-5H-benzo[e]-pyrimido [4,5-b][1,4]diazepin-9(6H)-one (2.6).*** 59%. mp: 154–155°C. $^1$H NMR: 8.04 (s, 1H), 7.24–7.17 (m, 3H), 6.98 (dd, 2H, $J_1$ = 7.5 Hz, $J_2$ = 1.8 Hz), 6.28 (s, 1H), 6.15 (s, 1H), 4.52–4.42 (m, 1H), 3.23–3.14 (m, 1H), 2.71–2.42 (m, 4H), 2.16–1.92 (m, 2H), 1.76–1.53 (m, 2H), 1.38–1.25 (m, 2H), 0.91 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR: 193.9, 156.6, 155.1, 149.5, 145.0, 140.8, 128.4, 126.8, 125.8, 119.1, 118.1, 57.9, 52.3, 35.6, 31.4, 29.9, 20.6, 19.8, 13.6. MS (ESI): *m*/*z* 383.2 [M+H$^+$].

***11-Butyl-4-chloro-10-(2-chlorophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.7).*** 41%. mp: 179–181°C. $^1$H NMR: 8.04 (s, 1H), 7.34 (d, 1H, $J$ = 7.5 Hz), 7.17–7.05 (m, 3H), 6.27 (s, 1H), 6.24 (s, 1H), 4.33–4.24 (m, 1H), 3.34–3.24 (m, 1H), 2.69–2.35 (m, 4H), 2.09–1.91 (m, 2H), 1.71–1.53 (m, 2H). 1.38–1.26 (m, 2H), 0.91 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR: 193.6, 156.2, 155.2, 150.2, 145.7, 138.6, 133.6, 130.5, 128.5, 127.3, 126.5, 120.2, 117.7, 56.7, 51.8, 35.7, 31.5, 30.0, 20.3, 20.0, 13.8. MS (ESI): *m*/*z* 417.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(2,4-dichlorophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.8).*** 45%. mp: 152–154°C. $^1$H NMR: 8.05 (s, 1H), 7.36 (s, 1H), 7.07–6.97 (m, 2H), 6.25 (s, 1H), 6.22 (s, 1H), 4.31–4.22 (m, 1H), 3.31–3.22 (m, 1H), 2.65–2.34 (m, 4H), 2.10–1.92 (m, 2H), 1.69–1.49 (m, 2H). 1.37–1.27 (m, 2H), 0.91 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR: 193.5, 156.2, 155.0, 150.4, 146.0, 137.4, 134.5, 133.7, 130.3, 128.2, 126.8, 120.1, 117.5, 56.4, 51.9, 35.8, 31.6, 30.1, 20.3, 20.0, 13.8. MS (ESI): *m*/*z* 451.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(3,4-dichlorophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.9).*** 65%. mp: 132–134°C. $^1$H NMR: 8.07 (s, 1H), 7.28 (s, 1H), 7.06 (dd, 1H, $J_1$ = 2.1 Hz, $J_2$ = 0.6 Hz), 6.84–6.80 (m, 1H), 6.33 (s, 1H), 6.09 (s, 1H), 4.50–4.41 (m, 1H), 3.21–3.11 (m, 1H), 2.74–2.44 (m, 4H), 2.18–1.94 (m, 2H), 1.71–1.49 (m, 2H). 1.37–1.26 (m, 2H), 0.91 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR: 193.9, 156.9, 154.9, 150.0, 145.8, 141.5, 132.6, 131.1, 130.4, 128.2,

125.3, 119.1, 117.6, 57.3, 52.4, 35.6, 31.6, 30.0, 20.7, 19.9, 13.7. MS (ESI): *m*/*z* 451.0 [M+H$^+$].

***11-Butyl-4-chloro-10-(4-fluorophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.10).*** 68%. mp: 146–148°C. $^1$H NMR: 8.05 (s, 1H), 6.97–6.86 (m, 4H), 6.31 (s, 1H), 6.10 (s, 1H), 4.50–4.40 (m, 1H), 3.22–3.13 (m, 1H), 2.73–2.44 (m, 4H), 2.19–1.93 (m, 2H), 1.72–1.49 (m, 2H), 1.42–1.23 (m, 2H), 0.91 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR: 194.0, 163.3, 160.0, 156.7, 155.2, 149.8, 145.3, 136.7, 127.7, 127.6, 119.3, 118.0, 115.6, 115.3, 57.7, 52.4, 35.7, 31.6, 30.1, 20.8, 20.0, 13.8. MS (ESI): *m*/*z* 401.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(4-cyanophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.11).*** 80%. mp: 51–53°C. $^1$H NMR: 8.08 (s, 1H), 7.51 (d, 2H, $J$ = 8.4 Hz), 7.10 (d, 2H, $J$ = 8.1 Hz), 6.34 (s, 1H), 6.18 (s, 1H), 4.50–4.40 (m, 1H), 3.23–3.14 (m, 1H), 2.74–2.45 (m, 4H), 2.17–2.00 (m, 2H), 1.70–1.54 (m, 2H). 1.36–1.26 (m, 2H), 0.91 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR: 193.9, 157.2, 154.7, 149.9, 146.6, 145.7, 132.3, 126.7, 118.9, 118.3, 117.5, 110.7, 57.7, 52.4, 35.5, 31.4, 29.9, 20.5, 19.8, 13.6. MS (ESI): *m*/*z* 408.2 [M+H$^+$].

***11-Butyl-4-chloro-10-(3-nitrophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.12).*** 80%. mp: 51–53°C. $^1$H NMR: 8.08 (s, 1H), 8.04 (d, 1H, $J$ = 7.8 Hz), 7.84 (s, 1H), 7.43–7.33 (m, 2H), 6.34 (s, 1H), 6.21 (s, 1H), 4.56–4.47 (m, 1H), 3.21–3.18 (m, 1H), 2.71–2.47 (m, 4H), 2.19–2.04 (m, 2H), 1.75–1.57 (m, 2H). 1.40–1.26 (m, 2H), 0.93 (t, 3H, $J$ = 6.9 Hz). $^{13}$C NMR: 193.9, 157.2, 154.8, 150.0, 148.4, 145.9, 143.4, 132.2, 129.6, 122.1, 121.2, 119.1, 117.1, 57.6, 52.5, 35.6, 31.5, 30.0, 20.7, 19.9, 13.7. MS (ESI): *m*/*z* 428.1 [M+H$^+$].

***11-Butyl-4-chloro-10-(4-nitrophenyl)-7,8,10,11-tetrahydro-5H-benzo[e] pyrimido[4,5-b][1,4]diazepin-9(6H)-one (2.13).*** 80%. mp: 51–53°C. $^1$H NMR: 8.09 (s, 1H), 8.07 (d, 2H, $J$ = 8.4 Hz), 7.16 (d, 2H, $J$ = 8.4 Hz), 6.34 (s, 1H), 6.23 (s, 1H), 4.51–4.41 (m, 1H), 3.26–3.17 (m, 1H), 2.76–2.47 (m, 4H), 2.20–1.93 (m, 2H), 1.74–1.50 (m, 2H). 1.39–1.24 (m, 2H), 0.90 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR: 193.9, 157.2, 154.7, 150.0, 148.8, 146.7, 145.8, 126.9, 123.7, 119.0, 117.6, 57.7, 52.4, 35.5, 31.5, 29.9, 20.6, 19.9, 13.7. MS (ESI): *m*/*z* 428.1 [M+H$^+$].

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## REFERENCES AND NOTES

[1] Nawrocka, W.; Sztuba, B.; Opolski, A.; Wietrzyk, J.; Kowalska, M. W.; Głowiak, T. Part II. Arch Pharm Pharm Med Chem 2001, 334, 3.

[2] Cortés, E. C.; Cornejo, A. L. V.; de Cortés, O. G.-M. J Heterocycl Chem 2007, 44, 183.

[3] Beccalli, E. M.; Broggini, G.; Paladino, G.; Zoni, C. Tetrahedron 2005, 61, 61.

[4] Tonkikh, N. N.; Strakovs, A.; Rizhanova, K. V.; Petrova, M. V. Chem Heterocycl Comp (Engl. Transl.) 2004, 40, 949.

[5] Xu, J.; Wang, C.; Zhang, Q. Heteroat Chem 2001, 12, 557.

[6] Chakrabarti, J. K.; Hotten, T. M.; Pullar, I. A.; Steggles, D. J. J Med Chem 1989, 32, 2375.

[7] Chakrabarti, J. K.; Hotten, T. M.; Pullar, I. A.; Tye, N. C. J Med Chem 1989, 32, 2573.

[8] Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Fanshawe, W. J.; Day, I. P.; Greenblatt, E. N.; Safir, S. R. J Med Chem 1979, 22, 725.

[9] Blache, Y.; Hichour, M.; Di Blasi, G.; Chezal, J.-M.; Viols, H.; Chavignon, O.; Teulade, J.-C.; Chapat, J.-P. Heterocycles 1999, 51, 1003.

[10] Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Bai, X. Org Lett 2005, 7, 1541.

[11] Xiang, J.; Zheng, L.; Chen, F.; Dang, Q.; Bai, X. Org Lett 2007, 9, 765.

[12] Zheng, L.; Yang, F.; Dang, Q.; Bai, X. Org Lett 2008, 10, 889.

[13] Che, X.; Zheng, L.; Dang, Q.; Bai, X. J Org Chem 2008, 73, 1147.

[14] Xiang, J.; Zheng, L.; Xie, H.; Hu, X.; Dang, Q.; Bai, X. Tetrahedron 2008, 64, 9101.

[15] Xiang, J.; Xie, H.; Wen, D.; Dang, Q.; Bai, X. J Org Chem 2008, 73, 3281.

[16] During the preparation of this manuscript, we have noticed a recent report by Raboisson, P. (McGowan, D.; Nyanguile, O.; Cummings, M. D.; Vendeville, S.; Vandyck, K.; Van den Broeck, W.; Boutton, C. W.; De Bondt, H.; Quirynen, L.; Amssoms, K.; Bonfanti, J.-F.; Last, S.; Rombauts, K.; Tahri, A.; Hu, L.; Delouvroy, F.; Vermeiren, K.; Vandercruyssen, G.; Van der Helm, L.; Cleiren, E.; Mostmans, W.; Lory, P.; Pille, G.; Van Emelen, K.; Fanning, G.; Pauwels, F.; Lin, T.-I.; Simmen, K.; Raboisson, P. Bioorg Med Chem Lett 2009, 19, 2492.)

[17] Kelley, J. L.; Bullock, R. M.; Krochmal, M. P.; McLean, E. W.; Linn, J. A.; Durcan, M. J.; Cooper, B. R. J Med Chem 1997, 40, 3207.

[18] Vanden Eynde, J.-J.; Mayence, A.; Maquestiau, A.; Anders, E. Bull Soc Chim Belg 1992, 101, 801.

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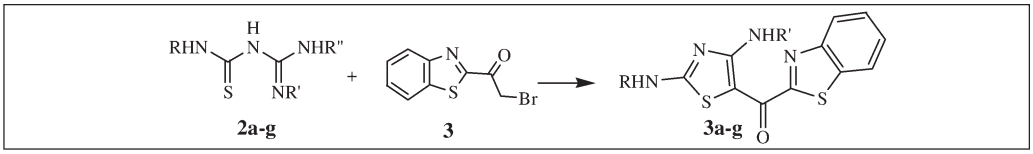


The synthesis of 2-(4-amino-2-alkylaminothiazol-5-oyl)benzothiazoles and 2-[2,4-bis(arylamino)thiazol-5-oyl]benzothiazoles as benzothiazoloylthiazole analogs of the cytotoxic marine alkaloid dendrodoine is reported. The highly decorated thiazole ring assembly was achieved using 2-bromoacetybenzothiazole to supply the C5 ring carbon and amidinothioureas of the type $R^1NH—CS—NH—C(=NHR^2)—(NHR^3)$ to provide the four ring atoms [C4—N3—C2—S1] in a [4+1] thiazole ring construction strategy. The antibacterial activity of these new analogs is reported.

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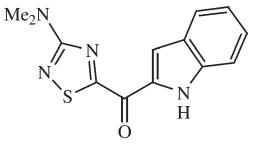
## INTRODUCTION

A recent review [1] on marine pigments highlights the rich variety of colored molecules that can be found in marine organisms. These pigments have structures that in many instances have no counterpart in any terrestrially derived molecules. Many among these are alkaloidal pigments. One among these, the pale yellow, bisheterocyclic, cytotoxic alkaloid dendrodoine, 3-*N*,*N*-dimethylamino-5-indol-3-oyl-1,2,4-thiadiazole 1, isolated from the tunicate *Dendrodoa grossularia* [2], is considered unique in being the first and only naturally occurring 1,2,4-thiadiazole derivative [1]. It is reported to be cytotoxic to lymphoma cells L1210 in culture [2,3].




**1**

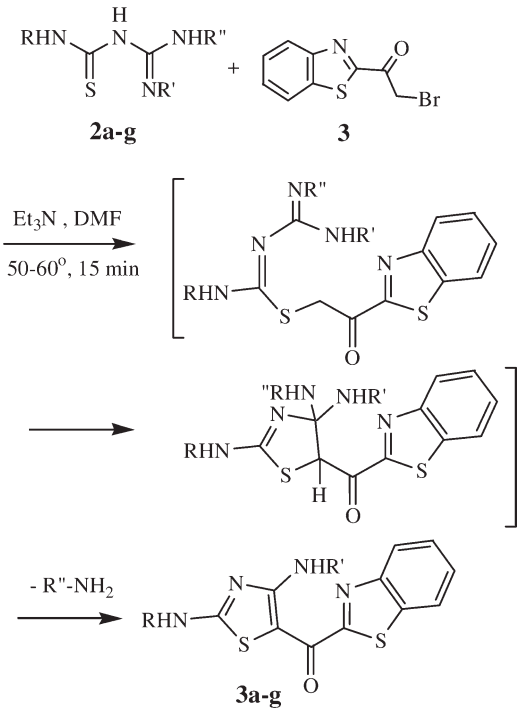
We have recently been interested in synthesizing [4] and cytotoxicity screening [5] of thiazole analogs of dendrodoine in the light of its reported cytotoxicity and the difficulty in its synthesis [6]. Two approaches were adopted by us; in the first, to overcome the limited opportunity for substitution positions in the 1,2,4-thiadiazole ring, it was replaced by a 1,3-thiazole ring [4a]. In the second, the indoloyl unit was varied to other benzofused heterobicyclic rings [7]. This allowed us to introduce much structural diversity leading to a large portfolio of dendrodoine analogs. We were also enthused by the recently reported *in vitro* cytotoxicity of bis(indolyl)thiazoles [8] and indolylthiazoles [9]. Further, noting the remarkable cytotoxic activity of benzothiazole derivatives as reviewed recently [10,11], we decided to extend our work on the synthesis and bioactivity screening of dendrodoine analogs to 2-(2,4-diaminothiazol-5-oyl)benzothiazoles.

## RESULTS AND DISCUSSION

Several modifications of the classic Hantzsch 2-aminothiazole synthesis have recently been developed for the direct ring assembly of highly decorated thiazole derivatives. Among such methods, the use cyanothioureas [12,13] RNH—CS—NH—CN, our reports [14–16] on the use of amidinothioureas RNH—CS—NH—C(=NH)—$NH_2$ and RNH—CS—NH—C(=NH)—$NHNO_2$, or the recent use of *S*-alkyldithiobiurets [17] RNH—CS—NH—C(SR)—$NH_2$, as the source of the four [S1—C2—N3—C4] ring atoms for the thiazole ring construction are noteworthy. The remaining ring C5 atom could be sourced from α-haloketones, which reacted with the above thioureas to afford 4-amino-5-acyl-2-(substituted amino)thiazoles. Nevertheless, our report [14,16] on the use of amidinothioureas of the type $R^1NH—CS—NH—C(=NHR^2)—(NHR^3)$ seems to be the only direct ring synthesis of 5-acyl-2,4-bis(substituted amino)thiazoles. Based on these considerations, we have now chosen the reaction between the amidinothiourea derivatives **2a–g** and 2-(2-bromoacetyl)benzothiazole 3 to access hitherto unreported 2-(4-amino-2-alkylaminothiazol-5-oyl)benzothiazoles and 2-[2,4-bis(arylamino)thiazol-5-oyl]benzothiazoles.

Accordingly, the reaction of 1-ethyl-3-(*N*-nitroamidino)thiourea 2a in *N*,*N*-dimethylformamide (DMF) with 2-(2-bromoacetyl)benzothiazole 3 afforded a yellow

**Scheme 1**




**2a, 4a:** R = $C_2H_5$, R' = H, R"= $NO_2$;
**2b, 4b:** R = *n*-$C_3H_7$, R' = H, R"= $NO_2$;
**2c, 4c:** R = *n*-$C_4H_9$, R' = H, R"= $NO_2$;
**2d, 4d:** R = Allyl, R'= H, R"= $NO_2$;
**2e, 4e:** R = R'=$C_6H_5$, R"=H;
**2f, 4f:** R = R' = 4-Cl$C_6H_5$, R"=H;
**2g, 4g:** R = R' = 4-Me$C_6H_5$, R"=H

crystalline compound which showed in the thin layer chromatogram a single fluorescent yellow spot. Based on the elemental analysis, the molecular composition of the compound was found to be $C_{13}H_{12}N_4OS_2$. The IR spectrum shows distinct bands at 3467, 3285, 3233, and 3175 $cm^{-1}$, which are ascribed to $\nu_{N-H}$ vibrations. The aliphatic C—H stretching bands were seen at 2972, 2928, and 2850 $cm^{-1}$ and a strong band at 1623 $cm^{-1}$ indicated the presence of a conjugated carbonyl group. The $^1$H NMR spectrum consisted of a three-hydrogen triplet at δ 1.18, due to methyl hydrogens. The peak due to the methylene hydrogens could not be seen as it appeared to be submerged in the broad solvent-based peak. The multiplet at δ 7.45–7.62 was assignable to the H-5 and H-6 of the benzothiazole ring. The two one-hydrogen doublets at δ 8.07 and 8.16 were attributed to H-4 and H-7 of the benzothiazole ring, respectively. The broad peak at δ 8.39 was due to the NH hydrogen of the NHR group. The FAB MS showed a strong $MH^+$ peak at m/z 305. Based on these, the compound was formulated as 2-(4-amino-2-ethylaminothiazol-5-oyl)benzothiazole **4a**; the reaction steps involved in its formation

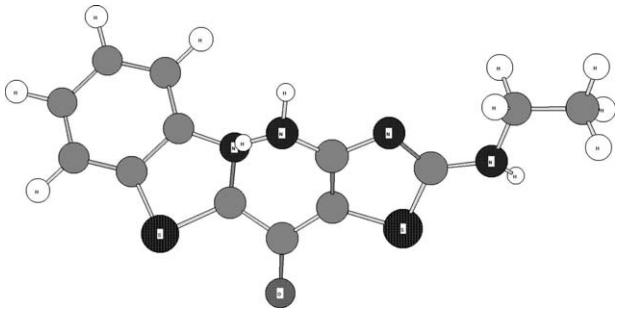


**Figure 1.** Energy minimized structure of **4a**.

is presented in Scheme 1. Three other thiazoloylbenzothiazoles **4b–d** were also synthesized. An interesting feature of the $^1$H NMR spectrum of **4a–d** was the appearance of the two hydrogens of the 4-amino group as two well separated broad singlets. For example, in the case of **4a**, these hydrogens were seen at δ 8.78 and 8.94. The results of energy minimized computations on **4a** obtained using MOPAC by the AM1 method are shown in Figure 1. These computed structures showed that one of the two hydrogens of the amino group could be strongly hydrogen bonded to the ring nitrogen of the benzothiazole unit. In addition, the 4-amino group in **4a** could also be amide like as it could be viewed as a vinylogous amide —CO—$C^5$=$C^4$—$NH_2$, which would also impede the rotation of the $C^4$—N bond.

Next, 1-phenyl-3(*N*,*N*′-diphenylamidino)thiourea **2e** was reacted with **3** to obtain a deep yellow compound with molecular composition $C_{23}H_{16}N_4OS_2$. Based on the FAB-MS, $^1$H and $^{13}$C NMR spectra, the structure of the compound was assigned as 2-[2,4-bis(phenylamino)thiazol-5-oyl]benzothiazole **4e**. In a similar reaction, two other 2-[2,4-diarylaminothiazol-5-oyl]benzothiazoles **4f–g** were also obtained.

To assess the bioactivity, the benzothiazoles **4a–g** were screened against the bacterial strains *Escherichia coli, Salomonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis* and the results are shown in Table 1.

**Table 1**

Antibacterial activity of benzothiazoloylthiazoles **4a–g**.

| Compound | *E. coli* | *S. typhii* | *S. aureus* | *B. subtilis* |
|---|---|---|---|---|
| **4a** | 9 | 8 | 7 | 7 |
| **4b** | 7 | 7 | NA | NA |
| **4c** | 7 | 8 | NA | NA |
| **4d** | 10 | 10 | NA | NA |
| **4e** | 8 | 7 | 6 | NA |
| **4f** | 8 | 8 | 10 | 10 |
| **4g** | 6 | 8 | NA | NA |
| **Penicillin G** | 12 | 12 | 13 | 12 |

Values are in diameter of zone of inhibition (mm) and average of three replicates.
NA, Not active.

## EXPERIMENTAL

Melting points are uncorrected and were determined by open capillary method using an immersion bath of silicon oil. Thin layer chromatography was performed using silica gel-G (E. Merck, India) coated on glass plates. The spots were visualized in iodine vapour or under UV light. The spectra were recorded on: JEOL DRX 300 or DPX 300 NMR spectrometer (300 MHz for $^1$H and 75 MHz for $^{13}$C NMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using Argon/Xenon, 6 KV, 10 mA as the FAB gas and m-nitrobenzyl alcohol as the matrix) for FAB mass spectra, and Nicolet 400D FTIR spectrometer fot IR spectra. Reagents and solvents were from Merck India and Fluka. Elemental analysis was done at Central Drug Research Institute, India. The antibacterial acticity was evaluated by the Kirby-Baur method [18].

**General procedure for the synthesis of 2-(2,4-diaminothiazol-5-oyl)benzothiazoles (4a–g).** A solution of 2-(2-bromoacetyl)benzothiazole **3** (0.254 g, 1 mmol), obtained from 2-(1-hydroxyethyl)benzothiazole [19,20], in DMF (2mL) was added to 1-alkyl-3-(*N*-nitroamidino)thiourea (**2a–d**) or 1-aryl-3-(*N*,*N*′-diarylamidino)thiourea (**2e–g**) (1 mmol) in DMF (2 mL). The reaction mixture was stirred well and triethylamine (0.3 mL, 2 mmol) was added and warmed at 50–60°C for 15 min. It was then cooled and poured into ice-cold water with constant stirring. The yellow precipitate thus obtained was filtered, washed with water, and dried. The crude product was purified by crystallization from methanol–water (2:1), then from benzene–petroleum ether (1:1) in the case of **4a–d**, and from ethanol–water (3:1) in the case of **4e–g**.

***2-(4-Amino-2-ethylaminothiazol-5-oyl)benzothiazole (4a).*** Yield: 65%, m.p. 255–256°C; *Anal*. found: C, 51.41: H, 3.90: N, 18.55%; calcd. for $C_{13}H_{12}N_4OS_2$ (304.39): C, 51.29: H, 3.97: N, 18.41%; IR (KBr) ν: 3467, 3285, 3233, 3175, 3067, 2972, 2928, 2850, 1623, 1592, 1558, 1450, 1351, 1093, 882, 818, 757, 722cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 1.18(t, $J$ = 7.0 Hz, 3H, $CH_3$), 3.35(br, 2H, $CH_2$), 7.45–7.62(m, 2H, H-5, H-6), 8.07(d, $J$ = 7.8 Hz, 1H, H-4), 8.16(d, $J$ = 7.8 Hz, 1H, H-7), 8.39(br, 1H, NH), 8.78(br, 1H, NH), 8.94(br, 1H, NH); FABMS: 305 ($MH^+$).

***2-[4-Amino-2-n-propylaminothiazol-5-oyl]benzothiazole (4b).*** Yield: 63%, m.p. 211–213°C; *Anal*. found: C, 52.95: H, 4.58: N, 17.45%; calcd. for $C_{14}H_{14}N_4OS_2$ (318.42): C, 52.80: H, 4.43: N, 17.60%; IR (KBr) ν: 3360, 3218, 3134, 3067, 2967, 2933, 2867, 1639, 1592, 1552, 1506, 1472, 1357, 1155, 1093, 891, 823, 778, 683, 622cm$^{-1}$; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 0.91(t, $J$ = 7.4 Hz, 3H, $CH_3$), 1.58(sextet, $J$ = 6.7 Hz, 2H, $CH_2$), 3.38(br, 2H, $CH_2$), 7.45–7.63(m, 2H, H-5, H-6), 8.06(d, $J$ = 6.9 Hz, 1H, H-4), 8.16(d, $J$ = 7.5 Hz, 1H, H-7), 8.40(br, 1H, NH), 8.79(br, 1H, NH), 8.95(br, 1H, NH); $^{13}$C NMR: (75 MHz, , DMSO-$d_6$) δ: 11.3, 21.9, 39.2, 91.1, 122.8, 123.8, 126.4, 126.8, 135.8, 139.3, 153.1, 169.5, 170.6, 171.3; FABMS: 319 ($MH^+$).

***2-[4-Amino-2-n-butylaminothiazol-5-oyl]benzothiazole (4c).*** Yield: 65%, m.p. 182–185°C; *Anal*. found: C, 54.33: H, 4.93: N, 16.59; calcd. for $C_{15}H_{16}N_4OS_2$ (332.44): C, 54.19: H, 4.85: N, 16.85%; IR (KBr) ν: 3352, 3279, 3198, 3162, 3050, 2962, 2917, 2858, 1634, 1600, 1539, 1465, 1357, 1309, 1152, 1081, 891, 818, 771, 737, 612cm$^{-1}$; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 0.90(t, $J$ = 7.4 Hz, 3H, $CH_3$), 1.35(sextet, $J$ = 7.3 Hz, 2H, $CH_2$), 1.51(quintet, $J$ = 7.1 Hz, 2H, $CH_2$), 3.33(br, 2H, $CH_2$), 7.45–7.64(m, 2H, H-5, H-6), 8.06(d, $J$ = 7.8 Hz, 1H, H-4), 8.17(d, $J$ = 7.5 Hz, 1H, H-7), 8.42(br, 1H, NH), 8.92(br, 1H, NH), 9.00(br, 1H, NH); FABMS: 333 ($MH^+$).

***2-[2-Allylamino-4-aminothiazol-5-oyl]benzothiazole (4d).*** Yield: 63%, m.p. 254–255°C; *Anal*. found: C, 53.29: H, 3.91: N, 17.57%; calcd. for $C_{14}H_{12}N_4OS_2$ (316.40): C, 53.14: H, 3.82: N, 17.71%; IR (KBr) ν: 3486, 3299, 3238, 3083, 3050, 2967, 2933, 2894, 2842, 1626, 1599, 1565, 1506, 1458, 1322, 1094, 1013, 958, 891, 825, 764, 729cm$^{-1}$; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 4.02(m, 2H, $CH_2$), 5.11–5.32(m, 2H, $CH_2$), 5.82–6.00(m, 1H, CH), 7.45–7.64(m, 2H, H-5, H-6), 8.07(d, $J$ = 7.8 Hz, 1H, H-4), 8.17(d, $J$ = 7.5 Hz, 1H, H-7), 8.43(br, 1H, NH), 8.77(br, 1H, NH), 9.09(br, 1H, NH); FABMS: 317 ($MH^+$).

***2-[2,4-Bis(phenylamino)thiazol-5-oyl]benzothiazole, (4e).*** Yield: 65%, m.p. 235–238°C; *Anal*. found: C, 64.31: H, 3.85: N, 13.25%; calcd. for $C_{23}H_{16}N_4OS_2$ (428.52): C, 64.46: H, 3.76: N, 13.08%; IR (KBr) ν: 3433, 3272, 3198, 3048, 1626, 1600, 1562, 1485, 1445, 1414, 1324, 1268, 912, 757, 690cm$^{-1}$; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 7.11–7.23(m, 2H, 2ArH), 7.38–7.50(m, 4H, 4ArH), 7.53–7.72(m, 4H, H-5, H-6, 2ArH), 7.77(d, $J$ = 8.1 Hz, 2H, 2ArH), 8.12(d, $J$ = 7.8 Hz, 1H, H-4), 8.23(d, $J$ = 7.8 Hz, 1H, H-7), 11.85(s, 1H, NH); $^{13}$C NMR: (75 MHz, , DMSO-$d_6$) δ: 91.1, 119.7, 120.1, 122.8, 123.7, 123.9, 124.3, 126.8, 127.0, 129.0, 129.2, 135.9, 138.7, 138.9, 152.8, 163.6, 169.6, 170.6, 172.1; FABMS: 429 ($MH^+$).

***2,4-Bis(4-chlorophenylamino)thiazol-5-oylbenzothiazole, (4f).*** Yield: 65%, m.p. 258–259°C; *Anal*. found: C, 55.69: H, 2.99: N, 11.41%; calcd. for $C_{23}H_{14}Cl_2N_4OS_2$ (497.42): C, 55.53: H, 2.84: N, 11.26%; IR (KBr) ν: 3428, 3275, 3207, 3066, 1631, 1572, 1497, 1424, 1324, 1269, 1221, 1186, 1095, 1021, 923, 826, 756, 628cm$^{-1}$; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 7.41-7.79(m, 10H, H-5, H-6, 8ArH), 8.08(d, $J$ = 9 Hz, 1H, H-4), 8.20(d, $J$ = 9 Hz, 1H, H-7), 11.76(s, 1H, NH); FABMS: 497 ($MH^+$).

***2,4-Bis(4-methylphenylamino)thiazol-5-oylbenzothiazole, (4g).*** Yield: 63%, m.p. 221–224°C; *Anal*. found: C, 65.51: H, 4.58: N, 12.53%; calcd. for $C_{25}H_{20}N_4OS_2$ (456.57): C, 65.76: H, 4.42: N, 12.27%; IR (KBr) ν: 3400, 3266, 3200, 3117, 3062, 2928, 2840, 1617, 1607, 1572, 1490, 1434, 1324, 1221, 1021, 923, 828, 764, 731, 620cm$^{-1}$; $^1$H NMR: (300 MHz, $CDCl_3$) δ: 2.30(s, 6H, $2CH_3$), 7.02–7.75(m, 10H, H-5, H-6, 8ArH), 8.10(d, $J$ = 7.8 Hz, 1H, H-4), 8.21(d, $J$ = 7.5 Hz, 1H, H-7), 11.86(s, 1H, NH); FABMS: 457 ($MH^+$).

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## REFERENCES AND NOTES

[1] Bandaranayake, W. M. Nat Prod Rep 2006, 23, 223.

[2] Heitz, S.; Durgeat, M.; Guyot, M.; Brassy, C.; Bachet, B. Tetrahedron Lett 1980, 21, 1457.

[3] Helbecque, N.; Moquin, C.; Bernier, J. L.; Morel, E.; Guyot, M.; Heinchart, J. P. Cancer Biochem Biophys 1987, 9, 271.

[4] (a) Reji, T. F. A. F.; Devi, S. K. C.; Thomas, K. K.; Sreejalekshmi, K. G.; Manju, S. L.; Francis, M.; Philip, S. K.; Bharathan, A.; Rajasekharan, K. N. Indian J Chem 2008, 47B, 1145; (b)

Sreejalekshmi, K. G.; Devi, S. K. C.; Rajasekharan, K. N. Tetrahedron Lett 2006, 47, 6179; (c) Manju, S. L.; Devi, S. K. C.; Rajasekharan, K. N. J Heterocycl Chem 2009, 46, 455.

[5] Sengupta, S.; Smitha, S. L.; Thomas, N. E.; Santoshkumar, T. R.; Devi, S. K. C.; Sreejalekshmi. K. G.; Rajasekharan, K. N. Br J Pharmacol 2005, 145, 1076.

[6] Hogan, I. T.; Sainsbury, M. Tetrahedron 1984, 40, 681.

[7] (a) Reji, T. F. A. F.; Rajasekharan, K. N. Indian J Chem 2009, 48B, 877; (b) Reji, T. F. A. F.; Rajasekharan, K. N. J Heterocycl Chem 2009, 46, 1011; (c) Reji, T. F. A. F.; Rajasekharan, K. N. J Saudi Chem Soc 2009, 13, 311.

[8] Jiang, B.; Gu, X. H. Bioorg Med Chem 2000, 8, 363.

[9] Moody, C. J.; Roffey, J. R. A.; Stephens, M. A.; Stratford, I. J. Anti-Cancer Drugs 1997, 8, 489.

[10] Edwards, P. Drug Discov Today 2006, 11, 671.

[11] Bradshaw, T. D.; Westwell, A. D. Curr Med Chem 2004, 11, 1009.

[12] Gewald, K.; Blauschmidt, P.; Mayer, P. J Prakt Chem 1967, 35, 97

[13] Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cruz-Lopez, O.; Cara, C. L.; Basso, G.; Viola, G.; Khedr, M.; Balzarini, J.; Mahboobi, S.; Sellmer, A.; Brancale, A.; Hamel, E. J Med Chem 2009, 52, 5551.

[14] Rajasekharan, K. N.; Nair, K. P.; Jenardanan, G. C. Synthesis 1986, 18, 353.

[15] Binu, R.; Thomas, K. K.; Jenardanan, G. C.; Rajasekharan, K. N. Org Prep Proced Int 1998, 30, 93.

[16] Rajasekharan, K. N.; Sulekha, A. Indian J Chem 1981, 20B, 549.

[17] Masquelin, T.; Obrecht, D. Tetrahedron 2001, 57, 153.

[18] James, G. C.; Natalie, S. Microbiology A Laboratory Manuel, 4th ed.; Addison-Wesley: Reading, MA, 1999, p 254.

[19] Sawhney, S. N.; Singh, J. Indian J Chem 1970, 8, 882.

[20] Gupta, R. R.; Ojha, K. G.; Kalwania, G. S.; Kumar, M. Heterocycles 1980, 14, 1145.

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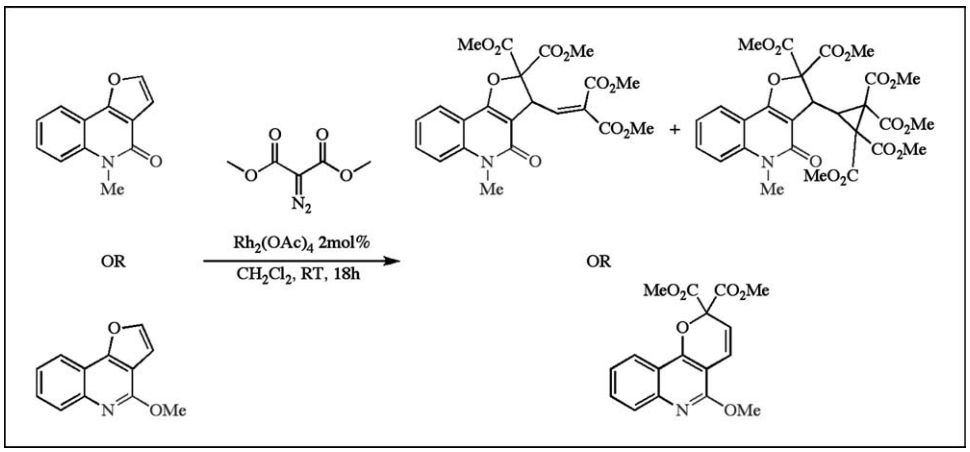


Novel double CH-insertion and rearrangement products (**5**, **6**, and **7**) were isolated from treatment of **1** or **2** with dimethyl diazomalonate (**3**) under dirhodiumtetrakis mediated carbenoid chemistry conditions. A new possible reaction pathway is suggested and discussed. Also other diazo compounds were tested.

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## INTRODUCTION

Furoquinolinones belong to a class of molecules exhibiting a wide variety of biological activities, including antifungal, antibacterial, antiviral (HIV), antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, antiarrhythmic, and sedative properties [1,2]. Examples of natural alkaloids containing the furoquinolinone core structure include oligophyline [3], araliopsine [4], and almeine [5] (Fig. 1).

These naturally occurring alkaloids, and others belonging to the furoquinolinone class of molecules, are obvious derivatives of a common core structural unit **1**, having a double bond in the **C** ring. Structure **1** is therefore a good choice for functionalization to important synthons for natural product synthesis and medicinal chemistry applications. To our knowledge, this potentially reactive core structure has not yet been exploited in synthesis.

It was envisaged that an electrophilic metal carbenoid, which is readily generated by metal catalyzed decomposition of a diazo reagent [6], could be used to probe reactivity of the **C** ring double bond of the furoquinolinone core structure. Previous studies on related structures have used metal carbenoid chemistry, such as simple furans [7], benzofurans [8], and tris-2-furylmethane derivatives [9].

## RESULTS AND DISCUSSION

We wish to report unexpected results from metal carbenoid-mediated chemistry using two analogues, **1** and **2**, as substrates and dimethyl diazomalonate (**3**) as the carbene precursor (Fig. 2). We have previously reported a novel synthesis of the common furoquinolinone core structure (**1**), describing the use of a palladium mediated intramolecular Heck coupling as a key step [10] and an alternative route to literature precedents [11]. The second core structure **2** was synthesized through modification of that protocol by using SEM in place of a methyl substituent as protecting group to facilitate formation of intermediate **9**. Treatment of **9** with dry HCl yielded the unprotected core structure **4**, which could easily be converted to the corresponding imine form **2** by further treatment with $POCl_3$ and sodium methoxide in two separate steps (Scheme 1). The carbene precursor **3** was synthesised by known methods [12].

All reactions were carried out in dichloromethane, with 2 mol % dirhodiumtetraacetate as catalyst and

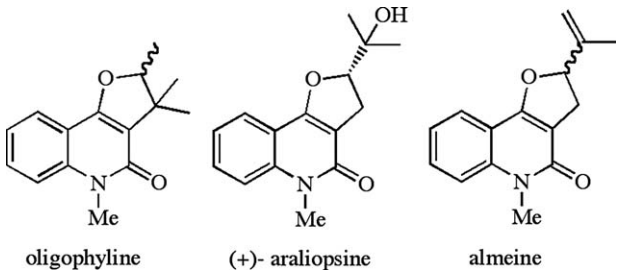



**Figure 1.** Natural alkaloids with furoquinolinone core structure.

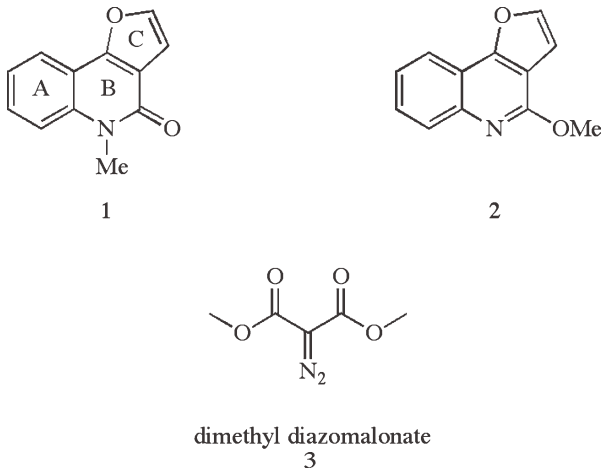



**Figure 2.** Starting materials (**1** and **2**) and carbene precursor (**3**).

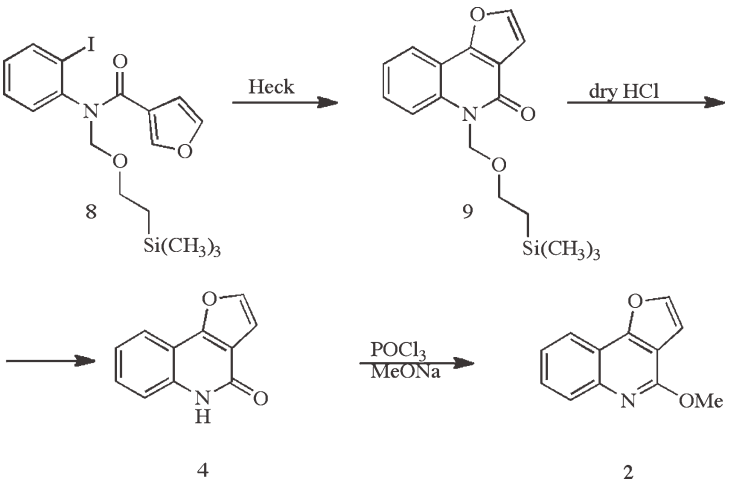
substrate **1** serving as a template for optimizing the reaction conditions. Treating **1** with **3** using previous reported literature procedures [8] with the aim of installing a cyclopropane functionality, did not consume starting material (**1**) in all cases (<5%). Optimized reaction conditions were found using 3.2 eq of **3** (Experimental), leading to 100% consumption of **1** and formation of furo products. Strikingly, the major product was the double CH-insertion product **5**, and the minor product was a cyclopropanated double CH-insertion product **6** (Scheme 2).

However, treatment of the analogue substrate **2** with **3**, under the same optimized conditions used as above, gave only the unsaturated product **7** (Scheme 3). Two aliquots of the carbene species must have reacted with one substrate giving two CH-insertions on the one scaffold, followed by ring opening of the furan ring, rearrangement and ring closure to give **5**. Due to the excess of the metal carbenoid present in the reaction mixture, product **5** can also react further to the minor product **6**. Opening of the furan ring has been noticed before for related structures under similar reaction conditions [7(d),13] This is similar here, indicated by the presence of the quarternary carbon at the C-2 position in both products **5** and **7**. Interestingly, when reacting **2** with **3**, only the pyrano structure **7** was produced.

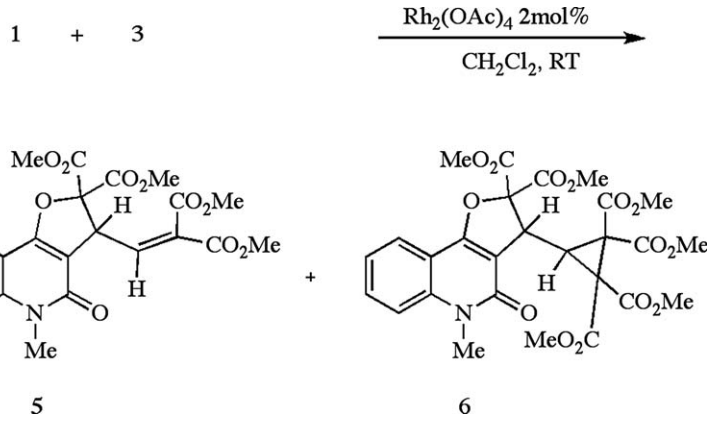
These quite different outcomes are most likely due to two different initial reaction intermediates/transition states **A** and **A'** forming from **1** and **2**, respectively, as substrates (Scheme 4). Possibly substrate **1** reacts with **3** in the C-3 position first, while substrate **2** reacts with **3** in the C-2 position. This suggests that intermediate **A** is formed and is sufficiently stable to undergo a second addition to form transition state **B**, followed by ring opening/ring closing to form **5** (Scheme 5).

In contrast, transition state **A'** cannot undergo such addition and is further stabilized by ring opening/rearrangement to give product **7** (Scheme 6). The ring closing pathway to form **7** proceeds most likely in a similar fashion as suggested for product **5**. These two early reaction intermediates/transition states (**A** and **A'**) can explain the two different outcomes observed and, ultimately, this reflects the inherent electronic differences

**Scheme 1**



**Scheme 2**

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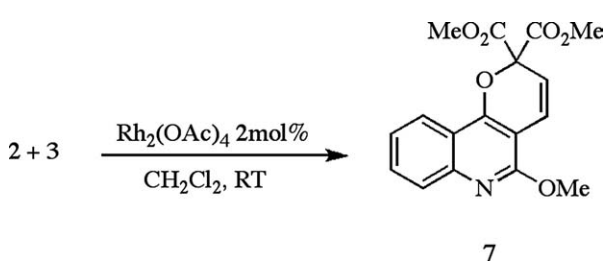
of **1** and **2**. Interestingly, it was noted product **7** does not react further in the presence of excess of **3**.

When changing dimethyl diazomalonate (**3**) for ethyl 2-diazopropionate (**8**) and optimizing the reaction protocol (Experimental), reaction of either **2** or **3** with **8** [14] gave the expected cyclopropanated outcomes **9** and **10** in isolated yields of 43 and 69%, respectively (Scheme 7). No ring opened product was observed in either case. Treatment of either **2** or **3** with the less stabilized carbene precursor 2-diazopropane under a range of conditions, including with/without catalyst and/or lowered/elevated temperatures, starting material was recovered quantitatively in all attempts.

In summary, three novel rearrangement products (**5**, **6**, and **7**) can be derived from two relatively similar substrates **1** and **2**, both belonging to the furoquionolinone class of molecules. The outcomes can be explained by different initial reaction intermediates/transition states, such as **A**, **B**, and **A'**, due to inherently different electronic properties of **1** and **2**. Thus, changing the relatively remote functionality from an amide to an imine (**1** to **2**) determines the reaction under the carbene chemistry conditions. Other reaction intermediates such as a dimerized diazomalonate in the presence of rhodium could possibly act as a carbene precursor. However, this may only be formed in higher concentrations of dimethyl diazomalonate, low consumption of **1** being observed until a certain excess of **3** is present. Alternatively, a direct rhodium mediated opening of the furan ring between the oxygen and C1 occurs [7(b),15]. Further, the expected cyclopropanated products **9** and **10** were obtained from treatment of **1** and **2** with ethyl 2-diazopropionate, however, no reaction was observed when using 2-diazopropane as the carbene precursor.

Most interestingly products **5**, **6**, and **7** are, to our knowledge, unprecedented rearrangement products. Thus, for product **5** (and **6**), this suggests a new reaction pathway is taking place and might serve as a useful application in related areas.

**Scheme 3**

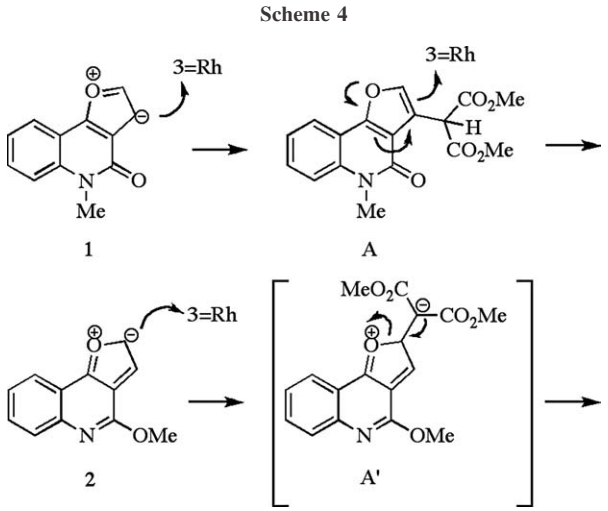



7

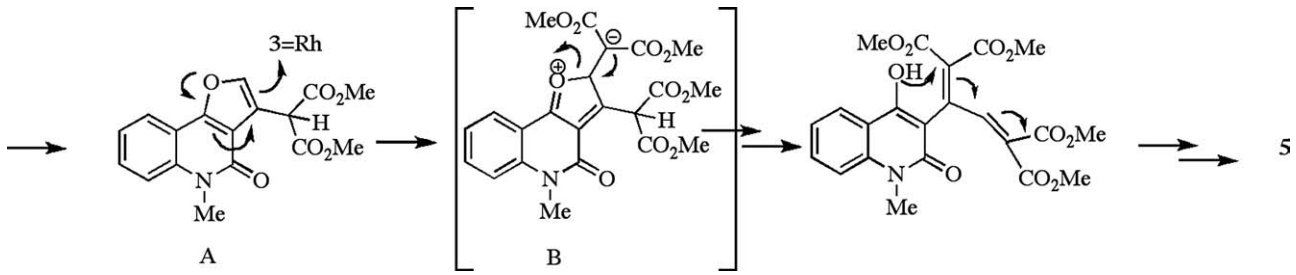
## EXPERIMENTAL

***N*-(2-Iodophenyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)-furan-3-carboxamide (8).** (2-(Chloromethoxy)ethyl)trimethylsilane (1.49 mL, 8.42 mmol) was added dropwise to a solution of *N*-(2-iodophenyl)furan-3-carboxamide (635 mg, 2.03 mmol) and sodium hydride (202 mg, 8.42 mmol) in THF (20 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was allowed to stir for 11 h (mean while slowly warming up to RT) and was then quenched by adding water (20 mL). The

**Scheme 4**



**Scheme 5**




reaction mixture was extracted with EtOAc (3 × 50 mL), washing the combined organic layers with 1M NaOH (30 mL), 1*M* HCl (30 mL) and brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (EtOAc:hexane/1:9) afforded 855 mg of **8** (95 %) as an oil. IR (KBr, $\nu_{max}$): 2946, 2921, 2357, 2324, 1655, 1581, and 1471 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 206.0 nm (14577), 226.2 nm (10829). $^1H$ NMR ($CDCl_3$, 500 MHz): δ 0.03 (s, 9H, $SiMe_3$), 0.99 (m, *J* 10 Hz, 2H, H-2‴), 3.77 (app d, *J* 5 Hz, 2H, H-1‴), 4.57 (d, *J* 10.5 Hz, 1H, H-1″), 5.81 (d, *J* 9 Hz, 1H, H-1b″), 6.28 (s, 1H, H-4), 6.73 (s, 1H, H-5), 7.16 (app t, *J* 7.5 Hz, 1H, H-4′), 7.20 (s, 1H, H-2), 7.37 (d, *J* 8.0 Hz, 1H, H-6′), 7.45 (app t, *J* 8.0 Hz, 1H, H-5′), 7.96 (d, *J* 8.0 Hz, 1H, H-3′). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 0.0 ($SiMe_3$), 18.5 (C-2‴), 66.9 (C-1‴), 77.3 (C-1″), 101.4 (C-2′), 111.4 (C-4), 121.9 (C-3), 129.7 (C-5′), 130.9 (C-4′), 132.0 (C-6′), 140.4 (C-3′), 142.5 (C-5), 143.8 (C-1′), 145.9 (C-2), 163.7 (C=O). MS (ESI): *m*/*z* 445 $[M+H]^+$, 467 $[M+Na]^+$, 910 $[2M+Na]^+$. Anal. Calcd. for $C_{17}H_{22}INO_3Si$: C, 46.05; H, 5.00; N, 3.16. Found: C, 46.09; H, 5.01; N, 3.02.

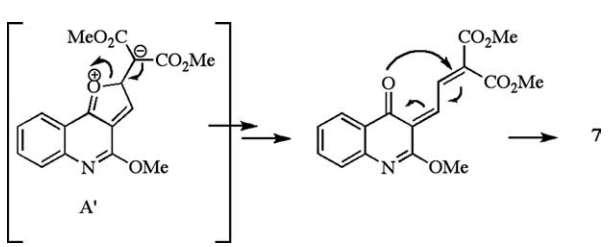
**5-((2-(Trimethylsilyl)ethoxy)methyl)furo[3,2-c]quinolin-4(5*H*)-one (9).** A mixture of **8** (90 mg, 0.20 mmol), KOAc (26 mg, 0.26 mmol), *n*-$Bu_4NCl$ (11 mg, 0.04 mmol), and PdO (2.5 mg, 0.02 mmol) was stirred in DMA (0.4 mL) at 150°C under a nitrogen atmosphere for 18 h. The crude mixture was then concentrated under reduced pressure followed by flash chromatography (EtOAc:hexane/15:85) to afford 55 mg of **9** (87%) as a slightly yellowish solid. Mp 61–62°C. IR (KBr, $\nu_{max}$): 3158, 3133, 2949, 2900, 1662, 1584, and 1499 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 227 nm (38358), 276 nm (7485), 286 nm (8934), 316 nm (9261), 331 nm (9435). $^1H$ NMR ($CDCl_3$, 500 MHz): δ -0.022 (s, 9H, H-SiMe3), 0.96 (t, *J* 8.5, 7.5 Hz, 2H, H-2″), 3.74 (t, *J* 8.5, 8 Hz, 2H, H-1″), 5.86 (s, 2H, H-1′), 7.08 (s, 1H, H-3), 7.35 (app t, *J* 7.5 Hz, 1H, H-8), 7.56 (app t, *J* 8.0 Hz, 1H, H-7), 7.65 (s, 1H, H-2), 7.72 (d, *J* 8.0 Hz, 1H, H-6), 8.02 (d, *J* 8.1 Hz, 1H, H-9). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 0.0 (SiMe3), 18.4 (C-2″), 66.6 (C-1″), 71.7 (C-1′), 108.8 (C-3), 113.7 (C-3a), 115.1 (C-9a), 116.8 (C-6), 121.3 (C-9), 123.1 (C-8), 129.8 (C-2), 137.9 (C-5a), 144.3 (C-7), 156.1 (C-9b), 160.2 (C=O). MS (ESI): *m*/*z* 316 [M+H]+, 338 [M+Na]+. Anal. Calcd. for $C_{17}H_{21}NO_3Si$: C, 64.73; H, 6.71; N, 4.44. Found: C, 64.76; H, 6.70; N, 4.45.

**Furo[3,2-c]quinolin-4(5*H*)-one (4).** To a premixed solution of acetyl chloride (43 mL), ethanol (73 mL) and water (5 mL), was added **9** (1.82 g, 5.77 mmol) at RT with stirring. After all substrate was dissolved, the reaction flask was fitted with a reflux condenser and heated to 80°C for 11 h, and the reaction mixture was then concentrated under reduced pressure. Purification was straightforward by flash chromatography when using (EtOAc:hexane/1:1) as eluent mixture which afforded 0.90 g of furo[3,2-*c*]quinolin-4(5*H*)-one (84%) as an off white solid. $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 7.04 (d, *J* 2.0 Hz, 1H, H-3), 7.25 (app t, *J* 7.4 Hz, 1H, H-8), 7.47 (app d, *J* 7.4 Hz, 1H, H-7), 7.53 (app t, *J* 7.4 Hz, 1H, H-9) 7.88 (d, *J* 7.4 Hz, 1H, H-6), 8.06 (d, *J* 2.0 Hz, 1H, H-2), 11.73 ( br s, 1H, NH). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 108.4, 111.9, 116.2, 116.7, 120.8, 122.9, 130.1, 137.7, 146.1, 156.1, 159.5. MS (ESI): *m*/*z* 185 $[M+H]^+$.

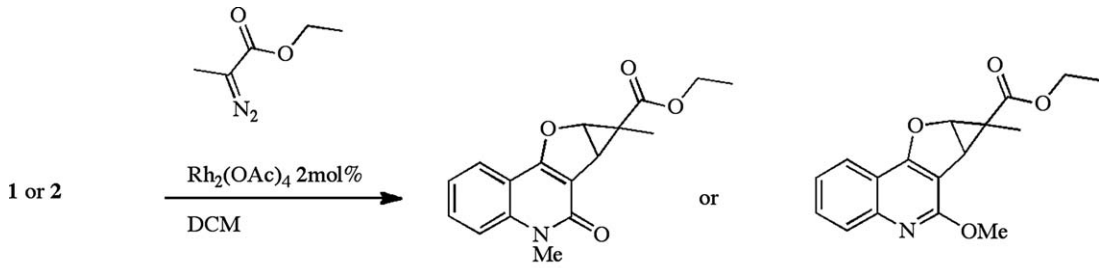
**(4-Chlorofuro[3,2-c]quinoline).** A mixture of furo[3,2-*c*]quinolin-4(5*H*)-one (0.87 g, 4.7 mmol), phosphorusoxychloride (10.0 mL) and water (0.5 mL) was refluxed at 135 °C for 4 h. The cold reaction mixture was quenched by adding water (10 mL) and with 25% ammonia. The aqueous layer was extracted with DCM (3 × 150 mL) and EtOAc (3 × 150 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure to afford 0.90 g of the desired 4-chlorofuro[3,2-*c*]quinoline (94%). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.03 (d, *J* 2.2 Hz, 1H, H-3), 7.64 (m, 1H, H-8), 7.73 (m, 1H, H-7), 7.82 (d, *J* 2.2 Hz, 1H, H-2), 8.14 (dd, *J* 8.0, 2.0 Hz, 1H, H-9), 8.25 (dd, *J* 7.4, 2.0 Hz, 1H, H-6). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 106.3, 116.6, 119.8, 120.1, 127.2, 128.8, 129.2, 144.3, 145.0, 145.2, 156.4. MS (ESI): *m*/*z* 204 $[M+H]^+$.

**4-Methoxyfuro[3,2-c]quinoline (2).** A mixture of the 4-chlorofuro[3,2-*c*]quinoline (125 mg, 0.49 mmol) and a methanolic solution of sodium methoxide (approximately 1.2 M, generated from 230 mg sodium in 10 mL of methanol) at RT under nitrogen atmosphere, was stirred until all starting material was consumed (monitored by TLC). The reaction mixture was extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (EtOAc:hexane/0 to 2.5:100 to 97.5) afforded 100 mg of **2** (80%). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 4.20 (s, 3H, OMe), 6.95 (m, 1H, H-3), 7.46 (app t, *J* 7.2 Hz, 1H, H-8), 7.61 (app t, *J* 7.2 Hz, 1H, H-7), 7.72 (m, 1H, H-2), 7.95 (app d, *J* 7.2 Hz, 1H, H-6), 8.15 (app d, *J* 7.2 Hz, 1H, H-9). $^{13}C$ NMR ($CDCl_3$, 100

**Scheme 6**



**Scheme 7**




**9** **10**

MHz): δ 53.7 (OMe), 105.4 (C-3), 111.4 (C-3a), 116.0 (C-9a), 120.1 (C-9), 124.4 (C-8), 127.7 (C-6), 128.6 (C-7), 144.3 (C-1), 144.5 (C-5a), 157.64 (C-9b), 157.68 (C-4). MS (ESI): *m*/*z* 200 $[M+H]^+$.

**Rearrangement/CH-insertion products (5) and (6).** To a solution of 1.30 (100 mg, 0.50 mmol) and dirhodium tetraacetate (5 mg, 0.01 mmol, 2 mol %) in DCM (2.5 mL) under a nitrogen atmosphere was added a solution of dimethyl diazomalonate (293 mg, 1.85 mmol, 3.7 eq) in DCM (0.5 mL) over 3 h period followed by 17 h stirring at ambient temperature (monitored by tlc). The crude was then filtered through a short silica plug using EtOAc as eluent (2 × 20 mL), dried with MgSO4 and concentrated *in vacuo*. Flash chromatography (EtOAc:hexane/1:1) afforded 180 mg of a clear oil as a mixture of the two products, **5** and **6**, in the ratio of 75:25. Reverse phase chromatography (HPLC, MeOH:$H_2O$/7:3) afforded an analytically pure sample of each product.

(**5**): Mp 179°C. IR (KBr, $\nu_{max}$): 3464, 3003, 2954, 1744, 1670, 1633, 1593, and 1437 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 226 (12355), 283 (1738), 292 (1922) nm. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 3.63 (s, 3H, NMe), 3.73 and 3.91 (2 × s, 2 × OMe, C-2′), 3.80 and 3.85 (2 × s, 2 × OMe, C-2), 5.61 (d, *J* 10.8 Hz, 1H, H-3), 6.73 (d, *J* 10.8 Hz, 1H, H-1′), 7.26 (dd, *J* 7.2, 3.0 Hz, 1H, H-8), 7.36 (d, *J* 8.4 Hz, 1H, H-6), 7.62 (app. t, *J* 7.8 Hz, 1H, H-7), 7.88 (d, *J* 7.8 Hz, 1H, H-9). $^{13}C$ NMR (CDCl3, 125 MHz) δ 29.4 (C-5), 46.7 (C-3), 52.8 and 53.1 (C-2′, 2 × OMe), 53.7 and 54.2 (C-2, 2 × OMe), 93.5 (C-2), 108.0 (C-2′), 111.7 (C-9a), 115.0 (C-6), 122.5 (C-8), 124.0 (C-9), 131.4 (C-3a), 132.5 (C-7), 141.4 (C-5a), 142.3 (C-1′), 159.9 (C-4), 161.9 (C-9b), 164.1, and 164.7 (C-2′, 2 × COOR), 165.1 and 166.1 (C-2, 2 × COOR) MS (ESI): *m*/*z* 460 $[M+H]^+$, 482 $[M+Na]^+$. HRMS Calcd. for $C_{22}H_{22}NO_{10}$ $[M+H]^+$: 460.1238. Found: 460.1252.

(**6**): Mp 199°C. IR (KBr, $\nu_{max}$): 3460, 3007, 2954, 1752, 1666, 1638, and 1433 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 229 (14802), 279 (2944), 290 (2931), 326 (2379) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.61 (d, *J* 11.0 Hz, 1H, H-3′), 3.66 (s, 3H, NMe), 3.73, 3.82, 3.87, and 3.95 (4 × s, 4 × OMe), 3.78 (s, 2 × OMe), 5.15 (d, *J* 11.0 Hz, 1H, H-3), 7.28 (m, 1H, H-8), 7.37 (d, *J* 8.5 Hz, 1H, H-6), 7.63 (app t, *J* 7.5 Hz, 1H, H-7), 7.88 (d, *J* 8.0 Hz, 1H, H-9). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 29.6 (C-5), 36.7 (C-3′), 43.7 (C-2′), 43.9 (C-3), 45.3 (C-1′), 53.0, 53.2, 53.5, 53.6, 53.7 and 53.9 (6 × OMe), 92.7 (C-2), 108.9 (C-3a), 111.9 (C-9a), 114.7 (C-6), 122.1 (C-8), 123.8 (C-9), 132.1 (C-7), 141.4 (C-5a), 160.1 (C-4), 161.1 (C-9b), 164.4 and 166.0 (C-1′, 2 x COOR), 166.2 and 166.3 (C-2′, 2 × COOR), 167.5 and 167.9 (C-2, 2 × COOR). (ESI): *m*/*z* 590 $[M+H]^+$, 612 $[M+Na]^+$. HRMS Calcd. for $C_{27}H_{28}NO_{14}$ $[M+H]^+$: 590.1504. Found: 590.1495.

**Dimethyl 5-methoxy-2*H*-pyrano[3,2-*c*]quinoline-2,2-dicarboxylate (7).** To a solution of **2** (100 mg, 0.5 mmol) and dirhodium tetraacetate (4.95 mg, 0.01 mmol, 2 mol %) in DCM (2.5 mL) under nitrogen atmosphere, was added a solution of dimethyl diazomalonate (293 mg, 1.85 mmol, 3.7 eq) in DCM (0.5 mL) over 3 h period followed by 17 h stirring at ambient temperature (monitored by tlc). The crude reaction mixture was then filtered through a short silica plug using EtOAc as eluent (2 × 20 mL), dried with MgSO4 and concentrated *in vacuo*. Flash chromatography (EtOAc:hexane/1:9) afforded 63 mg of **7** as a white solid (38%). Mp 85–86°C. IR (KBr, $\nu_{max}$): 3101, 3015, 2954, 1761, 1740, 1642, 1605, 1569, 1507, 1475 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 229 (4083), 254 (2936), 263 (2520), 317 (982) nm. $^1H$ NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 2 × 3H, 2 × COOMe), 4.09 (s, 3H, OMe), 6.05 (d, *J* 10.0 Hz, 1H, H-3), 6.97 (d, *J* 10.0 Hz, 1H, H-4), 7.39 (dd, *J* 7.0, 1.0 Hz, 1H, H-9), 7.62 (dd, *J* 7.0, 1.0 Hz, 1H, H-8), 7.77 (d, *J* 8.0 Hz, 1H, H-7), 8.19 (d, *J* 8.0 Hz, 1H, H-10). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 53.86 (C-2, 2 × COOMe), 53.89 (C-5, OMe), 101.4 (C-4a), 82.3 (C-2), 116.9 (C-3), 117.7 (C-10a), 120.9 (C-4), 122.4 (C-10), 124.2 (C-9), 127.2 (C-7), 130.7 (C-8), 147.2 (C-6a), 155.4 (C-10b), 158.7 (C-5), 167.0 (C-2, 2 × COOR). MS (ESI): *m*/*z* 330 $[M+H]^+$, 352 $[M+Na]^+$, 298 $[M-CH_3O]^+$. HRMS Calcd. for $C_{17}H_{16}NO_6$ $[M+H]^+$: 330.0972. Found 330.0960.

**Ethyl 5,7-dimethyl-6-oxo-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5]furo[3,2-*c*]quinoline-7-carboxylate (9).** To a solution of **2** (482 mg, 2.41 mmol) and dirhodium tetraacetate (24 mg, 0.05 mmol, 2 mol %) in DCM (15 mL) under a nitrogen atmosphere was added a solution of ethyl 2-diazopropanoate (**8**) (988 mg, 7.71 mmol, 3.2 eq) in DCM (5 mL) over 1 h period followed by 1 h stirring at ambient temperature. The crude reaction mixture was then filtered through a short silica plug using EtOAc as eluent (3 × 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Reverse phase flash chromatography (MeOH:$H_2O$/7:3) afforded 314 mg of **9** as a white solid (43%). Mp 141–142°C. IR (KBr, $\nu_{max}$): 3081, 2974, 2929, 1716, 1659, 1593, and 1569 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 224 (25226), 298 (3488), 324 (3880) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.93 (s, 3H, H-1′), 1.29 (t, *J* 7.2 Hz, 3H, H-2″), 3.50 (d, *J* 5.6 Hz, 1H, H-6b), 3.73 (s, 3H, NMe), 4.19 (q, *J* 7.2 Hz, 2H, H-1″), 5.18 (d, *J* 5.6 Hz, 1H, H-7a), 7.26 (dd, *J* 7.6, 1.2 Hz, 1H, H-2), 7.41 (d, *J* 8.4 Hz, 1H, H-4), 7.61 (dd, *J* 7.6, 1.6 Hz, 1H, H-3), 7.77 (dd, *J* 7.6, 1.2 Hz, 1H, H-1). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 6.6 (C-1′), 14.5 (C-2″), 20.2 (C-7), 29.6

(NMe), 34.4 (C-6b), 61.5 (C-1″), 72.8 (C-7a), 110.3 (C-6a), 111.8 (C-8b), 115.0 (C-4), 122.2 (C-2), 122.8 (C-1), 131.5 (C-3), 140.6 (C-4a), 161.1 (C-6), 164.0 (C-8a), 173.3 (COOR). MS (ESI): *m*/*z* 300 $[M+H]^+$, 322 $[M+Na]^+$. HRMS Calcd. for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$: 322.1049. Found: 322.1041.

**Ethyl 6-methoxy-7-methyl-7,7a-dihydro-6b*H*-cyclopropa[4,5]-furo[3,2-*c*]quinoline-7-carboxylate (10).** To a solution of **3** (100 mg, 0.50 mmol) and dirhodium tetraacetate (5 mg, 0.01 mmol, 2 mol %) in DCM (3.1 mL) under a nitrogen atmosphere was added a solution of ethyl 2-diazopropanoate (**8**) (209 mg, 1.60 mmol, 3.2 eq) in DCM (1 mL) over 1 h period followed by 1 h stirring at ambient temperature. The crude reaction mixture was then filtered through a short silica plug using EtOAc as eluent (2 × 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (EtOAc:hexane/5:95) afforded 103 mg of **10** as a white solid (69%). Mp 105°C. IR (KBr, $\nu_{max}$): 2979, 2949, 2938, 2899, 1707, 1637, 1604, and 1576 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 234 (52189), 320 nm (22709) nm. $^1H$ NMR ($CDCl_3$, 500 MHz): δ 0.86 (s, 3H, H-1′), 1.33 (t, *J* 6.0 Hz, 3H, H-2″), 3.48 (d, *J* 5.6 Hz, 1H, H-6b), 4.14 (s, 3H, OMe), 4.23 (q, *J* 6.0 Hz, 2H, H-1″), 5.25 (d, *J* 5.6 Hz, 1H, H-7a), 7.36 (dd, *J* 6.8, 1.2 Hz, 1H, H-2), 7.61 (dd, *J* 7.2, 1.6 Hz, 1H, H-3), 7.86 (m, 2H, H-4 and H-1). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 6.6 (C-1′), 14.5 (C-2″), 20.1 (C-7), 33.1 (C-6b), 53.7 (OMe), 61.6 (C-1″), 72.9 (C-7a), 106.5 (C-6a), 114.6 (C-8b), 121.1 (C-4), 124.0 (C-2), 127.5 (C-1), 130.1 (C-3), 147.4 (C-4a), 160.4 (C-6), 166.2 (C-8a), 173.7 (COOR). MS (ESI): *m*/*z* 300 $[M+H]^+$, 322 $[M+Na]^+$. HRMS Calcd. for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1230. Found: 300.1221.

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## REFERENCES AND NOTES

[1] Grundon, M. F. The Alkaloids: Quinoline Alkaloids Related to Anthranilic Acid; Academic Press: London, 1988, 32, 341.

[2] Michael, J. P. Nat Prod Rep 1998, 61, 595.

[3] Xu, W. H.; Xue, Z. Acta Chim Sin 1984, 42, 899.

[4] Vaquette, J.; Hifnawy, M. S.; Pousset, J. L.; Fournet, A.; Bouquet, A.; Cave, A. Phytochemistry 1976, 15, 743.

[5] Moulis, C.; Wirasutisna, K. R.; Gleye, J.; Loiseau, P.; Stanislas, E.; Moretti, C. Phytochemistry 1983, 22, 2095.

[6] (a) Dorwald, F. Z. Metal Carbenes in Organic Syntheses; Wiley-VCH, 1999; (b) Taber, D. F.; Joshi, P. V. In Modern Rhodium-Catalyzed Organic Reactions; Evans, P. A., Ed.; Wiley-VCH, 2005; p 357; (c) Davies, H. M. L.; Walji, A. M. In Modern Rhodium-Catalyzed Organic Reactions; Evans, P. A., Ed.; Wiley-VCH, 2005; p 301; (d) Doyle, M. P. In Modern Rhodium-Catalyzed Organic Reactions; Evans, P. A., Ed.; Wiley-VCH, 2005; p 341; (e) Davies, H. M. L.; Jin, Q. Proc Natl Acad Sci USA 2004, 101, 5472; (f) Davies, H. M. L.; Jin, Q. J Am Chem Soc 2004, 126, 10862.

[7] (a) Wenkert, E.; Khatuya, H.; Klein, P. S. Tetrahedron Lett 1999, 40, 5171; (b) Matlin, S. A.; Chan, L.; Catherwood, B. J Chem Soc Perkin Trans 1 1990, 89. (c) Davies, H. M. L.; Hedley, S. J Chem Soc Rev 2007, 36, 1109; (d) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. J Org Chem 1990, 55, 6203.

[8] Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. J Org Chem 1977, 42, 3945.

[9] Nair, V.; Thomas, S.; Mathew, S. C.; Vidya, N.; Rath, N.P. Tetrahedron 2005, 61, 9533.

[10] Lindahl, K.-F; Carroll, A.; Quinn, R. J.; Ripper, J. A. Tetrahedron Lett 2006, 47, 7493.

[11] (a) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Carroll, J. G.; Mackerracher, D.; Malone, J. F. J Chem Soc Perkin Trans 1 2000, 3397; (b) Bar, G.; Parsons, A. F.; Thomas, C. B. Tetrahedron 2001, 57, 4719; (c) Lee, Y. R.; Kim, B. S,; Kweon, H. I. Tetrahedron 2000, 56, 3867; (d) Pirrung, M. C.; Blume, F. J Org Chem 1999, 64, 3642.

[12] Doyle, M. P.; Davies, S. B.; Hu, W. Org Lett 2000, 2, 1145.

[13] (a) Davies, H. M. L.; Antoulinakis, E. G. Org React 2001, 57; (b) Manning, J. R.; DaviesH. M. L. Tetrahedron, 2008, 64, 6901; (c) Wood, J. L.; Moniz, G. A. Org Lett 1999, 1, 371; (d) Baird, M. S. Chem Rev 2003, 103, 1271.

[14] (a) Bachmann, S.; Fielenbach, D.; Jorgensen, K. A. Org Biomol Chem 2004, 2, 3044; (b) Benati, L; Nanni, D.; Spagnolo, P. J Org Chem 1999, 64, 5132; (c) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. J Org Chem 1996, 61, 2908.

[15] (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. Chem Rev 2010, 110, 704; (b) West, F. F. Modern Rhodium-Catalyzed Organic Reactions; Wiley-VCH, 2005, p 417.

# 1,3-Dipolar Cycloaddition of Nitrile Oxides with Symmetrical Tri- and Polycyclic Strained Olefins



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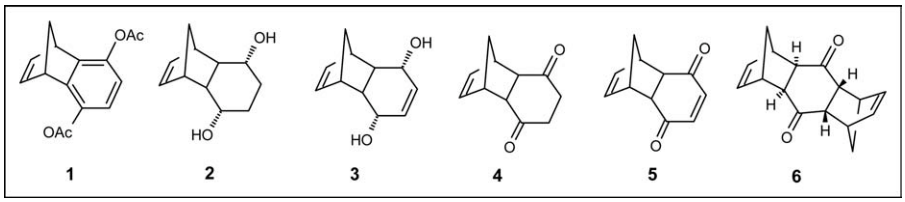


1,3-Dipolar cycloadditions of benzonitrile oxide and carbethoxyformonitrile oxide (CEFNO) with various facially perturbed polycyclic symmetrical dienophiles (**1**–**6**) were investigated. Cycloadditions took place chemoselectively at the norbornyl double bond and were found to be exclusively exo. Cycloadditions of benzonitrile oxide with dienophiles **4** and **5** led to mixture of inseparable products, however, that with CEFNO gave single products. Cycloadduct of dienophile **5** with CEFNO was found to be unstable, and it readily isomerized to more stable aromatic form.

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## INTRODUCTION

1,3-Dipolar cycloaddition of nitrile oxides are well documented [1] and provide efficient entries to the synthesis of isoxazolines [2]. Remarkable stereoselectivity has been observed in 1,3-dipolar cycloadditions with bicyclic systems [1a,3,4] and indeed, that with norbornene proceeds exclusively on the exo face [5]. Even unsymmetrically substituted norbornenes are reported to cycloadd completely stereoselectively [6]. The desired exo-isomers are the one in which oxygen of the dipole is attached to the more substituted center of the dipolarophiles (Scheme 1).

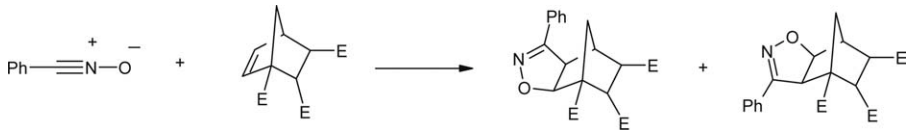
Formation of single regio- and stereoisomers were also noticed in the intramolecular cycloaddition of norbornene tethered nitrile oxides [6c]. Recently, Namboothiri *et al*. [7a] have studied the behavior of multi π-facial dipolarophiles, dicyclopentadiene (DCP), and its analogues toward nitrile oxides. In their study on DCP, the cycloaddition of nitrile oxide was found to be both chemo- and steroselective. However, cycloadducts were reported to be mixture of two regioisomers. In a similar study, Trivedi and coworkers [8] and Tanaka *et al*. [9] have also noticed comparable regio-, chemo-, and stereoselectivity during the cycloaddition of DCP with substituted acetonitrile oxides. As against this, the cycloadducts derived from Thiele's esters were regio-, stereo- and chemoselective [7].

It is interesting to note that the stereochemistry of Diels-Alder additions to norbornene systems, for example, 2,3-norbornenobenzoquinone (NPBQ) [10], 2,3-norbornanobenzoquinone (DNPBQ) have been extensively investigated by Mehata *et al*. [11]. However, complementory investigations involving the cycloaddition of facially perturbed dienophiles to 1,3-dipoles has not received matching attention. This study is, therefore, focused on the 1,3-dipolar cycloaditions of two different types of nitrile oxides *viz*. benzonitrile oxide and carbethoxyformonitrile oxide (CEFNO) toward multi π-facial tricyclic and polycyclic systems incorporating bicyclo-[2.2.1]-heptenyl moity (Figure 1).

## RESULTS AND DISCUSSION

Dipolarophile **1** was prepared by treatment of compound **5** with acetic anhydride and pyridine [10]. Compound **5** in turn was obtained by Diels-Alder cycloaddition of cyclopentadiene and *para*-benzoquinone (1:1 eq) [10]. Diels-Alder cycloaddition of cyclopentadiene and *para*-benzoquinone in 2:1 eq gave dipolarophile **6**. Dipolarophile **5** was reduced chemoselectively to dipolarophile **4** by using Zn and acetic acid. Chemoselective reduction of compounds **4** and **5** were carried out using $NaBH_4$ and $CeCl_3.7H_2O$ to get dipolarophiles **2** and **3**, respectively.

**Scheme 1**



Preference to the symmetrical dipolarophiles was given to negate regiochemistry question. The results presented here deal with both the questions of chemoselectivity and stereoselectivity. As Mayo *et al*. [6c] have noticed dependence of cycloadduct stereochemistry on the methods and conditions of generation of nitrile oxides. Therefore, we have adopted two methods for the generation of nitrile oxides. First one involves *in situ* preparation of benzonitrile oxide by commonly used bleach method in dichloromethane solvent, whereas second one involves *in situ* preparation of carbethoxyformonitrile oxide in ionic liquid medium as described by Taddei *et al* [12].

For initial studies, we have chosen dipolarophiles with only one double bond (**1** and **2**) so as to get rid of chemoselectivity aspect. In these cases, approach of dipole can take place from two faces of dipolarophiles leading to the possibility of two products. However, we observed that dipolarophiles **1** undergo cycloaddition with benzonitrile oxide **7a** giving exclusively exo cycloadduct **1a** (Scheme 2). In $^1$H-NMR disappearance of signal at δ 5.66 (s, 2 H) and appearance of signal at δ 4.16 (d, 1 H, $J$ = 8.1 Hz) for $H^a$ and 5.08 (d, 1 H, $J$ = 8.1 Hz) for $H^b$ confirmed formation of cycloadduct. The protons $H^a$ and $H^b$ appeared as doublets coupled only to each other but not to bridgehead protons indicating endo orientation [6c,7a]. Diol **2** also underwent cycloaddition with benzonitrile oxide affording exclusively exo-cycloadduct **2a** as indicated by spectral data (Scheme 2). Cycloaddition of **1** and **2** with carbethoxyformonitrile oxide **7b** took place similarly yielding corresponding cycloadducts **1b** and **2b**, respectively.

To further investigate cycloaddition reaction, we have increased the number of π-faces in dipolarophiles to two (two C=C). When dipolarophile **3** was subjected to cycloaddition to benzonitrile oxide, we observed remarkable stereoselectivity along with chemoselectivity. Cycloaddition took place selectively to the olefin of norbornene moity with exclusively exo selectivity giving rise to only one cycloadduct **3a** (Scheme 3). Similar results were obtained in cycloaddition of carbethoxyformonitrile oxide with dipolarophile **3** resulting in formation of cycloadduct **3b**.

Encouraged by these results, we attempted cycloaddition of benzonitrile oxide on more complex systems **4** and **5** containing three (two C=O and one C=C) and four (two C=O and two C=C) π-faces, respectively. In principle, dipolarophile **5** could react with either of the double bonds and/or with the carbonyl groups. In the event, if each of the π-component reacts with the dipole formation of upto three cycloadducts could be envisaged, provided the ''exo addition rule'' prevails [7]. However, the reaction ended up with a complex intractable mixture. To overcome the eventualities arising out of the side reactions due to multiple π-faces, it was decided to reduce the number of reactive sites by saturating the α,β-unsaturated double bond in the dienedione **5**. In such systems, amongst the constituents π-systems, the norbornenyl double bond is expected to deliver the cycloadducts in a chemoselective fashion. However, to our dismay, the cycloaddition reaction with benzonitrile oxide under the chosen condition ended up with the inseparable multiple products (Scheme 4).

However, when dipolarophile **4** was subjected to cycloaddition reaction with carbethoxyformonitrile oxide instead of multiple products as expected from our earlier studies only single product **9** was obtained. Cycloaddition took place chemoselectively to the olefinic double bond of dipolarophile **4**, and it was found to be exclusively exo product. Encouraged by these results, we expected similar chemo- and stereoselectivity in the cycloaddition of CEFNO to the dipolarophile **5**. Although the product of this cycloaddition was found to be pure by thin layer chromatography, the $^1$H and $^{13}$C-

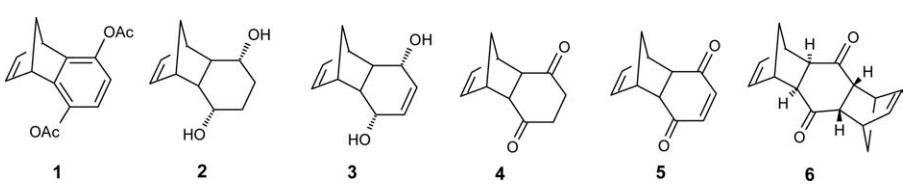
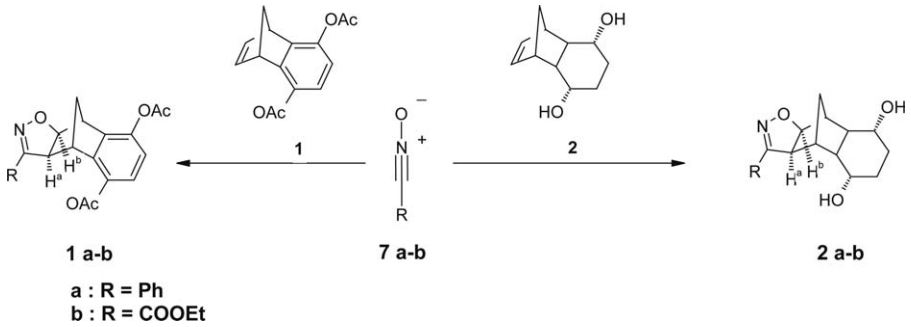


**Figure 1.** Symmetrically substituted dipolarophiles.

**Scheme 2**



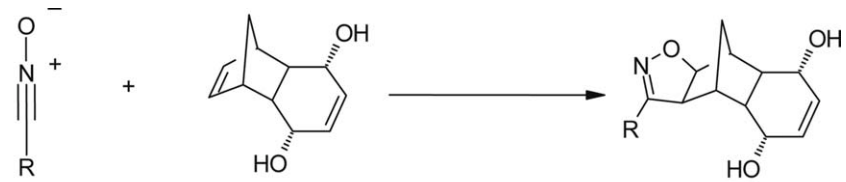

spectral data were little ambiguous and insufficient to confirm the exact structure of cycloadduct. The doublet observed in $^1$H spectra at δ 8.6 for two protons with $J$ = 8.7 Hz could not be explained. In $^{13}$C-spectra also, no signal for carbon of carbonyl was observed indicating absence of C=O group. IR spectrum showed strong absorptions in 3300–3600 cm$^{-1}$ range. To get the more details about the structure, spectral correlation studies were carried out. $^1$H-$^1$H COSY spectrum (Figure 2) showed only two correlations, one between proton of $CH_2$ and $CH_3$ of the ethyl group and another between two protons at δ 3.5 and δ 4.8 ppm. $^1$H-$^{13}$C HETCOR spectra (Figure 3) was more informative. It showed absence of correlation for two protons observed at 8.6 in $^1$H NMR spectrum and absence of protons on four carbon atoms (δ 128.40, 133.05, 143.97, and 144.71). Further, $D_2O$ exchange studies showed that doublet observed at 8.6 is $D_2O$ exchangeable. All these results led us to conclude the structure of adduct as **8** (Scheme 5). The cycloadduct was found to be exclusively exo as indicated by $^1$H-NMR spectrum.

As compound **5b** could not be obtained directly by cycloaddition of dipolarophile **5** with carbethoxyformonitrile oxide, we thought of preparing it by oxidation of cycloadduct **3b**. When we subjected the cycloadduct **3b** to PCC oxidation, expecting product **5b** as shown in Scheme 6, we ended up with **8** indicating that **5b** is not stable and gets isomerized to more stable form **8**. It further confirms the structure of cycloadduct of **3** with CEFNO as **3b**.

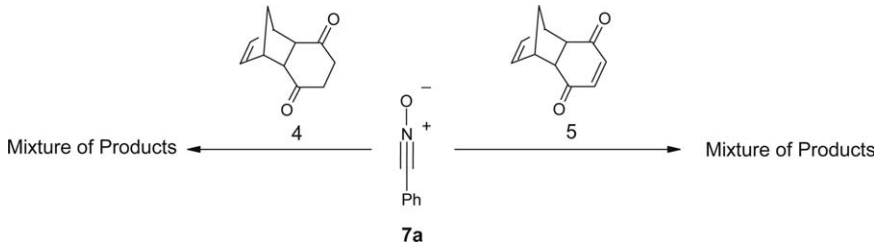
The next dipolarophile used for the study was endo-anti-endo bisadduct **6**. It has four π-faces (two C=C and two C=O). Although we were expecting behaviour of dipolarophile **6** in cycloaddition to benzonitrile oxide similar to that of **4** and **5**, we were surprised to observe exo monoadduct **6a** as the sole product as indicated by $^1$H and $^{13}$C spectral data. Cycloaddition of **6** with carbethoxyformonitrile oxide also resulted in similar results leading to formation of cycloadduct **6b** (Scheme 7).

In conclusion, we have studied the 1,3-dipolar cycloaddition of benzonitrile oxide and carbethoxyformonitrile oxide with various polycyclic dipolarophiles possessing norbornene moiety. Cycloaddition of dipolarophiles **1** and **2** with both the dipoles were found to be stereoselective as only exo cycloadduct was obtained. Dipolarophile **3** reacted with both the dipoles stereoselectively as well as chemoselectively at the norbornene double bond giving corresponding exo cycloadduct. Cycloaddition of dipolarophiles **4** and **5** with benzonitrile oxide led to the formation of mixture of products which could not be characterized; however, cycloaddition of **4** and **5** with carbethoxyformonitrile oxide gave corresponding cycloadducts stereoselectively and chemoselectively. Dipolarophile **6** also reacted with both the dipoles giving corresponding monoadduct stereo and chemoselectively. Hence, from the above study, we can

**Scheme 3**



**Scheme 4**




conclude that exo-rule prevails for the norbornene entities present in the polycyclic molecules.

## EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an atmosphere of $N_2$. Progress of reactions was monitored by TLC (silica gel 60 F254, 0.25 mm, Merck) and purification was effected using silica gel column chromatography. NMR spectra were recorded at 300 ($^1$H) and 75 ($^{13}$C) MHz on Jeol-300 MHz spectrophotometer. Chemical shifts (δ) were reported relative to TMS ($^1$H) and $CDCl_3$ ($^{13}$C) as the internal standards. IR spectra were recorded on a Nicolet Impact 400 series FTIR spectrophotometer. All commercial grade solvents were distilled before use.

**Preparation of dipolarophile 4.** To a solution of compound **6** (1.044 g, 6 mmol) in glacial acetic acid (60 mL) was added activated zinc (4.2 g, 64.2 mmol). The reaction mixture was stirred for 3 h at room temperature. The acetic acid was removed under high vacuum *via* dry ice-acetone trap. The residue was dissolved in diethyl ether and filtered through a pad of celite. The filtrate was washed with saturated aq. $NaHCO_3$ (120 mL), brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to furnish the product (0.580 g, 55%). Yellow oil. IR ($CHCl_3$): 3020, 2925, 1705, 1423, 1300 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.32–1.51 (m, 2H), 2.30 (m, 2H), 2.65 (m, 2H), 3.22 (s, 2H), 3.46 (s, 2H), 6.18 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 37.81, 47.31, 48.61, 51.71, 136.51, 209.55.

**Preparation of dipolarophile 2.** Compound **4** (0.35g, 2 mmol) was dissolved in a solution of cerium (III) chloride heptahydrate (1.5g, 4 mmol) in methanol (6 mL). The resulting solution was cooled to 0°C by external application of an ice bath. Sodium borohydride (0.15 g, 4 mmol) was then added at such a rate that the temperature of the reaction mixture did not rise significantly above 0°C. The reaction mixture was analyzed by TLC 2 h after addition of the sodium borohydride had been completed: The reaction was then quenched via addition of water (2.5 mL) and the resulting mixture was then extracted with chloroform and combined organic layer was concentrated *in vacuo* to yield crude diol. Recrystallization from DCM and petroleum ether afforded pure diol (0.099g, 27.76%). White solid, Mp 127–126°C. IR ($CHCl_3$): 3307, 3224, 2910, 1563, 1527 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.38 (dd, 2 H, $J$ = 7.5 and 8.0 Hz), 1.79 (s, 4 H), 1.86 (bs, 1 H), 2.38 (s, 2 H), 2.77 (bs, 1 H), 2.91 (s, 2 H), 4.12 (s, 2 H), 6.21 (s, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 27.04, 45.11, 45.83, 52.39, 67.04, 134.56.

**Procedure for PCC oxidation of 3b.** In a 50-mL round-bottomed flask fitted with a reflux condenser was suspended PCC (0.161 g, 0.75 mmol) in anhydrous dichloromethane (5 mL). Cycloadduct **3a** (0.073 g, 0.25 mmol) was added to it in small portions and stirring was continued till reaction goes to completion. The progress of reaction was monitored on TLC.

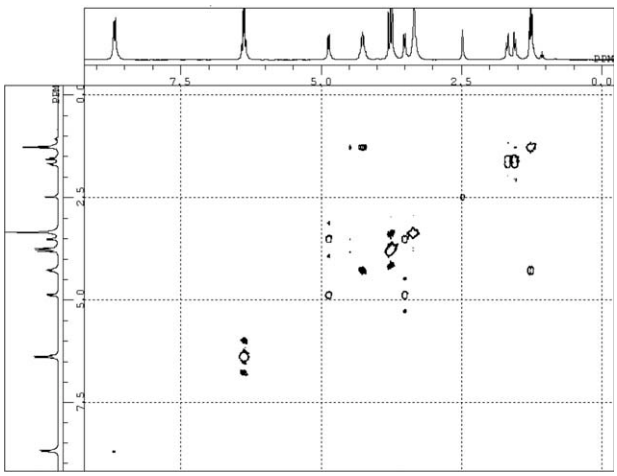


**Figure 2.** ($^1$H-$^1$H) COSY spectrum of compound **8**.

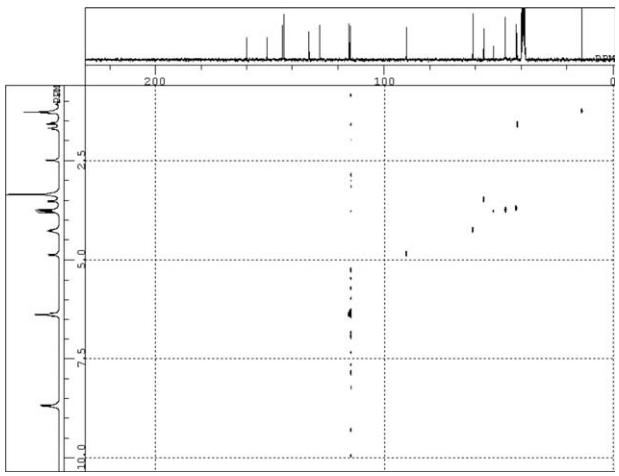
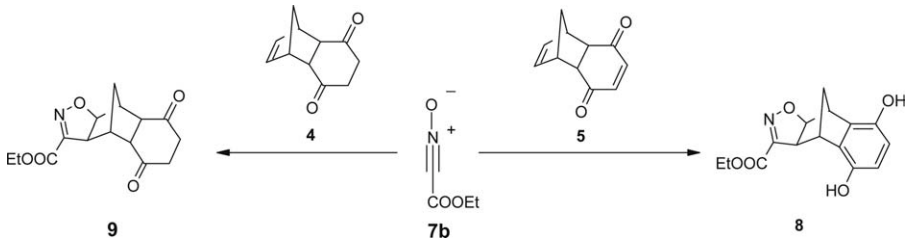


**Figure 3.** ($^{13}$C-$^1$H) HETCOR spectrum of compound **8**.

**Scheme 5**




After completion of the reaction, dichloromethane was removed under vacuum and product was extracted into diethyl ether (4 × 5 mL). All the extracts were dried by using anhydrous sodium sulfate and evaporated under reduced pressure to get the product which was purified by column chromatography, (0.055 g, 76%).

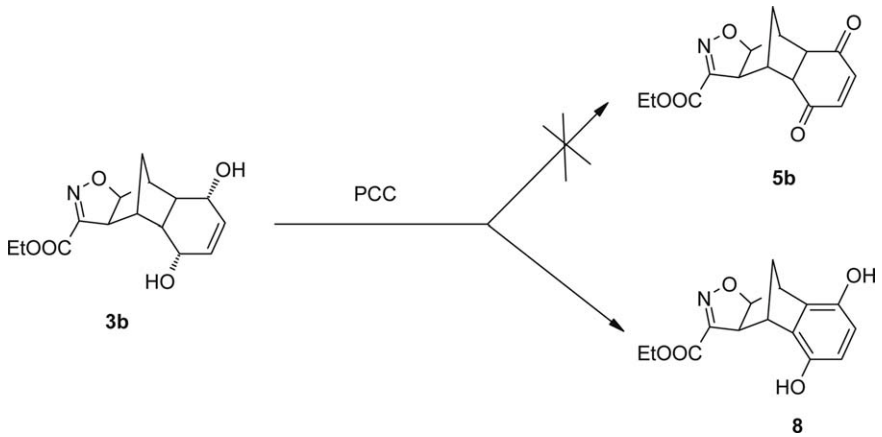
**General procedure for cycloaddition of benzonitrile oxides with dipolarophiles.** A solution of the benzaldoxime (dipole precursor) (1.2 mmol), dipolarophile (1 mmol) and triethylamine in dichloromethane (10 mL) was cooled to 0°C, sodium hypochlorite (4%, 10 mL) was added dropwise with stirring at 0°C. The reaction mixture was warm to room temperature and kept for 6–8 h with stirring. On disappearance of starting material (TLC), the reaction phases were separated and the aqueous phase was extracted with dichloromethane. The combined layers were washed with brine, dried with sodium sulphate, and the solvent evaporated under reduced pressure to yield crude cycloadduct. The crude product was chromatographed on a silica gel column. Thus, all cycloadducts were prepared following the aforementioned general protocol and characterized by IR, $^1$H-NMR, and $^{13}$C-NMR spectroscopy. The data for cycloadduct obtained from 1,3-dipolar cycloaddition are presented below.

**General procedure for cycloaddtion of carbethoxyformonitrile oxide with dipolarophiles.** In a typical experimental procedure, dipolarophile (1 mmol) was mixed with $NaHCO_3$ (1 mmol) in [bmim]$BF_4$ (0.5 g) ionic liquid. Ethyl chloroximidoacetate (1 mmol) was added, and the mixture was stirred at room temperature for 3–4 h when starting material disappeared (TLC); the reaction mixture was treated with diethyl ether to extract the product. Diethyl ether was removed under reduced pressure to get the product. In case of cycloaddition with dipolarophile **3**, due to poor solubility in diethyl ether, cycloadduct **3b** was isolated by dissolving ionic liquid in water followed by filtration. If required, the crude products were chromatographed on silica gel column. Cylcoadducts obtained were characterized by IR, $^1$H-NMR, and $^{13}$C-NMR spectroscopy.

***Compound 1a.*** White solid (89%), Mp 168–170°C. IR ($CHCl_3$): 1760, 1593, 1563 1483 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.87 (d, 1 H, $J$ = 9.0 Hz), 2.01 (d, 1 H, $J$ = 9.0 Hz), 2.32 (s, 3 H), 2.37 (s, 3 H), 3.43 (s, 1 H), 3.71 (s, 1 H), 4.16 (d, 1 H, $J$ = 8.1 Hz), 5.08 (d, 1 H, $J$ = 8.1 Hz), 6.83 (s, 2 H), 7.39–7.41 (m, 3 H), 7.77–7.79 (m, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.74, 20.81, 43.16, 44.66, 49.04, 56.99, 87.81, 120.90, 121.08, 126.89, 128.78, 128.93, 129.99, 137.01, 140.76, 142.25, 143.17, 156.16, 169.06, 169.30. HRMS (TOF, ES$^+$): $m/z$ [M + H]$^+$ calcd for $C_{22}H_{20}NO_5$: 378.1341; found: 378.1357.

***Compound 1b.*** White solid (70%), Mp 130–132°C. IR (KBr): 898, 1015, 1194, 1369, 1476, 1579, 1756, 2925, 2983 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, 9.0 Hz), 1.86 (d, 1 H, 9.0 Hz), 1.96 (d, 1 H, 12.0 Hz), 2.33 (s, 3 H), 2.36 (s, 3 H), 3.69 (s, 1 H), 3.71 (s, 1 H), 3.81 (d, 1 H, $J$ = 9.0 Hz), 4.36 (m, 2 H), 5.12 (d, 1 H, $J$ = 9.0 Hz), 6.84 (s, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.14, 20.74, 20.80, 43.03, 44.51, 48.90, 56.00, 62.02, 90.39, 121.17, 121.57,

**Scheme 6**



**Scheme 7**


136.50, 140.46, 142.43, 143.06, 151.19, 160.39, 169.84. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{19}H_{20}NO_7$: 374.1240; found: 374.1256.

***Compound 2a.*** Sticky mass (75%). IR ($CHCl_3$): 3351, 1611, 1574 $cm^{-1}$. $^1H$ NMR (300 Hz, $CDCl_3$): δ = 1.21 (d merged with other peak, 2 H, *J* = 10.5 Hz), 1.61 (d, 2 H, *J* = 10.2 Hz), 1.71 (d, 2 H, *J* = 12 Hz), 1.93 (d, 2 H, *J* = 14.7 Hz), 2.01 (s, 2 H), 2.62 (s, 1 H), 2.80 (s, 1 H), 4.27 (s, 1 H), 4.34 (s, 1 H), 5.01 (d, 1 H, *J* = 8.1 Hz), 5.76 (d, 1 H, *J* = 8.1 Hz), 7.35 (m, 3 H), 7.72 (m, 2 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 28.73, 28.79, 34.74, 40.87, 41.44, 44.26, 48.73, 51.11, 67.20, 67.80, 84.92, 126.97, 127.41, 128.69, 129.43, 129.66, 158.48. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_3$: 300.1600; found: 300.1614.

***Compound 2b.*** Yellow sticky oil (65%). IR (neat): 757, 829, 940, 1018, 1137, 1173, 1252, 1405, 1449, 1581, 1720, 2962, 3303 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.18–2.09 (m, 11 H), 2.70 (s, 1 H), 2.80 (s, 1H), 3.47–3.50 (m, 2 H), 4.17–4.34 (m, 4 H), 4.65 (d, 1 H, *J* = 9.0 Hz), 5.87 (d, 1 H, *J* = 9.0 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.97, 28.26, 28.41, 34.58, 40.88, 41.46, 44.06, 48.37, 49.83, 61.75, 66.84, 67.25, 87.90, 162.99, 161.32. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for:$C_{15}H_{22}NO_5$: 296.1498; found: 296.1484.

***Compound 3a.*** White solid (85%), Mp 196–198°C. IR ($CHCl_3$): 3397, 1655, 1460 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, 1 H, *J* = 6.9 Hz), 1.30 (d, 1 H, *J* = 11.4 Hz), 1.60 (s, 1 H), 1.67 (d, 1 H, *J* = 10.5 Hz), 2.58 (narrowly splitted triplet, 2 H), 2.68 (s, 1 H), 2.79 (s, 1 H), 3.85 (d, 1 H, *J* = 7.2 Hz), 4.45 (s, 1 H), 4.54 (s, 1 H), 4.72 (d, 1 H, *J* = 8.1 Hz), 5.73 (dd, 2 H, *J* = 10.5 and 10.2 Hz), 7.35–7.37 (m, 3 H), 7.81–7.84 (m, 2 H). $^{13}C$ NMR (75MHz, $CDCl_3$): δ = 34.23, 39.79, 40.69, 41.41, 45.50, 53.01, 65.84, 65.84, 85.57, 127.01, 128.62, 128.65, 129.32, 129.62, 130.34, 130.57, 157.19. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$: 298.1443; found: 298.1446.

***Compound 3b.*** White solid (69%), Mp 108–109°C. IR (KBr): 951, 1071, 1245, 1363, 1576, 1635, 1732, 2957, 3311, 3516 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, 3 H, *J* = 6.6 and 6.9 Hz, one peak merged in it), 1.55 (d, 1 H, *J* = 10.5 Hz), 1.92 (bs, $D_2O$ exch.), 2.58 (s, 2 H), 2.73 (s, 1 H), 2.80(s, 1 H), 3.61 (d, 1 H, *J* = 8.1Hz), 4.32 (m, 2 H), 4.43 (s, 2 H), 4.81 (d, 2 H, *J* = 8.1 Hz), 5.64 (d, 1 H, *J* = 9.9 Hz), 5.74 (d, 1 H, *J* = 9.9 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 14.09, 34.29, 39.93, 40.79, 41.06, 45.45, 51.89, 61.95, 65.61, 65.93, 88.47, 130.13, 130.95, 152.04, 160.97. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_5$: 294.1314; found: 294.1344.

***Compound 9.*** Yellow oil (62%). IR (KBr): 927, 1138, 1252, 1705, 2925 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, 3 H, *J* = 7.2 Hz, signal for 1 H merged in it), 1.57 (d, 1 H, *J* = 11.4 Hz), 2.47 (m, 2 H), 2.89 (m, 2 H), 3.15–3.23 (m, 4 H), 3.44 (d, 1 H, *J* = 9.0 Hz), 3.30–4.38 (m, 2 H), 4.75 (d, 1 H, *J* = 9.0 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 14.07, 31.85, 38.42, 38.69, 43.48, 47.36, 48.48, 50.54, 51.40, 62.16, 85.82, 151.65, 159.94, 207.60. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_5$: 292.1185; found: 292.1197.

***Compound 8.*** Brown solid (72%), Mp 220–222°C. IR (KBr): 821, 957, 1160, 1339, 1499, 1585, 1724, 2991, 3337, 3653 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 6.9 and 7.2 Hz), 1.56 (d, 1 H, *J* = 9.9 Hz), 1.69 (d, 1 H, *J* = 9.9 Hz), 3.52 (d, 1 H, *J* = 8.4 Hz), 3.74 (s, 1 H), 3.77(s, 1 H), 4.25–4.29 (m, 2 H), 4.87 (d, 1 H, *J* = 8.4 Hz), 6.36 (d, 1 H, *J* = 8.7 Hz), 6.40 (d, 1 H, *J* = 8.7 Hz), 8.67(s, 1 H, $D_2O$ exch.), 8.70(s, 1 H, $D_2O$ exch.). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 14.03, 42.25, 42.76, 47.34, 56.81, 61.59, 90.53, 115.07, 115.53, 128.46, 133.05, 143.97, 144.71, 151.47, 160.21. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}NO_5$: 290.1028; found: 290.1020.

***Compound 6a.*** White solid (87%), Mp176–178°C. IR ($CHCl_3$): 1690, 1563, 1494, 1444 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, 1 H, *J* = 10.8 Hz), 1.47 (d, 1 H, *J* = 8.7 Hz), 1.58 (m, 2 H), 2.68 (s, 2 H), 2.95 (s, 1 H), 3.13-3.16 (m, 2 H), 3.43 (s, 2 H), 3.56 (d, 1 H, *J* = 8.4 Hz), 4.65 (d, 1 H, *J* = 8.4 Hz), 6.37 (s, 2 H), 7.40 (m, 3 H), 7.78 (m, 2 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 31.13, 42.81, 46.76, 49.05, 50.66, 50.73, 51.45, 52.32, 54.20, 54.49, 83.27, 126.94, 128.56, 128.85, 129.99, 135.34, 135.51, 56.35, 210.52, 212.39. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{23}H_{26}NO_3$: 360.1600; found: 360.1607 $[M^+ + H]$.

***Compound 6b.*** Off-white solid (50%), Mp 140–141°C. IR (KBr): 932, 1125, 1256, 1690, 1721, 2922, 2983 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.23–1.63 (m, 7 H), 2.04 (s, 2 H), 2.66 (m, 2 H), 3.11 (m, 2 H), 3.40 (m, 3 H), 4.33 (m, 2 H), 4.70 (d, 1 H, *J* = 9.0 Hz), 6.35 (s, 2 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 14.06, 29.69, 31.30, 42.91, 46.70, 48.88, 50.61, 51.07, 51.23, 52.16, 54.05, 54.31, 62.05, 85.93, 135.41, 135.49, 151.71, 160.05, 210.53, 210.77. HRMS (TOF, $ES^+$): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_5$: 356.1498 ; found: 356.1496.

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## REFERENCES AND NOTES

[1] (a) Padwa, A. 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, 1984; Vols. 1 and 2; (b) Gothelf, K. V.; Jorgensen, K. A. Chem Rev 1998, 98, 863.

[2] (a) Kozikowski, A. P. Acc Chem Res 1984, 17, 410; (b) Curran, D. P. Advances in Cycloaddition; Jai: Greenwich, 1988; Vol 1, pp 129–189; (c) Torsaq, K. B. G. Nitrile Oxides, Nitrones and Nitronates in organic synthesis; VCH: New York, 1988; (d) Kanemasa, S.; Tsuge, O. Heterocycles 1990, 30, 719; (e) Namboothiri, I. N. N.; Hasner, A. Topics in Current Chemistry; Springer-Verlog: Berlin, 2001, Vol. 216, pp 1–43.

[3] Taniguchi, H.; Ikeda, T.; Yoshida, Y.; Imoto, E. Bull Chem Soc Jpn 1977, 50, 2694.

[4] De Micheli, C.; Gandolfi, R.; Oberti, R. J Org Chem 1980, 45, 1209.

[5] (a) Bianchi, G. De Micheli, C. Gandolfi, R. In The Chemistry of Double-bonded Functional Groups; Patai, S., Eds.; Interscience: London, 1977, Supplement a, Part I, Chapter 6; (b) Huisgen, R.; Grashey, R.; Sauen, J. In The Chemsitry of Alkenes; Patai, S., Ed.; Interscience: London, 1964; Chapter 11.

[6] (a) Yip, C.; Handerson, S.; Jordan, R.; Tam, W. Org Lett 1999, 1, 791; (b) Yip, C.; Handerson, S.; Trammer, G. K., Tam, W. J Org Chem 2001, 66, 276; (c) Mayo, P.; Hecnar, T.; Tam, W. Tetrahedron 2001, 57, 5931.

[7] (a) Namboothiri, I. N. N.; Rastogi, N.; Ganguly, B.; Shaik, M. M.; Cojocaru, M. Tetrahedron 2004, 60, 1453; (b) Alder, K.; Stein, G. Angew Chem 1937, 50, 510; (c) Martin, J. G.; Hill, R. K. Chem Rev 1961, 61, 537.

[8] Wankhede, K.; Vaidya, V. V.; Haran, H.; Salunkhe, M. M.; Trivedi, G. K. Synth commun 2008, 38, 2402.

[9] Tanaka, K.; Masuda, H.; Mitsuhashi, K. Bull chem Soc Jpn 1986, 59, 3901.

[10] (a) Meinwald, J.; Wiley, G. A. J Am Chem Soc 1958, 80, 3667; (b) Cookson, R. C.; Hill, R. R.; Hudec, J. J Chem Soc 1964, 3043.

[11] Mehata, G.; Padma, S.; Pattachi, V.; Pramanik, A.; Chandrasekhar, J. J Am Chem Soc 1990, 112, 2942 and references cited therein.

[12] Conti, D.; Rodriquez, M.; Sega, A.; Taddei, M. Tetrahedron Lett 2003, 44, 5327.

# 5a,10b-Dihydrobenzofuro[2,3-b]benzofuran Type Compounds and Related Products from *p*-Substituted Phenols and Glyoxal



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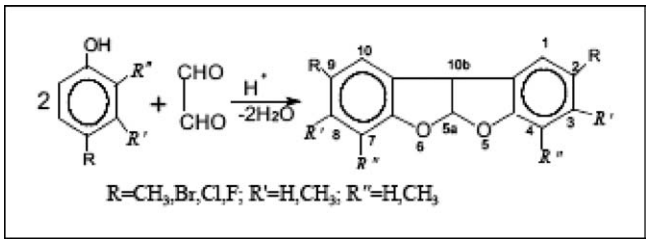


Condensation reactions of glyoxal with *p*-substituted phenol derivatives **1a–f** have been carried out and the corresponding 5a,10b-dihydrobenzofuro[2,3-b]benzofuran **4a–f** type compounds were obtained in good to excellent yields. The resulting dimeric products carrying methyl groups **4a–d** were converted to the corresponding carboxylic acid derivatives as the new polymer forming monomers. Many of these reactions gave novel structures. No definite product was obtained by the similar reactions of glyoxal with thiophenol and aniline in place of phenols.

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## INTRODUCTION

Some of dialdehydes and especially their synthetic equivalents are interesting reactive precursors in organic chemistry and are regarded as useful starting material for the preparation of the thermally stable polymers [1–9]. Condensation of unsubstituted phenols with glyoxal bisulfite or glyoxal has been reported to produce insoluble resins [10]. The reaction of 2-naphthol with glyoxal has been reported by Dischendorfer and assigned the reaction product after alkaline fusion as structure **5** with a benzofurobenzofuran moiety in its structure [8]. The preparation of novel aromatic compounds with one or two dihydrofurofuran moieties starting from 2-naphthol and glyoxal has been reported [11].

Recently, we have reported the possibility of using trifluoroacetic acid as suitable medium for the condensation of *p*-substituted phenolic compounds with malonaldehydetetramethyl acetal as very reactive protected dialdehyde [12]. In this context, we have also reported the synthesis of 1,1,4,4–tetrakis (2-hydroxyphenyl)butane type compounds from the condensation of phenols with 2,5-dimethoxytetrahydrofuran using trifluoroacetic acid as both solvent and catalyst [13]. In our previous studies, condensation reaction of *p*-substituted phenols with glutaraldehyde bisulfite in the presence of trifluoroacetic acid as both solvent and catalyst and formation of propano-dibenzo [2, 1 − *d* : 1′, 2′ −*g*] [1,3] dioxocin type compounds were reported [14].

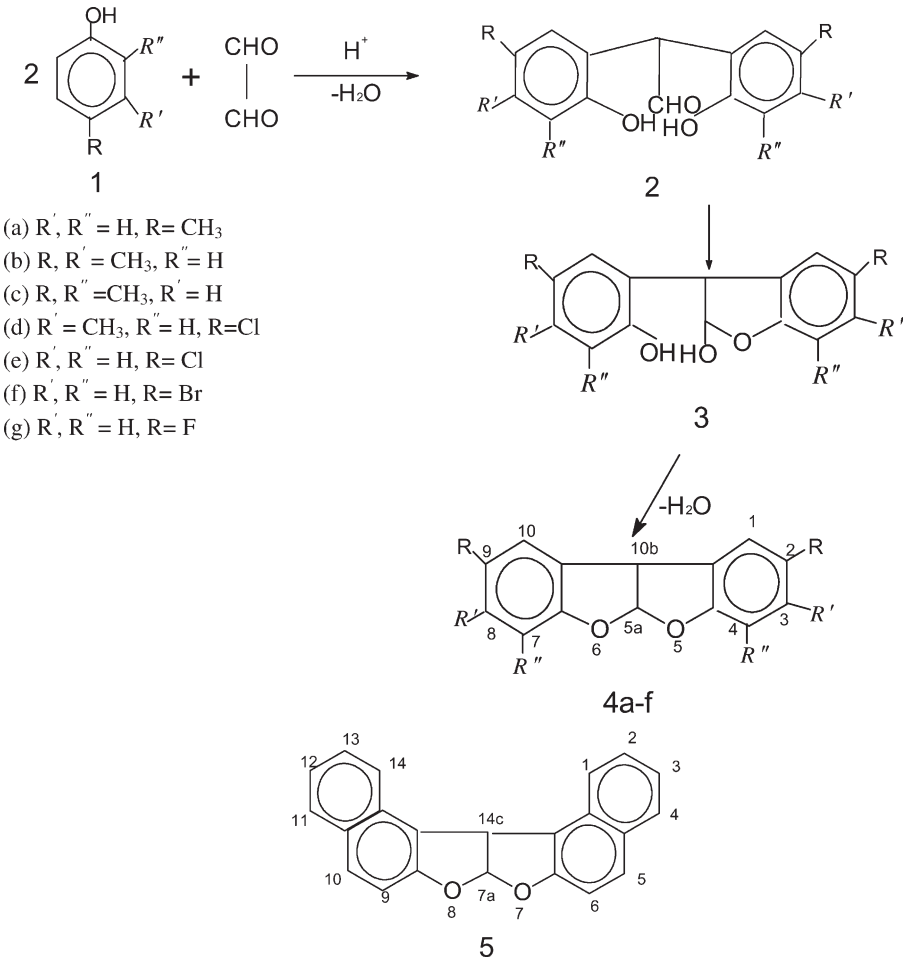
Condensation of 2-naphthol with glyoxal bisulfite in the presence of formic acid at 50–60°C has been shown to give dimeric product, namely 7a,14c-dihydronaphtho[2,1-b] naphtha [2′, 1′ : 5,6] furo[3,2-d] furan in only 22% yield [15]. The base catalyzed reaction of 2-naphthol with glyoxal was also investigated in which the final product was considered to be similar to that obtained from the acid catalyzed reaction [16–18].To the best of our knowledge, condensation reaction of *p*-substituted phenols with glyoxal has not been exploited for polymer forming monomers. However, the yield of formation of dimeric products was low and not enough for further transformations when we used sulphuric acid and formic acid as condensing agent [5,15,19].

To increase the yield in dimeric product and to examine more accurately the experimental conditions for the condensation reaction of *p*-substituted phenols and 2-naphthol with glyoxal and also in continuation of our research on the synthesis of thermally stable polymers from polymerisable monomers [20], we have also studied synthetic routes towards 5a,10b-dihydrobenzofuro[2,3-b]benzofuran type compounds as new model compounds and their related derivatives having suitable functional groups(e.g., dicarboxylicacid, dianhydride) which can be used as important monomers for the preparation of a variety of thermally stable polymers.

## RESULTS AND DISCUSSION

To study the possibility of using the reported method for condensation of 2-naphthol and glyxoalbisulfite with

**Scheme 1**




different phenols, we performed the reaction of phenols with glyoxalbisulfite under the reported conditions [15]. It was observed that this method cannot work for phenolic compounds. These observations led us to design another applied synthetic method for the condensation of *p*-substituted phenolic compounds with glyoxal. The possibility of condensation of different phenols with glyoxal bisulfite in acetic acid in the presence of sulfuric acid as catalyst were studied. Condensation of phenols with glyoxal bisulfite occurred and the corresponding 5a,10b-dihydrobenzofuro[2,3-b]benzofuran type compounds (**4a–f**) were obtained in low to moderate yields. To increase the yields of the products, we tried the same reactions using glyoxal solution in the presence of methane sulphonic acid as catalyst. The reaction of phenols carrying alkyl groups (**1a–c**) or having both alkyl and halogen (**4d**) gave excellent yields of their corresponding 5a,10b-dihydrobenzofuro [2, 3-b]benzofuran (**4a–f**). The reaction of phenols carrying only halogens (**1e,f**) gave moderate yields (Scheme 1).

For the study of structure–reactivity relationship, the reaction of *p*-substituted phenols having electron withdrawing substituents such as **1g** and 2,4-dichlorophenol with glyoxal under the same reaction condition was also investigated. No dimeric products as structure **4** with a benzofuro-benzofuran moiety (acetal type structure) in their structures were detected (Scheme 1). The results with the structurally different *p*-substituted phenolic compounds are shown in the Table 1.

It was found that the electron withdrawing groups retard the reaction and the electron donating substituents such as methyl were favorable in the reaction. These observations are in good agreement with the suggested mechanism as shown in Scheme 1.

We next decided to produce the dimeric product similar to that of **4a–f** but with sulfur or nitrogen in place of oxygen in the furan rings. However, we were not successful in using a similar reaction of glyoxal and thiophenols and/or aniline in place of phenols to reach our objective. No definite product was obtained by the reactions. When we treated glyoxal with aniline, for example, the expected product, a dihydroindole ring, was never produced. As is well-known, an amine and an aldehyde always react to produce a schiff base as a classical reaction.

**Table 1**

Reaction of phenolic compounds (**1a–f**) and 2-naphthol with glyoxal.

| Substrate | Method of preparation[a] | Reaction time (h) | Product (yield/%)[b] |
|---|---|---|---|
| **2-naphthol** | A | 1 | **5** (81) |
| | B | 1.5 | **5** (51) |
| **1a** | A | 1 | **4a** (86) |
| | B | 1.5 | **4a** (53) |
| **1b** | A | 1 | **4b** (83) |
| | B | 2.5 | **4b** (54) |
| **1c** | A | 1 | **4c** (81) |
| | B | 2.5 | **4c** (52) |
| **1d** | A | 1.5 | **4d** (80) |
| | B | 2 | **4d** (50) |
| **1e** | A | 1.5 | **4e** (28) |
| | B | 4 | **4e** (8) |
| **1f** | A | 2 | **4f** (29) |
| | B | 5 | **4f** (7) |
| **1g** | A | 2 | [c] |
| | B | 4 | – |

[a] A: glyoxal in $CH_3SO_3H$; B: glyoxalbisulfite in $H_2SO_4$.
[b] Yields refer to isolated products.
[c] No reaction.

Condensation of 2 moles of phenols (**1a–f**) with glyoxal solution and bisulfite occurs first through Friedel-Crafts reaction (one carbonyl group) to give **2** followed by an intramolecular acetalization reaction as suggested for the condensation of phenols with malonaldehyde tetramethyl acetal, 2,5-dimethoxytetrahydrofuran and glutaraldehyde [12–14], (Scheme 1).

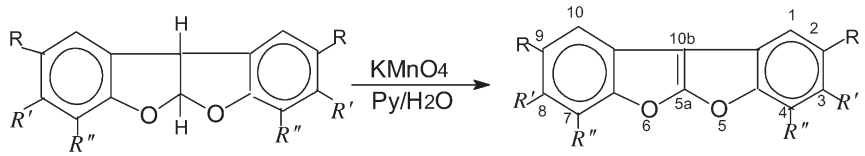
The structure of all compounds **4a–f, 5** were deduced from their IR, $^1$H, $^{13}$C-NMR and mass spectral data. The IR spectra show no carbonyl and hydroxyl groups. In all cases, the $^1$H-NMR spectra indicated that the compounds had the acetal structure. The spectra of all these compounds showed a doublet ($J$ = 6–7 Hz) in the region δ 4.8–5.82 (assigned to the hydrogen on the diarylmethyl carbon (10b-H), (14c-H) and a doublet ($J$ = 6–7 Hz) in the region δ 6.8–7 ppm assigned to the hydrogen on the acetal carbon (5a-H), (7a-H). The $^{13}$C-NMR spectra show two aliphatic resonances for the diaryl methyl (10b-C, 14C) in the region δ 48–50.85 and acetal carbons (5a-C, 7a-C) at region δ 111–112.4 ppm respectively, consistent with the overall mirror symmetry. In all of these compounds (**4a–f**,**5**) bands arising from the aromatic protons partially overlapped the doublet assigned to the hydrogen on the acetal carbon. It was found that, by expanding the NMR spectra in the aromatic region, the acetal hydrogen doublet was clearly separated from the bands attributed to the aromatic protons, and that overlapping was removed.

In conclusion, the simplicity of this method, good to excellent yields, readily available starting materials and the possibility of applying this method to phenols and naphthols make this method very useful for this type of transformation in organic synthesis.

To prepare the polymer forming monomers from dimeric products having two and tetramethyl groups (**4a–d**), we performed the ordinary aromatic side chain oxidation reaction of **4a–d** using $KMnO_4$ in the next stage. It was observed that the resulting reaction products had structures different from to that of our expected and a surprising result was obtained. Spectral investigations showed that aromatization had occurred in the products (**6a–d**) in addition to oxidation of the methyl groups as shown in Scheme 2.

The IR spectra of the compounds **6a–d** showed broad absorption bands around 2530–3500 (acidic H,s) and the acidic C=O stretching absorption in the region 1680–1715 cm$^{-1}$, confirming the presence of carboxylic acid groups in the structures. The $^1$H-NMR spectra showed no peaks associated with methyl groups and no doublets around 4.88–4.92 ppm for diaryl methyl protons (10b). There appeared only a complicated collection of peaks around the aromatic hydrogen region in the $^1$H-NMR spectra of the products. In other words, using $KMnO_4$ as an oxidizing agent causes a dehydrogenation reaction on 5a and 10b hydrogens which leads to the production of diacids **6a**, **6d** and tetra acids **6a**, **6c**, respectively. The tetra acid (**6b**) did not melt, but it underwent thermal

**Scheme 2**



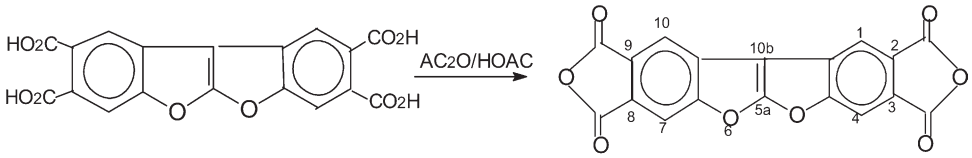

4

a) R′,R″ = H, R= $CH_3$
b) R, R′= $CH_3$,R″= H
c) R,R″ = $CH_3$, R'= H
d) R′ = $CH_3$,R″ =H, R= Cl

6

a) R′,R″ =H, R = $CO_2H$
b) R, R′= $CO_2H$, R″ =H
c) R, R″ = $CO_2H$ , R′ = H
d) R′ =$CO_2H$, R"= H, R = Cl

**Scheme 3**




**6b** **7**

cyclodehydration to the dianhydride. The $^1$H-NMR also show a peak in the region 12.8–13 ppm assigned to the acidic protons.

All the evidence, ie., no peaks for the 10b and 5a hydrogens in $^1$H-NMR spectra and a twofold difference between our expected molecular weights and that of experimental results in GC-MS, led us to the conclusion that the exact structures for the oxidation reaction products must be as structures **6a–d**, a series of molecules with fully aromatic structures (Scheme 2).

Finally, the dianhydride (**7**) was prepared by dehydration of the tetra acid (**6a**) in acetic acid and acetic anhydride (Scheme 3).

After compound **6b** was dehydrated into dianhydride **7**, the absorption bands of O—H and C=O stretching disappeared and the characteristic absorptions of the C=O groups in cyclic anhydride were observed at 1851 (asymmetric stretching) and 1782 (symmetric stretching) $cm^{-1}$, hence confirming the presence of an anhydride ring in the structure. The $^1$H-NMR spectrum of dianhydride (**7**) showed no acidic protons, and the remaining protons were only aromatic hydrogens. The mass spectral data completed the structural confirmation of dianhydride **7** in which the peak appeared at m/z 348 ($MH^+$, 100%)

In conclusion, we successfully prepared a series of new wholly aromatic polymer forming monomers from a relatively cheap raw material and through a high yield route, that involves the use of common, in expensive reagents. Specially, because of their complete aromatic structures, these monomers may be the good candidates in the synthesis of several types of heat stable polymers such as polyimide, polyamide, polyesters, polybenzimidazoles, etc. Synthesis and study of the corresponding polymers derived from the diacids (**6a**, **6d**) and dianhydride (**7**) and the preparation of their derivatives having several types of functional groups, to reach some kinds of polymers are underway and the results will be reported soon.

## EXPERIMENTAL

**Materials and instruments.** Solvents and chemical materials were obtained from Merck chemical company (Germany) and Fluka(Switzerland). Melting points were determined with a Buchi 535 melting point apparatus. IR and FTIR spectra were recorded using a Perkin–Elmer 781 and Unicam Matteson 1000 spectrometers, respectively. UV spectra were recorded on a Pharmacia biotech ultra spec 3000 model 80-2106-20 spectrometer. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a 250 MHz Bruker Avance DPX-250 and 400 MHz Bruker spectrometers using tetramethyl silane (TMS) as an internal standard at 25°C with frequencies of 400, 250, and 62.9 MHz for the $^1$H and $^{13}$C spectra, respectively. Mass spectra were recorded under electron impact at 70eV on a shimadzu GCMS-QP1000 Ex instrument. Elemental analysis was performed by RIPI.

**Glyoxal bisulfite.** To a solution of sodium bisulfite (30%) was added glyoxal in 2/1 mole ratio at room temperature. The bisulfite adduct was precipitated by addition of ethanol to the solution and dried *in vacuo* at 60°C.

**General procedures for (4a–f).** ***Method A.*** To a 500 mL round bottomed flask was charged with phenolic compound (**1a–f**) (0.10 mol) glyoxal, (0.05 mol of a 30% aqueous solution) and acetic acid (100 mL). The mixture was dissolved in acetic acid. Methane sulphonic acid (25–30 mL) was added drop by drop, with stirring, the temperature of the reaction mixture being kept between 30 and 35°C. During the addition of the methane sulphonic acid (20–50 min) the acetal began to precipitate from solution. The mixture was then stirred at 30–35°C until the total time of addition and stirring 1–2 h. The cooled reaction mixture was then poured into water (500 mL), and the crude product was collected by filtration and wash with water and ethanol. Details concerning the purification of each individual reaction product are given under the appropriate title in the following part of the experimental.

***Method B.*** In a fume cupboard, to a 500 mL round bottomed flask with a hot water bath $H_2O$ (150 mL), acetic acid (70 mL), glyoxal bisulfite(13 g, 0.05 mol) and phenolic compounds (**1a–f**) (0.1 mol) were added. The glyoxalbisulfite was dissolved upon stirring and increasing the temperature. After the temperature reached 80°C, concentrated sulfuric acid (40–45 mL) was added drop by drop and the temperature of the reaction mixture was kept between 85 and 90°C. During the addition of sulfuric acid (40–60 min) the reaction product began to precipitate from solution. The mixture was then stirred at 85–90°C until the total time of addition and stirring was 1.5–4 h. The cooled reaction mixture was filtered and the crude product was then poured into water (500 mL), collected by filtration and washed with water and ethanol. Reaction products were purified by appropriate methods specified below.

**2,9-Dimethyl-5a,10b-dihydrobenzofuro[2,3-b]benzofuran (4a). 4a** was obtained from **1a** and glyoxal following the general procedure and purified by recrystallizing from ethanol to give white solid; mp = 195–196°C(lit., 195°C, [6]); [Found: C, 80.50;

H, 5.84 $C_{16}H_{14}O_2$ requires C,80.67; H,5.88%]; UV($CH_2Cl_2$) λ 293.3 ($\varepsilon_{max}$ = 32440), 234.5 ($\varepsilon_{max}$ = 18940) $\nu_{max}$ (KBr) 2820–3030, 1245, 1185, 1000 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 2.31 (6*H,s*, *CH*$_3$), 4.81(1H, d, *J* 6.46 Hz, 10b-*H*), 6.81(1H, d, *J* 6.50 Hz, 5a-*H*), 6.61–7.20 (6H, m, Ar*H*); $\delta_C$ (62.9 MHz, $CDCl_3$)19.40 (*C*H$_3$), 50.10(10b-*C*), 111.60 (5a-*C*), 118.71, 122.65, 127.45, 131.65, 133.42(aromatic*C*), 157.05(=*C*O); m/z (EI) 238(100, $MH^+$), 195 (39.4), 165(18.1%)

**2,3,8,9-Tetramethyl-5a,10b-dihydrobenzofuro[2,3-b]benzofuran (4b). 4b** was obtained from **1b** and glyoxal following the general procedure and purified by recrystallizing from ethanol or acetic acid to give white solid; mp = 233–234°C; [Found: C, 81.16; H, 6.78 $C_{18}$ $H_{18}$ $O_2$ requires C, 81.20; H, 6.76%]; UV ($CH_2Cl_2$) λ 295.3 ($\varepsilon_{max}$ = 31140), 237.5 ($\varepsilon_{max}$ = 14940); $\nu_{max}$ (KBr) 3010–2900, 1260, 1160, 1055, 1000 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 2.165 (6*H, s* − *CH*$_3$), 2.18 (6*H, s* − *CH*$_3$), 4.88(1H, d, *J* 6.45 Hz, 10b*H*), 6.81(1H,d, *J* 6.48 Hz, 5a-*H*), 6.67(2H, s, Ar*H*), 7.10(2H, s, Ar*H*); $\delta_C$ (62.9MHz, $CDCl_3$)19.38, and 20.06 (*CH*$_3$), 50.20(10b–C),111.57(5a-*C*), 112.99, 124.56, 124.72, 130.18, 137.39(aromatic*C*), 156.03(=*C*O); m/z(EI)266 (100,$MH^+$), 251(16.3), 223(15.1), 208(29), 179(4.8), 165(5.3), 118(47), 69(45), 55(29), 40(100%).

**2,4,7,9-Tetramethyl-5a,10b-dihydrobenzofuro[2,3-b]benzofuran (4c).** (**4c**) was obtained from **1c** and glyoxal following the general procedure and purified by refluxing in ethanol and recrystallizing from acetic acid to give white solid; mp = 206–207°C(lit., 206°C, [6]); [Found: C, 81.19; H, 6.81. $C_{18}H_{18}O_2$ requires C, 81.20; H, 6.76%]; UV ($CH_2Cl_2$) 293.8 ($\varepsilon_{max}$ = 27,080), 233.7 ($\varepsilon_{max}$ = 28,200); $\nu_{max}$(KBr)3000-2900, 1210, 1135, 1075, 975 $cm^{-1}$; $\delta_H$(250MHz, $CDCl_3$) 2.23(6H, s,C*H*, 2.28(6H, s, *CH*$_3$), 4.91(1H, d, *J* 6.47 Hz, 10b-*H*), 6.86(1H, d, *J* 6.71Hz, 5a-*H*), 6.78 (2H, s, Ar*H*), 7.01(2H, s, Ar*H*); $\delta_c$ (62.9 MHz, $CDCl_3$) 15.03 and 20.77(*C*H$_3$), 50.85(10b-*C*), 111.80 (5a-*C*),19.81, 121.65, 126.61, 130.77, 132.45 (aromatic*C*),154.13(=*C*O); m/z(EI) 266 (100, $MH^+$), 251(39), 223(25.1), 179(14.8), 165(15.2) 118(52), 69(42), 55(22), 40(100%).

**2,9-Dichloro-3,8-dimethyl-5a,10b-dihydrobenzofuro[2,3-b]benzofuran (4d). 4d** was obtained from **1d** and glyoxal following the general procedure except that only 0.1 mole of glyoxal (rather than 0.05 mole) was used and purified by recrystallizing from acetic acid or tetrahydrofuran to give white solid; mp = 255–256 °C; [Found: C, 62.46; H, 3.76. $C_{16}$ $H_{12}Cl_2O_2$ requires C,62.54; H,3.908%]; UV ($CH_2$ $Cl_2$) λ 298.6($\varepsilon_{max}$ =12720), λ237.3($\varepsilon_{max}$ = 1040); $\nu_{max}$ (KBr)2990-2900, 1245, 1120, 1015, 975 $cm^{-1}$; $\delta_H$ (250 MHz,$CDCl_3$) 2.29(6*H,s*, *CH*$_3$), 4.92(1H, d, *J* 6.42Hz,10b-*H*, 6.86(1H, d, *J* 6Hz, 5a-*H*, 6.76 (2H, s,Ar*H*,7.29 (2H, s, Ar*H*); $\delta_c$ (62.9MHz,$CDCl_3$) 20.48(*C*H$_3$), 49.81 (10b-*C*), 112.39(5a-*C*),113.33, 125.84, 126.9, 129.87, 137.02 (aromatic*C*), 156.46(=*C*O); m/z (EI) 307(22.9, $MH^+$),308(65.1, $MH^+$+1), 309(9.90, $MH^+$+2), 310(9, $MH^+$+3), 306(100), 271(30.4), 243 (35.2), 208 (14.8), 180(10.5), 179(15.4), 165(22.6), 76(28.3), 51(50.9%).

**2,9-Dichloro-5a,10b-dihydrobenzofuro[2,3-b]benzofuran (4e). 4e** was obtained from **1e** and glyoxal following the general procedure, except that only 0.1 mole of glyoxal(rather than 0.05 mole)was used and purified by recrystallizing from acetic acid to give white solid; mp = 233–234°C (lit., 233–234°C, [5,6]); [Found: C, 60.10; H, 2.69. $C_{14}H_8Cl_2O_2$ requires C, 60.215; H, 2.867%]; UV ($CH_2Cl_2$) λ 298.6 ($\varepsilon_{max}$ = 17400), 233($\varepsilon_{max}$ =24110); $\nu_{max}$ (KBr) 2970, 1235, 1105, 1065, 975 $cm^{-1}$; $\delta_H$ (250 MHz, $CDCl_3$) 4.91 (1H, d, *J* 6.43Hz,10b-*H*), 6.48 (1H, d, *J* 6.73 Hz, 5a-*H*), 6.73–7.30 (6H, m, Ar*H*); m/z (EI) 278 (100, $MH^+$), 279 (14, $MH^+$+1) 280(65.8, $MH^+$+2), 243(28.8), 215(84.9), 217(26), 197(13.7), 169(53.4) 152(63), 89(28.8), 75(53.4), 63(57.5%).

**2,9-Dibromo-5a,10b-dihydrobenzofuro[2,3-b]benzofuran (4f). 4f** was obtained from **1f** and glyoxal following the general procedure, except that only 0.1 mole of glyoxal(rather than 0.05 mole)was used and purified by refluxing in ethanol and recrystallizing from acetic acid to give white solid; mp = 255–256°C, [Found: C, 44.30; H,2.18. $C_{14}H_8$ $Br_2O_2$ requires C, 45.652; H, 2.174%]; UV($CH_2Cl_2$) λ 298 ($\varepsilon_{max}$ = 29150), 244 ($\varepsilon_{max}$ = 28660); $\nu_{max}$ (KBr) 2955, 1230, 1105, 1025, 985 $cm^{-1}$; $\delta_H$(250 MHz, $CDCl_3$), 4.93(1H, d, *J* 7Hz, 10b-*H*, 6.82(1H, d, *J* 6.56Hz, 5a-*H*, 7.19–7.40 (6 H, m, Ar*H*; m/z (EI) 368(67.1, $MH^+$), 369 (9, *MH*$^+$ + 1), 370(32.1, $MH^+$+2), 371(2.6, $MH^+$+3), 366(33.8), 289(10.7), 287(10.3), 261(23.9), 259(25.2), 208(28.6), 180(44), 152(63.2), 134(20.1), 89(39.7), 76(73.5), 63 (100%).

**7a,14c-Dihydronaphtho[2,1-b]naphtho[2′,1′:5,6]furo[3,2-d]furan (5).** This compound has been obtained from the reaction of 2-naphthol with glyoxal following the general procedure and purified by recrystallizing from acetic acid or acetone to give white solid; mp = 236–237°C (lit., 236–237°C, [15,6]); [Found; C; 85.13; H,4.60. $C_{22}H_{14}O_2$ requires C, 85.14; H, 4.55%]; $\nu_{max}$ (KBr)845,805,735 $cm^{-1}$; $\delta_H$ (250 MHz, DMSO-$d_6$) 5.82 (1H, d, *J* 6 Hz, 14c-*H*), 7.20–8.40 (13H, m, ArH + 7a-*H*); $\delta_c$ (62.9 MHz, DMSO-$d_6$) 48.5 (d, 14c-*C*), 111.5, 114.4, 118.6, 122.9, 123.3, 126.4, 128.7, 129.5, 129.7, 130.1, 155.6 (aromatic *C*+7a-*C*); m/z (EI) 310(100, $MH^+$), 281(39%).

**General procedure for 6a–d.** A two-necked round bottomed flask with an effective stirrer, was charged with a solution of **6a–d** (0.032 mol) in a mixture of pyridine (200 mL) and water (100 mL). The temperature was elevated to near refluxing and $KMnO_4$ (0.29–0.58 mol) was added in small portions. Refluxing was continued for 8–24 h. After cooling to room temperature, the mixture was filtered and the residual $MnO_2$ was washed thoroughly with boiling water. The combined filtrates in an ice-water bath were acidified with hydrochloric acid. The white solid precipitate was filtered off, washed several times with water, and dried to afford **6a–d**. The products were purified by appropriate methods specified below.

**Benzofuro [2,3-b]benzofuran-2,3,8,10tetracarboxylic dianhydride(7).** In a 500 mL round bottomed flask, 8.7 g (0.025 mol) of tetra acid **6b** was suspended in 100 mL of glacial acetic acid and 200 mL of acetic anhydride. The mixture was boiled under reflux for 4h. Then, the mixture was filtered and left to crystallized overnight. The precipitated product was filtered out, washed with dry toluene, and dried to give white solid in 86% yield; [Found: C, 61.891; H,1.11. $C_{18}H_4O_8$ requires C, 62.08; H, 1.10%]; $\nu_{max}$ (KBr) 3125, 3051, 1858 (asym. C=O str.), 1780 (sym. C=O str.), 1629, 1439, 1185, 1152, 1130, 885 (C—O str.) $cm^{-1}$; $\delta_H$ (250MHz, DMSO-$d_6$) 8.78-8.32(s, 4H, Ar).

**Benzofuro[2,3-b]benzofuran-2,9-dicarboxylic acid (6a). 6a** was obtained from oxidation of **4a** with $KMnO_4$ (45.82g) in a 2:1 (v/v) pyridine: water mixture by heating to gentle reflux for 8h, following the general procedure and purified by recrystallizing from dilute ethanol to give white solid in 81 %yield; mp>300°C (lit. [19]); $\nu_{max}$(KBr) 3500-2800, 1680 (C=O str.), 1450, 1237, 1157 $cm^{-1}$; $\delta_H$ (400MHz, DMSO-$d_6$) 12.92(2H,

s,-O*H* ), 6.8–8.20(6H, m, Ar*H* ); m/z (EI) 296(100, $MH^+$), 269(45.8), 241(75.1%);

**Benzofuro[2,3-b]benzofuran-2,3,8,9-tetracarboxylic acid (6b). 6b** was obtained from oxidation of **4b** with $KMnO_4$ (91.649) in a 2:1 (v/v) pyridine: water mixture by heating to gentle reflux for 24h, following the general procedure and purified by recrystallizing from a mixture of ethanol/water(2:1 v/v) to give white solid in 82% yield; mp>300°C;[Found: C, 55.89; H, 2.791. $C_{18}H_8O_{10}$ requires C, 56.25; H, 2.783%], $\nu_{max}$ (KBr) 3445-2530, 1710(C═O str.), 1609, 1482, 1422(C─O str.), 1264 $cm^{-1}$; $\delta_H$(400MHz, DMSO-$d_6$) 12.81(4H, s, ─O*H*), 6.80–8.80 (4H, m, Ar*H*); m/z (EI) 366(84.6), 348 (94.5), 322 (27.2), 304 (32.6), 276 (95.7), 232 (14.5), 204 (48.6), 148 (35.8), 116(21.2), 98(62. 4), 74(100), 44(77.7%).

**Benzofuro[2,3-b]benzofuran–2,4,7,9-tetracarboxylic acid (6c). 6c** was obtained from oxidation of **4c** with $KMnO_4$(91.64g) in a 2:1(v/v) pyridine : water mixture by heating to gentle reflux for 24 h, following the general procedure and purified by recrystallizing from mixture of DMF/water (2:1 v/v) to give white solid in 84% yield; mp > 300°C;[Found: C, 56.89;H, 2.61. $C_{18}$ $H_8$ $O_{10}$ requires C, 56.25; H, 2.783%]; $\nu_{max}$ (KBr) 3450-2530, 1715 (C═O str.), 1609, 1482, 1450, 1421(C─O str.), 1265 $cm^{-1}$; $\delta_H$ (400 MHz, DMSO-$d_6$) 13(4H, s, ─O*H*), 6.80–8.80 (4H, m, Ar-*H*); m/z(EI) 384 (29.1, $MH^+$), 322(27), 294(23.9), 276(9.2), 266(15.9), 232(16.6), 204(41), 194(14.1), 166 (12.8), 98 (21), 79(100), 52(97%).

**2,9-Dichloro-benzofuro[2,3-b]benzofuran-3,8-dicarboxylic acid(6d). 6d** was obtained from oxidation of **4d** with $KMnO_4$ (55.4g) in a 2:1 (v/v) pyridine: water mixture by heating to gentle reflux for 12 h, following the general procedure and purified by recrystallizing from mixture of DMAc/water (2:1 v/v) to give white solid in 83% yield; mp>300 °C; [Found: C, 62.15; H, 3.32. $C_{16}H_{10}O_2Cl_2$ requires C, 62.95; H, 3.2787%]; $\nu_{max}$ (KBr) 3450-2800, 1695 (C═O str.), 1605, 1465, 1451,1425(C─O str.), 1240, 1145 $cm^{-1}$; $\delta_H$(400MHz, DMSO-d6) 13(2H, s-O*H*), 6.85–8.35(4H, m, Ar*H*); m/z(EI)305 (81,$MH^+$), 306(19, $MH^+$+1), 307(12.7, $MH^+$+2), 308 (9.1, $MH^+$+3), 261(100), 243(56), 217(41), 208(19), 180(29), 165(24), 76(32.2%).

## REFERENCES AND NOTES


[1] Mitsunobu, O.; Yamada, M. Bull Chem Soc Jpn 1967, 40, 2380.

[2] Weis, A. L.; Rosenbach, V. Tetrahedron Lett 1981, 22, 1453.

[3] Kashima, C.; Hibi, S.; Maruyama, T.; Omote, Y. Tetrahedron Lett 1986, 27, 2131.

[4] Kashima, C.; Hibi, S.; Maruyama, T.; Harada, K.; Omote, Y. J Heterocycl Chem 1987, 24, 913.

[5] Coxwoth, E. C. M. Can J Chem 1967, 45, 1777.

[6] Layer, R. W. J Heterocyclic Chem 1975, 12, 1067.

[7] Rosenthal, A.; Zaionchkovsky, A. Can J Chem 1960, 38, 2277.

[8] Dischendorfer, O. Monatsh 1940, 73, 45.

[9] Maravigna, P. J Polym Sci Chem Ed 1988, 26, 2475.

[10] Stevens, D. R.; Dobbs, A. C. U.S. Patent 2,515, 909 ( 1950); Chem Abstr 1950, 44, 9483.

[11] Fan, X.; Yanai, T.; Okazaki, H.; Yamaye, M.; Mizobe, H.; Kosugi, Y.; Kito, T. J Org Chem 1995, 60, 5407.

[12] Rahmatpour, A.; Banihashemi, A. Tetrahedron 1999, 55, 7271.

[13] Rahmatpour, A.; Banihashemi, A. J Chem Res 1999, 6, 390.

[14] Rahmatpour, A. J Chem Res 2002, 2, 118.

[15] Acuner Tunca, A.; Talinli, N.; Akar, A. Tetrahedron 1995, 51, 2109.

[16] Kito, T.; Yoshinaga, K.; Yamaye, M.; Mizobe, H. J Org Chem 1991, 56, 3336.

[17] Clerici, A.; Porta, O.; Arnone, A. J Org Chem 1990, 55, 1240.

[18] Fan, X.; Yamaye, M.; Kosugi, Y.; Okazaki, H.; Mizobe, H.; Yanai, T.; Kito, T. J Chem Soc Perkin Trans 2 1994, 2001.

[19] Banihashemi, A.; Pourabbas, B. Iran Polym J 1996, 5, 145.

[20] Rahmatpour, A. Polym Int, submitted.

# Three-Step Synthesis of 2,4-Diaryl-5,6,7,8-tetrahydroquinoline Derivatives

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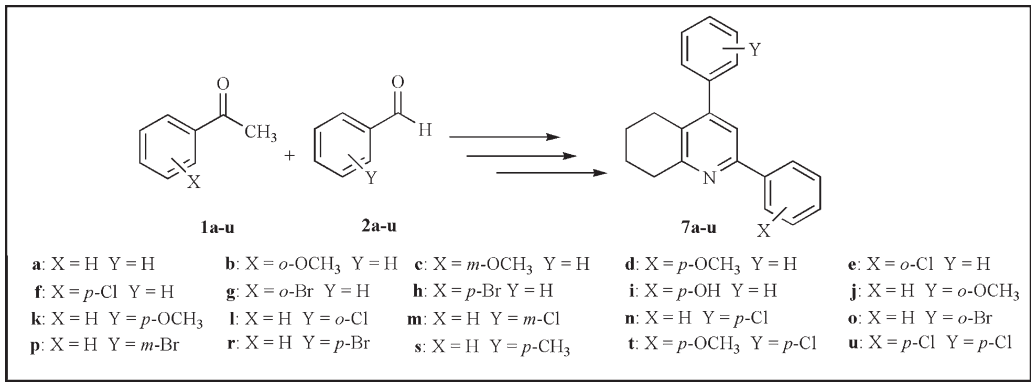


Addition of cylohexanone to chalcones, obtained from the appropriate acetophenone and benzaldehyde derivatives, under solvent-free conditions gave 1,5-diketones in good yields. Treatment of 1,5-diketones with ammonium acetate in acetic acid afforded directly 2,4-diaryl-5,6,7,8-tetrahydroquinoline derivatives **(7a–u)** in high yields. The structures of **7a–u** were elucidated by $^{1}$H NMR, $^{13}$C NMR, IR, and elemental analysis.

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## INTRODUCTION

The synthesis of oxygen, nitrogen, or sulfur-containing heterocycles is of importance in the organic and medicinal chemistry [1]. Among these structures, quinolines [2], tetrahydroquinolines [3], and their derivatives are excellent precursor of potential drugs [4]. Quinoline and their derivatives, which usually possess diverse biological activities, play important roles as versatile building blocks for the synthesis of natural products and as therapeutic agents [5]. In particular, 2-arylquinolines are biologically active and occur in structures of a number of antimalarial compounds and antitumor agents [6]. The biological activity of quinoline compounds has been found to possess antiasthmatic, antibacterial, antianflammatory, and antihypertensive properties [7]. Therefore, the synthesis of quinolines has attracted much attention in organic synthesis. The classic methods for the synthesis of quinolines include Skraup [8], Doebner-Von Miller [9], Conrad and Limbach [10], Combes [11], and Pfizinger [12] quinoline syntheses. A number of general synthetic methods have also been reported [13]. However, some of these methods suffer from several disadvantages such as harsh reaction conditions, multi steps, a large amount of promoters, and long reaction time [14].

In this study, we report that the synthesis of novel 2,4-diaryl-5,6,7,8-tetrahydroquinoline derivatives **7a–u** via cyclization of 1,5-diketones **5a–u** with ammonium acetate in acetic acid.

## RESULTS AND DISCUSSION

The general synthetic strategy used to prepare the chalcone derivatives (**3a–u**) was based on Claisen-Schmidt condensation, which was reported previously [15]. Chalcone derivatives (**3a–u**) were prepared by base-catalyzed condensation of appropriate substituted acetophenone with benzaldehyde in good yields (Scheme 1). All chalcone derivatives (**3a–u**) are well-known [16–26] according to our literature surveys. The structures of **3a–u** were characterized on the basis of spectral data (IR, $^{1}$H NMR, and $^{13}$C NMR) and comparison with authentic samples. After the structures of **3a–u** were determined, they were submitted to additional reaction of cyclohexanone (**4**). Addition of cyclohexanone to chalcones was performed according to our previously published method [27] in the presence of PTC (phase transfer catalyst = triethylammonium chloride) in solvent-free conditions. 1,5-Diketone derivatives **5a–u** were obtained in moderate to good yields (Scheme 1,

**Scheme 1**

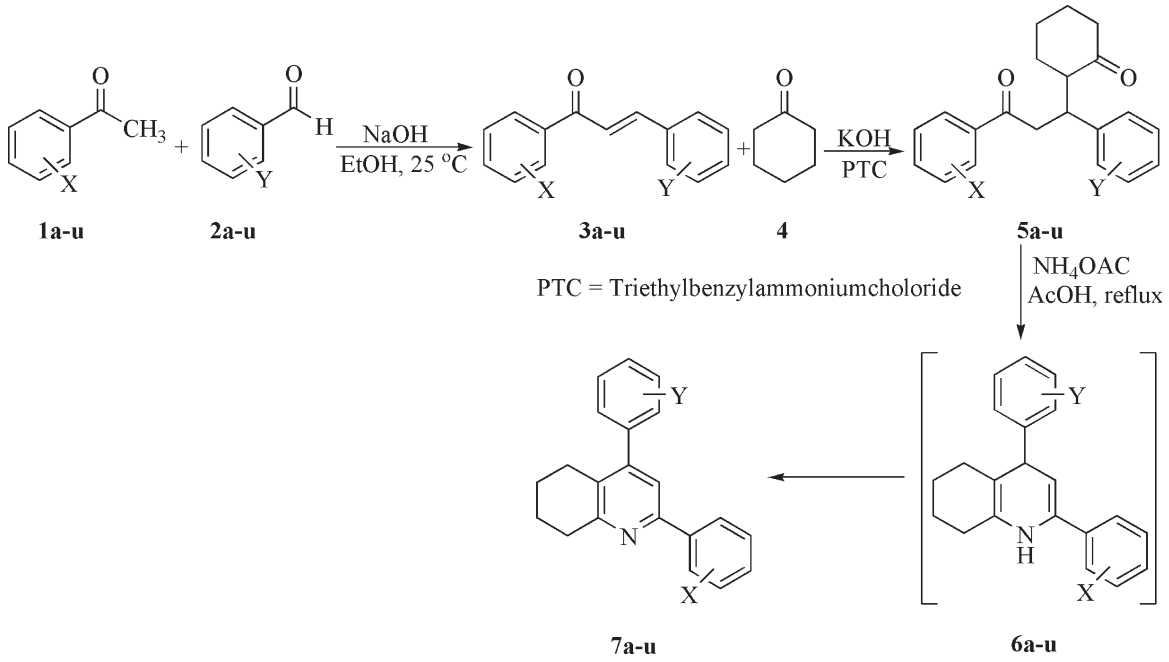


Table 1). In this series, the compounds **5a–g** are known in the literature [21,27–29]. The structures of other 1,5-diketones (**5h–u**) were determined by spectroscopic studies ($^1$H, $^{13}$C NMR, IR, and elemental analysis). In the $^1$H NMR spectrum of **5a–h**, the protons of $PhCOCH_2$ gave an AB system that is characteristic signals for these compounds. While part A of the AB system is shown as a doublet of doublet at $\delta = 3.50–3.42$ ($J = 15.7–16.7$ and 3.9–4.5 Hz) and that of part B is shown as a doublet of doublet at $\delta = 3.23–3.15$ ($J = 15.7–16.7$ and 9.5–9.6 Hz).

Treatment of 1,5-diketones **5a–u** with $NH_4OAc$ (ammonium acetate) in AcOH at reflux condition for 2.5–5 h afforded directly 2,4-diaryl-5,6,7,8-tetrahydroquinoline derivatives **7a–u** in excellent yields (Scheme 1, Table 2). The compounds **7a–u** were purified by column chromatography (on a silica gel) eluting $CHCl_3$/*n*-hexane (1:1).

**Table 1**

Synthesized 1,5-diketones (**5a–u**).

| Entry | Products | X | Y | Yield (%) |
|---|---|---|---|---|
| 1 | **5a** | H | H | 83 |
| 2 | **5b** | 2-$OCH_3$ | H | 40 |
| 3 | **5c** | 3-$OCH_3$ | H | 78 |
| 4 | **5d** | 4-$OCH_3$ | H | 78 |
| 5 | **5e** | 2-Cl | H | 65 |
| 6 | **5f** | 4-Cl | H | 72 |
| 7 | **5g** | 2-Br | H | 63 |
| 8 | **5h** | 4-Br | H | 56 |
| 9 | **5i** | 4-OH | H | 66 |
| 10 | **5j** | H | 2-$OCH_3$ | 77 |
| 11 | **5k** | H | 4-$OCH_3$ | 50 |
| 12 | **5l** | H | 2-Cl | 69 |
| 13 | **5m** | H | 3-Cl | 60 |
| 14 | **5n** | H | 4-Cl | 60 |
| 15 | **5o** | H | 2-Br | 50 |
| 16 | **5p** | H | 3-Br | 70 |
| 17 | **5r** | H | 4-Br | 90 |
| 18 | **5s** | H | 4-$CH_3$ | 94 |
| 19 | **5t** | 4-$OCH_3$ | 4-Cl | 97 |
| 20 | **5u** | 4-Cl | 4-Cl | 75 |

**Table 2**

Synthesized 2,4-diaryl-5,6,7,8-tetrahydroquinoline derivatives (**7a–u**).

| Entry | Products | X | Y | Yield (%) |
|---|---|---|---|---|
| 1 | **7a** | H | H | 82 |
| 2 | **7b** | 2-$OCH_3$ | H | 99 |
| 3 | **7c** | 3-$OCH_3$ | H | 83 |
| 4 | **7d** | 4-$OCH_3$ | H | 86 |
| 5 | **7e** | 2-Cl | H | 94 |
| 6 | **7f** | 4-Cl | H | 98 |
| 7 | **7g** | 2-Br | H | 66 |
| 8 | **7h** | 4-Br | H | 92 |
| 9 | **7i** | 4-OH | H | 80 |
| 10 | **7j** | H | 2-$OCH_3$ | 88 |
| 11 | **7k** | H | 4-$OCH_3$ | 71 |
| 12 | **7l** | H | 2-Cl | 87 |
| 13 | **7m** | H | 3-Cl | 99 |
| 14 | **7n** | H | 4-Cl | 90 |
| 15 | **7o** | H | 2-Br | 82 |
| 16 | **7p** | H | 3-Br | 98 |
| 17 | **7r** | H | 4-Br | 94 |
| 18 | **7s** | H | 4-$CH_3$ | 81 |
| 19 | **7t** | 4-$OCH_3$ | 4-Cl | 90 |
| 20 | **7u** | 4-Cl | 4-Cl | 97 |

Structures of **7a–u** were confirmed by their spectral (IR, NMR, and elemental analyses) data. In the $^1$H NMR spectrum of **7a–u**, the H4 proton gave a singlet (between $\delta = 7.60$ and 7.30 ppm) that is characteristic signals for these compounds. All spectral data are consistent with the titled compounds.

In conclusion, we have described a mild, efficient, and convenient method for the synthesis of 2,4-diaryl-5,6,7,8-tetrahydroquinoline derivatives from cheap and easily available materials such as acetophenone and benzaldehyde derivatives, cyclohexanone and ammonium acetate.

## EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recorded with Bruker AC 400 instruments. As internal standards, we used TMS ($\delta$ 0.00) for $^1$H NMR and $CDCl_3$ ($\delta$ 77.0) for $^{13}$C NMR spectroscopy. *J* values are given in hertz. The multiplicities of the signals in the $^1$H NMR spectra are abbreviated to s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and combinations thereof. IR spectra were recorded on a Jasco FT/IR-430 spectrometer. Elemental analyses were performed using a LECO CHNS 932 elemental analyzer. Melting points were measured on Electrothermal 9100 apparatus. All column chromatographies were performed on silica gel (60–230 mesh, Merck).

**General procedure for the synthesis of chalcones 3a–u.** To a solution of acetophenone derivative (1 mmol) in ethanol (20 mL) was added NaOH (8 mL, 2.5*M* NaOH) and benzaldehyde derivative (1 mmol) at room temperature. The mixture was stirred for 3 h. Then the mixture was washed with diluted HCl and extracted with $CHCl_3$. The organic layer was dried over $Na_2SO_4$ and the solvent was removed in vacuum. The residue was purified on a silica gel column eluting with $CHCl_3$/*n*-hexane (3:7) and/or crystallized from $CHCl_3$/*n*-hexane (3:7).

**General procedure for the synthesis of 1,5-diketones 5a–u.** To a mixture of chalcone (**1a**) (10 mmol) and cycylohexanone (**4**) (20 mmol) were added solid KOH (0.06% mol) with a few drop of water and PTC (benzyltrithylammonium chloride) (0.06% mol) and stirred for 3–4 h at room temperature. Then, the mixture was extracted with 20 mL of $CHCl_3$ and dried over $Na_2SO_4$. After the solvent was taken off in vacuum, the crude product was crystallized from $CCl_4$/hexane (3:1).

***2-(3-Oxo-1,3-diphenlpropyl)cyclohexanone (5a).*** Yield 83%; colorless crystals; mp 146–148°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.93–7.89 (m, 2H), 7.55–7.41 (m, 3H), 7.37–7.13 (m, 5H), 3.78–3.68 (m, 1H), 3.50 (dd, $J$ = 16.2, 4.1 Hz, 1H), 3.23 (dd, $J$ = 16.2, 9.5 Hz, 1H), 2.75–2.68 (m, 1H), 2.68–2.32 (m, 2H), 2.01–1.51 (m, 5H), 1.50–1.24 (m, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 215.6, 200.8, 144.1, 139.1, 134.8, 130.5 (2C), 130.4 (2C), 130.3 (2C), 130.2 (2C), 57.8, 46.2, 44.3, 43.1, 34.5, 30.5, and 26.1. IR (KCl): 3056, 33025, 2939, 2918, 2854, 1708, 1683, 1596, 1446, 1340, 1216, 746, 696, and 567 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 81.98; H, 7.22.

***2-(3-(2-Methoxyphenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5b).*** Yield 40%; colorless crystals; mp 108–111°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.43–6.85 (m, 9H), 3.86 (s, 3H), 3.80–3.68 (m, 1H), 2.72–2.63 (m, 1H), 3.44–3.33 (m, 2H), 2.72–2.28 (m, 3H), 1.95–1.24 (m, 5H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 215.4, 203.2, 160.1, 144.5, 134.9, 132.1, 130.9, 130.6 (2C), 130.2 (2C), 128.3, 122.5, 113.3, 57.9, 57.5, 50.8, 43.8, 42.6, 33.8, 30.3, and 25.6. IR (KCl): 3058, 3026, 2925, 2854, 1703, 1666, 1483, 1433, 1284, 1242, 1022, 752, 698, and 567 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.15; H, 7.48.

***2-(3-(3-Methxyphenyl)-3-oxo-1-phenylpropyl)cylohexanone (5c).*** Yield 78%; colorless crystals; mp 89–92°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.55–7.03 (m, 9H), 3.81 (s, 3H), 3.88–3.66 (m, 1H), 3.50 (dd, $J$ = 16.1, 4.0 Hz, 1H), 3.20 (dd, $J$ = 16.1, 9.6 Hz, 1H), 2.79–2.55 (m, 1H), 2.51–2.38 (m, 2H), 2.01–1.22 (m, 6H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 215.5, 200.6, 161.7, 143.9, 140.4, 131.4, 130.5 (2C), 130.4 (2C), 128.6, 122.8, 121.5, 114.5, 57.8, 57.4, 46.4, 44.4, 43.3, 34.5, 30.6, and 26.2. IR (KCl): 3058, 3028, 2931, 2912, 2852, 1709, 1678, 1581, 1431, 1259, 1049, 987, 700, and 573 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.20; H, 7.42.

***2-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5d).*** Yield 78%; colorless crystals; mp 128–130°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.91–7.89 (m, 2H), 6.91–6.87 (m, 2H), 7.88–7.14 (m, 5H), 3.84 (s, 3H), 3.75–3.69 (m, 1H), 2.75–2.69 (m, 1H), 3.42 (dd, $J$ = 15.7, 4.0 Hz, 1H), 3.17 (dd, $J$ = 15.7, 9.5 Hz, 1H), 2.55–2.48 (m, 1H), 2.02–1.92 (m, 1H), 1.80–1.50 (m, 5H), 1.31–1.10 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 213.9, 197.5, 163.5, 142.3, 130.4, 130.7 (2C), 128.7 (2C), 128.6 (2C), 126.8 (1C), 113.8 (1C), 56.1, 55.6, 44.1, 42.5, 41.5, 32.6, 28.7, and 24.2. IR (KCl): 3057, 3026, 2933, 2852, 1707, 1672, 1603, 1420, 1255, 1167, 984, 816, 698, and 565 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.30; H, 7.18.

***2-(3-(2-Chlorophenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5e).*** Yield 65%; colorless crystals; mp 120–124°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.43–7.11 (m, 9H), 3.71–3.59 (m, 1H), 3.46 (dd, $J$ = 16.6, 4.5 Hz, 1H), 3.23 (dd, $J$ = 16.6, 9.5 Hz, 1H), 2.72–2.60 (m, 1H), 2.55–2.34 (m, 2H), 1.99–1.22 (m, 6H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 215.2, 203.8, 143.7, 141.5, 132.7, 133.3, 132.2, 130.9, 130.5 (2C), 128.7 (2C), 57.7, 50.2, 44.2, 43.0, 34.2, 30.4, and 26.0. IR (KCl): 3058, 3026, 2933, 2918, 2854, 1705, 1691, 1431, 1369, 1122, 1072, 983, 750, 721, and 567 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}ClO_2$: C, 74.00; H, 6.21. Found: C, 73.74; H, 6.23.

***2-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5f).*** Yield 72%; colorless crystals; mp 113–116°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.94–7.83 (m, 2H), 7.42–7.29 (m, 2H), 7.27–7.12 (m, 5H), 3.68–3.61 (m, 1H), 3.54 (dd, $J$ = 15.8, 4.0 Hz, 1H), 3.15, (dd, $J$ = 15.8, 9.6 Hz, 1H), 2.74–2.66 (m, 1H), 2.51–2.35 (m, 2H), 2.02–1.21 (m, 6H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 215.7, 199.6, 143.7, 141.2, 137.4, 131.7 (2C), 130.7 (2C), 130.6 (2C), 130.3 (2C), 128.7, 57.8, 46.4, 44.5, 43.4, 34.7, 30.6, and 26.3. IR (KCl): 3057, 3024, 2939, 2918, 2852, 1707, 1685, 1589, 1446, 1398, 1215, 1095, 982, 816, 696, and 567 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}ClO_2$: C, 74.00; H, 6.21. Found: C, 73.68; H, 6.26.

***2-(3-(2-Bromophenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5g).*** Yield 63%; colorless crystals; mp 120–122°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.53–7.49 (m, 1H), 7.31–7.09 (m, 8H), 3.46 (dd, $J$ = 16.7, 4.4 Hz, 1H), 3.21

(dd, $J$ = 16.7, 9.5 Hz, 1H), 3.72–3.62 (m, 1H), 2.73–2.61 (m, 1H), 2.55–2.32 (m, 2H), 1.99–1.22 (m, 6H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ = 215.2, 204.5, 143.6, 143.6, 135.5, 133.3, 130.5 (2C), 130.5 (2C), 130.3, 129.2, 128.7, 120.6, 57.6, 49.9, 44.2, 42.9, 34.2, 30.4, and 26.0. IR (KCl): 3055, 3026, 2933, 2918, 2854, 1705, 1693, 1404, 1369, 1122, 1030, 983, 750, 698, and 567 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.08; H, 5.83.

***2-(3-(4-Bromophenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5h).*** Yield 56%; colorless crystals; mp 146–149°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, $J$ = 8.4 Hz, 2H), 7.55 (d, $J$ = 8.4 Hz 2H), 7.26 (t, $J$ = 7.2 Hz, 2H), 7.19–7.14 (m, 3H), 3.66 (td, $J$ = 8.8, 3.6 Hz, 1H), 3.50 (dd, $J$ = 15.6, 4.0 Hz, 1H), 3.15 (dd, $J$ = 16.0, 9.6 Hz, 1H), 2.72 (td, $J$ = 10.0, 4.2 Hz, 1H), 2.53–2.48 (m, 1H), 2.44–2.36 (m, 1H), 2.02–1.98 (m, 1H), 1.80–1.50 (m, 4H), 1.28–1.19 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.6, 197.89, 141.7, 135.7, 131.8 (2C), 129.8 (2C), 128.5 (2C), 128.3 (2C), 127.9, 126.7, 55.6, 44.4, 42.5, 41.4, 32.7, 28.6, and 24.3. IR (KCl): 3056, 3023, 2938, 2917, 2854, 1706, 1687, 1586, 1397, 1229, 1071, 982, 812, 698, and 569 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.08; H, 5.87.

***2-(3-(4-Hydroxyphenyl)-3-oxo-1-phenylpropyl)cyclohexanone (5i).*** Yield 66%; colorless crystals; mp 149–151°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, $J$ = 8.6 Hz, 2H), 7.28–7.23 (m, 3H), 7.19 (d, $J$ = 7.2 Hz, 2H), 6.81 (d, $J$ = 8.6 Hz, 2H), 3.75 (dt, $J$ = 9.6, 4.4 Hz, 1H), 3.42 (dd, $J$ = 16.1, 4.2 Hz 1H), 3.16 (dd, $J$ = 16.1, 9.2 Hz, 1H), 2.79–2.70 (m, 1H), 2.63–2.55 (m, 1H), 2.46–2.38 (m, 1H), 1.98–1.90 (m, 1H), 1.85–1.76 (m, 1H), 1.70–1.52 (m, 3H), 1.36–1.26 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 215.9, 197.6, 160.6, 141.9, 130.8 (2C), 129.6, 128.5 (2C), 128.4 (2C), 126.7, 115.3 (2C), 56.0, 43.9, 42.0, 41.2, 32.3, 28.5, and 23.6. IR (KCl): 3116, 3054, 3024, 2931, 2857, 1707, 1678, 1428, 1245, 1136, 984, 814, 699, and 567 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.12; H, 6.87.

***2-(1-(2-Methoxyphenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5j).*** Yield 77%; viscous oil. $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.91 (m, 2H), 7.54–7.47 (m, 1H), 7.43–7.38 (m, 2H), 7.23–7.05 (m, 2H), 6.88–6.80 (m, 2H), 3.74 (s, 3H), 3.50–3.30 (m, 2H), 2.99–2.97 (m, 1H), 2.55–2.26 (m, 2H), 1.99 (br s, 1H), 1.92–1.53 (m, 5H), 1.28–1.23 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 214.3, 199.5, 157.7, 137.2, 132.7, 130.2, 128.7, 128.4, 128.3 (2C), 128.2 (2C), 127.7, 127.3, 55.3, 42.9, 39.1, 32.8, 28.7, 27.7, and 24.4. IR (KCl): 3055, 2956, 2926, 2855, 1699, 1682, 1517, 1443, 1297, 1245, 1174, 987, 824, 725, and 566 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.32; H, 7.28.

***2-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5k).*** Yield 50%; colorless crystals; mp 136–139°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, $J$ = 7.2 Hz, 2H), 7.51 (t, $J$ = 7.2 Hz, 1H), 7.41 (t, $J$ = 7.2 Hz, 2H), 7.09 (d, $J$ = 8.4 Hz, 2H), 6.79 (d, $J$ = 8.4 Hz, 2H), 3.75 (s, 3H), 3.68 (m, 1H), 3.47 (dd, $J$ = 16.0, 4.0 Hz, 1H), 3.18 (dd, $J$ = 16.0, 9.6 Hz, 1H), 2,68 (m, 1H), 2.52–2.48 (m, 1H), 2.41–2.37 (m, 1H), 1.98–1.95 (m, 1H), 1.80–1.66 (m, 3H), 1.57–1.53 (m, 1H),1.28–1.24 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.8, 198.9, 158.1, 113.8 (2C), 128.4 (2C), 128.2 (2C), 56.0, 55.1, 44.4, 42.3, 40.4, 32.4, 28.6, and 24.1. IR (KCl): 3035, 2965, 2943, 2920, 2852, 1699, 1679, 1610, 1514, 1445, 1294, 1247, 1177, 1027, 987, 821, 723, and 563 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.20; H, 7.42.

***2-(1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5l).*** Yield 66%; colorless crystals; mp 126–128°C ($CCl_4$/*n*-hexane, 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.94 (dd, $J$ = 14.6 Hz, $J$ = 7.2 Hz, 2H), 7.48 (dd, $J$ = 14.6 Hz, $J$ = 7.2 Hz, 1H), 7.40 (t, $J$ = 7.6 Hz, 2H), 7.33–7.23 (m, 2H), 7.15 (t, $J$ = 7.2 Hz, 1H), 7.12–7.04 (m, 1H), 3.55 (dt, $J$ = 16.8, 3.6 Hz, 1H), 3.40 (dd, $J$ = 10, 3.6 Hz, 1H), 2.86–2.42 (m, 1H), 2.54–2.26 (m, 2H), 1.99 (br s, 1H), 1.85–1.50 (m, 5H), 1.48–1.59 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.0, 198.5, 139.8, 136.9, 134.0, 132.8, 129.8, 128.4 (2C), 128.1 (2C), 127.6, 127.0, 126.5, 53.4, 42.9, 42.7, 38.7, 32.6, 28.6, and 24.8. IR (KCl): 3085, 3061, 2936, 2928, 2859, 1698, 1680, 1592, 1574, 1447, 1223, 1119, 981, 748, and 687 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}ClO_2$: C, 74.00; H, 6.21. Found: C, 73.89; H, 6.25.

***2-(1-(3-chlorophenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5m).*** Yield 60%; colorless crystals; mp 124–127°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, $J$ = 7.6 Hz, 2H), 7.52 (t, $J$ = 7.2 Hz, 1H), 7.42 (t, $J$ = 7,6 Hz, 2H), 7.21–7.10 (m, 4H), 3.73 (m, 1H), 3.51 (dd, $J$ = 16.8, 4.0 Hz, 1H), 3.23 (dd, $J$ = 16.4, 9.6 Hz, 1H), 2.71 (m, 1H), 2.52–2.38 (m, 2H), 2.02–1.99 (m, 1H), 1.80–1.55 (m, 4H), 1.27–1.23 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.0, 189.3, 144.4, 128.5 (2C), 128.1 (2C), 134.2, 132.9, 129.7, 128.4, 126.9, 126.8, 55.5, 43.8, 42.8, 40.7, 32.6, 28.5, and 24.4. IR (KCl): 3083, 3059, 2932, 2924, 2858, 1698, 1681, 1593, 1571, 1449, 1360, 1232, 1127, 983, 748, and 685 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}ClO_2$: C, 74.00; H, 6.21. Found: C, 73.77; H, 6.22.

***2-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5n).*** Yield 60%; colorless crystals; mp 122–125°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, $J$ = 7.2 Hz, 2H), 7.52 (t, $J$ = 7.2 Hz, 1H), 7.42 (t, $J$ = 7.6 Hz, 2H), 7.23 (d, $J$ = 6.4 Hz, 2H), 7.13 (d, $J$ = 6.4 Hz, 2H), 3.72 (m, 1H), 3.51 (dd, $J$ = 16.4, 4.0 Hz, 1H), 3.21 (dd, $J$ = 16.4, 10.0 Hz, 1H), 2,71 (m, 1H), 2.51–2.47 (m, 1H), 2.42–2.37 (m, 1H), 2.03–1.99 (m, 1H), 1.80–1.53 (m, 4H), 1.26–1.20 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.1, 198.5, 129.8 (2C), 128.6 (2C) 128.5 (2C), 128.1 (2C), 140.6, 136.5, 132.9, 128.4, 132.2, 55.6, 43.9, 42.5, 40.5, 32.5, 28.5, and 24.4. IR (KCl): 3085, 3060, 2940, 2921, 2856, 1698, 1682, 1594, 1491, 1446, 1217, 1096, 984, 826, 750, and 688 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}ClO_2$: C, 74.00; H, 6.21. Found: C, 73.84; H, 6.23.

***2-(1-(2-Bromophenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5o).*** Yield 50%; colorless crystals; mp 92–95°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, $J$ = 8.2 Hz, 2H), 7.55–7.50 (m, 2H), 7.44 (t, $J$ = 7.2 Hz, 2H), 7.27–7.19 (m, 2H), 7.04 (t, $J$ = 7.6 Hz, 1H), 3.55 (dd, $J$ = 16.4, 4.4 Hz, 1H), 3.38 (dd, $J$ = 16.4, 9.6 Hz, 1H), 2.78–2.75 (m, 1H), 2.54–2.30 (m, 2H), 2.01–1.59 (m, 7H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 211.4, 198.6, 128.5 (2C), 128.2 (2C) 141.3, 136.8, 133.3, 132.9, 128.8, 127.8, 127.1, 125.2, 53.5, 42.3, 38.8, 38.3, 28.6, 27.6, and 25.0. IR (KCl): 3054, 3025, 2933, 2917, 2854, 1704, 1693, 1583, 1403, 1369, 1230, 1122, 983, 750, 698, and 566 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.26; H, 5.64.

***2-(1-(3-Bromophenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5p).*** Yield 70%; colorless crystals; mp 113–116°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, $J$ = 7.2 Hz, 2H), 7.52 (t, $J$ = 7.6 Hz, 1H), 7.42 (t, $J$ = 7.6 Hz, 2H), 7.34 (s, 1H), 7.30 (d, $J$

= 7.2 Hz, 1H), 7.17–6.96 (m, 2H), 3.71 (m, 1H), 3.50 (dd, *J* = 16.8, 4.0 Hz, 1H), 3.22 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.72–2.69 (m, 1H), 2.51–2.47 (m, 1H), 2.42–2.37 (m, 1H), 2.02–1.99 (m, 1H), 1.78–1.55 (m, 4H), 1.27–1.22 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 212.9, 198.3, 128.5 (2C), 128.1 (2C), 144.7, 122.6, 144.7, 136.8, 132.9, 131.2, 129.8, 27.3, 55.5, 43.8, 42.5, 40.7, 32.6, 28.5, and 24.4. IR (KCl): 3057, 2940, 2927, 2847, 1697, 1681, 1565, 1446, 1233, 1128, 979, 749, 687, and 590 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.31; H, 5.73.

***2-(1-(4-Bromopheyl)-3-oxo-3-phenylpropyl)cyclohexanone (5r).*** Yield 90%; colorless crystals; mp 122–125°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 6.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.71 (m, 1H), 3.51 (dd, *J* = 16.4, 3.6 Hz, 1H), 3.20 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.71–2.67 (m, 1H), 2.51–2.47 (m, 1H), 2.42–2.38 (m, 1H), 2.02–1.99 (m, 1H), 1.81–1.51 (m, 4H), 1.26–1.21 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.1, 198.5, 131.6 (2C), 130.2 (2C) 128.5 (2C), 128.1 (2C), 141.1, 136.8, 132.9, 120.4, 55.5, 43.9, 42.5, 40.5, 32.5, 28.5, and 24.4. IR (KCl): 3061, 2935, 2911, 2853, 1697, 1682, 1593, 1487, 1446, 1217, 1128, 1009, 824, 749, and 688 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.19; H, 5.56.

***2-(1-(4-Methylphenyl)-3-oxo-3-phenylpropyl)cyclohexanone (5s).*** Yield 94%; colorless crystals; mp 130–133°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.08–7.05 (m, 4H), 3.71 (m, 1H), 3.50 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.21 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.70 (m, 1H), 2.28 (s, 3H), 2.54–2.49 (m, 1H), 2.42–2.38 (m, 1H), 2.01–1.97 (m, 1H), 1.80–1.65 (m, 3H), 1.57–1.54 (m, 1H), 1.28–1.24 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): δ = 213.8, 198.9, 129.2 (2C), 128.4 (2C) 128.2 (2C), 128.2 (2C), 138.9, 137.0, 136.1, 132.8, 55.9, 44.3, 42.3, 40.7, 32.5, 28.6, 24.1, and 21.0. IR (KCl): 3033, 2942, 2923, 2857, 1698, 1671, 1596, 1449, 1249, 1125, 819, 760, 694, and 558 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.19; H, 7.56.

***2-(1-(4-Cholorophenyl)-3-(4-methokxyphenyl)-3-oxopropyl) cyclohexanone (5t).*** Yield 97%; colorless crystals; mp 131–134°C. $^1$H NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.71 (dt, *J* = 9.6, 3.9 Hz, 1H), 3.46 (dt, *J* = 15.9, 4.8 Hz, 1H), 3.12 (dd, *J* = 15.9, 9.9 Hz, 1H), 2.69 (dt, *J* = 9.9, 5.1 Hz, 1H), 2.54–2.23 (m, 2H), 2.05–1.45 (m, 5H), 1.29–1.15 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 213.2, 197.0, 163.4, 140.6, 132.2, 130.5 (2C), 129.9, 129.8 (2C), 128.6 (2C), 113.6 (2C), 55.6, 55.4, 43.6, 42.5, 40.7, 32.5, 28.5, and 24.3. IR (KCl): 3048, 3016, 2933, 2852, 1704, 1670, 1575, 1421, 1257, 1174, 981, 815, and 570 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{23}ClO_3$: C, 71.25; H, 6.25. Found: C, 71.04; H, 6.21.

***2-(1,3-Bis-(4-chlorophenyl)-3-oxopropyl)cyclohexanone (5u).*** Yield 75%; colorless crystals; mp 101–104°C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.50 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 3.69–3.61 (m, 1H), 3.55–3.43 (m, 1H), 3.16–3.06 (m, 1H), 2.72–2.63 (m, 1H), 2.51–2.33 (m, 2H), 2.01 (br s, 1H), 1.81–1.49 (m, 4H), 1.27–1.15 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 213.1, 197.3, 140.3, 139.4, 135.1, 132.3, 129.7 (2C), 129.6 (2C), 128.8 (2C), 128.7 (2C), 55.5, 44.1, 42.6, 40.7, 32.7, 28.6, and 24.5. IR (KCl): 3024, 2938, 2862, 1704, 1685, 1589, 1490, 1092, 1012, 984, 827, 756, and 530 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{20}Cl_2O_2$: C, 67.21; H, 5.37. Found: C, 67.14; H, 5.32.

**General procedure for synthesis of 2,4-diaryl-5,6,7,8-tetrahydroquinoline derivatives (7a-5u).** The 1,5-diketone (**5**) (1.5 mmol) and ammonium acetate ($NH_4OAc$) (4.5 mmol) were dissolved in acetic acid (10 mL) and refluxed for 2–5 h. After the removal of acetic acid in vacuum, the residue was added with $CHCl_3$ (30 mL) and washed with diluted $NaHCO_3$. Organic layer was dried over $Na_2SO_4$. Removal of the solvent in vacuum gave the 2,4-diaryl-5,6,7,8-tetrahydroqinoline derivative (**7**). The crude product was purified by column chromatography (on a silica gel) eluting with hexane/$CHCl_3$ (1:1).

***2,4-Diphenyl-5,6,7,8-tetrahydroquinoline (7a).*** Yield 82%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.5 Hz, 2H), 7.44–7.36 (m, 9H), 3.01 (t, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 6.2 Hz, 2H), 2.07–1.93 (m, 2H), 1.82–1.75 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.6, 154.3, 150.3, 139.7, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.1, 126.9, 119.5, 33.4, 27.3, 23.1, and 23.0. IR (KCl): 3060, 3027, 2977, 1582, 1494, 1446, 1236, 1018, 982, 846, 752, 700, and 665 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.23; H, 6.79; N, 4.98.

***2-(2-Methoxyphenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7b).*** Yield 99%; yellowish crystals, mp 90–93°C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.43–7.34 (m, 4H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.13 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 6.0, 2H), 1.99–1.93 (m, 2H), 1.80–1.74 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.2, 156.9, 152.9, 149.2, 139.8, 131.2, 129.6, 129.4, 128.8 (2C), 128.3 (2C) 128.1, 127.7, 123.4, 120.8, 111.3, 55.6, 33.1, 27.4, 23.2, and 23.1. IR (KCl): 3058, 3008, 2936, 1600, 1585, 1493, 1436, 1381, 1243, 1026, 890, 753, 701, and 665 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.69; H, 6.67; N, 4.24.

***2-(3-Methoxyphenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7c).*** Yield 93%; yellowish crystals, mp 99–102°C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.62 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.50–7.41 (m, 4H), 7.40–7.35 (m, 3H), 6.96 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.89 (s, 3H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 6.4 Hz, 2H), 2.00–1.94 (m, 2H), 1.81–1.75 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 160.01, 157.6, 154.1, 150.4, 139.6, 141.1, 129.7, 128.8, 128.6 (2C), 128.4 (2C), 127.9, 119.4 (2C), 112.2, 111.6, 55.4, 33.2, 27.4, 23.1, and 23.1. IR (KCl): 3057, 3007, 2936, 2860, 1583, 1541, 1494, 1455, 1262, 1215, 1161, 1044, 872, 755, 701, and 599 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.71; H, 6.45; N, 4.14.

***2-(4-Methoxyphenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7d).*** Yield 86%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.37–7.35 (m, 3H), 7.23 (t, *J* = 8.0 Hz, 1H), 7,00 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.11 (t, *J* = 6.5 Hz, 2H), 2.66 (t, *J* = 6.2 Hz, 2H), 1.99–1.93 (m, 2H), 1.80–1.74 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 160.1, 157.5, 153.9, 150.2, 139.9, 132.5, 128.6 (2C), 128.3 (2C), 128.1 (2C), 127.7 (2C), 118.4, 111.0 (2C), 55.3, 33.4, 27.3, 23.2, and 23.1. IR (KCl): 3058, 3007, 2935, 2859, 1608, 1587, 1513, 1450, 1248, 1172,

1032, 834, 754, 702, 666, and 570 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.63; H, 6.61; N, 4.28.

***2-(2-Chlorophenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7e).*** Yield 94%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.47–7.41 (m, 3H), 7.40–7.34 (m, 5H), 7.32–7.30 (m, 1H), 3.13 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 6.4 Hz, 2H), 2.00–1.94 (m, 2H), 1.81–1.76 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.6, 153.6, 149.4, 139.4, 139.3, 132.3, 131.6, 130.0, 129.3, 128.8, 128.7 (2C), 128.4 (2C), 127.9, 127.0, 123.1, 33.2, 27.4, 23.1, and 23.0. IR (KCl): 3058, 3010, 2945, 2868, 1584, 1542, 1497, 1371, 1094, 995, 832, 750, 702, and 668 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.76; H, 5.53; N, 4.21.

***2-(4-Chlorophenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7f).*** Yield 98%; yellowish crystals, mp 130–133°C. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.39 (s, 1H), 7.36 (t, *J* = 6.4 Hz, 2H), 7.29 (t, *J* = 6.4 Hz, 1H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.3 Hz, 2H), 1.98–1.92 (m, 2H), 1.80–1.71 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 152.9, 150.5, 139.5, 138.1, 134.5, 128.9, 128.8 (2C), 128.5 (2C), 128.4 (2C), 128.2 (2C), 127.9, 118.9, 33.3, 27.3, 23.1, and 23.0. IR (KCl): 3059, 3025, 2937, 2861, 1586, 1540, 1492, 1448, 1215, 1091, 1013, 835, 755, 701, and 666 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.73; H, 5.58; N, 4.34.

***2-(2-Bromophenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7g).*** Yield 66%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.32 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.47–7.37 (m, 6H), 3.12 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.00–1.94 (m, 2H), 1.85–1.77 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.4, 154.9, 149.4, 141.3, 139.3, 133.2, 131.6, 129.5, 128.8, 128.4 (2C), 128.7 (2C), 127.9, 127.6, 122.0, 123.0, 33.3, 27.3, 23.1, and 23.0. IR (KCl): 3057, 3027, 2935, 2859, 1583, 1540, 1494, 1447, 1381, 1217, 1025, 762, 701, 668, and 599 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 68.98; H, 4.93; N, 3.78.

***2-(4-Bromophenyl)-4-phenyl-5,6,7,8-tetrahydroquinoline (7h).*** Yield 92%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.46 (m, 2H), 7.39 (s, 1H), 7.36–7.34 (m, 2H), 7.27 (t, *J* = 8.0 Hz, 1H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6,4 Hz, 2H), 1.98–1.92 (m, 2H), 1.80–1.74 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 152.9, 150.5, 139.5, 138.5, 131.7 (2C), 128.9, 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.9, 122.9, 118.9, 33.3, 27.4, 23.1, and 23.0. IR (KCl): 3059, 3026, 2936, 2860, 1587, 1540, 1490, 1449, 1402, 1215, 1072, 1009, 832, 756, and 701 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.03; H, 4.94; N, 3.73.

***4-(4-Phenyl-5,6,7,8-tetrahydroquinolin-2-yl)phenol (7i).*** Yield 80%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.94 (br s, 1H—OH), 7.68 (d, *J* = 8.0 Hz, 2H), 7.47–7.39 (m, 3H), 7.33–7.27 (m, 3H), 6.80 (br d, *J* = 7.6 Hz, 2H), 3.14 (t, *J* = 6.0 Hz, 2H), 2.64 (t, *J* = 6.0 Hz, 2H), 1.99–1.88 (m, 2H), 1.75–1.71 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 158.3, 157.5, 156.7, 154.4, 151.7, 139.2, 129.5, 128.9, 128.7, 128.5, 128.4, 128.3, 128.0, 127.3, 119.8, 116.1, 31.9, 27.2, 22.8, and 22.7. IR (KCl): 3112, 3058, 2936, 2855, 1589, 1515, 1445, 1296, 1242, 1175, 1033, 832, 755, and 687 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.44; H, 6.29; N, 4.62.

***4-(2-Methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7j).*** Yield 88%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.2 Hz, 2H), 7.48–7.37 (m, 5H), 7.18 (dd, *J* = 7.2 Hz, 1.4 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.16–3.11 (m, 4H), 2.00–1.94 (m, 4H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.1, 156.3, 154.1, 147.6, 140.0, 130.3, 129.9, 129.4, 128.6, 128.3, 126.9, 120.6, 119.7, 110.8, 55.5, 33.4, 26.4, 23.2, and 22.8. IR (KCl): 3059, 2937, 2856, 2838, 1584, 1514, 1445, 1292, 1243, 1175, 1030, 835, 752, and 695 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.71; H, 6.69; N, 4.35.

***4-(4-Methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7k).*** Yield 71%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.6 Hz, 2H), 7.48–7.37 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 3.12 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 4 Hz, 2H), 1.99–1.93 (m, 2H), 1.81–1.75 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 159.3, 157.6, 154.3, 150.1, 139.7, 131.9, 128.9 (2C), 128.8, 128.7 (2C), 128.5, 126.9 (2C), 119.5, 113.8 (2C), 55.3, 33.2, 27.5, 23.2, and 23.1. IR (KCl): 3059, 2934, 2859, 2835, 1609, 1588, 1511, 1442, 1290, 1247, 1177, 1032, 833, 754, and 696 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.68; H, 6.70; N, 4.39.

***4-(2-Chlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7l).*** Yield 87%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.99 (br d, *J* = 8.0 Hz, 2H), 7.47–7.23 (m, 8H), 2.55 (t, *J* = 6.4 Hz, 2H), 2.46 (t, *J* = 6.0 Hz, 2H), 1.99–1.93 (m, 2H), 1.83–1.73 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.6, 154.2, 147.9, 139.6, 138.4, 132.6, 130.2, 129.6, 129.4, 129.3, 129.2, 128.6, 128.5, 126.9, 126.8, 118.9, 33.2, 26.4, 23.1, and 22.7. IR (KCl): 3061, 3028, 2937, 2859, 1592, 1537, 1444, 1267, 1084, 1004, 854, 756, 697, and 663 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.81; H, 5.64; N, 4.30.

***4-(3-Chlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7m).*** Yield 99%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 6.8 Hz, 2H), 7.40–7.36 (m, 5H), 7.25–7.22 (m, 1H), 3.12 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 1.99–1.88 (m, 2H), 1.81–1.73 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 154.4, 148.9, 118.9, 141.4, 139.4, 134.3, 129.7, 128.7 (2C), 128.6 (2C), 128.3, 127.9, 126.9 (2C), 126.8, 33.2, 27.2, 23.0, and 22.9. IR (KCl): 3061, 3030, 2937, 2860, 1586, 1541, 1443, 1380, 1216, 1078, 878, 755, and 697 $cm^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.74; H, 5.62; N, 4.33.

***4-(4-Chlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7n).*** Yield 90%; yellowish viscous oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.2 Hz, 2H), 7.47–7.40 (m, 4H), 7.32 (t, *J* = 4.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.63 (s, 1H), 3.11 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 6.4 Hz, 2H), 2.00–1.93 (m, 2H), 1.80–1.74 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 154.4, 149.2, 139.4, 138.0, 133.9, 129.9 (2C), 128.8 (2C), 128.7, 128.6 (2C), 128.5, 126.9 (2C), 119.0, 33.2, 27.3, 23.0, and 23.0. IR (KCl): 3061, 3029, 2937, 2861, 1599, 1491, 1444, 1215, 1091, 1015, 832, 759, 697, and 666

cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}ClN$: C, 78.86; H, 5.67; N, 4.38. Found: C, 78.85; H, 5.63; N, 4.31.

***4-(2-Bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7o).*** Yield 82%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): 8.05 (d, $J$ = 7.6 Hz, 2H), 7.71 (d, $J$ = 7.6 Hz, 1H), 7.48 (t, $J$ = 7.2 Hz, 2H), 7.42–7.39 (m, 3H), 7.30–7.23 (m, 2H), 3.20–3.11 (m, 2H), 2.62–2.55 (m, 1H), 2.48–2.39 (m, 1H), 2.00–1.94 (m, 2H), 1.84–1.78 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.8, 154.2, 149.5, 140.6, 139.6, 132.9, 130.1, 129.5, 128.9, 128.7 (2C), 128.6, 127.5, 126.9 (2C), 118.7, 122.6, 33.4, 26.6, 23.2, and 22.8. IR (KCl): 3060, 3031, 2936, 2859, 1596, 1543, 1442, 1382, 1216, 1025, 881, 758, and 695 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.20; H, 4.96; N, 3.81.

***4-(3-Bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7p).*** Yield 98%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, $J$ = 7.4 Hz, 2H), 7.56–7.52 (m, 2H), 7.46 (t, $J$ = 7.7 Hz, 2H), 7.38 (s, 1H), 7.36–7.27 (m, 3H), 3.11 (t, $J$ = 6.5 Hz, 2H), 2.65 (t, $J$ = 6.2 Hz, 2H), 2.01–1.92 (m, 2H), 1.81–1.76 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.9, 154.4, 148.7, 141.8, 139.5, 131.5, 130.8, 129.9, 128.7 (2C), 128.6, 128.2, 127.3, 126.9 (2C), 122.5, 118.8, 33.4, 27.2, 23.1, and 23.0. IR (KCl): 3061, 3011, 2937, 2860, 1586, 1541, 1475, 1444, 1215, 1072, 997, 879, 759, 698, and 666 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.12; H, 4.88; N, 3.79.

***4-(4-Bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (7r).*** Yield 94%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, $J$ = 7.2 Hz, 2H), 7.60 (d, $J$ = 8.8 Hz, 2H), 7.46 (t, $J$ = 8.0 Hz, 2H), 7.39 (t, $J$ = 8.0 Hz, 1H), 7.38 (s, 1H), 7.23 (d, $J$ = 8.8 Hz, 2H), 3.11 (t, $J$ = 6.5 Hz, 2H), 2.64 (d, $J$ = 6.3 Hz, 2H) 1.81–1.73 (m, 2H), 1.99–1.92 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.9, 154.5, 149.1, 139.5, 138.6, 131.6 (2C), 130.3 (2C), 128.9 (2C), 128.7 (2C), 128.6, 128.3, 122.1, 118.9, 33.2, 27.3, 23.1, and 23.0. IR (KCl): 3060, 3029, 2936, 2860, 1594, 1488, 1443, 1216, 1070, 1011, 827, 755, and 696 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{18}BrN$: C, 69.24; H, 4.98; N, 3.85. Found: C, 69.19; H, 4.92; N, 3.78.

***2-Phenyl-4-p-tolyl-5,6,7,8-tetrahydroquinoline (7s).*** Yield 81%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, $J$ = 8.8 Hz, 2H), 7.48 (t, $J$ = 7.8 Hz, 2H), 7.44 (s, 1H), 7.40 (t, $J$ = 7.2 Hz, 1H), 7.31–7.27 (m, 4H), 3.14 (t, $J$ = 6.6 Hz, 2H), 2.71 (t, $J$ = 6.3 Hz, 2H), 2.02–1.94 (m, 2H), 1.81–1.76 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.6, 154.3, 150.4, 139.7, 137.6, 136.8, 129.1 (2C), 128.7 (3C), 128.5 (2C), 128.4, 126.9 (2C), 119.4, 33.3, 27.4, 23.1, 23.1, and 21.3. IR (KCl): 3058, 3027, 2935, 2860, 1589, 1541, 1513, 1443, 1380, 1216, 1024, 820, 755, and 696 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.19; H, 6.98; N, 4.65.

***4-(4-Chlorophenyl)-2-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline (7t).*** Yield 90%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.93 (br d, $J$ = 6.4 Hz, 2H), 7.43 (br d, $J$ = 7.2 Hz, 2H), 7.31 (s, 1H), 7.26 (br d, $J$ = 6.4 Hz, 2H), 6.98 (br d, $J$ = 7.2 Hz, 2H), 3.85 (s, 3H), 3.08 (t, $J$ = 6.4 Hz, 2H), 2.62 (t, $J$ = 6.0 Hz, 2H), 1.96–1.90 (m, 2H), 1.79–1.74 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 160.2, 157.6, 154.1, 149.1, 138.2, 133.8, 132.0, 129.9, 128.6, 128.1, 127.6, 118.3, 114.1, 55.3, 33.2, 27.2, 23.1, and 23.0. IR (KCl): 3065, 3008, 2936, 2860, 2835, 1607, 1514, 1491, 1448, 1251, 1172, 1090, 1031, 832, 755, and 666 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{22}H_{20}ClNO$: C, 75.53; H, 5.76; N, 4.00. Found: C, 75.49; H, 5.70; N, 3.96.

***2,4-Bis(4-chlorophenyl)-5,6,7,8-tetrahydroquinoline (7u).*** Yield 97%; yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, $J$ = 8.0 Hz, 2H), 7.41 (br d, $J$ = 7.6 Hz, 2H), 7.39 (br d, $J$ = 7.32 Hz, 2H), 7.33 (s, 1H), 7.26 (d, $J$ = 8 Hz, 2H), 3.07 (t, $J$ = 6.8 Hz, 2H), 2.63 (t, $J$ = 6.4 Hz, 2H), 1.99–1.91 (m, 2H), 1.79–1.73 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.9, 153.0, 149.3, 137.8, 137.7, 134.7, 134.0, 130.3, 128.8, 128.6, 128.2, 118.7, 33.1, 27.3, 23.0, and 22.9. IR (KCl): 3015, 2938, 2862, 1597, 1539, 1491, 1446, 1215, 1090, 1014, 830, 755, and 665 cm$^{-1}$. *Anal*. *Calcd*. for: $C_{21}H_{17}Cl_2N$: C, 71.20; H, 4.84; N, 3.95 Found: C, 71.14; H, 4.79; N, 3.96.

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## REFERENCES AND NOTES

[1] Chabert, J. F. D.; Rostaing, S. P.; Bouchu, D.; Lemaire, M. Tetrahedron Lett 2006, 47, 1015.

[2] (a) Hoekstra, W. J.; Patel, H. S.; Liang, X.; Blanc, J. B. E.; Heyer, D. O.; Wilson, T. M.; Iannone, M. A.; Kadwell, S. H.; Miller, L. A.; Pearce, K. H.; Simmons, C. A.; Shearin, J. J Med Chem 2005, 48, 2243; (b) Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. J Med Chem 1994, 37, 2129.

[3] (a) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzerberger, S. M.; Varga, S. L. J Am Chem Soc 1995, 117, 6682; (b) Carling, R. W.; Leeson, P. D.; Moseleyy, A. M.; Smith, J. D.; Saywell, K.; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. Bioorg Med Chem Lett 1993, 3, 65.

[4] Michael, J. P. Nat Prod Rep 2001, 18, 543.

[5] (a) Michael, J. P. Nat Prod Rep 1997, 14, 605; (b) Balasubramanian, M.; Keay, J. G. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 245; (c) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. J Med Chem 2001, 44, 2374; (d) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. Eur J Med Chem 2000, 35, 1021; (e) Morimoto, Y.; Matsuda, F.; Shirahama, H. Synlett 1991, 202; (f) Isobe, M.; Nishikawa, T.; Yamamoto, N.; Tsukiyama, T.; Ino, A.; Okita, T. J Heterocycl Chem 1992, 29, 619.

[6] Atwell, G. J.; Baguley, B. C.; Denny, W. A. Med Chem 1989, 32, 396.

[7] Yang, D.; Jiang, K.; Li, J.; Xu, F. Tetrahedron 2007, 63, 7654.

[8] Skraup, H. Chem Ber 1880, 13, 2086.

[9] Doebner, O.; Miller, V. W. Chem Ber 1881, 14, 2812.

[10] Conrad, M.; Limbach, L. Chem Ber 1887, 20, 944.

[11] Combes, A. Comput Rend 1888, 106, 142.

[12] Pfitzinger, W. J Prakt Chem 1886, 33, 100.

[13] Kappe, C. O. Acc Chem Res 2000, 33, 879.

[14] Lin, X. F.; Cui, S. L.; Wang, Y. G. Tetrahedron Lett 2006, 47, 3127.

[15] Wattanasin, S.; Murphy, W. S. Synthesis 1980, 647.

[16] Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. Tetrahedron 1998, 54, 4085.

[17] Sasson, Y.; Cohen, M.; Blum, J. Synthesis 1973, 359.

[18] Batt, D. G.; Goodman, R.; Jones, D. G.; Kerr, J. S.; Mantegna, L. R.; McAllister, C.; Newton, R. C.; Nurnberg, S.; Welch, P. K.; Covington, M. B. J Med Chem 1993, 36, 1434.

[19] Singh, O. V.; Garg, C. P.; Kapoor, R. P. Synthesis 1990, 1025.
[20] Corey, E. J.; Zhang, F. Y. Org Lett 1999, 1, 1287.
[21] Zhang, F. Y.; Corey, E. J. Org Lett 2000, 2, 1097.
[22] Num, N. H.; Kim, Y.; You, Y. J.; Hong, D. H.; Kim, H. M.; Ahn, B. Z. Eur J Med Chem 2003, 38, 179.
[23] Hu, Y.; Liang, X.; Wang, J.; Zheng, Z.; Hu, X. J Org Chem 2003, 68, 4542.
[24] Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. J Am Chem Soc 2003, 125, 2582.
[25] Puschl, A.; Rudbeck, H. C.; Faldt, A.; Confante, A.; Kehler, J. Synthesis 2005, 291.
[26] Karaman, İ.; Gezegen, H.; Gürdere, M. B.; Dingil, A.; Ceylan, M. Chem Biodiversity 2010, 7, 400.
[27] Ceylan, M.; Gezegen, H. Turk J Chem 2008, 32, 55.
[28] Wang, J.; Li, H.; Zu, L.; Wang, W. Adv Synth Catal 2006, 425.
[29] Nikolaeva, T. G.; Petrova, N. V.; Kriven'ko, A. P. Chem Heterocycl Comp 1999, 35, 813.

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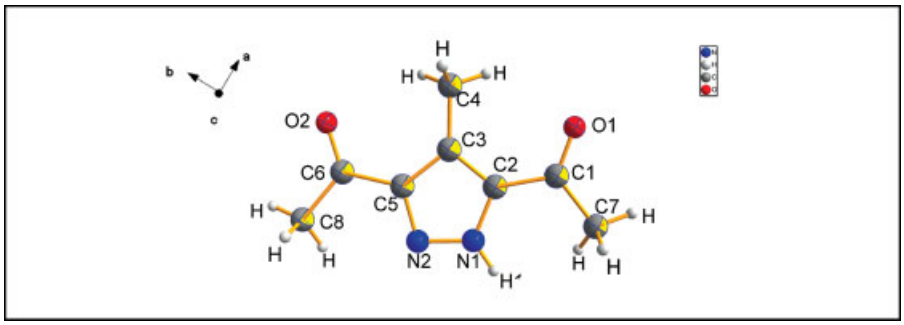


The 3,5-diacetyl-4-methylpyrazole diketone has been synthesized and its crystal structure has been determined. This diketone reacts with hydroxylamine hydrochloride to give the dioxime derivative. This reaction, conducted in presence of copper II ions, leads to the formation of $L_2M_2$ copper II complexes.

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## INTRODUCTION

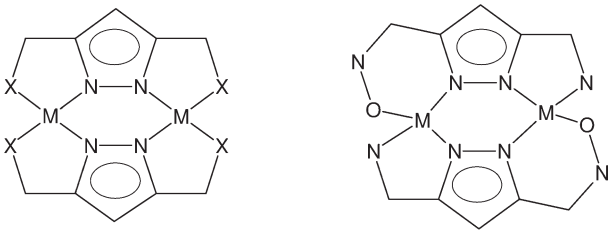
Research on transition metal complexes is a flourishing field with major interests focused on biological mimicry and cooperative phenomena in catalysis and magnetism. In this respect, pyrazol-based ligands have received a great deal of attention over the last decades due to their interesting coordination chemistry [1]. The pyrazole entity appears indeed particularly suited owing to its ability to bind simultaneously two metal centers in close proximity providing moreover an intramolecular pathway for spin-exchange interactions [2–9]. Further control of the metal–metal separation as well as the steric and electronic properties of the individual metal ions can be achieved by appropriates chelating side arms. Attached to the 3 and 5 positions of the heterocycle, these side arms are able to afford bis(μ-pyrazolato) bridged species $L_2M_2$.

In most cases, e.g. in type 1 complexes, the chelated metal atoms form only five-membered rings involving the four nitrogen atoms of the two depronated pyrazole rings and the four chelating heteroatoms bore by the 3,5-substituted side arms as shown in Scheme 1 [4–9]. Interestingly, the use of functional groups such as oximes as chelating side arms has a singular attractiveness. Oximes are indeed not only generally easy to prepare but can also take advantage of two different bridging modes as shown in Scheme 1 (type 2). In type 2 complexes, the metal atom can bind either to the N atom, either to the deprotonated O-atom of the oxime moiety thus forming a six-membered ring. In this purpose, we have already employed pyridazine and pyrazolate units, such as 3,6-diformylpyridazines [10,11], 3,6-dibenzoylpyridazines [10], and 3,5-diacetyl-4-methylpyrazole [12] and related dioxime species. The synthesis, crystal structure, and magnetic properties of two binuclear copper (II) complexes of the 3,5-diacetyl-4-methylpyrazole dioxime ($dampdoH_3$), involving the two bridging modes of the oxime function has been also reported [13]. In the present study, we describe the synthesis and crystal structure of the 3,5-diacetyl-4-methylpyrazole ligand used in a new one-step preparation of $L_2M_2$ copper II complexes.

## RESULTS AND DISCUSSION

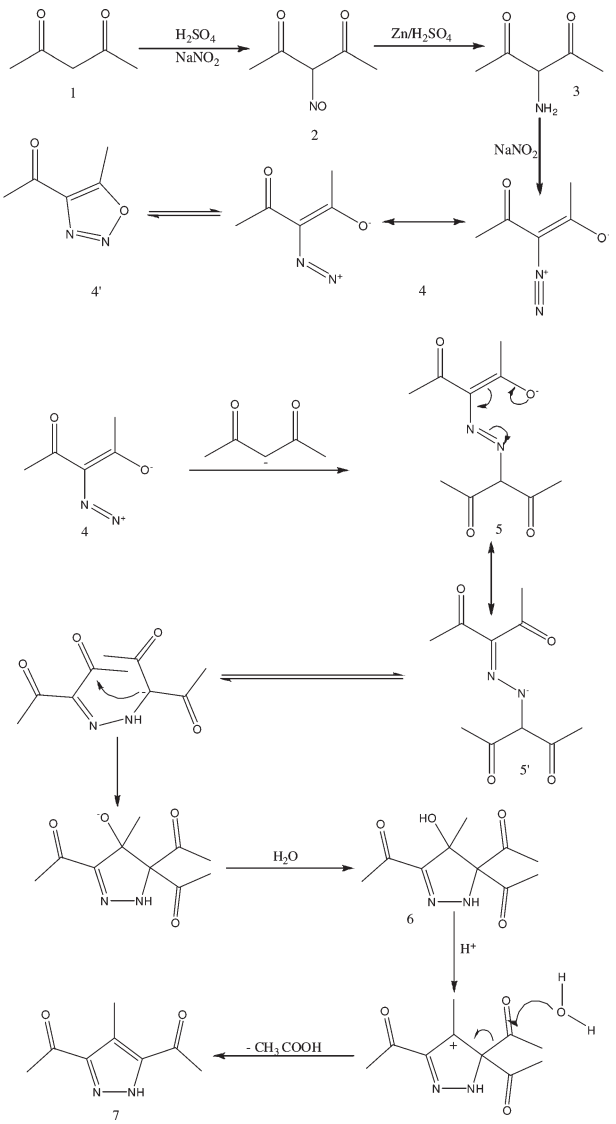
The 3,5-diacetyl-4-methylpyrazole is prepared by the method of Wolff [12]. Reduced by $Zn/H_2SO_4$, the isonitrosoacetylacetone (**2**) gives the aminoacetylacetone (**3**). This compound is then diazoted by sodium nitrite in acid medium (Scheme 2), affording the crude diazoacetylacetone (**4**) as an oily product which was in fact expected to be the 4-acetyl-5-methyl-oxadiazole (**4′**).

**Scheme 1.** $L_2M_2$ dinuclear complexes of pyrazolate anion.




To provide insight into the thermodynamics and kinetics of the possible internal cyclization of diazoacetylacetone (**4**) affording 4-acetyl-5-methyl-1,2,3-oxadiazole (**4′**), theoretical calculations were carried out at the B3LYP/6-31+g(d) DFT level. A thorough inspection of the frontier orbitals (HOMO and LUMO) of diazoacetylacetone (**4**) was first performed. The HOMO and LUMO for its most stable geometry in gas-phase show energy values of −7.5 and −2.7 eV, respectively. As depicted in Figure 1, the two frontier orbitals are distributed in the molecular plane. Although HOMO is mainly composed by lone pairs of the two carbonyl oxygen atoms, LUMO is an antibonding-π orbital located exclusively around the N≡N triple bond. This orbital distribution suggests that the unique pathway for the internal cyclization of diazoacetylacetone (**4**) should reside in the attack of one of carbonyl oxygen atom lone pairs at the π-orbital located on the terminal nitrogen atom of the diazonium moiety.

**Scheme 2.** Synthesis of 3,5-diacetyl-4-methylpyrazole.



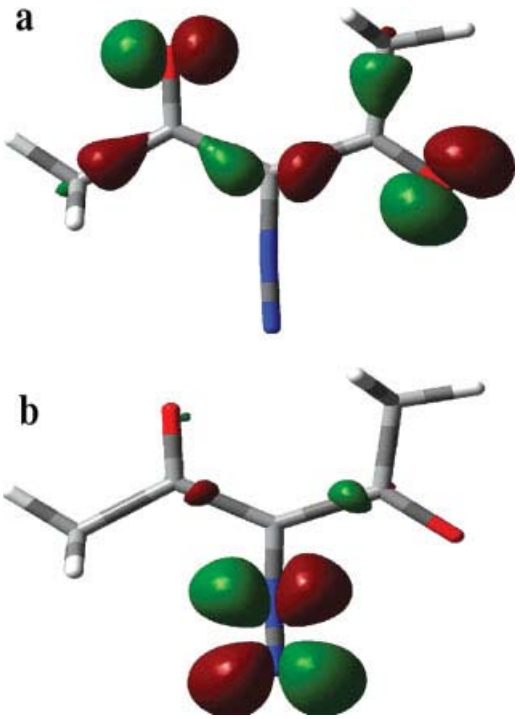




**Figure 1.** Isodensity surface plots of the HOMO (a) and LUMO (b) for the lowest-energy gas-phase geometry of diazoacetylacetone (**4**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

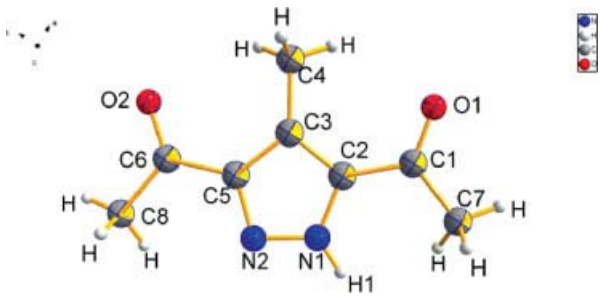



**Figure 2.** Perspective view of dampH structure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

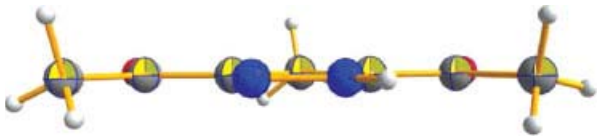


**Figure 3.** Projection view of dampH structure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The optimized geometry for transition state joining compounds (**4**) and (**4′**) on the potential energy surface has a single imaginary frequency ($\nu_i = 163\ cm^{-1}$) corresponding to the stretching vibration of the forming N—O bond. The distance of the N—O forming bond in transition state geometry is 1.902 Å. The reaction from diazoacetylacetone (**4**) leading to the formation of oxadiazole (**4′**) is predicted slightly endothermic (+7.3 kcal/mol in gas-phase and 8.5 kcal/mol in water). Diazoacetylacetone (**4**) is then thermodynamically more stable than 4-acetyl-5-methyl-1,2,3-oxadiazole (**4′**).

Furthermore, the barrier height calculated from diazoacetylacetone (**4**) is 8.0 kcal/mol (9.3 kcal/mol in water) indicating that formation of 4-acetyl-5-methyl-1,2,3-oxadiazole (**4′**) is not kinetically favored, at least at ambient temperature. This product is thus very unstable and must react immediately with carbanion of the 2,4-pentanedione as previously described [14]. This condensation and the subsequent heterocyclization give a pyrazoline (**6**), which was not isolated. In aqueous acidic medium, this compound gives the pyrazole (**7**) after elimination of acetic acid as described in Scheme 2. Slow evaporation of an ethanolic solution of **7** gives finally single crystals suitable for X-ray diffraction.

The main features of the crystal structure of compound dampH (**7**) result from the planarity of the whole entity (Figs. 2 and 3).

The crystal structure is formed by layers of planar dampH molecules stacked along the axis c direction.

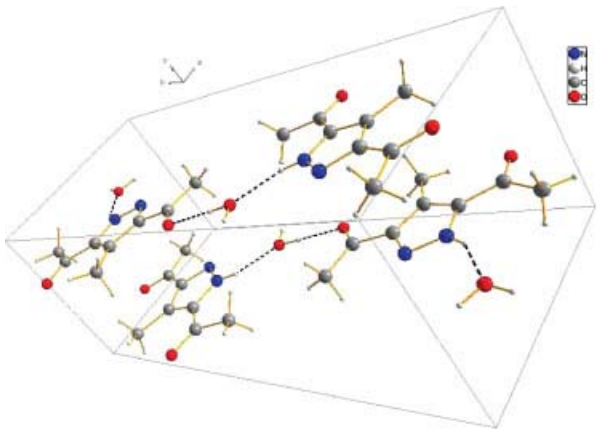
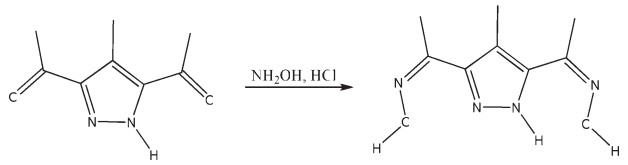


**Figure 4.** View of dampH crystal structure with its stabilizing hydrogen bond network (dashed lines). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Scheme 3.** Synthesis of $dampdoH_3$.




The layered crystal structure is also stabilized by an intermolecular hydrogen bond network forming dimeric ligand associations. The hydrogen bond interactions between two coplanar and adjacent 3,5-diacetyl-4-methylpyrazole ligands are mediated by a water molecule. The oxygen atom O3 of this water molecule gives an hydrogen bond with the hydrogen atom H1 bound to the nitrogen atom of pyrazole ring in the first ligand (O3—H1 = 1.9571 Å). Furthermore, one of the two hydrogen atoms H1w of the water molecule is also involved in a second hydrogen bond interaction with the oxygen atom O2 of the ketonic function of the second ligand molecule (H1w—O1 = 1.9207 Å) (Fig. 4).

This diketone (**7**) reacts with hydroxylamine hydrochloride to give the diacetyl dioxime derivative ($dampdoH_3$) as described in Scheme 3. On reaction with copper II cations $dampdoH_3$ leads to the bis(μ-pyrazolato) bridged $L_2M_2$ species [13] as described in Scheme 4, with L = dampdoH.

From $dampdoH_3$ ($H_2L$) and $CuCl_2{\cdot}6H_2O$, two structurally isomeric complexes $[Cu_2(HL)_2Cl_2]6H_2O$, which differ only from the hydrogen bonding, were previously obtained [10]. One of these complexes can be obtained directly from **7** by a one-step reaction with copper II ions in the presence of hydroxylamine hydrochloride. This reaction using $CuCl_2$, $CuClO_4$, $Cu(NO_3)_2$, or $CuSO_4$, leads, after several days, to the formation of dark green crystals of the copper II complexes previously described [13]. In this complex, the axial ligand is a chloride ion even in presence of perchlorate, nitrate, or sulphate ions, indicating that chloride ions are better complexing species.

**Scheme 4.** Dinuclear complex of $Cu_2(HL)_2^{2+}$.

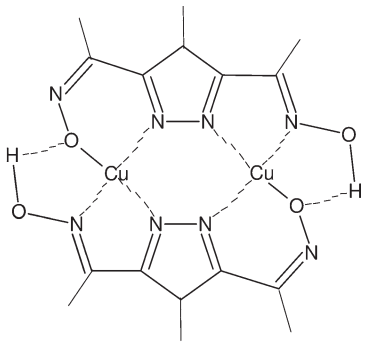


**Table 1**

Summary of the crystal data and structure refinement for dampH.

| | |
|---|---|
| Formula | $C_8H_{12}N_2O_3$ |
| Formula weight (g/mol) | 184.2 |
| Crystal system | Orthorhombic |
| Space group | Pbcm |
| $a$ (Å) | $a = 7.7798$ (10) |
| $b$ (Å) | $b = 18.337$ (3) |
| $c$ (Å) | $c = 6.7735$ (11) |
| $\alpha = \beta = \gamma$ (°) | 90 |
| $V$(Å$^3$) | 966.3 (2) |
| $Z$ | 4 |
| $D_{cal}$ (mg m$^{-3}$) | 1.266 |
| $T$ (K) | 296 |
| $F$(000) | 392 |
| Crystal size (mm) | 0.180 × 0.254 × 0.628 |
| μ (mm$^{-1}$) | 0.098 |
| Range of indices | $h$, −11 to 11; $k$, −26 to 23; $l$, −9 to 9 |
| Reflections measured | 13460 |
| $R_{int}$ | 2.64 |
| ($R_{all}$; $R_{2\sigma}$) | 7.43; 4.89 |
| ($wR_{all}$; $wR_{2\sigma}$) | 15.96; 14.08 |
| Number of parameters | 88 |
| Maximum peak in final $\Delta F$ map (eÅ$^{-3}$) | 0.28 |
| Minimum peak in final $\Delta F$ map (eÅ$^{-3}$) | −0.15 |

## EXPERIMENTAL

Melting points were determined on an IA 9000 series Electrothermal apparatus and are uncorrected. Elemental analyses of C, H, N, and S were performed at the Elemental Analysis service of CNRS, Vernaison, France. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker F.T. AC 300 spectrometer (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) using chloroform ($CDCl_3$) as solvent. Matrix-assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the correspondent compounds. All starting materials were of reagent grade and were used as purchased.

All theoretical calculations were performed using the Gaussian 03 suite of programs [15]. The gas-phase geometries of diazoacetylacetone (**4**), 4-acetyl-5-methyl-1,2,3-oxadiazole (**4′**), and related transition state were optimized using hybrid density functional theory (B3LYP) [16] and the 6-31+g(d) basis set. Frequency calculations were used to verify the nature of the computed stationary points. Geometries obtained for **4** and **4′** were real minima with all real vibrational frequencies while that of transition state was indeed a first-order saddle point with a single imaginary frequency. To ensure that the transition state joins the two compounds (**4**) and (**4′**) on the potential energy surface, an intrinsic reaction coordinate (IRC) [17] analysis was performed. Frequency calculations also allowed us to calculate the zero-point energy (ZPE) corrections, which were finally added to electronic energies. The energies computed in water include the ZPE-corrected electronic energy plus the solvation energy as obtained from the polarizable continuum model (PCM) [18].

Single crystals of 3,5-diacetyl-4-methylpyrazole hydrated (dampH) were obtained in the form of brown needles, by slow evaporation at room temperature in aqueous solution of dampH. A single crystal of compound **7** was mounted on a Brucker AXS SMART three-circle diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å), equipped with a CCD 4K two-dimensional detector [19]. A total of 1653 independent reflections were collected in the range of $2.22 < \theta < 31.03$ with $R_{int} = 2.64$. Data were corrected for Lorentz and polarization using program SaintPlus (Table 1). Atomic positions were determined using SHELXS [20] and refined using full matrix least squares [21]. Hydrogen positions were calculated and included in the final cycles of refinement in constrained positions and with fixed isotropic

**Table 2**

Bond distances (Å) and angles (°) for dampH.

| | | | |
|---|---|---|---|
| Bond distances | | | |
| N1—N2 | 1.327(2) | C3—C4 | 1.492(2) |
| N2—C5 | 1.351(2) | C5—C3 | 1.407(2) |
| N1—C2 | 1.363(2) | C5—C6 | 1.476(2) |
| C1—C7 | 1.498(3) | C6—O2 | 1.225(2) |
| C1—C2 | 1.468(2) | C6—C8 | 1.490(3) |
| C2—C3 | 1.395(2) | O1—C1 | 1.209(2) |
| Angles | | | |
| N2—N1—C2 | 113.0(1) | C2—C3—C4 | 128.0(1) |
| N1—N2—C5 | 104.6(1) | C5—C3—C4 | 128.5(1) |
| O1—C1—C2 | 120.1(1) | N2—C5—C3 | 112.1(1) |
| O1—C1—C7 | 121.8(2) | N2—C5—C6 | 118.4(1) |
| C2—C1—C7 | 118.1(2) | C3—C5—C6 | 129.5(1) |
| N1—C—C1 | 122.1(1) | O2—C6—C5 | 120.4(2) |
| C3—C2—C1 | 131.1(1) | C5—C6—C8 | 117.8(1) |
| N1—C2—C3 | 106.8(1) | O2—C6—C8 | 121.8(2) |
| C2—C3—C5 | 103.5(1) | | |

**Table 3**

Atomic coordinates and equivalent displacement for dampH.

| Atom | $x/a$ | $y/b$ | $z/c$ | $U$ (Å$^2$) |
|---|---|---|---|---|
| N1 | 0.6307(2) | 0.15617(7) | 1/4 | 0.0547(4) |
| N2 | 0.5408(2) | 0.21765(7) | 1/4 | 0.0557(4) |
| C1 | 0.9273(2) | 0.10700(9) | 1/4 | 0.0610(5) |
| C2 | 0.8038(2) | 0.16751(8) | 1/4 | 0.0521(4) |
| C3 | 0.8288(2) | 0.24286(9) | 1/4 | 0.0501(4) |
| C4 | 0.9949(2) | 0.28354(9) | 1/4 | 0.0599(5) |
| C5 | 0.6606(2) | 0.27101(8) | 1/4 | 0.0507(4) |
| C6 | 0.6021(2) | 0.34760(9) | 1/4 | 0.0570(5) |
| C7 | 0.8583(3) | 0.03073(9) | 1/4 | 0.0774(7) |
| C8 | 0.4134(3) | 0.36152(9) | 1/4 | 0.0828(7) |
| O1 | 0.0799(2) | 0.11936(9) | 1/4 | 0.1014(7) |
| O2 | 0.07067(2) | 0.39751(6) | 1/4 | 0.0772(5) |
| O3 | 0.3918(2) | 0.04499(7) | 1/4 | 0.0941(7) |
| $H_{N1}$ | 0.5845 | 0.1136 | 1/4 | 0.0660 |
| $H_{C4}$ | 0.9853 | 0.3255 | 0.1660 | 0.0900 |
| $H_{C4}$ | 0.0848 | 0.2524 | 0.2020 | 0.0900 |
| $H_{C4}$ | 0.0215 | 0.2989 | 0.3820 | 0.0900 |
| $H_{C1}$ | 0.3566 | 0.3249 | 0.1725 | 0.1240 |
| $H_{C1}$ | 0.3910 | 0.4087 | 0.1945 | 0.1240 |
| $H_{C1}$ | 0.3710 | 0.3599 | 0.3830 | 0.1240 |
| $H_{C6}$ | 0.8124 | 0.0195 | 0.3780 | 0.1160 |
| $H_{C6}$ | 0.9492 | −0.0028 | 0.2191 | 0.1160 |
| $H_{C6}$ | 0.7689 | 0.0266 | 0.1528 | 0.1160 |
| $H_{w1}$ | 0.363(3) | −0.002(2) | 1/4 | 0.089(8) |
| $H_{w2}$ | 0.294(4) | 0.067(2) | 1/4 | 0.101(9) |

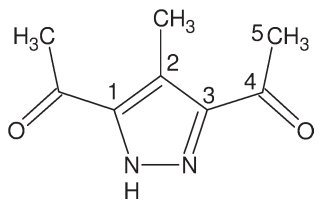
**Table 4**

Anisotropic displacement parameters for dampH.

| | U11 | U22 | U33 | U12 | U13 | U23 |
|---|---|---|---|---|---|---|
| N1 | 0.0412(7) | 0.0322(6) | 0.0907(11) | 0.0037(5) | 0 | 0 |
| N2 | 0.0408(6) | 0.0358(6) | 0.0905(11) | 0.0018(5) | 0 | 0 |
| C1 | 0.0485(9) | 0.0408(8) | 0.0935(14) | 0.0056(7) | 0 | 0 |
| C2 | 0.0418(8) | 0.0353(7) | 0.0794(12) | 0.0010(6) | 0 | 0 |
| C3 | 0.0388(7) | 0.0364(7) | 0.0752(11) | 0.0033(6) | 0 | 0 |
| C4 | 0.0405(8) | 0.0453(9) | 0.0939(13) | 0.0089(6) | 0 | 0 |
| C5 | 0.0407(7) | 0.0330(7) | 0.0786(11) | 0.0024(5) | 0 | 0 |
| C6 | 0.0481(8) | 0.0353(8) | 0.0876(13) | 0.0012(6) | 0 | 0 |
| C7 | 0.0737(13) | 0.0366(9) | 0.1218(19) | 0.0058(8) | 0 | 0 |
| C8 | 0.0491(10) | 0.0503(10) | 0.0149(2) | 0.0116(8) | 0 | 0 |
| O1 | 0.0444(7) | 0.0057(8) | 0.0204(2) | 0.0107(6) | 0 | 0 |
| O2 | 0.0588(8) | 0.0342(6) | 0.1385(14) | 0.0035(5) | 0 | 0 |
| O3 | 0.0448(7) | 0.0333(7) | 0.0204(2) | 0.0008(5) | 0 | 0 |

thermal parameters. Absorption corrections were not made due to the small value of the absorption coefficients (Table 1). Extinction was refined for all the three structures but was minimal. Figure 2 shows a perspective view of this compound with the numbering scheme, while in Table 2 bond distances and angles in the molecule (dampH) are reported. Atomic coordinates and equivalent displacement for dampH are reported in Table 3; anisotropic displacement parameters for dampH are reported in Table 4.

**General procedure for the synthesis of compounds 1, 4, and 7.** Starting material acetylacetone (**1**) was commercialized. The formula of the parent compounds with corresponding numbers to carbons scheme is given below.




**Synthesis of isonitroacetylacetone (2).** A suspension of acetylacetone (**1**) (50 g, 0.5 mol) in 7% sulphuric acid (500 mL) was stirred until it was completely dissolved. Sodium nitrite (35 g, 0.5 mol) in water (150 mL) was added, and the stirring was continued for 90 min. The reaction mixture was extracted with ether, dried (magnesium sulfate), filtered, and evaporated. The solid was recrystallized from ethanol: mp 75°C, yield 50 g, 77.5%.

**Synthesis of the acetylacetonate diazonium (4).** Isonitrosoacetylacetone 2 (10 g, 0.07 mol) dissolved in 30% sulphuric acid (100 mL) was cooled under 0°C. Zinc powder (15 g, 0.23 mol) was added, and the reaction mixture was allowed for 15 min. The limpid solution was filtered and diluted with water. A solution of sodium nitrite (6 g, 0.085 mol) in water (30 mL) was added and cooled. The reaction mixture was extracted with ether, and treated with 5% sodium carbonate. The residue was dried (magnesium sulfate), filtered, and evaporated to give an oil product: yield 4 g, 45%. The crude powder was used for the next step for the synthesis without further purification.

**Synthesis of 3,5-diacetyl-4-methylpyrazole (7).** A mixture of the acetylacetonate diazonium (**4**) (2 g, 0.016 mol), acetylacetone (**1**) (1.6 g, 0.015 mol), and sodium hydroxide (0.6 g, 0.015 mol) in water (30 mL) was heated at 50°C for 90 min. The resulting solution was concentrated under vacuum using a rotatory evaporator. After cooling, the obtained solution was neutralized by slow addition of aqueous sulfuric acid solution (0.5*M*). The obtained solid was filtered and recrystallized from ethanol: mp 112°C; yield 2 g, 75 %; $^1$H NMR ($CDCl_3$) δ (ppm) 10.78 (s, 1H); 2.51 (s, 6H); 2.46 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ (ppm) 192.96; 144.94; 121.58; 28.57; 10.21. MALDI-TOFMS: *m/z* 167 (M +1). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.08; N, 16.86. Found: C, 58.02; H, 5.98; N, 16.75.

**Synthesis of 3,5-diacetyl-4-methylpyrazole dioxime.** A solution of hydroxylamine hydrochloride (1.4 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in methanol/water solution (in ratio 50:50) was added to a solution of 3,5-diacetyl-4-methylpyrazole (1.5 g, 9 mmol) in water (20 mL) and heated under reflux for 2 h. After cooling, the solid product was filtered and recrystalized from ethanol: mp 218°C; yield 81%; $^1$H NMR (DMSO-d6) δ (ppm) 12.96 (s, H, NH); 11.33 (s, 1H, OH); 10.97 (s, 1H, OH); 2.27 (s, 3H); 2.14 (s, 6H); $^{13}$C NMR (DMSO-d6) δ (ppm) 150.39; 141.51; 134.62; 111.88; 11.70. MALDI-TOFMS: *m/z* 197 (M + 1). Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28,56. Found: C, 49.02; H, 5.98; N, 28.78.

**Preparation of complexes.** A solution of copper II chloride dehydrate (85 mg, 0.5 mmol) and hydroxylamine hydrochloride (69,5 mg, 1 mmol) in water (20 mL) was added to a solution of dampH (92 mg, 0.5 mmol) in ethanol (10 mL) and heated under reflux a few minutes. The mixture was filtered to remove any precipitated material. Slow evaporation at room temperature during 3 days affords dark green crystals which were filtered, washed with water and dried in vacuo. The crystals were found to have the formula $[Cu_2(dampdoH)_2Cl_2)_2H_2O]$ yield 110 mg; 70%. Anal. Calcd: C, 30.75; H, 4.20; Cl, 11.35; Cu, 20.35; N, 17.95; O, 15.40 Found: C, 30.69; H, 4.21; Cl, 11.37; Cu, 20.29; N, 18.00; O, 15.44.

## REFERENCES AND NOTES

[1] Mukherjee, R. Coordination Chem Rev 2000, 203, 151.

[2] Ajo, D. Inorg Chem 1988, 27, 2437.

[3] Pons, J.; López, X.; Benet, E.; Casabó, J.; Teixidor, F.; Sánchez F. J., Polyhedron, 1990, 9, 2839.

[4] Megumu, M.; Liang, P. W.; Mikiko, Y.; Takayoshi, K. S.; Masahiko, M.; Satoshi, K.; Susumo, K. J Chem Soc Dalton Trans 1995, 1, 4099.

[5] Röder, J. C.; Meyer, F.; Kaifer, E.; Pritzkow, H. Euro J Inorg Chem 2004, 8, 1646.

[6] Tanase, S.; Koval, I. A.; Bouwman, E.; De Gelder, R.; Reedijk, J. Inorg Chem 2005, 44, 7860.

[7] Du, M.; Chen, S. T.; Guo, Y. M.; Bu, X. H.; Ribas, J. J Mol Struct 2005, 737, 17.

[8] Teichgräber, J.; Leibeling, G.; Dechert, S.; Meyer, F. Z Anorg All Chem 2005, 631, 2613.

[9] De Geest, D. J.; Noble, A.; Moubaraki, B.; Murray, K. S.; Larsen, D.S.; Brooker, S. Dalton Trans 2007, 4, 467.

[10] Mernari, B.; Lagrenée, M. J Heterocyclic Chem 1996, 33, 2059.

[11] Abraham, F.; Lagrenée, M.; Sueur, S.; Mernari, B.; Bremard, C. J Chem Soc Dalton Trans 1991, 6, 1443.

[12] Wolff, L. Liebigs Ann Chem 1902, 325, 185.

[13] Mernari, B.; Abraham, F.; Lagrenée, M.; Drillon, M.; Legoll, P. J Chem Soc 1993, 11, 1707.

[14] Sachse, A.; Penkova, L.; Noel, G.; Dechert, S.; Varzatskii, O. A.; Fritsky, I. O.; Meyer, F. Synthesis 2008, 5, 800.

[15] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B. GAUSSIAN 03, revision B.05; Gaussian, Inc.: Pittsburgh, PA, 2003.

[16] (a) Becke, A. D. J Chem Phys 1993, 98, 5648; (b) Lee, C.; Yang, W.; Parr, R.G. Phys Rev B 1988, 41.

[17] (a) Fukui, K. J. Phys Chem 1970, 74, 4161; (b) Gonsalez, C.; Schlegel, H. B. J Chem Phys 1989, 90, 2154; (c) Gonsalez, C.; Schlegel, H. B. J Chem Phys 1990, 94, 5523.

[18] Tomasi, J.; Menucci, B.; Cammi, R. Chem Rev 2005, 105, 2999.

[19] Bruker AXS. SMART; Bruker AXS: Madison, Wisconsin, 1998.

[20] Sheldrick, G. M. Acta Cryst 1990, 46, 467.

[21] Sheldrick, G. M. SHELXL 97, Program for the Refinement of Crystal Structures; University of Gottingen: Germany, 1997.

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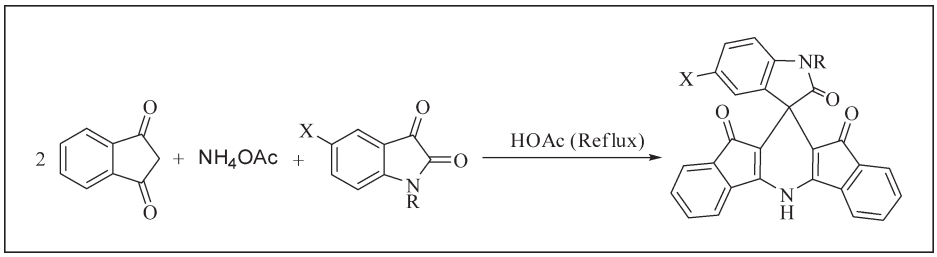


A one-pot and pseudo four-component synthesis of spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-trione derivatives by cyclo-condensation reaction of isatins, 1,3-indandione, and ammonium acetate in refluxing acetic acid is reported.

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## INTRODUCTION

Multicomponent reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [1,2]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [3,4]. As such processes avoid time consuming and costly purification processes, as well as protection–deprotection steps, they are inherently more environmentally benign and atom economic [5]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [6].

Indenone-fused heterocycles represent important biological and medicinal scaffolds. Thus, the indenopyridine skeleton is present in the 4-azafluorenone group of alkaloids, represented by its simplest member onychnine (Fig. 1) [7]. Indenopyrazoles (**A**) and indenopyridazines (**B**) have been investigated as cyclin-dependent kinase [8] and selective monoamine oxidase B (MAO-B) [9] inhibitors, respectively.

Further, indenopyridines (**C**) exhibit cytotoxic [10], phosphodiesterase inhibitory [11], adenosine A2a receptor antagonistic [12], anti-inflammatory/antiallergic [13], coronary dilating [14], and calcium modulating activities [15]. These compounds have also been investigated for the treatment of hyperlipoproteinemia and arteriosclerosis [16] as well as neurodegenerative diseases [17].

Indole and indoline fragments are important moieties of a large number of a variety of natural products and medicinal agents [18], and some of indolines, spiro-annulated with heterocycles in the 3-position, have shown high biological activity [19–21]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [22–24]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [25].

As part of our continuing efforts on the synthesis of biologically active heterocyclic compounds [26], we recently described an efficient synthesis of spiropyrimidoquinoline-pyrrolopyrimidines and spiroindoline-pyridodipyrimidines *via* a condensation reaction between amino-uraciles and isatines [27]. We have also developed an efficient synthesis of spiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaones via a reaction of isatins and 2-hydroxy-naphthoquinone in water [28].

Considering the important biological properties of spirooxindole fused heterocycles, we report herein a one-pot, pseudo four-component synthesis of spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-triones 4 through a one-pot condensation reaction of 1,3-indandione 1, ammonium acetate 2 and isatins 3 in refluxing acetic acid (Scheme 1).

## RESULTS AND DISCUSSION

In a pilot experiment, a mixture of 1,3-indandione **1**, ammonium acetate **2**, and isatin **3a** at refluxing acetic acid were stirred to afford the 5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione **4a** in 87% for 4 h.

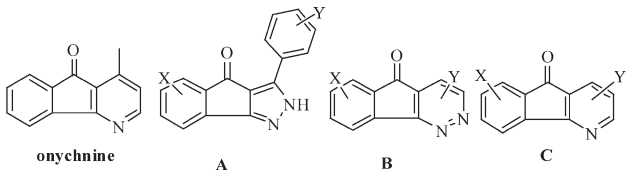



**Figure 1.** Representatives of important indenone-fused heterocycles

Encouraged by this success, we extended this reaction of 1,3-indandione **1** and ammonium acetate **2** with a range of other isatins **2b-l** under similar conditions, furnishing the respective 5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-triones **4b-l** in good yields. The optimized results are summarized in Table 1. We have shown that the use of a wide diversity of substituents in isatins **3** in this reaction makes possible the synthesis of libraries under similar circumstances.

$^1$H and $^{13}$C NMR spectra of the crude products clearly indicated the formation of spirooxindol fused diindenopyridines **4**. The nature of these compounds as 2:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate m/z value. Compounds **4a–l** are stable solids whose structures were established by IR, $^1$H and $^{13}$C NMR spectroscopy and elemental analysis.

For the investigation of the reaction mechanism, it is notable that when the 1,3-indandione **1**, ammonium acetate **2**, and isatin **3a** were reacted for 2 h, the intermediate **6** were isolated and characterized by spectroscopic methods. When intermediate **6** was reacted with $NH_4OAc$ **2** under the same reaction conditions, the product **4a** was obtained in 83% yield (Scheme 2).

Therefore, the formation of products **4** can be rationalized *via* initial addition of 1,3-indanedione **1** to the isatins **3** to yield intermediate **5**, which reacted further with another molecule of **1**. Finally, reaction of ammonium acetate **2** with the intermediate **6**, followed by cyclization afforded the corresponding product **4** (Scheme 3).

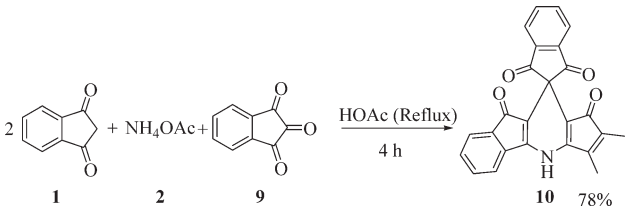
As expected, when the isatins **3** was replaced by acenaphthylene-1,2-dione **7**, 2*H*,5′*H*-spiro[acenaphthylene-1,11′-diindeno[1,2-*b*:2′,1′-*e*]pyridine]-2,10′,12′-trione **8** was obtained in 82% yield under the same reaction conditions (Scheme 4).

To further explore the potential of this protocol for spirofused heterocycle synthesis, we investigated reaction of 1,3-indandione **1** and ammonium acetate **2** with ninhydrine **9** and obtained 5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,2′-indene]-1′,3′,10,12-tetraone **10** in 78% yield (Scheme 3).

**Table 1**

Synthesis of spiro[diindenopyridine-indoline]-triones **4**.

| Product **4** | R | X | Yield (%) |
|---|---|---|---|
| **a** | H | H | 87 |
| **b** | Me | H | 85 |
| **c** | Et | H | 82 |
| **d** | $PhCH_2$ | H | 80 |
| **e** | H | Br | 91 |
| **f** | H | Me | 88 |
| **g** | H | F | 79 |
| **h** | H | $NO_2$ | 92 |
| **i** | Me | Br | 76 |
| **j** | Et | Br | 78 |
| **k** | Me | $NO_2$ | 79 |
| **l** | Et | $NO_2$ | 77 |

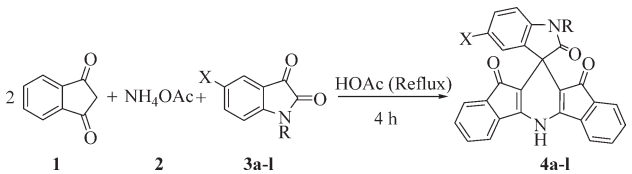



In conclusion, we have demonstrated an efficient and simple method for the preparation of some spirooxindole fused heterocycles using readily available starting materials. Prominent among the advantages of this new method are operational simplicity, good yields, and easy work-up procedures employed. Moreover, it is worth noting that two C—C and one two C—N bonds were formed with concomitant creation of a spirooxindoles in this one-pot, pseudo four-component process.

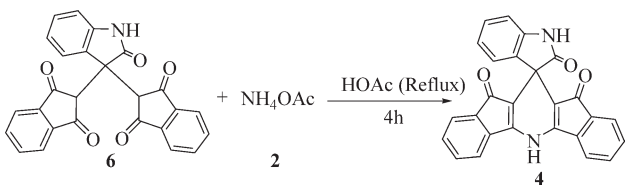
## EXPERIMENTAL

Melting points were measured on an Elecrtothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. $^1$H and $^{13}$C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using a Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

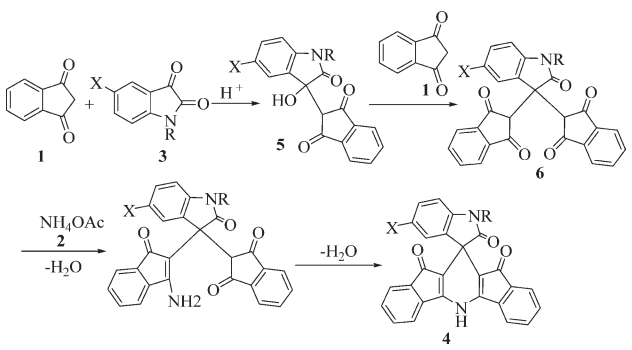
**Scheme 1**




**Scheme 2**



**Scheme 3**



Because of very low solubility of the products, we cannot report the $^{13}C$ NMR data for these products.

**Typical procedure for the preparation of 5*H*-Spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4a).** A mixture of 1,3-indandione **1a** (0.30 g, 2 mmol), ammonium acetate **2** (0.46 g, 3 mmol), and isatin **3a** (0.15 g, 1 mmol) in refluxing (5 mL) was stirred for 4 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with water (10 mL) and recrystallized by EtOH to afford the pure product **4a** as red powder (87%); m.p >300°C (dec). IR (KBr) ($\nu_{max}/cm^{-1}$): 3169, 2996, 1694, 1672, 1631. MS (EI, 70 eV) *m/z*: 402 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.83–7.74 (m, 12H, ArH), 10.66 (s, 1H, NH), 11.62 (s, 1H, NH). Anal. Calcd for $C_{26}H_{14}N_2O_3$: C, 77.60; H, 3.51; N, 6.96%. Found: C, 77.51; H, 3.45; N, 6.88%.

**1′-Methyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4b).** Dark red powder (85%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 2926, 1701, 1678, 1617. MS (EI, 70 eV) *m/z*: 416 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.27 (s, 3H, $NCH_3$), 7.07–8.53 (m, 12H, ArH), 11.13 (s, 1H, NH). Anal. Calcd for $C_{27}H_{16}N_2O_3$: C, 77.87; H, 3.87; N, 6.73%. Found: C, 77.95; H, 3.80; N, 6.66%.

**1′-Ethyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4c).** Red powder (82%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 3219, 2921, 1707, 1652 . MS (EI, 70 eV) *m/z*: 430 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.23–1.27 (m, 3H, $CH_3$), 3.78–3.80 (m, 2H, $NCH_2$), 6.90–7.80 (m, 12H, ArH), 11.63(1H, s, NH). Anal. Calcd for $C_{28}H_{18}N_2O_3$: C, 78.13; H, 4.21; N, 6.51%. Found: C, 78.01; H, 4.13; N, 6.62%.

**1′-Benzyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4d).** Dark red powder (80%); m.p = 270°C IR (KBr) ($\nu_{max}/cm^{-1}$): 3048, 1706, 1666, 1607. MS (EI, 70 eV) *m/z*: 492 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 5.00 (bs, 2H, $NCH_2$), 6.72–7.81 (m, 17H, ArH), 11.68 (s, 1H, NH). Anal. Calcd for $C_{33}H_{20}N_2O_3$: C, 80.47; H, 4.09; N, 5.69%. Found: C, 80.38; H, 4.01; N, 5.58%.

**5′-Bromo-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4e).** Red powder (91%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 3222, 2922, 1698, 1640, 1603. MS (EI, 70 eV) *m/z*: 482 ($M^+$+2), 480 ($M^+$). Anal. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.84–7.94 (m, 11H, ArH), 10.78 (s, 1H, NH), 11.66 (s, 1H, NH). Calcd for $C_{26}H_{13}BrN_2O_3$: C, 64.88; H, 2.72; N, 5.82%. Found: C, 64.81; H, 2.78; N, 5.89%.

**5′-Methyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4f).** Red powder (88%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 3169, 2996, 1682, 1645. MS (EI, 70 eV) *m/z*: 416 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 2.13 (s, 3H, $CH_3$), 6.72–7.76 (m, 11H, ArH), 10.53 (s, 1H, NH), 11.60 (s, 1H, NH). Anal. Calcd for $C_{27}H_{16}N_2O_3$: C, 77.87; H, 3.87; N, 6.73%. Found: C, 77.74; H, 3.77; N, 6.64%.

**5′-Fluoro-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4g).** Red powder (79%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 3048, 2901, 1681, 1640. MS (EI, 70 eV) *m/z*: 420 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.81–7.80 (m, 11H, ArH), 10.63 (s, 1H, NH), 11.66 (s, 1H, NH). Anal. Calcd for $C_{26}H_{13}FN_2O_3$: C, 74.28; H, 3.12; N, 6.66%. Found: C, 74.37; H, 3.06; N, 6.60%.

**5′-Nitro-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4h).** Red powder (92%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 3211, 3048, 1706, 1631, 1600. MS (EI, 70 eV) *m/z*: 447 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 7.07–8.15 (m, 11H, ArH), 11.36 (s, 1H, NH), 11.93 (s, 1H, NH). Anal. Calcd for $C_{26}H_{13}N_3O_5$: C, 69.80; H, 2.93; N, 9.39%. Found: C, 69.72; H, 2.86. N, 9.31%.

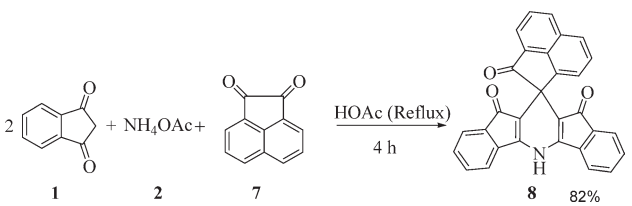
**5′-Bromo-1′-methyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12 -trione (4l).** Dark red powder (76%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 2917, 1680, 1640, 1608. MS (EI, 70 eV) *m/z*: 496 ($M^+$+2), 494 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.21 (s, 3H, NCH3), 7.04-7.81 (m, 11H, ArH), 11.72 (s, 1H, NH). Anal. Calcd for $C_{27}H_{15}BrN_2O_3$: C, 65.47; H, 3.05; N, 5.66%. Found: C, 65.35; H, 3.14; N, 5.75%.

**5′-Bromo-1′-ethyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4j).** Red powder (78%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 2931, 1714, 1667. MS (EI, 70 eV) *m/z*: 510 ($M^+$+2), 508 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.21 (bs, 3H, $CH_3$), 3.78 (bs, 2H, $NCH_2$), 7.06–7.79 (m, 11H, ArH), 11.96 (s, 1H, NH). Anal. Calcd for $C_{28}H_{17}BrN_2O_3$: C, 66.03; H, 3.36; N, 5.50%. Found: C, 66.14; H, 3.30; N, 5.59%.

**1′-Methyl-5′-nitro-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4k).** Red powder (79%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 2996, 1693, 1608. MS (EI, 70 eV) *m/z*: 461 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.33 (s, 3H, NCH3), 7.21–8.29 (m, 11H, ArH), 11.85(s, 1H, NH). Anal. Calcd for $C_{27}H_{15}N_3O_5$: C, 70.28; H, 3.28; N, 9.11%. Found: C, 70.19; H, 3.34; N, 9.04%.

**1′-Ethyl-5′-nitro-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,3′-indoline]-2′,10,12-trione (4l).** Red powder (77%); m.p > 300°C. IR (KBr) ($\nu_{max}/cm^{-1}$): 2964, 1692, 1645. MS (EI, 70 eV) *m/z*: 475 ($M^+$). $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.26 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_3$), 3.90 (q, $^3J_{HH}$ = 6.6 Hz, 2H, $NCH_2$), 7.27–8.27 (m, 11H, ArH), 11.83 (s, 1H, NH). Anal. Calcd for $C_{28}H_{17}N_3O_5$: C, 70.73; H, 3.60; N, 8.84%. Found: C, 70.67; H, 3.55; N, 8.91%.

**Scheme 4**



**2*H*,5′*H*-Spiro[acenaphthylene-1,11′-diindeno[1,2-*b*:2′,1′-*e*]pyridine]-2,10′,12′-trione (8).** Dark red powder (82%); m.p > 270°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3059, 1692, 1640. MS (EI, 70 eV) *m*/*z*: 437 ($M^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 7.14–8.29 (m, 15H, ArH, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_C$ (ppm) 51.5, 11.8, 120.5, 121.2, 121.3, 123.9, 125.0, 128.9, 129.3, 129.7, 130.2, 131.3, 132.9, 133.7, 1373.3, 137.9, 141.3, 143.9, 158.0, 190.5, 205.4. Anal. Calcd for $C_{30}H_{15}NO_3$: C, 82.37; H, 3.46; N, 3.20%. Found: C, 82.48; H, 3.38; N, 3.29%.

**5*H*-Spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridine-11,2′-indene]-1′,3′,10,12-tetraone (10).** Dark red powder (78%); m.p > 260°C dec. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2922, 1703, 1651. MS (EI, 70 eV) *m*/*z*: 415 ($M^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 7.29–8.09 (m, 12H, ArH), 11.94 (s, 1H, NH). Anal. Calcd for $C_{27}H_{13}NO_4$: C, 78.07; H, 3.15; N, 3.37%. Found: C, 77.97; H, 3.09; N, 3.29%.

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## REFERENCES AND NOTES

[1] Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[2] Dömling, A. Chem Rev 2006, 106, 17.

[3] El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. Org Lett 2006, 8, 4019.

[4] Zhu, J.; Bienaymé, H. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2005.

[5] Trost, B. M. Angew Chem Int Ed Engl 1995, 34, 259.

[6] Weber, L. Curr Med Chem 2002, 9, 2085.

[7] Zhang, J.; El-Shabrawy, A.-R. O.; El-Shanawany, M. A.; Schiff P. L.; Slatkin, D. J. J Nat Prod 1987, 50, 800.

[8] Nugiel, D. A.; Etzkorn, A.-M.; Vidwans, A.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Cox, S.; Czerniak, P. M.; Doleniak D.; Seitz, S. P. J Med Chem 2001, 44, 1334.

[9] Frédérick, R.; Dumont, W.; Ooms, F.; Aschenbach, L.; Van der Schyf, C. J.; Castagnoli, N.; Wouters J.; Krief, A. J Med Chem 2006, 49, 3743.

[10] Miri, R.; Javidnia, K.; Hemmateenejad, B.; Azarpira A.; Amirghofran, Z. Bioorg Med Chem 2004, 12, 2529.

[11] Heintzelman, G. R.; Averill K. M.; Dodd, J. H. PCT Int. Appl. WO 2002085894 A1 20021031, 2002.

[12] Heintzelman, G. R.; Averill, K. M.; Dodd, J. H.; Demarest, K. T.; Tang Y.; Jackson, P. F. Pat. Appl. Publ. U.S. Pat. 2004,082,578 A1 20,040,429, 2004.

[13] Cooper, K.; Fray, M. J.; Cross, P. E.; Richardson, K. Eur. Pat. Appl. EP 299727 A1 19890118, 1989.

[14] Vigante, B.; Ozols, J.; Sileniece, G.; Kimenis A.; Duburs, G. U. S. S. R. SU, 794006 19810107, 1989.

[15] Safak, C.; Simsek, R.; Altas, Y.; Boydag S.; Erol, K. Bull Chim Farm 1997, 136, 665.

[16] Brandes, A.; Loegers, M.; Schmidt, G.; Angerbauer, R.; Schmeck, C.; Bremm, K.-D.; Bischoff, H.; Schmidt, D.; Schuhmacher, J. Ger. Offen. DE 19627430 A1 19980115, 1998.

[17] Heintzelman, G. R.; Averill, K. M.; Dodd, J. H.; Demarest, K. T.; Tang Y.; Jackson, P. F. PCT Int. Appl. WO 2003088963 A1 20031030, 2003.

[18] Sundberg, R. J. The Chemistry of Indoles; Academic: New York, NY, 1996.

[19] Joshi, K. C.; Chand, P. Pharmazie 1982, 37.

[20] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J. Braz Chem Soc 2001, 12, 273.

[21] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. Bioorg Med Chem 2004, 12, 2483.

[22] Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39.

[23] Ma, J.; Hecht, S. M. Chem Commun 2004, 1190.

[24] Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. Farmaco. 2002, 57, 715.

[25] (a) Zhu, S.-L.; Ji, S.-J.; Zhang, Y. Tetrahedron 2007, 63, 9365; (b) Kumar, R. S.; Perumal, S. Terahedron Lett 2007, 48, 7164; (c) Redkin, R. Gr.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. Tetrahedron 2007, 63, 11444; (d) Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. Tetrahedron 2007, 63, 2057.

[26] (a) Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. Tetrahedron Lett 2007, 48, 8790; (b) Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 2375; (c) Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. J. Heterocycl Chem 2007, 44, 1009; (d) Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. Heterocycles 2008, 75, 87; (e) Dabiri, M.; Delbari, A. S.; Bazgir, A. Synlett 2007, 821; (f) Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2007, 63, 1770; (g) Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543; (h) Ghahremanzadeh, R. Shakibaei, G. I. Bazgir, A. Synlett 2008, 1129.

[27] (a) Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. Tetrahedron 2009, 65, 2005; (b) Dabiri, M.; Azimi, S. C.; Khavasi, h. R.; Bazgir, A. Tetrahedron 2008, 64, 7307.

[28] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. Terahedron Lett. 2008, 49, 5165.

# Iodine: Selectively Promote the Synthesis of Mono Substituted Quinazolin-4(3*H*)-ones and 2,3-Dihydroquinazolin-4(1*H*)-ones in One-Pot



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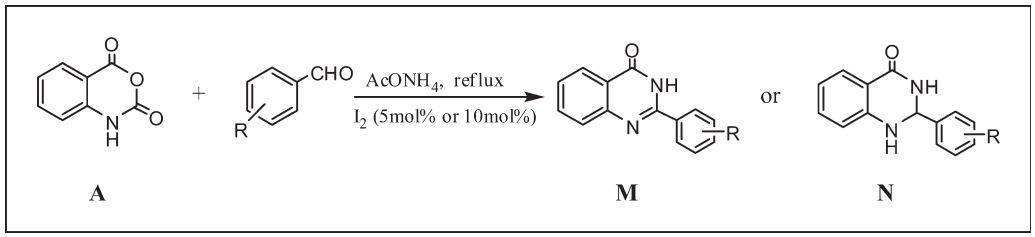


A general and versatile one-pot three-component procedure for the selective synthesis of mono substituted quinazolin-4(3*H*)-ones and 2,3-dihydroquinazolin-4(1*H*)-ones were described. The selectivity could be controlled by the ratio of iodine concentration.

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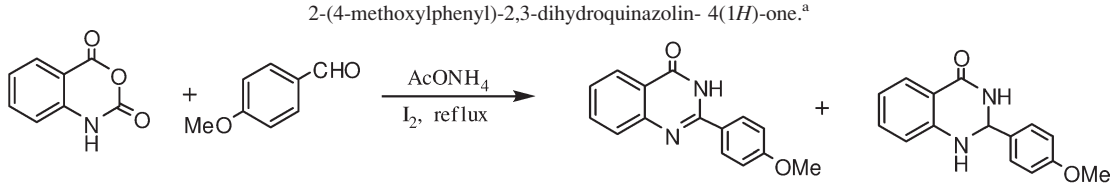
## INTRODUCTION

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of heterocycles with a broad spectrum of biological and pharmaceutical activities, such as antitumor, analgesic, anticancer, and diuretic [1–3]. Traditional procedure for the synthesis of these compounds involves the condensation of anthranilamides, as well as the reductive cyclization of *o*-nitrobenzamide or *o*-azidobenzamide with aldehydes or ketones in the presence of Brφnsted or Lewis acid catalyst [4–12]. On the other hand, quinazolin-4(3*H*)-ones, the oxidized products of 2,3-dihydroquinazolin-4(1*H*)-ones [13], were important precursors for the synthesis of natural and pharmacological compounds including febrifugine and isofebrifugine [14]. It can also be obtained by the cyclization of anthranilamides with aldehyde and other similar methods [15]. With the one-pot multicomponent reactions (MCRs) emerged as a powerful tool to routinely find out novel biologically active compounds [16], recently, various approaches to 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones, promoted by Brφnsted or Lewis acid, or by supported acid with the help of special instrument, were explored independently in a one-pot three-component protocol starting from isatoic anhydride **A**, primary amine, and aldehyde [17–23]. However, there is a paucity of efficient synthetic route to implement the selectivity of two such compounds, an extra-oxidize step was always required to complete the fusion of the quinazolin-4(3*H*)-ones. Although Chen reported quinazolin-4(3*H*)-ones could be obtained by employing DMSO as solvent instead of EtOH, which was utilized to prepare 2,3-dihydroquinazolin-4(1*H*)-ones in the same protocol [23], novel flexible strategies for selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones without toxicity, unavailable or expensive agent should benefit both synthetic and medicinal chemistry in terms of Green Chemistry.

As an oxidant, iodine is widely used for the oxidation of alcohols, aldehydes, sulfides, and amines; for the oxidation to aromatics; for the introduction of protecting groups; for the deprotection, and so on [24]. Meanwhile, iodine has a wide range of application as a mild Lewis acid catalyst in organic synthesis, such as the Michael addition, the mannich reaction, the hantzsch reaction and many other transformations [25,26]. However, a literature survey suggested that few studies have been performed on applying both the oxidizing and catalyzing abilities of iodine simultaneously to organic functional group conversions. As a cheap, less toxic, easily accessible, and eco-benign reagent, iodine would be more practical for organic synthesis if the selectivity could be controlled quantificationally via modulating the ratio in as much as the oxidizing ability require more iodine to fulfill. Herein, we would like to disclose a versatile procedure for the fabrication of mono substituted quinazolin-4(3*H*)-ones and 2,3-dihydroquinazolin-4(1*H*)-ones selectively in the presence of different ratio of iodine.

**Table 1**

The optimization of reaction conditions to synthesis 2-(4-methoxylphenyl)quinazolin-4(3*H*)-one and 2-(4-methoxylphenyl)-2,3-dihydroquinazolin- 4(1*H*)-one.[a]




**A** **M1** **N1**

| Entry | $I_2$ (mol %) | Solvent | A/$AcONH_4$ | *t* (min) | Yield (%)[b] | M1/N1[c] |
|---|---|---|---|---|---|---|
| 1 | 20 | EtOH | 1:1.2 | 25 | 86 | 100/0 |
| 2 | 20 | $H_2O$ | 1:1.2 | 15 | 77 | 100/0 |
| 3 | 20 | EtOH | 1:1.1 | 40 | 81 | 100/0 |
| 4 | 20 | EtOH | 1:1.3 | 30 | 85 | 100/0 |
| 5 | 20 | EtOH | 1:1.5 | 30 | 85 | 100/0 |
| 6 | 25 | EtOH | 1:1.2 | 25 | 86 | 100/0 |
| 7 | 20 | EtOH | 1:1.2 | 25 | 85[d] | 100/0 |
| 8 | 15 | EtOH | 1:1.2 | 60 | 91 | 97/3 |
| 9 | 10 | EtOH | 1:1.2 | 120 | 90 | 48/52 |
| 10 | 5 | EtOH | 1:1.2 | 70 | 89 | 1/99 |
| 11 | 0 | EtOH | 1:1.2 | 24h | 23 | 0/100 |

[a] Reaction conditions: 4-methoxylbenzaldehyde(5 mmol), was added to the solution containing **A**(5mmol), iodine, and $AcONH_4$ at room temperature, which was then increased to refluxing temperature.
[b] Isolated yield of **M**1 and **N**1 mixture.
[c] Determined by LC-MS.
[d] $N_2$ was used.

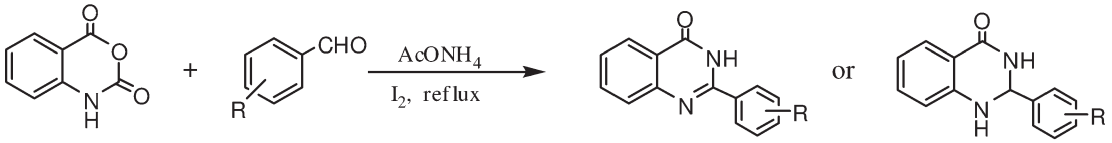
## RESULTS AND DISCUSSION

Following our continued interest in the iodine-catalyzed MCRs [26a–d], 20 mol % of iodine was initially selected to catalyze the model reaction of isatoic anhydride, 1.2 equiv. of ammonium acetate, and 4-methoxybenzaldehyde in refluxing ethanol, aimed at obtaining the compound **N**1. After 40 min stirring, the white flocs were totally precipitated from the reaction solution, the final pure product yielded in 63% after work up, unexpectedly melted at 241°C, which is the melt point of compound **M**1 exactly. Subsequent $^1$H NMR and LC-MS analysis certified that the white floc was just **M**1. Therefore, the optimization of the reaction conditions was carried out. First, the addition order of reactants was considered. As the enamine could be formed *in situ* and thus influence the yield of desired product, the aldehyde was added at last to the stirring solution at room temperature, which was increased to refluxing temperature as soon as possible, to our delight, the yields of product **M**1 could be up to 86%. With these conditions in hand, the solvent, ratio of **A** and $AcONH_4$, and the iodine concentration were screened subsequently. The results in Table 1 showed that refluxing the **A**, 4-methoxylbenzaldehyde and $AcONH_4$ rationed at 1:1:1.2 in the presence of 20 mol % of iodine about 25 min would provide the best result. Increasing the iodine amounts was ineffective for improvement of final yields. Interestingly, product **N**1 was detected and increased with the iodine concentration decreased from 20 mol % (Table 1, Entries 6–9), the pure product **N**1 could not be obtained until the amount of iodine reduced to 5 mol %, which was the right concentration to catalyze this three-compound reaction to give product **N**1, more iodine may present the oxidizing ability, resulting in mixed products of **M**1 and **N**1 (Table 1, Entries 8 and 9). As all the reactions were exposed in air, the $O_2$ may play the role of oxidant in the preparation of **M**1, so we employed the $N_2$ as an inert gas to perform the reaction (Table 1, Entry 7), and found that only the oxidated product **M**1 was detected in the reaction mixture by LC-Ms, which indicate that the catalytic iodine (20 mol %) played the roles of both catalyst and oxidant. Preliminary results unprecedentedly implied that we can selectively construct the structure of **M**1 and **N**1 promoted by 20 and 5 mol % of iodine, respectively.

In a comprehensive study, a sampling of the aldehydes was employed to explore the scope of this one-pot three-component reaction under optimal conditions (Table 2). Generally, all of the aldehydes participated smoothly and afforded the desired products in good to excellent yields, except for the 4-nitrobenzaldehyde yielded in 77% of **M** and 56% of **N** (Table 2, Entry 9 and 15). According to LC-MS monitoring of reaction mixtures, the benzylaldehyde and aromatic aldehydes bearing 4-Cl, 2-Cl, 4-Br demand more iodine to furnish the pure product **M** (Table 2, Entry 2, 4, 5, 8). The reaction time was slightly extended in the cases of producing pure product **N**.

**Table 2**

The preparation of 2-substituted-quinazolin-4(3*H*)-ones and 2-substituted-2,3-dihydroquinazolin- 4(1*H*)-ones.[a]




**A** **M** **N**

| Entry | R | $I_2$ (mol %) | *t* (min) | Yield (%)[b] | M/N[c] |
|---|---|---|---|---|---|
| 1 | 4-OMe | 20 | 25 | 86 | 100/0 |
| 2 | 4-Cl | 20 | 40 | 90 | 98/2 |
| | | 25 | 25 | 91 | 100/0 |
| 3 | 4-OH | 20 | 150 | 81 | 100/0 |
| 4 | H | 20 | 90 | 87 | 1/99 |
| | | 25 | 65 | 89 | 84/16 |
| | | 30 | 45 | 83 | 100/0 |
| 5 | 2-Cl | 20 | 60 | 94 | 3/97 |
| | | 30 | 45 | 93 | 99/1 |
| 6 | 4-$N(Me)_2$ | 20 | 15 | 92 | 100/0 |
| 7 | 3-Cl | 20 | 20 | 81 | 100/0 |
| 8 | 4-Br | 20 | 60 | 89 | 2/98 |
| | | 30 | 30 | 87 | 99/1 |
| 9 | 4-$NO_2$ | 20 | 90 | 77 | 100 |
| 10 | 4-OMe | 5 | 70 | 89 | 1/99 |
| 11 | H | 5 | 100 | 82 | 1/99 |
| 12 | 4-Cl | 5 | 55 | 95 | 0/100 |
| 13 | 4-$N(Me)_2$ | 5 | 120 | 91 | 0/100 |
| 14 | 4-Br | 5 | 90 | 91 | 0/100 |
| 15 | 4-$NO_2$ | 5 | 600 | 56 | 0/100 |

[a] Reaction conditions: 1 equiv. of aldehyde(5 mmol) was added to the solution containing **A**(5 mmol), iodine, and 1.2 equiv. of $AcONH_4$(5 mmol) at room temperature, which was then increased the to refluxing temperature.
[b] Isolated yield
[c] Determined by LC-MS

Besides, benzylaldehyde and 3-chlorobenzaldehyde provide somewhat lower yields and probable reason for this may be the lack of electron-influence.

Encouraged by these successes, we evaluated orthoester and *p*-toluidine for the MCR performance to furnish 3-substituted quinazolin-4(3*H*)-ones **E** and 2,3-dihydroquinazolin-4(1*H*)-ones **F** under the same conditions. Fortunately, the desired product 3-*p*-tolylquinazolin-4(3*H*)-one was favourably generated in 78% yield (Table 3, Entry 1). Thereafter, 5 mol % of iodine was tested aiming at constructing the structure 3-*p*-tolylquinazolin-2,3-dihydroquinazolin-4(1*H*)-one **F** (Fig. 1), whereas the same product 3-*p*-tolylquinazolin-4(3*H*)-one was obtained again in a 99% LC yield (Table 3, Entry 2). After carefully literature search, it was found that all of the methods reported [9,10,21] starting from orthoester were apt to form quinazolin-4(3*H*)-ones, for this may be the potential hydrogen-acquiring ability of —OEt dissociated from orthoester. Further attempt to optimize the conditions suggested that increasing the amount of amine up to 1.5 equiv. and replace the EtOH with $H_2O$ could improve the yield up to 89% and shorten the reaction time. As the pure product should be crystallized from EtOH, we chose EtOH as the solvent to exam other representative aromatic amine. As shown in Table 3, all of the substrates were compatible and the aromatic amine possessing electron-withdrawn group would lead to longer reaction time and slightly lower yield (Table 3, Entry 3).

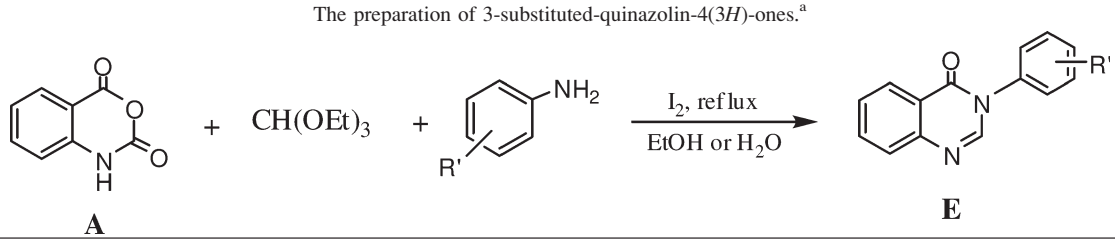
In conclusion, we have developed a novel and versatile method for the first time to selectively synthesize 2-substituted-quinazolin-4(3*H*)-ones and 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride, primary amine and various aldehydes in one-pot MCR protocol via modulating the iodine concentration, and also prepared 3-substituted-quinazolin-4(3*H*)-ones under the same conditions in the presence of 5 mol % of iodine. All of the reactions provided good to excellent yields of products that could be crystallized from the reaction solution. The operational simplicity, conditional generality, electively controllability made this method attractive to extensive application in organic chemistry.

## EXPERIMENTAL

The isatoic anhydride and iodine were obtained from commercial suppliers and used without further purification. All of the products are known and their physical data, mass data, and $^1H$

**Table 3**

The preparation of 3-substituted-quinazolin-4(3*H*)-ones.[a]



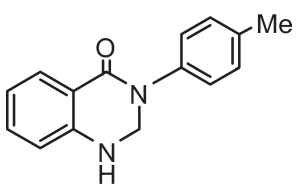

**A** **E**

| Entry | R′ | Solvent | $I_2$ (mol %) | *t* (min) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 4-Me | EtOH | 20 | 25 | 78 |
| | | EtOH | 5 | 30 | 75 |
| | | EtOH | 5 | 60 | 74[c] |
| | | EtOH | 5 | 25 | 88[d] |
| | | $H_2O$ | 5 | 15 | 89 |
| 2 | 4-OMe | EtOH | 5 | 25 | 93 |
| 3 | 4-Cl | EtOH | 5 | 200 | 81 |
| 4 | H | EtOH | 5 | 55 | 84 |

[a] Reaction conditions: 1 equiv. of othoester(5 mmol) was added to the solution containing **A**(5 mmol), iodine, and aromatic amine at room temperature, which was then increased the to refluxing temperature.
[b] Isolated yield.
[c] 1 equiv. of *p*-toluidine was added.
[d] 1.5 equiv. of *p*-toluidine was added.

NMR were essentially identical with those of authentic samples. Mass spectra were taken on an Agilent LC-MS 1100 series instrument in the electrospray ionization (positive ESI) mode. $^1$H NMR spectra were recorded at 300 MHz in DMSO-*d*6, and chemical shifts were reported in ppm from internal TMS (δ).

**The typical procedure for the preparation of 2-substituted-quinazolin-4(3*H*)-ones M.** 4-methoxylbenzaldehyde (0.68 g, 5 mmol), was added to the stirring solution containing **A**(0.815 g, 5 mmol), iodine(0.253 g, 1 mmol), and $AcONH_4$(0.462 g, 6 mmol) at room temperature in EtOH, then refluxing the mixture, after 25 min the white solid precipitated and EtOH was added till the solid dissolved again. The mixture was cooled to room temperature and the white flocs were crystallized slowly. After simple filtration and dryness, the product **M**1 was yielded in 86% (1.09 g, white flocs, m.p. 241°C). 2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (Table 2, Entry 1): $^1$H NMR(300 MHz, DMSO-*d*6) δ 3.81 (s, 3H), 7.04–7.07 (d, 2H), 7.42–7.47 (m, 1H), 7.65–7.68 (d, 1H), 7.76–7.78 (m, 1H), 8.08–8.11 (d, 1H), 8.14–8.17 (d, 2H), 12.53 (br s, NH); MS ($ES^+$) *m*/*z* 253(M + H); 2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (Table 2, Entry 2): $^1$H NMR(300 MHz, DMSO-*d*6) δ 7.52–7.57 (m, 1H), 7.62–7.65 (m, 2H), 7.74–7.76 (d, 1H), 7.83–7.88 (m, 1H), 8.15–8.22 (m, 3H), 12.83 (br s, NH); MS ($ES^+$) *m*/*z* 257(M + H).




**F**

**Figure 1.** The expected structure 3-*p*-tolylquinazolin-2,3-dihydroquinazolin-4(1*H*)-one **F**.

The 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones **N** were synthesized by a similar procedure except that 5 mol % of iodine(0.063 g, 0.25 mmol) was used. The products **N** were white flake. 2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, Entry 12): $^1$H NMR(300 MHz, DMSO-*d*6) δ 3.73 (s, 3H), 5.68 (s, 1H), 6.66–6.74 (m, 2H), 6.92 (d, 2H), 6.94 (s, NH), 7.23 (m, 1H), 7.39–7.41 (d, 2H), 7.58–7.60 (d, 1H), 8.21 (s, NH); MS ($ES^+$) *m*/*z* 255(M + H); 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, Entry 12): $^1$H NMR(300 MHz, DMSO-*d*6) δ 5.78 (s, 1H), 6.69–6.77 (m, 2H), 7.16 (s, NH), 7.22–7.28 (m, 1H), 7.44–7.53 (m, 4H), 7.60–7.63 (m, 1H), 8.36 (s, NH); MS ($ES^+$) *m*/*z* 259(M + H).

**The typical procedure for the preparation of 3-substituted-quinazolin-4(3*H*)-ones E.** Orthoester (5 mmol) was injected slowly into the stirring solution of **A**(0.815 g, 5 mmol), iodine(0.063 g, 0.25 mmol) and *p*-toluidine (0.8 g, 7.5 mmol) in EtOH at room temperature, increasing the temperature and refluxing the mixture 25 min followed by adding hot ethanol to further dissolve the solid formed, the product **E** was precipitated from the homogeneous solution slowly with the temperature decreased. Simple filtration and dryness would afford the pure 3-*p*-tolylquinazolin-4(3*H*)-one (1.04 g, 88%, white solid, m.p. 146–148°C) (Table 3, Entry 1): $^1$H NMR(300 MHz, DMSO-*d*6) δ 2.40 (s, 3H), 7.35–7.44 (m, 4H), 7.57–7.62 (m, 1H), 7.73–7.76 (d, 1H), 7.85–7.91 (m, 1H), 8.19–8.21 (d, 1H), 8.32 (s, 1H); MS ($ES^+$) *m*/*z* 237(M + H); 3-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (Table 3, Entry 2): $^1$H NMR(300MHz, DMSO-*d*6) δ 3.83 (s, 3H), 7.09–7.12 (m, 2H), 7.45–7.48 (m, 2H), 7.57–7.62 (m, 1H), 7.73–7.75 (m, 1H), 7.85–7.91 (m, 1H), 8.18–8.21 (m, 1H), 8.31 (s, 1H); MS ($ES^+$) *m*/*z* 253(M + H).

## REFERENCES AND NOTES

[1] Hour, M.; Huang, L.; Kuo, S.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. J Med Chem 2000, 43, 4479.

[2] Hamel, E.; Lin, C. M.; Plowman, J.; Wang, H.; Lee, K.; Paull, K. D. Biochem Pharmacol 1996, 51, 53.

[3] (a) Biressi, M. G.; Cantarelli, G.; Carissimi, M.; Catteneo, A.; Ravenna, F. Farmaco Ed Sci 1969, 24, 199; (b) Bhalla, P. R.; Walworth, B. L. Chem Abstr 1983, 98, 1669; (c) Bhalla, P. R.Walworth, B. L. Chem Abstr 1984, 100, 174857.

[4] Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webdter, W. J Org Chem 1969, 34, 887.

[5] Sharma, S. D.; Kaur, V. Synthesis 1989, 677.

[6] Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. J Med Chem 2000, 43, 2019.

[7] Su, W. K.; Yang, B. B. Aust J Chem 2002, 55, 695.

[8] Khurana, J. M.; Kukreja, G. J Heterocycl Chem 2003, 40, 677.

[9] Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Hu, H. Tetrahedron Lett 2003, 44, 3199.

[10] Shi, D. Q.; Shi, C. L.; Wang, J. X.; Rong, L. C.; Zhuang, Q. Y.; Wang, X. S. J Heterocycl Chem 2005, 40, 173.

[11] Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. J Org Chem 2005, 70, 6941.

[12] Liu, J. F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. Tetrahedron Lett 2005, 46, 1241.

[13] (a) Lopez, S. E.; Rosales, M. E.; Urdaneta, N.; Godoy, M. V.; Charris, J. E. J Chem Res Synop 2000, 258; (b) Abdel-Jalil, R. J.; Volter, W.; Saeed, M. Tetrahedron Lett 2004, 45, 3475.

[14] (a) Wolf, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. J Med Chem 1990, 33, 161; (b) Padia, J. K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, L. J Med Chem 1998, 41, 1042; (c) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. Tetrahedron Lett 1999, 40, 2175.

[15] For selected examples, see: (a) Takeuchi, H.; Haguvara, S.; Eguchi, S. Tetrahedron 1989, 45, 6375; (b) Takeuchi, H.; Haguvara, S.; Eguchi, S. J Org Chem 1991, 56, 1535. (c) Naleway, J. J.; Fox, C. M. J.; Robinhold, D.; Terpetsching, E.; Olsen, N. A.; Haugland, R. P. Tetrahedron Lett 1994, 35, 8569; (d) Abdel-Jalil, R. J.; Voelterb, W.; Saeed, M. Tetrahedron Lett 2004, 45, 3475; (e) Potewar, T. M.; Nadaf, R. N.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Synth Commun 2005, 35, 231.

[16] Zhu, J.; Bienaymé, H., Eds. Multicomponent Reaction; Wiley-VCH: Weinheim, 2005.

[17] Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Baghbanzadeh, M. Synlett 2005, 1155.

[18] Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgarya, G.; Mohammadi, A. A. Tetrahedron Lett 2005, 46, 6123.

[19] Baghbanzadeh, M.; Salehi, P.; Dabiri, M.; Kozehgarya, G. Synthesis 2006, 344.

[20] Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. Synth Commun 2006, 36, 2287.

[21] Lingaiaha, B. V.; Ezikiela, G.; Yakaiaha, T.; Reddyb, G. V.; Rao, P. S. Synlett 2006, 2507.

[22] Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. Green Chem 2007, 9, 972.

[23] Chen, J. X.; Wu, D. Z.; He, F.; Liu, M. C.; Wu, H. Y.; Ding, J. C.; Su, W. K. Tetrahedron Lett 2008, 49, 3814.

[24] Togo, H.; Iida, S. Synlett 2006, 2159.

[25] For selected examples, see: (a) Bandger, B. P., Shaikh, K. A. Tetrahedron Lett 2003, 44, 1959; (b) Ko, S.; Lin, C. C.; Tu, Z. J.; Wang, Y. F.; Wang, C. C.; Yao C. F. Tetrahedron Lett 2006, 47, 48; (c) Lee B. S.; Mahajan, S.; Janda K. D. Synlett 2005, 1325; (d) Prodeep, P. J Org Chem 2004, 69, 4005; (e) Zolfigol, M. A.; Salehi, P.; adi-Zad A. K.; Shayegh M. J Mol Catal A: Chem.,2007, 265, 88.

[26] (a) Ren Y. M.; Cai C. Monatsh Chem 2009, 140, 1434; (b) Ren Y. M.; Cai C. Catal Commun 2008, 9, 1017; (c) Ren, Y. M.; Cai, C. Synth Commun 2007, 37, 2221; (d) Ren, Y. M.; Cai, C. Catal Lett 2007, 118, 134; (e) Ren, Y. M.; Cai, C. Tetrahedron Lett 2008, 49, 7110.

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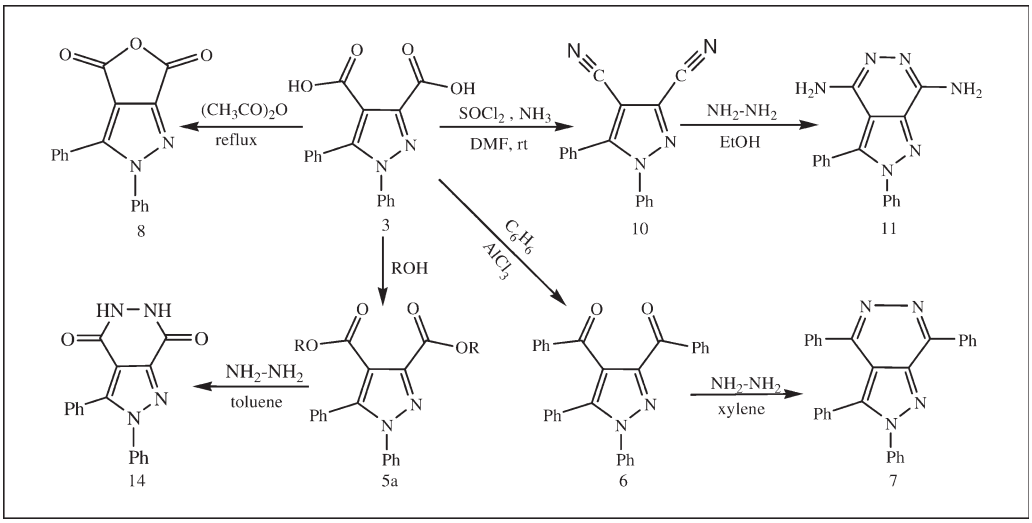


Compound of 4-(ethoxycarbonyl)-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **2** was obtained from the reaction of ethyl 4,5-dioxo-2-phenyl-4,5-dihydrofuran-3-carboxylate and 1-benzylidene-2-phenylhydrazine. A number of substitute pyrazole dicarboxylic acid derivatives (**4, 5a–c, 6, 7, 8, 9a–m, 10, 11, 12, 13, 14**) were synthesized from 1,5-diphenyl-1*H*-pyrazole-3,4-dicarboxylic acid **3** which was prepared from basic hydrolysis of **2**. Structures of synthesized compounds were characterized by $^{1}$H NMR, $^{13}$C NMR, Mass, FTIR, and elemental analysis.

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## INTRODUCTION

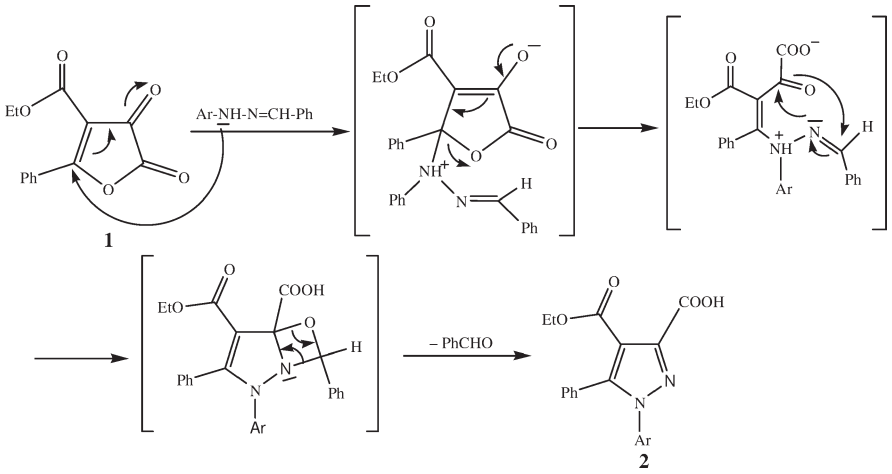
The chemistry of pyrazole derivatives have been the subject of much research because of their importance in various applications and their widespread potential biological and pharmacological activities such as antimicrobial, antiviral, antitumor, anti-inflammatory, pesticidal, antifungal, antidepressant, antipyretic, and analgesic [1–10]. Thus, these compounds have been the focus of high attention among medicinal chemists [11–16]. It is also known that biological activities of pyrazole derivatives which include substituted heteroaryl groups increase and that some pyrazolo-pyridazine compounds which include the same heteroaryl groups are used as a cure for many diseases [17–25].

Pyrazole-3-carboxylic acid derivatives in general are well-known nitrogen-containing heterocyclic compounds, and various procedures have been developed for their syntheses [26–31]. In the literature, there is not much research related to the reactions of derivatives of 1,5-diphenyl-1*H*-pyrazole-3,4-dicarboxylic acids although a number of new derivatives of pyrazoles some of which have bicyclic structure were synthesized [26–29]. In this research, we decided to extend our previous studies to satisfy this deficiency and to synthesize different derivatives of pyrazole compounds that show biological activity [20,21,26,29].

## RESULTS AND DISCUSSION

1,5-Diphenyl-1*H*-pyrazole-3,4-dicarboxylic acid **3**, which was our initial compound, was prepared after various reaction steps. First, ethyl 4,5-dioxo–2-phenyl-4,5–dihydrofuran–3-carboxylate **1** compound was prepared from the reactions of ethyl 3-oxo-3-phenylpropanoate and oxalyl dichloride [32,33]. Keeping in mind that H-active nucleophiles attack the C-2, C-3, and C-4 positions of furandiones and it starts the reactions in which intermediate products were formed, NH group attacks to

**Scheme 1**

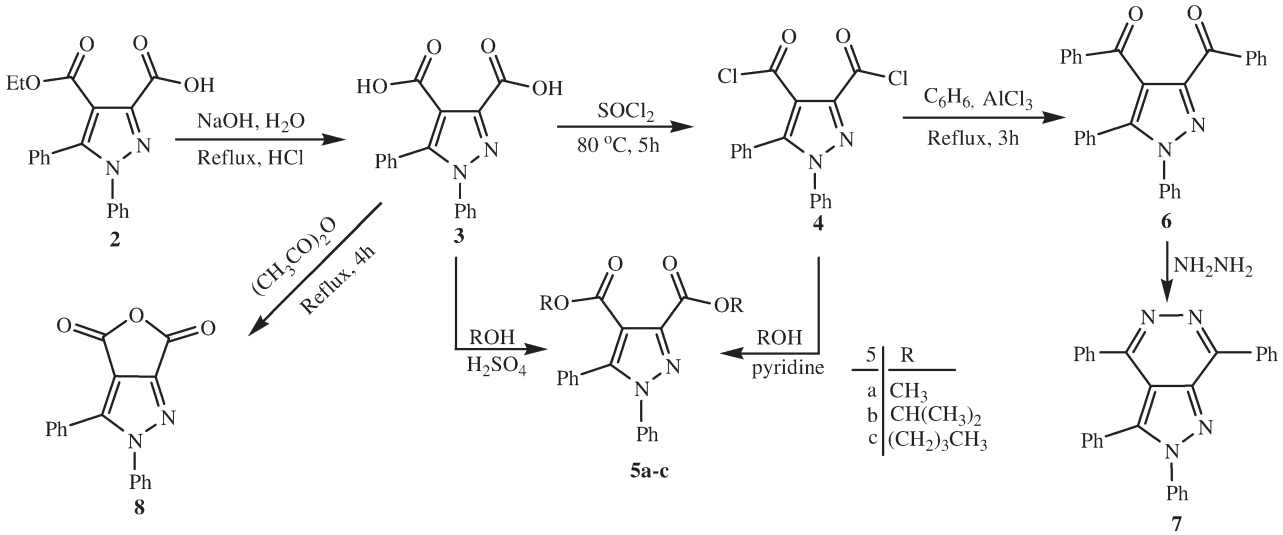


C-3 and C-4 positions of furandione in the condensation reaction of **1** with 1-benzylidene-2-phenylhydrazine in no solvent media [26,27,30]. The possible reaction steps of 4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazole-3-carboxylic acid **2** was given in Scheme 1.

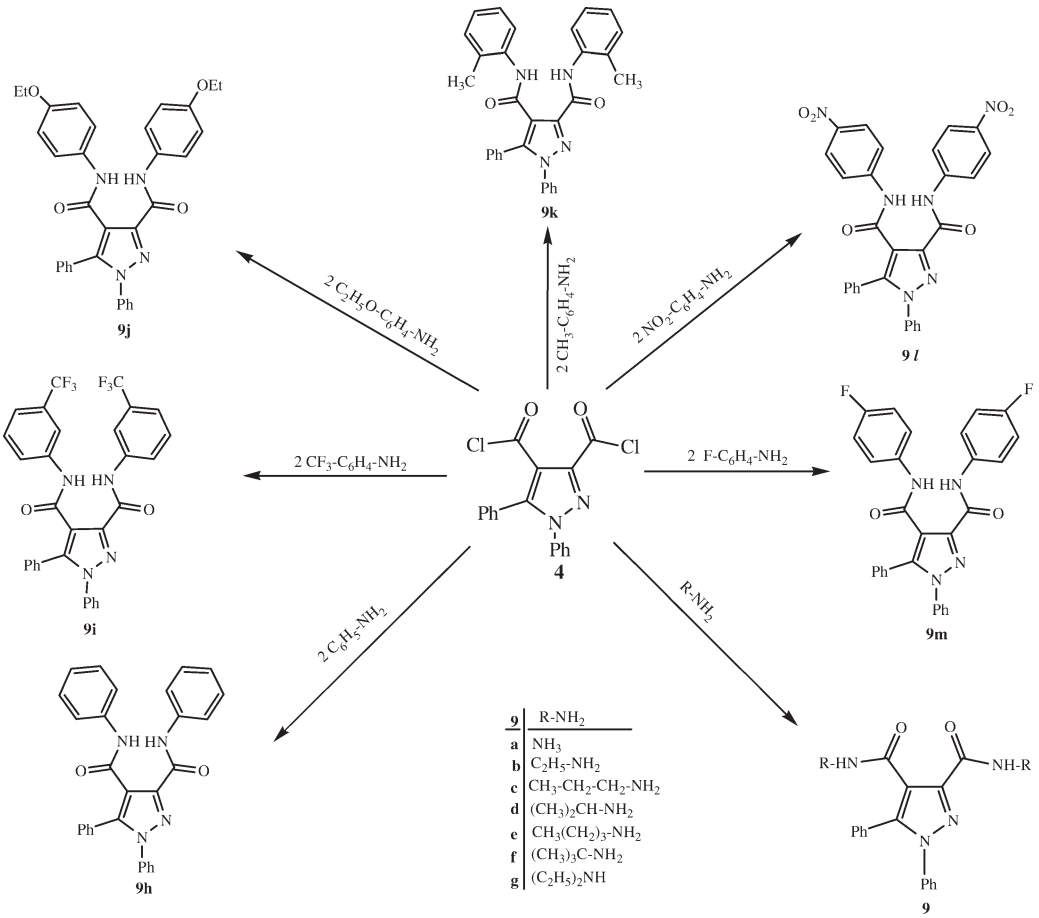
1,5-Diphenyl-1*H*-pyrazole-3,4-dicarboxylic acid **3** compound was prepared from the basic hydrolysis of **2** at a high yield (92%). The long reaction time increased the yield. The structure was confirmed with the characteristic IR absorption bands at 3354–2454 $cm^{-1}$ (COOH), 3064 $cm^{-1}$ (Ar CH ), 1670 $cm^{-1}$ (acid, C=O), 1597–1486 $cm^{-1}$ (C=C and C=N) and the $^{13}C$ NMR signals at $\delta = 163.75$ and $\delta = 164.61$ (acid, C=O). 306 m/z (M-2) value in mass spectra for **3** showed the existence of molecular ion structure.

Diester derivatives of Compound **3** were obtained in two different methods. In the first method, carboxylic groups of **3** were activated with $SOCl_2$ and gave the **4**. Afterward, the diester derivatives **5a–c** were obtained from the reaction of **4** with various alcohols with pyridine catalyst. However, it was understood from TLC works that synthesized products by this method contained impurity. This impurity was probably resulted from pyridine and was difficult to remove. In the second method, compound **3** gave the purer diester products **5a–c** about in yield of 61–75%. For this reason, the compound **3** was heated with various alcohols in benzene with sulfuric acid catalyst (Scheme 2). The second method was chosen in this study. On the other hand, heating the compound **4** in dry benzene with $AlCl_3$

**Scheme 2**



**Scheme 3**




catalyst [34] gave 1-phenyl-1H-pyrazole-3,4-diyl) bis(phenylmethanone **6** (Scheme 2).

$NH_2$ groups of hydrazine which have strong nucleophilic property attacks to benzoyl carbons when the compound **6** was heated with anhydrous hydrazine. In the second stage, cyclization occurred with the removal of two moles water, and pyrazolo-pyridazine derivative **7** was obtained (Scheme 2).

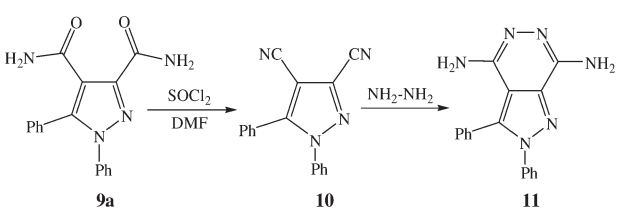
Moreover, heating of **3** in acetic anhydride caused the leaving of one mole water. As a result of this, furo[3,4-c] pyrazole-4,6-dione **8** (Scheme 2) was synthesized [35–37]. However, it was also observed from TLC controls that this compound was very sensitive to oxidation in air and returned to its initial compound. Therefore, it is suitable to handle this compound in desiccator by being dried with $P_2O_5$.

Derivatives of pyrazole-3,4-dicarboxamide **9a–m** were prepared easily by reaction of **4** with ammonia, substituted aryl amines, and a series of alkyl amines (Scheme 3). Structures of the compounds were confirmed with spectral data.

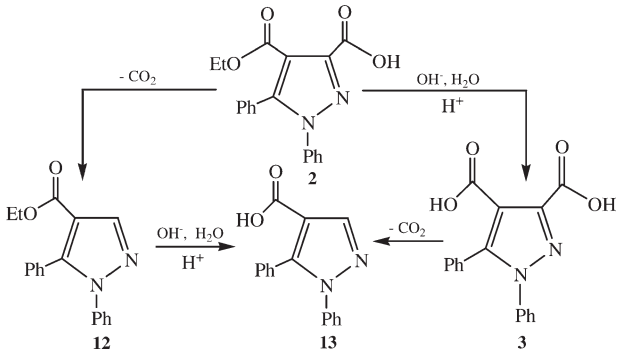
As a result of dehydration of **9a** in cold DMF and $SOCl_2$ mix, dinitrile **10** compound occurred at 96% yield [20,26]. Compound **10** showed characteristic IR absorption band at 2231 $cm^{-1}$ (C≡N). IR spectra of compound **10** showed no absorption bands corresponding to the COOH group such as 3300–2500 $cm^{-1}$ (COOH) and 1700–1750 $cm^{-1}$ (acid, C=O) like the 1,5-diphenyl-1*H*-pyrazole-3,4-dicarboxylic acid. Furthermore, $^{13}C$ NMR signals at $\delta$ = 110.77–110.80 ppm were related to carbon of nitrile (C≡N).

Reaction of **10** with anhydrous hydrazine in absolute ethanol led to the formation of the 2,3-diphenyl-2H-pyrazolo[3,4-d]pyridazine-4,7-diamine **11** in about 69% yield (Scheme 4). Structure of the compound was confirmed with spectral data (See Experiments).

**Scheme 4**



**Scheme 5**



As a result of decarboxylation of **2** at high temperature (200–220°C), the compound **12** was obtained and the compound **13** was synthesized after basic hydrolysis of **12**. It was understood from TLC and spectral data that basic hydrolysis of **12** and decarboxylation of **3** gave the same products 1,5-diphenyl-1*H*-pyrazole-4-carboxylic acid **13**. After decarboxylation of **3**, it was shown that leaving carboxyl group bonded the adjacent carbon to nitrogen (Scheme 5).

On the other hand, cyclo-condensation reaction of **2** and **5a** with hydrazine hydrate gave the same product pyrazolo[3,4-d]pyridazine-4,7-dione **14** [6,26]. IR, $^1$H NMR, and $^{13}$C NMR spectra [IR: 3158–2629), $^1$H NMR: 10.40 (br. s, 1H, NH—C=O), 5.30 (br. s, 1H, N=C—OH), $^{13}$C NMR: 161.79 and 161.58 (C=O, C-4), 156.58 and 152.33 (C=O, C-7)] showed evidence of the presence of a tautomeric equilibrium (HN—C=O↔N=C—OH) between the two tautomers (keto-enol) of compound **14** (Scheme 6).

In this research, a number of derivatives of substituted pyrazole dicarboxylic acids were gained to pyrazole chemistry and characterization of each compound were performed with the help of spectral data (See Experiments).

## EXPERIMENTS

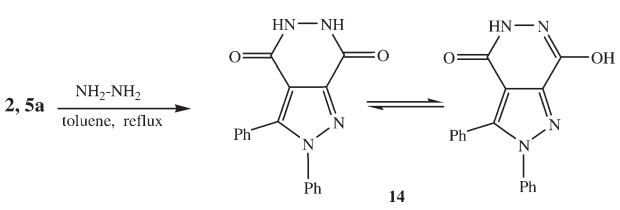
The optimum reaction conditions were determined considering the time, concentration, solvent, and structure of reactive compounds which were effective on yield and velocity of chemical reactions. Chemical compounds used in this research were at analytical purity, and the solvents were purified by using appropriate purifying agents and distillation. At the end of the each experiment, TLC was performed using DC Alufolien Kiesegel 60F/254 Merck and Camag TLC devices. Melting points were measured with Barnstead Electrothermal 9200 apparatus and were not corrected. IR spectrum data of compounds were determined by Mattson 1000 FTIR with using of KBr pellets. $^1$H NMR and $^{13}$C NMR spectra were evaluated by BRUKER DPX-400, (400MHz), and High Performance Digital FT-NMR (100MHz) spectrometers. Mass spectra data were determined by Varian Mat III 80 eV. Elemental analyses were carried out on a Leco CHNS-932 instrument.

**1,5-Diphenyl-1*H*-pyrazole-3,4-dicarboxylic acid (3).** Compound **2** of 0.336 g (1 mmol) was refluxed in solution of 0.1 g (2.5 mmol) NaOH for about 1.5 h. Mixed solution was cooled down to room temperature. It was stirred for a while by adding 1.5 mL concentrated HCl and water at equal volume. Precipitated white solid product was filtered and washed with water again. It was purified from water–ethanol mixture by crystallization. (283 mg, 92%); mp 224–225°C; IR (ν, cm$^{-1}$): 3354–2454 (OH, COOH), 3064 (CH, aromatic), 1670 (C=O), 1597–1486 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27–7.40 (m, 10H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.61 and 163.76 (C=O, acid), 144.85 (C–3), 144.31(C–5), 116.14 (C–4), 138.93, 130.53, 129.74, 129.52, 129.21, 128.67, 128.54, 126.32; MS(CI) m/z 306.0 (M–2, $COO^-$); Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.56; H, 3.65; N, 9.12.

**1,5-Diphenyl-1*H*-pyrazole-3,4-dicarbonyl dichloride (4).** Compound **3** of 0.308 g (1 mmol) was refluxed with excessive $SOCl_2$ at 80°C for about 5 h. Excessive $SOCl_2$ was evaporated. Remaining oily product was purified in ether–hexane mixture. (259 mg, 75%); mp 86–89°C; IR (ν, cm$^{-1}$): 3060 (CH, aromatic), 1735 (C=O), 1620–1487 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.00–7.72 (m, 10H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.39 and 161.09 (C=O), 146.54 (C–3), 143.96 (C–5), 120.35 (C-4), 137.82, 130.60, 130.09, 129.56, 129.35, 128.90, 126.13, 125.51; Anal. Calcd. for $C_{17}H_{10}Cl_2N_2O_2$: C, 59.15; H, 2.92; N, 8.12. Found: C, 59.35; H, 2.79; N, 8.10.

**General procedure for compounds 5a–c.** Compound **3 of** 1 mmol was dissolved in 10 mL dry benzene, and 2 mL alcohol (MeOH, *i*-PrOH, BuOH) and 0.2 mL $H_2SO_4$ was added to this solution. Mixture was refluxed for 4–5 h. After evaporation, some water was added to the product remaining at the bottom of the flask and transferred to separate funnel. 10 mL of ether was added

**Scheme 6**



to the mixture and was washed with 10% $Na_2CO_3$ solution. Ether was evaporated after separation of organic phase. The synthesized crude products **5a–c** were purified from hexane.

***Dimethyl-1,5-diphenyl-1H-pyrazole-3,4-dicarboxylate (5a).*** (205 mg, 61%); mp 96–97°C; IR (ν, $cm^{-1}$): 3002 (CH, aromatic), 2952 (CH, aliphatic), 1718 (C=O), 1596–1497 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39–7.23 (m, 10H, ArH), 4.00 and 3.78 (s, 6H, $2OCH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 163.48 and 162.31 (C=O), 144.86 (C–3), 143.21 (C–5), 115.56 (C–4), 52.63 and 52.25 ($2OCH_3$), 138.62, 130.05, 129.53, 128.99, 128.63, 128.38, 127.82, 125.63; Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.68; H, 4.89; N, 8.32.

***Diisopropyl-1,5-diphenyl-1H-pyrazole-3,4-dicarboxylate (5b).*** (239 mg, 61%); mp 96–97°C; IR (ν, $cm^{-1}$): 3059 (CH, aromatic), 2937 (CH, aliphatic), 1710 (C=O), 1599–1498 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39–7.24 (m, 10H, ArH), 5.36 and 5.12 (p, $J$ = 6.3 Hz, 2H, 2OCH), 1.45 and 1.27 (d, $J$ = 6.3 Hz, 12H, $2CH(CH_3)_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 162.51 and 161.80 (C=O), 144.41 (C–3), 144.09 (C–2), 115.93 (C–4), 69.54 and 68.73 (OCH), 21.83 and 21.57 ($CH_3$), 138.73, 130.11, 129.32, 128.92, 128.44, 128.24, 128.22, 125.63; Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.25; H, 6.19; N, 7.21.

***Dibutyl 1,5-diphenyl-1H-pyrazole-3,4-dicarboxylate (5c).*** (286 mg, 68%); mp 49–50°C; IR (ν, $cm^{-1}$): 3062 (CH, aromatic), 2959 (CH, aliphatic), 1719 (C=O), 1596–1498 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38–7.23 (m, 10H, ArH), 4.42 and 4.18 (t, $J$ = 6.8 Hz, 4H, $2OCH_2$), 1.81 (p, $J$ = 7.2 Hz, 4H, $2OCH_2CH_2CH_2$), 1.62–1.46 (m, 4H, $CH_2CH_2CH_3$ and $OCH_2CH_2CH_2$), 1.21 (h, $J$ = 7.5 Hz, 2H, $CH_2CH_2CH_3$), 0.99 and 0.86 (t, $J$ = 7.4 Hz, 6H, $2CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 163.03 and 162.31 (C=O), 144.64 (C–3), 143.94 (C–5), 115.49 (C–4), 65.60 and 64.99 ($OCH_2$), 30.65 and 30.41 ($CH_2CH_2CH_2$), 19.11 and 18.97 ($CH_2CH_2CH_3$), 13.75 and 13.64 ($CH_3$), 138.66, 130.10, 129.39, 128.92, 128.48, 128.31, 128.14, 125.58, 118.80; Anal. Calcd. for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.29; H, 6.79; N, 6.65.

**(1,5-Diphenyl-1*H*-pyrazole-3,4-diyl)bis (phenylmethanone) (6).** Compound **4** of 0.345 g (1 mmol) was dissolved in dry benzene, and 0.33 g (2.5 mmol) $AlCl_3$ was added to this solution. After cooling down of mixture which was refluxed for 3 h, organic phase was separated by adding some ether and ice water. Then ether was evaporated and the residue solid was recrystallized from ethanol–water mixture. (253 mg, 59%); mp 174–175°C; IR (ν, $cm^{-1}$): 3064 and 3028 (CH, aromatic), 1664 (C=O), 1617–1489 (C=C and C=N); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 8.20–7.23 (m, 20H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ (ppm): 191.04 and 187.16 (C=O, benzoyl), 149.43 (C–3), 144.01 (C–5), 123.85 (C–4), 139.04, 137.98, 136.47, 134.01, 133.80, 130.72, 130.70, 130.29, 129.82, 129.64, 129.39, 129.05, 129.02, 128.90, 128.07, 126.48; Anal. Calcd. for $C_{29}H_{20}N_2O_2$: C, 81.29; H, 4.70; N, 6.54. Found: C, 81.42; H, 4.65; N, 6.51

**2,3,4,7-Tetraphenyl-2*H*-pyrazolo[3,4-d]pyridazine (7).** Compound **6** of 1 mmol was dissolved in dry xylene, and 0.1 mL hydrazine was added and refluxed for 4 h. Then, solvent was evaporated and 10 mL ether was added to residue product and stirred for a while in cold. Precipitated yellow product was filtered, washed with water, and purified from ethanol–water mixture by crystallization. (343 mg, 81%); mp 194–196°C; IR (ν, $cm^{-1}$): 3057 and 3030 (CH, aromatic), 1590–1488 (C=C and C=N); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 7.57–7.01 (m, 20H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ (ppm): 156.57 and 149.93 (C–4 and C–7), 141.89, 139.85, 139.51, 137.01, 135.72, 135.35, 131.21, 130.80, 130.03, 129.53, 129.47, 129.41, 129.35, 129.13, 128.50, 128.32, 127.84, 127.28, 116.17 Anal. Calcd. for $C_{29}H_{20}N_4$: C, 82.05; H, 4.75; N, 13.20. Found: C, 81.93; H, 4.67; N, 13.28.

**2,3-Diphenyl-2*H*-furo[3,4-c]pyrazole-4,6-dione (8).** Compound **3 of** 0.308 g (1 mmol) was transferred to a flask. 2.5 mL acetic anhydride and 0.1 mL pyridine was added and refluxed for about 4 h. Excessive amount of solvent was evaporated. The residue product was purified from hexane and chloroform mixture by crystallization. (226 mg, 78%); mp 176–178°C; IR (ν, $cm^{-1}$): 3072 (CH, aromatic), 1810 and 1708 (C=O), 1628–1489 (C=C and C=N); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 7.30–7.01 (m, 10H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ (ppm): 164.46 and 164.15 (C=O), 146.99, 140.71, 139.12, 130.77, 129.41, 129.23, 129.03, 128.43, 126.33, 125.74, 116.25; MS(CI) m/z 291.0 (M+1); Anal. Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.48; H, 3.35; N, 9.72.

**1,5-Diphenyl-1*H*-pyrazole-3,4-dicarboxamide (9a).** Compound **4** of 0.345 g (1 mmol) was dissolved in $CCl_4$ and cooled down to 0°C. Excessive amount of $NH_3$ was added to this solution. To complete the reaction, mixture was stirred for about an hour at room temperature. Precipitated white product was washed with water and purified from ethanol by crystallization.

(217 mg, 71%); mp 286–287°C; IR (ν, $cm^{-1}$): 3308 and 3146 (NH), 3073 (CH, aromatic), 1650 (amide C=O), 1587–1489 (C=C and C=N); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 8.06 and 7.76 (br. 4H, $2NH_2$), 7.39–7.24 (m, 10H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ (ppm): 165.10 and 161.30 (C=O), 143.60 (C–3),

139.56 (C–5), 119.80 (C–4), 130.15, 129.81, 129.55, 129.12, 128.40, 128.31, 128.13, 123.50; MS(CI) m/z 307.1 (M+1); Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.61; H, 4.69; N, 18.27.

**General procedure for compounds 9b–m.** Compound **4** of 0.345 g (1 mmol) was dissolved in 10 mL dry xylene and 4 mmol aryl or alkyl amine compound was added. Mixture was refluxed for 3 h and solvent was evaporated. The crude product was washed with water and purified from an appropriate solvent.

***1,5-Diphenyl-N³,N⁴-diethyl-1H-pyrazole-3,4-dicarboxamide (9b).*** (304 mg, 84%); mp 138–139°C; (was crystallized from EtOH/$H_2O$); IR (ν, $cm^{-1}$): 3456 and 3291 (NH), 3077 (CH, aromatic), 2974 and 2930 (CH, aliphatic), 1644 (C=O), 1553–1496 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.35 (m, 2H, 2NH), 7.35–7.17 (m, 10H, ArH), 3.52 and 3.40 (p, $J$ = 3.6 Hz, 4H, $2CH_2$), 1.32 and 1.21 (t, $J$ = 7.3 Hz, 6H, $2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.15 and 161.36 (C=O), 148.38 (C–3), 142.56 (C–5), 117.34 (C–4), 34.49 and 34.08 ($NHCH_2$), 14.72 and 14.67 ($CH_3$), 138.78, 130.53, 129.85, 129.75, 128.85, 128.43, 127.95, 125.62; Anal. Calcd. for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.45; H, 6.21; N, 15.42.

***1,5-Diphenyl-N³,N⁴-dipropyl-1H-pyrazole-3,4-dicarboxamide (9c).*** (320 mg, 82%); mp 135–136°C; (was crystallized from chloroform/hexane); IR (ν, $cm^{-1}$): 3361 and 3256 (NH), 3059 (CH, aromatic), 2962 and 2874 (CH, aliphatic), 1634 (C=O), 1555–1492 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.37 (m, 2H, 2NH), 7.31–7.15 (m, 10H, ArH), 3.45 and 3.32 (q, $J$ = 6.8 Hz, 4H, $2NHCH_2CH_2$), 1.69–1.59 (m, 4H, $2CH_2CH_2CH_3$), 0,94–1,02 (m, 6H, $2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.26 and 161.52 (C=O), 148.31 (C–3), 142.66 (C–5), 117.32 (C–4), 41.56 and 41.39 ($NHCH_2$), 22.89 and 22.85 ($CH_2$—$CH_2$), 11.73 and 11.55 ($CH_3$), 138.77, 130.53, 129.86, 128.84, 128.42, 128.11, 127.95, 125.61; Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.63; H, 6.79; N, 14.32.

***1,5-Diphenyl-N³,N⁴-diisopropyl-1H-pyrazole-3,4-dicarboxamide (9d).*** (332 mg, 85%); mp 159–160°C; (was crystallized from ether/hexane); IR (ν, $cm^{-1}$): 3389 and 3249 (NH), 3036 (CH, aromatic), 2967 and 2931 (CH, aliphatic), 1656 (C=O), 1633–1492 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.21–10.19 (m, 2H, 2NH), 7.36–7.17 (m, 10H, ArH), 4.34 and 4.18 (m, 2H, $2NHCH(CH_3)_2$), 1.33 and 1.25 (d, $J$ = 6.6 Hz, 12H, $4CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.35 and 160.61 (C=O), 148.27 (C–3), 142.76 (C–5), 117.57 (C–4), 41.59 and 40.99 (NHCH), 22.72 and 22.70 ($CH(CH_3)_2$), 138.81, 130.52, 129.91, 128.85, 128.82, 128.42, 127.96, 125.72; Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.55; H, 6.82; N, 14.37.

***1,5-Diphenyl-N³,N⁴-dibutyl-1H-pyrazole-3,4-dicarboxamide (9e).*** (334 mg, 80%); mp 133–134°C; (was crystallized from ether/hexane); IR (ν, $cm^{-1}$): 3371 and 3256 (NH), 3033 (CH, aromatic), 2960, 2931 and 2871 (CH, aliphatic), 1657 (C=O), 1627–1493 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.34 and 7.51 (m, 2H, 2NH), 7.33–7.17 (m, 10H, ArH), 3.50 and 3.36 (q, $J$ = 7.1 Hz, 4H, $2NHCH_2CH_2$), 1.65–1.59 (m, 4H, $2CH_2CH_2CH_2$), 1.54–1.22 (m, 4H, $2CH_2CH_3$), 1.11–0.78 (m, 6H, $2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.23 and 161.45 (C=O), 148.30 (C–3), 142.68 (C–5), 117.34 (C–4), 39.35 and 39.19 ($NHCH_2$), 31.55 ($CH_2CH_2CH_2$), 20.37 and 20.16 ($CH_2CH_3$), 13.89 and 13.32 ($CH_3$), 138.79, 130.54, 129.88, 128.84, 128.40, 128.38, 127.95, 125.61; Anal. Calcd. for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.22; N, 13.39. Found: C, 71.59; H, 7.28; N, 13.45.

***1,5-Diphenyl-N³,N⁴-di-tert-butyl-1H-pyrazole-3,4-dicarboxamide (9f).*** (343 mg, 82%); mp 174–175°C; (was crystallized from ether/hexane); IR (ν, $cm^{-1}$): 3393 and 3268 (NH), 3069 (CH, aromatic), 2968 and 2929 (CH, aliphatic), 1665 (C=O), 1643–1489 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.44 and 7.39 (m, 2H, 2NH), 7.35–7.15 (m, 10H, ArH), 1.51 and 1.40 (s, 18H, $6CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.66 and 161.30 (C=O), 147.20 (C–3), 144.15 (C–5), 118.42 (C–4), 51.68 and 51.01 (NHC), 28.71 and 28.68 ($C(CH_3)_3$), 138.90, 130.40, 129.76, 128.92, 128.82, 128.28, 128.11, 125.74; Anal. Calcd. for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.22; N, 13.39. Found: C, 71.59; H, 7.25; N, 13.38.

***1,5-Diphenyl-N³,N³,N⁴,N⁴-tetraethyl-1H-pyrazole-3,4-dicarboxamide (9g).*** (322 mg, 77%); mp 134–135°C; (was crystallized from chloroform/hexane); IR (ν, $cm^{-1}$): 3063 (CH, aromatic), 2978 and 2940 (CH, aliphatic), 1656 (C=O), 1617–1496 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49–7.15 (m, 10H, ArH), 3.57 and 3.13 (q, $J$ = 7.1 Hz, 8H, $4NCH_2$), 1.09 and 0.74 (t, $J$ = 7.1 Hz, 12H, $4CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.46 and 162.68 (C=O), 145.63 (C–3), 139.42 (C–5), 119.97 (C–4), 43.49, 43.37, 40.31, 38.87 ($NCH_2$), 14.60, 13.36, 12.87, 12.44 ($CH_3$), 139.35, 131.53, 129.27, 128.91, 128.69, 128.54, 127.70, 125.02; Anal. Calcd. for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.22; N, 13.39. Found: C, 71.65; H, 7.25; N, 13.41.

***1,5,N³,N⁴,-Tetraphenyl-1H-pyrazole-3,4-dicarboxamide (9h).*** (357 mg, 78%); mp 209–210°C; (was crystallized from chloroform/hexane); IR (ν, $cm^{-1}$): 3465 (NH), 3030 (CH, aromatic), 1655 (C=O), 1599–1489 (C=C and C=N); $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.54 and 9.45 (s, 2H, 2NH), 7.85–7.10 (m, 20H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.64 and 159.35 (C=O), 149.55 (C–3), 142.18 (C–5), 118.14 (C–4), 139.07, 138.58, 137.13, 130.62, 130.60, 129.50,

129.22, 129.00, 128.80, 128.78, 128.16, 125.76, 125.13, 123.70, 120.67, 120.33; Anal. Calcd. for $C_{29}H_{22}N_4O_2$: C, 75.97; H, 4.84; N, 12.22. Found: C, 75.86; H, 4.92; N, 12.19.

***1,5-Diphenyl-N³,N⁴-bis(3-(trifluoromethyl) phenyl)-1H-pyrazole-3,4-dicarboxamide (9i).*** (434 mg, 73%); mp 202–203°C; (was crystallized from BuOH); IR (ν, $cm^{-1}$): 3464 and 3376 (NH), 3070 and 3023 (CH, aromatic), 1659 (C=O), 1626–1490 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 12.61 and 9.48 (s, 2H, 2NH), 8.10–7.23 (m, 18H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.88 and 159.34 (C=O), 150.10 (C–3), 141.56 (C–5), 123.69 and 123.37 ($\underline{C}F_3$), 116.92 (C–4), 139.41, 138.35, 137.48, 130.49, 129.86, 129.43, 129.23, 129.07, 129.05, 129.01, 128.23, 125.73, 121.77, 121.74, 120.32, 120.28, 117.76, 117.32, 117.28, 116.96; Anal. Calcd. for $C_{31}H_{20}F_6N_4O_2$: C, 62.63; H, 3.39; N, 9.42. Found: C, 62.48; H, 3.45; N, 9.45.

***1,5-Diphenyl-N³,N⁴-bis(4-ethoxyphenyl)-1H-pyrazole-3,4-dicarboxamide (9j).*** (410 mg, 75%); mp 210–211°C; (was crystallized from PhMe); IR (ν, $cm^{-1}$): 3459 and 3314 (NH), 3020 (CH, aromatic), 2857 (CH, aliphatic), 1665 (C=O), 1620–1501 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 12.44 and 9.23 (s, 2H, 2NH), 7.74–6.83 (m, 18H, ArH), 4.27–3.86 (m, 4H, $2O\underline{C}H_2$), 1.39–1.47 (m, 6H, $2CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.40 and 159.03 (C=O), 156.38 and 155.24 (C=C-OEt), 149.33 (C–3), 142.24 (C–5), 114.55 (C–4), 63.74 and 63.64 ($O\underline{C}H_2$), 14.89 ($CH_3$), 138.65, 132.23, 130.59, 129.95, 129.60, 129.11, 128.94, 128.68, 128.09, 125.73, 122.45, 121.77, 118.15, 114.91; Anal. Calcd. for $C_{33}H_{30}N_4O_4$: C, 72.51; H, 5.53; N, 10.25. Found: C, 72.45; H, 5.58; N, 10.24.

***1,5-Diphenyl-N³,N⁴-di-o-tolyl-1H-pyrazole-3,4-dicarboxamide (9k).*** (365 mg, 75%); mp 195–196°C; (was crystallized from PhMe); IR (ν, $cm^{-1}$): 3489 and 3381 (NH), 3029 (CH, aromatic), 2922 and 2865 (CH, aliphatic), 1658 (C=O), 1615–1485 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 11.84 and 9.28 (s, 2H, 2NH), 8.03–7.04 (m, 18H, ArH), 2.42 (s, 6H, $2CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.34 and 159.75 (C=O), 149.63 (C–3), 142.60 (C–5), 118.05 (C–4), 18.62 and 17.92 ($CH_3$), 138.78, 136.52, 135.12, 130.89, 130.71, 130.59, 130.39, 129.60, 129.15, 129.10, 129.02, 128.67, 128.17, 126.93, 126.18, 125.69, 125.64, 124.85, 124.50, 122.93; Anal. Calcd. for $C_{31}H_{26}N_4O_2$: C, 76.52; H, 5.39; N, 11.51. Found: C, 76.61; H, 5.32; N, 11.53.

***1,5-Diphenyl-N³,N⁴-bis(4-nitrophenyl)-1H-pyrazole-3,4-dicarboxamide (9l).*** (257 mg, 47%); mp 295–297°C; (was crystallized from EtOH/$H_2O$); IR (ν, $cm^{-1}$): 3468 and 3342 (NH), 3055 and 3006 (CH, aromatic), 1671 (C=O), 1627–1496 (C=C and C=N); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 12.31 and 10.71 (s, 2H, 2NH), 8.18–6.52 (m, 18H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ (ppm): 162.80 and 160.14 (C=O), 148.52 (C–3), 144.80 and 144.10 (C=$\underline{C}$-$NO_2$), 143.25 (C–5), 119.47 (C–4), 142.50, 138.60, 130.11, 129.73, 129.04, 128.12, 126.85, 126.51, 126.45, 125.48, 125.40, 125.16, 122.51, 120.82; Anal. Calcd. for $C_{29}H_{20}N_6O_6$: C, 63.50; H, 3.68; N, 15.32. Found: C, 63.39; H, 3.72; N, 15.33.

***1,5-Diphenyl-N³,N⁴-bis(4-fluorophenyl)-1H-pyrazole-3,4-dicarboxamide (9m).*** (400 mg, 81%); mp 227–228°C; (was crystallized from BuOH); IR (ν, $cm^{-1}$): 3356 (NH), 3039 and 3000 (CH, aromatic), 1679 (C=O), 1620–1499 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 12.50 and 9.33 (s, 2H, 2NH), 7.75–6.98 (m, 18H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 161.62 and 159.15 (C=O), 161.12 and 158.68 (C=$\underline{C}$-F), 149.72 (C–3), 141.86 (C–5), 115.19 (C–4), 138.49, 130.53, 129.28, 129.01, 128.86, 128.15, 125.72, 122.57, 122.49, 121.88, 121.81, 116.05, 115.82, 115.41; Anal. Calcd. for $C_{29}H_{20}F_2N_4O_2$: C, 70.44; H, 4.08; N, 11.33. Found: C, 70.32; H, 4.12; N, 11.35.

**1,5-Diphenyl-1H-pyrazole-3,4-dicarbonitrile (10).** Compound **9a** of 0.306 g (1 mmol) was dissolved in 5 mL DMF, and 0.292 mL (4 mmol) $SOCl_2$ was added. After stirring for 2 h in ice bath and 12 h in room temperature, some ice water was added to the mixture. Precipitated solid product was filtered and purified from ethanol–water mixture by crystallization.

(259 mg, 96%); mp 148–149°C; IR (ν, $cm^{-1}$): 3020 (CH, aromatic), 2231 (CN), 1595–1466 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52–7.24 (m, 10H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 110.80 and 110.77 (CN), 149.05 (C–5), 98.20 (C–4), 137.61, 131.23, 130.03, 129.63, 129.41, 129.16, 128.39, 125.27, 124.92; Anal. Calcd. for $C_{17}H_{10}N_4$: C, 75.54; H, 3.73; N, 20.73. Found: C, 75.65; H, 3.69; N, 20.78.

**2,3-Diphenyl-2H-pyrazolo[3,4-d]pyridazine-4,7-diamine (11).** Compound **10** of 1 mmol was dissolved in 10 mL absolute ethanol. 0.5 mL anhydrous hydrazine was added and refluxed for 5 h. The solvent was evaporated and residue compound was washed with ether and water. The crude product was purified from ethanol–water by crystallization.

(208 mg, 69%); mp 292–294°C; IR (ν, $cm^{-1}$): 3453 and 3350 (NH), 3057 and 3024 (CH, aromatic), 1626–1492 (C=C and C=N); $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46–7.18 (m, 10H, ArH), 4.81 (br. s, 4H, $NH_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 149.70 and 148.15 (N=$\underline{C}$-$NH_2$), 142.73 (C–3), 138.55, 130.22, 129.30, 129.22, 128.97, 128.78, 128.22, 126.57, 125.27, 114.22; Anal. Calcd. for $C_{17}H_{14}N_6$: C, 67.54; H, 4.67; N, 27.80. Found: C, 67.43; H, 4.75; N, 27.91.

**Ethyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (12).** Compound **2** of 0.336 g (1 mmol) was heated at 200°C until gas exiting finished. Solid at the bottom

was washed with ether and water, respectively. The crude product was purified from ethanol–water mixture by crystallization. (131 mg, 45%); mp 125–126°C; IR (ν, $cm^{-1}$): 3064, (CH, aromatic), 2978 (CH, aliphatic), 1741 (C=O, ester), 1620–1482 (C=C and C=N); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 8.19 (s, 1H, CH=N), 7.39–7.21 (m, 10H, ArH), 4.12 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 1.12 (t, $J$ = 7.1 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 162.50 (C=O, ester), 144.61 (C–3), 144.01 (C–5), 120.16 (C–4), 139.15, 130.71, 130.55, 130.12, 129.78, 128.80, 126.45, 123.65; MS(CI) m/z 293.1 (M+1); Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.82; H, 5.55; N, 9.57.

**1,5-Diphenyl-1*H*-pyrazole-4-carboxylic acid (13).** Compound **13** can be synthesized in two different methods.

***Method.*** Compound **3** of 0.308 g (1 mmol) was heated at 250°C until carbon dioxide gas exiting finished. The residue solid was washed with water and purified from xylene by crystallization.

***Method.*** Compound **12** of 0.292 g (1 mmol), 10 mL water, and 0.1 g (2.5 mmol) NaOH mixture was refluxed for about 1.5 h. Equal volume of water was added to mixture and cooled down to room temperature. The mixture was neutralized with 10% HCl solution and stirred approximately for half an hour to complete precipitation. Precipitated white product was filtered, washed with water, and purified from ethanol–water mixture by crystallization. (55–72%); mp 178–179 °C; IR (ν, $cm^{-1}$): 3420–2584 (OH, COOH), 3055 (CH, aromatic), 1689 (C=O), 1597–1498 (C=C and C=N); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 8.12 (s, 1H, CH=N), 7.28–7.03 (m, 10H, ArH), $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 164.27 (C=O), 145.15 (C–3), 142.68 (C–5), 114.42 (C–4), 139.37, 130.74, 129.09, 129.04, 128.97, 128.90, 128.03, 125.52; MS(CI) m/z 265.1 (M+1); Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.79; H, 4.51; N, 10.56.

**2,3-Diphenyl-5,6-dihydro-2*H*-pyrazolo[3,4-d] pyridazine-4,7-dione (14).** Compound **2** or **5a** of 1 mmol was dissolved in 10 mL dry toluene, and anhydrous hydrazine was added at 1/1 mole rate. The mixture was refluxed for about 5 h. Precipitate yellow product was filtered and purified from ethanol–water mixture by crystallization.

(60% and 73%); mp 316–318°C; IR (ν, $cm^{-1}$): 3158–2629 (NH), 3022 (CH, aromatic), 1642 (C=O), 1582–1490 (C=C and C=N); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 10.40 (br. s, 1H, NH), 5.30 (br. s, 1H, NH), 7.70–7.01 (m, 10H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 161.79, 161.58, 156.58 and 152.33 (C=O↔ =C–OH), 145.34, 143.32, 143.04, 142.53, 139.48, 139.03, 131.22, 130.71, 129.60, 129.41, 129.37, 129.31, 128.92, 128.41, 128.34, 127.88, 126.70, 126.12, 120.70, 116.51; 114.02; Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 66.93; H, 3.94; N, 18.48.

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## REFERENCES AND NOTES

[1] Katoch-Rouse, R.; Horti, A.G. J Label Compd Radiopharm 2003, 46, 93.

[2] Meschler, J. P.; Kraichely, D. M.; Wilken, G. H.; Howlett, A. C. Biochem Pharmacol 2000, 60, 1315.

[3] Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. J Med Chem 1985, 28, 256.

[4] Clause, G. W. Understanding Microbes: A Laboratory Textbook for Microbiology; W. H. Freeman and Company: New York, USA, 1989. p 571.

[5] Chornous, V. A.; Bratenko, M. K.; Vovk, M. V.; Sidorchuk, I. I. Pharm Chem J 2001, 35, 26.

[6] Akbas, E.; Berber, I. Eur J Med Chem 2006, 41, 904.

[7] Adnan, A. B.; Hesham, T. Y. F.; Sherif, A. F. R.; Baraka, A. Eur J Med Chem 2003, 38, 27.

[8] Badawey, E.; El-Ashmawey, I. M. Eur J Med Chem 1998, 33, 349.

[9] Thomson, W. T. Agricultural Chemicals-Book II Herbicides, 13th ed; Thomson Publications: California, USA, 1997. pp 268–278.

[10] Londershausen, M. Pestic Sci 1996, 48, 269.

[11] Bakavoli, M.; Feizyzadeh, B.; Rahimizadeh, M. Tetrahedron Lett 2006, 47, 8965.

[12] Mongin, F.; Quéguiner, G. Tetrahedron 2001, 57, 4059.

[13] Tominaga, Y.; Yoshioka, N.; Kataoka, S.; Aoyama, N.; Masunari, T.; Miike, A. Tetrahedron Lett 1995, 36, 8641.

[14] Zlicar, M.; Stanovnik, B.; Tišler, M. Tetrahedron 1992, 48, 7965.

[15] Stimac, A.; Stanovnik, B.; Tisler, M.; Golic, L. Tetrahedron 1990, 46, 6915.

[16] Chantegrel, B.; Hartmann, D.; Gelin, S. Tetrahedron 1977, 33, 45.

[17] Stevens, K. L.; Reno, M. J.; Alberti, J. B.; Price, D. J.; Kane-Carson, L. S.; Knick, V. B.; Shewchuk, L. M.; Hassell, A. M.; Veal, J. M.; Davis, S. T.; Griffin, R. J.; Peel, M. R. Bioorg Med Chem Lett 2008, 18, 5758.

[18] Johns, B. A.; Gudmundsson, K. S.; Allen, S. H. Bioorg Med Chem Lett 2007, 17, 2858.

[19] Kinoshita, T.; Warizaya, M.; Ohori, M.; Sato, K.; Neya, M.; Fujii, T. Bioorg Med Chem Lett 2006, 16, 55.

[20] Kasımoğulları, R.; Bülbül, M.; Günhan, H.; Güleryüz, H. Bioorg Med Chem 2009, 17, 3295.

[21] Bülbül, M.; Kasımoğulları, R.; Küfrevioğlu, Ö. İ. J Enzyme Inhib Med Chem 2008, 23, 895.

[22] Witherington, J.; Bordas, V.; Haigh, D.; Hickey, D. M. B.; Ife, R. J.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Ward, R. W. Bioorg Med Chem Lett 2003, 13, 1581.

[23] Witherington, J.; Bordas, V.; Gaiba, A.; Naylor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K.; Ward, R. W. Bioorg Med Chem Lett 2003 13, 3059.

[24] Bildirici, I.; Şener, A.; Atalan, E.; Battal, A.; Genç, H. Med Chem Res 2009, 18. 327.

[25] Bildirici, I.; Şener, A.; Tozlu, I. Med Chem Res 2007, 16, 418.

[26] Şener, A.; Kasımoğulları, R.; Şener, M. K.; Bildirici, İ.; Akçamur, Y. J Heterocycl Chem 2002, 39, 869.

[27] Akçamur, Y.; Şener, A.; İpekoğlu, A. M.; Kollenz, G. J Heterocycl Chem 1997, 34, 221.

[28] Akbaş, E.; Berber, İ.; Şener, A.; Hasanov, B. II Farmaco 2005, 60, 23.

[29] Şener, A.; Kasımoğulları, R.; Şener, M. K.; Genç, H. Chem Heterocycl Comp 2004, 40, 1039.

[30] Şener, A.; Bildirici, İ. Turk J Chem 2004, 28, 149.

[31] Şener, A.; Tozlu, İ.; Genç, H.; Bildirici, İ.; Arısoy, K. J Heterocycl Chem 2007, 44, 1077.

[32] Şener, A.; Genç, H.; Tozlu, İ.; Şener, M. K. Turk J Chem 2004, 28, 659.

[33] Stadler, A.; Zangger, K.; Belaj, F.; Kollenz, G. Tetrahedron 2001, 57, 6757.

[34] Noronha, R. G.; Fernandes, A. C.; Romao, C. C. Tetrahedron Lett 2009, 50, 1407.

[35] Kravchhenko, D. V.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. O.; Ivachtchenko, A. Il Farmaco 2005, 60, 804.

[36] Campaigne, E.; Hutchinson, J. H. J Heterocycl Chem 1970, 7, 655.

[37] Ganjian, I.; Khorshidi, M.; Lalezari, I. J Heterocyclic Chem 1991, 28, 1173.

# Selective Reduction of 2,4-Dinitro- and 4,5-Dinitroimidazole Derivatives Using Iron Dust



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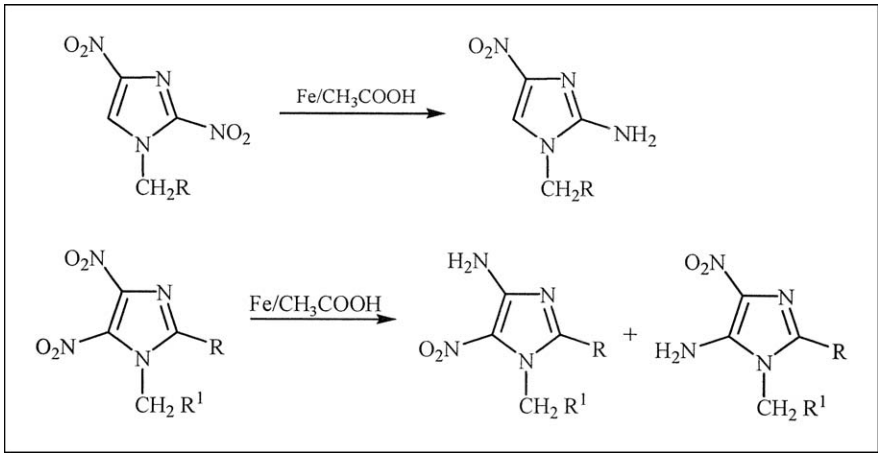


A series of *N*-substituted 2,4-dinitroimidazoles, 4,5-dinitroimidazoles, and 2-methyl-4,5-dinitroimidazoles have been selectively reduced to the corresponding aminonitroimidazole derivatives, using iron dust in glacial acetic acid at room temperature. 2,4-Dinitroimidazoles have been reduced to the 2-amino-4-nitro-derivatives only but 4,5-dinitroimidazoles have given 4-amino-5-nitro- or 5-amino-4-nitro-derivatives depended on the structure of the *N*-substituent.

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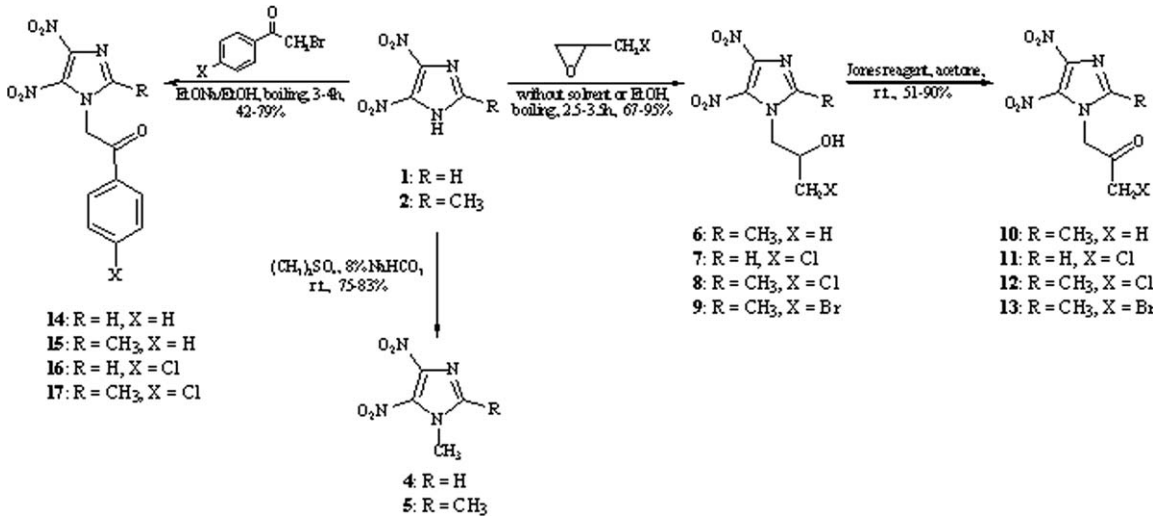
## INTRODUCTION

Imidazoles and their derivatives are very important group of compounds for their pharmacological properties [1,2]. Particularly, the nitroimidazole class of medicines mainly shows activity against bacteria [3,4]. Also, these drugs have become the important agents for treatment of serious infections caused by protozoa. Some of them have been tested against HIV [5]. 2-Nitroimidazoles played a major role as bioreductive markers for tumour hypoxia [6] and as radiosensitizers [7,8]. Our earlier investigations have been devoted to synthesis and antifungal as well as antibacterial properties of *N*-phenacyl-4,5-dinitroimidazole and 4-substituted amino-5-nitroimidazole derivatives, which have been prepared by nucleophilic displacement of the nitro group in 4,5-dinitroimidazole derivatives by primary or secondary amines [9,10].

Reduction of the nitro compounds has been one of the most important reactions in organic chemistry used as a routine method for the preparation of various nitrogen derivatives such as amines, nitrosocompounds, or hydroxylamines. The reported reduction methods of aromatic nitro compounds to prepare amino derivatives are very numerous. The reduction of the nitroazoles is readily achieved by using of one of many possible reagents like for instance iron in an acidic medium [11,12], hydrogen in the presence of palladium [13,14], Raney nickel [15] sodium borohydride [16]. Only limited number of all reduction methods have described the selective reduction of one nitro group in dinitro-compounds with remain unchanged of other functional groups. For example, reduction of 2,4-dinitrophenol using sodium sulfide has led to 2-amino-4-nitrophenol [17], but 4-amino-2-nitro-carboxamide mustard have been obtained by selective 4-nitro group reduction of 2,4-dinitrobenzamide derivative with $SnCl_2$ in concentrated HCl [18]. Lin and Sun [17] have found that using either Zn in $HCOONH_4$ or tin (II) chloride dihydrate can deliver traceless synthesis of 2-quinoxalinone analogues, an *o*-nitroaniline intermediate without further reduction of another nitro group under microwave irradiation or by conventional heating.

Products of reductions of nitroimidazole derivatives exhibit potential biological significance and are intermediates in syntheses of a variety of biologically active imidazoles. The compounds containing amino group in azoles ring can show good antimicrobial activity. In particular, the introduction of a bromine or two chlorine atoms or one phenyl group to the phenyl ring, except for the amino group in 2-amino-4(5)-arylimidazoles

**Scheme 1**




leads to compounds provided some antimicrobial activity [19]. Moreover, compound with the amino and the nitro groups have played important role as potent inhibitor of Coxackie virus B3 replication [20]. Synthetic 2-aminoimidazole derivatives including 2-aminohistamine have shown to have $H_1$ and $H_2$ receptor agonist and antagonist activity. Other 2-aminoimidazole derivatives are selective 5-$HT_3$ receptor antagonists, which may be potentially useful in the treatment of chemotherapy induced emesis [21]. Imidazole alkaloids containing the amino group at *C*-2 position in the heterocyclic ring also show interesting biological property such as anthelminthic activity (dorimidazole A, preclathridine A) [1].

## RESULTS AND DISCUSSION

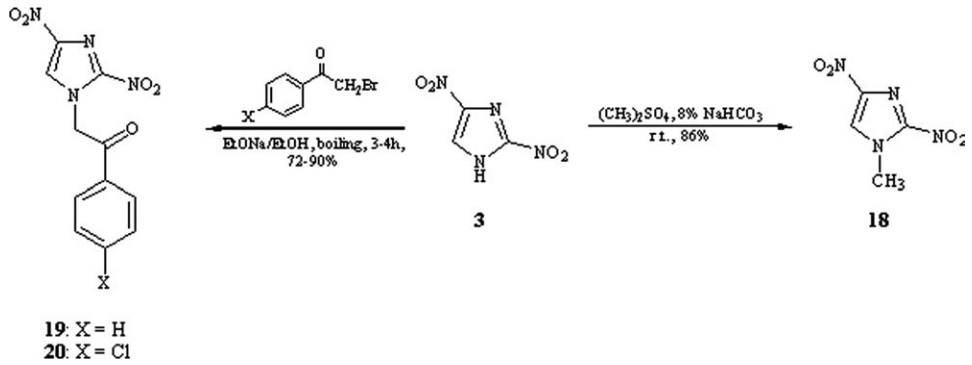
The reduction of *N*-substituted 2,4-dinitroimidazole, 4,5-dinitroimidazole, and 2-methyl-4,5-dinitroimidazole to the corresponding aminonitroderivatives by use of iron dust in glacial acetic acid at room temperature exhibits high selectivity. It is very surprising that iron dust in an acidic medium is capable of reducing one nitro group without further reduction of second nitro group. It is known that iron in the presence of acid is not selective agent [11]. In our experiments, treatment of dinitroimidazole derivatives with iron dust afforded, after purification, the crystalline aminonitro-compounds. Stability of these compounds depended on the position of the amino group, decreased in a series of 2-amino, 5-amino and 4-amino compounds.

The starting 4,5-dinitroimidazole (**1**), 2-methyl-4,5-dinitroimidazole (**2**), and 2,4-dinitroimidazole (**3**) were prepared according to the methods described in the literature [22,23]. The *N*-substituted derivatives of 4,5-dinitroimidazoles (**4–17**) were obtained in the reaction of **1** or **2** with $(CH_3)_2SO_4$, epoxypropane, epichlorohydrin, or phenacyl bromides in accordance with the method described in the literature [9,23,24]. The *N*-(2-hydroxypropyl) and *N*-(3-chloro-2-hydroxypropyl) compounds (**6–8**) were oxidized by Jones reagent to the desired carbonyl derivatives (**10–12**) [24]. Additionally, 2-methyl-4,5-dinitroimidazole was alkylated with epibromohydrin according to the method described for prepared epichlorohydrin derivatives [9]. The treatment of **2** with an excess of epibromohydrin (1:2) under reflux without solvent for about 3 h led to new 1-(3-bromo-2-hydroxypropyl)-2-methyl-4,5-dinitroimidazole (**9**). This new derivative was oxidized by Jones reagent to the 1-(3-bromo-2-oxopropyl)-2-methyl-4,5-dinitroimidazole (**13**) in accordance with the method described earlier [24]. Synthesis of *N*-substituted 4,5-dinitroimidazole derivatives **4–17** is shown in the Scheme 1.

Also, the 2,4-dinitroimidazole (**3**) was put on the reactions with $(CH_3)_2SO_4$ and phenacyl bromides according to the methods described in the literature [9,23,25]. The reactions of **3** with appropriate reagents resulted in the formation of *N*-substituted derivatives of 2,4-dinitroimidazole (**18–20**), as shown in the Scheme 2.

The *N*-methyl (**18**) and *N*-phenacyl derivatives of 2,4-dinitroimidazole (**19,20**) in the reduction gave only respective 2-amino-4-nitroimidazole with yield 54–82% (Scheme 3). When the reaction was complete, the excess of iron and its oxidation products were filtered off and the reaction mixture was diluted with water. The 2-amino-1-methyl-4-nitroimidazole (**21**) was isolated by extraction. After removal of the solvent, the crude product was crystallized. The precipitated crude reduction products (**22, 23**) were filtered off. A large, lipophilic phenacyl group facilitated obtaining the aminonitroderivatives. Reduction

**Scheme 2**




of *N*-substituted 2,4-dinitroimidazole derivatives **18**–**20** is shown in the Scheme 3.

The structures of **21–23** were confirmed by full spectral data. The infrared spectra showed absorptions at about 3400 and 3265 $cm^{-1}$ and also 1560 and 1300 $cm^{-1}$ indicative for the N—H and $NO_2$ resonances, respectively. The mass spectra exhibit strong molecular ions at 142, 246, and 280, respectively. In addition to the molecular ions, in spectra of compounds **22** and **23** strong signal (rel. int. 100%) corresponding to ion from phenacyl (*m*/*z* 105) or *p*-chlorophenacyl group (*m*/*z* 139) was observed. In the $^1H$ NMR spectra, the signals of the amino groups are as singlets at about 6.30 ppm, $CH_2$ protons of the phenacyl groups resonated as singlet at 5.56 and 5.54 ppm. The aromatic protons at *C*-5 position of the imidazole ring were observed at about 7.84 ppm.

Reduction of 4,5-dinitroimidazole alkyl derivatives led to *N*-alkylaminonitroimidazoles, as well. The iron dust in glacial acetic acid reduced with facility one nitro group but the second remained unreactive. In the same conditions, mixture of two isomers: 4-amino-5-nitro- and 5-amino-4-nitro- with predomination of the latter mentioned were formed (Scheme 4). The 4,5-diaminoimidazoles were not observed in the reaction mixtures. Formation of the aminonitroimidazoles depended on the position of the new formed amino group and yielding of 4-amino-compounds was the poorest. The low efficiency in reduction reactions of 4,5-dinitroimidazole alkyl derivatives probably is connected with structures and stability of compounds obtained. Moreover, the isolation of pure, definite, aminonitroderivatives was very inconvenient. Some of them were obtained after complex extraction, then purification by column chromatography and additional crystallization.

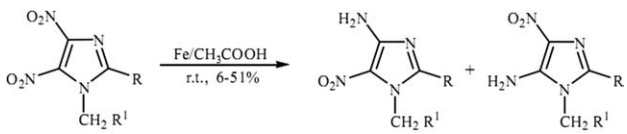
Reduction of *N*-substituted 4,5-dinitroimidazole derivatives **4**,**5**,**7–17** is shown in the Scheme 4.

Reaction of the compounds containing *N*-methyl group (**4, 5**) with iron dust afforded 4-amino-5-nitroimidazoles (**24, 25**) only that were separated after extraction with chloroform. In the reduction of the *N*-halohydroxypropyl derivatives (**7–9**) were formed 5-amino-4-nitro-compounds (**26–28**). These substances were obtained as solid products. Other 4,5-dinitroimidazoles (**10–17**) containing the carbonyl group in the chain

**Scheme 3**


| Substrate | R | Product |
|---|---|---|
| **18** | H | **21** |
| **19** | $C(O)C_6H_5$ | **22** |
| **20** | $C(O)C_6H_4$(*p*-Cl) | **23** |

**Scheme 4**




| Substrate | R | $R^1$ | 4-Amino derivatives | 5-Amino derivatives |
|---|---|---|---|---|
| **4** | H | H | 24 | |
| **5** | $CH_3$ | H | 25 | |
| **7** | H | $CH(OH)CH_2Cl$ | | 26 |
| **8** | $CH_3$ | $CH(OH)CH_2Cl$ | | 27 |
| **9** | $CH_3$ | $CH(OH)CH_2Br$ | | 28 |
| **10** | $CH_3$ | $C(O)CH_3$ | 29 | |
| **11** | H | $C(O)CH_2Cl$ | 30 | |
| **12** | $CH_3$ | $C(O)CH_2Cl$ | 31 | |
| **13** | $CH_3$ | $C(O)CH_2Br$ | 32 | |
| **14** | H | $C(O)C_6H_5$ | 33 | |
| **15** | $CH_3$ | $C(O)C_6H_5$ | 34 | 35 |
| **16** | H | $C(O)C_6H_4$(*p*-Cl) | 36 | |
| **17** | $CH_3$ | $C(O)C_6H_4$(*p*-Cl) | 37 | 38 |

at *N*-1 position of the imidazole ring provided mainly 4-amino-5-nitro- derivatives, after extraction **(29–34, 36, 37**). Only in the reduction of 2-methyl-4,5-dinitro-1-phenacylimidazole (**15**) and (**17**), the mixtures of two products were obtained. After reduction of **15**, isomers: 4-amino-2-methyl-5-nitro-1-phenacylimidazole (**34**) and 5-amino-2-methyl-4-nitro-1-phenacylimidazole (**35**) were obtained. Compound **35** was separated by the filtration and purified by crystallization. Dominating product, **34**, was obtained after extraction and was purified by column chromatography. Similarly, the 4-amino-1-(*p*-chlorophenacyl)-2-methyl-5-nitroimidazole **(37**) and 5-amino-1-(*p*-chlorophenacyl)-2-methyl-4-nitroimidazole **(38**) were obtained as products of the reduction of 1-(*p*-chlorophenacyl)-2-methyl-4,5-dinitroimidazole (**17**). These derivatives were separated by column chromatography. In all cases, 4,5-diamino derivatives were not observed.

The infrared spectra of **24–38** showed absorptions at about 3400 and 3260 $cm^{-1}$ and also 1560 and 1300 $cm^{-1}$ indicative for the N—H and $NO_2$ resonances, respectively. The mass spectra confirmed that only one nitro group in the dinitroimidazoles was reduced. The $^1H$ NMR spectra of new products provided evidence for the presence of the amino group. The $NH_2$ protons were observed as a singlet at about 7.40 ppm (**24, 25**) or within the range of 7.57–7.71 ppm (**26–38**). In the $^{13}C$ NMR spectra of **26–28**, signal for the carbon jointed with hydroxyl group was near 67 ppm. Moreover, the signal corresponded to the C=O group of **29–38** resonated in the range of 190.88–201.22 ppm. The position of the amino group in **26–38** was connected with the place of a signal of a methylene group at *N*-1 position of the heterocylic ring. In the $^{13}C$ NMR of **26–28**, the signal in the range 46.29–47.09 ppm was assigned to the $CH_2$ group. It is also observed that in the $^{13}C$ NMR of **29–32**, the resonances due to $CH_2$ occurred in the range 52.21–54.40 ppm. It is very interesting that the signals of the methylene groups of the pairs **34, 35** and **37, 38** occurred at different values: 52.01 and 50.27 ppm or 51.96 and 49.65 ppm, respectively. In the spectra of 5-amino-4-nitro-products, the signals of the carbons in the imidazole ring appeared in lower values, too. Additionally, the X-ray structures determination of the pair of isomers (**34,35**) facilitated the interpretation of NMR data and to determine the position of the amino group. The geometry of the molecules confirmed that the compound **35** is 5-amino-4-nitro- derivative but the second is 4-amino-5-nitro-isomer (**34**). The results obtained were in agreement with our interpretation of NMR spectra. The signals of the methylene group and carbon atoms of the imidazole ring of the all 5-amino-4-nitro compounds were shifted toward the lower field.

In conclusion, we have demonstrated very selective nitro group reduction method in the dinitroimidazole derivatives using iron dust in the acetic acid solution at room temperature. This method provided the products with the amino and the nitro group simultaneously. The presence of an electron-donating amino group at a position neighbouring to the nitro group can have influence on the many biological properties, which depended on the kind of substituents at positions *N*-1 and *C*-2 in the heterocyclic ring, as well.

To recapitulate, the *N*-derivatives of 2,4-dinitroimidazoles were reduced only to the 2-amino-4-nitro compounds. It was found that the reduction process among the *N*-derivatives of 4,5-dinitroimidazoles is more complicated, but it concerns mainly the 4-$NO_2$ group. Nitro group at *C*-5 position of imidazole ring is susceptible to reduction when there is a hydroxy group in the *N*-1 alkyl chain connected with tetrahedral carbon atom. Probably, some specific trigonal arrangements have the influence on the direction of nitro group reduction process.

## EXPERIMENTAL

Melting points were determined on a Boetius apparatus and were uncorrected. The $^1H$ and $^{13}C$ NMR spectra were recorded on Varian Gemini 300 VT spectrometer (300 and 75 MHz respectively). Chemical shifts (δ) are expressed in ppm, relative to tetramethylsilane (TMS) as an internal standard, using DMSO–$d_6$ as solvents. Coupling constants (*J* values) are expressed in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were recorded on a 402 AMD INTECTRA apparatus by the electron impact technique, operating at 75 eV. The infrared (IR) spectra were recorded in KBr tablets using a Specord 75–IR spectrophotometer and were expressed in $cm^{-1}$ scale. Elemental analysis was performed on a Vario EL III model of elemental analyzer and data of C, H, and N were within ±0.4% of calculated values. The progress of reactions and purity of products were controlled with thin-layer chromatography method (TLC) on silica gel plates (60 $F_{254}$ from Merck) in a $CHCl_3$/MeOH (9:1, v/v) as a developing system. The spots on the plates were observed in the UV light (λ = 254nm). Solid products of amino-nitro-derivatives were purified in the crystallization process using acetonitrile. Crude, oily products were purified by column chromatography on silica gel using the mixture of chloroform and methanol (50:0 → 50:5) as eluent. Among substances, which were used as substrates, the epichlorohydrin, epoxypropane, epibromohydrin, phenacyl bromides, and iron dust were commercial products. Compounds **4–8, 10–12**, and **14–18** were obtained according to the literature method [9,23–25].

**1-(3-Bromo-2-hydroxypropyl)-2-methyl-4,5-dinitroimidazole (9).** The 2-methyl-4,5-dinitroimidazole (3.44 g, 20 mmol) was added to epibromohydrin (3.42 mL, 40 mmol). The mixture was heated under reflux for about 3 h. Then, cooled and poured into the water. The precipitate was filtered off, washed with water, air-dried and crystallized from 40% EtOH as yellow needles; 5.40 g (87.5%); mp 103–105°C; $R_f$ = 0.64; IR: 3380, 1520, 1340; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 5.92 (m, 1H, OH), 4.49 (m, 1H, CH), 4.21 and 4.00 (2 m, 2H,

$CH_2Br$), 3.59 (m, 2H, N-$CH_2$), 2.49 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 145.42, 139.29, 130.68, 67.97, 50.09, 35.81, 13.72; ms: m/z 308 (2) and 310 (2) ($M^+$), 182 (100.0); Anal. calc. for $C_7H_9N_4O_5Br$: C, 27.29; H, 2.94; N, 18.19; found: C, 27.25; H, 2.98; N, 18.22.

**1-(3-Bromo-2-oxopropyl)-2-methyl-4,5-dinitroimidazole (13).** To a solution of **9** (3.10 g, 10 mmol) in acetone (50 mL), at room temperature was dropped Jones reagent (10 mL). After 24 h, *i*-PrOH (10 mL) was added. The dark green precipitate was filtered and washed with a small volume of acetone. The combined filtrates were poured into the water (200 mL) and the solution was held 2–3 days to afford the crystalline solid. The precipitate was filtered off, washed with water, air-dried, and crystallized from MeOH as yellow needless; 2.32 g (76.0%); mp 117–119°C; $R_f$ = 0.64; IR: 1720, 1510, 1380; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 5.54 (s, 2H, $CH_2$), 4.59 (s, 2H, $CH_2Br$), 2.43 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 193.95, 146.10, 140.06, 129.42, 53.28, 33.62, 13.31; ms: m/z 308 (15) and 306 (16) ($M^+$), 156 (100); Anal. calc. for $C_7H_7N_4O_5Br$: C, 27.47; H, 2.92; N, 18.31; found: C, 27.52; H, 2.97; N, 18.28.

**General procedure for synthesis of *N*-phenacyl-2,4-dinitroimidazole derivatives (19–20).** The solution of Na (1.38 g, 60 mmol) in absolute EtOH (40 mL) was added dropwise under stirring to a solution of 2,4-dinitroimidazole (**3**) (7.90 g, 50 mmol) in absolute ethanol (50 mL). Subsequently, a solution of phenacyl bromide or *p*-chlorophenacyl bromide (50 mmol) in absolute ethanol (100 mL) was dropped and heated under reflux for 4 h. The mixture was cooled and the precipitate was filtered off, air-dried, and crystallized from EtOH.

***2,4-Dinitro-1-phenacylimidazole (19).*** This compound was obtained as cream needles (EtOH), 12.50 g (90.6%); mp 123–125°C; $R_f$ = 0.64; IR: 1680, 1526, 1320; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.72 (s, 1H, 5-Im), 8.09 (m, 2H, 2,6-Ph), 7.76 (m, 1H, 4-Ph), 7.66 (m, 2H, 3,5-Ph), 6.27 (s, 2H, $CH_2$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 190.84, 142.30, 141.69, 134.87, 133.34, 129.27, 128.27, 126.86, 57.24; ms: *m*/*z* 276 (28) ($M^+$), 105 (100); Anal. calc. for $C_{11}H_8N_4O_5$: C, 47.86; H, 2.92; N, 20.29; found: C, 47.90; H, 2.94; N, 20.32.

***1-(*p*-Chlorophenacyl)-2,4-dinitroimidazole (20).*** This compound was obtained as cream needles (EtOH), 11.20 g (72.2%); mp 154–156°C; $R_f$ = 0.62; IR: 1680, 1526, 1320; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.71 (s, 1H, 5-Im), 8.12 (m, 2H, 2,6-Ph), 7.74 (m, 2H, 3,5-Ph), 6.26 (s, 2H, $CH_2$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 190.02, 142.29, 141.65, 139.80, 132.05, 130.18, 129.42, 126.85, 57.16; ms: m/z 312 (11), 310 (32) ($M^+$), 139 (100); Anal. calc. for $C_{11}H_7N_4O_5Cl$: C, 42.61; H, 2.27; N, 18.07; found: C, 42.58; H, 2.24; N, 18.10.

**General procedure for synthesis of Aminonitroimidazoles (21–38).** Appropriate *N*-substituted 2,4-dinitro-, 4,5-dinitro-, or 2-methyl-4,5-dinitroimidazole derivatives (2 mmol) were dissolved in glacial AcOH (25 mL), and the excess of iron dust (0.37 g, 6.60 mmol) was added. The resulting mixtures were then left for about 3 days at room temperature shaking them from time to time. Upon completion reaction, the excess of iron and its oxidation products were filtered off, and the reaction mixtures were diluted with water (75 mL). The precipitated crude products were filtered off. If products not solidified, then the filtrate was extracted with $CHCl_3$ (4 × 5 mL) and the combined organic phases were dried ($MgSO_4$), filtered off. After removal of the solvents, the crude product was purified by column chromatography on silica gel. All new products were crystallized from MeCN.

***2-Amino-1-methyl-4-nitroimidazole (21).*** This compound was obtained as yellow needles (MeCN), 0.15 g (53.6%); mp 216–218°C; $R_f$ = 0.18; IR: 3425, 3265, 1627, 1554, 1300; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.88 (s, H, 5-Im), 6.23 (s, 2H, $NH_2$), 3.44 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 149.38, 143.29, 119.93, 32.30; ms: m/z 142 (68) ($M^+$), 42 (100); Anal. calc. for $C_4H_6N_4O_2$: C, 33.82; H, 4.25; N, 39.44; found: C, 33.86; H, 4.20; N, 39.42.

***2-Amino-4-nitro-1-phenacylimidazole (22).*** This compound was obtained as yellow needles (MeCN), 0.40 g (81.3%); mp 243–245°C; $R_f$ = 0.41; IR: 3400, 3270, 1680, 1627, 1560, 1295; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.03 (m, 2H, 2,6-Ph), 7.84 (s, H, 5-Im), 7.73 (m, H, 4-Ph), 7.60 (m, 2H, 3,5-Ph), 6.31 (s, 2H, $NH_2$), 5.56 (s, 2H, $CH_2$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 192.16, 149.51, 143.63, 134.34, 134.06, 128.92, 128.11, 119.67, 51.83; ms: m/z 246 (14) ($M^+$), 105 (100); Anal. calc. for $C_{11}H_{10}N_4O_3$: C, 53.68; H, 4.09; N, 22.76; found: C, 53.73; H, 4.11; N, 22.81.

***2-Amino-1-(*p*-chlorophenacyl)-4-nitroimidazole (23).*** This compound was obtained as yellow needles (MeCN), 0.42 g (75.0%); mp 260–262°C; $R_f$ = 0.43; IR: 3375, 3265,1675, 1634, 1565, 1285; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.05 (m, 2H, 2,6-Ph), 7.82 (s, H, 5-Im), 7.70 (m, 2H, 3,5-Ph), 6.33 (s, 2H, $NH_2$), 5.54 (s, 2H, $CH_2$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 191.33, 149.48, 143.64, 138.87, 133.03, 130.00, 129.05, 119.54, 51.83; ms: m/z 282 (6) and 280 (18) ($M^+$), 139 (100); Anal. calc. for $C_{11}H_9N_4O_3Cl$: C, 47.17; H, 3.23; N, 20.00; found: C, 47.15; H, 3.26; N, 20.05.

***4-Amino-1-methyl-5-nitroimidazole (24).*** This compound was obtained as yellow needles (MeCN), 0.03 g (10.7%); mp 157–160°C; $R_f$ = 0.18; IR: 3405, 3265, 1620, 1540, 1350; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.72 (s, 1H, 2-Im), 7.40 (s, 2H, $NH_2$), 3.76 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 153.23, 143.56, 121.09, 34.83; ms: m/z 142 (51) ($M^+$), 42 (100); Anal. calc. for $C_4H_6N_4O_2$: C, 33.82; H, 4.25; N, 39.44; found: C, 33.86; H, 4.26; N, 39.45.

***4-Amino-1,2-dimetylo-5-nitroimidazole (25).*** This compound was obtained as yellow needles (MeCN), 0.09 g (29.0%); mp 265–268°C; $R_f$ = 0.43; IR: 3405, 3265, 1625, 1555, 1380; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.47 (s, 2H, $NH_2$), 3.70 (s, 3H, N-$CH_3$), 2.27 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 153.20, 152.66, 120.32, 32.88, 13.84; ms: m/z 156 (100) ($M^+$); Anal. calc. for $C_5H_8N_4O_2$: C, 38.47; H, 5.16; N, 35.89; found: C, 38.51; H, 5.21; N, 35.93.

***5-Amino-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole (26).*** This compound was obtained as dark yellow pales (MeCN), 0.14 g (31.9%); mp 160–162°C; $R_f$ = 0.05; IR: 3360, 3325, 3225, 1625, 1560, 1340; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.57 (s, 2H, $NH_2$), 7.20 (s, 1H, 2-Im), 5.71 (s, 1H, OH), 3.90 (m, 2H, N-$CH_2$), 3.68 (m, 2H, $CH_2Cl$), 3.58 (m, 1H, CH); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 143.39, 132.56, 128.06, 67.80, 47.34, 47.19; ms: m/z 222 (19) and 220 (44) ($M^+$), 70 (100); Anal. calc. for $C_6H_9N_4O_3Cl$: C, 32.75; H, 4.12; N, 25.46; found: C, 32.80; H, 4.15; N, 25.47.

***5-Amino-1-(3-chloro-2-hydroxypropyl)-2-methyl-4-nitroimidazole (27).*** This compound was obtained as light yellow pales (MeCN), 0.16 g (34.1%); mp 206–208°C; $R_f$ = 0.25; IR: 3360, 3325, 3300, 1625, 1560, 1400; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.61 (s, 2H, $NH_2$), 5.72 (s, 1H, OH), 3.91 (m, 2H, N-

$CH_2$), 3.78 (m, 2H, $CH_2Cl$), 3.64 (m, 1H, CH), 2.23 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 144.61, 140.30, 126.80, 67.78. 47.56, 46.29, 13.44; ms: m/z 236 (16) and 234 (45) ($M^+$), 55 (100); Anal. calc. for $C_7H_{11}N_4O_3Cl$: C, 35.91; H, 4.73; N, 23.93; found: C, 35.92; H, 4.75; N, 23.96.

***5-Amino-1-(3-bromo-2-hydroxypropyl)-2-methyl-4-nitroimidazole (28).*** This compound was obtained as yellow needles (MeCN), 0.14 g (25.4%); mp 195–197°C; $R_f$ = 0.19; IR: 3380, 3350, 3250, 1625, 1565, 1345; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.61 (s, 2H, $NH_2$), 5.74 (m, 1H, OH), 3.70 (m, 5H, $CH_2CH(OH)CH_2Br$), 2.23 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 144.40, 140.09, 126.64, 67.34, 47.09, 37.23, 13.50; ms: m/z 280 (7) and 278 (7) ($M^+$), 80 (100); Anal. calc. for $C_7H_{11}N_4O_3Br$: C, 30.24; H, 3.98; N, 20.15; found: C, 30.22; H, 4.03; N, 20.18.

***4-Amino-2-methyl-5-nitro-1-(2-oxopropyl)-imidazole (29).*** This compound was obtained as yellow pales (MeCN), 0.20 g (51.3%); mp 232–234°C; $R_f$ = 0.26; IR: 3420, 3350, 1720, 1620, 1520, 1340; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.60 (s, 2H, $NH_2$), 5.13 (s, 2H, $CH_2$), 2.20 (s, 6H, 2x$CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 201.22, 153.16, 153.09, 120.29, 107.08, 54.40, 26.83, 13.59; ms: m/z 198 (100.0) ($M^+$); Anal. calc. for $C_7H_{10}N_4O_3$: C, 42.44; H, 5.08; N, 28.28; found: C, 42.48; H, 5.05; N, 28.30.

***4-Amino-1-(3-chloro-2-oxopropyl)-5-nitroimidazole (30).*** This compound was obtained as yellow needles (MeCN), 0.08 g (18.2%); mp 215°C; $R_f$ = 0.23; IR: 3405, 3360, 1710, 1610, 1500, 1300; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.71 (s, 1H, 2-Im), 7.61 (s, 2H, $NH_2$), 5.25 (s, 2H, N—$CH_2$), 4.68 (s, 2H, $CH_2Cl$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 195.94, 153.11, 144.29, 119.96, 53.57, 46.98; ms: m/z 220 (26) and 218 (75) ($M^+$), 68 (100); Anal. calc. for $C_6H_7N_4O_3Cl$: C, 33.05; H, 3.23; N, 25.69; found: C, 33.09; H, 3.26; N, 25.69.

***4-Amino-1-(3-chloro-2-oxopropyl)-2-methyl-5-nitroimidazole (31).*** This compound was obtained as yellow needles (MeCN), 0.20 g (43.5%); mp 270°C; $R_f$ = 0.20; IR: 3395, 3260, 1725, 1625, 1540, 1390; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.65 (s, 2H, $NH_2$), 5.24 (s, 2H, N—$CH_2$), 4.68 (s, 2H, $CH_2Cl$), 2.23 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 195.73, 153.44, 153.12, 120.12, 52.21 46.99, 13.62; ms: m/z 234 (18), 232 (50) ($M^+$), 67 (100); Anal. calc. for $C_7H_9N_4O_3Cl$: C, 36.23; H, 3.90; N, 24.14; found: C, 36.20; H, 3.89; N, 24.15.

***4-Amino-1-(3-bromo-2-oxopropyl)-2-methyl-5-nitroimidazole (32).*** This compound was obtained as yellow crystals (MeCN), 0.21 g (38.5%); mp 186–189°C; $R_f$ = 0.29; IR: 3395, 3260, 1725, 1625, 1540, 1360; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 7.65 (s, 2H, $NH_2$), 5.23 (s, 2H, N—$CH_2$), 4.68 (s, 2H, $CH_2Br$), 2.24 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 195.72, 153.44, 153.11, 120.11, 52.21, 46.98, 13.61; ms: m/z 278 (7), 276 (7) ($M^+$), 67 (100); Anal. calc. for $C_7H_9N_4O_3Br$: C, 30.46; H, 3.28; N, 20.30; found: C, 30.42; H, 3.26; N, 20.27.

***4-Amino-5-nitro-1-phenacylimidazole (33).*** This compound was obtained as dark yellow pales (MeCN), 0.10 g (20.4%); mp 219–221°C; $R_f$ = 0.30; IR: 3400, 3250, 1670, 1626, 1510, 1350; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.01 (m, 2H, 2,6-Ph), 7.65 (m, 3H, 3,4,5-Ph), 7.69 (s, 2H, $NH_2$), 7.23 (s, 1H, 2-Im), 5.64 (s, 2H, $CH_2$); $^{13}C$ NMR NMR (75 MHz, DMSO–$d_6$): δ = 191.49, 153.65, 144.06, 134.18, 133.75, 129.01, 128.32, 120.42, 50.55; ms: m/z 246 (6) ($M^+$), 105 (100); Anal. calc. for $C_{11}H_{10}N_4O_3$: C, 53.69; H, 4.09; N, 22.77; found: C, 53.72; H, 4.10; N, 22.74.

***4-Amino-2-methyl-5-nitro-1-phenacylimidazole (34).*** This compound was obtained as light yellow pales (MeCN), 0.16 g (30.1%); mp 227–229°C; $R_f$ = 0.45; IR: 3400, 3250, 1680, 1620, 1500, 1340; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.06 (m, 2H, 2,6-Ph), 7.68 (m, 5H, 3,4,5-Ph, $NH_2$), 5.84 (s, 2H, $CH_2$), 2.28 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 192.52, 153.66, 153.28, 134.06, 133.94, 128.80, 128.07, 120.42, 52.01, 13.70; ms: m/z 260 (27) ($M^+$), 105 (100); Anal. calc. for $C_{12}H_{12}N_4O_3$: C, 55.41; H, 4.65; N, 21.54; found: C, 55.42; H, 4.62; N, 21.54.

***5-Amino-2-methyl-4-nitro-1-phenacylimidazole (35).*** This compound was obtained as yellow needles (MeCN), 0.03 g (5.8%); mp 265–267°C; $R_f$ = 0.28; IR: 3495, 3265, 1665, 1625, 1555, 1355; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.06 (m, 2H, 2,6-Ph), 7.69 (m, 5H, 3,4,5-Ph, $NH_2$), 5.63 (s, 2H, $CH_2$), 2.10 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 192.80, 146.08, 142.11, 135.40, 134.40, 129.83, 129.06, 127.17, 50.27, 13.44; ms: m/z 260 (53) ($M^+$), 105 (100); Anal. calc. for $C_{12}H_{12}N_4O_3$: C, 55.41; H, 4.65; N, 21.54; found: C, 55.40; H, 4.67; N, 21.50.

***4-Amino-1-(*p*-chlorophenacyl)-5-nitroimidazole (36).*** This compound was obtained as yellow pales (MeCN), 0.12 g (21.4%); mp 245–248°C; $R_f$ = 0.23; IR: 3440, 3255, 1680, 1625, 1565, 1300; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.06 (m, 2H, 2,6-Ph), 7.73 (s, 1H, 2-Im), 7.69 (m, 2H, 3,5-Ph), 7.61 (s, 2H, $NH_2$), 5.85 (s, 2H, $CH_2$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 191.78, 153.16, 144.22, 138.90, 132.57, 129.79, 129.05, 120.33, 53.39; ms: m/z 282(3), 280 (10) ($M^+$), 139 (100); Anal. calc. for $C_{11}H_9N_4O_3Cl$: C, 47.18; H, 3.24; N, 20.01; found: C, 47.20; H, 3.28; N, 19.98.

***4-Amino-1-(*p*-chlorophenacyl)-2-methyl-5-nitroimidazole (37).*** This compound was obtained as dark yellow pales (MeCN), 0.06 g (10.2%); mp 270–272°C; $R_f$ = 0.43; IR: 3440, 3255, 1680, 1625, 1565, 1300; $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.07 (m, 2H, 2,6-Ph), 7.70 (m, 4H, 3,5-Ph, $NH_2$), 5.82 (s, 2H, $CH_2$), 2.27 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 191.70, 153.64, 153.24, 138.80, 132.76, 129.97, 128.92, 120.36, 51.96, 13.68; ms: m/z 296 (10), 294 (32) ($M^+$), 139 (100); Anal. calc. for $C_{12}H_{11}N_4O_3Cl$: C, 49.01; H, 3.77; N, 19.05; found: C, 49.04; H, 3.78; N, 19.09.

***5-Amino-1-(*p*-chlorophenacyl)-2-methyl-4-nitroimidazole (38).*** This compound was obtained as cream needles (MeCN), 0.08 g (13.5%); mp 220°C; $R_f$ = 0.25; IR: 3420, 3250, 1680, 1625, 1540, 1320. $^1H$ NMR (300 MHz, DMSO–$d_6$): δ = 8.06 (m, 2H, 2,6-Ph), 7.71 (m, 4H, 3,5-Ph, $NH_2$), 5.61 (s, 2H, $CH_2$), 2.10 (s, 3H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO–$d_6$): δ = 190.88, 144.91, 139.65, 138.78, 132.75, 130.05, 128.76, 126.58, 49.65, 12.84; ms: m/z 296 (10), 294 (31) ($M^+$), 139 (100); Anal. calc. for $C_{12}H_{11}N_4O_3Cl$: C, 49.01; H, 3.77; N, 19.05; found: C, 49.03; H, 3.75; N, 19.09.

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## REFERENCES AND NOTES

[1] De Luca, L. Curr Med Chem 2006, 13, 1.

[2] Mital, A. Sci Pharm 2009, 77, 497.

[3] Barry, C. E.; Boshoff, H. I. M.; Dowd, C. S. Curr Pharm Des 2004, 10, 3239.

[4] Edwards, D. I. J Antimicrob Chemother 1993, 31, 9.

[5] Silvestri, R.; Artico, M.; De Martino, G.; Ragno, R.; Massa, S.; Loddo, R.; Murgioni, Ch.; Loi, A. G.; La Colla, P.; Pani, A. J Med Chem 2002, 45, 1567.

[6] Hodgkiss, R. J. Anti-Cancer Drug Des 1998, 13, 687.

[7] Kasai, S.; Nagasawa, H.; Yamashita, M.; Masui, M.; Kuwasaka, H.; Oshodani, T.; Uto, Y.; Inomata, T.; Oka, S.; Inayama, S.; Hori, H. Bioorg Med Chem 2001, 9, 453.

[8] Hori, H.; Jin, C.-Z., Kiyono, M.; Kasai, S.; Shimamura, M.; Inayama, S. Bioorg Med Chem 1997, 5, 591.

[9] Zaprutko, L.; Gajdziński, M.; Michalska, W.; Pietkiewicz, K.; Lutomski, K.; Łukaszewski, Z.; Wrzeciono, U. Pharmazie 1989, 44, 817.

[10] Zaprutko, L.; Olender, D.; Gzella, A. Monatsch Chem 2003, 134, 1145.

[11] Castera, C.; Crozet, M. D.; Crozet, M. P.; Vanelle, P. Heterocycles 2005, 65, 337.

[12] Grehn, L.; Ding, L.; Ragnarsson, U. Acta Chem Scand 1990, 44, 67.

[13] Palmer, B. D.; Zijl, P.; Denny, W. A.; Wilson, W. R. J Med Chem 1995, 38, 1229.

[14] Helal, C. J.; Kang, Z.; Lucas, J. C.; Bohall, B. R. Org Lett 2004, 6, 1853.

[15] Suwiński, J.; Walczak, K. Pol J Chem 1994, 68, 678.

[16] Suwiński, J.; Wagner, P. Tetrahedron 1996, 52, 9541.

[17] Lin, M.-J.; Sun, C.-M. J Comb Chem 2006, 8, 455.

[18] Cavalleri, B.; Volpe, G.; Arioli, V.; Perenti, F. Arzneim--Forsch/Drug Res 1977, 27, 1889.

[19] Makarov, V. A.; Riabova, O. B.; Granik, V. G.; Dahse, V. M.; Stelzner, A.; Wutzler, P.; Schmidtke, M. Bioorg Med Chem Lett 2005, 15, 37.

[20] Little, T. L.; Webber, S. E. J Org Chem 1994, 59, 7299.

[21] Chen, B.-C.; Chao, S. T.; Sundeen, J. E.; Tellew, J.; Ahmad, S. Tetrahedron Lett 2002, 43, 1595.

[22] Bulusu, S.; Damavarapu, R.; Autera, J. R.; Behrens, R., Jr.; Minier, L. M.; Villanueva, J.; Jayasuriya, K.; Axenrod, T. J Phys Chem 1995, 99, 5009.

[23] Novikov, S. S.; Khmel'nitskii, L. I.; Lebedev, O. V.; Sevast'yanova, V. V.; Epishina, L. V. Khim Geterotsikl Soedin 1970, **6**, 503.

[24] Olender, D.; Żwawiak, J.; Lukianchuk, V.; Lesyk, R.; Kropacz, A.; Fojutowski, A.; Zaprutko, L. Eur J Med Chem 2009, 44, 645.

[25] Sehgal, R. K.; Webb, M. W.; Agrawal, K. C. J Med Chem 1981, 24, 601.

# Facile Synthesis of 2,4-Diamino-6-alkyl- or 6-Aryl-Pyrimidine Derivatives

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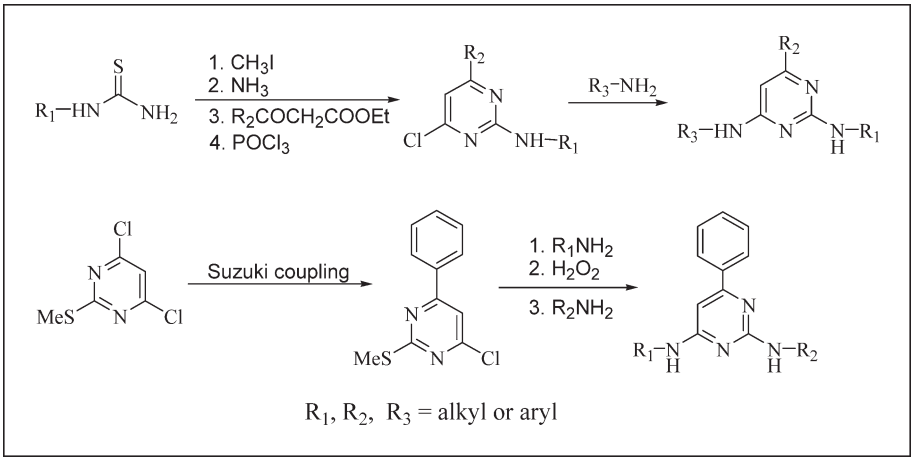


Facile methods were developed to prepare a series of 6-phenyl and 6-alkyl-2,4-diaminopyrimidine derivatives. The pyrimidine ring of the final products was constructed by treatment of a 1,3-dicarbonyl derivative with an amidine or guanidine. The 6-phenyl-pyrimidine derivatives were also prepared by Suzuki coupling reaction, using 2-methylthio-4,6-dichloropyrimidine as the starting material.

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## INTRODUCTION

As part of our efforts in search of malaria prophylactic and/or therapeutic agents, a series of imidazolidinedione (IZ) derivatives was found to possess profound activity against liver stage malarias in rodent and nonhuman primate models [1–4]. Subsequently, the IZ compounds were found to metabolize to *s*-triazine derivatives in microsomal preparations and in rodents [4]. Active in mice tests, the *s*-triazines were considered the active metabolite of the IZ compounds. This finding prompted us to develop methods to prepare a series of *N,N′*-di-substituted 2,4-diamino-1,3,5-triazines and 2,4-diamino-pyrimidine derivatives as potential antimalarial agents. This report focused on the method development for the synthesis of the latter class of compounds.

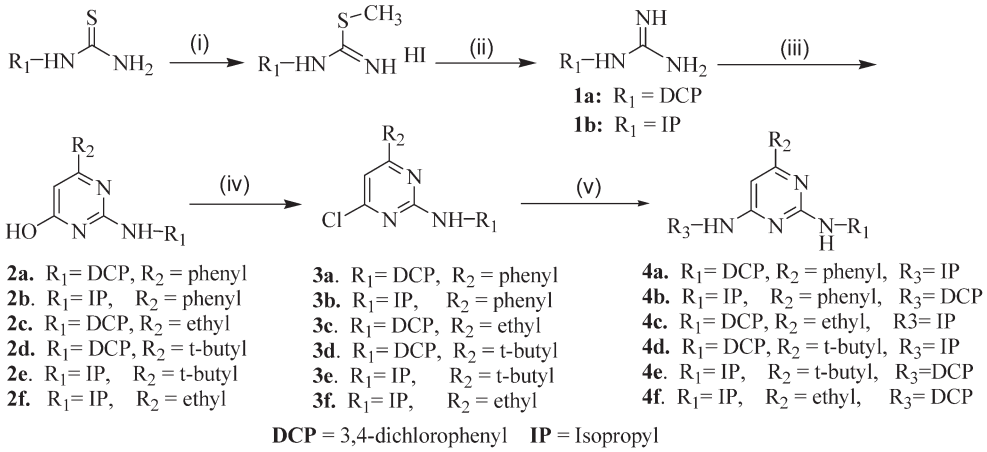
Polyamino-pyrimidines play a very important role in biological and pharmaceutical chemistry. A number of applications as therapeutic agents have been documented [5]. The most general method for the synthesis of 2,4,6-trisubstituted pyrimidines involves the treatment of two essential starting materials, a 1,3-dicarbonyl component and a N—C—N fragment such as urea, amidine, or guanidine [6,7]. The other method involved Suzuki coupling or Grignard reactions to insert various aryl or alkyl groups into 2,4,6-trichloropyrimidine [8] followed by stepwise amination with appropriate amines.

In this study, facile methods were developed to prepare substituted 6-alkyl or 6-aryl-2,4-diaminopyrimidines.

## RESULTS AND DISCUSSION

Methods were developed to prepare substituted 6-alkyl or 6-arylpyrimidine-2,4-diamines. The pyrimidine ring of the desired products was constructed by condensation of a 1,3-dicarbonyl component with an amidine, isopropylguanidine, or 3,4-dichloroguanidine as shown in Scheme 1. The hydroxypyrimidines (**2a–f**) obtained were converted to the corresponding chloropyrimidines (**3a–f**) in high yields with phosphorus oxychloride [9–11]. The amination of chloropyrimidine derivatives was achieved via acid- or base-mediated nucleophilic substitution [12]. Hartung et al. reported that the chloro group of chloropyrimindines can be easily displaced with an aromatic amine under acidic conditions, but it can only be displaced by an aliphatic amino group under basic

**Scheme 1.** Synthesis of 6-phenyl or alkyl-2,4-diaminopyrimidine derivatives.

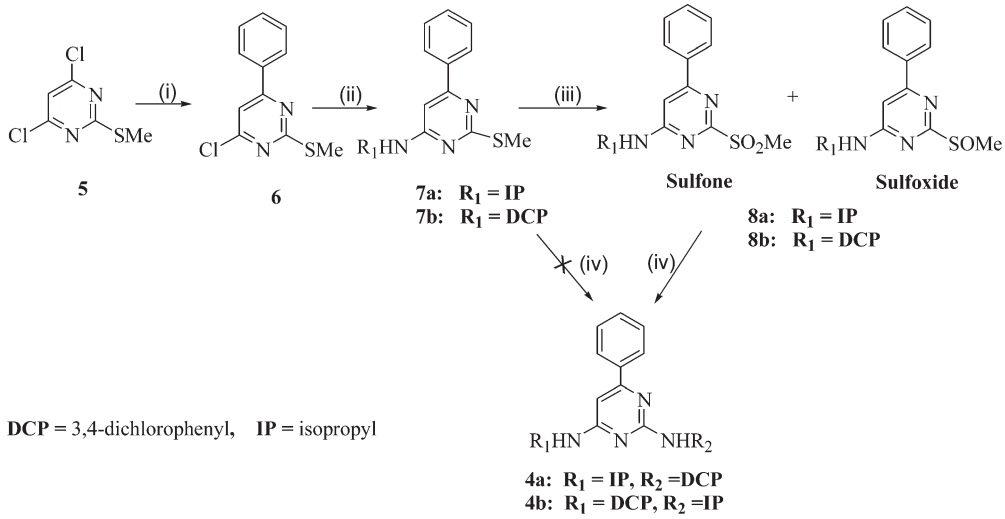



*Reagents and Conditions*: (i) $CH_3I$, acetone, reflux; (ii) $NH_3$, EtOH, 100 °C; (iii) $R_2COCH_2COOEt$, DMF, 100 °C, 48hr; (iv) $POCl_3$; (v) $R_3NH_2$, 110 °C.

conditions [12]. The method was adapted to insert the 3, 4-dichloroanilino, and the isopropylamino groups into the pyrimidine ring in high yield under the acidic and basic conditions, respectively (Scheme 1). Likewise, 4-alkyl analogs **4c–f** were prepared using ethyl propionylacetate or ethyl pivaloylacetate as 1,3-dicarbonyl component.

The Suzuki coupling method was an alternative approach used to make the 2,4-diamino-6-phenylpyrimidine derivatives (**4a** and **4b**) (Scheme 2). Initially, the Suzuki coupling reaction was attempted using 2,4,6-trichloropyrimidine as the starting material to introduce a phenyl group at either the 4- or 6-position, followed by amination. However, the success of this approach depends on the relative reactivity of the 2- and 4-chloro groups toward amination reactions, allowing for insertion of an amino group selectively to either 2- or 4-position of the pyrimidine ring. Although the Suzuki reaction of 2,4,6-trichloropyrimidine gave a good yield of 2,4-dichloro-6-phenyl-pyrimidine, the followed up

**Scheme 2.** Method involved Suzuki reaction on 4,6-dichloro-2-methylthiopyrimidine.




*Reagents and Conditions*: (i) $C_6H_5B(OH)_2$, $Pd(OAC)_2II$, TPP, $Na_2CO_3$, Glyme, reflux, 18h; (ii) $R_1NH_2$, 1-butanol, reflux, 6h; (iii) 30% $H_2O_2$, $NaWO_4$, EtOAc/toluene (1:1 v/v), 0 °C for 30 min then RT for 2h; (iv) $R_2NH_2$, neat, 140 °C, 2h.

amination gave a mixture consisting almost equal amount of 2-amino- and 4-aminopyrimidine derivatives. The low selectivity of 2,4-dichloro-6-phenyl-pyrimidine in the amination reaction led us to use 4,6-dichloro-2-methylthio-pyrimidine as the starting material. On treatment with phenylboronic acid in the presence of triphenylphosphine and palladium acetate, 4,6-dichloro-2-methylthio-pyrimidine (**5**) gave 4-chloro-2-methylthio-6-phenylpyrimidine (**6**) in very high yield. The first amination of compound **6** gave intermediate **7a** or **7b** readily, whereas the second amination on the 2-methylthio group failed to produce the desired products **4a** and **4b** [13–15]. Thus, oxidative activation of the 2-methylthio group in **7a** and **7b** was necessary before the amination reaction on the 2-position can be carried out. The oxidation was achieved by treatment of the 2-methylthiopyrimidine derivative with hydrogen peroxide under the catalysis of sodium tungstate dehydrate [14,15]. The mixture of sulfone and sulfoxide (**8**) formed was used without purification for further reactions with 3, 4-dichloroaniline or isopropylamine to give the products **4a** (11%) and **4b** (84%), respectively. The striking disparity in yields between **4a** and **4b** is, most likely, a result of difference in nucleophilicity of the two amines used.

The major difference between the two methods used in Scheme 1 (Method 1) and Scheme 2 (Method 2) to prepare compounds **4a** and **4b** is the order of introduction of 2-amino, 4-amino-, and 6-phenyl groups to the pyrimidine ring. The former method assembled the 2-amino and the 6-phenyl groups during the formation of the pyrimidine ring followed by insertion of the arylamino or alkylamino group at either 2- or 4-posion under the acidic or basic conditions, respectively. The overall yield of the Method 1 is good and the reaction conditions are mild. The latter method as described in Scheme 2 started from the commercially available starting material 4,6-dichloro-2-methylthio-pyrimidine. The 6-phenyl substituent was constructed first by the Suzuki coupling reaction followed by stepwise amination reactions to yield the substituted 2, 4-diamino-6-phenylpyrimidines **4a** or **4b**. The yield of the 2nd nucleophilic substitution reaction is good when alkylamines were used, but poor when aromatic amines were the nucleophiles.

In conclusion, the method described in Scheme 1 is superior to that of Scheme 2 for the preparation of the desired pyrimidine derivatives **4a-f**, with better yield, milder reaction conditions and cheaper reagents.

## EXPERIMENTAL

Melting points were determined on a Mettler FP62 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed using HPTLC-HLF normal phase 150 microns silica gel plates (Analtech, Newark, DE). Visualization of the developed chromatogram was performed by UV absorbance, or spreading with aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using a Horizon HPFC System (Biotage, Charlottesville, VA) with Flash 25M or 40M cartridges (KP-Sil™ Silica, 32–63 μm, 60 Å). Preparative TLC was performed using silica gel GF Tapered Uniplates (Analtech, Newark, DE). $^1$H NMR and $^{13}$C NMR spectra were recorded in deuteriochloroform, unless otherwise noted, on a Bruker Avance 300 spectrometer (Bruker Instruments, Wilmington, DE). Chemical shifts are reported in parts per million on the δ scale from an internal standard of tetramethylsilane. Combustion analyses were performed by Atlantic Microlab, (Norcross, GA). Where analyses are indicated by symbols of the elements, the analytical results obtained were within +/− 0.4% of the theoretical values.

**2-(3,4-Dichlorophenylamino)-4-hydroxy-6-phenylpyrimidine (2a).** Ethyl benzoylacetate (15 mL) was added dropwise to a suspension of 3,4-dichlorophenylguanidine (**1a**, 7.23g. 35.4 mmol) [2] in 100 mL of anhydrous DMF. The mixture was heated at 100°C for 48 h. After cooling, the reaction mixture was poured into 500 mL of ice water. The precipites were collected, washed with water, and dried to give 64% yield of compound **2a** as a pink solid. The product was used for further reactions without purification. $^1$H NMR ($CD_3OD$): δ 8.24 (d, 1H, $J$ = 2.4Hz), 8.00 (m, 2H), 7.57 (m, 2H), 7.47 (m, 3H), 6.45 (s, 1H). ms: $m/z$ 331 ($M^+$).

**4-Hydroxy-2-isopropylamino-6-phenylpyrimidine (2b).** Ethyl benzoylacetate (11.7 mL) was added dropwise to a suspension of isopropylguanidine (**1b**) [2] (2.3 g, 22.7 mmol) in 50 mL of anhydrous DMF. The reaction mixture was heated at 100°C for 3 days. After cooling, the solution was poured into crushed ice water. The mixture was extracted with EtOAc three times and the EtOAc extracts were combined, washed with water, and brine successively, dried over $Na_2SO_4$ and evaporated to dryness in vacuole. The residue was applied to a silica gel flash column and eluted with 2.5% MeOH in $CHCl_3$ to give 35% yield of compound **2b** as a white solid. $^1$H NMR ($CDCl_3$): δ 8.01 (d, 2H, $J$ = 3.6 Hz), 7.48 (m, 3H), 6.24 (s, 1H), 4.37 (m, 1H), 1.36 (d, 6H, $J$ = 6.6 Hz). ms: $m/z$ 229 ($M^+$).

**2-(3,4-Dichlorophenylamino)-6-ethyl-4-hydroxy-pyrimidine (2c).** Compound **2c** was prepared by the same method for the preparation of **2a**, using ethyl propionylacetate as starting material to yield 75% of **2c** as a white solid. $^1$H NMR ($CD_3OD$) δ 8.06 (d, 1H, $J$ = 2.2 Hz), 7.46 (dd, 1H, $J$ = 2.2 Hz, 8.7 Hz), 7.42 (d, 1H, $J$ = 8.7 Hz), 5.82 (s, 1H), 2.54 (q, 2H, $J$ = 7.5 Hz), 1.25 (t, 3H, $J$ = 7.5 Hz). ms: $m/z$ 283 ($M^+$).

**6-*t*-Butyl-2-(3,4-dichlorophenylamino)-4-hydroxy-pyrimidine (2d).** The title compound was prepared by the same method as for the preparation of **2a**, using ethyl pivaloylacetate as starting material to yield 60% of **2d** as an off-white solid. $^1$H NMR ($CD_3OD$): δ 8.22 (s, 1H), 7.41 (m, 2H), 5.93 (s, 1H), 1.28 (s, 9H). ms: $m/z$ 311 ($M^+$).

**6-*t*-Butyl-4-hydroxy-2-isopropylamino-pyrimidine (2e).** Compound **2e** was prepared by the same method as for the preparation of **2b**, using ethyl pivaloylacetate as starting material to afford the product as a white solid (33% yield). $^1$H NMR ($CDCl_3$): δ 5.73 (s, 1H), 4.17 (m, 1H), 1.21 (m, 15H). ms: $m/z$ 209 ($M^+$).

**6-Ethyl-4-hydroxy-2-isopropylamino-pyrimidine (2f).** Compound **2f** was prepared by the same method as for the preparation of **2b**, using ethyl propionylacetate as starting material to give 31% yield of the desired product as a white solid. $^1$H NMR ($CDCl_3$): δ 6.04 (s, 1H), 4.17 (m, 1H), 2.45 (q, 2H, $J$ = 7.2 Hz), 1.25 (t, 3H, $J$ = 7.2 Hz), 1.21 (d, 6H, $J$ = 6.6 Hz). ms: $m/z$ 181 ($M^+$).

**4-Chloro-2-(3,4-dichlorophenylamino)-6-phenylpyrimidine (3a).** 2-(3, 4-Dichlorophenylamino)-4-hydroxy-6-phenylpyrimidine (**2a**) in 100 mL of $POCl_3$ was stirred at room temperature overnight. The excess $POCl_3$ was removed under reduced pressure to give a gummy residue which solidified upon addition of excessive amount of crushed ice. The solid was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford the desired compound **3a** in 82% yield as a light yellow solid. $^1$H NMR ($CDCl_3$): δ 8.07 (m, 3H), 7.56 (m, 3H), 7.46 (m, 1H), 7.42 (d, 1H, $J$ = 8.7 Hz), 7.24 (s, 1H). ms: $m/z$ 349 ($M^+$).

**4-Chloro-2-isopropylamino-6-phenylpyrimidine (3b).** The title compound was prepared by the same method for the preparation of **3a**, using hydroxyl intermediate **2b** as the starting material giving the desired 4-chloro product **3b** as light yellow oil in 47% yield. $^1$H NMR ($CDCl_3$): δ 8.01 (d, 2H, $J$ = 3.6 Hz), 7.48 (m, 3H), 6.97 (s, 1H), 4.28 (m, 1H), 1.27 (d, 6H, $J$ = 6.5 Hz). ms: $m/z$ 247 ($M^+$).

**2-(3,4-Dichlorophenylamino)-4-chloro-6-ethylpyrimidine (3c).** The title compound was prepared by the same method as for the preparation of **3a**, using compound **2c** as the starting material, to give 75% yield of the desired compound as off-white solid. $^1$H NMR ($CDCl_3$,): δ 8.06 (s, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 6.70 (s, 1H), 2.70 (q, 2H, $J$ = 7.5 Hz), 1.30 (t, 3H, $J$ = 7.5 Hz). ms: $m/z$ 301 ($M^+$).

**6-*t*-Butyl-4-chloro-2-(3,4-dichlorophenylamino)-pyrimidine (3d).** Compound **3d** was prepared by the same method as for the preparation of **3a**, using **2d** as the starting material to give 83% yield of the product as off-white solid. $^1$H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.38 (s, 2H), 6.83 (s, 1H), 1.38 (s, 9H). ms: $m/z$ 329 ($M^+$).

**6-*t*-Butyl-4-chloro-2-isopropylamino-pyrimidine (3e).** Compound **3e** was prepared from **2e** using the same method as for the preparation of **3a**; giving 50% yield of the desired compound as white oil. $^1$H NMR ($CDCl_3$): δ 6.55 (s, 1H), 4.97 (brs, 1H), 4.15 (m, 1H), 1.25 (m, 15H). ms: $m/z$ 227 ($M^+$).

**4-Chloro-6-ethyl-2-isopropylamino-pyrimidine (3f).** Compound **3f** was prepared by the same method as for the preparation of **3a**, starting from **2f** to get the desired compound as white oil in 47% yield. $^1$H NMR ($CDCl_3$): δ 6.44 (s, 1H), 5.04 (brs, 1H), 4.15 (m, 1H), 2.58 (q, 2H, $J$ = 7.2 Hz), 1.25 (m, 9H). ms: $m/z$ 199 ($M^+$).

**2-(3,4-Dichlorophenylamino)-4-isopropylamino-6-phenylpyrimidine.HCl (4a)**

***Method 1.*** 4-Chloro-2-(3,4-dichlorophenylamino)-6-phenylpyrimidine (**3a**, 5g) in 100 mL of isopropylamine was heated in a sealed tube at 110°C overnight. Upon cooling, the reaction mixture was poured into ice water and the mixture was extracted with EtOAc three times. The EtOAc extracts were combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was applied to a silica gel flash column and eluted with hexane: EtOAc (10:1, v/v) to give the desired product **4a** as light yellow solid in 90% yield, mp 277.6°C (decomposed). $^1$H NMR ($CDCl_3$): δ 8.16 (br, 1H), 7.95 (m, 2H), 7.47 (m, 3H), 7.33 (d, 2H, $J$ = 1.8 Hz), 7.00 (brs, 1H), 6.28 (s, 1H), 4.72 (s, 1H), 4.14 (m, 1H), 1.32 (d, 6H, $J$ = 6.4Hz). ms: $m/z$ 372 ($M^+$). *Anal*. calcd. for $C_{19}H_{18}Cl_2N_4$.HCl: C, 55.69; H, 4.67; N, 13.67; Cl, 25.96. Found: C, 55.80; H, 4.65; N, 13.66; Cl, 25.90.

***Method 2.*** A mixture of sulfone/sulfoxide **8a** (2.0 g) and 3,4-dichloroaniline (3.34 mL, 3.0 equiv) was heated in a sealed tube at 140°C for 2 h. The mixture was cooled and the crude product was purified by a silica gel flash column, eluting with hexane/EtOAc (4:1 v/v) to give the desired compound **4a** in 11% yield. The NMR and MS spectra data are identical to compound **4a** prepared by method 1 as shown in Scheme 1.

**4-(3,4-Dichlorophenylamino)-2-isopropylamino-6-phenylpyrimidine (4b)**

***Method 1.*** Concentrated hydrochloric acid (1.5 mL) was added to a solution of 4-chloro-2-isopropylamino-6-phenylpyrimidine (**3b**) (886 mg) and 3,4-dichloroaniline (815 mg, 1.5 equiv) in 15 mL of isopropanol. The reaction mixture was heated at 100°C overnight. The crude product was purified by silica gel flash column chromatography and eluted with 2.5% MeOH in $CH_2Cl_2$ to give the desired compound as an off-white solid, yield 97%, mp 79.7°C. $^1$H NMR ($CDCl_3$): δ 7.93 (m, 3H), 7.43 (m, 2H), 7.37 (s, 1H), 7.28 (d, 1H, $J$ = 2.6 Hz), 7.25 (d, 1H, $J$ = 2.6 Hz), 6.48 (s, 1H), 6.36 (s, 1H), 4.98 (br, 1H), 4.25 (m, 1H), 1.32 (d, 6H, $J$ = 6.4 Hz). $^{13}$C NMR: ($CDCl_3$) δ 163.21, 161.89, 161.74, 141.51, 138.41, 131.35, 130.68, 130.27, 129.01, 126.74, 122.72, 120.45, 119.27, 92.51, 79.64, 42.77, 23.00. ms: $m/z$ 374 ($M^+$). *Anal*. calcd. for $C_{19}H_{18}Cl_2N_4$.HCl: C, 55.69; H, 4.67; N, 13.67; Cl, 25.96. Found: C, 55.40; H, 4.62; N, 13.50; Cl, 25.69.

***Method 2.*** The mixture of sulfone/sulfoxide **8b** (3.0g) and isopropylamine (6.21mL, 10.0 equiv) was heated in a sealed tube at 140°C for 20 min. The mixture was cooled and the crude product was purified by silica gel flash column chromatography and eluted with hexane/EtOAc (4:1 v/v) to give compound **4b** in 84% yield. The NMR and MS spectra data are identical to compound **4b** prepared by method 1 as shown in Scheme 1.

**2-(3,4-Dichlorophenylamino)-6-ethyl-4-isopropylamino-pyrimidine (4c).** Compound **4c** was prepared by the same method as for the preparation of **4a**, using **3c** as starting material to give the gummy desired compound. The product was dissolved in anhydrous ether and 2.0*M* HCl ether solution was added to form HCl salt. The HCl salt was recrystallized from hexanes/$CHCl_3$ to give a white solid in 95% yield, mp 211.3°C. $^1$H NMR ($CD_3OD$): δ 8.02 (s, 1H), 7.55 (d, 1H, $J$ = 8.7 Hz), 7.42 (d, 1H, $J$ = 8.7 Hz), 6.05 (s, 1H), 4.24 (m, 1H), 2.65 (q, 2H, $J$ = 7.5 Hz), 1.31 (m, 9H). $^{13}$C NMR ($CDCl_3$): δ 170.9, 162.9, 159.3, 140.2, 132.2, 129.9, 123.8, 120.0, 117.8, 94.0, 42.8, 30.7, 22.8, 12.7. ms: $m/z$ 324 ($M^+$). *Anal*. calcd. for $C_{15}H_{18}Cl_2N_4$: C, 55.39; H, 5.58; N, 17.23; Cl, 21.80. Found: C, 55.18; H, 5.67; N, 16.95; Cl, 22.05.

**6-*t*-Butyl-2-(3,4-dichlorophenylamino)-4-isopropylamino-pyrimidine (4d).** Compound **4d** was prepared by the same method as for the preparation of **4a**, starting from **3d** to give the desired compound in 99% yield as an off-white solid, mp 125.8–126.5°C. $^1$H NMR ($CDCl_3$): δ 8.20 (s, 1H), 7.30 (m, 2H), 7.05 (br, 1H), 5.88 (s, 1H), 4.59 (s, 1H), 4.08 (m, 1H), 1.30 (s, 9H), 1.25 (d, 6H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$): δ 177.1, 162.9, 158.9, 140.5, 132.2, 129.9, 123.5, 119.9, 117.5, 91.9, 42.7, 37.1, 19.3, 22.9. ms: $m/z$ 352 ($M^+$). *Anal*. calcd.

for $C_{17}H_{22}Cl_2N_4$: C, 57.79; H, 6.28; N, 15.86; Cl, 20.07. Found: C, 58.01; H, 6.18; N, 15.80; Cl, 20.05.

**6-*t*-Butyl-4-(3,4-dichlorophenylamino)-2-isopropylamino-pyrimidine (4e).** Compound **4e** was prepared by the same method as for the preparation of **4b**, using 6-t-butyl-4-chloro-2-isopropylamino-pyrimidine (**3e**) as starting material to give the desired compound as a white solid in 71% yield, mp 249.5–250.8°C. $^1$HNMR ($CDCl_3$): δ 11.94 (s, 1H), 11.04 (s, 1H), 8.30 (d, 1H, $J$ = 6.9 Hz), 8.25 (s, 1H), 7.71 (d, 1H, $J$ = 8.7 Hz), 7.33 (d, 1H, $J$ = 6.9 Hz), 6.78 (s, 1H), 4.14 (m, 1H), 1.36 (s, 9H), 1.32 (t, 6H, $J$ = 6.5 Hz). ms: $m/z$ 352 ($M^+$). *Anal*. calcd. for $C_{17}H_{22}Cl_2N_4$.HCl: C, 52.39; H, 5.95; N, 14.38; Cl, 27.29. Found: C, 52.46; H, 5.96; N, 14.33; Cl, 27.16.

**4-(3,4-dichlorophenylamino)-6-ethyl-2-isopropylamino-pyrimidine (4f).** Compound **4f** was prepared by the same method as for the preparation of **4b**, using compound **3f** as the starting material to afford the desired compound as a pink solid in 92% yield, mp 251.3°C (decomposed).$^1$H NMR ($CDCl_3$): δ 7.92 (d, 1H, $J$ = 2.5 Hz), 7.33 (d, 1H, $J$ = 8.7 Hz), 7.20 (dd, 1H, $J$ = 2.5Hz, 8.7Hz), 6.47 (br, 1H), 5.80 (s, 1H), 4.82 (d, 1H, $J$ = 7.0 Hz), 4.11 (m, 1H), 2.48 (q, 2H, $J$ = 7.6 Hz), 1.25 (d, 6H, $J$ = 6.5 Hz), 1.21 (t, 3H, $J$ = 7.6 Hz). $^{13}$C NMR ($CDCl_3$): δ 161.7, 158.8, 154.1, 138.7, 131.5, 131.1, 126.3, 122.7, 121.4, 95.9, 43.9, 25.8, 22.3, 11.8. ms: $m/z$ 324 ($M^+$). *Anal*. calcd. for $C_{15}H_{18}Cl_2N_4$.HCl: C, 49.81; H, 5.29; N, 15.49; Cl, 29.41. Found: C, 49.98; H, 5.28; N, 15.52; Cl, 29.31.

**4-Chloro-2-methylthio-6-phenylpyrimidine (6).** A catalytic amount of palladium acetate (0.286 g, 0.05 equiv) and triphenylphosphine (0.668 g, 0.10 equiv) were added to the solution of 4,6-dichloro2-methylthio-pyrimidine (**5**) (5.0 g, 25.42 mmol), phenylboronic acid (3.10 g, 1.0 equiv), and sodium carbonate (8.3 g, 3.1 equiv dissolved in a minium amount of water) in 250 mL of glyme. The reaction mixture was heated to reflux for 18 h, and the solvent was removed under reduced pressure. The crude product was extracted with methylene chloride and the extracts were combined, washed with water three times, dried over $Na_2SO_4$ and evaporated to dryness. The residue was purified by flash column chromatography, using hexane/ethyl acetate as eluent to yield compound **6** as a white solid in 84% yield, mp 59.8°C. $^1$H NMR ($CDCl_3$): δ 8.06 (m, 2H), 7.68 (m, 3H), 7.38 (s, 1H), 1.54 (s, 3H). $^{13}$C NMR ($CDCl_3$): δ 173.55, 165.29, 161.53, 135.31, 131.66, 128.98, 127.35, 111.70, 14.41. ms: $m/z$ 236 ($M^+$).

**4-Isopropyl-amino-2-methylthio-6-phenylpyrimidine (7a).** A suspension of 4-chloro-2-methylthio-6-phenylpyrimidine (**6**, 2.0g) and isopropylamine (1.0 mL, 1.5 equiv) in 100 mL of 1-BuOH was heated under reflux for 6 h. The solution was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with hexane/EtOAc (8:2 v/v) to yield 68% of the desired compound **7a**, mp 89.6°C. $^1$H NMR ($CDCl_3$): δ 7.98 (d, 2H, $J$ = 6.0 Hz), 7.43 (m, 3H), 6.38 (s, 1H), 4.77 (br, 1H), 4.10 (m, 1H), 1.54 (s, 3H), 1.27 (d, 6H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$): δ 171.5, 162.7, 162.0, 137.7, 94.9, 42.8, 22.7, 14.0. ms: $m/z$ 259 ($M^+$).

**4-(3,4-Dichlorophenylamino)-2-methylthio-6-phenylpyrimidine (7b).** The title compound was prepared by the same method as for the preparation of **7a** using 3,4-dichloroaniline as nucleophile to give compound **7b** in 65% yield. $^1$H NMR ($CD_3OD$): δ 8.13 (d, 1H, $J$ = 2.4 Hz), 7.82 (m, 2H), 7.62 (m, 3H), 7.57 (s, 1H), 7.54 (d, 1H, $J$ = 2.4 Hz), 6.85 (s, 1H), 2.73 (s, 3H). $^{13}$C NMR ($CD_3OD$):: δ 169.6, 160.3, 157.5, 137.3, 132.1, 131.8, 130.4, 129.1, 127.9 127.1, 123.3, 121.1, 99.7, 13.1. ms: $m/z$: 361 ($M^+$). *Anal*. calcd. for $C_{17}H_{13}Cl_2N_3S$: C, 56.36, H, 3.62, Cl, 19.57, N, 11.60. Found: C, 56.74, H, 3.98, Cl, 20.08, N, 12.10.

**4-Isopropylamino-2-methanesulfonyl/sulfinyl-6-phenylpyrimidine (mixture of sulfone and sulfoxide) (8a).** 4-Isopropylamino-2-methylthio-6-phenylpyrimidine (**7a)** (2.0g, 7.7 mmol) was dissolved in 50 mL of ethyl acetate/toluene mixture. Water (2 ml) was added to the solution followed by a catalytic amount of sodium tungstate dihydrate (0.18 g, 0.1 equiv). The mixture was cooled to 0°C and hydrogen peroxide (30% aqueous solution, 1.69 mL, 10 equiv) was added dropwise. The reaction was stirred for 30 min, warmed to room temperature, and monitored by TLC until the disappearance of the starting material **7a** (~2 h). The mixture was cooled to 0°C again and excess $H_2O_2$ was decomposed carefully by addition of saturated sodium sulfide (20 mL). The organic layer was separated, concentrated under vacuum at 50°C to a volume of 100 mL. The mixture was cooled to room temperature and diluted with hexanes (20 mL). Compound **8a**, as a mixture of sulfone and sulfoxide, precipitated out from the solution, was collected and washed with hexanes to give **8a** in yield 71%. The product was used for further reaction without purification. $^1$H NMR ($CD_3OD$): δ 7.50 (d, 2H, $J$ = 6.0 Hz), 7.27 (m, 3H), 6.77 (s, 1H), 4.77 (m, 1H), 1.59 (s, 6H), 1.32 (d, 6H, $J$ = 6.4 Hz). $^{13}$C NMR (DMSO-d6): δ 166.3, 163.2, 160.7, 136.2, 131.2, 129.4, 127.5, 126.9, 103.1, 98.8, 42.7, 22.4. ms: $m/z$ 291 ($M^+$).

**4-(3,4-Dichlorophenylamino)-2-methanesulfonyl/sulfinyl-6-phenylpyrimidine (mixture of sulfone and sulfoxide) (8b).** Compound **8b** was prepared from **7b** according to the same method for the preparation of **8a** to give the desired product in 74 % yield. $^1$H NMR (DMSO-d6): δ 10.59 (s, 1H), 8.18 (d, 1H, $J$ = 2.8 Hz), 8.10 (m, 2H), 7.64 (m, 3H), 7.60 (d, 1H, $J$ = 2.8 Hz), 7.40 (s, 1H), 2.73 (s, 3H). ms: $m/z$ 393 ($M^+$).

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## REFERENCES AND NOTES

[1] Guan, J.; Zhang, Q.; Gettayacamin, M.; Karle, J. M.; Ditusa, C. A.; Milhous, W. K.; Skillman, D. R.; Lin, A. J. Bioorg Med Chem 1991, 13, 699.

[2] Zhang, Q.; Guan, J.; Sacci, J.; Ager, A.; Ellis, W.; Milhous, W. K.; Kyle, D.; Lin, A. J. J Med Chem 2005, 48, 6472.

[3] Lin, A. J.; Zhang, Q.; Guan, J.; Milhous, W. K. US Pat. 7,101,902, 2006.

[4] Guan, J.; Wang, X.; Smith, K.; Ager, A.; Gettayacamin, M.; Kyle, D. E.; Milhous, W. K.; Kozar, M. P.; Magill, A. J.; Lin, A. J. J Med Chem 2007, 50, 6226.

[5] Montebugnoli, D.; Bravo, P.; Brenna, E.; Mioskowski, C.; Panzeri, W.; Viani, F.; Volonterio, A.; Wagner, A.; Zanda, M. Tetrahedron 2003, 59, 7147.

[6] Joule, J. A.; Mills, K. Heterocyclic Chemistry; Blackwell science: Oxford, UK, 2006. pp 194–232.

[7] Hill, M. D.; Movassaghi, M. Chem Euro J 2008, 14, 6836.

[8] Schomasker, J. M.; Delia, T. J. J Org Chem 2001, 66, 7125.

[9] Gong, B.; Hong, F.; Kohm, C.; Jenkins, S.; Tulinsky, J.; Bhatt, R.; Vries, P.; Singer, J. W.; Klein, P. Bioorg Med Chem Lett 2004, 14, 2303.

[10] Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Durieu, V.; Gillard, M.; Lebon, F.; Lengele, S.; Quere, L.; Keulen, B. Bioorg Med Chem Lett 2006, 16, 1834.

[11] Biagi, G.; Giorgi, I.; Livi, O.; Scarton, VV.; Lucacchini, A. IL Farmaco 1997, 52, 61.

[12] Hartung, C. G.; Backes, A. C.; Felber, B.; Missio, A.; Philipp, A. Tetrahedron 2006, 62, 10055.

[13] Nagamatsu, T.; Islam R.; Ashida, N. Heterocycles 2007, 72, 573.

[14] Liverton, N. J.; Butcher, J. W.; Claiborne, C. F.; Claremon D. A.; Libby, B. E.; Nguyen, K. T.; Pitzenberger, S. M.; Selnick, H. G.; Smith, G. R.; Tebben, A.; Vacca, J. P.; Varga, S. L.; Agarwal, L.; Dancheck, K.; Forsyth, A. J.; Fletcher, D. S.; Frantz, B.; Hanlon, W. A.; Harper, C. F.; Hofsess, S. J.; Kostura, M.; Lin, J.; Luell, S.; O'Neill, E. A.; Orevillo, C. J.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Visco, D. M.; O'Keefe, S. J. J Med Chem 1999, 42, 2180.

[15] Barvian, M.; Boschelli, D. H.; Cossrow, J.; Dobrusin, E.; Fattaey, A.; Fritsch, A.; Fry, D.; Harvey, P.; Keller, P.; Garrett, M.; La, F.; Leopold, W.; McNamara, D.; Quin, M.; Trumpp-Kallmeyer, S.; Toogood, P.; Wu, Z.; Zhang, E. J Med Chem 2000, 43, 4606.

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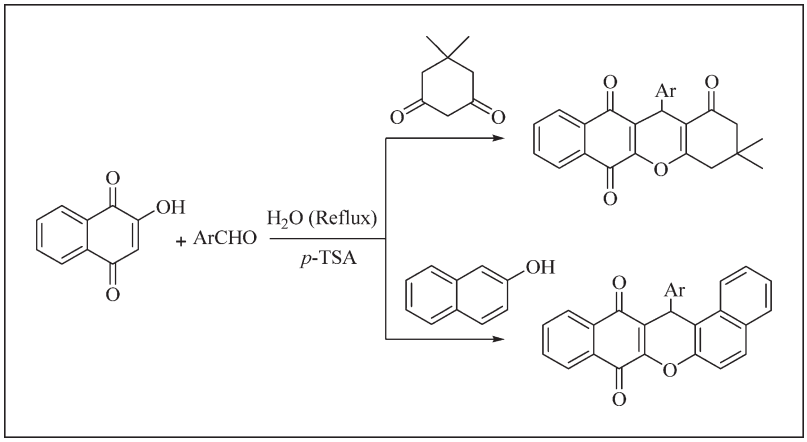


A clean, one-pot and three-component synthesis of new dibenzo[*a*,*i*]xanthene-diones derivatives by cyclo-condensation reaction of 2-hydroxynaphthalene-1,4-dione, aromatic aldehydes and dimedone or 2-naphthol in aqueous media is reported.

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## INTRODUCTION

*ortho*-Quinone methides (*o*-QMs) are highly reactive intermediates that have been extensively harnessed by nature. Despite the general knowledge of *o*-QMs for over a century these intermediates still lie outside the synthetic mainstream [1,2]. Very recently, Pettus described the methods by which *o*-QMs are prepared, the benefits and limitations associated with each method as well as current applications in total synthesis [3]. The pseudo three-component condensation reaction of 2-naphthol with aldehydes in the presence of various catalysts to form xanthenes has been studied widely. The reaction proceeds through the *in situ* formation of *ortho*-quinone methides with 2-naphthol acting as a nucleophile [4]. However, the three-component condensation reactions of 2-naphthol and aldehydes with other nucleophiles is rarely reported in literature [5].

Xanthenes and benzoxanthenes have been reported to posses diverse biological and therapeutic properties, such as antibacterial [6], antiviral [7], and anti-inflammatory activities [8], as well as photodynamic therapy [9] and for antagonism of the paralyzing action of zoxazolamine [10]. The other useful applications of this heterocycles are as dyes [11], fluorescent materials for visualization of biomolecules [12], and in laser technologies [13]. Therefore, a number of methods have been reported for the preparation of xanthene derivatives [4,5f–h, 14–17].

Molecules with the naphthoquinone structure constitute one of the most interesting classes of compounds in organic chemistry, because of their biological properties, their industrial applications, and their potential as intermediates in the synthesis of heterocycles [18]. Naphthoquinone moiety occurs in different natural products, including β-lapachone **A**, α-xiloidone **B**, lambertellin **C**, WS-5995A **D**, and pyranokunthone B **E** [19]. Compounds **F** and **G** were extracted from marine actinomycete strain CNQ-525 bacteria; these bacteria were isolated from ocean sediments, which were collected at a depth of 152 m near La Jolla, California (Fig. 1). Compounds **F** and **G** possess significant antibiotic properties and cancer cell cytotoxicities activities [20].

In continuation of our previous works on synthesis of heterocycles containing naphthoquinone or xanthene moiety [21–25], herein we report a simple and efficient method for the preparation of benzo[*b*]xanthene-triones and dibenzo[*a*,*i*]xanthene-diones in aqueous media.

## RESULTS AND DISCUSSION

We found that a mixture of 2-hydroxynaphthalene-1,4-dione **1**, 2-naphthol **2** and aromatic aldehydes **3a–i**,

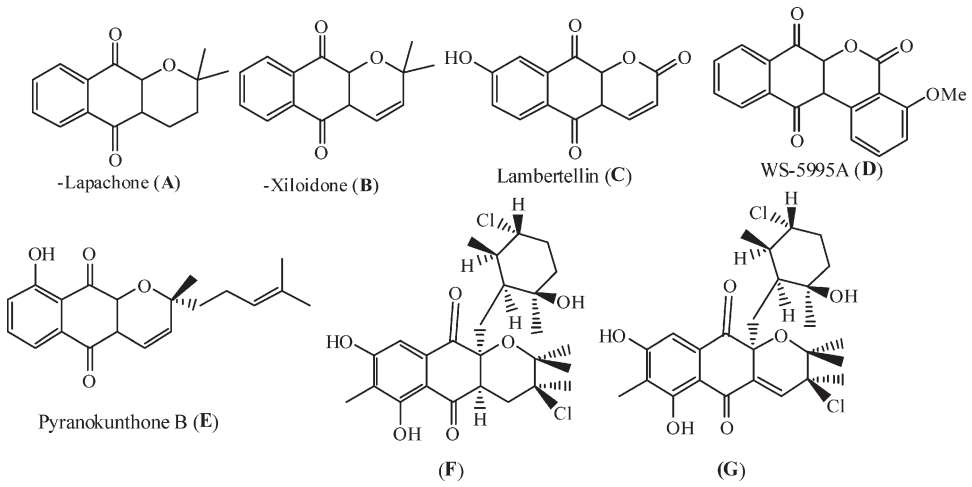



**Figure 1.** Examples of biologically active naphthoquinone derivatives.

in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and readily available catalyst at refluxing water for 8–10 h, afforded 14-aryl-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-diones **4a–i** in 83–91% yields (Scheme 1). The optimized results are summarized in Table 1. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields.

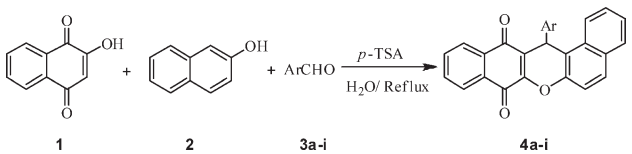
The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA and over long period of time (24 h) the yields of products were low (<30%).

When this reaction was carried out with aliphatic aldehyde, such as butanal or pentanal, TLC and $^1$H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products, the yield of the expected product was very poor.

By referring to the literature [4], the formation of products **4** can be rationalized by initial formation of *ortho*-quinone methides intermediate **5**. Subsequent addition of **1** to the intermediate **5**, followed by elimination of water afforded the corresponding products **4** (Scheme 2).

To further explore the potential of this protocol for xanthene synthesis, we investigated reaction of 1,3-cyclohexadione **6** instead of 2-naphthol **2** and obtained 3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione **7a–i**, in good yields for 14–16 h (Scheme 3). The optimized results are summarized in Table 2.

**Scheme 1**




The nature of the compounds **4** and **7** as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4** and **7** are stable solids whose structures are fully supported by IR, NMR spectroscopy, and elemental analysis.

In summary, a novel, simple, convenient, and practical method for the synthesis of substituted benzo[*b*]xanthene-triones and dibenzo[*a*,*i*]xanthene-diones has been reported by one-pot and three component reaction using *p*-TSA as an inexpensive and readily available catalyst. This protocol includes some important aspects like the use of water as a ''green'' reaction medium, high atom economy, mild reaction conditions, and excellent yields.

## EXPERIMENTAL

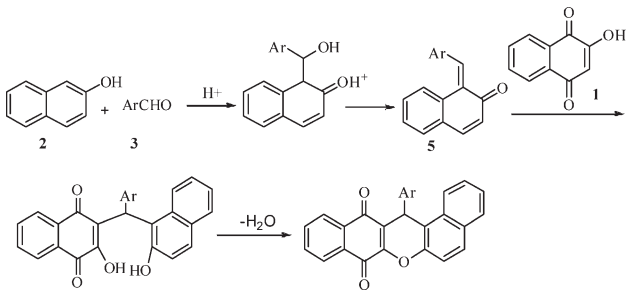
Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at

**Table 1**

Synthesis of dibenzo[*a*,*i*]xanthene-diones **4**.

| Product **4** | Ar | Time (h) | Yield (%) |
|---|---|---|---|
| a | $C_6H_5$ | 10 | 88 |
| b | 4-Cl—$C_6H_4$ | 9 | 83 |
| c | 4-Br—$C_6H_4$ | 10 | 89 |
| d | 4-F—$C_6H_4$ | 8 | 85 |
| e | 4-MeO—$C_6H_4$ | 10 | 84 |
| f | 4-Me—$C_6H_4$ | 10 | 87 |
| g | 4-HO—$C_6H_4$ | 10 | 78 |
| h | 3-$NO_2$—$C_6H_4$ | 8 | 91 |
| i | 2-Cl—$C_6H_4$ | 9 | 87 |

**Scheme 2**



300.13 and 75.47 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

**Typical procedure for preparation of 14-phenyl-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-dione (4a).** A mixture of benzaldehyde (0.11 g, 1 mmol), 2-naphtol (0.140 g, 1 mmol), 2-hydroxynaphthalene-1,4-dione (0.17 g, 1 mmol), *p*-TSA (0.1 g) was refluxed in water (5 mL) for 10 h (TLC). At the end of the reaction, the precipitate formed was collected by filtration and washed with ethanol to afford the pure product **4a**. Orange powder (88%); m.p. 294–297°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3054, 1703, 1656; $^1$H NMR (DMSO-$d_6$): $\delta_H$ 5.09 (1H, s, CH), 7.16–8.08 (15H, m, H-Ar). MS (*m*/*z*) 388 ($M^+$). Anal. Calcd (%) for $C_{27}H_{16}O_3$: C, 83.49; H, 4.15. Found C, 83.55; H, 4.10.

**Selected Characterization Data.**

***14-(4-Chlorophenyl)-8H-dibenzo[a,i]xanthene-8,13(14H)-dione(4b).*** Yellow powder (83%); m.p. 281–284°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3044, 1699, 1663; $^1$H NMR (DMSO-$d_6$): $\delta_H$ 5.77 (1H, s, CH), 7.24 (2H, d, $J$ = 7.4 Hz, H-Ar), 7.39 (2H, d, $J$ = 7.4 Hz, H-Ar), 7.46–7.51 (2H, m, H-Ar). 7.67–7.74 (2H, m, H-Ar). 7.86 (1H, d, $J$=7.1 Hz, H-Ar), 7.90–8.02 (4H, m, H-Ar), 8.20 (1H, d, $J$=7.1 Hz, H-Ar). MS (*m*/*z*, %) 422 ($M^+$). Anal. Calcd (%) for $C_{27}H_{15}ClO_3$: C, 76.69; H, 3.58. Found C, 76.61; H, 3.52.

**14-(4-Bromophenyl)-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-dione (4c).** Yellow powder (89%); m.p. 294–298°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3075, 1704, 1663; $^1$H NMR (DMSO-$d_6$): $\delta_H$ 5.89 (1H, s, CH), 7.27–7.34 (4H, m, H-Ar), 7.45 (2H, t, $J$ = 6.8 Hz, H-Ar). 7.50–7.62 (2H, m, H-Ar), 7.79 (1H, t, $J$ = 7.6 Hz, H-Ar). 7.85–7.92 (3H, m, H-Ar), 8.11–8.18 (2H, m, H-Ar). MS (*m*/*z*, %) 468 ($M^+$ + 2), 466 ($M^+$). Anal. Calcd (%) for $C_{27}H_{15}BrO_3$: C, 69.39; H, 3.24. Found C, 69.30; H, 3.33.

Due to very low solubility of the product **4a–c**, we cannot report the $^{13}$C NMR data for this product.

**12-phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (7a).** Orange powder (82%); mp: 263–265°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2926, 1678, 1606. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 0.94 (3H, s, $CH_3$), 1.07 (3H, s, $CH_3$), 2.15 and 2.31 (2H, AB system, $J$ = 16.2 Hz, $CH_2$), 2.67 (2H, s, $CH_2$), 4.88 (1H, s, CH), 7.10–7.15 (1H, m, H-Ar), 7.21–7.32 (2H, m, H-Ar), 7.43–7.46 (2H, m, H-Ar). 7.80–7.91 (3H, m, H-Ar) 7.99–8.07 (1H, m, H-Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_c$ 26.9, 28.9, 32.4, 32.7, 40.1, 113.6, 124.2, 126.2, 126.5, 127.2, 128.7, 128.8, 129.0, 130.9, 131.4, 134.6, 135.0, 143.2, 149.5, 163.4, 177.5, 183.2, 196.3. MS (*m*/*z*) 384 ($M^+$). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24;%. Found: C, 78.21; H, 5.29%.

**Scheme 3**

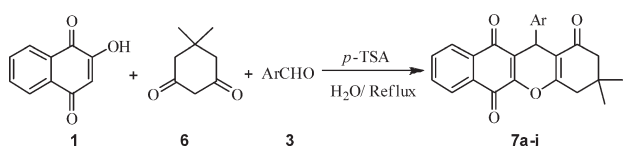


**Table 2**

Synthesis of dibenzo[*a*,*i*]xanthene-diones **7**.

| Product **7** | Ar | Time (h) | Yield (%) |
|---|---|---|---|
| a | $C_6H_5$ | 16 | 82 |
| b | 4-Cl—$C_6H_4$ | 15 | 90 |
| c | 4-Br—$C_6H_4$ | 16 | 86 |
| d | 4-F—$C_6H_4$ | 14 | 82 |
| e | 4-$NO_2$–$C_6H_4$ | 14 | 84 |
| f | 4-Me—$C_6H_4$ | 16 | 83 |
| g | 2-Cl—$C_6H_4$ | 16 | 87 |
| h | 3-$NO_2$—$C_6H_4$ | 15 | 81 |
| I | 3-Br—$C_6H_4$ | 16 | 80 |

**12-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (7b).** Yellow powder (90%); mp: 282–284°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2932, 1663, 1618, 1594. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 0.94 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.15 and 2.31 (2H, AB system, $J$ = 16.2 Hz, $CH_2$), 2.67 (2H, s, $CH_2$), 4.89 (1H, s, CH), 7.28–7.37 (4H, m, H-Ar), 7.83–7.90 (3H, m, H-Ar), 8.03–8.06 (1H, m, H-Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_c$ 26.9, 29.0, 32.5, 33.7, 33.5, 50.5, 113.7, 124.2, 126.2, 126.5, 127.2, 128.6, 129.1, 130.9, 131.4, 134.6, 135.0, 143.2, 149.5, 163.4, 183.3, 196.4. MS (*m*/*z*) 418 ($M^+$). Anal. Calcd for $C_{25}H_{19}ClO_4$: C, 71.69; H, 4.57%. Found: C, 71.78; H, 4.50%.

**12-(4-Bromophenyl)-3,3-dimethyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (7c).** Yellow powder (86%); mp: 268–270°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2957, 1660, 1616, 1579. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 0.94 (3H, s, $CH_3$), 1.07 (3H, s, $CH_3$), 2.15 and 2.31 (2H, AB system, $J$ = 15.9 Hz, $CH_2$), 2.67 (2H, s, $CH_2$), 4.88 (1H, s, CH), 7.10–7.12 (2H, d, $J$ = 8.4 Hz, H-Ar), 7.42–7.45 (2H, m, H-Ar), 7.83–7.90 (3H, m, H-Ar), 8.03–8.06 (1H, m, H-Ar). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta_c$ 27.3, 29.0, 32.4, 33.7, 40.7, 50.5, 113.3, 123.8, 123.9, 126.6, 126.8, 129.7, 130.4, 131.4, 134.1, 134.7, 146.9, 149.3, 149.6, 163.4, 177.5, 196.0. MS (*m*/*z*) 464 ($M^+$), 462 ($M^+$). Anal. Calcd for $C_{25}H_{19}BrO_4$: C, 64.81; H, 4.13%. Found: C, 64.73; H, 4.20%.

## REFERENCES AND NOTES

[1] Dömling, Wan, P.; Backer, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. Cancer J. Chem. 1996, 74, 465.

[2] Desimoni, G.; Tacconi, G. Chem. Rev. 1975, 75, 651.

[3] Van De Water, R. W.; Pettus, T. R. R. Tetrahedron 2002, 58, 5367.

[4] (a) Rajitha, B.; Kumar, B. S.; Reddy, Y. T.; Reddy, P. N.; Sreenivasulu, N. Tetrahedron Lett. 2005, 46, 8691; (b) Khosropour, A. R.; Khodaei, M. M.; Moghannian, H. Synlett 2005, 955; (c) Ko, S.; Yao, C.-F. Tetrahedron Lett. 2006, 47, 8827.

[5] (a) Cimarelli, C.; Palmieri, G.; Volpini, E. Tetrahedron: Asymmetry 2002, 13, 2417; (b) Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. Tetrahedron Lett 2002, 43, 8367; (c) Szatmári, I.; Lázár, L.; Fülöp, F. Tetrahedron Lett. 2006, 47, 3881; (d) Saidi, M. R.; Azizi, N. Tetrahedron: Asymmetry 2003, 14, 389; (e) Khosropour, A. R.;

Khodaei, M. M.; Moghannian, H. Synlett 2005, 916. (f) Khurana, J. M.; Magoo, D. Tetrahedron Lett. 2009, 50, 4777; (g) Li, J.; Tang, W.; Lu, L.; Su, W. Tetrahedron Lett. 2008, 49, 7117; (h) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Srinivas, Y. Synlett 2007, 3107.

[6] Hideu, T.; Teruomi, J. Jpn. Pat. 56,005,480, 1981.

[7] Lamberk, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J. PCT Int. Appl. WO 9706178, 1997.

[8] Poupelin, J. P.; Saint-Rut, G.; Fussard-Blanpin, O.; Narcisse, G.; Uchida-Ernouf, G.; Lakroix, R. Eur J Med Chem 1978, 13, 67.

[9] Ion, R.-M.; Frackowiak, D.; Planner, A.; Wiktorowicz, K. Acta Biochim Pol 1998, 45, 833.

[10] Saint-Ruf, G.; De, A.; Hieu, H. T. Bull Chim Ther 1972, 7, 83.

[11] Banerjee, A.; Mukherjee, A. K. Stain Technol. 1981, 56, 83.

[12] Knight, C. G.; Stephenes, T. Biochem. J. 1989, 258, 683.

[13] Sirkecioglu, O.; Tulinli, N.; Akar, A. J Chem Res (S) 1995, 502.

[14] Van Allan, J. A.; Giannini, D. D.; Whitesides, T. H. J Org Chem 1982, 47, 820.

[15] Bekaert, A.; Andrieux, J.; Plat, M. Tetrahedron Lett 1992, 33, 2805.

[16] Jha, A.; Beal, J. Tetrahedron Lett 2004, 45, 8999.

[17] Knight, D. W.; Little, P. B. J Chem Soc Perkin Trans 1 2001, 1771.

[18] Thomson R H. Naturally Occurring Quinones, 4th ed.; Chapman & Hall: London, 1997.

[19] Noroozi Tisseh, Z.; Azimi, S. C.; Mirzaei, P.; Bazgir, A. Dyes Pigments 2008, 79, 273.

[20] Bazgir, A.; Noroozi Tisseh, Z. Dyes Pigments 2009, 83, 258.

[21] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. Tetrahedron Lett 2008, 49, 5165.

[22] Seyyedhamzeh, M.; Mirzaei, P.; Bazgir, A. Dyes Pigments 2008, 76, 836.

[23] Imani Shakibaei, G.; Mirzaei, P.; Bazgir, A. Appl Catal A: Gen 2007, 325, 188.

[24] Amini, M. M.; Seyyedhamzeh, M.; Bazgir, A. Appl Catal A: Gen 2007, 323, 242.

[25] Imani Shakibaei, G.; Mirzaei, P.; Bazgir, A. Appl Catal A: Gen 2007, 325, 188.

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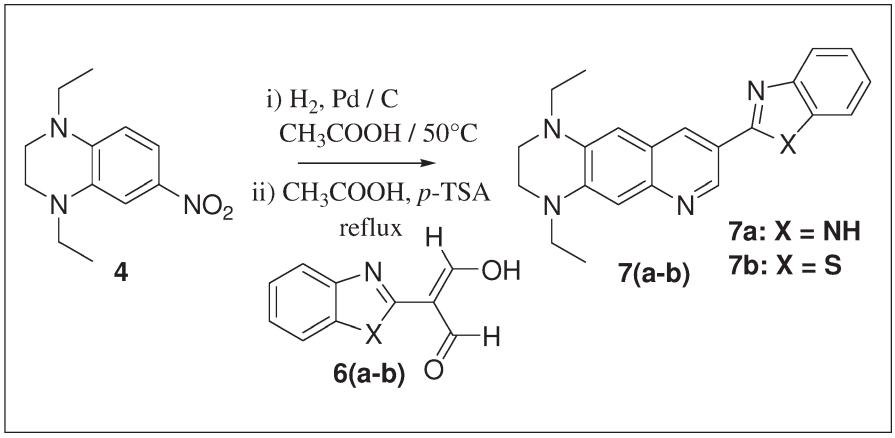


1,4-Diethyl-1,2,3,4-tetrahydro-6-nitroquinoxaline **4** was synthesized by alkylative reduction of 6-nitroquinoxaline. Catalytic reduction of **4** followed by cyclocondensation with heterocyclic malondialdehydes afforded novel 8-(heteroaryl)-1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxalines. The solutions of these novel compounds having 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline framework as an electron releasing system showed absorption in the range of 424–426 nm in the visible region and exhibited brilliant bluish-green fluorescence. The thermogravimetric curve obtained by thermogravimetric analysis displayed that these fluorophores possess excellent thermal stability with one-step thermal decomposition.

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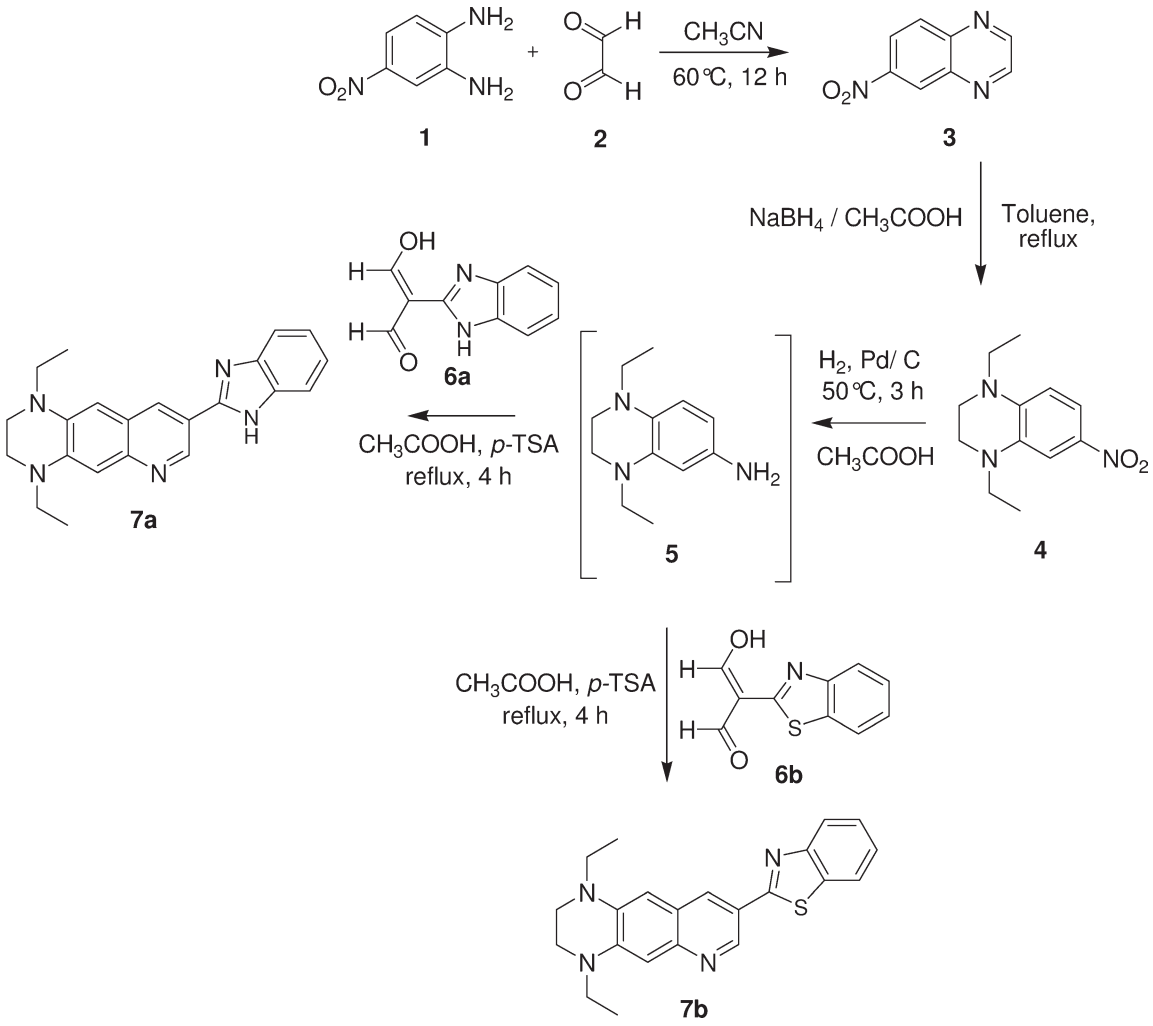
## INTRODUCTION

The structural diversity, stability, and biological importance of heterocycles have made them attractive synthetic targets over many years, and they have found potential applications in various fields of science and technology. Especially in the field of colorants, heterocycles have gained extreme importance because of their planar and rigid π-conjugation system. Many heterocycles based on rigid ring systems such as coumarins [1], thiazoles [2], benzimidazoles [3], pyrazines [4], naphthalimides [5], and oxadiazoles [6] are well-established fluorescent dye chromophores. Heterocyclic fluorescent compounds have been extensively investigated for various potential applications including tunable dye lasers [7], molecular probes for biochemical research [8], and traditional textile and polymer fields [9].

Quinoxaline is one of the interesting heterocyclic systems. Many quinoxaline scaffolds are found as a core unit in a number of biologically active compounds [10,11]. Its derivatives are used in the development of novel organic dyes and organic semiconductors [12]. Fluorescent styryl dyes based on fused quinoxaline system are reported in the literature. In earlier work from our laboratory, the versatility of quinoxaline has been demonstrated [13–16]. Quinoxalines can be easily reduced to 1,2,3,4-tetrahydroquinoxalines by reducing agents such as lithium aluminium hydride [17] and sodium borohydride [18] in excellent yields. Sequential reduction and alkylation of N-heterocycles such as indole to N-alkylated indoline and quinoline to 1,2,3,4-tetrahydroquinoline by sodium borohydride and trifluoroacetic acid is well known [19–22]. Quinoxalines can also be sequentially reduced and dialkylated using sodium borohydride and carboxylic acids. 6-Nitroquinoxaline has been subjected to similar reductive alkylation using sodium borohydride and glacial acetic acid to obtain 1,4-diethyl-1,2,3,4-tetrahydro-6-nitroquinoxaline [23]. The 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline framework is rigid and highly electron rich. We have

**Scheme 1.** Synthetic pathway of compounds **7a–7b**.




reported mono- and bis-styryl dyes derived from 1,4-diethyl-1,2,3,4-tetrahydro-6-methoxyquinoxaline [24]. These dyes having orange to violet hue displayed pronounced bathochromicity and good thermal stability. A series of highly fluorescent coumarin derivatives based on 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline framework, synthesized by us, exhibited excellent bathochromicity [25]. These results encouraged us to envisage that, the molecular structures possessing a strong electron donating and rigid 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline unit in conjugation with heterocyclic π-conjugated system should exhibit brilliant fluorescence and display absorption maxima in the yellow region of the electromagnetic spectrum.

In this communication, we report the synthesis and spectroscopic properties of novel pyrido[2,3-g]quinoxaline derivatives having 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline framework as an electron releasing unit in conjugation with electron accepting heterocycles like benzimidazole and benzothiazole. The electronic properties of these highly fluorescent compounds were analyzed by UV-vis absorption spectroscopy and fluorescence emission spectroscopy. The fluorescent compounds **7a** and **7b** were also evaluated for thermal stability by thermogravimetric analysis. The spectroscopic properties of these pyrido[2,3-g]quinoxaline derivatives were compared with the closely related coumarin analogs **8a**–**8b** and styryl derivatives **9a**–**9b**.

## RESULTS AND DISCUSSION

**Synthesis of compounds 7a–7b.** Substituted 1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxalines **7a–7b** were synthesized by cyclocondensation of 6-amino-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline **5** and suitable malondialdehyde derivatives **6a–6b** as depicted in Scheme 1. 4-Nitro-1,2-phenylenediamine **1** was condensed with glyoxal **2** in dry acetonitrile to obtain 6-nitroquinoxaline **3** in excellent yield. Reductive

**Table 1**
Spectral properties of compounds **7a–7b** in toluene, chloroform, hexane, and methanol.

| | Toluene | | | | Chloroform | | | | Hexane | | | | Methanol | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compd. | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | ε (l mol$^{-1}$ cm$^{-1}$) | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | ε (l mol$^{-1}$ cm$^{-1}$) | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | ε (l mol$^{-1}$ cm$^{-1}$) | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | ε (l mol$^{-1}$ cm$^{-1}$) |
| **7a** | 418 | 497 | 79 | 34,404 | 422 | 502 | 80 | 33,290 | 412 | 483 | 71 | 33,611 | 424 | 512 | 88 | 29,854 |
| **7b** | 423 | 519 | 96 | 25,956 | 426 | 520 | 93 | 26,591 | 418 | 507 | 89 | 26,666 | 426 | 533 | 107 | 25,469 |

alkylation of 6-nitroquinoxaline with sodium borohydride and glacial acetic acid in dry toluene yielded 1,4-diethyl-6-nitro-1,2,3,4-tetrahydroquinoxaline **4** as a bright red solid, which was then hydrogenated over 10% palladium charcoal in glacial acetic acid to afford 6-amino-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline **5**. The catalyst was filtered under nitrogen atmosphere and filtrate was immediately used for further reactions as the amino compound **5** was unstable and rapidly oxidized. The reaction of 6-amino-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline **5** with appropriate malondialdehyde derivatives **6a–6b** took place readily in glacial acetic acid in the presence of equivalent amount of *p*-toluenesulphonic acid to yield 8-(heteroaryl)-1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxalines **7a–7b**. This cyclocondensation reaction proceeded in a facile manner owing to the presence of electron releasing 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline framework. The structures of the compounds were confirmed by FT-IR, $^1$H NMR spectroscopy, mass spectrometry, and elemental analysis. The results are summarized in the experimental section.

**Spectral characteristics of compounds 7a–7b.** Basic spectral characteristics of the chromophores such as absorption maxima ($\lambda_{max}$), emission maxima ($\lambda_{em}$), and extinction coefficient (ε) were measured in different solvents and are presented in Tables 1 and 2. The electronic absorption spectra of the compounds **7a–7b** displayed absorption maxima in the visible region from 412 to 427 nm. Compound **7a** showed absorption maxima at 412 nm in hexane, lowest among two derivatives, whereas compound **7b** showed well-pronounced absorption maxima at 427 nm in DMF which is the highest between the two derivatives. To investigate the influence of solvents on the absorption maxima of compounds **7a** and **7b**, their absorption spectra were measured in different solvents such as toluene, chloroform, ethyl acetate, hexane, methanol, DMF, acetonitrile, and ethyl acetate. The solvents differ considerably in polarity and ability to form H-bonds. From the presented values in Tables 1 and 2, it is apparent that practically no solvatochromism was observed. Only in the case of **7a** in hexane, significant hypsochromic shift in the absorption maxima was noticed. Figure 1 displays absorption maxima of the compounds **7a–7b** in methanol.

These 8-(heteroaryl)-1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxalines were expected to be strongly fluorescent in view of the conjugation of rigid and electron rich 1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxaline ring with electron accepting heterocycles. To our delight, both compounds exhibited strong bluish-green fluorescence with large Stokes shift values (Tables 1 and 2). Especially, fluorophore **7b** containing benzothiazole ring showed remarkably high Stokes shift value of 107 in methanol. Figure 2 displays emission maxima of

**Table 2**
Spectral properties of compounds **7a–7b** in DMF, acetonitrile and ethyl acetate.

| | DMF | | | | Acetonitrile | | | | Ethyl acetate | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compd. | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | $\varepsilon$ (l mol$^{-1}$ cm$^{-1}$) | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | $\varepsilon$ (l mol$^{-1}$ cm$^{-1}$) | $\lambda_{max}$ (nm) | $\lambda_{em}$ (nm) | Stokes shift | $\varepsilon$ (l mol$^{-1}$ cm$^{-1}$) |
| **7a** | 423 | 505 | 82 | 28,054 | 421 | 506 | 85 | 29,095 | 418 | 494 | 76 | 30,940 |
| **7b** | 427 | 528 | 101 | 24,995 | 425 | 527 | 102 | 24,235 | 421 | 519 | 98 | 24,972 |

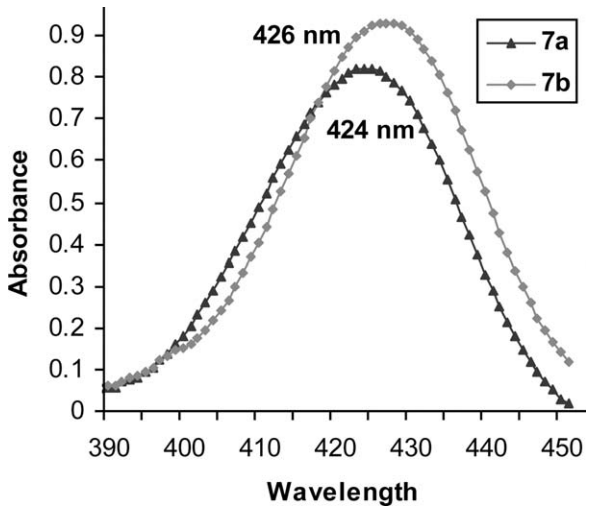



**Figure 1.** Absorption maxima of compounds **7a–7b** in methanol.

the compounds **7a–7b** in methanol. Figure 3 shows photographs of the fluorophores **7a** and **7b** in UV light (366 nm).

As stated earlier, the fluorophores **7a** and **7b** have rigid and electron rich 1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxaline ring in conjugation with electron accepting heterocycles. The situation is rather similar to the coumarin fluorophores **8a** and **8b** (Table 3) reported by us [25]. Also, the styryl dyes **9a** and **9b** (Table 3) were derived from the same electron donor and acceptors [24]. In short, compounds **7a–7b** are structural analogs of compounds **8a–8b** and **9a–9b**. Hence, the spectral properties of **7a** and **7b** in methanol were also compared with the established dyes **8a–8b** and **9a–9b**. The comparative data are summarized in Table 3. Compounds **7a** and **7b** showed intense yellow hue with absorption maxima at 424 and 426 nm, respectively, whereas compounds **8a** and **8b** showed bright orange

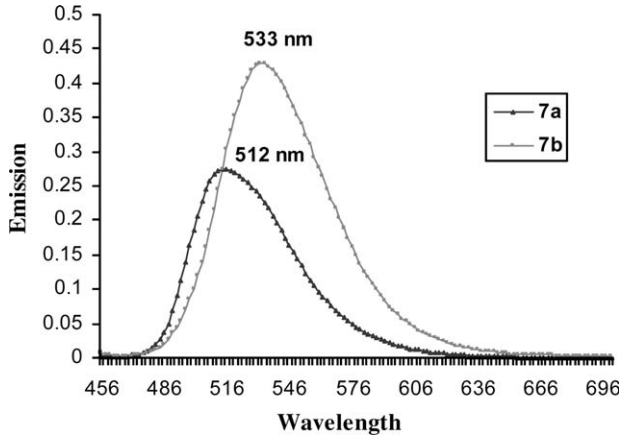



**Figure 2.** Emission maxima of compounds **7a–7b** in methanol.

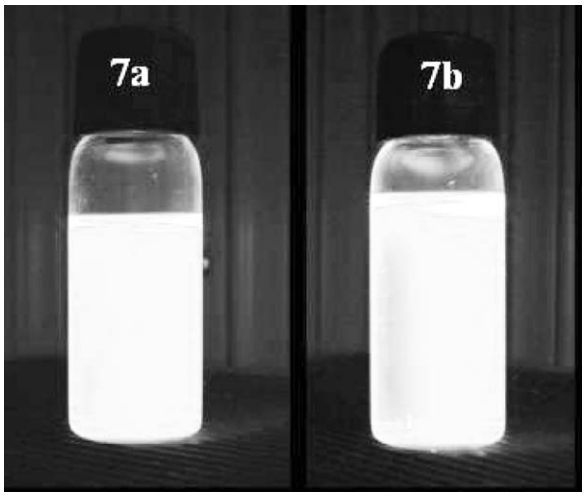
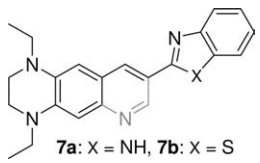
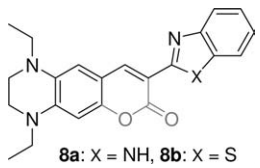
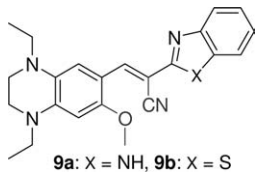
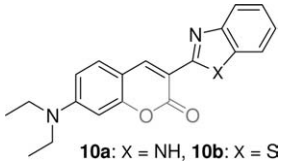



**Figure 3.** Photographs of fluorophores **7a–7b** in UV light (366 nm).

hue and absorbed at 483 and 501 nm, respectively. The large bathochromic shift in the case of **8a** and **8b** is clearly due to the presence of lactone ring. The compounds **8a** and **8b** were highly fluorescent, as it is usual with coumarin compounds. Stokes shift value of **8a** was almost close to that of **7a**, whereas Stokes shift value of **8b** was lower than that of **7b**. It must be noted that the styryl dyes **9a** and **9b**, having same electron donating 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline skeleton in conjugation with electron accepting benzimidazole and benzothiazole rings, respectively, were nonfluorescent. The absence of fluorescence was probably due to lack of rigidity provided by pyrido ring as in the case of compounds **7a–7b** and lactone ring as in the case of compounds **8a–8b**. However, the styryl dyes **9a** and **9b** showed remarkably higher bathochromic shift with absorption maxima at 501 and 528 nm, respectively, owing to the presence of an additional electron

**Table 3**

Spectral properties of compounds **7a**–7**b**, **8a**–**8b**, **9a**–**9b**, and **10a**–**10b** in methanol.

| Structure | Compd. | $\lambda_{max}$ (nm) | ε (l mol$^{-1}$ cm$^{-1}$) | $\lambda_{em}$ (nm) | Stokes shift | Quantum yield[a] (Φ) |
|---|---|---|---|---|---|---|
|  **7a**: X = NH, **7b**: X = S | **7a** | 424 | 24,054 | 512 | 88 | 0.1 |
| | **7b** | 426 | 25,469 | 533 | 107 | 0.14 |
|  **8a**: X = NH, **8b**: X = S | **8a** | 483 | 24,600 | 574 | 91 | 0.28 |
| | **8b** | 501 | 33,900 | 598 | 97 | 0.34 |
|  **9a**: X = NH, **9b**: X = S | **9a** | 501 | 29,218 | – | – | – |
| | **9b** | 528 | 25,514 | – | – | – |
|  **10a**: X = NH, **10b**: X = S | **10a** | 435 | 52,200 | 480 | 45 | 0.62 |
| | **10b** | 465 | 54,000 | 491 | 26 | 0.7 |

[a] Quantum yields were measured in methanol using Rhodamine-6G (Φ = 0.94) as standard [26,27].

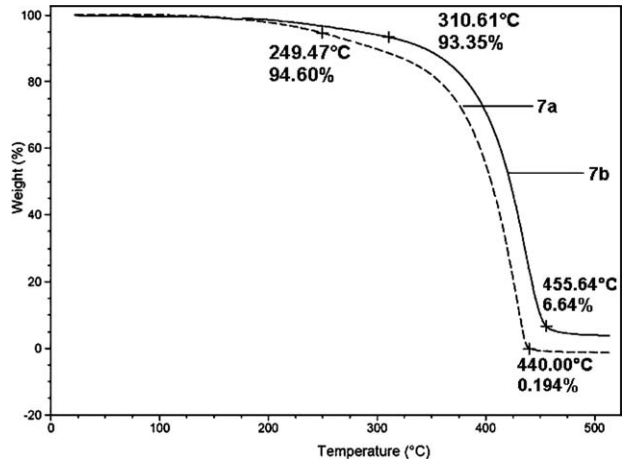



**Figure 4.** Thermogravimetric curves of fluorophores **7a–7b**.

accepting cyano group. In all the three classes, the compounds **7b**, **8b**, and **9b** having benzothiazole ring underwent bathochromic shift relative to their respective analogs having benzimidazole ring, owing to high electronegativity of sulfur atom in the ring.

To complement this study, spectral properties of fluorescent compounds **7a–7b** and **8a–8b** were compared with that of commonly encountered commercial fluorescent coumarin dyes **10a** (Coumarin 535) and **10b** (Coumarin 540) (Table 3) having same electron accepting groups. As expected, the rigid coumarins **8a** and **8b** showed significant bathochromic shift in absorption maxima compared with the nonrigid coumarins **10a** and **10b**. The compounds **10a** and **10b**, however, have remarkably high molar extinction coefficient values and absorb at longer wavelength compared with quinoxaline derivatives **7a** and **7b**. The Stokes shift values of compounds **10a** and **10b** are lower than that of compounds **7a–7b** and **8a–8b**. The fluorescence quantum yields ($\Phi$) of the compounds were measured in methanol using Rhodamine-6G ($\Phi = 0.94$) [26,27] as standard. Compound **7b** showed $\Phi$ value of 0.14 which is marginally higher than that of **7a** ($\Phi = 0.1$). The fluorescence quantum yields of compounds **7a** and **7b** were found to be lower than that of coumarin derivatives. Although, the quinoxaline derivatives **7a–7b** possess similar electron donor and acceptor groups as coumarins **8a–8b** and **10a–10b**, they exhibit significant hypsochromic shift in absorption maxima and lower fluorescence quantum yields. The lower fluorescence in quinoxaline derivatives is due to the absence of lactone framework in coumarins which impart rigidity, high electronegativity, and excellent planarity to the molecule.

**Thermal properties of fluorophores 7a and 7b.** The fluorophores were subjected to the thermogravimetric analysis to investigate their thermal stability. The change in weight of the compound was measured as a function of temperature. Figure 4 displays thermograph of the fluorophores **7a** and **7b**. The thermogravimetric curves for the compounds show a clear plateau followed by a sharp and smooth decomposition curve. The loss in weight of the compound **7a** was rapid when heated above 250°C. This fact indicates that the compound is stable up to 250°C after which it decomposes rapidly and decomposition completes at 440°C. Among the two compounds, compound **7b** in particular showed excellent thermal stability up to 310°C. Rapid decomposition of **7b** occurred when it was heated above 310°C. The decomposition completed at about 455°C. Both the fluorophores underwent one-step thermal decomposition. Coumarin chromophores **8a–8b** and styryl dyes **9a–9b** also showed thermal stability above 250°C with smooth, one step thermal decomposition curve [24,25].

## CONCLUSION

In conclusion, novel 8-(heteroaryl)-1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxalines are valuable as new fluorescent chromophores having absorption maxima at 412–427 nm and emission maxima at 502–533 nm in different solvents. These compounds did not show any appreciable solvatochromism and have lower fluorescence quantum yields than coumarins having same electron donating and accepting groups. The compounds displayed good thermal stability.

## EXPERIMENTAL

All melting points were uncorrected and are in °C. IR spectra were recorded on a Bomem Hartmann and Braun MB-Series FT-IR spectrometer (KBr). $^1$H NMR spectra were recorded on Varian 300 MHz mercury plus spectrometer, and chemical shifts are expressed in $\delta$ ppm using TMS as an internal standard. Mass spectra were recorded on Micromass: Q-T of micro (YA-105) mass spectrometer. Microanalysis for C, H, N, and S were performed on Thermofignnin elemental analyzer. Electronic spectra were recorded on Spectronic spectrophotometer. The fluorescence maxima of the compounds were recorded on Jasco FP-1520 fluorimeter. Thermogravimetric analysis was carried out on SDT Q600 v8.2 Build 100 model of TA instruments.

**Synthesis of 6-amino-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline (5).** 1,4-Diethyl-1,2,3,4-tetrahydro-6-nitroquinoxaline **4** [23] (5.0 g, 0.021 moles) and catalytic amount of palladium on charcoal (10%) in glacial acetic acid (100 mL) were stirred in Parr hydrogenator at 50°C under an atmosphere of hydrogen until think layer chromatography (TLC) (eluent: 10% ethyl acetate in *n*-hexane) of the reaction mixture showed no red colored spot of reactant. The reaction mixture was then filtered under nitrogen atmosphere to separate the catalyst. 6-Amino-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline **5** thus obtained was not isolated and subsequently used for further reaction immediately after filtration as it was found to be unstable [23]. (The

pale yellow reaction mixture was filtered under nitrogen blanket as it turns black on exposure to air).

**General method for the synthesis of compounds (7a–7b).** Above reaction mixture, appropriate malondialdehyde derivative **6a** or **6b** [28] (0.021 moles) and *p*-toluenesulphonic acid (*P*-TSA) (3.6 g, 0.021 moles) were heated to reflux under nitrogen atmosphere for 4 h. The reaction mixture was then cooled to room temperature, neutralized with dilute sodium hydroxide solution (10%) maintaining the temperature below 15°C. Dark brown solid obtained was filtered, washed with water and dried. The crude compound was purified by column chromatography on activated neutral aluminium oxide using toluene–ethyl acetate (7:3) system.

**8-(Benzimidazol-2-yl)-1,4-diethyl-1,2,3,4-tetrahydropyrido[2,3-g]quinoxaline (7a).** (5.17 g, 69%); mp 160–162°C; ir (KBr) $\nu_{max}$ $cm^{-1}$: 3090–3015, 2900–2850, 1688, 1612, 1279; $^1H$ NMR: δ 1.20 (t, $J = 7.1$ Hz, 3H, $CH_3$), δ 1.26 (t, $J = 7.1$ Hz, 3H, $CH_3$), δ 3.15–3.21 (m, 2H), δ 3.29 (q, $J = 7.1$ Hz, 2H, $CH_2$), δ 3.39 (q, $J = 7.1$ Hz, 2H, $CH_2$), δ 3.47–3.53 (m, 2H), δ 6.69 (s, 1H, phenyl proton), δ 7.03 (s, 1H, phenyl proton), δ 7.31–7.37 (m, 2H, protons on benzimidazole ring), δ 7.53–7.58 (m, 1H, proton on benzimidazole ring), δ 7.72–7.77 (m, 1H, proton on benzimidazole ring), δ 8.55 (d, $J = 1.95$ Hz, 1H, proton *para* to N of pyrido ring), δ 9.26 (d, $J = 1.95$ Hz, 1H, proton *ortho* to N of pyrido ring), Anal. Calcd for $C_{22}H_{23}N_5$: C, 73.92; H, 6.49; N, 19.59. Found: C, 73.95; H, 6.48; N, 19.55; ms: *m*/*z* 358 ($M^+$+H).

**8-(Benzthiazol-2-yl)-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline (7b).** (5.74 g, 73%); mp 174–176°C; ir (KBr) $\nu_{max}$ $cm^{-1}$: 3100–3010, 2911–2850, 1682, 1608, 1280; $^1H$ NMR: δ 1.21 (t, $J = 6.9$ Hz, 3H, $CH_3$), δ 1.28 (t, $J = 6.9$ Hz, 3H, $CH_3$), δ 3.13–3.18 (m, 2H), δ 3.31 (q, $J = 6.9$ Hz, 2H, $CH_2$), δ 3.41 (q, $J = 6.9$ Hz, 2H, $CH_2$), δ 3.49–3.54 (m, 2H), δ 6.71 (s, 1H, phenyl proton), δ 7.04 (s, 1H, phenyl proton), δ 7.31–7.51 (m, 2H, phenyl protons on benzthiazole ring), δ 7.87–7.91 (m 1H, phenyl proton on benzthiazole ring), δ 8.03–8.07 (m, 1H, phenyl proton on benzthiazole ring), δ 8.42 (d, $J = 2.42$ Hz, 1H, proton *para* to N of pyrido ring), δ 9.11 (d, $J = 2.42$ Hz, 1H, proton *ortho* to N of pyrido ring); Anal. Calcd for $C_{22}H_{22}N_4S$: C, 70.56; H, 5.92; N, 14.96; S, 8.56. Found: C, 70.59; H, 5.88; N, 14.97; S, 8.57; ms: *m*/*z* 375 ($M^+$+H).

## REFERENCES AND NOTES


[1] (a) O'kennedy, R. In Coumarins: Biology, Applications and Mode of Action; Thomes, R. D., Ed.; Wiley: New York, 1997; (b) Murray, R. D. H.; Mendez, J.; Brown, S. A. The Natural Coumarins: Occurrence, Chemistry and Biochemistry; Wiley: New York, 1982; (c) Zahradnik, M. The Production and Application of Fluorescent Brightening Agents; Wiley: New York, 1982; (d) Griffiths, J.; Miller, V.; Bahra, G. S. Dyes Pigm 1995, 28, 327.

[2] Subnis, R. W.; Rangnekar, D. W. J Heterocycl Chem 1990, 27, 417.

[3] Rajadhyaksha, D. D.; Rangnekar, D. W. J Chem Tech Biotech 1986, 36, 300.

[4] Shriai, K.; Yanagisawa, A.; Takahashi, H.; Fukunishi, K.; Matsuoka, M. Dyes Pigm 1986, 39, 49.

[5] (a) Mitchell, K.; Brown, R.; Yuan, D.; Chang, S.-C.; Utech, R.; Lewis, D. J Photochem Photobiol A Chem 1998, 115, 57; (b) Cosnard, F.; Wintgens, V. Tetrahedron Lett 1998, 39, 2751; (c) Ramachandram, B.; Sankaran, N.; Karmakar, R.; Saha, S.; Samanta, A. Tetrahedron 2000, 56, 7041.

[6] Rangnekar, D. W.; Phadke, R. C. Dyes Pigm 1985, 6, 293.

[7] (a) Matsuoka, M. J Soc Dyers Colour 1989, 105, 167; (b) Jones, G.; Jackson, W. R.; Choi, C.; Bergmark, W. R. J Phys Chem 1985, 89, 294.

[8] (a) Mao, F.; Subnis, R. W.; Naleway, J.; Nelson, R.; Hanglano, P. U.S. Pat. 5,576,421 (1996); (b) Christie, R. M. Rev Prog Col 1993, 23, 1.

[9] (a) Gold, H. In Chemistry of Synthetic Dyes; Venkataraman, K., Ed.; Academic Press: London, 1971; Vol. 5, pp 535–679; (b) Hunger, K. Industrial Dyes; WILEY-VCH: Weiheim, 2003, pp 569–577; (c) Kodiro, K.; Inoue, Y. J Am Chem Soc 2003, 125, 421.

[10] (a) Wiseloge, F. W. In Advances in Heterocyclic Chemistry; Armarego, W. L. F., Ed.; Academic Press: New York, 1963; Vol. 1, pp 304; (b) Burguete, A.; Pontiki, E.; Litina, D. H.; Villar, R.; Vicente, E.; Solano, B. Bioorg Med Chem Lett 2007, 17, 6439; (c) Seitz, L. E.; Suling, W. J.; Reynolds, R. C. J Med Chem 2002, 46, 6345.

[11] Yan, L.; Liu, F. W.; Dai, G. F.; Liu, H. Bioorg Med Chem Lett 2007, 17, 609.

[12] (a) Belgoderre, E.; Bossio, R.; Chimichi, S.; Parini, V.; Pepino, R. Dyes Pigm 1983, 4, 59; (b) Jaung, J.; Matsuoka, M.; Fukunishi, K. Dyes Pigm 1996, 31, 141.

[13] Rangnekar, D. W.; Sonawane, N. D.; Subnis, R. W. J Heterocycl Chem 1998, 35, 1353.

[14] Rangnekar, D. W.; Phadke, R. C. Bull Chem Soc Jpn 1986, 59, 1245.

[15] Rangnekar, D. W.; Subnis, R. W. J Heterocycl Chem 1992, 29, 65.

[16] Rangnekar, D. W.; Subnis, R. W. J Heterocycl Chem 1991, 28, 1105.

[17] Hamer, J.; Holliday, R. F. J Org Chem 1963, 28, 2488.

[18] Robert, C. B.; Robert, A. O. J Org Chem 1979, 44, 1719.

[19] Gribble, G. W.; Lord, P. D.; Skotnicki, J. D.; Eaton, S. J.; Johnson, J. J Am Chem Soc 1974, 96, 7812.

[20] Gribble, G. W.; Heald, P. W. Synthesis 1975, 10, 650.

[21] Gribble, G. W.; Ferguson, D. J Chem Soc Chem Commun 1975, 13, 535.

[22] Gribble, G. W.; Hoffman, J. Synthesis 1977, 12, 859.

[23] Gloster, D. F.; Cincotta, L.; Foley, J. W. J Heterocycl Chem 1999, 36, 25.

[24] Satam, V. S.; Rajule, R. N.; Bendre, S. R.; Bineesh, P.; Kanetkar, V. R. J Heterocycl Chem 2009, 46, 221.

[25] Jagtap, A. R.; Satam, V. S.; Rajule, R. N.; Kanetkar, V. R. Dyes Pigm 2009, 82, 84.

[26] Bäumler, W.; Penzkofer, A. Chem Phys 1990, 140, 75.

[27] Wei, P.; Bi, X.; Wu, Z.; Xu, Z. Org Lett 2005, 7, 3199.

[28] (a) Bahar, M. H.; Sabata, B. K. Indian J Chem Sect B 1981, 20, 328; (b) Chandramohan, M. R.; Seshadri, S. Indian J Chem 1972, 10, 573.

# Synthesis of New 1,1′-Carbonyl-bis[3-aryl(heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] and Trifluoromethyl Derivatives through Ring-Opening Reactions

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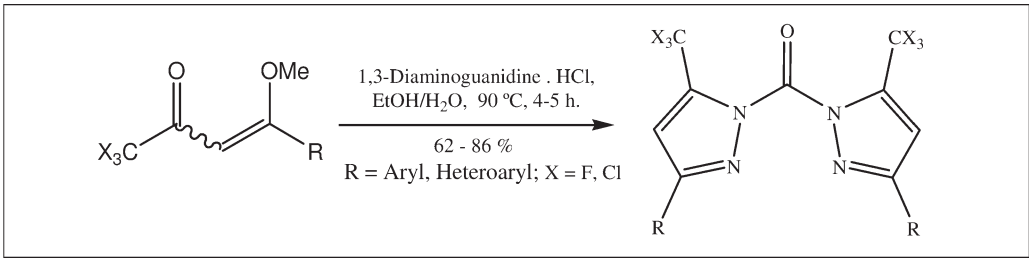


Two new series of 1,1′-carbonyl-bis[3-aryl(heteroaryl)-5-trihalomethyl-1*H*-pyrazoles], where aryl = $C_6H_5$, 4-$CH_3C_6H_4$, 4-$FC_6H_4$, 4-$OCH_3C_6H_4$, 4-$NO_2C_6H_4$, 4,4′-BiPh, 1-naphthyl, and heteroaryl = 2-thienyl and 2-furyl have been synthesized, in a one-pot methodology, from the reaction of 4-methoxy-4-aryl(heteroaryl)-1,1,1-trihalobut-3-en-2-ones with 1,3-diaminoguanidine monohydrochloride. The heterocycles were obtained regioselectively in good yields (62–86%) and in a short reaction time. Ring-opening reactions with 1,2-dinuleophiles and the synthesis of ethyl carboxylate derivative from a pyrazolycarbohydrazide is also reported.

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## INTRODUCTION

The linked pyrazole ring represents an interesting block for synthesis strategies as well as studies on their biological and chemical properties. Moreover, pyrazoles are a class of heterocyclic compounds with many derivatives, and of note, the fluorinated pyrazoles have been demonstrated to play key pharmacophore functions in many pharmaceutical and agrochemical fields [1,2].

The introduction of fluorine(s) into heterocyclic rings is still limited and the trifluoromethyl substituted α,β-unsaturated ketones represent a practical way to access such compounds [3–11]. In recent years, the synthesis of trifluoromethyl pyrazoles has drawn much attention and the literature has reported a series of specific 5-$CF_3$ substituted pyrazoles. The main synthetic methods to prepare such compounds involve CCC and NN atom fragments in cyclization reactions of substituted hydrazines or derivatives thereof with 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [3–9].

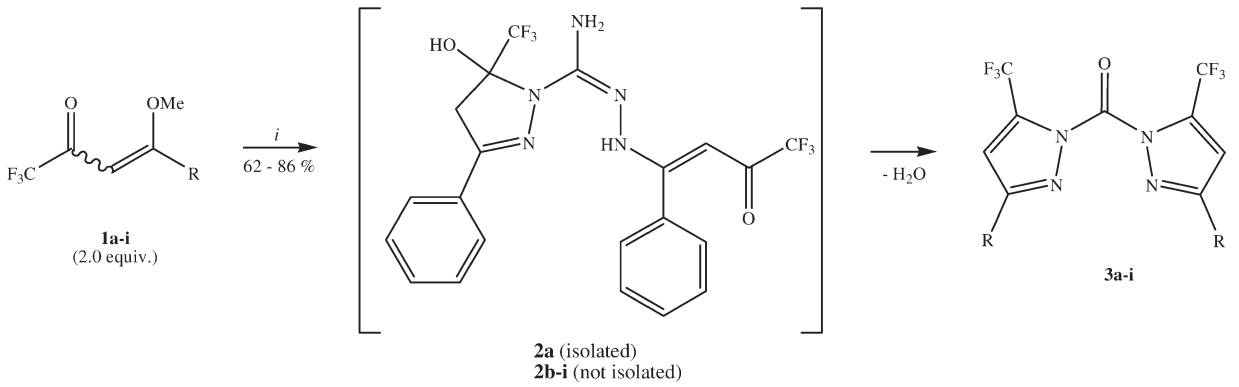
This [3+2] cyclization approach has been shown to be an efficient method to prepare such compounds, where the pyrazole ring is linked to another pyrazole. On the other hand, carbonyl-bispyrazoles are not so common in the literature. For instance, new synthetic routes to obtain these compounds and studies on their potential as pharmaceuticals and agrochemicals have been relatively little explored [10–12].

1,1′-Carbonyl-bispyrazoles have been most commonly synthesized by substitution reaction involving phosgene and other derivatives with pyrazoles [13–19]. However, this synthetic procedure is efficient only when the starting materials are symmetric substituted or nonsubstituted pyrazoles, because nonsymmetric 3- or 5-substituted pyrazoles may exist in two tautomeric structures in solution and their $N^1$-substitution reactions lead undoubtedly to three possible carbonyl-bispyrazoles isomers.

Soliman and Darwish [13] have reported that substituted 3,5-dimethyl-1*H*-pyrazoles reacted with ethyl chloroformate, in the presence of anhydrous potassium carbonate, giving bis-(3,5-dimethyl-1*H*-pyrazole)methanone, in good yields, as a possible hypoglycemic agent. However, a very limited scope is observed when the bis-pyrazole synthesized by this procedure has only methyl substituents at the position 3 and 5 of both pyrazole rings.

More recently, Higgs and Carrano [20] reported the synthesis of carbonyl-bispyrazoles prepared by the

**Scheme 1.** Synthetic route to prepare bis-pyrazoles **3**. Reagents and conditions: (*i*) 1,3-diaminoguanidine. HCl (1.0 equiv), EtOH/$H_2O$, 90°C, 4–5 h.




| 1-3 | a | b | c | d | e | f | g | h | i |
|---|---|---|---|---|---|---|---|---|---|
| R | $C_6H_5$ | 4-$CH_3C_6H_4$ | 4-$FC_6H_4$ | 4-$OCH_3C_6H_4$ | 4-$NO_2C_6H_4$ | 4,4'-$BiC_6H_4$ | 2-Naphthyl | 2-Thienyl | 2-Furyl |

reaction of 3,5-substituted 1*H*-pyrazoles (R and $R^1$ = H, $CH_3$, *i*-Pr) with phosgene, using triethylamine in anhydrous THF as solvent. In this procedure, symmetric carbonyl-bispyrazoles (R = $R^1$ = H or $CH_3$) were obtained, except when R = H and $R^1$ = *i*-Pr. In the previous example, a mixture of isomeric bis-pyrazoles was not obtained due to a steric hindrance between the *i*-propyl substituents.

Recently, we have reported the one-step and regioselective procedure for the synthesis of a novel series of 1,1′-carbonyl-bis[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles] [21] from the cyclocondensation reactions of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones with carbohydrazide. Subsequently, as an example, 1,1′-carbonyl-bis(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole) was subjected to dehydration reactions, using acetic acid/ethanol [22,23], at reflux for 4 h or sulfuric acid/ethanol [24] at reflux for 4 h. In both the cases, the aromatic 1*H*-pyrazole was obtained with the simultaneous removal of the carbonyl function. Because of the relative elimination difficulty, the presence of trifluoromethyl, and the carbonyl groups at positions 5 and 1 of the pyrazole, respectively, another synthetic procedure was performed. After a review of the literature and in an attempt to obtain the aromatic bis-pyrazole, we chose thionyl chloride/pyridine [24,25] as the dehydration agent. Again, the isolation of 1*H*-pyrazole was observed with the cleavage of both C(O)—N bonds.

## RESULTS AND DISCUSSION

As an alternative strategy for the synthesis of trifluoromethylated aromatic bis-pyrazoles, in this study we describe firstly the full regioselective synthesis and characterization of a new series of 1,1′-carbonyl-bis(3-substituted-5-trifluoromethyl-1*H*-pyrazoles) (**3**) from the reaction of trifluoromethyl vinyl ketones (**1**) with 1,3-diaminoguanidine monohydrochloride (Scheme 1).

In principle, β-alkoxyvinyl trihalomethyl ketones (**1a–i** and **8a–f**) are prepared by trihaloacetylation reaction of acetals derived from ketones, according to the previously described procedures [5,26–28].

1,1′-carbonyl-bis(3-substituted-5-trifluoromethyl-1*H*-pyrazoles) (**3a–i**) were obtained from the reaction of two equivalents of 4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1a–i**) and one equivalent of 1,3-diaminoguanidine monohydrochloride, in a one-pot reaction and in 62 to 86% yields. All reactions were carried out in ethanol/water (20:1), monitored by TLC, and the optimal reaction time and temperature were 4–5 h at 90°C. After this time, the compounds (**3a–i)** were isolated by extraction with chloroform/water (1.5:1). The organic layer was dried and evaporated under reduced pressure. The products (**3a–i**) were purified by recrystallization from *iso*-propyl ether, to give pure yellow solids.

According to our previous experience, trifluoromethyl vinyl ketones **1a–i** readily react with substituted hydrazines to give only 5-$CF_3$ substituted pyrazoles [3–9]. In this study, we found that 1,3-diaminoguanidine monohydrochloride reacted specifically as a bis-1,2-dinucleophile with enones **1a–i** and **8a–f** to give bis-pyrazoles linked through a carbonyl carbon. As for the reaction mechanism, firstly, the cyclization of enones **1a–i** takes place furnishing 1,1′-carbonyl-bis(4,5-dihydro-pyrazole) intermediates linked through an imino group. These intermediates undergo *in situ* water elimination and hydrolysis of the imino group to give the respective bis-pyrazoles **3a–i**. The evidence of this mechanism is given

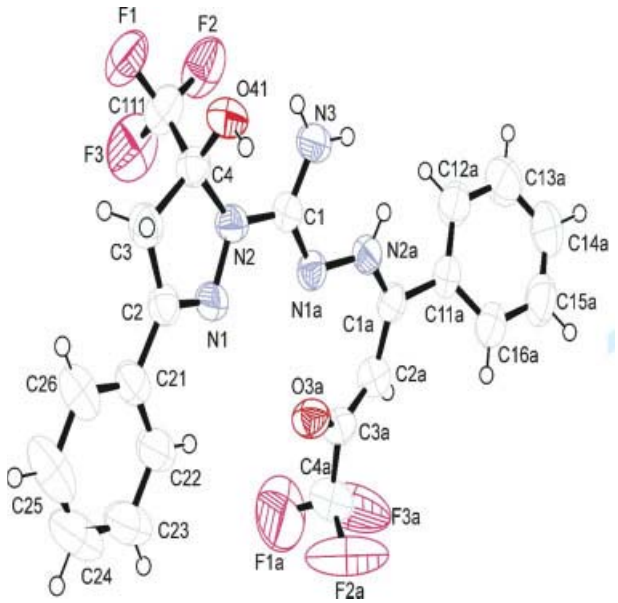



**Figure 1.** ORTEP plot of the intermediate **2a**. Thermal ellipsoids are shown at the 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

by the isolation of the intermediate **2a**, the only intermediate that was isolated and whose was structure confirmed by single-crystal x-ray diffraction (Fig. 1) [29].

The optimal condition to isolate product **3a** together with a trace of the intermediate **2a** was when the reaction was carried out in ethanol/water, at 90°C for 3 h.

The structures of **3a–i** and **9a–f** were deduced from their NMR spectra ($^1$H and $^{13}$C) and by comparison with NMR data of other pyrazoles formerly synthesized in our laboratory [5–9].

The symmetrical carbonyl heterocycles **3a–i** show a symmetrical pattern with one set of signals for the hydrogens and carbons of the 3-substituted pyrazole rings. The compounds **3a–i** show the $^1$H NMR chemical shifts in DMSO-$d_6$ for the H-4 as a sharp singlet in the range of 5.85–6.41 ppm. The signals for the other aromatic hydrogens are in the range of 6.53–8.23 ppm.

The compounds **3a–i** present the typical $^{13}$C chemical shifts of pyrazole rings at an average of 148.1 ppm (C-3) and 86.7 ppm (C-4). The C-5 exhibit signals at around 169.3 and appear as a characteristic quartet with $^2J$ = 28 Hz, because they are attached to a $CF_3$ group. The $CF_3$ group shows a typical quartet at an average of 118.2 ppm, with $J_{C\text{-}F}$ = 291 Hz. The $^{13}$C chemical shifts of the other aromatic carbons present a signal in the range of 113.2–147.3 ppm. The carbonyl carbon interfacing the two pyrazole rings shows signals in the range of 185.6 ppm.

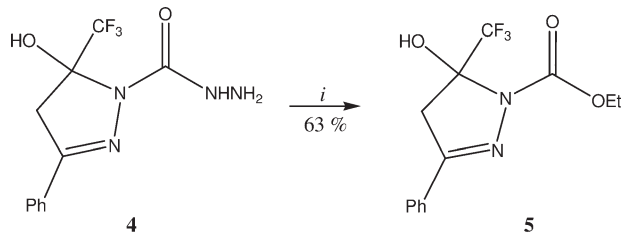
Subsequently, aiming to obtain examples of heterocyclic derivatives, the reaction of carbohydrazide **4** with a 1,3-diketone (2,4-pentanedione) was performed. In this case, the well-known ester **5** [30] was isolated in 63% yield, instead the desired nonsymmetrical bis-pyrazole, showing an interesting and promising employment of pyrazolyl carbohydrazides such as **4** (Scheme 2). Compound **4** was obtained when the reaction of pure carbohydrazide [$(NH_2NH)_2CO$] and 4-methoxy-4-phenyl-1,1,1-trifluorobut-3-en-2-one was carried out at a molar ratio 1:1, in ethanol, according to the literature [21].

Finally, the new ketone **3b** was subjected to reactions with phenylhydrazine [31] and hydroxylamine hydrochloride [32] to verify the possibility of an induced ring-opening reaction followed by recyclization with these two dinucleophiles (Scheme 3).

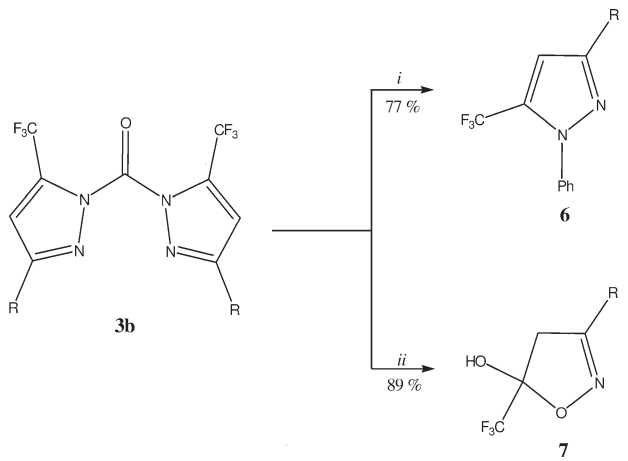
Although **3b** is not the best precursor to synthesize pyrazole **6** and isoxazoline **7**, these well-known heterocycles were easily isolated in good yields (77–89%) from this type of reaction.

In addition to the interest inherent in the chemical attributes of these novel trifluoromethylated condensation products **3**, it seemed appropriate to evaluate the cyclization reactions involving now the β-alkoxyvinyl trichloromethyl ketones **8a–f** and 1,3-diaminoguanidine monohydrochloride (Scheme 4).

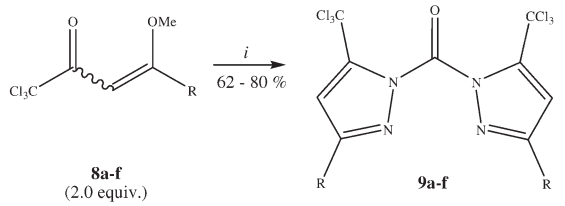
**Scheme 2.** Synthesis of nonsymmetrical ketone **5**. Reagents and conditions: (*i*) 2,4-pentanedione, EtOH, reflux, 20 h.




**Scheme 3.** Preparation of pyrazole **6** and isoxazole **7** from ketone **3b**. Reagents and conditions: (*i*) $NH_2NHPh$, EtOH, reflux, 4 h; (*ii*) $NH_2OH{\cdot}HCl$, Py, $H_2O$, 45°C, 24 h (R = 4-Tolyl).



**Scheme 4.** Synthetic route to prepare bis-pyrazoles **9**. Reagents and conditions: (*i*) 1,3-diaminoguanidine. HCl (1.0 equiv), EtOH/$H_2O$, 90°C, 4–5 h.




**8a-f** (2.0 equiv.) **9a-f**

| 8-9 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| R | $C_6H_5$ | 4-$CH_3C_6H_4$ | 4-$ClC_6H_4$ | 4-$BrC_6H_4$ | 4-$NO_2C_6H_4$ | 2-Thienyl |

We reported now the results of reactions of ketones **8** with 1,3-diaminoguanidine monohydrochloride which were expected to deliver 1,1′-carbonyl-bis(5-trichloromethyl-1*H*-pyrazoles) **9a–f** bearing an carbonyl moiety on the newly formed bis-trichoromethyl substituted heterocyclic system. We carried out the reactions of 4-methoxy-1,1,1-trichlorobut-3-en-2-ones **8** with 1,3-diaminoguanidine monohydrochloride, in 2:1 molar ratio, respectively, and in ethanol/water (20:1) as solvent.

When the mixtures were heated at 90°C, after stirring for 4–5 h, the TLC showed that the reactions proceeded smoothly and gave the products **9** in 62–80% yields (Scheme 4). The derivatives **9** were all stable, white crystalline solids, which showed no significant signs of decomposition after being stored for many months under refrigeration and were unaffected by the recrystallization method.

NMR spectroscopic studies alone allow convincing structural assignments for this heterocyclic system and consequently unequivocal determination of structures of **9**. The symmetrical carbonyl heterocycles **9a–f** show a symmetrical pattern with one set of signals for the hydrogens and carbons of the 3-substituted pyrazole rings. The compounds **9a–f** show the $^1$H NMR chemical shifts in DMSO-$d_6$ for the H-4 as a sharp singlet in the range of 6.21–6.98 ppm. The signals for the other aromatic hydrogens are in the range of 7.21–8.30 ppm.

The compounds **9a–f** present the typical $^{13}$C chemical shifts of pyrazole rings in average of 175.0 ppm (C-3) and 85.6 ppm (C-4). The carbonyl carbon bonding the two pyrazole rings shows signals in the range of 182.8 ppm. The two $CCl_3$ groups show a typical singlet in average of δ 98.9 ppm. All the signals are consistent with $^1$H and $^{13}$C NMR chemical shifts of the pyrazoline moieties for these symmetrical systems.

In conclusion, we have developed a useful, simple, and convenient procedure to obtain new 1,1′-carbonyl-bis[3-aryl(heteroaryl)-5-trihalomethyl-1*H*-pyrazoles] (**3**, **9**), starting from the cyclocondensation reactions with β-alkoxyvinyl trihalomethyl ketones (**1**, **8**) and 1,3-diaminoguanidine monohydrochloride in a one-pot method leading to high yields (62–86%). In addition, the reaction was proven to be regioselective because only the 1,1′-carbonyl-bis(5-trihalomethyl-1*H*-pyrazole) isomer was isolated. Moreover, we think that alkylcarboxylate heterocycles such as **5** and many other ring-opening reactions can be induced in this new heterocyclic system using several dinucleophiles.

## EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus. $^1$H and $^{13}$C NMR spectra were acquired on a Bruker DPX 200 spectrometer ($^1$H at 200.13 MHz and $^{13}$C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in DMSO-$d_6$ for **3**, **5**, **9** and in $CDCl_3$ for **6** and **7**, using TMS as internal reference. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and He was used as the carrier gas.

**Synthetic procedures. General procedure for the preparation of 1,1′-carbonyl-bis[3-aryl(heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] (3a–i, 9a–f).** A stirred mixture of 4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1a–i**) or 4-methoxy-1,1,1-trichlorobut-3-en-2-ones (**8a–f**) (2.0 mmol) and 1,3-diaminoguanidine monohydrochloride (1.0 mmol), diluted in ethanol (20 mL) and water (1 mL) was heated in an oil bath for 4–5 h at 90°C. After cooling, water (10 mL) was added to the reaction and the product extracted with chloroform (2 × 15 mL). The organic layer was dried ($Na_2CO_3$) and evaporated under reduced pressure. The solid residues were recrystallized from iso-propyl ether to give white solids.

**1,1′-Carbonyl-bis(3-phenyl-5-trifluoromethyl-1*H*-pyrazole) (3a).** This compound was obtained as a yellow solid, yield 75%, Mp. 211–212°C. $^1$H NMR (DMSO-$d_6$) δ = 7.75–7.79 (m, 4H, aromatic-H), 7.38–7.42 (m, 6H, aromatic-H), 5.94 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 186.1 (C=O), 169.3 (C-5, $J$ = 28), 141.7 (C-3), 130.2; 128.1; 126.8; 126.6 (aromatic-C); 118.2 (q, $CF_3$, $J$ = 291), 87.3 (C-4).

**1,1′-Carbonyl-bis[3-(4-tolyl)-5-trifluoromethyl-1*H*-pyrazole] (3b).** This compound was obtained as a yellow solid, yield 80%, Mp. 241–243°C. $^1$H NMR (DMSO-$d_6$) δ = 7.69 (d, 4H, Ar); 7.21 (d, 4H, Ar); 5.91 (s, 2H, H-4); 2.32 (s, 3H, Me). $^{13}$C NMR (DMSO-$d_6$) δ = 185.6 (C=O); 169.3 (q, $^2J$ = 28, C-5), 152.9 (C-3), 128.7, 128.5, 126.7, 126.5 (6C, Ar), 122.1 (q, $^1J$ = 291, $CF_3$), 86.8 (C-4), 20.7 (Me).

**1,1′-Carbonyl-bis[3-(4-fluorophenyl)-5-trifluoromethyl-1H-pyrazole] (3c).** This compound was obtained as a yellow solid, yield 79%, Mp. 179–181°C. $^1$H NMR (DMSO-$d_6$) δ = 7.85 (t, 4H, Ar), 7.20 (t, 4H, Ar), 5.91 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 184.5 (C=O), 169.3 (q, $^2J$ = 28, C-5), 138.1 (C-3), 129.1, 129, 114.9, 114.7 (6C, Ar), 118.1 (q, $^1J$ = 291, $CF_3$), 86.9 (C-4).

**1,1′-Carbonyl-bis[3-(4-methoxyphenyl)-5-trifluoro-methyl-1*H*-pyrazole] (3d).** This compound was obtained as a yellow solid, yield 81%, Mp. 242–244°C. $^1$H NMR (DMSO-$d_6$) δ =

7.76 (d, 4H, Ar), 6.93 (d, 4H, Ar), 5.90 (s, 2H, H-4), 3.78 (s, 3H, OMe). $^{13}$C NMR (DMSO-$d_6$) δ = 173.4 (C=O), 168.5 (q, $^2J$ = 28, C-5), 160.9 (C-3), 134.1, 128.5, 128.3, 113.2 (4C, Ar), 119.3 (q, $^1J$ = 291, $CF_3$), 86.5 (C-4), 55.1 (OMe).

**1,1′-Carbonyl-bis[3-(4-nitrophenyl)-5-trifluoromethyl-1*H*-pyrazole] (3e).** This compound was obtained as a yellow solid, yield 62%, Mp. 258–260°C. $^1$H NMR (DMSO-$d_6$) δ = 8.23 (d, 4H, Ar), 7.99 (d, 4H, Ar), 5.94 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 183.1 (C=O), 170.2 (q, $^2J$ = 28, C-5), 148.1 (C-3), 147.3, 127.8, 123.5, 123.3 (4C, Ar), 118.3 (q, $^1J$ = 292, $CF_3$), 87.7 (C-4).

**1,1′-Carbonyl-bis[3-(4,4′-biphenyl)-5-trifluoromethyl-1*H*-pyrazole] (3f).** This compound was obtained as a yellow solid, yield 83%, Mp. 170–172°C. $^1$H NMR (DMSO-$d_6$) δ = 8.02 (s, 4H, Ar), 7.71–7.76 (m, 8H, Ar), 7.45 (d, 6H, Ar), 6.41 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 187.3 (C=O), 170.5 (q, $^2J$ = 31, C-5), 143.2 (C-3), 138.9, 137.7, 137.4, 128.8, 127.9, 127.7, 126.6, 126.5 (8C, Ar), 119.2 (q, $^1J$ = 287, $CF_3$), 89.2 (C-4).

**1,1′-Carbonyl-bis[3-(1-naphthyl)-5-trifluoromethyl-1*H*-pyrazole] (3g).** This compound was obtained as a yellow solid, yield 74%, Mp. 186–188°C. $^1$H NMR (DMSO-$d_6$) δ = 7.98–8.07 (m, 4H, Ar), 7.70–7.75 (m, 2H, Ar), 7.43–7.60 (m, 8H, Ar), 6.37 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 177.5 (C=O), 176.5 (q, $^2J$ = 33, C-5), 132.8 (C-3), 132.4, 129.8, 129.6, 128.2, 127.5, 126.8, 126.1, 126, 125.1, 123.7 (10C, Ar), 115.7 (q, $^1J$ = 293, $CF_3$), 94.4 (C-4).

**1,1′-Carbonyl-bis[3-(thien-2-yl)-5-trifluoromethyl-1*H*-pyrazole] (3h).** This compound was obtained as a yellow solid, yield 86%, Mp. 237–239°C. $^1$H NMR (DMSO-$d_6$) δ = 7.63 (d, 2H, Thienyl), 7.56 (d, 2H, Thienyl), 7.08 (d, 2H, Thienyl), 5.89 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 178.9 (C=O), 168.9 (q, $^2J$ = 28, C-5), 149 (C-3), 129.7, 127.8, 126.9, 126.7 (4C, Thienyl), 118.7 (q, $^1J$ = 291, $CF_3$), 86.7 (C-4).

**1,1′-Carbonyl-bis[3-(fur-2-yl)-5-trifluoromethyl-1*H*-pyrazole] (3i).** This compound was obtained as a yellow solid, yield 67%, Mp. 259–261°C. $^1$H NMR (DMSO-$d_6$) δ = 7.69 (s, 2H, Furyl), 6.90 (d, 2H, Furyl), 6.53–6.54 (m, 2H, Furyl), 5.85 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 175.8 (C=O), 169.4 (q, $^2J$ = 28, C-5), 155.3 (C-3), 144, 143.8, 111.7, 111.6 (4C, Furyl), 118.9 (q, $^1J$ = 291, $CF_3$), 86.8 (C-4).

**1,1′-Carbonyl-bis(3-phenyl-5-trichloromethyl-1*H*-pyrazole) (9a).** This compound was obtained as a white solid, yield 80%, Mp. 150–152°C. $^1$H NMR (DMSO-$d_6$) δ = 7.43–7.53 (m, 2H, Ar), 7.42–7.48 (m, 8H, Ar), 6.21 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 185.6 (C=O), 175.2 (C-3), 141.8 (C-5), 130.1, 128.6, 128.1, 126.4 (4C, Ar), 100.4 ($CCl_3$), 83.4 (C-4).

**1,1′-Carbonyl-bis(3-tolyl-5-trichloromethyl-1*H*-pyrazole) (9b).** This compound was obtained as a white solid, yield 62%, Mp. 204–206°C. $^1$H NMR (DMSO-$d_6$) δ = 7.68 (d, 4H, Ar), 7.21 (d, 4H, Ar), 6.36 (s, 2H, H-4), 2.33 (s, 6H, Me). $^{13}$C NMR (DMSO-$d_6$) δ = 185.8 (C=O), 174.6 (C-3), 139.6 (C-5), 129.1, 128.6, 128.2, 126.5 (4C, Ar), 100.8 ($CCl_3$), 82.9 (C-4), 20.9 (Me).

**1,1′-Carbonyl-bis[3-(4-chlorophenyl)-5-trichoromethyl-1*H*-pyrazole] (9c).** This compound was obtained as a white solid, yield 76%, Mp. 168–169°C. $^1$H NMR (DMSO-$d_6$) δ = 7.77 (d, 4H, Ar), 7,44 (d, 4H, Ar), 6.98 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 184.1 (C=O), 177.9 (C-3), 138.4 (C-5), 130.7, 130.4, 129.1, 129.0 (6C, Ar), 94.6 ($CCl_3$), 89.5 (C-4).

**1,1′-Carbonyl-bis[3-(4-bromophenyl)-5-trichoromethyl-1H-pyrazole] (9d).** This compound was obtained as a white solid, yield 64%, Mp. 142–144°C. $^1$H NMR (DMSO-$d_6$) δ = 7.72 (d, 4H, Ar), 7.60 (d, 4H, Ar), 6.3 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 184.1 (C=O), 175.3 (C-3), 140.9 (C-5), 131.7, 131.0, 130.0, 128.5 (6C, Ar), 100.3 ($CCl_3$), 83.2 (C-4).

**1,1′-Carbonyl-bis[3-(4-nitrophenyl)-5-trichoromethyl-1*H*-pyrazole] (9e).** This compound was obtained as a white solid, yield 73%, Mp. 191–193°C. $^1$H NMR (DMSO-$d_6$) δ = 8.30 (d, 4H, Ar), 7.71 (d, 4H, Ar), 6.32 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 178.7 (C=O), 174.9 (C-3), 148.2 (C-5), 140.5, 129.8, 123.8, 123.2 (4C, Ar), 97.0 ($CCl_3$), 91.8 (C-4).

**1,1′-Carbonyl-bis[3-(thien-2-yl)-5-trichoromethyl-1*H*-pyrazole] (9f).** This compound was obtained as a white solid, yield 68%, Mp. 183–185°C. $^1$H NMR (DMSO-$d_6$) δ = 7.61 (d, 2H, Thienyl), 7.50 (d, 2H, Thienyl), 7.08 (d, 2H, Thienyl) 6.29 (s, 2H, H-4). $^{13}$C NMR (DMSO-$d_6$) δ = 179 (C=O), 174.7 (C-3), 149.6 (C-5), 129.4, 128.7, 127.8, 126.3 (4C, Thienyl), 100.4 ($CCl_3$), 82.9 (C-4).

**General procedure for the synthesis of ethyl 5-(trifluoromethyl)-3-phenyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole-1-carboxylate (5).** A solution of 5-trifluoromethyl-3-(phenyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazolylcarbohydrazide (**4**) (1 mmol) and 2,4-pentanedione (1 mmol), in ethanol as solvent (4 mL) was stirred under reflux for 20 h. After the reaction time, the solvent was removed under reduced pressure. The solid residue was recrystallized from ethanol and isolated in high purity.

**Ethyl 5-(trifluoromethyl)-3-phenyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole-1-carboxylate (5).** This compound was obtained as a white solid, yield 63%, Mp. 127–129°C [30]. $^1$H NMR (DMSO-$d_6$) δ = 8.08 (s, 1H, OH), 7.76–7.74 (m, 2H, Ar), 7.47 (s, 3H, Ar), 4.23 (q, 2H, $CH_2$, $J$ = 7), 3.86 (d, 1H, H-4a, $J$ = 19), 3.55 (d, 1H, H-4b, $J$ = 19), 1.26 (t, 3H, $CH_3$, $J$ = 7). $^{13}$C NMR (DMSO-$d_6$) δ = 151.08 (C=O), 150.79 (C-3), 130.17, 130.09, 128.46, 126.2 (Ar), 123.4 (q, $CF_3$, $J$ = 285), 91,2 (q, $J$ = 41), C-5), 61.4 (C-4), 44.4 ($CH_2$), 13.9 ($CH_3$). GC-MS (EI, 70 eV): $m/z$ (%) = 302 ($M^+$, 19), 212 (46), 189 (42), 161 (100), 77 (72).

**General procedure for the synthesis of 3-(4-methylphenyl)-5-(trifluoromethyl)-1H-1-phenylpyrazole (6).** A stirred solution of ketone (**3b**) (2 mmol) with phenylhydrazine (2 mmol) in 15 mL of dry ethanol was stirred at 80°C during 4 h. After the reaction time, the solvent was removed under reduced pressure, and the product **6** was dried under reduced pressure, and isolated in high purity.

**3-(4-Methylphenyl)-5-(trifluoromethyl)-1H-1-phenylpyrazole (6).** This compound was obtained as an oil, yield 77%. $^1$H NMR ($CDCl_3$) δ = 7.34 (s, 5H, Ar), 7.11 (s, 4H, Ar), 6.72 (s, 1H, H-4), 2.34 (s, 3H, $CH_3$). GC-MS (EI, 70 eV): $m/z$ (%) = 302 ($M^+$, 100), 281 (19), 233 (5), 77 (10).

**General procedure for the synthesis of 5-hydroxy-3-(4-methylphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (7).** To a stirred solution of ketone (**3b**) (2 mmol) in pyridine (2 mmol), was added a solution of hydroxylamine hydrochloride (2 mmol) in $H_2O$ (1 mL). The mixture was stirred at 45°C for 24 h. After 24 h, water (25 mL) was added and extracted with diethyl ether (3 × 15 mL). The organic layer was dried with $Na_2CO_3$, filtered and evaporated under reduced pressure. The solid was recrystallized from diethyl ether and obtained in high purity.

**5-Hydroxy-3-(4-methylphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (7).** This compound was obtained as a yellow solid, yield 89%, Mp. 62–63°C. $^1$H NMR ($CDCl_3$) δ = 7.53 (d, 2H, Ar, $J$ = 8), 7.23 (d, 2H, Ar, $J$ = 8), 3.66 (d, 1H, H-4a, $J$ = 18), 3.47 (d, 1H, H-4b, $J$ = 18), 2.39 (s, 3H, $CH_3$). GC-MS (EI, 70 eV): $m/z$ (%) = 245 ($M^+$, 100), 176 (30), 133 (21), 91 (53).

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## REFERENCES AND NOTES

[1] Krishnaiah, A.; Narsaiah, B. J Fluorine Chem 2002, 115, 9.

[2] (a) Touzot, A.; Soufyane, M.; Berber, H.; Toupet, L.; Mirand, C. J Fluor Chem. 2004, 125, 1299; (b) Smith, C. D.; Tchabanenko, K.; Adlington, R. M.; Baldwin, J. E. Tetrahedron Lett 2006, 47, 3209.

[3] (a) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. Tetrahedron 2007, 63, 7753. (b) Song, L.; Chu, Q.; Zhu, S. J Fluorine Chem 2001, 107, 107.

[4] Bonacorso, H. G.; Martins, D. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. Synthesis 2004, 809.

[5] Bonacorso, H. G.; Cechinel, C. A.; Oliveira, M. R.; Costa, M. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. J Heterocycl Chem 2005, 6, 1055.

[6] Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; Silva, L. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. J Braz Chem Soc 2005, 16, 868.

[7] Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; Silva, L. B.; Wastowski, A. D.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. J Heterocycl Chem 2005, 42, 631.

[8] Bonacorso, H. G.; Lewandowski, H.; Drekener, R. L.; Costa, M. B.; Pereira, C. M.; Wastowski, A. D.; Peppe, C.; Martins, M. A. P.; Zanatta, N. J Fluorine Chem 2003, 122, 159.

[9] Martins, M. A. P.; Blanco, R. F.; Pereira, C. M.; Beck, P.; Brondani. S.; Cunico, W.; Zimmermann, N. E. K.; Bonacorso, H. G.; Zanatta, N. J Fluorine Chem 2002, 118, 69.

[10] (a) Denisova, A. B.; Sosnovskikh, V. Y.; Dehaen, W.; Toppet, S.; Meervelt, L. V.; Bakulev, V. A. J Fluor Chem 2002, 115, 183; (b) Shawali, A. S.; Sherif, S. M.; El-Merzabani, M. M.; Darwish, M. A. A. J Heterocycl Chem 2009, 46, 548.

[11] Hanamoto, T.; Hakoshima, Y.; Egashira, M. Tetrahedron Lett 2004, 45, 7573.

[12] Angerman, A.; Franke, H.; Geisler, J.; Johann, G.; Rees, R. Schering AG, U.S. Pat. 4,008,200 (1991).

[13] Soliman, R.; Darwish, S. A. S. J Med Chem 1983, 11, 1959.

[14] Sheludyakov, V. D.; Shedulyakova, S. V.; Kuznetsova, M. G.; Silkina, N. N.; Mironov, V. F. Zh Obshch Khim 1980, 4, 875.

[15] Scherer, J.; Klausener, A.; Soellner, R. Patent DE 10,035,011 (2002).

[16] Esteves-Souza, A.; Echevarría, A.; Vencato, I.; Jimeno, M. L.; Elguero, J. Tetrahedron 2001, 57, 6147.

[17] Byers, P. K.; Canty, A. J.; Honeyman, R. T.; Gardinier, J. R.; Reger, D. L. Inorg Synth 2004, 34, 30.

[18] Tang, L.; Jia, W.; Wang, Z.; Wang, H. J Organomet Chem 2002, 649, 152.

[19] Katritsky, A. R.; Rees, C. W.; Scriven, E. F. V. Comprehensive Heterocyclic Chemistry II, Vol. 3; Elsevier Science: New York, 1996.

[20] Higgs, T. C.; Carrano, C. J. Inorg Chem 1997, 36, 291.

[21] Bonacorso, H. G.; Cechinel, C. A.; Deon, E. D.; Sehnem, R. C.; Luz, F. M.; Martins, M. A. P.; Zanatta, N. ARKIVOC 2009, ii, 174.

[22] Bonacorso, H. G.; Cechinel, C. A.; Oliveira, M. R.; Costa, M. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. J Heterocycl Chem 2005, 6, 1055.

[23] Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. J Fluorine Chem 1998, 92, 23.

[24] Bonacorso, H. G.; Wentz, A. P.; Lourega, R. V.; Cechinel, C. A.; Moraes, T. S.; Coelho, H. S.; Zanatta, N.; Martins, M. A. P.; Hoerner, M.; Alves, S. H. J Fluorine Chem 2006, 127, 1066.

[25] Padwa, A. J Org Chem 1965, 30, 1274.

[26] Siqueira, G. M.; Flores, A. F. C.; Clar, G.; Zanatta, N.; Martins, M. A. P. Quim Nova 1994, 17, 24; Chem Abstr 1995, 122, 187063.

[27] Flores, A. F. C.; Brondani, S.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 8701.

[28] Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. Curr Org Synth 2004, 1, 391.

[29] Crystallographic data for the structure of **2a**, reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 707315. Copies of the data can be obtained free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44–1233-336033 or e-mail: deposit@ccdc.com.ac.uk).

[30] Goldfarb, D. S. U.S. Pat. 2,009,163,545 (2009), 57pp.

[31] Taillefer, M.; Cristau, H. J.; Cellier, P.; Spindler, J. F. Patent FR 2,840,303 (2003).

[32] Martins, M. A. P.; Siqueira, G. M.; Giovani, P.; Bonacorso, H. G.; Zanatta, N. J Heterocycl Chem 1996, 33, 1619.

# New Tandem Cyclo- and/or Addition Reactions between *N*-Arylisoindolines with Benzyne and Dimethyl Acetylenedicarboxylate



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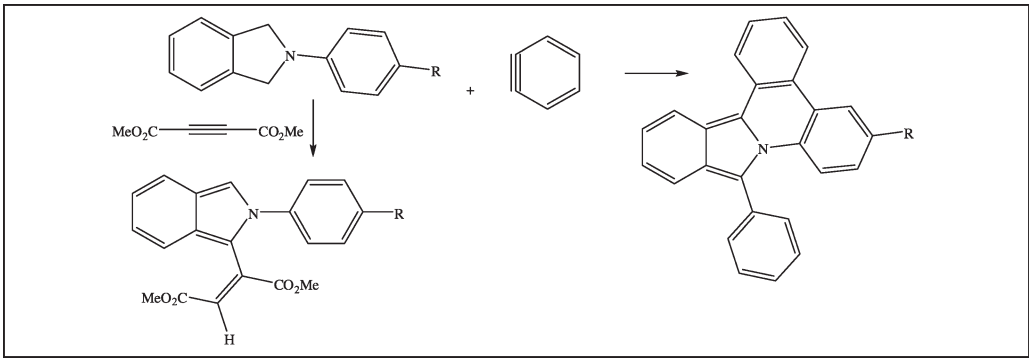


Reaction of *N*-arylisoindolines with benzyne afforded predominantly 10-arylisoindolo[2,1-*f*]phenanthridines. On the other hand, *N*-arylisoindolines react with dimethyl acetylenedicarboxylate to give dimethyl 2-(2-aryl-2*H*-isoindol-1-yl)fumarates. Possible reaction mechanisms are discussed.

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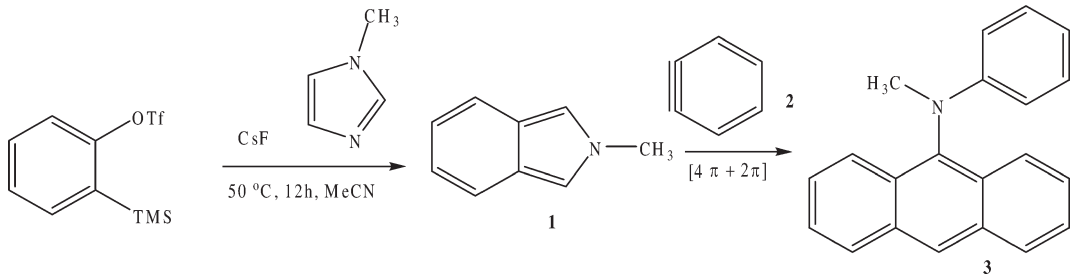
## INTRODUCTION

Previously, it was demonstrated that *N*-arylisoindolines underwent charge-transfer complexation [1,2] and deep seated chemical transformations with 1,4-benzo- or 1,4-naphthoquinones [2] under initial α-H-atom abstraction to give α-oxygenated products [3,4]. Also and in a multistep reaction, 3,3′-(2-aryl-2*H*-isoindol-1,3-ylene)-di-(1,4-naphthoquinone-2-carbonitriles) have been formed in 25–61% yield from a series of *N*-aryl-isoindolines with (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile in aerated pyridine [5]. On the other side, *N*-arylisoindolines react with ethenetetracarbonitrile (TCNE) in aerated benzene with the formation of [3-(2-aryl-3-dicyanomethylene-2,3-dihydro-1*H*-isoindol-1-ylidene)-2-aryl-2,3-dihydro-1*H*-isoindol-1-ylidene]propanedinitriles, *N*-aryl-3-dicyanomethylene-isoindol-2-ones, and *N*-aryl-phthalimides as well as ethanetetracarbonitrile [4,6]. The highly reactive parent system, benzyne, reacts with imine compounds to give (*o*-anilinobenzyhydryl)-aniline [7] and phenanthridine derivatives [8] as well as acridines [8] *via* [2π + 2π] and/or [4π + 2π] cycloaddition reactions. We investigated the cycloaddition reactions of aromatic diimines [9], azomethine compounds having [2.2]paracyclophane [10] and ethenyl-[2.2]-paracyclophanes [11] with selected dienophiles including benzyne aiming to synthesize various heterocycles and heterophanes. Synthesis of biologically active heterocycles has also been one of our interests [12,13]. Aryne chemistry has been applied to the synthesis of aryl amines in a tandem reaction including two Diels-Alder reactions, with three benzyne molecules reacting with one imidazole molecule (Scheme 1) [14]. The reaction proceeds *via* formation of 2-methyl-2*H*-isoindole (**1**), which reacted with two more molecules of benzyne (**2**) to give the corresponding *N*-methyl-*N*-phenylanthracen-9-amine (**3**, Scheme 1) [14]. Accordingly, we were encouraged to investigate the reaction of *N*-arylisoindolines **4a–d** [2,15] with benzyne (**2**) and dimethyl acetylenedicarboxylate (DMAD, **11**).

## RESULTS AND DISCUSSION

Herein, we report the cycloaddition reactions of *N*-arylisoindolines **4a–d** with benzyne (dehydrobenzene, **2**), which was generated by diazotization of 1,2-anthranilic acid [11,16–19]. We chose *N*-arylisoindolines **4a–d** bearing electron donating and withdrawing substituents on the benzene ring, to examine their effect on the course of reaction. Scheme 2 outlines the reaction of **4a–d** with **2** in dry acetonitrile under $N_2$ atmosphere.

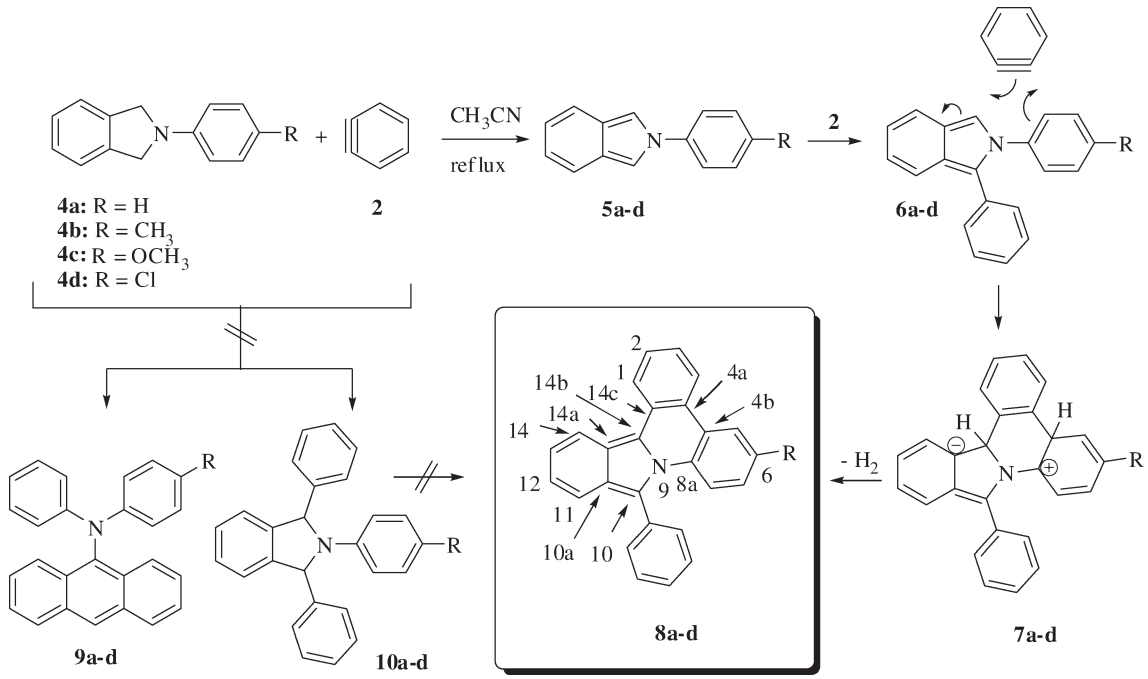
**Scheme 1.** Reaction of *N*-methylisoindolone with benzene.



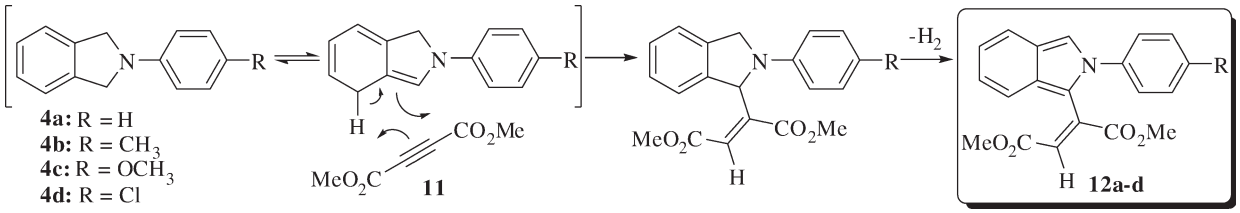

The reaction proceeded to yield, after chromatographic purification and recrystallization, compounds **8a–d** (58–68%) (Scheme 2). The NMR and mass spectra, and elemental analyses, confirm the addition of two molecules of **2** to **4** (Scheme 2).

NMR spectra confirmed the absence of the isoindoline $CH_2$ protons and their corresponding carbons. In **8a**, a double-doublet at $\delta_H = 8.46$ corresponded to H-11 ($J =$ 7.8, 1.2 Hz). Another multiplet at $\delta_H = 8.40$–8.34 was assigned to H-8,12,13,14. Another two double-doublets at $\delta_H = 8.00$ and 7.76 corresponded to H-5 and H-4 ($J =$ 7.8, 1.2 Hz), respectively. The $^{13}C$ NMR spectrum of **8a** showed C-14b, C-10a, C-4a, C-8a at $\delta_C = 150.2$, 141.0, 137.4, and 131.0, respectively. The absence of the symmetrical anthracene ring system from the $^{13}C$ NMR spectra [20] excluded the formation of compounds **9a-d**. One can also envision that the regioisomers **10a–d** might be formed. Of compounds **10a–d,** 1,2,3-triphenylisoindole (**10a**) is known [21]. However, the NMR spectra of **10a** should show the molecular symmetry, which is absent from **8a**. Autoxidation of **10a** is reported to give ring opening, not closure to **8a** [22]; thus, we exclude **10a–d** as intermediates in our pathways leading to **8a–d**. Published syntheses of isoindoles from isoindolines proceed *via N*-oxidation, followed by *O*-acylation and elimination [17,23]. However, benzyne is reported to oxidize dihydropyridines to pyridines [24], presumably by a hydrogen-transfer mechanism like a diimide reduction. We, therefore, propose that **2** oxidizes isoindolines **4a–d** to the corresponding isoindoles **5a–d**, which undergo electrophilic substitution by **2,** selectively at C-1 [25], to give compounds **6a–d**. (The order of these steps may be reversed: see below) Subsequently, compounds **6a–d** react with a second molecule of **2** by intermolecular cycloaddition, followed by oxidation *in situ* to produce the stable heterocyclic compounds **8a–d**. Interestingly, the reaction of isoindolines having electron-donating substituents in the arylidene groups, such as **4b** and **4c**, with

**Scheme 2.** Reaction of *N*-arylisoindolines **4a–d** with benzyne (**2**). **8a**: 6 h, 62%; **8b**: 8 h, 64%; **8c**: 4 h, 68%; **8d**: 10 h, 58%.



**Scheme 3.** Reaction of *N*-arylisoindolines **4a–d** with DMAD (11). **12a**: 14 h, 82%; **12b**: 14 h, 82%; **12c**: 12 h, 87%; **12d**: 18 h, 78%.




**2** yielded the main products **8b**,**c** in higher percentage yields compared with **8d**.

Surprisingly, the reactions of **4a–d** with dimethyl acetylenedicarboxylate (DMAD, **11**), in refluxing ethanol, afforded dimethyl 2(2-aryl-2*H*-isoindole-1-yl)fumarates **12a–d** (Scheme 3). Structure **12a** has formula $C_{20}H_{17}NO_4$, consistent with the molecular ion of $m/z$ = 335. The $^1$H NMR spectrum of **12a** showed the two methyl esters as two singlets at $\delta_H$ = 3.86 and 3.78. Another singlet at $\delta_H$ = 7.00 denoted the vinylic H of the ethylenic bond. The $^{13}$C NMR spectrum of **12a** showed two carbonyl carbons at $\delta_C$ = 170.0 and 168.5. The remaining carbons of **12a** showed signals at $\delta_C$ = 138.9, 138.4, 127.6, 123.2, 120.5, 120.0, 118.8, 116.2, 115.2, 112.8, 102.0, 52.0, and 51.7 corresponding to (Ar-C—N), (vinylic-C-2′), (Ar-CH-6), (Ar-CH-7), (Ar-CH-5), (C-1), (Ar-CH-4), (CH-3), (C-3a), (vinylic-CH-1′), (C-7a), (ester-CH3) and (ester-$CH_3$), respectively. Formally, compounds **12a–d** arise by ene reaction between **11** and a tautomer of **4a–d**, followed by oxidation (Scheme 3). The same kind of sequence can be written for reaction of **4a–d** with benzyne, which would lead the substitution invoked above (Scheme 2) to occur before oxidation.

## CONCLUSIONS

In conclusion, *N*-arylisoindolines react with benzyne to form arylisoindolophenanthridines and with DMAD to form (2-aryl-2*H*-isoindol-1-yl)fumarates. The mechanisms of these transformations are uncertain but appear to involve both concerted reactions and oxidations.

## EXPERIMENTAL SECTION

**General.** Melting points are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were measured in deuterochloroform solutions on Bruker AM-400 or AV-400 spectrometers (400.13 MHz for 1H and 100.6 MHz for 13C). The AV-400 was purchased with assistance from the National Science Foundation (CHE 03-42251). For preparative thin layer chromatography (PLC), glass plates (20 × 48 cm) were covered with a slurry of silica gel Merck $PF_{254}$ and air-dried using the solvents listed for development. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in Assiut Microanalysis Center of Assiut University. Mass spectroscopy was performed with a Finnigan Mat 8430 spectrometer at 70 eV Institute of Organic Chemistry, TU-Braunschweig. Germany. IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets.

**Starting materials.** 2-Aryl-2,3-dihydro-1*H*-isoindoles **4a–d** were prepared according to published procedures [2,15]. Dimethyl acetylene-dicarboxylate (DMAD, **10**) was bought from Fluka.

**Reaction of isoindolines 4a-d with benzyne (2).** Benzenediazonium carboxylate was prepared by the procedure described in [16–19]. Under nitrogen atmosphere, 6 mmol of benzyne (**2**) precursor was slowly added to the stirred and refluxed solutions of **4a–d** (2 mmol) in dry acetonitrile (250 mL) for 1 h. The reaction mixture was refluxed till the consumption of the starting materials was completed (reaction progress monitored by TLC analysis) in 4–10 h. The solvent was concentrated and the residue was filtered off. The precipitate was washed with dichloromethane (200 mL). The filtrate was then concentrated in vacuum and the residue was applied to PLC using toluene as an eluent. The migrating zones contained the products **8a–d** were recrystallized from the stated solvents. All zones were extracted with acetone and the products recovered.

***10-Phenylisoindolo[2,1-f]phenathridines (8a).*** Yellow crystals (0.213 g, 62%), mp 240°C (ethanol); [Found: C, 90.80; H, 4.90; N, 4.00. $C_{26}H_{17}NO$ requires C, 90.93; H, 4.99; N, 4.08%]; $\nu_{max}$ (potassium bromide) 3030–3000 (m, Ar-CH), 1580 (m, olefinic-CH) cm$^{-1}$; $\delta_H$ = 8.46 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-11), 8.40–8.34 (m, 4H, H-8,12,13,14), 8.00 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-5), 7.76 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-4), 7.60–7.58 (m, 6H, Ar-H), 7.50–7.38 (m, 4H, Ar-H); $\delta_C$ = 150.2 (C-14b), 141.0 (C-10a), 137.4 (C-4a), 133.4 (Ph-C), 131.0 (C-8a), 130.0 (Ar-CH-*p*), 129.2 (Ar-CH-*p*), 128.6 (Ar-2CH-*m*), 128.4 (Ar-2CH-*o*), 128.0, 127.6, 127.4, 127.0, 126.6 (Ar-CH), 126.4 (C-14a), 125.9, 125.6 (Ar-CH), 124.8 (C-4b), 124.0 (CH-11), 123.4 (CH-12), 123.0 (CH-13), 122.8 (CH-14), 118.0 (C-14c), 116.8 (C-10); m/z (70 eV, EI): 343 [M$^+$] (100), 266 (30), 242 (18), 192 (20), 168 (28), 92 (20), 78 (24%).

***6-Methyl-10-phenylisoindolo[2,1-f]phenathridines (8b).*** Yellow crystals **8b** (0.229 g, 64%), mp 260°C (methanol); [Found: C, 90.60; H, 5.39; N, 4.08. $C_{27}H_{19}N$ requires C, 90.72; H, 5.36; N, 3.92%]; $\nu_{max}$ (potassium bromide): 3065–3008 (m, Ar-CH), 2980–2870 (w, aliph.—CH), 1582 (m, olefinic-CH) cm$^{-1}$; $\delta_H$ = 8.38 (dd, $J$ = 7.6, 1.2 Hz, 2H, H-11,14), 8.40–8.28 (m, 2H, H-12,13), 7.86 (m, 2H, H-5,4), 7.76–7.52 (6H, m), 7.40–7.30 (4H, m), 2.34 (s, 3H, $CH_3$); $\delta_C$ = 149.6 (C-14b), 141.2 (C-10a), 137.0 (C-4a), 133.0, 132.6 (Ar-C), 128.9 (C-8a), 128.4 (Ar-CH-*p*), 127.6 (Ar-2CH-*m*), 127.0 (Ar-2CH-*o*), 126.9 (C-14a), 126.6, 126.2, 125.8, 125.6, 125.4, 125.0, 124.8 (Ar-CH), 124.4 (C-4b), 124.0 (CH-11),

123.6 (CH-12), 123.2 (CH-13), 122.6 (CH-14), 118.2 (C-14c), 116.6 (C-10), 21.8 ($CH_3$); m/z (70 eV, EI): 357 [M+] (100), 342 (26), 264 (28), 242 (28), 190 (26), 168 (32), 92 (32), 78 (44%).

***6-Methoxy-10-phenylisoindolo[2,1-f]phenathridines (8c).*** Yellow crystals (0.254 g, 68%), mp 290°C (acetonitrile); [Found: C, 86.70; H, 5.10; N, 3.68. $C_{27}H_{19}NO$ requires C, 86.84; H, 5.13; N, 3.75%]; $\nu_{max}$ (potassium bromide) 3080–3012 (m, Ar-CH), 2988–2860 (m, aliph.—CH), 1590 (s, olefinic-CH) $cm^{-1}$; $\delta_H$ = 8.38 (dd, $J$ = 7.6, 1.0 Hz, 2H, H-11,14), 8.30–8.20 (m, 2H, H-12,13), 7.94 (t, $J$ = 7.8 Hz, 1H, H-8), 7.90 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-1), 7.80 (dd, $J$ = 7.8, 1.2 Hz, 2H, H-5,4), 7.52–7.40 (6H, m), 7.30–7.18 (2H, m), 3.90 (s, 3H, $OCH_3$); $\delta_C$ = 158.0 ($H_3CO$-Ar-C), 148.0 (C-14b), 141.2 (C-10a), 135.8 (C-4a), 133.2 (Ph-C), 128.6 (Ph-CH-*p*), 128.0 (Ph-2CH-*m*), 127.2 (Ph-2CH-*o*), 127.0 (C-8a), 126.9 (C-14a), 126.8, 126.6, 126.0, 125.4, 125.0 (Ar-CH), 124.6 (C-4b), 123.8 (CH-11), 123.6 (CH-12), 123.0 (CH-13), 122.8 (CH-14), 122.6 (CH-7), 117.6 (C-14c), 115.0 (C-10), 104.0 (CH-5), 55.8 ($OCH_3$); m/z (70 eV, EI): 373 [$M^+$] (100), 356 (18), 342 (26), 264 (28), 242 (30), 190 (34), 168 (22), 109 (22), 92 (30), 78 (34%).

***6-Chloro-10-phenylisoindolo[2,1-f]phenathridines (8d).*** Yellow crystals (0.219 g, 58%), mp 250°C (ethyl acetate); [Found: C, 82.50; H, 4.20; Cl, 9.50; N, 3.62. $C_{26}H_{16}ClN$ requires C, 82.64; H, 4.27; Cl, 9.38; N, 3.71%]; $\nu_{max}$ (potassium bromide) 3060–3009 (m, Ar-CH), 1585 (s, olefinic-CH) $cm^{-1}$; $\delta_H$ = 8.45 (dd, $J$ = 7.8, 1.2 Hz, 2H, H-8), 8.30 (t, $J$ = 7.6 Hz, 1H, H-14), 8.20 (t, $J$ = 7.6 Hz, 1H, H-11), 8.08 (t, $J$ = 7.6 Hz, 1H, H-13), 8.04 (dd, $J$ = 7.6, 1.2 Hz,, 1H, H-5), 7.90–7.64 (10H, m); $\delta_C$ = 149.0 (C-14b), 141.6 (C-10a), 136.2 (C-4a), 133.4 (Ph-C), 130.6 (CH-3), 131.2 (CH-7), 130.0 (CH-8), 129.6 (CH-2), 129.4 (C-8a), 129.2 (Ar-2CH-*m*), 128.6 (CH-1), 128.4 (Ar-CH-*p*), 128.0 (CH-1), 127.8 (Ar-2CH-*o*), 127.0 (Ar-C—Cl), 126.6 (C-14a), 125.8 (C-4b), 124.0 (CH-14), 123.6 (CH-5), 123.2 (CH-11), 123.0 (CH-12), 122.8 (CH-13), 119.2 (C-14c), 116.0 (C-10); m/z (70 eV, EI): 378 [M+1] (30), 377 [$M^+$] (100), 344 (23), 342 (34), 266 (28), 242 (20), 192 (26), 168 (30), 112 (28), 92 (20), 78 (24%).

**Reaction of isoindolines 4a–d with dimethyl acetylenedicarboxylate (DMAD, 11).** A mixture of **4a–d** (1 mmol) with **11** (0.142 g, 1 mmol) in absolute ethanol (50 mL) was refluxed for 12–18 h (the reaction was followed by TLC analysis). The solvent was removed under vacuum. The residue was applied on column chromatography (silica gel) using dichloromethane as eluent. The separated products **12a–d** were recrystallized from the stated solvents.

***Dimethyl 2-(2-phenyl-2H-isoindol-1-yl)fumarate (12a).*** Yellow crystals (0.275 g, 82%), mp 220°C (methanol); [Found: C, 71.50; H, 5.08; N, 4.18. $C_{20}H_{17}NO_4$ requires C, 71.63; H, 5.11; N, 4.18%]; $\nu_{max}$ (potassium bromide): 3090–3008 (m, Ar-CH), 2980–2860 (m, aliph.—CH), 1730–1712 (br, s, CO), 1586 (s, olefinic-CH) $cm^{-1}$; $\delta_H$ = 8.38 (t, $J$ = 7.6 Hz, 1H, H-4), 8.30 (t, $J$ = 7.8 Hz, 1H, H-6), 8.10 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-5), 8.06 (dd, $J$ = 7.6, 1.2 Hz, 1H, H-5), 7.36–7.20 (5H, m), 7.00 (s, 1H, vinylic-H-2′), 6.96 (s, 1H, H-3), 3.86 (s, 3H, $CH_3$-ester), 3.78 (s, 3H, $CH_3$-ester); $\delta_C$ = 170.0 (CO-ester), 168.5 (CO-ester), 138.9 (Ar-C—N), 138.4 (vinylic-C-2′), 129.0 (Ph-2CH-*m*), 126.8 (Ar-CH-*p*), 127.6 (Ar-CH-6), 122.4 (Ar-2CH-*o*), 123.2 (Ar-CH-7), 120.5 (Ar-CH-5), 120.0 (C-1), 118.8 (Ar-CH-4), 116.2 (CH-3), 115.2 (C-3a), 112.8 (vinylic-CH-1′), 102.0 (C-7a), 52.0 (ester-$CH_3$), 51.7 (ester-$CH_3$); m/z (70 eV, EI): 335 [$M^+$] (100), 320 (22), 305 (24), 277 (18), 266 (30), 250 (18), 212 (40), 192 (20), 168 (28), 92 (20), 78 (24%).

***Dimethyl 2-(2-(4′-methylphenyl)-2H-isoindol-1-yl)fumarate (12b).*** Yellow crystals (0.293 g, 84%), mp 240°C (ethanol); [Found: C, 72.30; H, 5.34; N, 4.00. $C_{21}H_{19}NO_4$ requires C, 72.19; H, 5.48; N, 4.01%]; $\nu_{max}$ (potassium bromide) 3085–3008 (m, Ar-CH), 2982–2840 (m, aliph.—CH), 1728–1715 (br, s, CO), 1586 (s, olefinic-CH) $cm^{-1}$; $\delta_H$ = 8.36 (t, $J$ = 7.8 Hz, 1H, H-4), 8.32 (t, $J$ = 7.6 Hz, 1H, H-6), 8.08 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-5), 8.00 (dd, $J$ = 7.8, 1.2 Hz, 1H, H-5), 7.36 (d, $J$ = 7.7 Hz, 2H), 7.20 (d, $J$ = 7.8 Hz, 2H), 7.10 (s, 1H, vinylic-H-2′), 6.90 (s, 1H, H-3), 3.90 (s, 3H, $CH_3$-ester), 3.86 (s, 3H, $CH_3$-ester), 2.34 (s, 3H, $CH_3$-Ar); $\delta_C$ = 169.4 (CO-ester), 168.8 (CO-ester), 138.6 (Ar-C—N), 138.2 (vinylic-C-2′), 135.4 (Ar-C), 129.2 (Ph-2CH-m), 127.2 (Ar-CH-6), 124.4 (Ar-2CH-*o*), 123.2 (Ar-CH-7), 120.5 (Ar-CH-5), 120.2 (C-1), 119.2 (Ar-CH-4), 116.4 (CH-3), 115.4 (C-3a), 113.0 (vinylic-CH-1′), 102.2 (C-7a), 52.2 (ester-CH3), 51.2 (ester-$CH_3$), 22.4 (Ar-$CH_3$) m/z (70 eV, EI): 349 [$M^+$] (100), 335 (24), 320 (20), 304 (18), 276 (26), 266 (30), 250 (18), 207 (34), 192 (20), 168 (28), 92 (40), 78 (34%).

***Dimethyl 2-(2-(4′-methoxyphenyl)-2H-isoindol-1-yl)fumarate (12c).*** Yellow crystals (0.318 g, 87%), mp 202°C (methanol); [Found: C, 68.90; H, 5.20; N, 3.90. $C_{21}H_{19}NO_5$ requires C, 69.03; H, 5.24; N, 3.83%]; $\nu_{max}$ (potassium bromide) 3090–3006 (m, Ar-CH), 2980–2850 (m, aliph.—CH), 1730–1712 (br, s, CO), 1585 (s, olefinic-CH) $cm^{-1}$; $\delta_H$ = 8.40 (t, $J$ = 7.6 Hz, 1H, H-4), 8.34 (t, $J$ = 7.8 Hz, 1H, H-6), 8.12 (dd, $J$ = 7.6, 1.2 Hz, 1H, H-5), 8.05 (dd, $J$ = 7.6, 1.2 Hz, 1H, H-5), 7.56 (d, $J$ = 7.8 Hz, 2H), 6.90 (d, $J$ = 7.8 Hz, 2H), 6.96 (s, 1H, vinylic-H-2′), 6.90 (s, 1H, H-3), 3.92 (s, 3H, CH3-ester), 3.80 (s, 3H, $CH_3$-ester), 3.92 (s, 3H, $CH_3O$-Ar); $\delta_C$ = 169.7 (CO-ester), 168.2 (CO-ester), 156.9 (CH3O-Ar-C), 138.5 (Ar-C—N), 139.0 (vinylic-C-2′), 127.2 (Ar-CH-6), 124.4 (Ar-2CH-*o*), 123.4 (Ar-CH-7), 120.5 (Ar-CH-5), 120.2 (C-1), 119.6 (Ar-CH-4), 118.2 (Ar-2CH-*m*), 116.4 (CH-3), 115.4 (C-3a), 113.4 (vinylic-CH-1′), 102.2 (C-7a), 52.0 (ester-$CH_3$), 51.0 (ester-$CH_3$), 50.8 (Ar-$OCH_3$); m/z (70 eV, EI): 365 [$M^+$] (100), 350 (14), 334 (16), 320 (20), 306 (22), 280 (24), 222 (30), 192 (20), 91 (38), 78 (36%).

***Dimethyl 2-(2-(4′-chlorophenyl)-2H-isoindol-1-yl)fumarate (12d).*** Yellow crystals (0.288 g, 78%), mp 162°C (methanol); [Found: C, 64.96; H, 4.36; Cl, 9.59; N, 3.79. $C_{20}H_{16}ClNO_4$ requires C, 64.80; H, 4.30; Cl, 9.70; N, 3.70%]; $\nu_{max}$ (potassium bromide): 3060–3005 (m, Ar-CH), 2980-2770 (m, aliph.—CH), 1732–1710 (br, s, CO), 1586 (s, olefinic-CH) $cm^{-1}$; $\delta_H$ = 8.30–8.26 (m, 2H, H-4,7), 8.12–8.08 (m, 2H, H-6,7), 7.42 (d, $J$ = 7.8 Hz, 2H), 7.30 (d, $J$ = 7.8 Hz, 2H), 7.03 (s, 1H, H-3), 6.95 (s, 1H, vinylic-H-2′), 3.95 (s, 3H, $CH_3$-ester), 3.86 (s, 3H, $CH_3$-ester); $\delta_C$ = 170.0 (CO-ester), 169.2 (CO-ester), 136.5 (Ar-C—N), 138.2 (vinylic-C-2′), 131.0 (Ar-C-Cl), 129.0 (Ar-2CH-*o*), 127.0 (Ar-CH-6), 123.2 (Ar-CH-7), 120.4 (Ar-2CH-*m*), 120.3 (Ar-CH-5), 120.0 (C-1), 119.4 (CH-3), 119.2 (Ar-CH-4), 114.4 (C-3a), 112.0 (vinylic-CH-1′), 101.2 (C-7a), 52.4 (ester-CH3), 51.2 (ester-CH3); m/z (70 eV, EI): 370 [M+1] (32), 369 [$M^+$] (100), 354 (24), 352 (26), 340 (14), 339 (18), 334 (22), 312 (16), 310 (18), 227 (20), 226 (24), 192 (24), 114 (42), 91 (38), 78 (39%).

## REFERENCES AND NOTES

[1] Nour El-Din, A. M.; Mourad, A. E.; Hassan, A. A.; Döpp, D. Z Phys Chem (Leipzig) 1988, 269, 832.

[2] Hassan, A. A. Bull Soc Chim Fr 1991, 128, 544.

[3] Döpp, D.; Hassan, A. A.; Nour El-Din, A. M.; Mourad, A. E. In Proceedings of the 5th International Symposium on Organic Free Radicals; Fischer, E.; Heimgartner, H., Eds.; Springer: Berlin, 1988; p 41.

[4] Döpp, D.; Hassan, A. A.; Mourad, A. E.; Nour El-Din, A. M.; Angermund, K.; Krüger, C.; Lehman, C. W.; Rust, J. Tetrahedron 2003, 59, 5073.

[5] Döpp, D.; Hassan, A. A.; Nour El-Din, A. M.; Mourad, A. M.; Lehmann, C. W.; Rust, J. Tetrahedron 2006, 62, 11618.

[6] Hoberg, H.; Milchereit, A. Liebigs Ann Chem 1972, 766, 146.

[7] Nakayama, T.; Midorikawa, H.; Yoshida, M. Bull Chem Soc Jpn 1975, 48, 1063.

[8] Fishwick, C. W. G.; Gupta, R. C.; Storr, R. C. J Chem Soc Perkin Trans 1 1984, 2827.

[9] Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A. E. Tetrahedron 1999, 55, 1111.

[10] Aly, A. A.; Mourad, A. E.; El-Shaieb, K. M.; Hopf, H. Synth Commun 2001, 31, 637.

[11] Aly, A. A.; Hopf, H.; Ernst, L. Eur J Org Chem 2000, 3021.

[12] El-Emary, T. I.; Bakhite, E. A. Pharmazie 1999, 54, 106.

[13] El-Emary, T. I. Polym J Chem 1996, 70, 1143.

[14] Xie, C.; Zhang, Y. Org Lett 2007, 9, 781.

[15] Mourad, A. E.; Nour El-Din, A. M.; Hassan, A. A.; Döpp, D. Bull Soc Chim Belg 1986, 95, 1045.

[16] Wittig, G.; Closs, G.; Mindermann, F. Liebigs Ann Chem 1955, 594, 89.

[17] Kreher, R. P.; Feldhoff, U.; Seubert, J.; Schmitt, D. Chem-Ztg 1987, 111, 155.

[18] (a) Paquette, L. A.; Shen, C. C.; Krause, J. A. J Am Chem Soc 1989, 111, 2351; (b) Paquette, L. A.; Shen, C. C. J Am Chem Soc 1990, 112, 1159.

[19] Aly, A. A. Tetrahedron 2003, 59, 6067.

[20] Bovey, F. A. Nuclear Magnetic Resonance Spectroscopy, 2nd ed.; Academic: San Diego, 1988.

[21] Theilacker, W.; Schmidt, W. Liebigs Ann Chem 1957, 605, 43.

[22] Ahmed, M.; Kricka, L. J.; Vernon, J. M. J Chem Soc Perkin Trans11975, 71.

[23] Kreher, R. P.; Kohl, N. Chem-Ztg 1986, 110, 299.

[24] Sadeghi, M. M.; Memarian, H. R.; Khosropour, A. R. J Sci I R Iran 1998, 9, 240.

[25] Joule, J. A.; Mills, K. Heterocyclic Chemistry, 4th ed.; Blackwell: Oxford, 2000; p 392.

# A DIC Mediated Expeditious Small Library Synthesis and Biological Activity of Thiazolidin-4-one and 1,3-Thiazinan-4-one Derivatives



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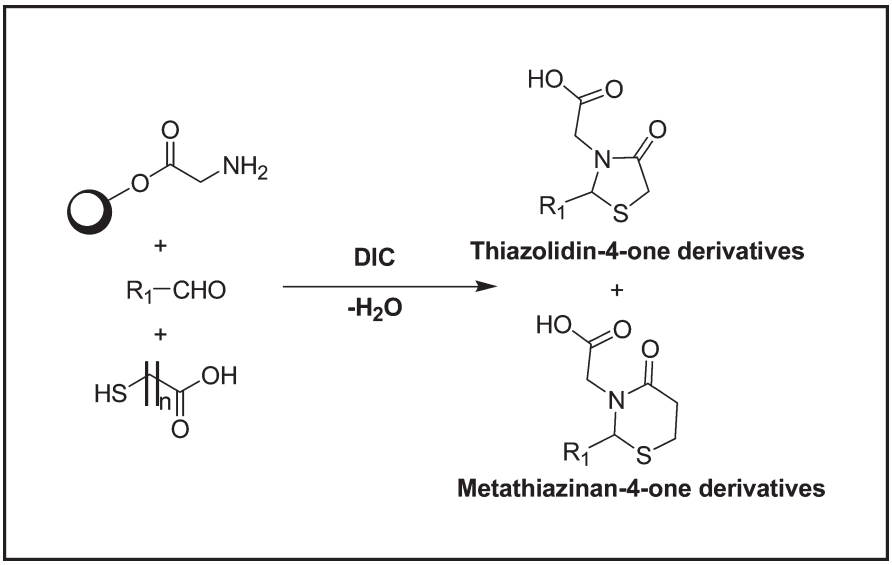


A diisopropylcarbodiimide (DIC) mediated small library of thiazolidin-4-one and 1,3-Thiazinan-4-one derivatives were efficiently synthesized using one pot three component condensation of amino acid, aldehyde, and mercapto carboxylic acid on a polymer support. The study shows significantly higher yields of the thiazolidin-4-one derivatives thereby indicating a lower dependence on the nature of the amino acid and aldehyde components. As an obvious extension of this protocol, the reactions were performed using heterocyclic aldehydes and substituted hindered aromatic aldehydes instead of simple aromatic aldehydes. The synthesized library compounds were also screened for their antifungal acitivity against these three pathogenic fungi: *Candida albicans (Ca), Candida parapsilosis (Cp)*, and *Cryptococcus neoformans (Cn)*.

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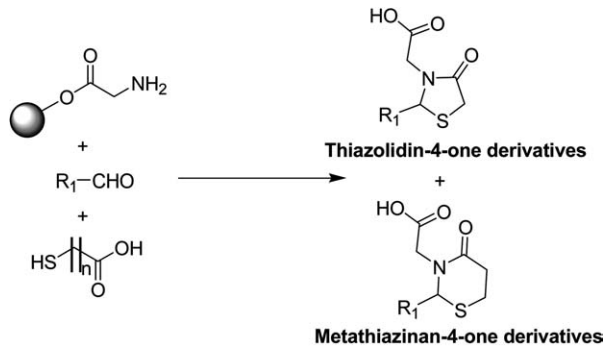
## INTRODUCTION

The categorical imperative of modern drug discovery is to produce better clinical candidates that are less prone to failure at later stage. Solid phase organic synthesis is regarded as one of the key disciplines for providing constant supply of chemical compounds that may be monitored for their biological activity on the vastly increasing number of biological targets. Solid phase organic synthesis together with high throughput synthesis and efficient data management, undoubtedly lead to acceleration in the process of drug discovery [1].

There are numerous biologically active molecules whose framework includes a five-membered and six-membered ring containing two hetero atoms. Thiazolidin-4-one and thiazinan-4-one are biologically important scaffolds known to be associated with several biological activities. These structures contain one **S** and one **N** atom in skeleton as heterocyclic atoms [2–3].

Several protocols for the synthesis of thiazolidin-4-one and thiazinan-4-one derivatives are available in the literature [4–12] (Scheme 1). Essentially these are three component reactions involving an amine, a carbonyl compound and a mercapto acid. The process can be either a one-pot three-component condensation or a two-step process. The reaction has been suggested to proceed via imine formation followed by the attack of sulfur nucleophile on the imine carbon. The last step involves intramolecular cyclization with the elimination of water to give the final compound. This step appears to be

**Scheme 1.** Schematic representation for synthesis of thiazolidin-4-one and metathiazinan-4-one derivatives on solid support.




critical for obtaining high yields. Therefore, variations have been affected in this step to facilitate removal of water. Most commonly used protocols utilize azeotropic distillation, molecular sieves, and use of other desiccants like anhydrous zinc chloride [13], sodium sulfate [14], or magnesium sulfate [15]. These protocols require prolonged heating at 70–80°C for 17–20 h and give moderate to good yields. More recently, an improved protocol has been reported wherein *N*,*N*-dicyclohexylcarbodiimide (DCC) or 2-(1H-benzotrizole-1-yl)-1,1,3,3 tetramethyluraniumhexafluorophospate (HBTU) is used as an acid amine coupling and dehydrating agent to accelerate intramolecular cyclization, resulting in faster reaction and improved yields [16,17]. First time Holmes *et al*. [18] reported solution and polymer-supported synthesis of thiazolidin-4-one and thiazinan-4-one derivatives, derived from amino acids. In amino acids, the carboxylic acid function serves as an anchor group for attachment to the site of support. The condensation of this support bound amine with several aldehydes and mercapto acetic acids in a one-pot reaction, afforded desired products. A series of experiments were performed using different proportions to optimize the ratio of reactants. The ratio of reactants in 1:2:3 for amino acid, aldehyde, and mercapto acetic acid, respectively, as in case of solution phase HBTU protocol gave poor yields. Quantitative yields were obtained by using the ratio of reactants in 1:4:6 for amino acid, aldehyde, and mercapto acetic acid, respectively. This is in agreement with the earlier observation by Holmes *et al*. In a typical experiment, amino acid and aldehyde were shaken in dry tetrahydrofuran (THF) for 15 min, followed by addition of mercapto acetic acid and HBTU, and shaking of reaction mixture for an additional 5 h. The resin was then filtered, washed successively with *N*,*N*′-dimethyl formamide (DMF) (3 × 2 mL), methanol (MeOH) (3 × 2 mL), dichloromethane (DCM) (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum. After cleavage of the final compounds from the resin by treating it with trifluroacetic acid (TFA): dichloromethane (DCM) (1:1) mixture, the desired products in almost quantitative yields were obtained. It was observed that in the case of phenylalanine, the yields were significantly lower than that with glycine, using HBTU in both the reactions. Fast decomposition of HBTU and steric hindrance could be a major reason for lower yield with phenylalanine.

Previous studies suggest that the use of carboxylate activating reagents have facilitated cyclization [19]. Therefore it was thought to explore *N, N*′-diisoproplylcarbodiimide (DIC) as a coupling and dehydrating agent by keeping *N*,*N*- dicyclohexylcarbodiimide (DCC) mediated protocol in mind, which is usually used in solid phase peptide coupling reactions [20–21]. The generality of the DIC mediated reactions have been demonstrated by synthesizing a variety of thiazolidin-4-one and thiazinan-4-one derivatives. In previous study, it was observed that sterically hindered amino acids react sluggishly during cyclization and lead to poor yields or sometimes do not react at all. To avert these shortcomings, in this study, sterically hindered amino acids were examined and the results obtained were excellent (Table-2).

*Candida albicans, Candida parapsilosis*, and *Cryptococcus neoformans* are the common opportunistic fungi responsible for infections. Out of these *Candida albicans* infections may become problematic in severely immunocompromised patients and may induce oral candiasis,

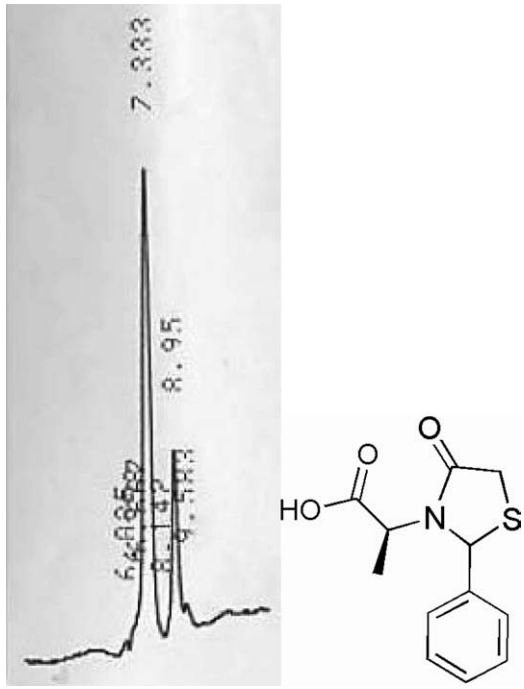
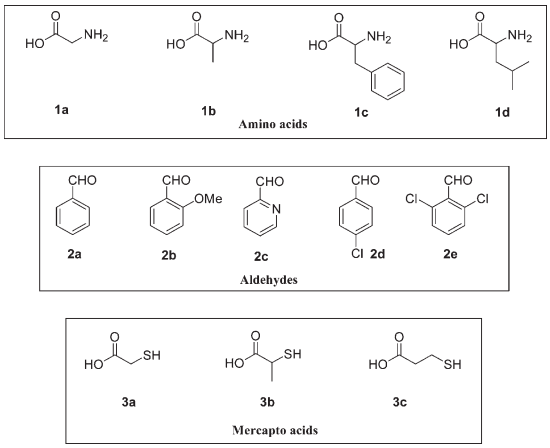



**Figure 1.** The HPLC data of the final compound VI. HPLC trace of diastereomeric thiazolidin-4-one (VI) (7.333 and 8.95 min) after TFA cleavage from solid support at 220 nm.

oesophageal candiasis, and vaginal candiasis. *Candida parapsilosis* is second to *Candida albicans* as a cause of candida endocarditis. Approximately 25% of candidal endocarditis cases reported have been caused by *Candida parapsilosis*. On the contrary *Cryptococcus neoformans* is the causative agent of cryptococcosis, which is the leading cause of morbidity and mortality due to fungi in patients with AIDS. Thus, there is urgent need for more effective and novel antifungal therapies. Therefore in the first instance, synthesized library compounds were screened for their antifungal activity, against these three pathogenic fungi: *Candida albicans (Ca), Candida parapsilosis (Cp)*, and *Cryptococcus neoformans (Cn)*.

**Table 1**

Building blocks for solid phase synthesis.




## EXPERIMENTAL

The reagents used in the study are figured in Table 1. Unless otherwise stated, the materials were of the highest grade available from commercial sources and used without further purification. The solvents and reagents were purchased from the following sources: Wang resin (1% divinylbenzene, 200–400 mesh, 0.5–1.2 mmol/g substitutions) from Novabiochem; Fmoc protected amino acids, *N*,*N*′-diisopropylcarbodiimide, piperidine, diisopropylamine, and trifluoroacetic acid from Aldrich and mercapto acid derivatives from Lancaster.

The reactions on solid phase were optimized using polypropylene syringes of 5 mL capacity (Becton and Dickinson) with fritt (12 mm diameter and 2 mm thickness for 5 mL syringes) inserted at the bottom of the syringes. They were shaken on an orbital shaker (IKA-Vibrax-VXR). The syringes were capped at the bottom with Leur positive (VSG-0419, Roland Vetter) cap. The compounds after cleavage from the resin were dried under $N_2$. $^1$H NMR spectra were obtained on Brucker Evans DRX-600 spectrometer and chemical shifts (δ) were reported in ppm relative to TMS. Because of solubility properties, the solvents used was $CDCl_3$. RP-HPLC analysis of crude products was carried using a 5 μm, 4.8 × 150 mm C-18 reverse-phase column with a linear gradient of Acetonitrile:Water (80:20 v/v) with 100 μL TFA over 25 min. The flow rate was 0.4 mL/min, and UV detection was observed at 220 nm. The retention time of compounds has been expressed in minutes as $t_R$ (Fig. 1). Mass spectra were recorded using electron spray ionization (ESI) technique or FAB.

**Ninhydrine test for aliphatic primary amines.** Ninhydrine test is used to detect the presence and absence of free aliphatic $-NH_2$ group on resin beads after de-protection of Fmoc group. The test was performed by taking small aliquot of the resin in an eppendorf followed by the addition of few drops of following solutions:

1. 80% solution of phenol in absolute alcohol.
2. 2% solution of aqueous KCN (0.001*M*) in Pyridine.
3. 5% solution of Ninhydrine in absolute alcohol.

The eppendorf was then heated at 100°C in a water bath, for 5 min. and colour of the beads was examined. The presence of free aliphatic $-NH_2$ group of amino acids was indicated by blue resin beads (Positive Ninhydrine test), whereas its absence was confirmed by colorless beads (Negative Ninhydrine test).

## GENERAL PROCEDURE

**Loading of amino acid on resin.** The Wang resin (500 mg) was swelled by shaking on an orbital shaker (IKA-Vibrax-VXR) at 600 rpm in 5 mL DCM:DMF (1:1) for 30 min. The resin was then filtered and washed with DMF. The resin so obtained was then coupled with a preactivated solution of amino acid (5 equiv., 2.825 mmol), DIC (3 equiv., 1.695 mmol, 267.38 μL) and DMAP (3 equiv., 1.695 mmol, 207 mg) in dry DMF (2 mL) and the reaction mixture was allowed to shake at room temperature for 6–7 h. The resin was filtered and washed, successively, with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum. A second repeat cycle was made with a preactivated solution of amino acid (2 equiv., 1.13 mmol), DIC (1.5 equiv., 0.847 mmol, 133.5 μL) and DMAP (1.5 equiv., 0.847 mmol, 103.5 mg) in dry DMF (2 mL), and the reaction mixture was allowed to shake at room temperature for 6–7 h to achieve complete loading of amino acids on resin. The resin was filtered and washed, successively, with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum. (Scheme 2).

**Deprotection of Fmoc groups of resin bound amino acids.** This was carried out by treating the resin twice with 30% (v/v) piperidine/DMF solution at room temperature for 15 and 25 min, respectively. Then the resin was filtered and washed successively with DMF (3 × 2

mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum.

**Preparation of resin bound thiazolidin-4-one and thiazinan-4-one derivatives.** The Fmoc-deprotected amino acids loaded Wang resin (200 mg in a polypropylene syringe) was swelled in dry THF for 30 min. After 30 min (hetero)/aromatic aldehyde (4 eq.) in THF was added and shook on an orbital shaker (IKA-Vibrax-VXR) at 600 rpm for 30 min. Then, an appropriate mercapto acid (6 eq.) was poured into the reaction mixture. After 5 min diisopropylcarbodiimide (DIC) (4 eq.) was added to the reaction mixture. The reaction mixture was then allowed to shake at room temperature for 8 h. Diisopropylurea (DIU) was separated during reaction was removed by washing. The resin was then filtered, washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum.

**Cleavage of final compounds (I–XXIII).** The final compounds (Table 2) were cleaved from the resin by treating it with TFA:DCM (1:1) mixture. The resulting mixture was filtered and the filtrate was evaporated to dryness in vacuum.

## ANTIFUNGAL ACTIVITY

The $IC_{50}$ values of library compounds were determined against the test fungi by using micro-broth dilution technique as per guidelines of NCCLS M-27A [22]. $IC_{50}$ values of standard antifungal (Miconazole) and synthetic compounds were measured in 96 well tissue culture plate (CellStar Greiner Bio One, Germany) using RPMI 1640 media buffered with MOPS [3-(*N*-Morpholino) propanesulfonic acid, Sigma]. Starting inocula of test culture were maintained at 1.0–5.0 × 103 cfu/mL. A solution of 2 mg/mL of library compounds in 10% DMSO was used. Microtitre plates were incubated at 35°C in a moist dark chamber and $IC_{50}$ and MIC values were recorded spectrophotometrically (Softmax pro 4.3, Versamax microplate reader, molecular devices) after 48 h for *candida albicans* and *candida parapsilosis* and 72 h for *cryptococcus neoformans*. The antifungal

**Scheme 2.** DIC mediated synthesis of thiazolidin-4-one and metathiazinan-4-one derivatives. Reagents and conditions: (i) 5 mL DCM:DMF (1:1), 30 min (ii) 10 equiv. FmocAA-OH (1a–d), 5 equiv. DMAP, 5 equiv. DIC, dry DMF, rt, 600 rpm, 6h. (iii) 20% piperidine in dry DMF, rt, two cycles of 15 and 30 min, respectively. (iv) 4 equiv. aldehyde(2a–e), 6 equiv. mercapto acid (3a–c), 4 equiv. DIC, rt, 8 h. (v) 20% TFA/DCM, rt, 1h.

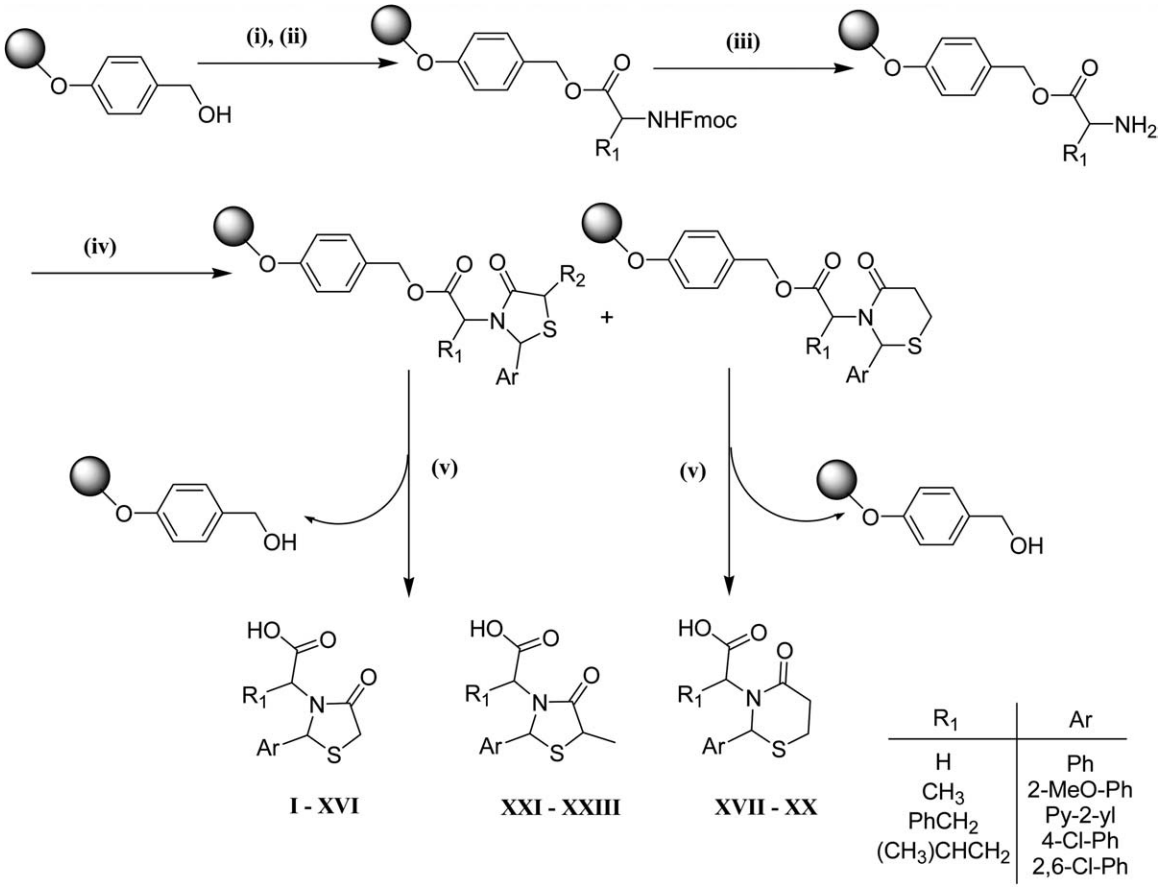


**Table 2**

Data of compounds synthesized on solid phase.

| Entry | Building blocks | | | Overall yields[a] (%) | M.Wt | ESI-MS *m/z* $(M+H)^+$ |
|---|---|---|---|---|---|---|
| | Amino acids | Aldehydes | Mercapto acids | | | |
| I | 1a | 2a | 3a | 98 | 237 | 238 |
| II | 1a | 2b | 3a | 90 | 267 | 268 |
| III | 1a | 2c | 3a | 96 | 238 | 239 |
| IV | 1a | 2d | 3a | 66 | 271 | 272 |
| V | 1a | 2e | 3a | 95 | 306 | 307 |
| VI | 1b | 2a | 3a | 90 | 251 | 252 |
| VII | 1b | 2b | 3a | 63 | 281 | 282 |
| VIII | 1b | 2c | 3a | 55 | 252 | 253 |
| IX | 1b | 2d | 3a | 30 | 285 | 286 |
| X | 1c | 2a | 3a | 75 | 327 | 328 |
| XI | 1c | 2b | 3a | 42 | 357 | 358 |
| XII | 1c | 2c | 3a | 53 | 328 | 329 |
| XIII | 1c | 2d | 3a | 28 | 361 | 362 |
| XIV | 1c | 2e | 3a | 58 | 396 | 397 |
| XV | 1d | 2a | 3a | 89 | 293 | 294 |
| XVI | 1d | 2b | 3a | 42 | 323 | 324 |
| XVII | 1a | 2c | 3c | 68 | 252 | 253 |
| XVIII | 1b | 2a | 3c | 40 | 265 | 266 |
| XIX | 1c | 2a | 3c | 80 | 341 | 342 |
| XX | 1c | 2b | 3c | 32 | 371 | 372 |
| XXI | 1b | 2c | 3b | 62 | 266 | 267 |
| XXII | 1c | 2b | 3b | 36 | 371 | 372 |
| XXIII | 1d | 2a | 3b | 40 | 307 | 308 |

[a] The overall yields are based on the initial loading of hydroxymethyl resin.

activity of library compounds has been summarized in Table 3.

## RESULTS AND DISCUSSION

**Physicochemical data.** ***(4-Oxo-2-pyridin-2-yl-thiazolidin-3-yl)-acetic acid (III).*** mp semisolid on RT: IR (KBr) 1681.81, 1745.46; $^1$H NMR ($CDCl_3$, 600 MHz) δ 2.56 (bs, 1H, OH), 3.44 (d, $J$ = 18.0 Hz, 1H, $NCH_2$), 3.76 (d, $J$ = 15.6 Hz, 1H, $H_A$), 3.82 (dd, $J$ = 15.6, 1.2 Hz, 1H, $H_B$), 4.39 (d, $J$ = 18.0 Hz, 1H, $NCH_2$), 6.01 (s, 1H, C-2), 7.40 (m, 1H, $H_5$-Py), 7.58 (d, $J$ = 7.8 Hz, 1H, $H_3$-Py), 7.88 (m, 1H, $H_4$-Py), 8.53 (d, $J$ = 4.8 Hz, 1H, $H_6$-Py); $^{13}$C NMR (CDCl3) δ 32.18, 45.00, 63.13, 122.88, 124.72, 139.23, 147.82, 157.82, 169.73, 172.11.

***2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-propionic acid (VI).*** mp 176–182°C (3:1 mixture of diastereomers): IR (KBr) 1664.45, 1685.67, 1743.53; $^1$H NMR ($CDCl_3$, 600 MHz) δ major isomer 1.25 (d, $J$ = 7.8 Hz, 3H, $CH_3$), 3.67 (d, $J$ = 16.2 Hz, 1H, $H_A$), 3.85 (dd, $J$ = 16.2, 1.2 Hz, 1H, $H_B$), 4.21 (q, $J$ = 7.2 Hz, 1H, C*H*$CH_3$), 5.20 (bs, 1H, OH), 5.75 (s, 1H, C-2), 7.35–7.45 (m, 5H, Ph); minor isomer, 1.41 (d, $J$ = 7.8 Hz, 3H, $CH_3$), 3.73 (q, $J$ = 7.2 Hz, 1H, C*H*$CH_3$), 3.77 (s, 2H, CH2), 5.20 (bs, 1H, OH), 5.74 (s, 1H, C-2), 7.35–7.45 (m, 5H, Ph); 13C NMR (CDCl3) δ major isomer 14.24, 32.41, 52.60, 63.24, 127.11, 128.23, 129.11, 137.78, 172.35, 172.96; minor isomer 14.38, 33.10, 53.46, 65.69, 127.11, 128.23, 129.82, 139.74, 172.35, 172.96.

***2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-3-phenyl-propionic acid (X).*** mp 75–81°C (3:1 mixture of diastereomers): IR (KBr) 1681.81, 1745.46; $^1$H NMR ($CDCl_3$, 600 MHz) δ major isomer 3.23–3.27 (m, 1H, $CH_2$-Ph), 3.31–3.48 (m, 1H, $CH_2$-Ph), 3.66–3.76 (m, 2H, $H_A$ & $H_B$), 3.89 (q, $J$ = 6.0, 0.5H, CH), 5.07 (q, $J$ = 6.0, 0.5H, CH), 6.74 (bs, 1H, OH), 6.87 (s, 0.5H, C-2), 6.98 (s, 0.5H, C-2), 7.14–7.41 (m, 7H, Ar-H), 7.48 (t, $J$ = 7.2, 1H, H5-benzyl), 7.68 (d, $J$ = 7.20, 2H, $H_{2\&6}$-Ph); $^{13}$C NMR (CDCl3) δ major isomer (32.66, 33.00), (33.10, 34.30), (58.97, 59.25), (65.49, 65.94), (126.65, 127.12), (128.48, 128.53), (128.62, 128.69), (128.84, 129.05), (129.24, 129.45), (129.72, 132.00), (133.48, 135.77), (136.44) 137.39), (172.22, 172.49), (173.67, 174.02).

The above findings draw attention to address the scope and limitations of the present protocol. The work concentrated on aldehydes having electron-donating and electron-withdrawing substituents. It is evident from the yields that the present method obviates the limitations of earlier methods and is more versatile. Furthermore, this method shows significantly higher yields of the thiazolidin-4-one derivatives thereby indicating a lower dependence on the nature of the amino acid and aldehyde components (Table 2). As an obvious extension of this

**Table 3**

$IC_{50}$ values for synthesized library compounds (I–XXIII).

| Entry | *Ca* $IC_{50}$ [μ*M*] | *Cp* $IC_{50}$ [μ*M*] | *Cn* $IC_{50}$ [μ*M*] |
|---|---|---|---|
| I | 82.37 | 82.37 | 53.45 |
| II | 79.49 | 79.49 | 79.49 |
| III | 78.61 | 78.61 | 78.61 |
| IV | 77.51 | 77.51 | 77.51 |
| V | 83.33 | 75.33 | 52.91 |
| VI | 78.12 | 78.12 | 43.28 |
| VII | 79.61 | 79.61 | 21.17 |
| VIII | 27.14 | 20.22 | 22.50 |
| IX | 79.61 | 79.61 | 33.91 |
| X | 78.49 | 52.90 | 24.01 |
| XI | 79.55 | 79.55 | 48.05 |
| XII | 80.64 | 80.64 | 15.16 |
| XIII | 78.67 | 56.17 | 49.80 |
| XIV | 22.01 | 13.54 | 12.16 |
| XV | 81.30 | 57.23 | 28.94 |
| XVI | 80.38 | 56.51 | 35.85 |
| XVII | 80.51 | 80.51 | 30.27 |
| XVIII | 75.24 | 52.89 | 23.70 |
| XIX | 55.36 | 56.28 | 47.09 |
| XX | 78.12 | 78.12 | 43.28 |
| XXI | 81.27 | 98.25 | 43.16 |
| XXII | 84.14 | 81.27 | 82.64 |
| XXIII | 78.16 | 79.52 | 78.32 |
| Standard (miconazole) | 05.12 | 08.22 | 01.32 |
| Control | 85.23 | 98.48 | 92.54 |

protocol, the reactions were performed using heterocyclic aldehydes and substituted hindered aromatic aldehydes instead of simple aromatic aldehydes. The corresponding thiazolidin-4-one derivatives were obtained in quantitative yield. Generally, low yields of thiazolidin-4-one derivatives were reported in the literature when amino acids were used as a source of amine; however, with this protocol, excellent to moderate yields were obtained. The versatility of the protocol and to further enhance the scope of this reaction, efforts were made on adaptation of the method for synthesis of thiazinan-4-one, another biologically active chromophore. It is apparent from the variety of reactants that this method has the potential to generate a battery of thiazolidin-4-one and thiazinan-4-one derivatives by solid phase combinatorial synthesis.

The results for the antifungal assay of the synthesized library compounds are summarized in Table 3. As is evident that out of 23 synthesized molecules, compound XIV exhibited best inhibitions in comparison to others with $IC_{50}$ values of 22.01 μ*M* against *Ca*, 13.54 μ*M* against *Cp*, and 12.16 μ*M* against *Cn*.

Our studies thus suggest that activity is strongly dependent on the nature of the substituent at C-2 and N-3 positions of thiazolidin-4-one ring. In particular, a high activity level was observed for compounds possessing a 2,6-dihalophenyl group at C-2 position and a phenethyl ring at N-3 position.

The results presented in this study indicate that changes at C-2 position of thiazolidin-4-one moiety, except for 2,6-dihalophenyl, may lead to reduction in antifungal activity of these compounds. However, introduction of phenethyl moiety at the N-3 position in the thiazolidin-4-one ring is well-supported.

## REFERENCES AND NOTES

[1] Terret, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. Tetrahedron 1995, 51, 8135.

[2] (a) Barreca, M. L.; Chimirri, A.; Luca, L. D.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappalà, M.; Balzarini, J.; Clercq, E. D.; Pannecouque, C.; Witvrouw, M. Bioorg Med Chem Lett 2001, 11, 1793; (b) Barreca, M. L.; Balzarini, J.; Chimirri, A.; Clercq, E. D.; Luca, L. D.; Höltje, H. D.; Höltje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappalà, M. J Med Chem 2002, 45, 5410; (c) Goel, B.; Ram, T.; Tyagi, R.; Bansal, A.; Kumar, A.; Mukherjee, D.; Sinha, J. N. Eur J Med Chem 1999, 34, 265; (d) Taddei, A.; Folli, C.; Moran, O. Z.; Fanen, P.; Verkman, A. S.; Galietta L. J. V. FEBS Lett 2004, 558, 52; (e) Allen, S.; Newhouse, B.; Anderson, A. S.; Fauber, B.; Allen, A.; Chantry, D.; Eberhardt, C.; Odingo, J.; Burgess, E. L. Bioorg Med Chem Lett 2004, 14, 1619; (f) Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. Bioorg Med Chem 2005, 13, 6771; (g) Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouquec, C.; De Clercq, E. Bioorg Med Chem 2007, 15, 1725; (h) Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouquec, C.; De Clercq, E. Bioorg Med Chem 2007, 15, 3134.

[3] Verma, A.; Saraf S. K. Eur J Med Chem 2008, 43, 897.

[4] Dains, F. B.; Krober, O. A. J Am Chem Soc 1939, 61, 1830.

[5] Damico, J. J.; Harman, M. W. J Am Chem Soc 1955, 77, 476.

[6] Bon, V.; Tisler, M. J Org Chem 1962, 27, 2878.

[7] Rao, R. P. J Indian Chem Soc 1961, 38, 784.

[8] Bhargava, P. N.; Chaurasia, M. R. J Pharm Sci 1969, 58, 896.

[9] Chaubey, V. N.; Singh, H. Bull Chem Soc Jpn 1970, 43, 2233.

[10] Wilson, F. J.; Burns, R. J Chem Soc 1922, 121, 870.

[11] Bougault, J.; Cattelain, E.; Chabrier, P.; Quevauviller, A. Bull Soc Chim Fr 1949, 16, 433.

[12] Surrey, A. R.; Cutler, R. A. J Am Chem Soc 1954, 76, 578.

[13] Srivastava, S. K.; Srivastava, S. L.; Srivastava, S. D. J Indian Chem Soc 2000, 77, 104.

[14] Shrama, R. C.; Kumar, D. J Indian Chem Soc 2000, 77, 492.

[15] Baraldi, P. G.; Simoni, D.; Moroder, F.; Manferdini, S.; Mucchi, L.; Vecchia, F. D. J Heterocycl Chem 1982, 19, 557.

[16] Srivastava, T.; Haq, W.; Katti, S. B. Tetrahedron 2002, 58, 7619.

[17] Rawal, R. K.; Srivastava, T.; Haq, W.; Katti S. B. J Chem Res 2004, 5, 368.

[18] Holmes, C.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. J Org Chem 1995, 60, 7328.

[19] Srivastava, T.; Haq, W.; Katti, S. B. Tetrahedron. 2002, 58, 7619.

[20] Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. Tetrahedron Lett 1975, 14, 1219.

[21] Carpino, L. A. J Am Chem Soc 1993, 115, 4397.

[22] Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. NCCLS Approval Standard Document M27-A. National Committee for Clinical Laboratory Standards: Wayne, PA, 1997.

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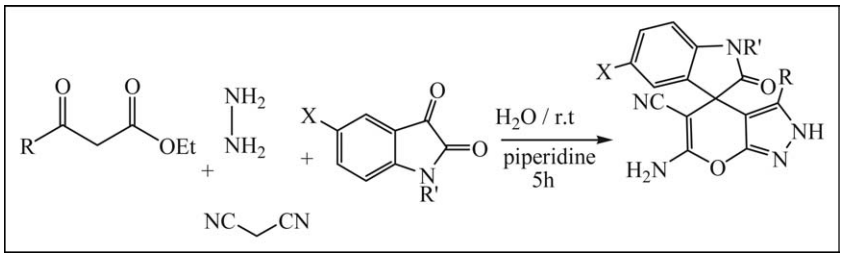


Piperidine catalyzes efficiently the one-pot, four-component reaction of β-ketoesters, hydrazine hydrate, malononitrile, and isatines in aqueous media. The reaction was done at room temperature and the spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitriles were obtained with high yields and purity *via* an easy work-up procedure. These compounds were also investigated *in vitro* for antibacterial activities.

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## INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry because the strategies of MCR offer significant advantages over conventional linear-type syntheses. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of ''drug-like'' molecules for biological screening, as the combination of three or more small molecular weight building blocks in a single operation leads to a high combinatorial efficacy [1,2]. Designing of MCRs in water is another attractive area in chemistry [3] because water is a cheap, safe, and environmentally benign solvent. There is need for developing MCRs in water with a suitable catalyst and without the use of any harmful organic solvents.

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents [4]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhance biological activity [5–7]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [8–10]. Therefore, a number of methods have been reported for the preparation of spirooxindole-fused heterocycles [11–14].

Substituted amino-pyrans take a significant place among the six-membered oxygen-containing heterocycles. Some of them possess anticancer and antimicrobial activity [15,16]. Serotonin receptor modulators (pteropodine and its stereoisomers), natural alkaloids, containing both spiro-indole and pyran cycles, were isolated from stem bark of *Uncaria tomentosa* (Fig. 1) [8]. Several spiroheterocycles, containing both indole and pyran heterocycles, possess anticonvulsant and analgetic [17], herbicidal [18], and antibacterial activities [19]. Similarly, pyrano[2,3-*c*]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry [20–22].

As part of our continuing efforts on the synthesis of biologically active heterocyclic compounds [23–32], especially spirooxindole derivatives [33–35], we report herein a novel and clean synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitriles 5 through a one-pot, four-component condensation reaction of β-ketoesters 1, hydrazine hydrate 2, malononitrile 3, and isatins 4 in water (Scheme 1).

## RESULTS AND DISCUSSION

We found that the one-pot, four-component condensation reaction of β-ketoesters **1a,b**, hydrazine hydrate **2**, malononitrile **3**, and isatins **4** proceeded rapidly in water at ambient temperature and were complete after 5 h to afford spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitriles **5a–l**, in high yields (Table 1). $^{1}H$ and $^{13}C$ NMR spectra of the crude products clearly indicated the formation of spirooxindol-fused pyranopyrazole **5**. The nature of these compounds as 1:1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate m/z values. Compounds **5a–l** are stable solids whose structures were

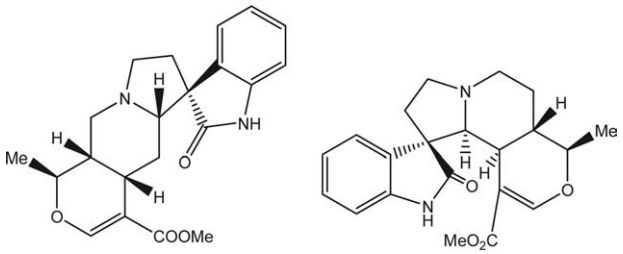



**Figure 1.** Spirooxindole natural alkaloid.

established by IR, $^{1}H$ and $^{13}C$ NMR spectroscopy, and elemental analysis. The structures of **5j** were confirmed by a single-crystal X-ray analysis [36] (Fig. 2).

The results were good in terms of yields and product purity in the presence of piperidine, whereas without piperidine the yields of products were very low (<40%) even after 24 h.

To the best of our knowledge, this new procedure provides the first example of an efficient and four-component method for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitriles. This method, based on four-component piperidine-catalyzed reaction in water, is the most simple and convenient and would be applicable for the synthesis of different types of spiroindoline-pyranopyrazoles.

For the investigation of the reaction mechanism, it is notable that when the ethyl acetoacetate **1a**, hydrazine hydrate **2**, malononitrile **3**, and isatin **4a** were reacted for 1 h, the intermediate **6** and **7** were isolated and characterized by spectroscopic methods. When intermediate **6** and **7** were isolated and reacted in the presence of piperidine under the same reaction conditions, the product **5a** was obtained in 75% yield (Scheme 2).

According to the results, the formation of products **5** can be rationalized by initial formation of pyrazol-5-ol **6** *via* condensation of **1** and **2**. Subsequent Michael-type addition of **6** to the intermediate **7** (formed *in situ* by reaction of the malononitrile **3** and isatin **4**), followed by cyclization and tautomerization afforded the corresponding products **5** (Scheme 3).

To further explore the potential of this protocol for spiro-heterocyclic synthesis, we investigated reaction of acenaphthylene-1,2-dione **8** instead of isatin **4** and

**Scheme 1**

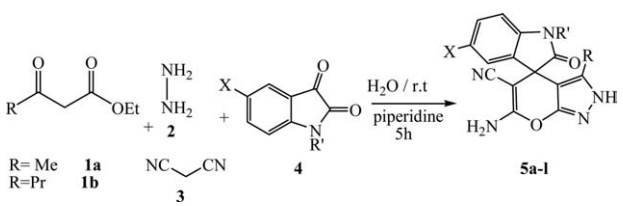



**Table 1**

Synthesis of spiroindoline-pyranopyrazoles **5**.

| Product **5** | R | R′ | X | Yield (%) |
|---|---|---|---|---|
| **A** | Me | H | H | 89 |
| **B** | Me | Me | H | 85 |
| **C** | Me | Et | H | 80 |
| **D** | Me | $PhCH_2$ | H | 85 |
| **E** | Me | H | Br | 95 |
| **F** | Me | Me | Br | 93 |
| **G** | Me | Et | Br | 90 |
| **H** | Me | H | $NO_2$ | 94 |
| **I** | n-Pr | H | H | 92 |
| **J** | n-Pr | Me | H | 90 |
| **K** | n-pr | H | Br | 97 |
| **L** | n-Pr | H | $NO_2$ | 95 |

obtained spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile **9** in 87% yield (Scheme 4).

Finally, all synthesized compounds were screened for antimicrobial activity. The microorganisms used in this study were *Escherichia coli* ATCC 25922, *Pseudomonas aeruginusa* ATCC 85327, (Gram-negative bacteria), *Enterococcus faecalis* ATCC 29737, *Bacillus subtilis* ATCC 465, *Bacillus pumilus* PTCC 1114, *Micrococcus luteus PTCC* 1110, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Sterptococcus mutans* PTCC 1601 (Gram-positive bacteria). The minimum inhibitory concentration of the synthesized compounds determined by microdilution method [37] and compared to two commercial antibiotics (Table 2).

As can be seen from Table 2, good to improved antibacterial activity was observed for most of the compounds against all species of Gram positive and Gram negative bacteria used in the study. Almost, all of the

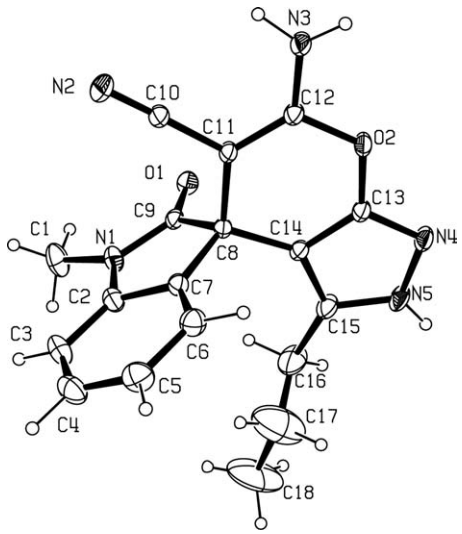
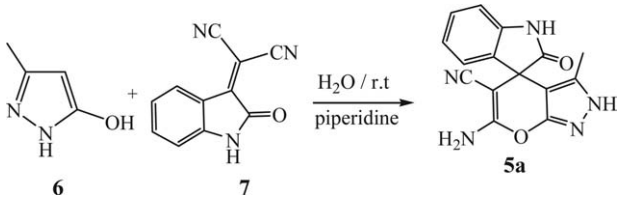
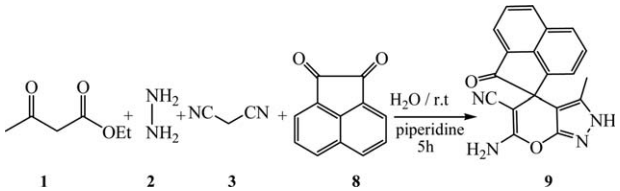



**Figure 2.** X-ray crystal structure of **5j**.

**Scheme 2**



**Scheme 4**



compounds were found to be more active than Gentamicin against all tested strains.

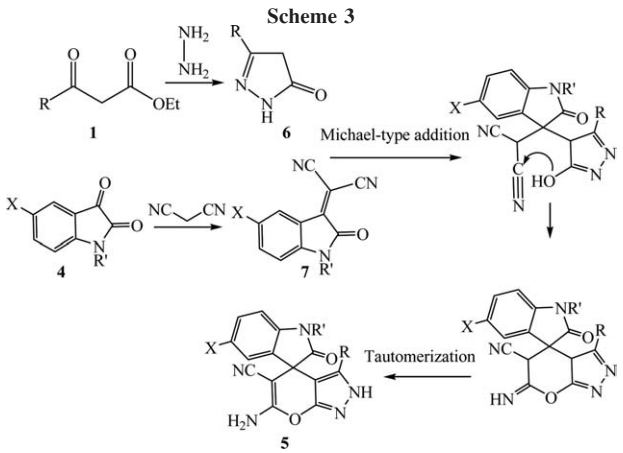
In conclusion, we have developed a facile, one-pot and four-component procedure for the preparation of 1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitriles of potential synthetic and biological interest. The method is simple, starts from readily accessible commercial reagents, and provides biologically interesting spirooxindol derivatives in good yields. Almost most of the compounds exhibited good to excellent antibacterial activity against all the tested strains.

## EXPERIMENTAL

Melting points were taken on an Electrothermal 9100 apparatus and left uncorrected. IR spectra were obtained on a Shimadzu IR-470 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solutions in DMSO using TMS as internal standard. All of the chemicals were purchased from Fluka, Merck, and Aldrich and used without purification.

**Typical procedure for the preparation of 6′-amino-3′-methyl-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5a).** To a magnetically stirred solution of ethyl acetoacetate **1a** (1 mmol) and hydrazine hydrate 96% **2** (1 mmol) in water (5 mL) for 0.5 h were added isatin **4a** (1 mmol), malononitril **3** (1 mmol), and piperidine (0.3 mmol) at room temperature. The mixture was finally stirred for 4.5 h. After completion of the reaction (TLC), the reaction mixture was filtered off and the residue was washed with water (10 mL) and then residue recrystallized from EtOH to afford the pure product **5a** as brown powder (89%). m.p. 224°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3383, 3332, 2182, 1714. MS (EI, 70 eV) *m*/*z*: 293 (M$^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.52 (3H, s, $CH_3$), 6.88–7.25 (6H, m, H-Ar, and $NH_2$), 10.60 (1H, s, NH), 12.28 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 9.4, 47.7, 55.5, 95.8, 110.1, 119.2, 122.9, 124.9, 129.3, 133.1, 135.1, 141.9, 155.7, 162.9, 178.4. Anal. Calcd. for $C_{15}H_{11}N_5O_2$:C, 61.43; H, 3.78; N, 23.88. Found: C, 61.38; H, 3.74; N, 23.80%.

**Scheme 3**



**6′-Amino-1,3′-dimethyl-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5b).** Cream powder (85%); m.p. 262°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3374, 3329, 2188, 1709. MS (EI, 70 eV) *m*/*z*: 307 (M$^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.44 (3H, s, $CH_3$), 3.19 (3H, s, $CH_3$), 7.08–7.33 (6H, m, H-Ar, and $NH_2$), 12.30 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 9.3, 26.7, 47.4, 55.1, 95.6, 109.1, 119.1, 123.6, 124.6, 129.5, 132.3, 135.2, 143.3, 155.6, 163.0, 176.7. Anal. Calcd for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79%. Found: C, 62.59; H, 4.21; N, 22.73%.

**6′-Amino-5-bromo-3′-methyl-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5e).** Cream powder (95%); m.p. 243°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3343, 3132, 2182, 1709. MS (EI, 70 eV) *m*/*z*: 373 (M$^+$), 371 (M$^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.58 (3H, s, CH3), 6.87–7.44 (5H, m, H-Ar, and NH2), 10.76 (1H, s, NH), 12.34 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 9.5, 47.9, 54.9, 95.1, 112.2, 114.6, 119.1, 127.7, 132.2, 135.2, 135.5, 141.2, 155.6, 162.9, 178.0. Anal. Calcd. for $C_{15}H_{10}BrN_5O_2$: C, 48.41; H, 2.71; N, 18.82%. Found: C, 48.45; H, 2.64; N, 18.74%.

**6′-Amino-3′-methyl-5-nitro-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5h).** Dark red powder (80%); m.p. 270°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3048, 1706, 1666, 1607. MS (EI, 70 eV) *m*/*z*: 492 (M$^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 5.00 (bs, 2H, $NCH_2$), 6.72–7.81 (m, 17H, ArH), 11.68 (s, 1H, NH). Anal. Calcd for $C_{33}H_{20}N_2O_3$: C, 80.47; H, 4.09; N, 5.69%. Found: C, 80.38; H, 4.01; N, 5.58%.

**6′-Amino-3′-propyl-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5i).** Cream powder (92%); m.p. 230°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3322, 3183, 2192, 1716. MS (EI, 70 eV) *m*/*z*: 321 (M$^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 0.52 (3H, t, 3JHH= 7.2 Hz, CH3), 0.94–1.16 (2H, m, CH2), 1.85 (2H, t, 3JHH = 7.5 Hz, CH2), 6.88–7.26 (6H, m, H-Ar and NH2), 10.61 (1H, s, NH), 12.29 (1H, s, NH). $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 13.8, 21.4, 26.3, 47.8, 55.7, 95.5, 110.0, 119.2, 122.9, 125.1, 129.4, 133.5, 139.6, 141.9, 155.5, 162.8, 178.8. Anal. Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79%. Found: C, 63.50; H, 4.76; N, 21.70%.

**6′-Amino-1-methyl-2-oxo-3′-propyl-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5j).** Cream powder (90%); m.p. 251°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3388, 3316, 2196, 1710. MS (EI, 70 eV) *m*/*z*: 335 (M$^+$). $^1$H NMR (300

**Table 2**

MIC (μg/mL) values of products **5** and **9**.

| | Products | | | | | | | | | | | | | Standard | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **5a** | **5b** | **5c** | **5d** | **5e** | **5f** | **5g** | **5h** | **5i** | **5j** | **5k** | **5l** | **9** | Tetracycline | Gentamicin |
| *Bacillus subtilis* | 16 | 8 | 4 | 4 | * | 32 | 16 | 16 | 32 | 24 | 4 | 8 | 16 | 4 | * |
| *Bacillus pumilus* | 6 | 4 | 2 | <2 | <2 | 8 | 4 | 2 | 64 | 32 | 16 | 32 | 32 | 8 | * |
| *Micrococcus luteus* | 2 | 2 | 2 | <2 | 8 | 16 | 4 | 2 | 16 | 16 | 8 | 64 | 4 | 4 | * |
| *Staphylococcus aureus* | 8 | 6 | 4 | 4 | 8 | 2 | 16 | 32 | 2 | 2 | * | * | 16 | 4 | * |
| *Staphylococcus epidermidis* | 6 | 2 | 2 | 2 | 8 | <2 | 2 | 8 | 64 | 32 | * | * | 8 | <2 | * |
| *Sterptococcus mutans* | 6 | 4 | 2 | <2 | 128 | 16 | 2 | 64 | 4 | 4 | 6 | 8 | 32 | 2 | * |
| *Escherichia coli* | 4 | 2 | 2 | 2 | 4 | 2 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | * | 4 |
| *Enterococcus faecalis* | 6 | 4 | 2 | 2 | 8 | 16 | 4 | 4 | 32 | 16 | 2 | 4 | 2 | 8 | * |
| *Pseudomonas aeruginosa* | 8 | 4 | 2 | 4 | 2 | 2 | 2 | <2 | <2 | <2 | 4 | 4 | 8 | * | 8 |

* Not active.

MHz, DMSO-$d_6$): $\delta_H$ 0.50 (3H, t, 3JHH = 7.2 Hz, CH3), 0.93–1.03 (2H, m, CH2), 1.66–1.82 (2H, m, CH2), 3.18 (3H, s, CH3), 7.04–7.37 (4H, m, H-Ar), 7.26 (2H, s, NH2), 12.31 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$): $\delta_c$ = 13.8, 21.4, 26.3, 26.7, 47.4, 55.2, 95.3, 109.1, 119.0, 123.7, 124.7, 129.5, 132.6, 139.5, 143.3, 155.4, 162.9, 177.0. Anal. Calcd. for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88%. Found: C, 64.43; H, 5.16; N, 20.94%.

**4-Methyl-1*H*-pyrrol-2-ol (6).** White powder; m.p. 219–222°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3314, 3324, 2199, 1687. MS (EI, 70 eV) *m*/*z*: 98 ($M^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 2.35 (3H, s, CH3), 5.81 (1H, s, CH),12.86 (1H, s, NH).

**2-(2-Oxoindolin-3-ylidene)malononitrile (7).** Brick-red powder; m.p. 215–217°C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3236, 3016, 2232, 1611. MS (EI, 70 eV) *m*/*z*: 3195 ($M^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.91–7.86 (4H, m, H-Ar), 11.20 (1H, s, NH).

**6′-Amino-3′-methyl-2-oxo-2*H*,2′*H*-spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (9).** Brown powder (87%); m.p. 246°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3414, 3320, 2187, 1714. MS (EI, 70 eV) *m*/*z*: 328 ($M^+$). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 1.05 (3H, s, CH3), 7.31 (2H, s, NH2), 7.45–8.40 (6H, m, H-Ar), 12.26 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$): $\delta_c$ = 9.5, 52.1, 56.2, 96.7, 119.3, 121.7, 123.0, 125.4, 129.4, 129.9, 130.4, 131.0, 133.1, 135.1, 141.4, 141.5, 155.7, 162.9, 204.3. Anal. Calcd. for $C_{19}H_{12}N_4O_2$: C, 69.51; H, 3.68; N, 17.06.%. Found: C, 69.57; H, 3.64; N, 17.11%.

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## REFERENCES AND NOTES

[1] Domling, A.; Ugi, I. Angew Chem Int Ed Engl 2000, 39, 3168.

[2] Dömling, A. Chem Rev 2006, 106, 17.

[3] Herrerias, C. I.; Yao, X.; Li, Z.; Li, C. Chem Rev 2007, 107, 2546.

[4] Sundberg, R. J. The Chemistry of Indoles; Academic: New York, NY, 1996.

[5] Joshi, K. C.; Chand, P. Pharmazie 1982, 37, 1.

[6] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[7] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. Bioorg Med Chem 2006, 12, 2483.

[8] Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39.

[9] Ma, J.; Hecht, S. M. Chem Commun 2004, 1190.

[10] Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. Farmaco 2002, 57, 715.

[11] Zhu, S.-L.; Jia, S.-J.; Zhang, Y. Tetrahedron 2007, 63, 9365.

[12] Kumar, R. S.; Perumal, S. Tetrahedron Lett 2007, 48, 7164.

[13] Redkin, R. Gr.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. Tetrahedron 2007, 63, 11444.

[14] Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. Tetrahedron 2007, 63, 2057.

[15] Al-Haiza, M. A.; Mostafa, M. S.; El-Kady, M. Y. Molecules 2003, 8, 275.

[16] Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zho, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. J Med Chem 2004, 47, 6299.

[17] Joshi, K. C.; Jain, R.; Sharma, K. J Indian Chem Soc 1988, 65, 202.

[18] Joshi, K. C.; Jain, R.; Arora, S. J Indian Chem Soc 1988, 65, 277.

[19] Higashiyama, K.; Otomasu, H. Chem Pharm Bull 1988, 28, 648.

[20] El-Tamany, E. S.; El-Shahed, F. A.; Mohamed, B. H. J Serb Chem Soc 1999, 64, 553.

[21] Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; Ghorab, M. M. Egyp J Biotechnol 2003, 13, 73.

[22] Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. Z Naturforsch C 2006, 61, 1.

[23] Bazgir, A.; Mohammadi Khanaposhtani, M.; Abolhasani Soorki, A. Bioorg Med Chem Lett 2008, 18, 5800.

[24] Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. Tetrahedron Lett 2007, 48, 8790.

[25] Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 2375.

[26] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. J Heterocycl Chem 2007, 44, 1009.

[27] Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. Heterocycles 2008, 75, 87.

[28] Dabiri, M.; Delbari, A. S.; Bazgir, A. Synlett 2007, 821.

[29] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2007, 63, 1770.

[30] Dabiri, M.; Delbari, A. S.; Bazgir, A. Heterocycles 2007, 71, 543.

[31] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. Tetrahedron Lett 2008, 49, 5165.

[32] Ghahremanzadeh, R.; Imani Shakibaei, G.; Bazgir, A. Synlett 2008, 1129.

[33] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. Tetrahedron 2009, 65, 2005.

[34] Dabiri, M.; Azimi, S. C.; Khavasi, H. R.; Bazgir, A. Tetrahedron 2008, 64, 7307.

[35] Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. J Comb Chem 2009, 11, 341.

[36] X-Ray data for **5j**: $C_{18}H_{17}N_5O_2$, $M = 335.37$ g/mol, monoclinic system, space group C2/c, $a = 18.0812(12)$, $b = 8.0724(7)$, $c = 23.3904(16)$ Å, $\beta = 95.122(5)^\circ$, $V = 3400.4(4)$ Å$^3$, $Z = 8$, Dc $= 1.31$ g cm$^{-3}$, $\mu$(Mo-K$\alpha$) $= 0.090$ mm$^{-1}$, crystal dimention of 0.30 mm $\times$ 0.21 mm $\times$ 0.12 mm. The structure was solved by using SHELXS. The structure refinement and data reduction were carried out with SHELXL of the X-Step32 suite of programs [38]. The nonhydrogen atoms were refined anisotropically by full matrix least-squares on $F^2$ values to final $R1 = 0.0853$, wR2 $= 0.1987$, and $S = 1.092$ with 256 parameters using 4600 independent reflection ($\theta$ range $= 1.75$–$29.32^\circ$). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **5j** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 732154, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

[37] NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, which Grows Aerobically, 5th ed.; Approved Standard M7-A5, NCCLS: Villanova, PA, 2000.

[38] X-STEP32 Version 1.07b, X-ray structure evaluation package, Stoe & Cie, Darmstadt, Germany, 2000.

# A Practical and Stereoselective Synthesis of (+/−)-*trans*-4-Benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine



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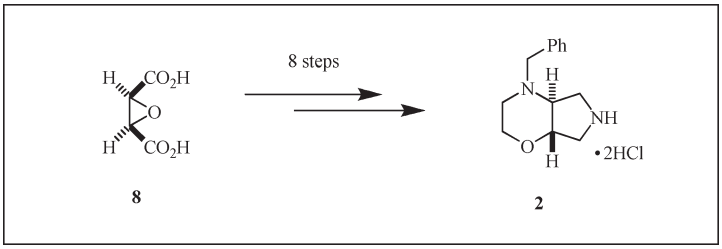


**8** **2**

*trans*-Octahydropyrrolo[3,4-*b*][1,4]oxazine is an important heterocycle within the pharmaceutical industry for the preparation of biologically active analogs, including the phase III drug, finafloxacin. A practical synthesis of the title compound (**2**) is described in eight steps and ca. 10% overall yield. The key synthetic step is the formation of the pyrrolo[3,4-*b*][1,4]oxazine core **20** *via* a one pot double *N*-alkylation of the corresponding bis-tosylate **18** with 4-nitrobenzenesulfonamide. Subsequent removal of the nosyl group occurred under mild conditions.

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## INTRODUCTION

The morpholine ring is utilized extensively in drug discovery research. Due to its hydrophilic nature, medicinal chemists will often look for opportunities to incorporate morpholine into their analogs as a means to increase solubility. Within a chemical series, morpholine, with its lower pKa compared to isosteric piperidine (8.3 *vs*. 11.1), has been shown to reduce hERG activity [1], which is an early indicator of cardiovascular risk. Numerous drugs incorporating the morpholine ring have been approved for the treatment of human diseases; a snapshot of some recent examples is shown in Chart 1, including linezolid (Zyvox®) [2], gifitinib (Iressa®) [3], and reboxetine [4]. Finafloxacin, which is currently undergoing clinical trials for the treatment of *Helicobacter pylori (H. pylori)* infections [5], possesses a morpholine ring fused onto a pyrrolidine ring, giving rise to the *trans*-pyrrolo[3,4-*b*][1,4]oxazine heterocycle. The ring fusion restricts the spatial orientation of the morpholine ring compared to the unfused analog; this restriction is presumably important for optimal binding to the biological receptor. In addition, the pyrrolidine nitrogen provides a chemical handle for attaching the heterocycle to the analog of interest.

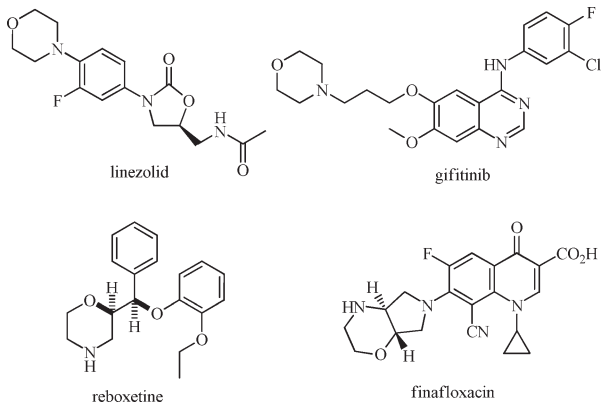
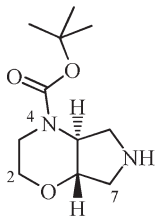
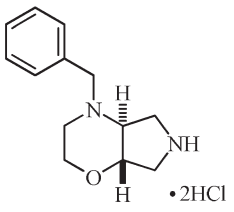



**Chart 1.**

Recently, Hong *et al*. [6] have disclosed a synthesis of enantiomerically pure (4a*S*,7a*S*)-*tert*-butyl hexahydro pyrrolo [3,4-*b*][1,4]oxazine-4(4a*H*)-carboxylate [(4a*S*,7a*S*)-**1**], wherein the morpholine nitrogen is differentially protected with respect to the pyrrolidine nitrogen. In connection with our own medicinal chemistry efforts, we were also interested in preparing this novel heterocycle wherein the morpholine nitrogen was selectively protected. We detail below a stereoselective synthesis of (+/−)-*trans*-4-benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine (**2**).



(*4aS, 7aS*)-**1**



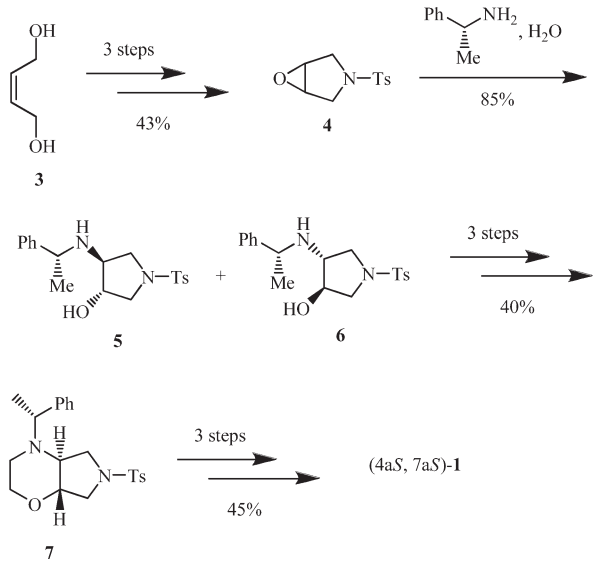
**2**

## RESULTS AND DISCUSSION

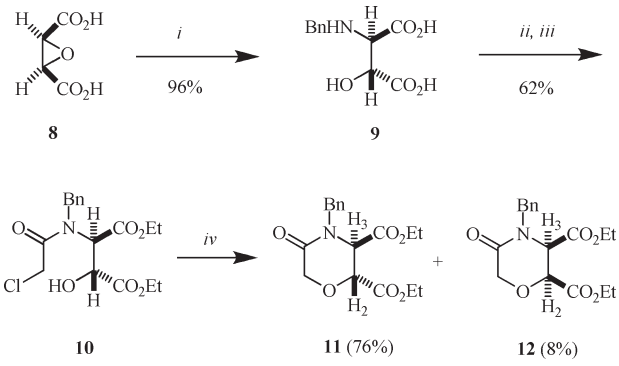
Hong prepared enantiomerically pure pyrrolo[3,4-*b*][1,4]oxazine (4a*S*,7a*S*)-**1** by a ten step synthesis outlined in Scheme 1 [6]. Thus, epoxypyrrolidine **4** was prepared in three steps from commercial (*Z*)-but-2-ene-1,4-diol (**3**). Opening epoxide **4** with (*R*)-α-methylbenzylamine led to diastereomers **5** and **6**, which were readily separated by solvent extraction and crystallization techniques. Treatment of diastereomer **5** with chloroacetyl chloride, followed by exposure to base effected ring closure, and subsequent reduction of the lactam carbonyl afforded the intact pyrrolo[3,4-*b*][1,4]oxazine heterocycle **7**. Exchanging the α-methylbenzyl protecting group on N(4) for a *tert*-butoxycarbonyl (BOC) group and deprotection of the pyrrolidine nitrogen led to pyrrolo[3,4-*b*][1,4]oxazine (4a*S*,7a*S*)-**1**.

Our approach toward synthesizing the *trans*-fused pyrrolo[3,4-*b*][1,4]oxazine heterocycle focused on stereoselectively preparing a 2,3-disubstituted morpholine wherein the sustituents at C(2) and C(3) are *trans* with respect to each other. Thus, the known dicarboxylic acid **9** [7], prepared in near quantitative yield from commercial *cis*-epoxysuccinic acid (**8**), served as the logical starting point (Scheme 2). Esterification of **9** with absolute ethanol and hydrogen chloride, generated *in situ*

**Scheme 1**



**Scheme 2.** Reagents and conditions: (i) $BnNH_2$ (excess), $H_2O$, reflux, 3 h; (ii) AcCl, EtOH, 0°C, 1h; add substrate, reflux, 72 h; (iii) chloroacetyl chloride, $CH_2Cl_2$-aq. 1 *N* NaOH, 0°C, 15 min; (iv) NaH (1.8 eq.), THF-$CH_3CN$-DMF (90:5:5), 0°C, 1 h.



from ethanol and acetyl chloride, provided the corresponding diester in good yield. Esterification with ethanol in the presence of thionyl chloride was also effective; however, the yield was significantly lower, and chromatography was necessary to remove the impurities formed during the reaction. Treatment of the diester with chloroacetyl chloride under Shotten-Baumann conditions afforded α-chloroacetamide **10**. Under these conditions, 5–10% of the corresponding *o*-acylated product was formed along with 1–2% of di-acylated product. However, the *o*-acylated product could be easily removed by extracting the crude reaction mixture with aqueous hydrochloric acid. Subjection of chloroalcohol **10** to sodium hydride gave rise, after purification, to a 9:1 mixture [8] of morpholinones **11** and **12**, respectively. Fortuitously, whereas the desired *trans*-diester **11** was a solid (mp 117–118°C), the undesired *cis*-diester **12** was an oil. Thus, a simple trituration of the product mixture efficiently removed the undesired **12**, affording a 76% yield of pure **11**.

The structural assignments of **11** and **12** were based on a combination of 1D and 2D NMR experiments. For *trans*-diester **11**, the vicinal coupling constant between $H_2$ and $H_3$ was 1.7 Hz, which suggested that the ester groups adopt a pseudo *trans*-diaxial orientation to avoid $A^{1,2}$ strain between the C(3) ester moiety and the benzylic hydrogens (Fig. 1). This interpretation is consistent

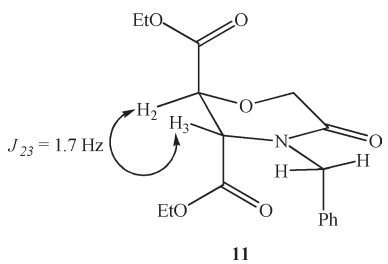
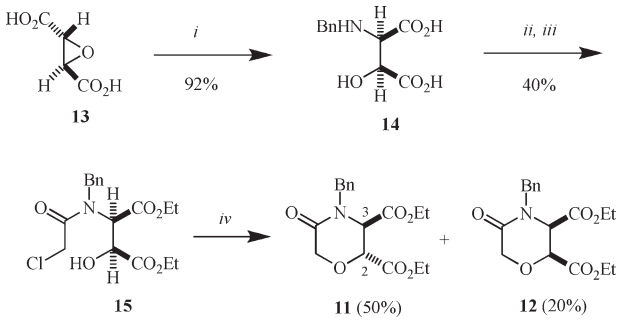


**Figure 1.** 3D representation of diester **11.** Arrow shows vicinal coupling relationship.

**Scheme 3.** Reagents and conditions: (i) $BnNH_2$ (excess), $H_2O$, reflux, 3 h; (ii) AcCl, EtOH, 0°C; add substrate, reflux, 72 h; (iii) chloroacetyl chloride, $CH_2Cl_2$-aq. 1.0 *N* NaOH, 0°C, 15 min; (iv) NaH (1.8 eq.), THF-$CH_3CN$-DMF (90:5:5), 0°C, 1 h.




with observations made by others on similar ring systems [9]. Also, once the pyrrolidine ring was fused onto **11** (*vide infra*), the $H_2$–$H_3$ vicinal coupling constant changed to ca. 9 Hz, which is consistent with a *trans*-diaxial orientation of the two vicinal hydrogens. The $H_2$–$H_3$ vicinal coupling constant for *cis*-diester **12** was 2.7 Hz, which is consistent with an axial-equitorial orientation of the two ester moieties.

Unexpectedly, subjection of alcohol **15**, prepared according to Scheme 3, to identical cyclization conditions [NaH (1.8 eq.), THF-$CH_3CN$-DMF (90:5:5), 0°C, 30 min] afforded a 2.5:1 mixture of **11** and **12**, respectively [8]. Clearly, equilibration of one of the esters is taking place during the reaction. Furthermore, it is likely that equilibration is occurring after ring closure based on the following observations: (1) resubmitting pure *trans*-diester **11** to the cyclization conditions for 30 min led to a 10:1 mixture of **11** and **12**, respectively. Likewise, resubmitting pure *cis*-diester **12** to the cyclization conditions for 30 min led to a 6:1 ratio of **11** and **12**, respectively; (2) stopping the cyclization reaction of **10** prior to completion (Scheme 2) and analysis of the reaction mixture found no evidence of diastereomer **15**.

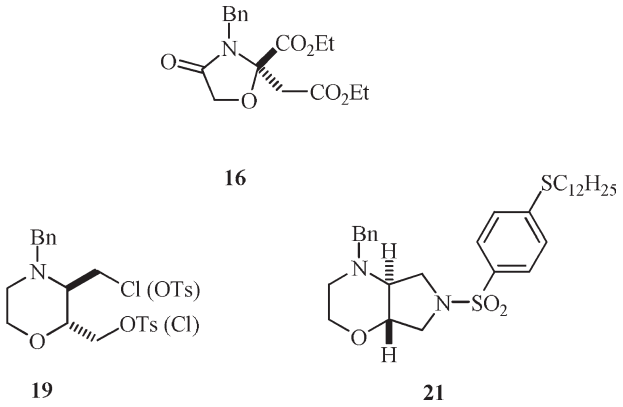
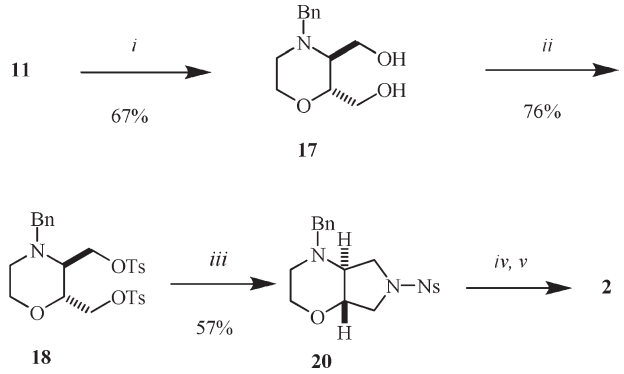



**Chart 2.**

**Scheme 4.** Reagents and conditions: (i) $LiAlH_4$ (5.0 eq.), THF, 0° → room temperature, 30 min, room temperature → reflux, 30 min; (ii) $Ts_2O$ (3.0 eq.), pyridine (3.0 eq.), $CH_2Cl_2$, 0°C, 30 min; (iii) 4-nitrobenzenesulfonamide (3.0 eq.), DBU (2.0 eq.), $CH_3CN$, 70°C, 2 h; (iv) $C_{12}H_{25}SH$ (2.0 eq.), $LiOH•H_2O$ (2.0 eq.), DMF, room temperature, 2 h, 77%; (v) 4 *M* HCl-dioxane, MeOH, room temperature→40°C, 60%.

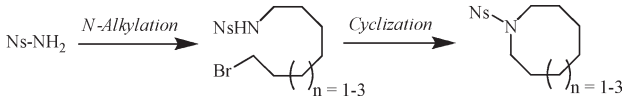



Interestingly, prolonged exposure of either **11** or **12** to sodium hydride in tetrahydrofuran at 0°C resulted, in addition to decomposition, in the formation of a new product, which, based on spectral data, we have assigned as ethyl 3-benzyl-2-(2-ethoxy-2-oxoethyl)-4-oxooxazolidine-2-carboxylate (**16**, Chart 2) [10].

With the stereochemistry at C(2) and C(3) secure, efforts were directed toward installing the remaining pyrrolidine ring. Toward this end, reduction of **11** with lithium aluminum hydride afforded diol **17** (Scheme 4). Bis-tosylate **18** was realized in 76% yield by treating diol **17** with tosic anhydride. The use of tosyl chloride in pyridine led, in addition to bis-tosylate **18**, a significant amount of monotosylate-monochloride products **19** (Chart 2).

Fukuyama has popularized the use of 2-nitro- and 4-nitrobenzenesulfonamide (2-Ns-$NH_2$, Ns-$NH_2$, respectively) as useful starting materials for the efficient construction of cyclic secondary amines [11]. The protocol involves a two-step alkylation-cyclization sequence (Scheme 5). Since this two-step protocol was primarily developed for the preparation of medium-sized rings, we were curious as to whether a pyrrolidine ring could be formed in a single pot *via* a double *N*-alkylation with Ns-$NH_2$. While we could find no examples of pyrrolidine ring formation *via* a double *N*-alkylation with Ns-$NH_2$, pyrrolidine ring formation *via* double *N*-alkylation with *para*-toluenesulfonamide (Ts-$NH_2$) is well precedented [12], including one example by Hong *et al*. [6] to prepare (4a*S*,7a*S*)-**1**. However, Ts-$NH_2$ was a less

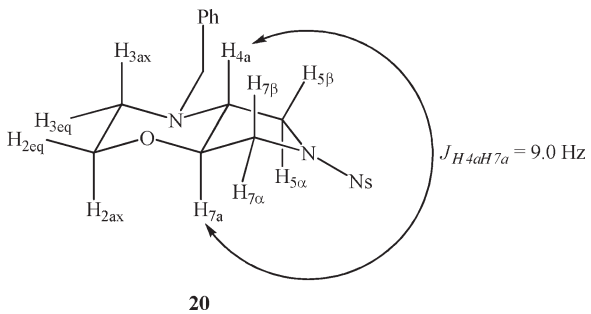
**Scheme 5.** Fukuyama's nitrobenzenesulfonamide methodology for the construction of secondary cyclic amines.



attractive nucleophile to us in that subsequent removal of the tosyl group typically requires either strongly reducing conditions, such as sodium naphthalide, or strongly acidic conditions. On the contrary, the nosyl group is typically removed under mild conditions [11]. We were pleased to find that heating an acetonitrile solution of bis-tosylate **18** with 4-nitrobenzenesulfonamide in the presence of DBU gave rise (57%) to pyrrolo[3,4-*b*][1,4]oxazine **20** (Scheme 4). While other bases, such as sodium hydride, potassium carbonate, or diisopropylethylamine, did effect ring closure, the reactions did not go to completion, even when additional base was added. No other organic-soluble product could be isolated from this reaction. Given the presence of DBU and the ease of bis-tosylate **18** forming an anti-periplanar relationship between the carbon-oxygen bond of one of the tosylates and the axial carbon-hydrogen bond at C(2) or C(3), it is possible that the elimination pathway was competing with substitution. However, no elimination byproducts could be isolated upon workup. That pyrrolo[3,4-*b*][1,4]oxazine **20** possessed a *trans*-ring fusion was readily confirmed based on the large coupling constant (9.0 Hz) between the bridgehead protons, $H_{4a}$ and $H_{7a}$ in the $^1$H-NMR spectrum (Fig. 2). Additional 2D NMR experiments on **20** were also in support of the proposed structure (data not shown).

Cleavage of the nosyl group to afford pyrrolo[3,4-*b*][1,4]oxazine **2** was realized in 77% yield *via* treatment of sulfonamide **20** with dodecanethiol in the presence of lithium hydroxide [13] (Scheme 4). Under these conditions, ca. 15% of aryl thioether **21** was formed (Chart 2). This was not surprising given others have also observed this byproduct during thiol-mediated deprotection of nosyl-protected cyclic amines [14]. Wuts *et al*. [14a] has further observed that 2-nitrobenzenesulfonamide (2-Ns-$NH_2$) was less likely to produce the corresponding byproduct. Unfortunately, the use of 2-Ns-$NH_2$ in the pyrrolidine cyclization reaction led to inferior yields (20% *vs*. 57%).

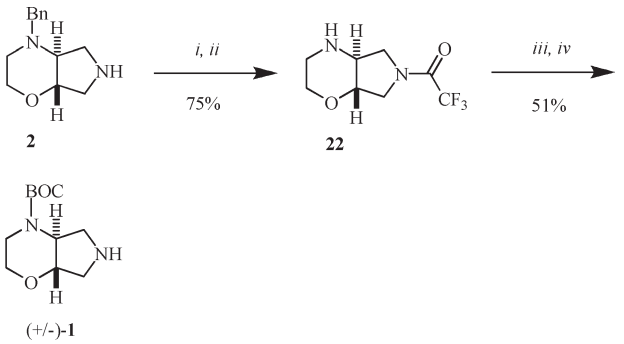
As a final proof of structure, we have converted benzyl-protected pyrrolo[3,4-*b*][1,4]oxazine **2** into




**20**

**Figure 2.** 3D Representation of compound **20**. Arrow shows vicinal coupling relationship.

**Scheme 6.** Reagents and conditions: (i) $(CF_3CO)_2O$ (2.0 eq.), $Et_3N$ (4.0 eq.), $CH_2Cl_2$, 0°C → room temperature, 1.5 h; (ii) $H_2$, 10% Pd/C, MeOH, 42 psi, room temperature, 48 h; (iii) $(BOC)_2O$, $CH_2Cl_2$, room temperature, 24 h; (iv) $K_2CO_3$ (2.0 eq.), MeOH-water (5:1), room temperature, 1 h.




Hong's BOC-protected pyrrolo[3,4-*b*][1,4]oxazine **1** by the sequence outlined in Scheme 6. Thus, trifluoroacetylation of **2** and subsequent hydrogenolysis of the benzyl group led to amine **22**, which should serve as a useful intermediate for the preparation of pyrrolo[3,4-*b*][1,4]oxazine analogs connected through N(4). BOC protection of N(4) and hydrolysis of the trifluoroacetamide group afforded (+/−)-**1**. The spectral properties of our racemic (+/−)-**1** were consistent with those of (4a*S*,7a*S*)-**1** [6,15].

## CONCLUSIONS

In summary, we have reported a practical and stereoselective eight-step synthesis of (+/−)-*trans*-4-benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine (**2**) from inexpensive starting materials and reagents. Only two intermediates required chromatographic purification; otherwise, the remaining compounds were purified by precipitation or trituration. The conditions developed for the one pot double *N*-alkylation-pyrrolidine ring formation using 4-nitrobenzenesulfonamide and DBU will likely be of general interest to the synthetic community.

## EXPERIMENTAL

Proton ($^1$H), carbon ($^{13}$C), and fluorine ($^{19}$F) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Assignments of key NMR signals were made by a combination of gHSQC, gHMBC, and ROESY experiments. Stereochemical assignments for compounds **11**, **12**, **20** and (+/−)-**1** were made based on a combination of ROESY and non-overlapping *J* coupling constants. Infrared (IR) spectra were recorded on a Bruker Vector 33 FTIR. High resolution mass spectra (MS) were acquired on an Agilent 1200 series LCMS TOF with UV detection. Combustion analyses were performed by QTI Intertek, Whitehouse, NJ. Melting points were recorded on an ®Electrothermal Mel-Temp 3.0 device and are uncorrected.

Reactions were monitored by thin layer chromatography (TLC) using Analtech silica gel GF 250 micron plates. The plates were visualized either by UV inspection or by staining with an ammonium molybdate/ ceric sulfate mixture. Flash chromatography was performed as described by Still *et al*. [16] using Aldrich column chromatography grade silica gel (200–400 mesh). All reagents were purchased from either the Aldrich Chemical Co. or TCI America Chemical Co. and used without further purification. All solvents were HPLC grade unless otherwise stated. Anhydrous solvents were purchased from EMD Chemical Co. and used as supplied.

***N*-Benzyl-*threo*-β-hydroxy-DL-aspartic acid (9).** This compound was prepared according to the procedure of Liwscitz [7] with slight modification:

To a stirred solution of *cis*-epoxysuccinic acid (8, 30 g, 227 mmol) in water (50 mL), benzylamine (84 mL, 770 mmol) was added. The mixture was heated to reflux for 3 h. The mixture was cooled to room temperature, followed by the addition of 15% aqueous sodium hydroxide until pH = 13. The aqueous layer was extracted with ether (3×) to remove the benzylamine. The ethereal layer was discarded. The aqueous layer was acidified with concentrated hydrochloric acid to pH = 4, which caused a white precipitate to form. The precipitate was filtered and washed with water. The pH of the mother liquor was re-adjusted to 4 with concentrated hydrochloric acid and additional precipitation occurred. The precipitate was filtered, washed with water. The combined precipitates were dried *in vacuo* to afford 52 g (96%) of 9 as a white solid: $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11.0–10.0 (br s, 2H), 7.35–7.22 (m, 5H), 4.25 (d, 1H, $J$ = 5.5 Hz), 3.92 (ABq, 2H, $J_{AB}$ = 12.9 Hz, $\Delta\nu_{AB}$ = 61.6 Hz), 3.58 (d, 1H, $J$ = 5.9 Hz); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 173.5, 171.0, 137.1, 129.2, 128.9, 128.1, 69.79, 61.55, 50.75; high resolution MS (ESI) Calcd. for $C_{11}H_{14}NO_5$ [M + H] *m*/*e* 240.0892. Found: 240.0866. An analytical sample was prepared *via* recrystallization from water: mp 224–225°C (dec.) (Ref. [7] 225–226°C).

**Diethyl *N*-benzyl-*threo*-β-hydroxy-DL-aspartate.** To a stirred solution of dry ethyl alcohol (550 mL) at 0°C, acetyl chloride (54 mL, 760 mmol) was added. After complete addition, the solution was stirred at 0°C for 1 h. To this solution, diacid **9** (45.0 g, 190 mmol) was added, and the whole mixture was heated to reflux for 72 h. The mixture was cooled to room temperature, and the ethanol was removed *in vacuo* to afford a clear oil. The oil was partitioned between ether and saturated aqueous potassium carbonate solution. The ethereal layer was washed with aqueous potassium carbonate solution and brine. The ethereal layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 43 g (77%) of diethyl *N*-Benzyl-*threo*-β-hydroxy-DL-aspartate as a white solid: $R_f$ 0.31 (hexanes-ethyl acetate, 3:1), IR ($CH_2Cl_2$) 3490, 3347, 3028, 2982, 2906, 2872, 1741, 1465, 1454, 1258, 1190, 1107, 740, 700 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.46 (d, 1H, $J$ = 2.7 Hz), 4.22 (q, 2H, $J$ = 7.0 Hz), 4.25–4.16 (m, 1H), 4.13–4.05 (m, 1H), 3.74 (ABq, 2H, $J_{AB}$ = 13.3 Hz, $\Delta\nu_{AB}$ = 124 Hz), 3.59 (d, 1H, $J$ = 2.8 Hz), 1.26 (t, 3H, $J$ = 6.8 Hz), 1.16 (t, 3H, $J$ = 7.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 139.5, 128.3, 128.2, 127.1, 72.10, 62.03, 61.93, 61.43, 52.15, 14.17, 14.00; high resolution MS (ESI) Calcd. for $C_{15}H_{22}NO_5$ [M + H] *m*/*e* 296.1529. Found: 296.1492. An analytical sample was prepared *via* recrystallization from hexanes-ethyl acetate: mp 40–41°C. Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.06; H, 7.13; N, 4.67.

**Diethyl 2-(*N*-benzyl-2-chloroacetamido)-*threo*-3-hydroxysuccinate (10).** To a rapidly stirred solution of diethyl *N*-Benzyl-*threo*-β-hydroxy-DL-aspartate (20.0 g, 67.7 mmol) in dichloromethane (160 mL) at 0°C, ice cold sodium hydroxide (102 mL of a 1.0 *M* aqueous solution) was added, followed by dropwise addition of a solution of chloroacetyl chloride (8.1 mL, 102 mmol) in dichloromethane (8.0 mL). After complete addition, the mixture was stirred at 0°C for 15 min. Sodium hydroxide (20 mL of a 1.0 *M* aqueous solution) was added, followed by separation of the layers. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The remaining oil was dissolved in ether and extracted three times with 3.0 *M* aqueous hydrochloric acid (to remove *o*-acylated byproduct). The ethereal layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford an oil. Trituration of the oil in hexanes-ether (9:1) gave 20.2 g (80%) of **10** as a white solid: mp 69–71°C; $R_f$ 0.20 (hexanes-acetone, 85:15); IR ($CH_2Cl_2$) 3427, 2984, 1738, 1660, 1452, 1267, 1026, 737 cm$^{-1}$; 1H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H), 4.95–4.83 (m, 2H), 4.69 (ABq, 2H, $J_{AB}$ = 17.2 Hz, $\Delta\nu_{AB}$ = 85.6 Hz), 4.25–4.10 (m, 4H), 4.00–3.85 (m, 2H), 1.51 (br s, 1H), 1.25 (t, 3H, $J$ = 7.0 Hz), 1.18 (t, 1H, $J$ = 7.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 171.5, 169.2, 167.4, 135.4, 128.9, 128.1, 126.9, 70.94, 62.26, 62.13, 62.03, 53.58, 41.43, 13.99, 13.91; high resolution MS (ESI) Calcd. for $C_{17}H_{23}ClNO_6$ [M + H] *m*/*e* 372.1247. Found: 372.1208. Anal. Calcd. for $C_{17}H_{22}ClNO_6$: C, 54.92; H, 5.96; N, 3.77. Found: C, 54.87; H, 5.73; N, 3.70.

**Diethyl *trans*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (11) and diethyl *cis*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (12).** To a stirred suspension of sodium hydride (60% oil dispersion, 1.98 g, 49.4 mmol) in dry tetrahydrofuran (150 mL) at 0°C under nitrogen atmosphere, a solution of alcohol **10** (10.2 g, 27.4 mmol) in tetrahydrofuran-acetonitrile (50 mL, 4:1) *via* canula was added. After complete addition, DMF (10 mL) was added, and the mixtue was stirred at 0°C for 1 h. Once the reaction was complete (TLC monitoring), it was poured over a rapidly stirred solution of 10% aqueous acetic acid (100 mL). Note: once the cyclization was complete, the mixture becomes dark orange in color. If the reaction was not quenced shortly after the orange color appeared, 4-oxooxazolidine **16** began to form. In latter runs, we found that adding solid alcohol **10** directly to a 0°C suspension of 1.4 equivalents of sodium hydride in tetrahydrofuran-acetonitrile-DMF (9:0.5:0.5) for 1 h minimized the formation of **16**. The mixture was concentrated *in vacuo* to a volume of ca. 80 mL. The remaining liquid was extracted with ethyl acetate. The organic layer was extracted with saturated aqueous potassium carbonate solution (to remove carboxylic acid byproducts). The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The organic layer was passed through a short plug of silica gel to remove base-line impurities. The organic layer was concentrated *in vacuo* to a tan solid. Trituration of the remaining solid in hexanes-ether (9:1) gave 5.9 g (64%) of **11** as a fluffy white solid. The mother liquor was concentrated *in vacuo* and purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (70:30) afforded

an additional 1.1 g of **11** as a fluffy white solid (76% combined yield of **11**). Further elution afforded 0.70 g (8%) of *cis*-diester **12** as a clear oil.

***trans*-Diester 11.** $R_f$ 0.32 (hexanes-acetone, 85:15); IR ($CH_2Cl_2$) 2987, 2941, 1738, 1657, 1454, 1426, 1296, 1137, 737, 702 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (m, 5H), 4.68 (m, 1H), 4.57 (ABq, 2H, $J_{AB}$ = 14.8 Hz, $\Delta\nu_{AB}$ 676 Hz), 4.50 (ABq, 2H, $J_{AB}$ = *13.2 Hz*, $\Delta\nu_{AB}$ = 184 Hz), 4.23 (d, 1H, $J$ = 1.8 Hz), 4.20 (dq, 2H, $J$ = 7.4, 2.3 Hz), 4.05 (m, 1H), 3.75 (m, 1H), 1.23 (t, 3H, $J$ = 7.4 Hz), 1.00 (t, 3H, $J$ = 7.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 168.5, 168.0, 166.3, 135.1, 128.9, 128.6, 128.0, 72.88, 64.80, 62.51, 61.93, 58.61, 48.79, 14.05, 13.73; high resolution MS (ESI) Calcd. for $C_{17}H_{22}NO_6$ [M + H] *m*/*e* 336.1478. Found: 336.1441. An analytical sample was prepared *via* recrystallization from hexanes-ethyl acetate: mp 117–118°C. Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.95; H, 6.23; N, 4.12.

***cis*-Diester 12.** $R_f$ 0.15 (hexanes-acetone, 85:15); IR ($CDCl_3$) 2984, 1750, 1669, 1453, 1209, 1140, 1028, 704 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 4.65 (ABq, 2H, $J_{AB}$ = 14.9 Hz, $\Delta\nu_{AB}$ = 576 Hz), 4.47 (ABq, 2H, $J_{AB}$ = 17.2 Hz, $\Delta\nu_{AB}$ = 62.5 Hz), 4.42 (d, 1H, $J$ = 2.7 Hz), 4.23–4.03 (m, 5H), 1.24 (t, 3H, $J$ = 7.0 Hz), 1.18 (t, 3H, $J$ = 7.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 167.2, 166.1, 166.1, 135.1, 128.9, 128.6, 128.1, 74.67, 67.75, 62.51, 62.05, 59.09, 49.35, 14.06, 14.01; high resolution MS (ESI) Calcd. for $C_{17}H_{22}NO_6$ [M + H] *m*/*e* 336.1478. Found: 336.1441. Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.64; H, 6.24; N, 4.12.

**4-Oxooxazolidine 16.** $R_f$ 0.34 (hexanes-acetone, 85:15); IR ($CHCl_3$) 2983, 1735, 1717, 1404, 1266, 1182, 1057, 1028, 704 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 4.54 (ABq, 2H, $J_{AB}$ = 16 Hz, $\Delta\nu_{AB}$ = 45 Hz); 4.47 (ABq, 2H, $J_{AB}$ = 14 Hz, $\Delta\nu_{AB}$ = 38 Hz); 4.06–3.87 (m, 4H), 2.90 (ABq, 2H, $J_{AB}$ = 15 Hz, $\Delta\nu_{AB}$ = 108 Hz); 1.15 (t, 6H, $J$ = 7 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 170.4, 167.9, 167.6, 135.4, 128.5, 128.1, 127.7, 93.1, 67.3, 62.1, 60.9, 43.72, 39.3, 13.80, 13.65; high resolution MS (ESI) Calcd. for $C_{17}H_{22}NO_6$ [M + H] *m*/*e* 336.1478. Found: 336.1441. Anal. Calcd. for $C_{17}H_{21}NO_6 \bullet 0.25H_2O$: C, 60.07; H, 6.38; N, 4.12. Found: C, 59.94; H, 6.15; N, 4.02.

***trans*-(4-Benzylmorpholine-2,3-diyl)dimethanol (17).** To a stirred suspension of lithium aluminum hydride (3.71 g, 97.7 mmol) in dry tetrahydrofuran (250 mL) at 0°C, a solution of diester **11** (6.55 g, 19.5 mmol) in tetrahydrofuran (50 mL) *via* canula was added. After complete addition, the mixture was warmed to room temperature for 30 min, followed by heating to reflux for 30 min. The mixture was cooled to 0°C, and 3.7 mL of water was added dropwise, followed by sodium hydroxide (3.7 mL of a 3.0 *M* aqueous solution), followed by 11 mL of water. The mixture was stirred at room temperature for 15 min, followed by the addition of ethyl acetate and anhydrous potassium carbonate. After further stirring for 15 min, the mixture was filtered, and the precipitate was washed with ethyl acetate. The filtrate was concentrated *in vacuo* to afford an oil. The crude product was purified by flash chromatography on silica gel. Elution with ethyl acetate gave 3.1 g (67%) of **17** as a clear oil: $R_f$ 0.23 EtOAc; IR ($CH_2Cl_2$) 3650, 3550, 30390, 3005, 1450, 1400, 1275, 1130, 1075, 925 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.00 (dd, 1H, $J$ = 12.1, 3.5 Hz), 3.82, (m, 1H), 3.78 (ddd, 1H, $J$ = 11.7, 3.5, 1.9 Hz), 3.71–3.65 (m, 2H), 3.64 (ABq, 2H, $J_{AB}$ = 13.3 Hz, $\Delta\nu_{AB}$ = 392 Hz), 3.58 (td, 1H, $J$ = 11.3, 1.9 Hz), 3.55 (m, 1H), 2.73, (br s, 1H), 2.67 (dm, 1H, $J$ = 11.8 Hz), 2.45 (m, 1H), 2.33 (td, 1H, $J$ = 11.3, 3.5 Hz), 2.07 (br s, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 137.9, 128.1, 127.8, 126.7, 77.31, 64.99, 62.64, 62.19, 58.02, 50.54; high resolution MS (ESI) Calcd. for $C_{13}H_{20}NO_3$ [M + H] *m*/*e* 238.1472. Found: 238.1437. %Water (KF): 2.07. Anal. Calcd. for $C_{13}H_{19}NO_3 \bullet 2.07\%$ $H_2O$: C, 64.48; H, 8.13; N, 5.78. Found: C, 64.15; H, 8.17; N, 5.74.

***trans*-(4-Benzylmorpholine-2,3-diyl)bis(methylene) bis(4-methylbenzenesulfonate) (18).** To a stirred solution of diol **17** (1.00 g, 4.21 mmol) in dichloromethane (40 mL) at 0°C, pyridine (1.0 mL, 12.6 mmol), followed by *p*-toluenesulfonic anhydride (4.13 g, 12.6 mmol) was added. The mixture was stirred at 0°C for 30 min. The mixture was diluted with ether and water. The organic layer was washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to an amber oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (80:20 → 70:30), followed by further elution with hexanes-ethyl acetate-triethylamine (58:40:2) afforded 1.75 g (76%) of **18** as a clear oil: $R_f$ 0.25 (hexanes-ethyl acetate, 3:1); $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 2H, $J$ = 8.2 Hz), 7.72 (d, 2H, $J$ = 8.6 Hz), 7.30 (d, 2H, $J$ = 8.2 Hz, 7.28 (d, 2H, $J$ = 8.4 hz), 7.25–7.10 (m, 5H), 4.26 (dd, 1H, $J$ = 10.9, 5.4 Hz), 4.23–4.18 (m, 2H), 4.15 (td, 1H, $J$ = 10.5, 3.9 Hz), 3.69–3.65 (m , 1H), 3.63–3.54 (m, 1H), 3.51 (ABq, 2H, $J_{AB}$ = 13.3 Hz, $\Delta\nu_{AB}$ = 188 Hz), 3.47–3.38 (m, 1H), 2.66–2.60 (m, 1H), 2.56–2.48 (m, 1H), 2.39 (s, 6H), 2.21–2.13 (m, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 145.1, 144.9, 137.6, 132.7, 132.4, 130.0, 129.8, 128.6, 128.3, 128.0, 127.9, 127.2, 72.55, 68.32, 65.29, 63.13, 58.43, 57.81, 48.29, 21.61; low resolution MS (ESI) *m*/*e* 546 [M + H]. Note: In our hands, bis-tosylate **18** decomposed at room temperature under nitrogen atmosphere by ca. 20% (based on the $^1$H-NMR spectrum) over a two week period. In latter runs, bis-tosylate **18** was stored at 0°C and used in the next reaction within a 24 h period, which minimized decomposition.

***trans*-4-Benzyl-6-(4-nitrophenylsulfonyl)octahydro- pyrrolo[3,4-b][1,4]oxazine (20).** To a stirred solution of 4-nitrobenzenesulfonamide (1.44 g, 7.15 mmol) and DBU (0.71 mL, 4.76 mmol) in dry acetonitrile (10 mL) at 70°C, a solution of bis-tosylate **18** (1.30 g, 2.38 mmol) in acetonitrile (5.0 mL) *via* canula was added. After complete addition, the mixture was stirred at 70°C and monitored by TLC. Once the starting material had been consumed (ca. 2 h), the mixture was diluted with ether-ethyl acetate (1:1) and water. The organic layer was washed five times with 1.0 *M* aqueous sodium hydroxide solution (to remove excess 4-nitrobenzenesulfonamide). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered through a short pad of silica gel (to remove baseline impurities), and concentrated *in vacuo* to an orange solid. Trituration of the crude product in hexanes-ether afforded 560 mg (58%) of **20** as a tan solid: $R_f$ 0.23 (hexanes-ethyl acetate, 3:1); IR ($CH_2Cl_2$) 3104, 3060, 2988, 2871, 2822, 1532, 1351, 1266, 1172, 1140, 740 $cm^{-1}$; $^1$H-NMR (500 MHz, $CD_3CN$) δ 8.45 (d, 2H, $J$ = 8.2 Hz), 8.06 (d, 2H, $J$ = 8.2 Hz), 7.38–7.33 (m, 5H), 3.85 (dd, 1H, $J$ = 11.7, 3.7 Hz), 3.69 (dd, 1H, $J$ = 8.0, 8.0 Hz), 3.65 (dd, 1H, $J$ = 9.2, 6.8 Hz), 3.57 (td, 1H, $J$ = 11.8, 2.67), 3.43 (ABq, 2H, $J_{AB}$ = 13.3 Hz, $\Delta\nu_{AB}$ = 160 Hz), 3.11 (dd, 1H, $J$ = 10.4, 9.2 Hz), 2.95 (dd,

1H, $J$ = 10.8, 9.7 Hz), 2.63 (ddd, 1H, $J$ = 12.1, 2.67, 1.24 Hz), 2.12 (ddd, 1H, $J$ = 10.8, 9.0, 7.1 Hz); $^{13}$C-NMR (125 MHz, $CD_3CN$) δ 156.6, 142.5, 137.7, 129.1, 128.6, 128.3, 127.4, 124.7, 77.9, 67.7, 65.2, 60.6, 52.0, 49.4, 48.6; high resolution MS (ESI) Calcd. for $C_{19}H_{22}N_3O_5S$ [M + H] *m*/*e* 404.1312. Found: 404.1274. An analytical sample was prepared *via* recrystallization from hexanes-ethyl acetate: mp 155–157°C. Anal. Calcd. for $C_{19}H_{21}N_3O_5S$: C, 56.56; H, 5.25; N, 10.41. Found: C, 56.21; H, 4.89; N, 10.21.

***trans*-4-Benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine dihydrochloride (2).** To a stirred solution of sulfonamide **20** (600 mg, 1.49 mmol) in DMF (2.0 mL), dodecanethiol (0.71 mL, 2.97 mmol) and lithium hydroxide hydrate (125 mg, 2.97 mmol) were added. The mixture was stirred at room temperature for 2 h. The mixture was diluted with hexanes-ethyl acetate (1:1) and 1.0 *M* aqueous hydrochloric acid, and the layers were separated. The organic layer was extracted with aqueous hydrochloric acid, and the combined aqueous layers were back extracted with 1:1 hexanes-ethyl acetate. The organic layers were discarded, and the aqueous layer was basified with 50% aqueous sodium hydroxide to pH = 13. The aqueous layer was extracted twice with dichloromethane-methanol (9:1). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 250 mg (77%) of the free base of **2** as a brown semi-solid: $R_f$ 0.40 (chloroform-methanol-ammonium hydroxide, 90:9:1); $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.27–7.18 (m, 5H), 3.85 (dd, 1H, $J$ = 11.7, 3.5 Hz), 3.67 (m, 1H), 3.57 (ddd, 1H, $J$ = 10.1, 9.0, 7.0 Hz), 3.46 (ABq, 2H, $J_{AB}$ = 12.9 Hz, $\Delta\nu_{AB}$ = 168 Hz), 3.43–3.25 (br s, 1H), 3.22–3.11 (m, 2H), 2.85 (t, 1H, $J$ = 10.1 Hz), 2.71 (t, 1H, $J$ = 10.1 Hz), 2.63, dm, 1H, $J$ = 12.1 Hz), 2.27 (ddd, 1H, $J$ = 11.0, 9.0, 6.7 Hz), 2.09 (td, 1H, $J$ = 12.2, 3.6 Hz); $^{13}$C (100 MHz, $CDCl_3$) δ 137.5, 129.1, 128.2, 127.3, 80.34, 68.08, 66.97, 61.42, 52.60, 46.75, 46.29; low resolution MS (ESI) *m*/*e* 219 [M + H].

To a solution of the above semi-solid (250 mg) in methanol (3 mL), a 4.0 *M* solution of hydrogen chloride in dioxane (1.0 mL) was added. The solution was warmed to 40°C in a water bath for 10 min, followed by concentration *in vacuo*. Trituration of the remaining residue in ethyl acetate afforded 200 mg (60%) of **2** as a white solid: mp 253–255°C; $^1$H-NMR (400 MHz, $D_2O$) δ 7.41–7.34 (m, 5H), 4.26 (ABq, 2H, $J_{AB}$ = 12.9 Hz, $\Delta\nu_{AB}$ = 48.31 Hz), 4.11 (dd, 1H, $J$ = 13.3, 3.9 Hz), 4.00 (ddd, 1H, $J$ = 11.0, 10.2, 7.5 Hz), 3.76 (td, 1H, $J$ = 12.5, 2.4 Hz), 3.64–3.56 (m, 2H), 3.47 (ddd, 1H, $J$ =11.4, 10.1, 7.4 Hz), 3.33 (dm, 1H, $J$ = 10.5 Hz), 3.14–3.05 (m, 3H); $^{13}$C-NMR (100 MHz, $D_2O$) δ 130.5, 130.0, 128.9, 127.7, 74.27, 64.87, 61.46, 59.82, 50.94, 43.05, 41.61; high resolution MS (ESI) $C_{13}H_{19}N_2O$ [M + H] *m*/*e* 219.1525. Found: 219.1491. %Water (KF): 0.47. Anal. Calcd. for $C_{13}H_{18}N_2O\bullet 2HCl\bullet 0.47\%\ H_2O$: C, 53.35; H, 6.94; N, 9.57. Found: C, 52.97; H, 6.81; N, 9.35.

**2,2,2-Trifluoro-1-(*trans*-hexahydropyrrolo[3,4-*b*][1,4] oxazin-6(2H)-yl)ethanone (22).** To a stirred suspension of **2** (100 mg, 0.34 mmol) in dichloromethane (3 mL) at 0°C were added triethylamine (190 μL, 1.37 mmol) and trifluoroacetic anhydride (95 μL, 0.69 mmol). The mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was diluted with dichloromethane and washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to an oil. The crude product was purified by chromatography on silica gel. Elution with hexanes-ethyl acetate-triethylamine (75:24:1) afforded 85 mg (79%) of 2,2,2-trifluoro-1-(*trans*-hexahydropyrrolo[3,4-*b*][1,4] oxazin-6(2H)-yl)ethanone as an oil: $R_f$ 0.62 (hexanes-ethyl acetate, 1:1); $^1$H-NMR [400 MHz, $CDCl_3$, two rotomers present (1:1)] δ 7.30–7.18 (m, 5H), 3.98–3.58 (m, 4H), 3.41–3.08 (m, 3H), 2.67 (t, 1H, $J$ = 12.5 Hz), 2.37 (m, 1H), 2.18 (m, 1H); $^{13}$C-NMR [100 MHz, $CDCl_3$, two rotomers present (1:1)] δ 156.1 (q, $J$ = 37 Hz), 155.9 (q, $J$ = 37 Hz), 136.7, 136.5, 129. 1, 129.0, 128.4, 128.3, 127. 7, 127.6, 116.0 (q, $J$ = 286 Hz), 115.9 (q, $J$ = 285 Hz), 78.14, 77.01, 67.94, 67. 89, 65.69, 63.85, 61.32, 61.01, 52.34, 52.08, 48.24, 48.15, 47.76, 47.72; $^{19}$F-NMR [376 MHz, methanol-$d_4$, 2 rotomers present (1:1)] δ − 73.68, −73.90; low resolution MS (ESI) *m*/*e* 315 [M + H].

The product from above (85 mg, 0.27 mmol) was dissolved in methanol (15 mL), and 80 mg of 10% palladium on activated carbon was added. The suspension was placed in a Parr hydrogenation bottle and hydrogenated (42 PSI, room temperature) for 48 h. The reaction mixture was filtered through Celite and washed with methanol. The solution was concentrated *in vacuo* to afford 57 mg (95%) of **22** as an oil: $R_f$ 0.40 (hexanes-ethyl acetate, 1:1); $^1$H-NMR [400 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 3.90–3.77 (m, 3H), 3.70–3.59 (m, 1H), 3.50–3.39 (m, 1H), 3.34 (t, 0.5H, $J$ = 10.1 Hz), 3.26–3.15 (m, 1H), 3.06 (t, 0.5H, $J$ = 11.3 Hz); 3.00–2.73 (m, 3H), 1.91 (br s, 1H); $^{13}$C-NMR [100 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 156.1 (q, $J$ = 37 Hz), 155.9 (q, $J$ = 37 Hz); 116.0 (q, $J$ = 284 Hz); 78.90, 77.74, 68.05, 67.99, 59.31, 57.68, 48.54, 48.50, 47.80, 47.62, 45.83, 45.72; $^{19}$F-NMR [376 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ −72.51, −72.76; low resolution MS (ESI) 225 [M + H].

***tert*-Butyl (+/−)-*trans*-hexahydropyrrolo[3,4-*b*][1,4] oxazine-4(4a*H*)-carboxylate [(+/−)-1].** To a stirred solution of **22** (55 mg, 0.25 mmol) in dichloromethane (1.0 mL), di-*tert*-butyl dicarbonate (60 mg, 0.27 mmol) was added. The mixture was stirred under nitrogen atmosphere for 4 h. The reaction mixture was purified by chromatography on silica gel. Elution with heptane-ethyl acetate (9:1 → 1:1) afforded 55 mg (70%) of *tert*-butyl *trans*-6-(2,2,2-trifluoroacetyl)hexahydropyrrolo[3,4-*b*][1,4]oxazine-4(4a*H*)-carboxylate as an oil: $R_f$ 0.58 (hexanes-ethyl acetate, 1:1); $^1$H-NMR [400 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 4.43 (m, 0.5H), 4.35 (m, 0.5H), 4.00–3.94 (m, 1H), 3.93–3.75 (m, 3H), 3.69–3.59 (m, 2H), 3.57–3.42 (m, 1H), 3.34 (t, 0.5H, $J$ = 10.6 Hz), 3.20 (t, 0.5H, $J$ = 10.9 Hz), 3.11–2.87 (m, 2H), 1.40 (s, 9H); $^{13}$C-NMR [100 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 160.0 (q, $J$ = 37 Hz), 159.9 (q, $J$ = 37 Hz), 155.3, 155.2, 116.0 (q, $J$ = 288 Hz), 115.9 (q, $J$ = 288 Hz), 81.50, 78.51, 77.49, 67.40, 67.37, 57.96, 56.59, 49.06, 48.97, 46.67, 46.61, 28.15, 28.09; $^{19}$F-NMR [376 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ −72.22, −72.63; high resolution MS (ESI) Calcd. for $C_{13}H_{19}N_2O_4F_3Na$ [M + Na] *m*/*e* 347.1222. Found: 347.1189.

To a stirred solution of *trans*-6-(2,2,2-trifluoroacetyl) hexahydropyrrolo[3,4-*b*][1,4]oxazine-4(4a*H*)-carboxylate (27 mg, 0.83 mmol) in methanol-water (600 μL, 5:1) at room temperature, potassium carbonate (23 mg, 0.17 mmol) was added. The mixture was stirred at room temperature for 1 h. The mixture was diluted with water and ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford 18 mg (95%) of (+/−)-**1** as an oil:

$R_f$ 0.42 (dichloromethane-methanol-ammonium hydroxide, 89:10:1); $^1$H-NMR (500 MHz, $CD_3CN$) δ 3.99 (ddd, 1H, $J$ = 11.8, 3.9, 1.56 Hz), 3.81 (ddd, 1H, $J$ = 13.5, 3.06, 1.53 Hz), 3.64 (td, 1H, $J$ = 11.9, 3.1 Hz), 3.6–3.5 (br m, 1H), 3.48 (app. q, 1H, $J$ = 9.6 Hz), 3.15–2.90 (br m, 2H), 2.99–2.94 (m, 1H), 2.91 (ddd, 1H, $J$ = 13.5, 12.0, 3.8 Hz), 2.85–2.68 (br m, 1H), 1.46 (s, 9H); $^{13}$C-NMR (125 MHz, $CD_3CN$) δ 155.9, 81.3, 79.8, 67.2, 59.9, 47.8, 45.0, 44.6, 27.9; high resolution MS (ESI) Calcd. for $C_7H_{13}N_2O_3$ [M – $^t$Bu + 2H] *m/e* 173.0945. Found: 173.0920.

***N*-Benzyl-*erythro*-β-hydroxy-DL-aspartic acid (14).** This material was prepared according to the established procedure with slight modification:

To a stirred solution of (+/−)-*trans*-epoxysuccinic acid (**13**, 20.0 g, 151 mmol) in deionized water (70 mL), benzylamine (50 mL, 460 mmol) was added. The mixture was heated to reflux under nitrogen atmosphere. A precipitant began to form after ∼15 min at reflux. After 4 h of heating, the reaction was cooled to room temperature and treated with 2.5 N aqueous sodium hydroxide (∼140 mL) to adjust the pH to ∼11. The aqueous layer was extracted with ether (4 × 100 mL) to remove the benzylamine. The aqueous layer was acidified with concentrated hydrochloric acid to pH ∼4 (ca. 19 mL), which caused a white precipitate to form. The precipitate was collected by suction filtration, washed with water (2 × 100 mL) and dried *in vacuo* (vacuum oven, 65°C, house vacuum) to afford 30.4 g (84%) of **14** as a white solid: $^1$H-NMR (400 MHz, $D_2O$) δ 7.41 (s, 5H), 4.10–4.34 (m, 3H), 3.81 (d, 1H, $J$ = 4.1 Hz); $^{13}$C-NMR (100 MHz, $D_2O$) δ 175.9, 170.1, 130.6, 129.9, 129.6, 129.2, 70.24, 64.06, 50.60; high resolution MS (ESI) Calcd. for $C_{11}H_{14}NO_5$ [M + H] *m/e* 240.0892. Found: 240.0866. An additional 3.0 g of **20** was obtained from the filtrates upon standing overnight. Combined yield: 92%.

**Diethyl *N*-benzyl-*erythro*-β-hydroxy-DL-aspartate.** To a stirred solution of dry ethyl alcohol (250 mL) at 0°C under nitrogen atmosphere, acetyl chloride (18 mL, 250 mmol) was added dropwise. After complete addition, the reaction was stirred at 0°C for 30 min. Diacid **14** (12.0 g, 50 mmol) was added in one portion, and the suspension was slowly heated to reflux for 72 h. The reaction mixture was filtered, and the collected precipitate (unreacted **14**) was set aside. The filtrate was concentrated under reduced pressure. The remaining residue was partitioned between ether (100 mL) and half-saturated aqueous potassium carbonate solution (50 mL). The ethereal layer was extracted with potassium carbonate solution. The combined aqueous layers were back-extracted with ether. The combined ethereal layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 6.1 g (41%) of diethyl *N*-Benzyl-*erythro*-β-hydroxy-DL-aspartate as a tan oil: $R_f$ 0.20 (heptane-ethyl acetate, 75:25); IR ($CDCl_3$) 3475, 2983, 1734, 1189, 1116, 1026, 739, 669 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 4.51 (d, 1H, $J$ = 3.4 Hz), 4.29–4.15 (m, 4H), 3.98 (d, 1H, $J$ = 13.0 Hz), 3.77 (d, 1H, $J$ = 13.0 Hz), 3.71 (d, 1H, $J$ = 3.1 Hz), 3.43 (br s, 1H), 2.30 (br s, 1H), 1.29 (t, 6H, $J$ = 7.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 171.9, 171.0, 139.3, 128.5, 128.3, 127.2, 71.83, 63.23, 61.81, 61.38, 52.60, 14.18, 14.13; high resolution MS (ESI) Calcd. for $C_{15}H_{22}NO_5$ [M + H] *m/e* 296.1529. Found: 296.1492. Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.87; H, 7.23; N, 4.73.

**Diethyl 2-(*N*-benzyl-2-chloroacetamido)-*erythro*-3-hydroxysuccinate (15).** To a stirred solution of diethyl *N*-benzyl-*erythro*-β-hydroxy-DL-aspartate (5.0 g, 17 mmol) in dichloromethane (40 mL) in an ice-brine bath (−10°C) under nitrogen atmosphere, sodium hydroxide (25 mL of 1.0 N aqueous solution) was added. The mixture was vigorously stirred while a solution of chloroacetyl chloride (2.0 mL, 25 mmol) in dichloromethane (4.0 mL) was added dropwise *via* syringe (addition time ∼10 min). Halfway through the addition, the reaction mixture began to thicken. The ice-brine bath was replaced with an ice bath. After complete addition, the reaction mixture was stirred at 0°C for an additional 15 min. Sodium hydroxide (10 mL of a 1.0 *N* aqueous solution) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The remaining residue was dissolved in ether (100 mL) and extracted with 3 *N* hydrochloric acid (to remove *o*-acylated byproduct). The ethereal layer was washed with brine (2×), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford 6.2 g (99%) of **15** as a viscous tan oil: $R_f$ 0.17 (heptane-ethyl acetate, 75:25); IR ($CDCl_3$) 3462, 2983, 1738, 1163, 1203, 1127, 1203, 1025, 669 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.43–7.23 (m, 5H), 5.56 (s, 1H), 4.96–4.81 (m, 2H), 4.44 (br s, 1H), 4.31 (q, 2H, $J$ = 7.2 Hz), 4.26–4.00 (m, 4H), 3.71 (d, 1H, $J$ = 2.4 Hz), 1.34 (t, 3H, $J$ = 7.2 Hz), 1.24 (t, 3H, $J$ = 7.1 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 171.4, 168.8, 167.6, 136.6, 129.0, 127.8, 126.1, 70.85, 62.70, 62.02, 61.34, 51.17, 41.61, 14.11, 13.97; high resolution MS (ESI) Calcd. for $C_{17}H_{23}ClNO_6$ [M + H] *m/e* 372.1247. Found: 372.1208. %Water(KF): 0.46. Anal. Calcd. for $C_{17}H_{22}ClNO_6$•0.46% $H_2O$: C, 54.66; H, 5.98; N, 3.75. Found: C, 54.32; H, 5.98; N, 3.61.

**Diethyl *trans*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (11) and diethyl *cis*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (12).** To a stirred suspension of sodium hydride (60% oil dispersion, 0.22 g, 5.5 mmol) in dry tetrahydrofuran (25 mL) at 0°C under nitrogen atmosphere, a solution of alcohol **15** (0.99 g, 2.7 mmol) in tetrahydrofuran-acetonitrile (5 mL, 4:1) was added dropwise *via* syringe (addition took ∼10 min). During the addition, the reaction turned from a grey suspension to a yellow suspension. After complete addition, the reaction mixture was stirred at 0°C for 30 min. The reaction mixture was poured into a rapidly stirred solution of 10% aqueous acetic acid (20 mL). The mixture was concentrated *in vacuo* to a volume of ca. 15 mL. The remaining residue extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 1.0 *N* aqueous sodium hydroxide solution (to remove minor carboxylic acid byproducts), brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford an orange solid (0.9 g). The crude product was purified by Biotage® on silica gel. Elution with heptane-ethyl acetate (95:5) afforded 0.45 g (50%) of *trans*-product **11** as a white solid and 0.18 g (20%) of *cis*-product **12** as an oil. The spectral properties of compounds **11** and **12** from this experiment were identical in all respects to compounds **11** and **12** obtained above.

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## REFERENCES AND NOTES

[1] Sisko, J. T.; Tucker, T. J.; Bilodeau, M. T.; Buser, C. A.; Ciecko, P. A.; Coll, K. E.; Fernandes, C.; Gibbs, J. B.; Koester, T. J.; Kohl, N.; Lynch, J. J.; Mao, X.; McLoughlin, D.; Miller-Stein, C. M.; Rodman, L. D.; Rickert, K.W.; Sepp-Lorenzino, L.; Shipman, J. M.; Thomas, K. A.; Wong, B. K.; Hartman, G. D. Bioorg Med Chem Lett 2006, 16, 1146.

[2] Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. J Med Chem 2008, 51, 1981.

[3] Barker, A. J.; Gibson, K. H.; Grundy, W.; Godfrey, A. A.; Barlow, J. J.; Healy, M. P.; Woodburn, J. R.; Ashton, S. E.; Curry, B. J.; Scarlett, L.; Henthorn, L.; Richards, L. Bioorg Med Chem Lett 2001, 11, 1911.

[4] Kasper, S.; El Giamal, N.; Hilger, E. Expert Opin Pharmacother 2000, 1, 771.

[5] Vasiliou, S.; Vicente, M.; Castaner, R. Drugs Future 2009, 34, 451.

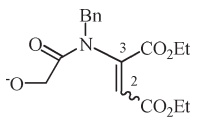
[6] Hong, J.; Zhang, Z.; Lei, H.; Cheng, H.; Hu, Y.; Yang, W.; Liang, Y.; Das, D.; Chen, S.-H.; Li, G. Tetrahedron Lett 2009, 50, 2525.

[7] Liwschitz, Y.; Rabinsohn, Y.; Haber, A. J Chem Soc 1962, 3589.

[8] Ratios are based on the integrations of the benzylic hydrogens in the $^1$H NMR spectrum of the crude reaction mixture.

[9] (a) Norman, B. H.; Kroin, J. J Org Chem 1996, 61, 4990; (b) Cushman, M.; Castagnoli, N., Jr. J Org Chem 1973, 38, 440; (c) Burdzhiev, N. T.; Stanoeva, E. R. Tetrahedron 2006, 62, 8318; (d) Johnson, F. Chem Rev 1968, 68, 375.

[10] The formation of 4-oxooxazolidine **16** could arise *via* base-catalyzed-elimination of either **11** or **12** to afford ring-opened intermediate **23**, followed by conjugate addition of the alkoxide at C(3),




**23**

[11] Kan, T.; Fukuyama, T. Chem Commun 2004, 40, 353.

[12] (a) Bornstein, J.; Shields, J. E. Organic Syntheses; Wiley: New York, 1973; Vol. 5, p 1064; (b) Ballini, R.; Bosica, G.; Mase, A.; Petrini, M. Eur J Org Chem 2000, 2927.

[13] (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. Tetrahedron Lett 1995, 38, 6373; (b) Matoba, M.; Kajimoto, T.; Node, M. Synth Commun 2008, 39, 1194.

[14] (a) Wuts, P. G. M.; Northius, J. M. Tetrahedron Lett 1998, 39, 3889; (b) Lencina, C. L.; Dassonville-Klimp, A.; Sonnet, P. Tetrahedron Asymmetry 2008, 19, 1689.

[15] Due to severe line broadening of the C(5) and C(7) protons in the $^1$H NMR spectrum of (+/−)-**1** ($CDCl_3$), exact comparison of our spectra of (+/−)-1 to Hong's reported $^1$H NMR spectra of (4aS,7aS)-1 was difficult [6]. However, we believe our structure of (+/−)-1 to be correct based on extensive 1D and 2D NMR experiments performed in $CD_3CN$, where the line broadening was less severe.

[16] Still, W. C.; Kahn, M.; Mitra, A. J Org Chem 1978, 43, 2923.

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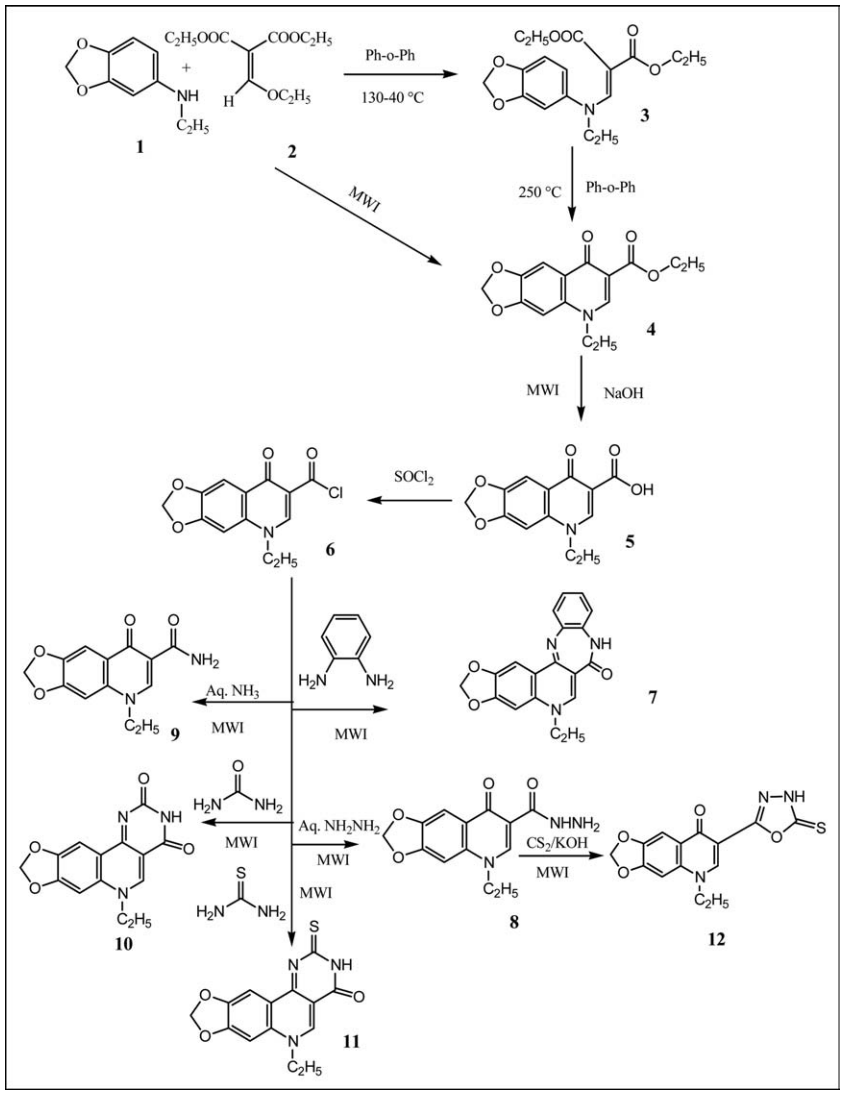



The Gould-Jacob type of reaction for the synthesis of ethyl 5-ethyl-8-oxo-5,8-dihydro-[1,3]-dioxolo[4,5-g]quinoline-7-carboxylate **4** has been carried out conventionally by the condensation between *N*-ethyl-3,4-methylenedioxyaniline **1** and diethyl ethoxymethylenemalonate **2** gave the unsaturated ester **3** and thermal cyclization in refluxing diphenyl oxide gave quinolone ethyl ester **4** and the results obtained were compared with single step microwave irradiation under solvent free conditions for the synthesis of **4**. The esters on basic hydrolysis formed free acid **5,** which, upon treatment with thionyl chloride gave the acid chloride **6**. Treatment of acid chloride with *o*-phenylenediamine, hydrazine hydrate, ammonia, urea, and thiourea gave the amides (**7–11**). $CS_2$ treatment in presence of KOH on **8** gave **12**. We prepared **7–12** derivatives by conventional as well as microwave irradiation. These compounds have been characterized on the basis of IR, $^1$H NMR, MS, and elemental analysis. All the compounds prepared herein were screened for their antibacterial activity. Compounds **4**, **5** possess promising antibacterial activity and compound **8** showed significant antibacterial activity.

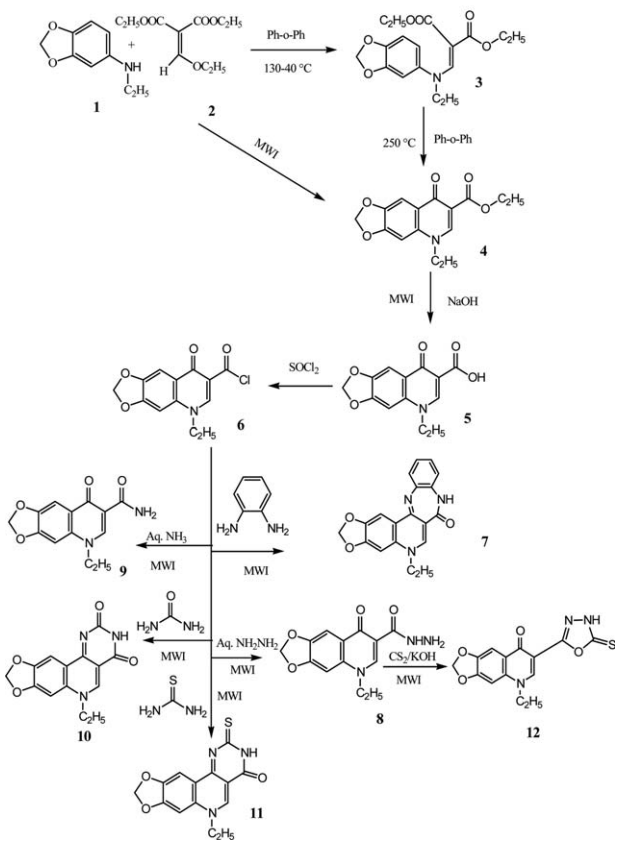
## INTRODUCTION

Nalidixic acid and its quinolone analogs for example oxolinic acid, norfloxacin, pefloxacin, ciprofloxacin, and ofloxacin have been used for treatment of various bacterial infections (urology, ophthalmology) [1]. The purpose of this investigation was to provide a novel and more advantageous method that the synthesis of 5-ethyl-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid **5** and its chloride **6** and then different derivatives of amides **7–12** by conventional as well as microwaves irradiation and comparative study of both the method have been carried out. The solvent free reactions [2–6] under microwave condition are especially for providing an environmentally benign system. Thus microwave assisted synthesis becomes a part of ''Sustainable chemistry''. Microwave accelerated organic synthesis is an effective and an alternative route proposed during the last decade due to drastic reduction in the reaction time, to minimize cumbersome work-up and better yield [7–10]. We report herein the synthesis of quinolone derivatives and related compounds using conventional as well as microwave methodologies and comparative study of both the method have been carried out. These compounds were evaluated for antibacterial activity *in vitro* and *in vivo* in comparison with nalidixic acid [11–14].

## RESULTS AND DISCUSSION

The aim of this work was to synthesize 5-ethyl-8-oxo-5, 8-dihydro-[1,3]dioxolo[4,5-g] quinoline -7- carboxylic acid (oxolinic acid) and its chloride **6** and different derivatives of amides. In conventional method, *N*-ethyl methylene dioxyaniline **1** was condensed with EMME **2** at 130–140°C for 1.5–2 h to obtain unsaturated ester **3**, which on thermal cyclization in boiling diphenyl oxide at 250°C for 2–3 h provided quinolone ethyl ester **4** in 70% overall yield on the basis of compound **1**. On the other hand, single step microwave assisted reaction of **1** with EMME **2** without solvent (Method B) provided identical compound **4** within 8–10 min in 88% overall yield (Scheme 1). Thus microwave assisted synthesis quinolone ethyl ester **4** has remarkable advantages over the conventional techniques because of easier work up, better yield, rapid and solvent free cleaner reaction. Compound **4** on hydrolysis gave compound **5**, which upon treatment with thionyl chloride gave acid chloride **6**. Treatment of this acid chloride **6** with *o*-phenylenediamine, hydrazine hydrate, ammonia solution, urea, and thiourea gave the amides **7–11** and Compound **8** when refluxed with ethanol and carbon disulfide in presence of potassium hydroxide yielded the corresponding 5-ethyl-7-(5-thioxo-4, 5-dihydro-[1,3,4] oxadiazol-2-yl)-5-H-[1, 3] dioxolo [4, 5-g] quinolin-8-one **12** by conventional heating as well as under microwave irradiation (Scheme 1). The comparison between conventional and microwave methodologies has been shown in Table 1. Compounds obtained from both methods were identical and were confirmed on the basis of TLC, mp, elemental, and spectral analysis.

**Scheme 1**




In conclusion, we have developed a simple, fast, solvent free, and high yielding method for the synthesis quinolone derivatives and related compounds, in which compounds **4** and **5** displayed very promising activity as expected (*in vitro* as well as *in vivo* activity better than the standard Nalidixic acid), whereas synthesized novel compound 8 exhibited significant antibacterial activity. Rest of the novel compounds displayed weak antibacterial activity.

## EXPERIMENTAL

Melting points were determined in open capillaries on a BÜCHI melting point apparatus B-540 and are uncorrected. Infrared (ir) spectra were recorded on a PerkinElmer paragon 1000 FTIR spectrophotometer (potassium bromide pellets). The $^1$H NMR spectra were recorded on Varians 400 MHz spectrophotometer in deuteriodimethyl sulfoxide using TMS as internal standard and the chemical shifts are expressed in ppm.

**Table 1**

A comparison between conventional and microwave assisted synthesis of quinolone derivatives and related compounds.

| Compound no. | Conventional (Method A) Time (h) | Yield (%) | Microwave (Method B) Time [c] (min) | Yield (%) | Melting point (°C) |
|---|---|---|---|---|---|
| **4** | 3 | 70 | 4 | 88 | 169–73 |
| **5** | 2 | 82 | 4 | 93 | 313–14 |
| **6** | 12 | 86 | – | – | 245–47 |
| **7** | 10 | 60 | 4 | 87 | 335–37 |
| **8** | 03 | 78 | 4 | 92 | 300–02 |
| **9** | 01 | 77 | 2 | 92 | 288–90 |
| **10** | 03 | 70 | 4 | 88 | 285–87 |
| **11** | 03 | 70 | 4 | 86 | 265–68 |
| **12** | 24 | 71 | 5 | 86 | 260–63 |

Mass spectral (MS) data were obtained using an Agilent 1100LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 metanol/water. Microwave irradiation was carried out in modified microwave oven fitted with a condenser BPL microwave oven, Model BMO 700T, (2450 MHz, 700 W). The purity of compounds was checked by TLC using silica gel G plates.

**Synthesis of 5-ethyl-8-oxo-5, 8-dihydro-[1, 3] dioxolo[4, 5-g] quinoline-7-carboxylic acid (5).** ***Three step conventional method A.*** *Step 1: 2-[(Benzo[1,3]dioxolo-5-yl-ethyl-amino) methylene]-malonic acid diethyl ester (3).* A mixture of benzo[1,3]dioxol-5yl-ethyl-amine **1** (3.30 g, 0.02 mol), diethyl ethoxy methylenemalonate **2** (4.40 g, 0.02 mol), and diphenyl oxide (10 mL) was heated at 130–140°C for 1.5 h, and the alcohol generated from reaction mixture was allowed to escape. The reaction mixture was keep for further step.

*Step 2: Ethyl 5-ethyl-8-oxo-5, 8-dihydro-[1,3]dioxolo [4, 5-g] quinoline-7-carboxylate (4).* 2-[(Benzo[1,3]dioxolo-5-yl-ethyl-amino)-methylene]-malonic acid diethyl ester **3** (6.70 g) was dissolved in boiling diphenyl oxide (10 mL) and heated at 250°C for 1.5–2 h. The liberated alcohol was collected in a Dean-Stark trap. Then the mixture was cooled to room temperature, the resulting solid was filtered and washed with petroleum ether and dried *in vacuo*, yielding 4.1 g (70%) of (**4),** mp 169–173°C (ref. [15], mp 172–173°C).

*Step 3: 5-Ethyl-8-oxo-5, 8-dihydro-[1, 3] dioxolo [4, 5-g] quinoline-7- carboxylic acid (5).* This compound was obtained in 82% yield as a white solid, (ref. [16,17]).

***Two step microwave assisted method B.*** *Step 1: Ethyl 5-ethyl-8-oxo-5, 8-dihydro-[1, 3] dioxolo [4, 5-g] quinoline-7-carboxylate (4).* A neat mixture of benzo[1,3]dioxol-5yl-ethyl-amine **1** (3.30 g, 0.02 mol) and diethyl ethoxymethylenemalonate **2** (4.40 g, 0.02 mol) was taken in an open Pyrex tube and subjected to microwave irradiation in domestic microwave oven (BPL, BMO 700T) at an output of about 700 watts for specified time given in (Table 1). Progress of reaction was monitored through TLC at an interval of 45 sec. On completion, the reaction mixture was allowed to cool at room temperature; the resulting solid was filtered and washed with petroleum ether and dried *in vacuo*, to give 5.1 g (88%) of **4**.

mp 169–173°C (ref. [15], mp 172–173°C).

*Step 2: 5 - Ethyl-8-oxo-5, 8-dihydro-[1, 3] dioxolo [4, 5-g] quinoline-7- carboxylic acid (5).* A neat mixture of ethyl 5-ethyl-8-oxo-5, 8-dihydro-[1, 3] dioxolo [4, 5-g] quinoline -7-carboxylate **4** (4.0 g, 0.014 mol) was dissolved in 20 mL of 10% NaOH. The reaction mixture was subjected to microwave irradiation in Pyrex glass round bottle flask attached with air condenser from outside with special arrangement for 3 min. After cooling at room temperature, the reaction mixture was acidified using concentrated HCl. The resulting precipitated was filtered and washed with water, and recrystallized from aqueous DMF to give 3.4 g (93%) of **5**.

***5-Ethyl-8-oxo-5,8-dihydro-[1,3]-dioxolo[4,5-g]quinoline -7-carbonyl chloride (6).*** This compound was obtained in 86% yield as a light brown solid (ref. [17,18]).

***5-Ethyl-5,8-dihydro-[1,3]dioxolo-5,8,13-triaza-benzo[5,6]cyclohepta[1,2-a]naphthalen-7-one(7).*** *Method A.* To a solution of **6** (0.28 g, 0.001 mol) in 10 mL of xylene was added *o*-phenylenediamine (0.162 g, 0.0015 mol) and the reaction mixture was refluxed for 8–10 h. The liberated water was collected in Dean-Stark trap. After the mixture was cooled to room temperature, the solid precipitated was filtered and recrystallized from ethanol to afford 0.20 g (60%) of 7 as dark yellow solid.

*Method B.* To a solution of compound **6** (0.28 g, 0.001 mol), *o*-phenylenediamine (0.162 g, 0.0015 mol) in 10 mL of xylene, acidic alumina (2 g) was added. The reaction mixture was stirred well, air dried, and subjected to the MWI intermittently at 30 s intervals for specified time (Table 1). On completion of reaction as monitored by TLC, the product was extracted into ethanol (3 × 5 mL). Removal of solvent under reduced pressure yielded the product, which was recrystalized from ethanol to give 0.29 g (87%) of (**7**) as dark yellow solid.

mp 335–337°C; IR (KBr): 3422, 3218, 2924, 2853, 1676, 1624, 1599, 1555, 1538, 1500, 1473, 1455, 1376, 1299, 1277, 1254, 1202, 1032 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.39 (t, 3H), 4.70 (q, 2H), 6.43 (s, 2H), 7.08–7.21 (m, 3H) 7.56 (d, d 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.10 (s, 1H), 10.50 (s, 1H); MS (ESI, *m/z*):334 $[M+H]^+$. Anal.Calcd. For $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.76; H, 4.36; N, 12.54.

***5-Ethyl-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g] quinoline -7-carbohydrazide (8).*** *Method A.* To a solution of **6** (0.42 g, 0.0015 mol) dissolved in 10 mL of ethanol was added hydrazine hydrate (2.5 mL). The mixture was stirred for 1 h at room temperature, and then poured into water. The precipitate was collected by filtration and recrystallized from ethanol to give 0.32 g (78%) of **8** as yellow solid.

*Method B.* To a solution of compound **6** (0.42 g, 0.0015 mol) and hydrazine hydrate (2.5 mL) in ethanol (10 mL) acidic alumina (2 g) was added. The reaction mixture was stirred well, air dried, and subjected to MWI intermittently at 30 s intervals for specified time (Table 1). On completion of

reaction, as monitored by TLC the product was extracted into ethanol (3 × 5 mL). Removal of solvent under reduced pressure yielded the product, which was recrystallized from ethanol to give 0.38 g (92%) of **8** as yellow solid.

mp 300–302°C; IR (KBr): 3400, 3245, 2986, 1647, 1618, 1592, 1506, 1474, 1375, 1269, 1256, 1238, 1197, 1038 $cm^{-1}$; MS (ESI, *m/z*):276 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.87; H, 4.56; N, 15.54.

***5-Ethyl-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g] quinoline-7-carboxamide (9).*** *Method A*. This compound was obtained in 77% yield as a white solid (ref. [19]).

*Method B*. To a solution of **6** (0.28 g, 0.001 mol), ammonia solution (5 mL) in ethanol, basic alumina (2 g) was added. The reaction mixture was stirred well, air dried, and subjected to MWI intermittently at 30 s intervals for specified time (Table 1). On completion of reaction, as monitored by TLC the product was extracted into ethanol (3 × 5 mL). Removal of solvent under reduced pressure yielded the product which was recrystallized from ethanol to give 0.24 g (92%) of **9** as a white solid. mp 334–336°C; (lit. ref. [19] 336°C).

***6-Ethyl-6H-8, 10-dioxa-1, 3, 6 triaza-cyclopenta [b] phenanthrene-2, 4-dione (10).*** *Method A*. A mixture of **6** (0.28 g, 0.001 mol), urea (0.1 g, 0.002 mol), 5% aq. KOH (2 mL) and methanol (10 mL) was refluxed for 2 h and cooled. The precipitate obtained after dilution with water was filtered, washed with water, and recrystallized from methanol to give 0.20 g (70%) of **10** as a white solid.

*Method B*. To a solution of compound **6** (0.28 g, 0.001 mol), urea (0.1 g, 0.002 mol) in methanol (10 mL), 5% aq KOH (2 mL), and basic alumina 2 g was added. The reaction mixture was stirred well, air dried, and subjected to MWI intermittently at 30 s intervals for specified time (Table 1). On completion of reaction, as monitored by TLC the product was extracted into ethanol (3 × 5 mL). Removal of solvent under reduced pressure yielded the product which was recrystallized from methanol to give 0.25 g (88%) of **10** as a white solid.

mp 285–287°C; IR (KBr): 3431, 2926,2853,1721, 1685, 1658, 1604, 1574, 1557, 1508, 1472, 1416, 1335, 1292, 1251, 1216, 1181, 1114, 1084,1024 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.42 (t, 3H), 4.66 (q, 2H), 6.35 (s, 2H), 7.74 (s, 1H), 8.26 (s, 1H), 9.11 (s, 1H), 15.62 (s, 1H); MS (ESI, *m/z*):286 $[M+H]^+$. Anal.Calcd. For $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.85; H, 3.95; N, 14.85.

***6-Ethyl – 2- thioxo-2, 6 dihydro-3H-8, 10-dioxa-1, 3, 6 triaza-cyclopenta [b] phenanthrene - 4-one (11).*** *Method A*. A mixture of **6** (0.28 g, 0.001 mol), thiourea (0.15 g, 0.002 mol), 5% aq. KOH (2 mL), and methanol (10 mL) was refluxed for 2 h and cooled. The precipitate obtained after dilution with water was filtered, washed with water, and recrystallized from methanol to give 0.21 g (70%) of **11** as a white solid.

*Method B*. To a solution of **6** (0.28 g, 0.001 mol), thiourea (0.15 g, 0.002 mol) in methanol (10 mL), 5% aq KOH 2 mL, and basic alumina 2 g was added. The reaction mixture was stirred well; air dried, and subjected to MWI intermittently at 30 s intervals or specified time (Table 1).On completion of reaction, as monitored by TLC, the product was extracted into ethanol (3 × 5 mL). Removal of solvent under reduced pressure yielded the product, which was recrystallized from methanol to give 0.26 g (86%) of **11** as a white solid.

mp 265–268°C; IR (KBr): 3401, 3061, 2363, 1708, 1629, 1553, 1499, 1471, 1433, 1396, 1370, 1272, 1250, 1221, 1166, 1037, 1017 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.42 (t, 3H), 4.66 (q, 2H), 6.35 (s, 2H), 7.74 (s, 1H), 8.26 (s, 1H), 9.11 (s, 1H), 15.62 (s,1H); MS (ESI, *m/z*):302$[M+H]^+$.Anal.Calcd. For $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95. Found: C, 55.70; H, 3.88; N, 14.05.

***5-Ethyl -7-(5-thioxo-4, 5-dihydro-[1, 3, 4] oxadiazol-2-yl)-5-H-[1, 3] di-oxolo [4, 5-g] quinolin-8-one (12).*** *Method A*. A mixture of **8** (0.30 g, 0.0011 mol), $CS_2$ (0.68 g, 0.009 mol), and KOH (0.22 g, 0.004 mol) in ethanol 30 mL was heated under reflux for 10 h, cooled to room temperature, and diluted with water (4 mL) was heated under reflux until the evolution of $H_2S$ had ceased. The reaction mixture was cooled to room temperature, and poured into water and acidification with HCl. The resulting precipitated was filtered and washed with water and recrystallized from methanol to give 0.25 g (71%) of **12**.

*Method B*. To a solution of (**8**) (0.30 g, 0.0011 mol), $CS_2$ (0.68 g, 0.009 mol) and KOH (0.22 g, 0.004 mol) in ethanol 20 mL dissolved in water (4 mL) were added. The reaction mixture was subjected to microwave irradiation in a Pyrex glass round bottle flask attached with water condenser from outside with special arrangement for 4 min (Table 1). On completion of reaction, as monitored by TLC the reaction mixture was cooled to room temperature and poured into water and acidification with HCl. The resulting precipitated was filtered and washed with water and recrystallized from methanol to give 0.3 g (86%) of **12**.

mp 260–263°C; IR (KBr): 3442, 3171, 3050, 2901, 1650,1621, 1595, 1519, 1483, 1392, 1269, 1255, 1230, 1197,1039 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.35 (t, 3H), 4.40 (q, 2H), 6.19 (s, 2H), 7.48 (s, 1H), 7.52 (s, 1H) 8.58 (s, 1H), 11.26 (s, 1H); MS (ESI, *m/z*):318 $[M+H]^+$. Anal.Calcd. for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24. Found: C, 52.88; H, 3.36; N, 13.54.

Caution: Although we did not have any accident in this work, it is highly recommended that the reaction should be performed in an efficient hood.

***In vitro* antibacterial activity**. Minimal inhibitory concentrations (MICs) were determined by means of an agar dilution method, using Mueller Hinton agar plates containing a series of twofold dilutions of drug. Overnight cultures in Mueller Hinton broth were used for precultures of tested strains. MICs were determined after overnight incubation at 37°C, with an inoculum equivalent to 1:100 dilution of an 18 h culture in Mueller Hinton broth (about$10^8$ cells/mL). Each inoculum was seeded onto agar plates by using an inoculum-replicating apparatus and transferred by a 0.005 mL (about $10^4$ cells) calibrated loop. The MIC was the lowest drug concentration that inhibited the development of visible growth on agar plate.

The *in vivo* antibacterial activities of drugs were determined in the systemic infections of mice with bacteria. Ten female Swiss albino mice weighing 18 to 22 g were used for each dose level. Microorganisms grown on Mueller Hinton agar plates were suspended in physiological saline solution. Mice were intraperitoneally challenged with bacteria. Mice infected with *Escherichia coli* ML 4707 were treated at 1 h after infection. Mice infected with *Klebsiella pneumoniae* ML 4730 and *Proteus morganii* ML 4731 were treated, respectively, at 1, 6, and 24 h and then immediately and at 3 h after infection. Drugs to be tested were administered PO. The total number of surviving mice was recorded 1 week after infection, and the

**Table 2**

Biological activity.

| Compound no. | MIC (μg/mL) | $ED_{50}$(PO) (mg/kg bw) |
|---|---|---|
| **4** | 16 | 30 |
| **5** | 0.5 | 4.7 |
| **7** | 256 | >50 |
| **8** | <4 | 15 |
| **9** | >512 | >50 |
| **10** | 256 | >50 |
| **11** | 256 | >50 |
| **12** | 256 | >50 |
| Nalidixic acid | 4.0 | 12.5 |

amount of a single dose (milligrams per kilogram body weight) that gave protection to 50% of the infected mice was estimated as $ED_{50}$ (Table 2).

## REFERENCES AND NOTES

[1] (a) Lesher, G. Y.; Froelich, J. E.; Gruett, M. D.; Bailey, J. H.; Brundage, R. P. J Med Pharma Chem 1962, 5, 1063; (b) Albrecht, R. Prog Drug Res 1977, 21, 9; (c) Radl, S. Cesk Farm 1987, 36, 180.

[2] Loppy, A.; Petit, A.; Hamelin, J.; Texier-Boulet, F.; Jacquault, P.; Mathe, D. Synthesis 1998, 1213.

[3] Varma, R. S Pure Appl Chem 2001, 73, 193.

[4] Harmonised Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures; OECD Series on Testing and Assessment Number 33; ENV/JM/MONO(2001)6; OECD: Paris, 2001.

[5] Oussaid, I.; Thach, N.; Loupy, A. Tetrahedron Lett 1997, 38, 2451.

[6] Tanaka, K.; Toda, F. Chem Rev 2000, 100, 1025.

[7] Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipokowska, Z. Heterocycles 1990, 30, 741.

[8] Caddick, S. Tetrahedron 1995, 51, 10403.

[9] Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Tetrahedron 2001, 57, 9225.

[10] Kappe, C. O. Angew Chem Int Ed Engl 2004, 43, 6250.

[11] CLSI. CLSI document M2-A7, Wayne, PA, 2001.

[12] Turner, F. J.; Ringel, S. M.; Martin, J. F.; Storino, P. J.; Daly, J. M.; Schwartz, B. S. Antimicrob Agents Chemother (Bethesda) 1967, 7, 475.

[13] Nagate, T.; Kurashige, S.; Mitsuhashi, S. Antimicrob Agents Chemother 1980, 17, 203.

[14] Litchfield, J. T.; Wilcoxon, F. J Pharmacol 1948, 92, 99.

[15] Agui, H.; Mitani, T.; Nakashita, M.; Nakagome, T. J Hetrocycl Chem 1971, 8, 357.

[16] Kaminsky, D.; Meltzer, R. I. U.S Pat. 3,172,811 (1965).

[17] Kaminsky, D.; Meltzer, R. I. J Med Chem 1968, 11, 160.

[18] Loubinoux, B.; Colin, J. L.; Thomas, V. Eur J Med Chem 1991, 26(4), 461.

[19] Agui, H.; Nakagome, T. J Hetrocyclic Chem 1976, 13, 765.

# Preparation and Evaluation of Antibacterial Activity of Some New 1,2,4-Triazole Derivatives



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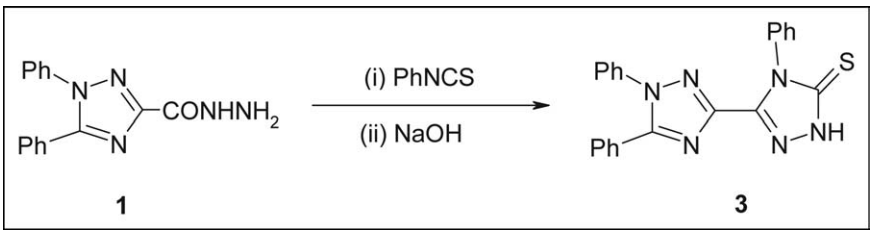


Cyclizations of 1,5-diphenyl[1,2,4]triazole-3-carbohydrazide **1** and the thiosemicarbazide **2** (derived from **1** by addition to phenylisothiocyanate) under various conditions afforded novel biheterocyclic systems. The newly prepared compounds were screened for their antibacterial activity. The results showed that several of these compounds exhibited significant antibacterial activity.

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## INTRODUCTION

Many compounds consisting of five-membered heterocyclic rings such as triazoles, oxazdiazoles, and thiadiazoles were synthesized and evaluated for their biological activities [1–5]. During recent years, microorganisms have increased their resistance against commonly used antibiotics. Therefore, it was crucial to develop new antimicrobial and antiviral compounds [6]. Studies on 1,2,4-triazole compounds have a wide range in the area of pharmacology [7–14]. 4-Thiazolidinones are known to possess antibacterial [15–20], antifungal [21], antiviral [22,23], and antituberculosis [24] properties (Fig. 1).

4-Thiazolidinones have a novel mechanism for action that involves the inhibition of bacterial protein synthesis at a very early stage [25,26]. The traditional method for the preparation of thiazolidinones includes the reaction of an aromatic amine with substituted benzaldehyde in the presence of mercaptoacetic acid [26,27]. In addition, the method reported recently for the synthesis of thiazolidinones involved the reaction of thiosemicarbazides with chloroacetic acid [25]. During the recent years, there has been a broad investigation on different classes of thiadiazoles, many of which were found to possess an extensive spectrum of pharmacological activities [28–32]. Also, 1,2-pyrazole derivatives were found to possess various biological activities [33,34].

The cyclization of relatively small and linear molecules is one of the most common methods leading to the formation of heterocyclic compounds. For example, compounds that contain a thiosemicarbazide structure can be considered as suitable precursors for this purpose [34–37]. The $NH_2$ group of the hydrazide structure behaves as a good nucleophile in most reactions leading to formation of new heterocyclic rings such as 1,2,4-triazoles, 1,3,4-thiadiazoles [37–39].

In view of these facts, hereby we report the preparation of new 1,2,4-triazoles, connected to another heterocyclic ring such as 1,2,4-triazole, 1,3,4-thiadiazole, and 1,3-thiazolidin-4-one rings.

## RESULTS AND DISCUSSION

The structure of the prepared compounds was elucidated using IR, $^1$H NMR, $^{13}$C NMR, and mass spectroscopic methods besides elemental analyses. The pathways leading to the products obtained have been depicted in Schemes 1 and 2. The key intermediate in this study is the 1,5-diphenyl-1*H*-[1,2,4]triazole-3-carboxylic acid hydrazide **1**, which was prepared according to a previously described procedure [40].

Acid hydrazide **1** and thiosemicarbazide **2** are of considerable interest as building blocks for nitrogen and/or sulfur containing heterocyclic systems, which might show biological activities. Therefore, our attempts are to prepare new five-membered heterocycles of expected biological activities utilizing compounds **1** and **2** as starting material.

When compound **1** was refluxed with phenylisothiocyanate, the expected thiosemicarbazide **2** was obtained in good yield. In the IR spectrum of compound **2**, the hydrazone NH stretching frequencies were observed at 3291, 3198, and 3146 $cm^{-1}$. The absorption band at

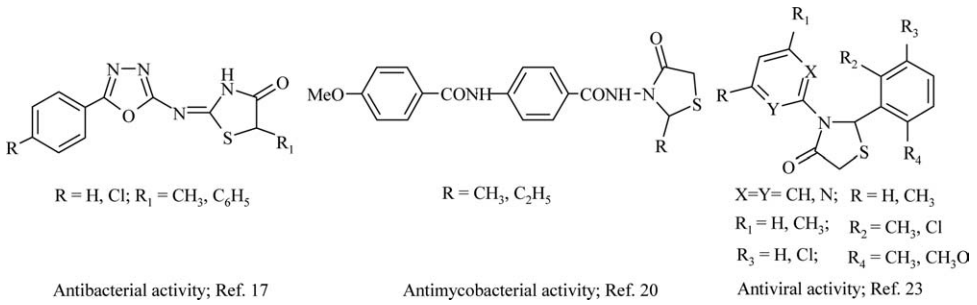
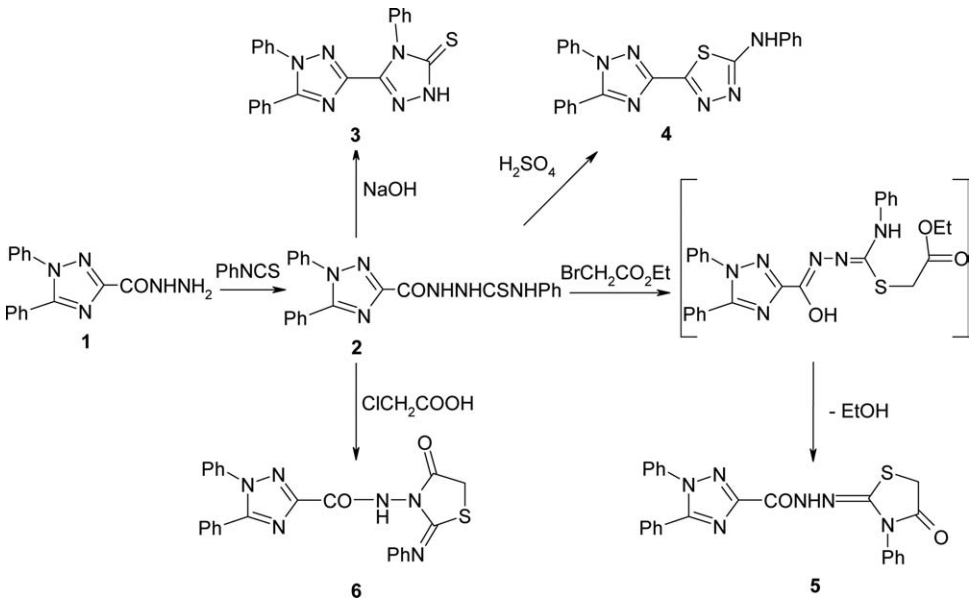


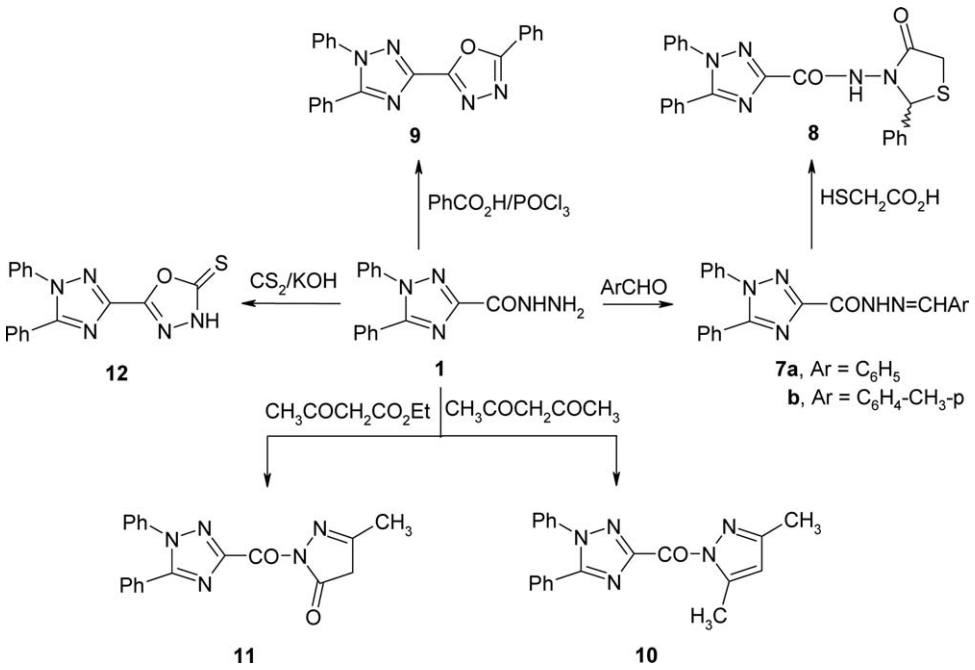

**Figure 1**

1666 $cm^{-1}$ is due to the presence of C=O stretch. The C=S stretching frequency was observed at 1373 $cm^{-1}$. Further evidence for the formation of compound **2** was obtained by recording its mass spectrum. The mass spectrum of **2** showed the molecular ion at *m*/*z* 414 corresponding to $C_{22}H_{18}N_6OS$ and the base peak at *m*/*z* 220. Alkaline cyclization of the thiosemicarbazide **2** using 2*N* sodium hydroxide solution afforded the corresponding 4,1′,5′-triphenyl-1,4-dihydro-1′*H*-[3,3′]bi[1,2,4] triazolyl]-5-thione **3**. This reaction began with nucleophilic attack of thiosemicarbazide N-5 to carbonyl group in the side chain of compound **2**. The structure of compound **3** was confirmed on the basis of elemental analysis, IR, $^1$H NMR, $^{13}$C NMR, and mass spectroscopic methods. It is interesting to note that compound **3** is present in solid state in thionic form, C=S, as indicated by its IR spectrum, which showed the absence of absorption in the region of 2500–2660 $cm^{-1}$ cited for SH group [41] and the presence of maximum at 1455 $cm^{-1}$ characteristic for C=S group. Moreover, in the $^1$H NMR spectrum of compound **3**, NH was observed as singlet at 9.32 ppm, therefore it was proved that compound **3** was found in thionic form also in DMSO. Furthermore, reacting thiosemicarbazide **2** with cold concentrated sulfuric acid resulted in the formation of the corresponding N-phenyl[5-(1,5-diphenyl-1*H*-[1,2,4]triazol-3-yl)-[1,3,4]thiadiazol-2-yl]-amine **4**. The reaction involved the nucleophilic attack of the C=S sulfur atom on the carbonyl C of compound **2**. In the $^1$H NMR spectrum of compound **4** the presence of only one singlet for NH group integrated for one proton confirming the cyclization at the side chain of triazole ring in compound **2** to afford the thiadiazole **4**. Also, the mass spectrum of compound **4** gave molecular ion peak in agreement with its molecular formula. The thiazolidinone derivative **5** was obtained from the treatment of thiosemicarbazide **2** with ethyl bromoacetate in the presence of anhydrous sodium acetate in absolute ethanol. The first

**Scheme 1**



**Scheme 2**




step of this reaction is thought to be an S-alkylation of **2**. The second step is a release of ethanol to give thiazolidinone **5**, the IR spectrum of which showed the lactam C=O stretching band at 1708 $cm^{-1}$. The mass spectrum was also in agreement with the formation of thiazolidinone ring. In an extension of the above reaction to obtain another thiazolidinone derivative **6**, thiosemicarbazide **2** undergoes a ring closure reaction, on boiling in ethanol with monochloroacetic acid. The structure of compound **6** was elucidated on the basis of IR, $^1H$ NMR, and mass spectra as well as correct elemental analysis. The IR of **6** exhibited absorption bands at 3212 due to NH group and at 1719, 1665 $cm^{-1}$ because of two carbonyl groups. $^1H$ NMR of **6** revealed a singlet at 3.62 because of $CH_2$ of thiazolidinone ring and singlet at 9.01 ppm for NH.

Additionally, the condensation of the acid hydrazide **1** with a variety of aromatic aldehydes in ethanol leading to the formation of compounds **7a**, **b**. Structure elucidation of the Schiff's bases **7a**, **b** was based on microanalysis and spectral data (Tables 1 and 2). 1,5-Diphenyl-1*H*-[1,2,4]triazole-3-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide **8** was obtained by refluxing the Schiff's base **7a** and thioglycolic acid in dry benzene for 10 h using a Dean-Stark water separator. The thiazolidinone **8** was characterized by IR absorption bands at

**Table 1**

Analytical data of the new compounds.

| Comp. No. | Molecular formula | mp (°C) | Yield (%) | Elemental analyses found (calcd.) | | | |
|---|---|---|---|---|---|---|---|
| | | | | %C | %H | %N | %S |
| **2** | $C_{22}H_{18}N_6OS$ | 215 | 80 | 63.64 (63.75) | 4.57 (4.38) | 20.11 (20.28) | 7.80 (7.74) |
| **3** | $C_{22}H_{16}N_6S$ | 285 | 84 | 66.77 (66.65) | 3.86 (4.07) | 21.33 (21.20) | 7.86 (8.09) |
| **4** | $C_{22}H_{16}N_6S$ | 179 | 85 | 66.42 (66.65) | 4.24 (4.07) | 21.00 (21.20) | 8.21 (8.09) |
| **5** | $C_{24}H_{18}N_6O_2S$ | 210 | 82 | 63.61 (63.42) | 4.24 (3.99) | 18.35 (18.49) | 7.22 (7.05) |
| **6** | $C_{24}H_{18}N_6O_2S$ | 202 | 78 | 63.57 (63.42) | 3.78 (3.99) | 18.32 (18.49) | 7.15 (7.05) |
| **7a** | $C_{22}H_{17}N_5O$ | 175 | 81 | 72.12 (71.92) | 4.51 (4.66) | 19.13 (19.06) | – |
| **7b** | $C_{23}H_{19}N_5O$ | 187 | 88 | 72.22 (72.42) | 5.00 (5.02) | 18.57 (18.36) | – |
| **8** | $C_{24}H_{19}N_5O_2S$ | 220 | 80 | 65.55 (65.29) | 4.24 (4.34) | 15.59 (15.86) | 7.33 (7.26) |
| **9** | $C_{22}H_{15}N_5O$ | 195 | 68 | 72.47 (72.32) | 4.00 (4.14) | 18.89 (19.17) | – |
| **10** | $C_{20}H_{17}N_5O$ | 240 | 75 | 70.06 (69.96) | 4.82 (4.99) | 20.11 (20.40) | – |
| **11** | $C_{19}H_{15}N_5O_2$ | 225 | 82 | 66.23 (66.08) | 4.16 (4.38) | 20.03 (20.28) | – |
| **12** | $C_{16}H_{11}N_5OS$ | 165 | 74 | 59.63 (59.80) | 3.71 (3.45) | 21.52 (21.79) | 10.14 (9.98) |

**Table 2**

Spectral data for the new compounds.

| Comp. No. | Spectral data |
|---|---|
| **2** | IR (KBr, $cm^{-1}$): 3291, 3198, 3146 (NH), 1666 (C=O), 1604 (C=N) and 1373 (C=S).<br>ms: *m/z* (%): 414 ($M^+$, 15.30). |
| **3** | IR (KBr, $cm^{-1}$): 3129, 1598 (C=N) and 1455 (C=S).<br>$^1$H NMR (DMSO-$d_6$, δ ppm): 7.01–7.48 (15H, m, aromatic protons) and 9.32 (1H, s, NH).<br>$^{13}$C NMR (DMSO-$d_6$, δ ppm): arom-C: [123.8 (2CH), 125.7 (4CH), 126.1 (2CH), 128.0 (1CH), 128.8 (6CH), 135.4 (1C), 137.5 (2C)], 154.0 (C5-triazole ring), 157.4 (C3 & C′3-triazole rings), 181.5 (C=S).<br>ms: *m/z* (%): 396 ($M^+$, 42.10). |
| **4** | IR (KBr, $cm^{-1}$): 3187 (NH) and 1599 (C=N).<br>$^1$H NMR (DMSO-$d_6$, δ ppm): 5.10 (1H, s, NH) and 6.91–7.33 (15H, m, aromatic protons )<br>ms: *m/z* (%): 396 ($M^+$, 13.80). |
| **5** | IR (KBr, $cm^{-1}$): 3330 (NH), 1708 (C=O), 1688 (C=O) and 1612 (C=N).<br>$^1$H NMR (DMSO-$d_6$, δ ppm): 3.67 (2H, s, $CH_2$ of thiazolidinone ring), 7.11–7.42 (15H, m, aromatic protons) and 9.23 (1H, s, NH).<br>ms: *m/z* (%): 454 ($M^+$, 42.71) |
| **6** | IR (KBr, $cm^{-1}$): 3212 (NH), 1719 (C=O), 1665 (C=O) and 1605 (C=N).<br>$^1$H NMR (DMSO-$d_6$, δ ppm): 3.62 (2H, s, $CH_2$ of thiazolidinone ring), 7.05–7.38 (15H, m, aromatic protons) and 9.01 (1H, s, NH).<br>ms: *m/z* (%): 454 ($M^+$, 12.80) |
| **7a** | IR (KBr, $cm^{-1}$): 3242 (NH), 1685 (C=O) and 1601 (C=N).<br>ms: *m/z* (%): 367 ($M^+$, 26.37). |
| **7b** | IR (KBr, $cm^{-1}$): 3222 (NH), 1680 (C=O) and 1589 (C=N).<br>ms: *m/z* (%): 381 ($M^+$, 37.14). |
| **8** | IR (KBr, $cm^{-1}$): 3251 (NH), 1722 (C=O) and 1704 (C=O).<br>$^1$H NMR (DMSO-$d_6$, δ ppm): 3.41 (1H, d, equatorial proton of thiazolidinone at C-5), 3.81 (1H, d, axial proton of thiazolidinone at C-5), 5.68 (1H, s, CH of thiazolidinone at C-2), 7.21–7.35 (15H, m, aromatic protons) and 9.51 (1H, s, NH).<br>$^{13}$C NMR (DMSO-$d_6$, δ ppm): 39.2 (C5-thiazolidinone ring), 55.9 (C2-thiazolidinone ring), arom-C: [124.5 (1CH), 125.0 (2 CH), 126.4 (3CH), 127.5 (3CH), 128.7 (6CH), 136.3 (1C), 137.4 (1C), 138.2 (1C)], 154.5 (C5-triazole ring), 158.4 (C-3 triazole ring), 165.7 (C=O), 167.6 (C4-thiazolidinone ring).<br>ms: *m/z* (%): 441 ($M^+$, 27.08). |
| **9** | IR (KBr, $cm^{-1}$): 1599 (C=N).<br>ms: *m/z* (%): 365 ($M^+$, 30.67). |
| **10** | IR (KBr, $cm^{-1}$): 1670 (C=O).<br>$^1$H NMR (DMSO-$d_6$, δ ppm):1.63, 1.81 (6H, 2s, $2CH_3$), 5.40 (1H, s, C4- pyrazole ring), 6.89–7.24 (10H, m, aromatic protons).<br>$^{13}$C NMR (DMSO-$d_6$, δ ppm): 8.2 ($2CH_3$), 109.6 (C4-pyrazole ring), arom-C: [124.3 (1CH), 125.1 (2 CH), 126.5 (2CH), 127.5 (1CH), 128.3 (4CH), 136.1 (1C), 137.7 (1C)], 149.9 (C3 & C5-pyrazole ring), 154.2 (C5-triazole ring), 159.5 (C-3 triazole ring), 169.6 (C=O).<br>ms: *m/z* (%): 343 ($M^+$, 47.51). |
| **11** | IR (KBr, $cm^{-1}$): 1728 (C=O) and 1688 (C=O).<br>$^1$H NMR (DMSO-$d_6$, δ ppm): 2.01 (3H, s, $CH_3$), 3.26 (2H, s, $CH_2$ of pyrazolone ring) and 7.12–7.37 (10H, m, aromatic protons).<br>ms: *m/z* (%):345 ($M^+$, 52.49). |
| **12** | IR (KBr, $cm^{-1}$): 3321 (NH).<br>$^1$H NMR (DMSO-$d_6$, δ ppm) 6.99–7.50 (10H, m, aromatic protons) and 10.85 (1H, s, NH).<br>ms: *m/z* (%): 321 ($M^+$, 25.47). |

3251, 1722, and 1704 $cm^{-1}$ for NH and the two C=O groups, respectively. Its $^1$H NMR exhibited two signals appearing as doublets at 3.41 ppm and 3.81 ppm because of the nonequivalent geminal $CH_2$ protons [42]. This splitting was not observed with derivatives **5**, **6**, and **11** which may be attributed to the lacking of the asymmetric carbon atom. A convenient method for the preparation of oxadiazole derivative **9** was deduced from refluxing the acid hydrazide **1** with an equimolar amount of benzoic acid in the presence of an excess of phosphorous oxychloride. The IR spectrum of compound **9** showed no absorption for NH groups, this indicating the cyclization of **1** into oxadiazole **9**. Also, the mass spectrum of **9** gave a molecular ion at *m/z* 365 corresponding to $C_{22}H_{15}N_5O$. The hydrazide **1** was allowed to react with acetyl acetone and ethyl acetoacetate to give dimethyl pyrazole derivative **10** and methyl pyrazolone derivative **11**, respectively. The IR of **11** showed absorption band at 1728 $cm^{-1}$ characteristical for the pyrazole carbonyl group. $^1$H NMR spectra of

compounds **10** and **11** showed singlets at 1.81 ppm and 2.01 ppm assigned for the methyl groups, respectively. The preparation of oxadiazole-2-thione **12** was achieved, according to a reported method of Young and Wood [43], by adopting a simple one-pot procedure that involves reacting **1** with carbon disulfide under strong basic conditions followed by acidification with diluted HCl. The oxadiazole derivative **12** was characterized by IR which showed band at 3321 $cm^{-1}$ attributed to NH. The $^1H$ NMR spectrum of **12** displayed the NH resonance of the oxadiazole ring at 10.85 ppm.

## ANTIBACTERIAL STUDIES

The newly prepared compounds were screened for their antibacterial activity against Gram positive (*Bacillus subtitis* and *Streptococci*) and Gram negative (*Klebsiella pneumoniae* and *Escherichia coli*) bacterial strains by the disc diffusion method [44], and the results are summarized in Table 3. The results obtained showed that Schiff's bases **7a** and **7b** were found to be the most active compounds against the employed microorganisms; this is probably due to their ability to increase the penetration in the bacterial cell [45]. In addition, the substituted thiazolidinones **5**, **6**, and **8** as well as the substituted pyrazole **11** exhibited promising activity against both Gram positive and negative bacteria. However, the pyrazole derivative **10** exhibited a low activity against Gram positive only. No satisfactory level of inhibition was observed with the other compounds.

## CONCLUSIONS

This study reports a successful preparation and characterization of new 1,2,4-triazole derivatives. The antibacterial study revealed that, compounds **5**, **6**, **7a**, **7b**, **8**, and **11** showed low to moderate antibacterial activities. This result suggesting that Schiff's base, thiazolidinone, and pyrazole moieties play an important role in enhancing the antibacterial activities of this class of compounds.

**Table 3**

Screening for antibacterial activity of the new compounds (diameter zones of inhibitions in mm).

| | Gram positive | | Gram negative | |
|---|---|---|---|---|
| Comp. No. | *Bacillus subtitis* | *Streptococci* | *Klebsiella pneumoniae* | *Escherichia coli* |
| **3** | – | – | – | – |
| **4** | – | – | – | – |
| **5** | 5 | 10 | 12 | 11 |
| **6** | 9 | 12 | 11 | 10 |
| **7a** | 20 | 23 | 18 | 19 |
| **7b** | 21 | 18 | 20 | 15 |
| **8** | 19 | 23 | 22 | 17 |
| **9** | – | – | – | – |
| **10** | 11 | 12 | – | – |
| **11** | 18 | 10 | 10 | 12 |
| **12** | – | – | – | – |
| Control (DMSO) | – | – | – | – |

## EXPERIMENTAL

**Chemistry.** Melting points were determined in open-glass capillaries on a Stuart electric melting point apparatus and were uncorrected. Elemental analyses were performed by the Microanalysis center, Faculty of Science, Cairo University. Infrared spectra were recorded on Satellite 2000 spectrometer using KBr discs. Mass spectra were determined on GC-MS (QP/000 EX) Shimadzu spectrometer at an ionizing voltage of 70 eV. Nuclear magnetic resonance spectra were recorded on Varin Mercury 300 MHz spectrometer using TMS as an internal standard; chemical shifts are reported in δ units. Solvents were dried by standard procedures. Reaction progress and purity of the compounds were checked by TLC, making use of silica gel plates (Silica gel F254 on aluminum sheets).

***Preparation of thiosemicarbazide 2.*** A solution of **1** (0.01 mol) and equimolar amount of phenylisothiocyanate in 50 mL of ethanol was heated under reflux for 5 h. The solid product obtained after concentration of the solution was collected by filtration and recrystallized from methanol to give yellow crystals.

***Preparation of 4,1′,5′-triphenyl-1,4-dihydro-1′H-[3,3′]bi[[1,2,4]triazolyl]-5-thione 3.*** The thiosemicarbazide **2** (0.01 mol) in sodium hydroxide (2*N*, 15 mL) was refluxed for 8 h. The solution was cooled and neutralized using diluted hydrochloric acid. The formed solid was collected by filtration, washed with water, and recrystallized from methanol to give colorless crystals.

***Preparation of N-phenyl[5-(1,5-diphenyl-1H-[1,2,4]triazol-3-yl)-[1,3,4]thiadiazol-2-yl]-amine 4.*** To an ice-cold stirred solution of thiosemicarbazide **2** (0.01 mol) in absolute ethanol (10 mL), concentrated sulfuric acid (10 mL) was added over a period of 30 min, the stirring was maintained at room temperature for an additional 5 h. Then, the reaction mixture was poured onto ice/water mixture. The solid was filtered off and recrystallized from dioxane to give colorless crystals.

***Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid (4-oxo-3-phenyl-thiazolidin-2-ylidene)-hydrazide 5.*** A mixture of **2** (0.01 mol), ethyl bromoacetate (0.01 mole), and anhydrous sodium acetate (0.03 mol) in ethanol (30 mL) was refluxed for 5 h. The solid product obtained after concentration of the reaction mixture was collected by filtration and recrystallized from methanol to give pale yellow crystals.

***Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid (4-oxo-2-phenylimino-thiazolidin-3-yl)-amide 6.*** A solution of **2** (0.01 mol) in ethanol (30 mL) was treated with monochloroacetic acid (0.01 mol), and the reaction mixture was refluxed for 5 h. The solid product obtained after concentration of the solution was collected by filtration and recrystallized from ethanol to give yellow crystals.

***Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid benzylidene-hydrazide 7a, b.*** A solution of **1** (0.01 mol) and an appropriate aldehyde (0.01 mol) in ethanol (30 mL)

was refluxed for 5 h. The solid separated upon cooling was filtered and recrystallized from dioxane to give yellow crystals.

***Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide 8.*** A mixture of **7a** (0.01 mol) and thioglycolic acid (0.01 mol) was refluxed in dry benzene (75 mL) for 10 h, using a Dean-Stark water separator. The solvent was evaporated, and the reaction mixture was neutralized with cold dilute sodium bicarbonate solution. The formed solid was filtered off, dried, and recrystallized from ethanol to give yellow crystals.

***Preparation of 2-(1,5-diphenyl-1H-[1,2,4]triazol-3-yl)-5-phenyl-[1,3,4]oxadiazole 9.*** A mixture of **1** (0.01 mol) and benzoic acid (0.01 mol) in $POCl_3$ (15 mL) was refluxed for 10 h. The reaction mixture was slowly poured onto ice/water mixture and then neutralized with sodium bicarbonate solution. The solid formed was filtered, washed with water, and recrystallized from ethanol to give pale yellow crystals.

***Preparation of compounds 10 and 11.*** A mixture of **1** (0.01 mol) and acetyl acetone or ethyl acetoacetate (0.01 mol) in ethanol (50 mL) was refluxed for 5 h. The solid product obtained after concentration and cooling of the solution was collected by filtration and recrystallized from dioxane to give yellow crystals.

***Preparation of 5-(1,5-diphenyl-1H-[1,2,4]triazol-3-yl)-3H-[1,3,4] oxadiazole-2-thione 12.*** To a mixture of **1** (0.01 mol) in ethanol (50 mL) was added a solution of potassium hydroxide (0.015 mol) in ethanol (50 mL), followed by carbon disulfide (30 mL). The reaction mixture was refluxed for 20 h. The solid product obtained after cooling and acidification with dilute HCl was collected by filtration and recrystallized from ethanol to give yellow crystals.

**Antibacterial assay.** Antibacterial screening of prepared compounds was done by the paper disc agar diffusion method [44] against Gram positive (*B. subtitis* and *Streptococci*) and Gram negative (*K. pneumoniae* and *E. coli*) strains. The compounds were dissolved in DMSO at a concentration of 1 mg $mL^{-1}$. Antibacterial activity of DMSO against the test microorganisms was investigated and was found to be nil. The nutrient agar medium was sterilized by autoclaving at 120°C for 15 min; the Petri dishes were sterilized in hot air oven at 160°C for an hour. Into each sterilized Petri plate, about 30 mL of molten agar medium inoculated with the respective strain of bacteria (6 mL inoculums to 300 mL of nutrient medium) was transferred. The plates were left at room temperature to allow solidification. Six-millimeter diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37°C. The antibacterial activity was evaluated by measuring the diameter of the inhibition zone. All the experiments were carried out in doublet, and the average value was reported. The antibacterial activity results were summarized in Table 3.

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## REFERENCES AND NOTES

[1] Labanauskas, L.; Udrenaite, E.; Gaideles, P.; Brukstus, A. Il Farmaco 2004, 59, 255.

[2] Karaku, S.; Rollas, S. Il Farmaco 2002, 57, 577.

[3] Sun, S.; Lou, H.; Gao, G.; Fan, P.; Ma, B.; Ge W.; Wang, X. J Pharm Biomed Anal 2004, 34, 1117.

[4] Turan-Zitouni, G.; Kaplancikli, Z. A.; Erol, K.; Kiliç, F. S. Il Farmaco 1999, 54, 218.

[5] Forumadi, A. R.; Mirzaei, M.; Shafiee, A. Il Farmaco 2001, 56, 621.

[6] Dixit, P. P.; Patil, V. J.; Nair, S.; Jain, S.; Sinha, N.; Arora, S. K. Eur J Med Chem 2006, 41, 423.

[7] Van Rhee, A. M.; Diddiqi, S. M.; Melman, N.; Shi, D.; Padgett, W. L.; Daly, J. W.; Jacobson, K. A. J Med Chem 1996, 39, 398.

[8] Yasuma, T.; Oda, T.; Hazama, M.; Taketomi, S. WO 98 09, 958 (1998); Chem Abstr 1998, 128, 217366v.

[9] Mari, S. L. Eur J Med Chem 2009, 44, 827.

[10] İkizler, A.; Demirbaş, N.; İkizler, A. A. J Heterocycl Chem 1996, 33, 1765.

[11] İkizler, A.; Demirbaş, N.; Demirbas, A.; Ikizler, A. A. Pol J Chem 1996, 70, 1114.

[12] İkizler, A. A.; Uçar, F.; Demirbas, N.; Yasa, I.; Demirbas, A.; Genzer, T. Indian J Pharm Sci 1999, 61, 271.

[13] Meo, P.; Noto, R.; Weber, G. J Heterocycl Chem 1993, 30, 765.

[14] Anders, C. J.; Bronson, J. J.; D'Andrea, S. V.; Deshpande, M. S.; Falk, P. J.; Grand-Young, K. A.; Harte, W. E.; Ho, H. T.; Misco, P. F.; Robertson, J. G.; Stock, D.; Sun Y.; Walsh, A. W. Bioorg Med Chem Lett 2000, 10, 715.

[15] Castro, A.; Castano, T.; Encinas, A.; Porcal, W.; Gil, C. Bioorg Med Chem 2006, 14, 1644.

[16] Demirbas, A.; Sahin, D.; Demirbas, N.; Karaoglu, S. A. Eur J Med Chem 2009, 44, 2896.

[17] Kocabalkanli, A.; Ates, Ö.; Ötük, G. Arch Pharm Med Chem 2001, 334, 35.

[18] Bonde, C. G.; Gaikwad, N. J. Bioorg Med Chem 2004, 12, 2151.

[19] Ates, Ö.; Kocabalkanli, A.; Saniş-Ötük, G.; Ekinci, A. C.; Vidin, A. Arzneim Forsch/Drug Res 1997, 47, 1134.

[20] Küçükgüzel, S. G.; Oruç, E. E.; Rollas, S.; Şahin, F.; Özbek, A. Eur J Med Chem 2002, 37, 197.

[21] Fahmy, H. T. Y. Boll Chim Farm 2001, 140, 422.

[22] Barreca, M. L.; Chimirri, A.; De Clercq, E.; Monoforte, A. M.; Monforte, P.; Pannecouque, C.; Zappala, M. Farmaco 2003, 58, 115.

[23] Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Luca, L. D.; Monoforte, A. M.; Monforte, P.; Pannecouque, C.; Zappala, M. Farmaco 2004, 59, 33.

[24] Ulusoy, N. Arzneim Forsch/Drug Res 2002, 52, 565.

[25] Bonde, C. G.; Gaikwad, N. J Bioorg Med Chem 2004, 12, 2151.

[26] Yu, D.; Huiyuan, G. Bioorg Med Chem Lett 2002, 12, 857.

[27] Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. Bioorg Med Chem 2005, 13, 6771.

[28] Srivasta, T.; Haq, W.; Katti, S. B. Tetrahedron 2002, 58, 7619.

[29] Ottana, R.; Maccari, R.; Baccera, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. Bioorg Med Chem 2005, 13, 4243.

[30] Lednicer, D.; Mitscher, L. A.; George, G, I. Organic Chemistry of Drug Synthesis, Vol. 4; Wiley: New York, 1990; p 95.

[31] Rehman, N. Z.; Anwar, C. J.; Ahmed, S. Bull Korean Chem Soc 2005, 26, 1771.

[32] Knadler, M. P.; Bergstrom, R. F.; Callaghan, J. T.; Rubin, A. Drug Metab Dispos 1986, 14, 175.

[33] Kalluraya, B.; Isloor, A. M.; Shenoy, S. Indian J Heterocycl Chem 2001, 11, 159.

[34] Kalluraya, B.; Isloor, A. M.; Priya, F. V.; Jagadeesha, R. L. J Heterocycl Chem 2004, 13, 245.

[35] Varvarasou, A.; Siatra-Papastaikoudi, T.; Tsotunis, A.; Tsatili-Kakoulidou, A.; Vamvakides, A. Il Farmaco 1998, 53, 320.

[36] Reiter, J.; Pongo, L.; Dvortsak, P. J Heterocycl Chem 1987, 24, 1685.

[37] Demirbas, N.; Demirbas, A.; Karaoglu, S. A.; Çelik, E. ARKIVOC 2005, i, 75.

[38] Demirbas, A. Turk J Chem 2004, 28, 311.

[39] Demirbas, N.; Karaoglu, S. A.; Demirbas, A.; Sancak, K. Eur J Med Chem 2004, 39, 793.

[40] Brown, E. J.; Polya, J. B. J Chem Soc 1962, 575.

[41] Güleman, N. N.; Doğan, H. N.; Rollas, S.; Johansson, C.; Çelik, C. Farmaco 2001, 56, 953.

[42] Kücükgüzel, S. G.; Oruç, E. E.; Rollas, J.; Şahin, F.; Özbek, A. Eur J Med Chem 2002, 37, 197.

[43] Young, R. W.; Wood, K. H. J Am Chem Soc 1955, 77, 400.

[44] Cruickshank, R.; Duguid, J. P.; Marmion, R. H. A. Swain, Medicinal Microbiology, 12th ed.; Churchill Livingstone: London, 1975; Vol. II, p 196.

[45] Mahendra, S.; Gorentla, V.; Suresh, K.; Varaprasad, D.; Suresh, T.; Kalyan, C.; Rachit, S. Eur J Med Chem 2007, 42, 807.

# Stereoselective Synthesis of Cyclopropyl Indolyl Ketones with Indolylidene and Arsonium Ylide



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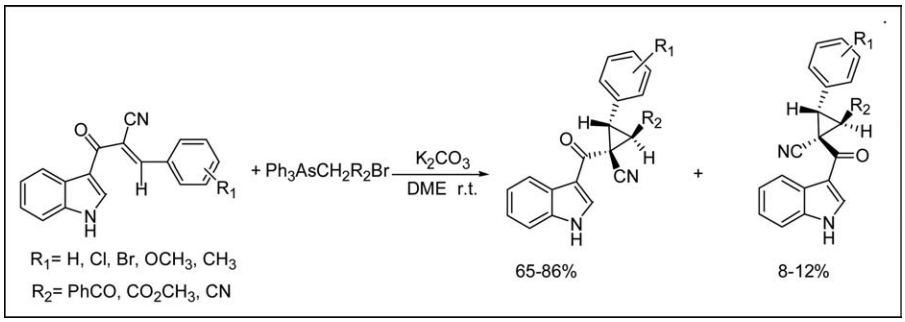


An efficient approach for stereoselective synthesis of cyclopropyl indolyl ketone from olefin and arsonium ylied was achieved. Its advantages are of mild condition, high yield, and good stereoselectivity. In addition, the one-pot cycloproparation of olefins with bromides and triphenylarsine was studied.

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## INTRODUCTION

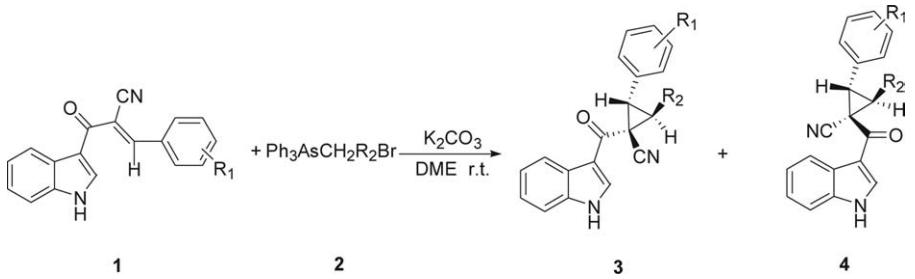
Cyclopropyl ketones occupy an important position in cyclopropane chemistry owing to their wide utility as potent synthetic blocks which have been extensively applied for the synthesis of complex molecules including heterocycles [1]. Therefore, the great efforts have been made to develop new method for synthesis of cyclopropyl ketones [2].

In recent years, the concept of privileged structures, which repeated occurrence in biologically active molecules, become important for the design and synthesis of drug candidates. The indole framework is a versatile and important structural motif frequently found in natural products, pharmaceuticals, and other synthetic compounds [3]. Thus, it is not surprising that a great deal of attention has been directed to development of efficient routes for the synthesis of these interesting compounds. Now, we become interested in the design and synthesis of the cyclopropyl indolyl ketones. Because of their unique ring strain and high reactivity, these novel cyclopropanes may serve as new and useful building blocks for construction of complex indoles. To the best of our knowledge, no approaches have been previously reported for synthesis of cyclopropyl indolyl ketones. Here, we report an effect procedure for preparation of cyclopropyl indolyl ketones *via* cyclopreparation of indolylidene with arsonium ylide (Scheme 1).

The needed indolylidenes were prepared according to the reported literature [4]. We tested some bases first. In the model experiment, a mixture of indolylidene **1a** (1 equiv), benzoylmethyltriphenylarsonium bromide **2a** (1.1 equiv) and base (3 equiv) in dimethoxyethane (DME) was stirred at room temperature to give compound **3a** and **4a**. The results showed that the $K_2CO_3$ as base provided the highest yield (entry 1, Table 1). And then, the screening for a suitable solvent was performed in the presence of $K_2CO_3$ at room temperature. It was found that DME was the best solvent for this reaction. The results were listed in Table 1. At the same time, the results in Table 1 also showed that bases, solvents, and temperature have no obvious influence on the ratio of product **3** and **4**.

To investigate the scope of this reaction, some indolyldienes and arsenium salts are examined with the optimized conditions and the results are shown in Table 2. It is worth noting that only compounds **3e–k** were obtained (entries 6–11, Table 2), when methoxycarbonylmethyltriphenylarsonium bromide and cyanomethyltriphenylarsonium bromide were used as arsonium salts instead of benzoylmethyltriphenylarsonium bromide.

**Scheme 1**




1 2 3 4

The structures of compounds **3a–k** and **4a–d** were characterized by $^1$H NMR, $^{13}$C NMR, MS, IR, elemental analysis, and X-ray diffraction (Fig. 1; Table 3). The relative configurations of product **3** and **4** are confirmed from NOE experiments of compounds **3b** (Fig. 2) and **4b** (Fig. 3). The cyclopropyl hydrogen with a trans configuration is deduced by the absence of NOE correlation between two protons situated at adjacent carbons in the cyclopropane ring of these compounds.

One-pot methodology has recently attracted increasing attention. Because it offers significant advantages such as a reduction in the number of synthetic steps, energy consumption and waste production, and high efficiency [5]. Thus, considerable efforts have been taken in developing new one-pot process. Our attention turned next to one-pot cyclopropanation reaction with triphenylarsine and bromide. (Scheme 2).

Initial studies focused on screening the optimum reaction conditions, in the model experiments, a mixture of triphenylarsine **6** (0.1 equiv), methyl bromoacetate **5** (1.2 equiv), indolyidiene **1** (1.0 equiv), and bases (3.0 equiv) in solvent (5 mL) was stirred under reflux. The results are shown in Table 4. We found that the highest yield of cyclopropane **3f** was obtained in acetonitrile/$K_2CO_3$ system (entry 2, Table 4). Then, the amount of $Ph_3As$ was tested under the similar condition. Through an effort to investigate the reaction condition, we chose 0.75 equiv of $Ph_3As$ /acetonitrile/$K_2CO_3$ system as the optimum reaction condition. Because the amount of triphenylarsine changes from 0.75 equiv to 1 equiv, the differences in the yield and rate of cyclopropanation are not significant (entries 10 and 11, Table 4).

The scope of the one-pot of cyclopropanation with indolyidienes and bromides in the presence of trephenylarsine was further explored. The results are shown in Table 5.

A plausiblemechanism for the formation of product **3** and **4** is shown in Scheme 3. (1) The arsonium yilde **B** is generated from arsonium salt **A** with $K_2CO_3$ as base. (2) The ylide **B** nucleophilically attacks the olefin **C** to result in either transition state **D** or **E**. Apparently, the **E** should be favored over **D**, with the latter being higher energy given the steric repulsion between bulky X and Ar groups in the conformation of **D**. (3) The six-membered ring, locking conformation of intermediate **F**, is formed by nonbonding interactions between the negatively polarized oxygen in enolate ion and positively polarized X group, and the product **3** is given *via* cyclopropanation reaction. (4) When the X is benzoyl group, the intermediate **G** is formed due to the steric repulsion between bulky benzoyl and indolyl groups, and then the product **4** is yielded from **G**.

In conclusion, we have developed an efficient approach for stereoselective synthesis of cyclopropyl indolyl ketone from olefin and arsonium ylied. The advantages of this approach are of mild condition, high yield, and good stereoselectivity. In addition, the one-pot cycloproparation of olefins with bromides and triphenylarsine was also studied.

**Table 1**

Optimization of reaction condition of indolylidene with arsonium salt.

| Entry | $R_1$ | $R_2$ | Base | Solvent | Temperature (°C) | Time (h) | Yield (%) **3** | Yield (%) **4** |
|---|---|---|---|---|---|---|---|---|
| 1 | 4-Cl | COPh | $K_2CO_3$ | DME | r.t. | 2 | 68 | 12 |
| 2 | 4-Cl | COPh | $KF.2H_2O$ | DME | r.t. | 4 | 60 | 15 |
| 3 | 4-Cl | COPh | $NaHCO_3$ | DME | r.t. | 28 | 58 | 14 |
| 4 | 4-Cl | COPh | $K_2CO_3$ | chloroform | r.t. | 3.5 | 56 | 14 |
| 5 | 4-Cl | COPh | $K_2CO_3$ | acetonitrile | r.t. | 2.5 | 60 | 18 |
| 6 | 4-Cl | COPh | $K_2CO_3$ | DME | 0 | 4.5 | 67 | 15 |
| 7 | 4-Cl | COPh | $K_2CO_3$ | DME | −15 | 6 | 68 | 15 |

DME, dimethoxyethane.

**Table 2**

Synthesis of cyclopropyl indolyl ketones with indolyldienes and arsenium salts.

| Entry | Product | R1 | R2 | Reaction time (h) | Yield **3**(%)[a] | Yield **4**(%)[a] |
|---|---|---|---|---|---|---|
| 1 | **a** | H | COPh | 2 | 71 | 10 |
| 2 | **b** | 4-Cl | COPh | 2 | 68 | 12 |
| 3 | **c** | 3-Br | COPh | 1.5 | 73 | 8 |
| 4 | **d** | 4-$OCH_3$ | COPh | 2 | 65 | 12 |
| 5 | **e** | H | $CO_2CH_3$ | 3 | 76 | 0 |
| 6 | **f** | 4-Cl | $CO_2CH_3$ | 3 | 85 | 0 |
| 7 | **g** | 3-Br | $CO_2CH_3$ | 3.5 | 72 | 0 |
| 8 | **h** | 4-$CH_3$ | $CO_2CH_3$ | 3 | 79 | 0 |
| 9 | **i** | 4-$OCH_3$ | $CO_2CH_3$ | 4 | 70 | 0 |
| 10 | **j** | H | CN | 1 | 78 | 0 |
| 11 | **k** | 4-Cl | CN | 1.5 | 85 | 0 |

[a]Isolated yield

## EXPERIMENTAL

**General Experimental Conditions.** All reagents and solvents were obtained from commercial sources and used without purification. All melting points were uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. $^1$H NMR spectra were recorded at a Bruker AM-500, using $CD_3COCD_3$ as solvent and TMS as internal reference. Mass spectra were taken with a HP5989A mass spectrometer at an ionizing voltage of 70 eV. Elemental analyses were measured on the elementar vario EL III. X-Ray crystal data were collected with Bruker Smart Apex2 CCD

**General procedure for preparing 3a–k and 4a–d.** A mixture of indolylidene 1 (1 mmol), arsonium bromide **2** (1.1 mmol) and $K_2CO_3$ (0.414 g, 3 mmol) in dimethoxyethane (DME) (5 mL) was stirred at room temperature. The completion of the reaction was determined by TLC. The DME was removed off under reduced pressure, and the residue was run on a silica-gel chromatographic column (eluant: petroleum ether–ethyl acetate (v: v = 6:1)). The desired products **3** and **4** can be obtained and triphenylarsine recovered, respectively.

**General procedure of one-pot method for 3a–k and 4a–d.** A mixture of indolyidiene 1 (1 mmol), bromide **5** (1.2 mmol), triphenylarsine 6 (0.225 g, 0.75 mmol), and $K_2CO_3$ (0.414 g, 3 mmol) was stirred in the refluxing $CH_3CN$ (5 mL). The completion of the reaction was determined by TLC.The $CH_3CN$ was removed off under reduced pressure, and the residue was run on a silica-gel chromatographic column (eluant: petroleum ether–ethyl acetate (v: v = 6:1)). The desired products **3** and **4** can be obtained and triphenylarsine recovered, respectively.

***Trans-2-benzoyl-1-(1H-indole-3-carbonyl)-3-phenyl-cyclopropanecarbonitrile (3a).*** This compound was obtained as white solid, mp 110–111°C (petroleum ether–ethyl acetate (v:v = 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 4.03 (d, $J$ = 8.0 Hz, 1H), 4.56 (d, $J$ = 8.0 Hz 1H), 7.22-7.28 (m, 2H), 7.41–7.42 (m,1H), 7.44–7.57 (m, 5H), 7.64–7.69 (m, 3H), 8.19–8.21 (m, 3H), 8.44 (s, 1H), 11.21 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 36.0, 37.3, 38.0, 113.1, 115.7, 118.7, 122.7, 123.5, 124.6, 126.9, 129.1, 129.3, 129.4, 129.6, 134.4, 134.6, 135.3, 137.6, 137.8, 180.6, 192.3; IR

**Table 3**

Selected bond lengths and bond angels of compound **3f**.

| Compound **3f** | Lengths (A) | Angels(deg) |
|---|---|---|
| C(4)-C(7) | 1.482(4) | |
| C(7)-C(9) | 1.510(4) | |
| C(7)-C(8) | 1.509(4) | |
| C(8)-C(10) | 1.475(4) | |
| C(8)-C(9) | 1.527(4) | |
| C(9)-C(12) | 1.450(4) | |
| C(9)-C(13) | 1.535(4) | |
| C(9)-C(7)-C(8) | | 60.75(19) |
| C(7)-C(8)-C(9) | | 59.65(18) |
| C(7)-C(9)-C(8) | | 59.60(19) |
| C(5)-C(4)-C(7) | | 123.2(3) |
| C(3)-C(4)-C(7) | | 118.8(3) |
| C(4)-C(7)-C(9) | | 122.9(2) |
| C(4)-C(7)-C(8) | | 124.1(2) |
| C(10)-C(8)-C(7) | | 117.9(3) |
| C(10)-C(8)-C(9) | | 118.9(3) |
| C(12)-C(9)-C(7) | | 116.2(2) |
| C(12)-C(9)-C(8) | | 114.9(2) |
| C(7)-C(9)-C(13) | | 120.0(2) |
| C(12)-C(9)-C(13) | | 113.2(2) |
| C(8)-C(9)-C(13) | | 122.9(2) |

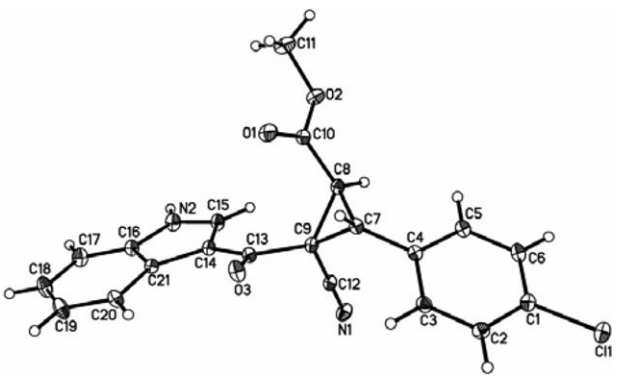



**Figure 1.** X-ray crystal structure of **3f**.

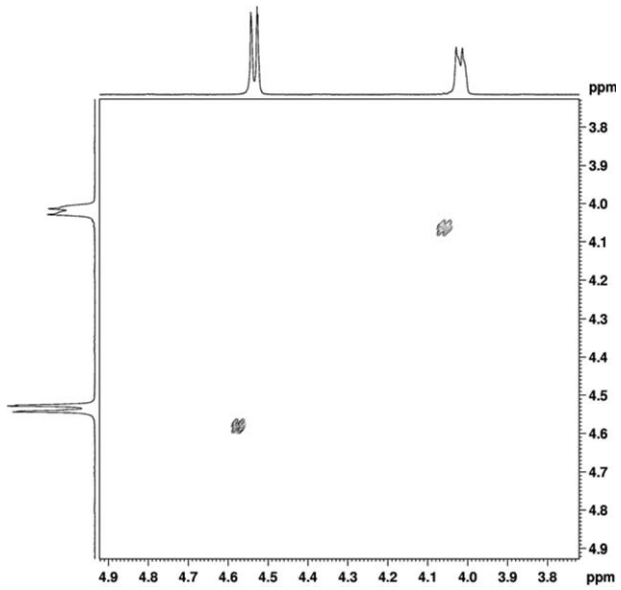



**Figure 2.** NOE spectrum of compound **3a**.

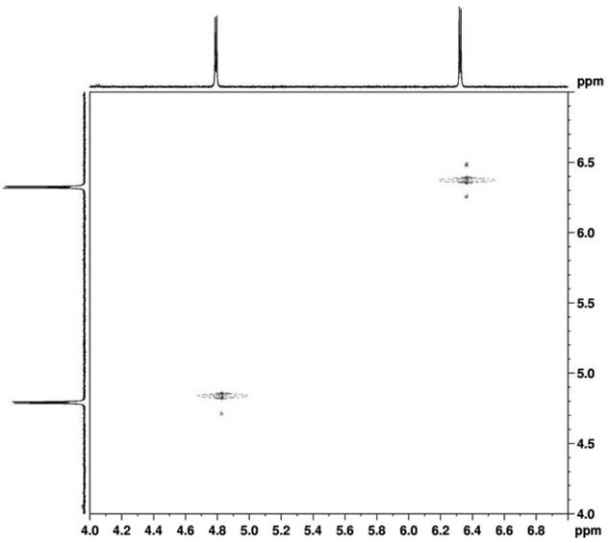



**Figure 3.** NOE spectrum of compound **3b**.

(potassium bromide): 3356, 2234 (CN), 1679 (CO), 1642 (CO), 1423, 750 $cm^{-1}$; ms (m/z) (%): 390 ($M^+$, 16), 388 (100); Anal. calcd. for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.15; H, 4.87; N, 6.96.

***Trans-2-benzoyl-1-(1H-indole-3-carbonyl) -3-(4-chlorophenyl)-cyclopropanecarbonitrile (3b).*** This compound was obtained as white solid, mp 112–113°C (petroleum ether–ethyl acetate (v:v =1:1) ); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 4.03 (d, $J$ = 8.0 Hz, 1H), 4.56 (d, $J$ = 8.0 Hz 1H), 7.21–7.24 (m, 2H), 7.51–7.57 (m, 5H), 7.64–7.67 (m, 1H), 7.71–7.72 (m, 2H), 8.16–8.20 (m, 3H), 8.43 (s, 1H), 11.22 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 35.2, 37.2, 38.1, 113.1, 115.6, 118.6, 122.7, 123.5, 124.7, 126.9, 129.4, 129.6, 129.7, 131.2, 133.6, 134.5, 134.6, 135.4, 137.6, 137.7, 180.4, 192.1; IR (potassium bromide): 3366, 2234 (CN), 1679 (CO), 1641 (CO), 1423, 751 cm-$^1$; ms (m/z) (%): 426 ($M^+$ +1, 1), 425 ($M^+$, 4), 319 (100); Anal. calcd. for $C_{26}H_{17}ClN_2O_2$: C, 73.50; H, 4.03; N, 6.59. Found: C, 73.32; H, 4.23; N, 6.81.

***Trans-2-benzoyl-1-(1H-indole-3-carbonyl) -3-(3-bromo-phenyl)-cyclopropanecarbonitrile (3c).*** This compound was obtained as white solid, mp 214–215°C (petroleum ether–ethyl acetate (v:v = 1:1); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 4.05 (d, $J$ = 8.0 Hz, 1H), 4.64 (d, $J$ = 8.0 Hz 1H), 7.21–7.28 (m, 3H), 7.44–7.47 (m, 3H), 7,51–7.52 (m, 1H), 7.54–7.57 (m, 1H), 7.60–7.67 (m, 1H), 7.70–7.72 (m, 1H), 7.90–8.21 (m, 3H), 8.43 (s, 1H), 11.21 (br s 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 35.1, 37.2, 38.0, 113.1, 115.6, 118.5, 122.7, 123.2, 123.5, 124.7, 126.9, 128.7, 129.4, 129.6, 131.5, 132.1, 132.2, 134.5, 135.4, 137.4, 137.6, 137.7, 180.3, 192.0. IR (potassium bromide): 3352, 2236 (CN), 1675 (CO), 1615 (CO), 1433, 746 $cm^{-1}$; ms (m/z) (%): 471 ($M^+$ +2, 1), 470 ($M^+$ +1, 4), 469 ($M^+$, 2), 105 (100). Anal. calcd. for $C_{26}H_{17}BrN_2O_2$: C, 66.54; H, 3.65; N, 5.97. Found: C, 66.20 ; H, 3.74; N, 5.87.

***Trans-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(4-methoxy-phenyl)-cyclopropanecarbonitrile (3d).*** This compound was obtained as white solid, mp 161°C (petroleum ether–ethyl acetate (v:v = 1:1) ); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.85 (s, 3H), 3.94 (d, $J$ = 8.0 Hz, 1H), 4.44 (d, $J$ = 8.0 Hz 1H), 7.03–7.05 (m, 2H), 7.20–7.27 (m, 2H), 7.51–7.53 (m,1H), 7.54–7.64 (m, 2H), 7.66–7.67 (m, 3H), 8.15–8.19 (m, 3H), 8.43 (s, 1H), 11.20 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 35.8, 37.3, 38.3, 55.6, 113.1, 115.0, 115.8, 118.9, 122.7, 123.5, 124.6, 126.3, 126.9, 129.4, 129.6, 130.6, 134.4, 135.3, 137.6, 137.9, 160.7, 181.0, 192.4; IR (potassium bromide): 3220, 2233 (CN), 1677 (CO), 1637 (CO), 1425, 750 $cm^{-1}$; ms (m/z) (%): 420 ($M^+$, 7), 315 (100); Anal. calcd. for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 76.95; H, 4.98; N, 6.47.

**Scheme 2**

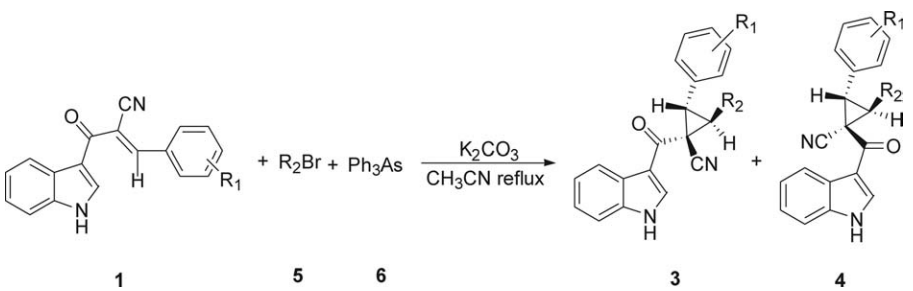


**Table 4**

Optimization of one-pot cyclopropanation reaction condition.

| Entry | $R_1$ | $R_2$ | Base | Solvent | Triphenylarsine (equiv) | Temp (°C ) | Time (h) | Yield **3f**(%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | chloroform | 0.1 | reflux | 48 | 47 |
| 2 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | acetonitrile | 0.1 | reflux | 3 | 55 |
| 3 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | DME | 0.1 | reflux | 2.5 | 45 |
| 4 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | nitromethane | 0.1 | reflux | | 0 |
| 5 | 4-Cl | $CO_2CH_3$ | $NaHCO_3$ | acetonitrile | 0.1 | reflux | 40 | 38 |
| 6 | 4-Cl | $CO_2CH_3$ | $KF.2H_2O$ | acetonitrile | 0.1 | reflux | 48 | ? |
| 7 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | acetonitrile | 0.05 | reflux | 7 | 40 |
| 8 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | acetonitrile | 0.25 | reflux | 2.5 | 63 |
| 9 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | acetonitrile | 0.5 | reflux | 2.5 | 66 |
| 10 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | acetonitrile | 0.75 | reflux | 2 | 72 |
| 11 | 4-Cl | $CO_2CH_3$ | $K_2CO_3$ | acetonitrile | 1 | reflux | 2 | 75 |

***Trans-1,3-dihydro-2-cyano-2-(1H-indole-3-carbonyl)-3-phenyl-cyclopropanecarboxylic acid methyl ester (3e).*** This compound was obtained as white solid, mp 165–166°C (petroleum ether–ethyl acetate (v:v = 1:1) ); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.56 (d, $J$ = 8.0 Hz, 1H), 3.57 (s, 3H), 3.78 (d, $J$ = 8.0 Hz 1H), 7.28–7.33 (m, 2H), 7.40–7.43 (m, 1H), 7.46–7.49 (m, 2H), 7.55–7.60 (m, 3H), 8.26-8.28 (m, 1H), 8.46 (s, 1H), 11.33 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 34.5, 34.8, 34.9, 52.9, 113.2, 115.6, 118.3, 122.7, 123.6, 124.8, 126.9, 129.1, 129.2, 129.6, 134.0, 135.4, 137.8, 168.0, 180.4; IR (potassium bromide): 3400, 2241 (CN), 1730 (CO), 1660 (CO), 1425, 755 cm$^{-1}$; ms (m/z) (%): 345 ($M^+$ +1, 4), 344 ($M^+$, 24), 285 (100); Anal. calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 72.98; H, 4.89; N, 8.42.

***Trans-1,3-dihydro-3-(4-chlorophenyl)-2-cyano-2-(1H-indole-3-carbonyl)-cyclopropanecarboxylic acid methyl ester (3f).*** This compound was obtained as white solid, mp 226–227°C (petroleum ether–ethyl acetate (v:v = 1:1) ); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (s, 3H), 3.60 (d, $J$ = 8.0 Hz, 1H), 3.80 (d, $J$ = 8.0 Hz 1H), 7.28–7.33 (m, 2H), 7.49–7.51 (m, 2H), 7.58–7.60 (m, 3H), 8.26–8.28 (m, 1H), 8.48 (s, 1H), 11.34 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 34.2, 34.7, 34.8, 52.9, 113.2, 115.5, 118.2, 122.6, 123.6, 124.8, 126.9, 129.7, 131.0, 133.1, 134.6, 135.5, 137.7, 167.8, 180.0; IR (potassium bromide): 3399, 2241 (CN), 1733 (CO), 1657 (CO), 1426, 753 cm$^{-1}$; ms (m/z) (%): 379 ($M^+$ +1, 10), 378 ($M^+$, 22), 319 (100); Anal. calcd. for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.49; H, 4.09; N, 7.53.

***Trans-1,3-dihydro-3-(4-bromophenyl)-2-cyano-2-(1H-indole-3-carbonyl)-cyclopropanecarboxylic acid methyl ester (3g).*** This compound was obtained as white solid, mp 231–232°C (petroleum ether–ethyl acetate (v:v= 1:1) ); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (s, 3H), 3.67 (d, $J$ = 8.0 Hz, 1H), 3.80 (d, $J$ = 8.0 Hz 1H), 7.28–7.33 (m, 2H), 7.42–7.45 (m, 1H), 7.58–7.61 (m, 3H), 7.77–7.78 (m, 1H). 8.26–8.27 (m, 1H), 8.48 (s, 1H), 11.34 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 34.2, 34.6, 34.8, 52.9, 113.2, 115.5, 118.1, 122.6, 123.2, 123.6, 124.8, 126.9, 128.4, 131.6, 132.1, 132.2, 135.5, 136.8, 137.7, 167.7, 180.0; IR (potassium bromide): 3395, 2242 (CN), 1728 (CO), 1657 (CO), 1426, 753 cm$^{-1}$; ms (m/z) (%): 425 ($M^+$ +2, 4), 424 ($M^+$ +1, 18), 423 ($M^+$, 5), 365 (100), 363 (100); Anal. calcd. for $C_{21}H_{15}BrN_2O_3$: C, 59.59; H, 3.57; N, 6.62. Found: C, 59.75; H, 3.81; N, 6.40.

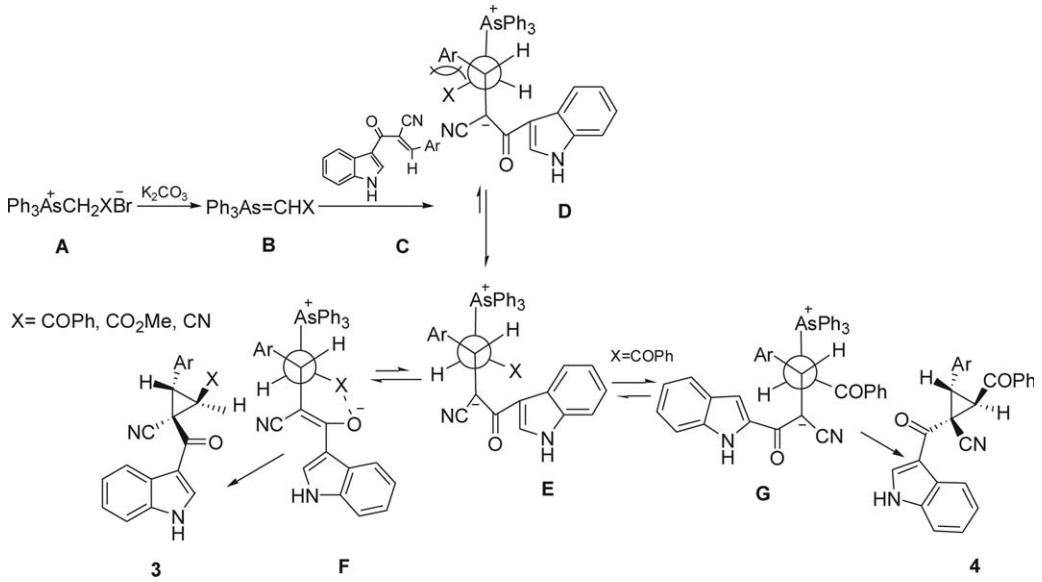
***Trans-1,3-dihydro-2-cyano-2-(1H-indole-3-carbonyl)-3-(4-methylphenyl)-cyclopropanecarboxylic acid methyl ester (3h).*** This compound was obtained as white solid, mp 203–204°C (petroleum ether–ethyl acetate (v:v = 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 2.36 (s, 3H), 3.51 (d, $J$ = 7.5 Hz, 1H), 3.59 (s, 3H), 3.73 (d, $J$ = 7.5 Hz 1H), 7.23–7.33 (m, 4H), 7.42–7.44 (m, 2H), 7.58–7.60 (m, 1H), 8.26–8.28 (m, 1H), 8.46 (s, 1H), 11.31 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone) δ 21.1, 34.5, 34.8, 34.9, 52.8, 113.2, 115.6, 118.4, 122.7, 123.6, 124.7, 126.9, 129.1, 130.3, 131.0, 135.4, 137.8, 138.9, 168.0, 180.5; IR (potassium bromide): 3398, 2240 (CN), 1732 (CO), 1658 (CO), 1426, 754 cm$^{-1}$; ms (m/z)

**Table 5**

Cyclopropanation of olefin with triphenylarsine and bromide *via* one-pot reaction.

| Entry | Product | R1 | R2 | Reaction time (h) | Yield **3**(%) | Yield **4**(%) |
|---|---|---|---|---|---|---|
| 1 | **a** | H | COPh | 2 | 48 | 5 |
| 2 | **b** | 4-Cl | COPh | 2 | 58 | 7 |
| 3 | **c** | 3-Br | COPh | 2.5 | 55 | 5 |
| 4 | **d** | 4-$OCH_3$ | COPh | 3 | 50 | 8 |
| 5 | **e** | H | $CO_2CH_3$ | 3.5 | 65 | 0 |
| 6 | **f** | 4-Cl | $CO_2CH_3$ | 2 | 72 | 0 |
| 7 | **g** | 3-Br | $CO_2CH_3$ | 5 | 68 | 0 |
| 8 | **h** | 4-$CH_3$ | $CO_2CH_3$ | 6 | 60 | 0 |
| 9 | **i** | 4-$OCH_3$ | $CO_2CH_3$ | 4.5 | 66 | 0 |
| 10 | **j** | H | CN | 7 | 30 | 0 |
| 11 | **k** | 4-Cl | CN | 15 | 35 | 0 |

**Scheme 3**




(%): 358 ($M^+$, 26), 299 (100); Anal. calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.92; H, 4.88; N, 7.57.

***Trans-1,3-dihydro-2-cyano-2-(1H-indole-3-carbonyl)-3-(4-methoxyphenyl)-cyclopropanecarboxylic acid methyl ester (3i).*** This compound was obtained as white solid, mp 196–197°C (petroleum ether–ethyl acetate (v:v= 1:1) ); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.49 (d, $J$ = 8.0 Hz 1H), 3.60 (s, 3H), 3.72 (d, $J$ = 8.0 Hz, 1H), 3.83 (s, 3H), 7.00–7.03 (m, 2H), 7.27–7.32 (m, 2H), 7.46–7.49 (m, 2H), 7.57–7.60 (m, 1H), 8.26–8.28 (m, 1H), 8.46 (s, 1H), 11.31 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 34.6, 34.7, 52.8, 55.6, 113.1, 113.2, 115.0, 115.6, 118.5, 122.6, 123.6, 124.7, 125.7, 126.9, 130.4, 135.4, 137.7, 160.7, 168.1, 180.6; IR (potassium bromide): 3340, 2239 (CN), 1731 (CO), 1658 (CO), 1427, 753 $cm^{-1}$; ms (m/z) (%): 374 ($M^+$, 48), 315 (100); Anal. calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.35; H, 5.02; N, 7.21.

***Trans-2,3-dihydro-1-(1H-indole-3-carbonyl)-3-phenyl-cyclopropane-1,2-dicarbonitrile (3j).*** This compound was obtained as white solid, mp 193–194°C (petroleum ether–ethyl acetate (v:v= 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (d, $J$ = 9.0 Hz 1H), 3.64 (d, $J$ = 9.0 Hz, 1H), 7.30–7.34 (m, 2H), 7.45–7.48 (m, 1H), 7.50–7.53 (m, 2H), 7.63–7.64 (m, 1H), 7.71–7.72 (m, 2H), 8.29–8.31 (m, 1H), 8.86 (s, 1H), 11.45 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 20.5, 32.3, 37.0, 113.3, 115.0, 115.8, 117.6, 122.9, 123.8, 124.9, 127.4, 129.7, 129.8, 130.4, 131.8, 135.7, 137.4, 180.0; IR (potassium bromide): 3278, 2245 (CN), 1615 (CO), 1425, 753 $cm^{-1}$; ms (m/z) (%): 311($M^+$, 100); Anal. calcd. for $C_{20}H_{13}N_3O$: C, 77.16; H, 4.21; N, 13.50. Found: C, 77.39; H, 4.57; N, 13.30.

***Trans-2,3-dihydro-3-(4-chlorophenyl)-1-(1H-indole-3-carbonyl)-cyclopropane-1,2-dicarbonitrile (3k).*** This compound was obtained as white solid, mp 201–202°C (petroleum ether–ethyl acetate (v:v = 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (d, $J$ = 9.0 Hz 1H), 3.66 (d, $J$ = 9.0 Hz, 1H), 7.29–7.35 (m, 2H), 7.55–7.57 (m, 2H), 7.62–7.64 (m, 1H), 7.74–7.76 (m, 2H), 8.28–8.30 (m, 1H), 8.60 (s, 1H), 11.46 (br s, 1H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 20.8, 32.3, 36.2, 113.3, 115.1, 115.7, 117.5, 122.9, 123.9, 125.0, 127.4, 129.8, 130.8, 132.2, 135.3, 135.7, 137.4, 180.0; IR (potassium bromide): 3350, 2244 (CN), 1602 (CO), 1435, 751 $cm^{-1}$; ms (m/z) (%): 346 ($M^+$ +1, 33), 345 ($M^+$, 85), 144 (100); Anal. calcd. for $C_{20}H_{12}ClN_3O$: C, 59.59; H, 3.57; N, 6.62. Found: C, 59.81; H, 3.29; N, 6.49.

***Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-phenyl-cyclopropanecarbonitrile (4a).*** This compound was obtained as white solid, mp 220–221°C (petroleum ether–ethyl acetate (v:v = 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 4.97 (d, $J$ = 5.0 Hz, 1H), 6.32 (d, $J$ = 5.0 Hz 1H), 7.12–7.15 (m, 2H), 7.23–7.26 (m, 3H), 7.37–7.40 (m, 1H), 7.44–7.47 (m, 3H), 7.56–7.62 (m, 2H), 7.72–7.75 (m, 1H), 8.01–8.07 (m, 2H), 8.29 (s, 1H), 11.15 (br s, 1 H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 51.0, 79.8, 89.8, 104.4, 112.1, 117.3, 121.2, 121.6, 122.9, 125.2, 127.8, 128.0, 128.9, 129.0, 129.1, 129.2, 134.0, 134.2, 136.3, 140.9, 165.7, 193.3. IR (potassium bromide): 3292, 2196 (CN), 1706 (CO), 1610 (CO), 1163, 745 $cm^{-1}$; ms (m/z) (%): 390 ($M^+$, 20), 285 (100); Anal. calcd. for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.12; H, 4.80; N, 6.93.

***Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(4-chlorophenyl)-cyclopropanecarbonitrile (4b).*** This compound was obtained as white solid, mp 212–213°C (petroleum ether–ethyl acetate (v:v = 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 4.85 (d, $J$ = 5.0 Hz, 1H), 6.34 (d, $J$ = 5.0 Hz 1H), 7.12–7.15 (m, 1H), 7.22–7.26 (m, 1H), 7.50 (s, 4H), 7.56–7.58 (m, 1H), 7.60–7.63 9m, 2H), 7.72–7.76 (m, 1H), 7.99–7.80 (m, 1H), 8.00–8.09 (m, 2H), 8.29 (s, 1H), 11.17 (br s, 1 H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 51.1, 80.3, 90.4, 105.2, 113.1, 118.0, 122.1, 122.5, 123.9, 126.0, 129.8, 130.0130.1, 130.2, 130.5, 134.2, 134.9, 135.0, 137.2, 140.7, 166.8, 194.0; IR (potassium bromide) 3265, 2202 (CN), 1703 (CO), 1611(CO), 1162, 747 $cm^{-1}$.; ms (m/z) (%):426 ($M^+$ +1, 5), 425 ($M^+$, 6), 105 (100); Anal. calcd. for $C_{26}H_{17}ClN_2O_2$: C, 73.50; H, 4.03; N, 6.59. Found: C, 73.29; H, 4.26; N, 6.79.

***Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(3-bromophenyl)-cyclopropanecarbonitrile (4c).*** This compound was obtained as white solid, mp 194–195°C (petroleum ether–ethyl acetate (v:v= 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 4.88 (d, $J$ = 5.0 Hz, 1H), 6.39 (d, $J$ = 5.0 Hz 1H), 7.11–7.14 (m, 1H), 7.22–7.25 (m, 1H), 7.41–7.44 (m, 1H), 7.55–7.57 (m, 2H), 7.60–7.63 (m, 3H), 7.66 (s, 1H), 7.73–7.76 (m,1H), 7.97–7.99 (m, 1H), 8.09–8.11 (m, 2H), 8.30 (s, 1H), 11.21 (br s, 1H); $^{13}$C nmr (125 MHz, hexadeuteroacetone): δ 51.1, 80.1, 90.3, 105.2, 113.1, 118.0, 122.1, 122.5, 123.9, 126.0, 127.8, 129.8, 130.1, 130.2, 131.6, 131.9, 132.0, 134.9, 135.1, 137.2, 144.4, 166.8, 193.9; IR (potassium bromide) 3264, 2203 (CN), 1705 (CO), 1611 (CO), 1165, 747 cm$^{-1}$; ms (m/z) (%): 471 ($M^+$ +2, 2), 470 ($M^+$ +1, 11), 469 ($M^+$, 12), 105 (100); Anal. calcd. for $C_{26}H_{17}BrN_2O_2$: C, 66.54; H, 3.65; N, 5.97. Found: C, 66.39; H, 3.71; N, 5.82.

***Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(4-methoxyphenyl)-cyclopropanecarbonitrile (4d).*** This compound was obtained as white solid, mp 211–212°C (petroleum ether–ethyl acetate (v:v = 1:1)); $^1$H NMR (500 MHz, hexadeuteroacetone): δ 3.83 (s, 3H), 4.71 (d, $J$ = 5.0 Hz, 1H), 6.27 (d, $J$ = 5.0 Hz 1H), 6.99–7.00 (m, 1H), 7.01–7.02 (m, 1H), 7.12–7.15 (m, 2H), 7.22–7.26 (m, 1H), 7.35–7.38 (m, 2H), 7.56–7.61 (m, 1H), 7.71–7.75 (m, 2H), 8.02–8.05 (m, 3H), 8.06 (s, 1H), 11.15 (br s, 1 H); $^{13}$C NMR (125 MHz, hexadeuteroacetone): δ 51.5, 55.6, 81.0, 90.8, 105.4, 113.0, 115.4, 118.2, 122.0, 122.6, 123.8, 126.1, 129.7, 129.8, 130.0, 133.5, 134.9, 135.0, 137.2, 160.5, 166.3, 194.2; IR ((potassium bromide) 3274, 2199 (CN), 1703 (CO), 1611 (CO), 1164, 743 cm$^{-1}$; ms (m/z) (%): 420 ($M^+$, 13), 315 (100); Anal. calcd. for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 76.89; H, 4.88; N, 6.52.

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## REFERENCES AND NOTES

[1] (a) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. Tetrahedron 2001, 57, 987; (b) Bertozzi, F.; Gustalsson, M.; Olsson, R. Org lett 2002, 4, 3147; (c) Wurz, R. P.; Charette, A. B. Org lett 2005, 7, 2313; (d) Liu. L.; Montgomery, J. J Am Chem Soc 2006, 128, 5348; (e) Yang, Y.-H.; Shi, M. Org lett 2006, 8, 1709; (f) Yadav, J. S.; Subba Reddy, B. V.; Chandrakanth, D.; Satheesh, G. Tetrahedron lett 2007, 48, 8040; (g) Rashid, M. A.; Iqbal, I.; Rasool, N.; Imran, M.; Langer, P. Tetrahedron lett 2008, 49, 4266.

[2] (a) Wurz, R. P.; Charette, A. B. Org lett 2003, 5, 2327; (b) Concellón, J. M.; Rodriguez-Solla, H.; Méjica, C.; Blanco, E. G. Org lett 2007, 9, 2981.

[3] (a) Joule, J. A.; Mills, K. Heterocyclic Chemistry, 4 th ed.; Blackwell Science: Oxford, 2000; (b) Sundberg, R. J. Indoles; Academic Press: London, 1996; (c) Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; Knoell, J.; Krahl, M. P.; Reddy, K. R.; Knolker, H.-J. Curr Org Chem 2005, 9, 1601; (d) O'Connor, S. E.; Maresh, J. J Nat Prod Rep 2006, 23, 532.

[4] Slätt, J.; Romero, I.; Bergman, J. Synthesis 2004, 2760.

[5] (a) Motokura, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Tetrahedron Lett 2004, 45, 6029; (b) Rajapakse, H. A.; Zhu, H.; Young, M. B.; Mott, B. T. Tetrahedron Lett 2006, 47, 4827; (c) Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. J Org Chem 2006, 71, 4312; (d) Savitha, V.; Niveditha, S. K.; Muralidharan, D.Perumal, P. T. Tetrahedron Lett 2007, 48, 2943; (e) Parenty, A. D. C.; Song, Y.-F.; Richmond, C. J.; Cronin, L. Org Lett 2007, 9, 2253.

# Synthesis of Carbonyl Dyes from 1-Hydroxy-2-Acetonaphthone and 2-Fluorobenzophenone



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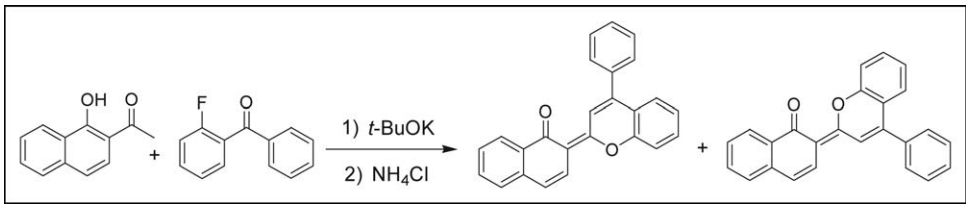


The reaction between 1-hydroxy-2-acetonaphthone and 2-fluorobenzophenone in basic medium afforded two diastereoisomeric carbonyl dyes whose structures were unambiguously established using spectroscopic methods. A mechanism for the formation of these dyes involving a base-catalysed addition followed by dehydration and intramolecular aromatic nucleofilic substitution is proposed.

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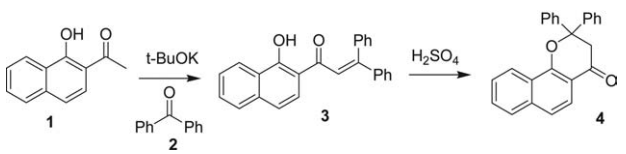
## INTRODUCTION

Reaction between 1-hydroxy-2-acetonaphthone **1** and benzophenone **2** in the presence of sodium *tert*-butoxide is known to produce, after acid treatment, mainly 2,2-diphenylnaphthopyran-4-one **4**, a useful compound in the synthesis of photochromic naphthopyrans [1,2]. The reaction involves a base-catalysed addition of **1** to **2** followed by dehydration that provides the yellow intermediate **3**. Then the acid catalyzed intramolecular 1,4-addition of the phenolic hydroxyl group to the α,β-conjugated ketone produces the diphenylnaphthopyran-4-one **4** (Scheme 1) [3]. This low yielding reaction (56%) requires an excess of base and ketone and is thus far limited to diarylketones [4–6].

Recently, we have reported that the reaction between **1** and 2-fluorobenzophenone **5** in the presence of 5 equivalents of potassium *tert*-butoxide in toluene under reflux, followed by reflux in AcOH/HCl gives rise to a small amount of a blue dye (5.7%). Spectroscopic characterization using high-resolution NMR techniques established the highly conjugated structure **6** for this product [7].

**Scheme 1.** Synthesis of 2,2-diphenylnaphthopyran-4-one **4**.



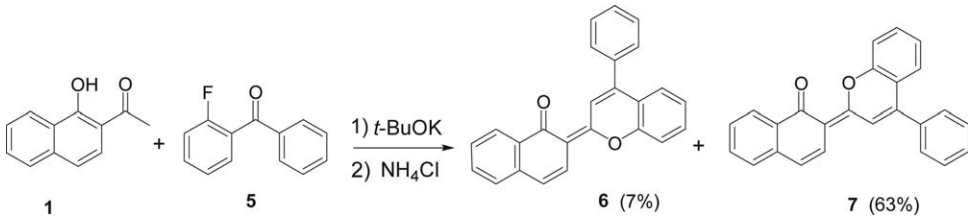

## RESULTS AND DISCUSSION

To improve the yield and understand how this dye is formed, we re-investigated this reaction and found out that, in fact, two different dyes are formed after the first step of the reaction between **1** and **5** (*t*-BuOK in toluene under reflux). $NH_4Cl$(aq) hydrolysis of the basic reaction mixture afforded a yellow dye **7** (less polar, 63% yield) as well as a small amount of the already known dye **6** (more polar, 7% yield) (Scheme 2).

Spectroscopic characterization of the new yellow dye **7** using DEPT, COSY, HMBC, HSQC provided the complete assignment of all proton and carbon resonances and showed that this compound is a diastereoisomer of the previously isolated dye **6** (Table 1). Long-range C—H correlations in the HMBC spectrum established the connectivity between all atoms and are shown in Figure 1.

The spectroscopic data for compounds **7** and **6** are quite similar. Both exhibit the same molecular formula and similar patterns in the Mass spectra and in the $^{1}H$ and $^{13}C$ NMR spectra. The main differences between these two diastereoisomeric dyes in the NMR spectra were the chemical shifts of protons H-3′ found at 6.04 (s) for dye **7** and at 9.12 (s) for dye **6** and the chemical shift of the carbonyls found at 195.36 ppm for **7** and at 183.58 ppm for **6**. The NOESY spectrum showed an important correlation between H-3′and H-3 for compound **7**, which was not observed for compound **6** and thus establishes a *Z*-configuration for the double bond between carbons 2 and 2′ of dye **7**.

**Scheme 2.** Synthesis of dyes **6** and **7**.




The UV-vis spectra of these two dyes are very different. While the blue dye **6** exhibits a large band in the visible spectrum with a maximum at 538 nm (ε 1.1 × $10^4$), a sub-maximum at 577 nm (ε 1.1 × $10^4$), and two shoulders at 504 nm (ε 0.83 × $10^4$) and 630 nm (ε 0.50 × $10^4$), the yellow dye **7** presents a maximum at 394 nm (ε 0.74 × $10^4$) (Figure 2). The lower $\lambda_{max}$ for dye **7** suggests a less efficient conjugation that may be due to the repulsion between the oxygen atoms at C-2′ and C-1 that would led to a less planar structure of this *Z*-isomer.

The formation of both dyes under basic medium led us to propose the following mechanism: subsequent to the base-catalyzed addition between **1** and **5**, proton transfer and dehydration would form the phenolate **A**, which might adopt two configurations, that upon intramolecular nucleophilic aromatic substitution would lead to the two diastereoisomeric dyes **6** and **7** (Scheme 3) [8,9].

Although both dyes were formed under basic conditions, a small amount of the blue dye **6** was also formed when the yellow dye **7** was refluxed in acid medium (AcOH/HCl). This can be explained through an acid catalyzed isomerization of **7** to **6** (Scheme 4).

## EXPERIMENTAL

The reagents were obtained from Aldrich and were used as supplied. Solvents were of analytical grade. The reactions were monitored by thin-layer chromatography on aluminum plates precoated with Merck silica gel 60 F254 (0.25 mm). Melting point was determined in capillary tubes and are

**Table 1**

NMR spectral data for dyes **6** and **7**.

| | Dye **6** | | Dye **7** | |
|---|---|---|---|---|
| Atom | 1H (*J* in Hz) | 13C | 1H (*J* in Hz) | 13C |
| 1 | | 183.58, *s* | | 195.36, *s* |
| 2 | | 111.21, *s* | | 113.96, *s* |
| 3 | 7.66, *d* (9.6) | 123.18, *d* | 7.80, *d* (8.8) | 124.59, *d* |
| 4 | 6.73, *d* (9.6) | 119.53, *d* | 7.25[a] | 118,11, *d* |
| 4a | | 137.78, *s* | | 137.28, *s* |
| 5 | 7.42, *d* (7.6) | 127.25, *d* | 7.74, *d* (8.0) | 127.35, *d* |
| 6 | ~7.55[a] | 131.84, *d* | 7.62, *ddd* (1.3,6.9, 8.0) | 130.04, *d* |
| 7 | 7.36, *dd* (7.5; 8.0) | 126.38, *d* | 7.51, *ddd* (1.0,7.0, 8.0) | 125.77, *d* |
| 8 | 8.34, *d* (8.0) | 126.90, *d* | 8.45, *d* (8.0) | 124.35, *d* |
| 8a | | 132.59, *s* | | 125.18, *s* |
| 2′ | | 162.44, *s* | | 163.54, *s* |
| 3′ | 9.12, *s* | 120.74, *d* | 7.48, *s* | 124.15, *d* |
| 4′ | | 150.14, *s* | | 147.72, *s* |
| 4′a | | 121.38, *s* | | 126.59, *s* |
| 5′ | ~7.55[a] | 126.47, *d* | 7.10[a] | 128.18, *d* |
| 6′ | 7.25, *dd* (7.5; 7.6) | 124.81, *d* | 7.15, *d* (8.9) | 123.96, *d* |
| 7′ | ~7.58[a] | 132.03, *d* | 7.20[a] | 131.20, *d* |
| 8′ | ~7.51[a] | 117.12, *d* | 7.05[a] | 115.50, *d* |
| 8′a | | 153.34, *s* | | 148.52, *s* |
| 1″ | | 136.05, *s* | | 140.28, *s* |
| 2″ and 6″ | ~7.52[a] | 128.77, *d* | 7.45[a] | 128.58, *d*[b] |
| 3″ and 5″ | ~7.62[a] | 128.98, *d* | 7.45[a] | 127.86, *d*[b] |
| 4″ | ~7.52[a] | 129.54, *d* | 7.40[a] | 129.70, *d* |

All $^1$H-$^{13}$C connectivities were assigned by HMBC and HSQC and the multiplicities were determined by DEPT experiments.
[a] Approximate central values due to overlapped signals.
[b] The values may be interchanged.

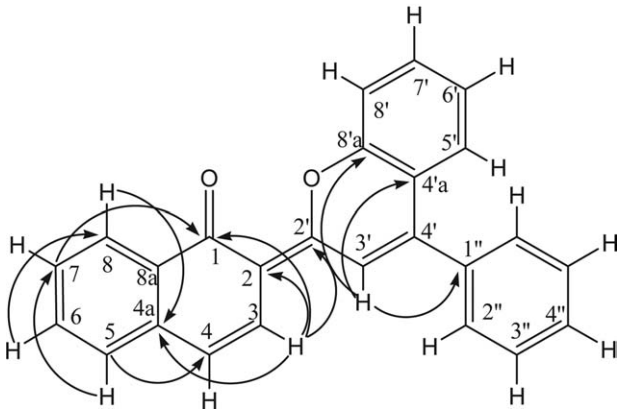


**Figure 1.** Long-range C—H correlations obtained from HMBC for dye **7**.

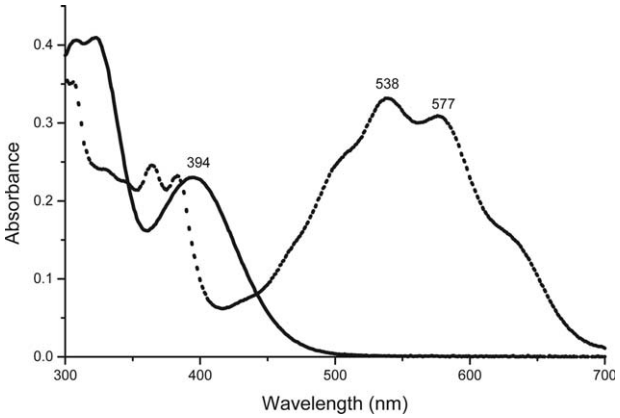



**Figure 2.** UV/vis spectra of compounds **6** and **7** ($3.1 \times 10^{-5}$ M, $CH_2Cl_2$).

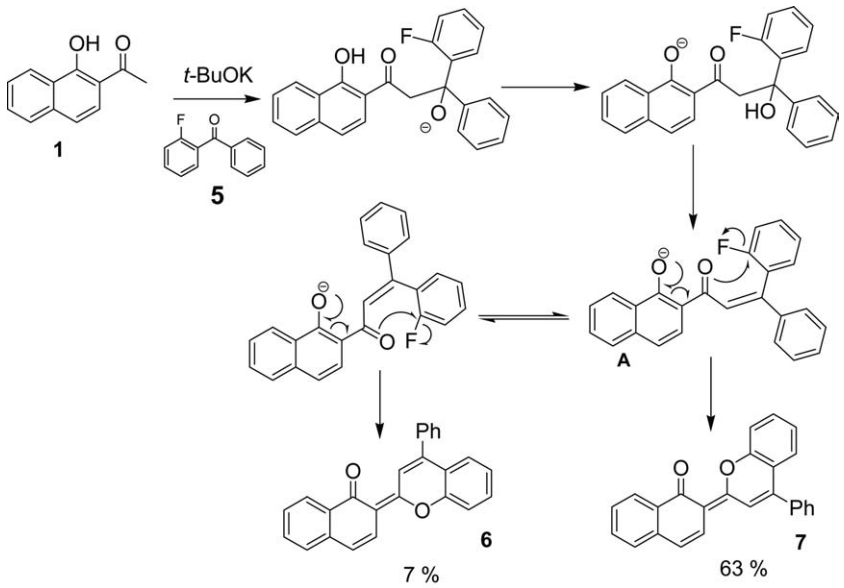
uncorrected. The new compounds were determined to be >95% pure by $^1$H NMR spectroscopy. UV-Vis spectra were recorded on a CARY 50 Varian spectrophotometer. IR spectra were obtained on a Perkin-Elmer FTIR 1600 spectrometer using KBr disks (wavenumbers in $cm^{-1}$). Electronic impact mass spectra were measured on a AutoSpecE spectrometer. The $^1$H and $^{13}$C NMR spectra were recorded at 298 K in $CDCl_3$ using a Bruker ARX400 spectrometer (at 400.13 for $^1$H and 100.62 MHz for $^{13}$C). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Resonance multiplicities for $^{13}$C were established via the acquisition of DEPT spectra. Heteronuclear $^1$H-$^{13}$C HSQC and HMBC experiments were carried out using standard procedures.

**General procedure for the synthesis of dyes (6) and (7).** 1-Hydroxy-2-acetonaphthone **1** (0.186 g, 1.0 mmol) and potassium *tert*-butoxide (0.336 g, 3 mmol) in toluene (15 mL) were refluxed for 20 min. 2-Fluorobenzophenone **2** (0.400 g, 2.0 mmol) was added and the reaction mixture was refluxed for another 40 min. The dark red solution was hydrolyzed with $NH_4Cl$ (aq) and then extracted with $Et_2O$ (3 × 20 mL). The organic extracts were dried over anhydrous $Na_2SO_4$ and evaporated leaving a deep red residue, which was purified by column chromatography (2–10% ethyl acetate/petroleum ether) over silica gel. Two compounds were isolated: **7**, 0.220 g (63%) and **6**, 0.025 g (7%).

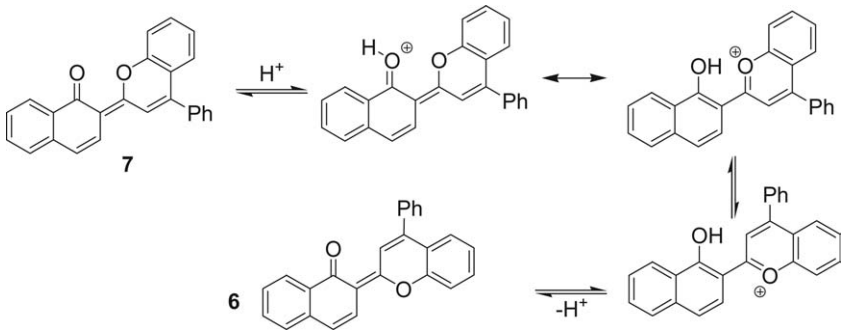
**(2Z)-2-(4′-phenyl-2H-chromen-2′-ylidene)naphthalene-1(2H)-one (7).** This compound was obtained as a yellow powder, mp 130°C dec. IR: 3060, 3026, 2976, 1620, 1594, 1569, 1450, 1320, 1254, 1203, 1059. For $^1$H NMR and $^{13}$C NMR data see Table 1. MS: *m*/*z* (%): 348 (75), 331 (12), 291 (8), 271 (14), 170 (100). Exact mass for $C_{25}H_{16}O_2$: 348.1150; Found 348.1146.

**(2E)-2-(4′-phenyl-2H-chromen-2′-ylidene)naphthalene-1(2H)-one (6).** This compound was obtained as blue needles, mp 155–158°C. IR: 3050, 2923, 2852, 1624, 1593, 1541, 1505, 1468, 1371, 1315, 1273, 1235, 955, 923. For $^1$H NMR

**Scheme 3.** Mechanism for the formation of dyes **6** and **7** from 1-hydroxy-2-acetonaphthone **1** and 2-fluorobenzophenone **5**.



**Scheme 4.** Acid catalysed isomerization of dye **7** to dye **6**.




and $^{13}C$ NMR data see Table 1. MS: *m*/*z* (%): 348 (100), 331 (25), 289 (10), 271 (40). Exact mass for $C_{25}H_{16}O_2$: 348.1150; Found 348.1148.

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## REFERENCES AND NOTES

[1] Hepworth, J. D.; Heron, B. M. In Functional Dyes; Kim, S. H., Ed.; Elsevier: Amsterdam, 2006; Chapter 3, pp 85–135.

[2] Van Gemert, B. In Organic Photochromic and Thermochromic Compounds. Main Photochromic Families, Crano, J. C., Guglielmetti, R., Eds.; Plenum Press: New York, 1998; Vol. 1, p 111.

[3] Coelho, P. J.; Carvalho, L. M.; Vermeersch, G.; Delbaere, S. Tetrahedron 2009, 65, 5369.

[4] Cottam, J.; Livingstone, R. J Chem Soc 1964, 5228.

[5] Kabbe, H. D.; Widdig, A. Angew Chem Int Ed Engl 1982, 21, 247.

[6] Nelly, S. E.; Vanderplas, B. C. J Org Chem 1991, 56, 1325.

[7] Coelho, P. J.; Carvalho, L. M. Dyes Pigm 2008, 78, 173.

[8] Santamaria, A.; Moreno-Manas, M.; Pleixats, R. Arkivoc 2007, 4, 234.

[9] Del Buttero, P.; Molteni, G.; Papagni, A.; Pilati, T. Tetrahedron 2003, 59, 5259.

# Synthesis, Complexation, and Biological Activity Studies of 4-Aminomethyl-7,8-dihydroxy Coumarines and Their Crown Ether Derivatives



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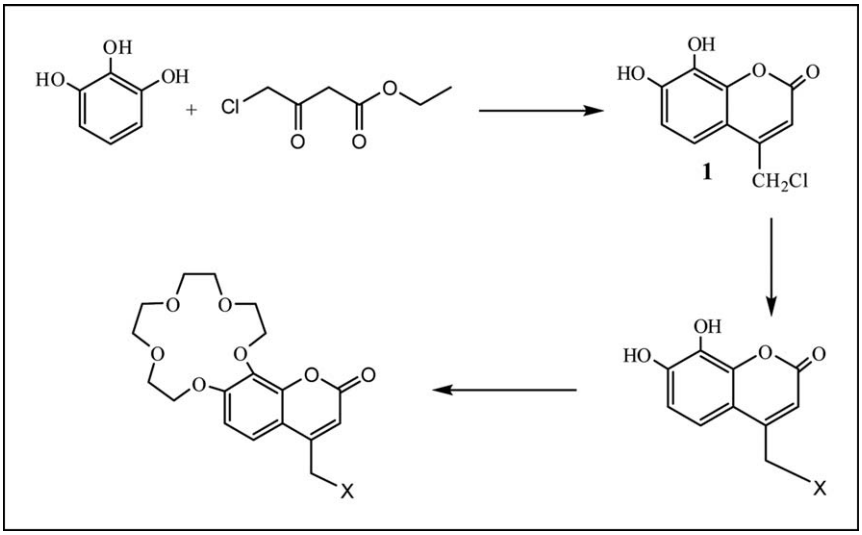


The article focuses synthesis of novel 4-aminomethyl-7,8-dihydroxy coumarins and their crown ether derivatives. The purified novel coumarins and their crown ether derivatives were identified by $^{1}H$ NMR, $^{13}C$ NMR, mass spectrometry and elemental analysis. The 1:1 binding constants of $Ca^{2+}$, $Mg^{2+}$, $Fe^{2+}$, $Zn^{2+}$, $Ni^{2+}$, $Cd^{2+}$, $Co^{2+}$, and $Mn^{2+}$ ions at 25°C ± 0.1 with the 4-aminomethyl-7,8-dihydroxy coumarins and their crown ether derivatives estimated using extraction procedure with Inductively Coupled Plasma-Atomic Emission Spectroscopy in dichloromethane/water membrane systems. Synthesized compounds were investigated for complexation and biological activity properties. Best results in biological activity studies were observed for antioxidant activity.

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## INTRODUCTION

Coumarins are members of the class of compounds called benzopyrones and display a variety of pharmacological properties [1] depending on their substitution pattern. They are also known to possess antifungal and antibacterial properties [2,3], natural [4], and synthetic origin [5]. The diverse biological activity of chromenone derivatives as anticoagulants and antithrombotics is well known [6].

3-Alkyl and 4-alkylcoumarins are well known [7] for their anthelmintic, hypnotic, insecticidal, antifungal activities, and anticoagulant effect on blood and diuretic properties. Extensive work has been done on the synthesis [8] of these classes of compounds. Methylene halide that is attached at the 4th position is a very highly reactive group in coumarins. Some coumarine compounds obtained from reaction of coumarin-4-methylene halide group with various amino compounds have been investigated for complexation [9], biological [10], photopysical [11,12], and spectroscopic [13–15] properties.

Macrocyclic molecules have attracted much attention because of their potential use in a variety of chemical processes, complexation ability, selective complexing

agents for metal ions, and photoinduced electron transfer since its discovery by Pedersen [16,17]. The complexation selectivity of crown ethers has often been explained in terms of the size-fit concept that the crown ether forms a more stable complex with the cation which is more suitable in size for the crown ether cavity. From many investigations of crown ether and cation interactions it was determined that crown ethers can form variable complexes with cations that are too large to fit into the macrocyclic cavity [18–23]. This led to the synthesis of new crown ethers derivatives which are attachment of functional side arm.

In ion-pair extractive separation of metal cations using a neutral chelation reagent and a counter anion, selection of the chelation reagent is one of the most important factors to realize preferable separation. Especially, investigation of effect of steric structure around electron donor atoms in the reagent on the separation ability is very important for the development of novel reagents having high separation performance. The determination of complexation constants of organic ligands-metal ion complexes in water can be examined with different methods by following the extraction of metals to the varied organic solvents with organic ligands [24–29]. The solvent extraction of metal cations which contains macrocyclic ligands is preferred to use for its easy determination by spectrophotometric methods [23,30,31].

We report in this study the synthesis, complexation, and biological activity studies of novel 4-aminomethyl-7,8-dihydroxy coumarins and their crown ether derivatives.

## RESULTS AND DISCUSSION

**Synthesis of compounds.** 4-chloromethyl 7,8-dihydroxy coumarin compound (**2**) was synthesized by reaction of 1,2,3-trihydroxybenzene with ethyl-4-chloroacetoacetate. The 4-aminomethyl coumarins (**2–9**) were synthesized at room temperature by stirring and then refluxing the reaction mixture of amino compound and triethylamine with 4-chloromethyl coumarin in dry acetone. (Scheme 1). Next stage, the substituted 4-aminomethyl coumarin crown ether derivatives (**10–17**) were synthesized by refluxing 4-aminomethyl coumarins, tetraethyleneglycole ditosylate and $Na_2CO_3$ in $CH_3CN$ for 3–4 days.

**Complexation studies.** $K_{ex}$ is extraction equilibrium constant; $[M^{+m}]$ and $[MLA_m]$ are the concentrations of metal cation in aqueous phase and organic phase, respectively. $K_{D,L}$ denotes a distribution constant of ligand between organic solvent and water [25,32,33]. Extraction values, complexation, and distribution constants of synthesized ligands collected in Table 1.

$$M^{+m}_{(aq)} + L_{(org)} + mA_{(aq)} \overset{K_{ex}}{\rightleftharpoons} (MLA_m)_{(org)}, \quad (1.1)$$

$$K_{ex} = \frac{[MLA_m]_{(org)}}{[M^{+m}]_{(aq)}[L]_{(org)}[A]^m_{(aq)}}, \quad (1.2)$$

$$K_{D,L} = [L]_{(org)}/[L]_{(L)}. \quad (1.3)$$

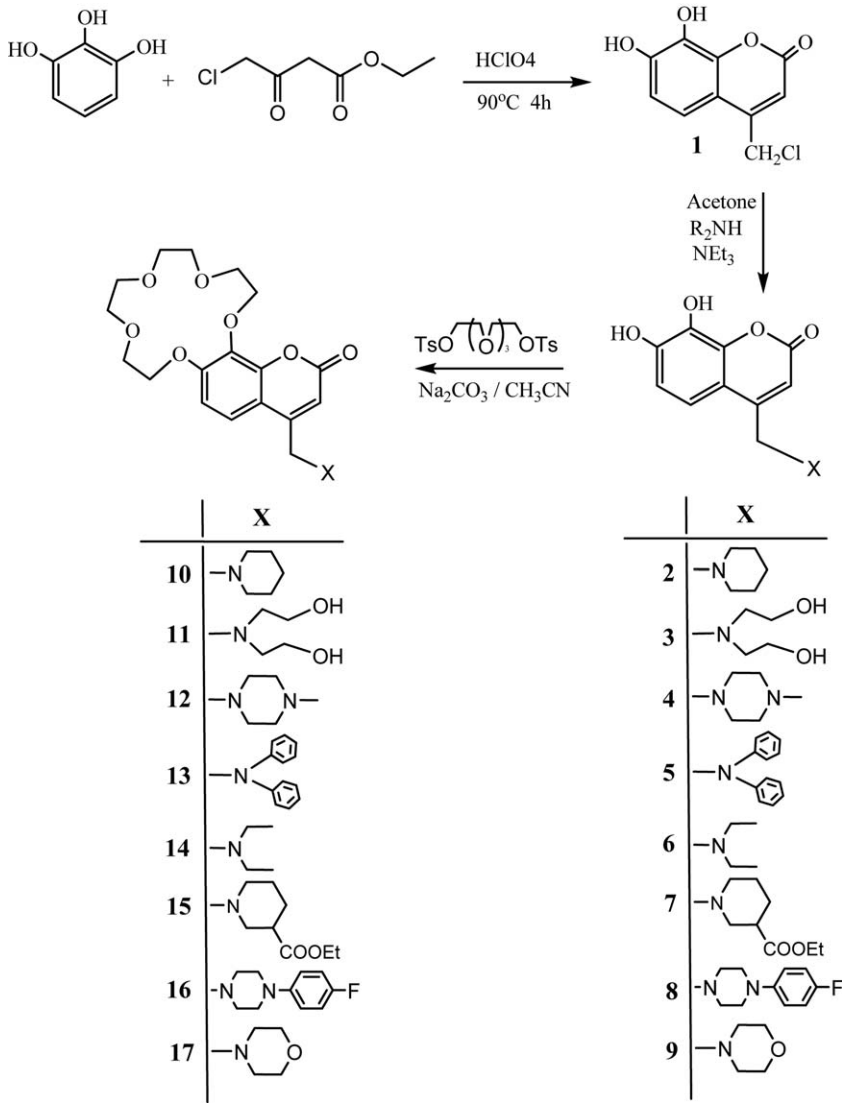
The complexation of metal cations $Ca^{2+}$, $Mg^{2+}$, $Fe^{2+}$, $Zn^{2+}$, $Ni^{2+}$, $Cd^{2+}$, $Co^{2+}$, and $Mn^{2+}$ have been examined with the synthesized ligands and extracting solvent. Association constants based on 1:1 stoichiometry of various metal complexes of these ligands were calculated from eqs. (1.1)–(1.3) (see Table 1) as the interactions of the ligands with different metal ions in dichloromethane solvent media. Assuming that formation of 1:1 complexes of the metal cations have been extracted at the natural pH of the aqueous metal salt solutions. The results are interesting, namely, the binding order of hydroxycoumarin compounds observed for only **3**,**7**,**8**, and **9** as ($Ni^{2+} > Co^{2+} > Mn^{2+} > Fe^{2+} > Ca^{2+} > Zn^{2+} > Cd^{2+} > Mg^{2+}$), ($Cd^{2+} > Ca^{2+} > Co^{2+} > Fe^{2+} > Ni^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+}$), ($Co^{2+} > Ni^{2+} > Cd^{2+} > Mn^{2+} > Fe^{2+} > Ca^{2+} > Zn^{2+} > Mg^{2+}$), ($Co^{2+} > Cd^{2+} > Fe^{2+} > Ca^{2+} > Zn^{2+} >>> Ni^{2+} = Mn^{2+} = Mg^{2+}$), respectively. It is found that the values of stability constants of coumarine crown derivatives were nearly in the same range for most examined metal cations except for $Cd^{2+}$ and $Co^{2+}$ cations. $Cd^{2+}$ is found to be the best extracted metal cation for the coumarine crowns. It followed by $Co^{2+}$ for all synthesized coumarine crown derivatives. One of the most important findings was the increase in $Mg^{2+}$ selectivity for only **8** and **11** among the all examined ligands. However, the five hydroxycoumarins (**1**,**2**,**4**,**5**, and **6**) and two coumarin crown compounds (**10** and **13**) did not show any complexation towards metal cations.

The synthesized compounds were tested for antibacterial (Table 2), antituberculosis (Table 2), antifungal (Table 2), and antioxidant (Table 3) activity. High values were obtained in antimicrobial activity studies especially for some hydroxycoumarin compounds. Best results in biological activity studies were observed for antioxidant activity. In comparison with the control substance, extremely high values have been obtained for **2**,**3**,**4**,**6**, and **8** ligands.

## EXPERIMENTAL

**General.** The starting chemicals were purchased from Aldrich or Merck unless otherwise cited. $CaCl_2$, $MgCl_2$, $ZnCl_2$, $CoCl_2$, $FeSO_4$, $MnCl_2$, $NiCl_2$, and $CdCl_2$ were analytical grade reagents from Fluka dried over $P_2O_5$ for 48 h at 0.1

**Scheme 1.** Synthesized compounds.




torr. The $CH_2Cl_2$ used was of analytical reagent grade. FT-IR spectra have taken as a KBr pellet with a Perkin Elmer Spectrum spectrometer, model BX-II, High resolution EI mass spectra have been obtained with Agilent 1100 LC/MSD, NMR spectra have been obtained with a Bruker-Specrospin AvanceDPX-400 Ultra-Shield $^1$H: 400 MHz $^{13}$C: 100 MHz. CPX and TMS was the initial standard. All melting points reported are uncorrected. The concentrations of metal ions in the aqueous phases have been determined spectroscopically: ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES): Perkin Elmer Optima 3100 XL).

**Organic synthesis.** ***4-Chloromethyl-7,8-dihydroxy-2H-chromen-2-one(1).*** A mixture of pyrogallol (0.03 mol), ethyl 4-chloroacetoacetate (0.06 mol) and $HClO_4$ (10 mL, 70%) was heated to 90°C for 4 h. The resulting mixture was cooled, diluted with water and the precipitates were collected by filtration. The dried crude product was purified by recrystallisation from ethanol. Yield (brown):48%. mp; 105–107°C. $^1$H NMR (400 MHz, Acetone/TMS) δ(ppm): 7.5 (s), 7.2 (d), 6.9 (d), 6.6 (s), 6.4 (s), 4.9 (s).

***General synthesis of 4-aminomethyl 7,8-dihydroxy coumarins.*** A mixture of 4-chloromethyl-7,8-dihydroxy coumarin (0.010 mol), amino compound (0.010 mol) and acetone (300 mL) was stirred to room temparature under $N_2$ for 24 h. Triethyl amine (0.010 mol) added and stirred for 1 h and then the mixture was refluxed for 3 h. After the removal of solution by evaporation, the resulting mixture was triturated with water, and the precipitates were collected by filtration. The crude product was dried under vacuum.

***7,8-Dihydroxy-4-piperidine-1-ylmethyl-2H-chromen-2-one(2).*** Yield (brown); 71%. mp; 65–68°C. $^1$H NMR (400 MHz, Acetone/TMS) δ(ppm): 7.73 (s), 7.28 (dd), 6.85 (dd), 6.38 (s), 6.33 (s), 4.72 (s), 2.65 (m), 1.7 (m), 1.36 (m).

***4-{(Bis-(2-hydroxy-ethyl)-amino)-methyl}-7,8-dihydroxy-2H-chromen-2-one (3).*** Yield (darkgreen); 67%. mp; 155–159°C. $^1$H NMR (400 MHz, Acetone/TMS) δ(ppm): 7.78 (s),

**Table 1**

$K_{D,L}$, % Ext, and Log $K_{ex}$ values for extraction of synthesized compounds in $CH_2Cl_2$ with $Ca^{2+}$, $Mg^{2+}$, $Fe^{2+}$, $Zn^{2+}$, $Ni^{2+}$, $Cd^{2+}$, $Co^{2+}$, and $Mn^{2+}$ ions at 25°C ± 0.1.[a]

| | | Cations | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ligand | Value | $Zn^{2+}$ | $Cd^{2+}$ | $Ni^{2+}$ | $Ca^{2+}$ | $Mn^{2+}$ | $Co^{2+}$ | $Fe^{2+}$ | $Mg^{2+}$ |
| **1** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **2** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **3** | $K_{D,L}$ | 0.26 | 0.14 | 2.65 | 0.68 | 1.19 | 1.78 | 0.77 | – |
| | % Ext | 20.49 | 12.30 | 72.57 | 40.52 | 54.37 | 64.09 | 43.46 | – |
| | Log $K_{ex}$ | 8.41 | 8.06 | 10.34 | 9.08 | 9.55 | 9.94 | 9.18 | – |
| **4** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **5** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **6** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **7** | $K_{D,L}$ | 0.63 | 1.98 | 1.41 | 1.86 | 0.31 | 1.80 | 1.64 | – |
| | % Ext | 38.69 | 66.39 | 58.56 | 65.02 | 23.86 | 64.35 | 62.10 | – |
| | Log $K_{ex}$ | 9.02 | 10.04 | 9.71 | 9.98 | 8.53 | 9.95 | 9.85 | – |
| **8** | $K_{D,L}$ | 0.70 | 1.34 | 2.33 | 0.86 | 0.95 | 3.63 | 0.88 | 0.09 |
| | % Ext | 41.02 | 57.23 | 69.93 | 46.13 | 48.72 | 78.40 | 46.91 | 8.23 |
| | Log $K_{ex}$ | 9.10 | 9.66 | 10.21 | 9.27 | 9.35 | 10.69 | 9.29 | 7.82 |
| **9** | $K_{D,L}$ | 11.22 | 1.88 | – | 1.41 | – | 3.01 | 1.50 | – |
| | % Ext | 85.21 | 65.24 | – | 58.48 | – | 75.08 | 59.99 | – |
| | Log $K_{ex}$ | 5.76 | 9.99 | – | 9.71 | – | 10.48 | 9.77 | – |
| **10** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **11** | $K_{D,L}$ | 1.27 | 2.49 | 2.19 | 0.48 | 0.90 | 2.46 | 1.04 | 0.04 |
| | % Ext | 55.96 | 71.31 | 68.61 | 32.23 | 47.27 | 71.14 | 50.99 | 4.12 |
| | Log $K_{ex}$ | 9.61 | 10.28 | 10.14 | 8.81 | 9.30 | 10.27 | 9.43 | 7.47 |
| **12** | $K_{D,L}$ | 1.03 | 2.51 | 1.35 | 0.85 | 0.56 | 1.95 | 1.10 | – |
| | % Ext | 50.84 | 71.49 | 57.41 | 45.95 | 35.97 | 66.09 | 52.28 | – |
| | Log $K_{ex}$ | 9.43 | 10.28 | 9.67 | 9.26 | 8.93 | 10.02 | 9.48 | – |
| **13** | $K_{D,L}$ | – | – | – | – | – | – | – | – |
| | % Ext | – | – | – | – | – | – | – | – |
| | Log $K_{ex}$ | – | – | – | – | – | – | – | – |
| **14** | $K_{D,L}$ | 1.72 | 2.73 | 1.71 | 1.06 | 0.67 | 2.28 | 0.95 | – |
| | % Ext | 63.23 | 73.22 | 63.03 | 51.56 | 40.21 | 69.52 | 48.79 | – |
| | Log $K_{ex}$ | 9.90 | 10.38 | 9.89 | 9.45 | 9.07 | 10.19 | 9.36 | – |
| **15** | $K_{D,L}$ | 1.32 | 3.12 | 1.55 | 1.24 | 0.72 | 1.80 | 1.72 | – |
| | % Ext | 56.92 | 75.71 | 60.82 | 55.30 | 41.71 | 64.26 | 63.22 | – |
| | Log $K_{ex}$ | 9.65 | 10.52 | 9.80 | 9.59 | 9.12 | 9.94 | 9.90 | – |
| **16** | $K_{D,L}$ | 1.46 | 3.23 | 1.88 | 0.63 | 0.66 | 2.49 | 0.85 | – |
| | % Ext | 59.40 | 76.33 | 65.29 | 38.59 | 39.71 | 71.31 | 45.92 | – |
| | Log $K_{ex}$ | 9.74 | 10.56 | 9.99 | 9.02 | 9.05 | 10.28 | 9.26 | – |
| **17** | $K_{D,L}$ | 1.68 | 2.72 | 1.64 | 0.86 | 0.97 | 2.32 | 0.91 | – |
| | % Ext | 62.69 | 73.13 | 62.18 | 46.26 | 49.32 | 69.86 | 47.76 | – |
| | Log $K_{ex}$ | 9.88 | 10.37 | 9.86 | 9.27 | 9.37 | 10.20 | 9.32 | – |

[a] Corr. coefficient 0.999.

7.24 (d), 6.9 (d), 6.71 (s), 6.38 (s), 4.89 (s), 3.15 (m), 2.82 (br).

***Bis-(4-piperazinyl methyl-7,8-dihydroxy)-2H-chromen-2-one(4).*** Yield (darkgreen); 63%. mp; 82–84°C. $^1$H NMR (400 MHz, Acetone/TMS) δ(ppm): 7.38 (d), 6.93 (d), 6.86 (d), 6.41 (s), 6.3 (s), 4.91 (s), 3.84 (t).

***4-((N,N-diphenylamino)-methyl)-7,8-dihydroxy-2H-chromen-2-one(5).*** Yield (brown); 77%. mp; 60–62°C. $^1$H NMR (400

**Table 2**

Antibacterial, antituberculosis, antifungal, and antimicrobial activities results of synthesized compounds.

| | Inhibiton zone (mm) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ligands | *M. tuberculosis*[a] | *M. simiae* | *M. kansasii* | *M. terrae* | *M. szulgai* | *E. coli* | *S. aureus* | *C. albicans* | *M. smegmatis* |
| **1** | NT | NT | NT | NT | NT | NA | NA | NA | NA |
| **2** | NT | NT | NT | NT | NT | 7 | NA | NA | NA |
| **3** | NA | NA | 9 | NA | 9 | 5 | 7 | NA | 7 |
| **4** | NA | NA | NA | NA | 6 | NA | NA | 6 | 7 |
| **5** | NT | NT | NT | NT | NT | NA | NA | NA | NA |
| **6** | NT | NT | NT | NT | NT | 7 | NA | NA | NA |
| **7** | NA | NA | 6 | NA | 5 | 6 | NA | 7 | 7 |
| **8** | NA | NA | NA | 3 | 5 | 5 | NT | 6 | 6 |
| **9** | NT | NT | NT | NT | NT | NA | NA | 7 | NA |
| **10** | NA | NA | NA | NA | 9 | 7 | NA | NA | 8 |
| **11** | NT | NT | NT | NT | NT | NA | NA | 8 | NA |
| **12** | NT | NA | NA | NA | NA | NA | NA | NA | 13 |
| **13** | NT | NT | NT | NT | NT | NA | NA | NA | NA |
| **14** | NT | NT | NT | NT | NT | NA | NA | 6 | NA |
| **15** | NA | NA | NA | NA | NA | 6 | NA | NA | 12 |
| **16** | NT | NT | NT | NT | NT | NA | NA | 6 | NA |
| **17** | NA | NA | NA | NA | NA | NA | NA | NA | 7 |
| Rifampicin | NT | NT | NT | NT | NT | NT | NT | NT | 35 |

NA: not active, NT: not tested.
[a] MIC values (μg/mL).

MHz, Acetone/TMS) δ(ppm): 7.41 (s), 7.22 (dd), 7.11 (d), 6.91 (d), 6.84 (dd), 6.38 (s), 4.88 (s).

***4-(N,N-diethylamino)methyl-7,8-dihydroxy-2H-chromen-2-one(6).*** Yield (yellow); 82%. mp; 79–82°C. $^1$H NMR (400 MHz, Acetone/TMS) δ(ppm): 7.56 (s), 7.25 (d), 6.93 (d), 6.65 (s), 6.4 (s), 4.91 (s), 3.1 (m), 2.12 (t).

***1-(7,8-Dihydroxy-2-oxo-coumarin-4-ylmethyl)-piperidine-3-carboxylic acid ethyl ester (7).*** Yield (brown); 71%. mp; 101–103°C. $^1$H NMR (400 MHz, acetone/TMS) δ(ppm): 7.65 (s). 7.03 (s), 6.84 (s), 6.65 (s), 6.33 (s), 4.53 (s), 3.4 (m), 2.52 (m), 1.68 (m), 1.50 (t).

***4-(4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl)-7,8-dihydroxy-2H-chromen-2-one (8).*** Yield (brown); 70%. mp; 94–96°C. $^1$H NMR (400 MHz, Acetone/TMS) δ(ppm): 7.36 (d), 6.99 (m), 6.85 (d), 6.32 (s), 3.73 (s), 3.18 (m), 2.72 (m).

***7,8-dihydroxy-4-(morpholinomethyl)-2H-chromen-2-one(9).*** Yield (yellow); 78%. mp; 199–202°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.8 (d), 7.2 (d), 6.7 (s), 4.7 (s), 3.2 (t), 2.4 (t).

***General synthesis of 4-aminomethyl 7,8-coumarin crown ethers.*** A mixture of 4-alkylamino substitued 7,8-dihydroxy coumarin (0.005 mol), tetraethylenglycole ditosylate (0.005 mol), $Na_2CO_3$ (0.01 mol) and 700 mL $CH_3CN$ was refluxed for 3–4 days under $N_2$. After the removal of solution by evaporation, the residue was extracted with $CHCl_3$, the organic layer washed with water and dried on $MgSO_4$. After the evaporation of $CHCl_3$, the residue was purified by column chromatography on silicagel (chloroform–methanol).

***20-Piperidine-1-ylmethyl-2,5,8,11,14,17-hexaoxa-tricyclo(13.8.0.0$^{16,21}$)tricosa-1(23),15,19,21-tetraen-18-on (10).*** Yield (yellow solid); 33%, mp; >300°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.7 (d), 7.15 (d), 6.3 (s), 4.78 (s), 4.03 (t), 3.93 (t), 3.6 (m),1.87 (m), 1.69 (m). $^{13}$C NMR (100 MHz) δ(ppm): 158, 149, 143.5, 139.34, 128.64, 125.95, 122, 112.88, 103, 71.88, 71.00, 70.9, 70.48, 70.24, 68.6, 69.1, 65, 60.22, 60.02, 42, 21.9. EI-MS (*m/z*). $M^+$ :434(8), 351(100), 219(47). Elemental Analysis: Anal. Calcd. for C, 63.73; H, 7.21; N, 3.23; O, 25.84; Found: C, 63.69; H, 7.18; N, 3.28; O, 25.85.

***20-{(Bis-(2-hydroxy-ethyl)-amino)-methyl}-2,5,8,11,14,17-hexaoxa-tricyclo(13.8.0.0$^{16,21}$)tricosa-1(2),15,19,21-tetraen-18-on (11).*** Yield (yellow); 19%, mp; 217–220°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.4 (d), 7.08 (d), 6.79 (s), 4.72 (s), 3.35 (m), 2.47 (t), 4.2 (m), 3.6 (m), 2.64 (t). $^{13}$C NMR (100 MHz) δ(ppm): 166.78, 153.43, 144.4, 132, 131.2, 129,

**Table 3**

Antioxidant activity results.

| Compounds | TEAC CUPRAC |
|---|---|
| **1** | NA |
| **2** | 1.28 |
| **3** | 2.40 |
| **4** | 3.64 |
| **5** | NA |
| **6** | 2.26 |
| **7** | NA |
| **8** | 0.89 |
| **9** | NA |
| **10** | NA |
| **11** | NA |
| **12** | NA |
| **13** | NA |
| **14** | NA |
| **15** | NA |
| **16** | NA |
| **17** | NA |
| Askorbik acid | 0.93/0.96[a] |
| Tocopherol | 0.97/1.01[a] |

[a] Values in literature.

110, 108.65, 102.73, 71.65, 71.19, 70.88, 70.32, 69.73, 68.69, 68.16, 67.66, 53, 49.8, 39.65. EI-MS (*m/z*). $M^+$: 453(7), 391(57), 358(100), 351(75). Elemental Analysis: Anal. Calcd. for C, 58.27; H, 6.89; N, 3.09; O, 31.75; Found: C, 58.20; H, 6.99; N, 3.00; O, 31.81.

***16,16′-(piperazin-1,4-düilbis(methylen))bis(5,6,8,9,11,12-hexahidro-2H-(1,4,7,10,13) pentaoxa cyclopentadeca (2,3-h)chromen-18(3H)-one) (12).*** In this procedure tetraethylenglycole ditosylate and $Na_2CO_3$ was used twofold. Yield (yellow); 19%, mp; 285–290°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.75 (d), 7.11 (d), 6.4 (s), 4.4 (s), 3.9 (m), 3.7 (m), 2.6 (m). $^{13}$C NMR (100 MHz) δ(ppm): 163.55, 142, 140.4, 138.55, 130.23, 128.6, 126, 113.45, 101.11, 70.77, 70.44, 70.29, 69.88, 69.08, 68.73, 68.11, 67.24, 53, 43, 39.87. EI-MS (*m/z*). $M^+$: 783(100), 611.5(74). Elemental Analysis: Anal. Calcd. for C, 61.37; H, 6.44; N, 3.58; O, 28.61; Found: C, 61.27; H, 6.53; N, 3.58; O, 28.62.

***20-((Diphenylamino)-methyl)-2,5,8,11,14,17-hexaoxa-tricyclo(13.8.0.0$^{16,21}$)tricosa-1(23),15,19,21-tetraen-18-on (13).*** Yield (yellow); 29%, mp; 270–275°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.45 (d), 7.09 (d), 6.9 (m), 6.2 (s), 4.65 (s), 4.1 (m), 3.32 (m). $^{13}$C NMR (100 MHz) δ(ppm): 161, 147.65, 145.23, 142.95, 127, 123.2, 118.2, 116.56, 110.43, 109.33, 107.46, 107.33, 101, 71.39, 71.28, 71.05, 70.8, 70.46, 68.77, 68.39, 68.04, 36.55. EI-MS (*m/z*). $M^+$: 517(17), 439(21), 416(48), 384(100), 300(52). Elemental Analysis: Anal. Calcd. for C, 69.62; H, 6.04; N, 2.71; O, 21.64; Found: C, 69.56; H, 6.01; N, 2.78; O, 21.65.

***20-Diethylaminomethyl-2,5,8,11,14,17-hexaoxa-tricyclo (13.8.0.0$^{16,21}$) tricosa-1(23),15,19,21-tetraen-18-on (14).*** Yield (yellow); 23%, mp; 278–280. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.49 (d), 7.1 (d), 6.87 (s), 6.3 (s), 4.7 (s), 4.1 (m), 3.5 (t), 2.48 (q), 2.26 (t). $^{13}$C NMR (100 MHz) δ(ppm): 161, 145.4, 142.2, 138.55, 132.22, 128.61, 125, 101, 107, 71.37, 71.06, 70.65, 70.29, 70, 69.64, 68.91, 68.21, 56, 41.21, 36.55. EI-MS (*m/z*). $M^+$: 422.5(100), 407(32), 253(45), 219(47). Elemental Analysis: Anal. Calcd. for C, 62.69; H, 7.41; N, 3.32; O, 26.57; Found: C, 62.75; H, 7.43; N, 3.35; O, 26.47.

***1-(18-Oxo-2,5,8,11,14,17-hexaoxa-tricyclo(13.8.0.0$^{16,21}$)tricosa-1(23),15,19,21-tetraen-20-ylmethyl)-piperidine-3-carboxylic acid ethyl ester (15).*** Yield (brown); 35%, mp; >310. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.75 (d), 7.13 (d), 6.27 (s), 4.67 (s), 4.1 (m), 3.6 (m), 2.32 (m), 1.25 (m). $^{13}$C NMR (100 MHz) δ(ppm): 172, 161, 145, 142.65, 140.11, 128.65, 125.94, 113, 112, 109, 71.85, 71.22, 70.75, 70.50, 70.32, 69.86, 68.56, 68.24, 59.60, 58, 57.7, 56.5, 55.29, 40, 36.35. EI-MS (*m/z*). $M^+$: 506(17), 489(52), 475(17), 316(45), 302(100). Elemental Analysis: Anal. Calcd. for C, 61.77; H, 6.98; N, 2.77; O, 28.48; Found: C, 61.70; H, 7.02; N, 2.71; O, 28.57.

***20-(4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl)-2,5,8,11,14,17-hexaoxa-tricyclo (13.8.0.0$^{16,21}$) tricosa-1(23),15,19,21-tetraen-18-on (16).*** Yield (brown); 37%, mp; 276–280°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS): 7.47 (d), 7.1 (d), 7.0 (m), 4.7 (s), 3.7 (m), 3.6 (m), 2.5 (m). $^{13}$C NMR (100 MHz): 167, 140, 139, 133, 131.55, 130.46, 128.9, 128.34, 126.65, 124.98, 116, 115.89, 111.76, 70.79, 70.68, 70.43, 70.12, 69.69, 69.17, 68.49, 68.04, 54, 50.88, 39. EI-MS (*m/z*). $M^+$: 529(100). Elemental Analysis: Anal. Calcd. for C, 63.62; H, 6.29; F, 3.59; N, 5.30; O, 21.19; Found: C, 63.57; H, 6.27; F, 3.61; N, 5.33; O, 21.22.

***16-(morpholinomethyl)-5,6,8,9,11,12-hexahidro-2H-(1,4,7,10,13) pentaoxacyclopentadeca (2,3-H) chromen-18(3H)-on (17).*** Yield (yellow); 27%, mp; 255–260°C. $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ(ppm): 7.5 (d), 7.1 (d), 7.0 (s), 4.5 (s), 3.5 (m), 2.4 (t). $^{13}$C NMR (100 MHz) δ(ppm): 161, 150.22, 146.26, 137.98, 133, 128.59, 110, 108.9, 103, 71.84, 71.12, 70.95, 70.42, 69.75, 69.4, 69, 68.78, 67.66, 56.63, 44.3. EI-MS (*m/z*). $M^+$: 436(100). Elemental Analysis: Anal. Calcd. for C, 60.68; H, 6.71; N, 3.22; O, 29.39; Found: C, 60.61; H, 6.75; N, 3.27; O, 29.37.

## EXTRACTION PROCEDURE

The extraction measurements were done in 100 mL glass thermostated cell compartment with a mechanical stirrer where a solution 10 mL ($1 \times 10^{-5}$ *M*) of an aqueous salt and ligand in $CH_2Cl_2$ organic solvent in appropriate concentration were placed and stirred for 120 min at 25 ± 0.1°C and subsequently allowed to stand for 60 min to complete the phase separation. The optimum concentrations of the ligands were determined by extracting the alkali salts with 10 mL aliquot of various concentrations of the ligands ($1 \times 10^{-5}$ *M*).

After extraction, the metal concentrations in the aqueous phase were determined using ICP-AES. Each value was the average of three subsequent measurements. Complexation and distribution constants summarized in Table 1.

## BIOLOGICAL ASSESSMENTS

Antibacterial and antifungal activities studies; Disc diffusion method was used [34]. The compounds were tested against standard bacterial strains; *E. coli*, *S. aureus*, *M. smegmatis*, *M. tuberculosis*, *M. simiae*, *M. kansasii*, *M. terrae*, *M. szulgai*, and a fungi *C. albicans*. Disc diffusion method was applied for the determination of antimicrobial activities of the samples. Compounds were dissolved in dichloromethane ($CH_2Cl_2$) and then filter-sterilized using a 0.20-μm membrane filter. A suspension of the tested microorganism (0.1 mL of $10^8$ cells/mL) was spread over the surface of agar plates (MHA and SDA). Filter papers having a diameter of 6 mm, soaked with 10 μL of samples and 10 μg compound in solution were placed on the inoculated agar plates. Before incubation all petri dishes were kept in the refrigerator (4°C) for 2 h. Then they were incubated at 37°C for 24 h for bacteria and at 30°C for 48 h for the yeasts. The diameters of the inhibition zones were measured in millimeters. The biological activity results of synthesized compounds are displayed in Table 2.

## ANTIOXIDANT ACTIVITY STUDIES

Antioxidant activity studies were measured by using the cuprac method in the literature [35]. Antioxidant activity studies results are showed in Table 3.

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## REFERENCES AND NOTES


[1] Hoult, J. R. S.; Payd, M. Gen Pharmacol 1996, 27, 713.

[2] Campo, A. D.; Fazzi, P. L. Riv Ist Sieroterap Ital 1958, 33, 389.

[3] Kumari, S. S.; Rao, K. S. R. M.; Rao, N. V. S. Proc Indiana Acad Sci 1973, 77, 149.

[4] Hossain, C. F.; Okuyama, E.; Yamazaki, M. Chem Pharm Bull 1996, 44, 1535.

[5] Rendenbach-Muller, B.; Schelcker, R.; Traut, M.; Weifenbach, H. Bioorg Med Chem Lett 1994, 4, 1195.

[6] Mitra, A. K.; Karchudhuri, A. N.; Misra, S. K.; Mmukhopadhyay, A. K. J Indian Chem Soc 1998, 75, 66.

[7] (a) Deana, A. A.; Stokker, G. E.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Russo, H. F.; Watson, L. S. J Med Chem 1983, 26, 580; (b) Gordon, M.; Grover, S. H.; Strothers, J. B. Can J Chem 1973, 51, 2092; (c) Polonsky, J.; Baskevitch, Z.; Cagnoli-Bellavita, N.; Buckwalter, B. L.; Wenkert, E. J Am Chem Soc 1972, 94, 4367.

[8] (a) Staunton, J. In Comprehensive Organic Chemistry, 1st ed.; Pergamon Press Ltd.: Headington Hill Hall, Oxford, 1979; Vol. 4, pp 646–658; (b) Hepworth, J. D. In Comprehensive Heterocyclic Chemistry, 1st ed., Part 2B; Pergamon Press Ltd.: Headington Hill Hall, Oxford, 1984; Vol. 3, pp 799–883.

[9] Kele, P.; Orbulescu, J.; Calhoun, L.; Gawley, R. E.; Leblanc, R. M. Tetrahedron Lett 2002, 43, 4413.

[10] Kalkhambkar, R. G.; Kulkarni, G. M.; Kamanavalli, C. M.; Premkumar, N.; Asdaq, S. M. B.; Sun, C. M. Eur J Med Chem 2008, 43, 2178.

[11] Schade, B.; Hagen, V.; Schmidt, R.; Herbrich, R.; Krause, E.; Eckardt, T.; Bendig, J. J Org Chem 1999, 64, 9109.

[12] Furuta, T.; Samuel, S.; Wang, H.; Dantzker, J. L.; Dore, T. M.; Bybeei, W. J.; Callaway, E. M.; Denk, W.; Tsien, R. Y. Proc Natl Acad Sci USA 1999, 96, 1193.

[13] Eckardt, T.; Hagen, V.; Schade, B.; Schmidt, R.; Schweitzer, C.; Bendig, J. J Org Chem 2002, 67, 703.

[14] Wang, W.; Li, H. Tetrahedron Lett 2004, 45, 8479.

[15] Sui, G.; Kele, P.; Orbulescu, J.; Huo, Q.; Leblanc, R. M. Lett Pept Sci 2002, 8, 47.

[16] Pedersen, C. J. J Am Chem Soc 1967, 89, 2495.

[17] Salan, Ü.; Bulut, M. Heterocycles 2006, 68, 237.

[18] Pedersen, C. J. J Am Chem Soc 1970, 92, 386.

[19] Mallinson, P. R.; Truter, M. R. J Chem Soc Perkin Trans 2 1972, 1818.

[20] Remoorter, F. P.; Boer, F. P. Inorg Chem 1974, 13, 2071.

[21] Cram, D. J.; Cram, J. M. Science 1974, 183, 803.

[22] Wong, K. H.; Bourgoin, M. D. J.; Staid, J. J Chem Soc Chem Commun 1974, 715.

[23] Gokel, G. W. Chem Soc Rev 1992, 21, 39.

[24] Cakir, U.; Cicek, B. Transition Metal Chem 2004, 29, 263.

[25] Cakir, U.; Ozer, M.; Icen, M. A.; Ugras, H. I.; Bulut, M. Dyes Pigm 2004, 60, 177.

[26] Takeda, Y.; Endo, K.; Katsuta, S.; Ouichi, M. Talanta 2001, 54, 575.

[27] Katsuta, S.; Tsuchiya, F.; Takeda, Y. Talanta 2000, 51, 637.

[28] Takeda, Y.; Kawarabayashi, A.; Takahashi, K.; Kudo, Y. Bull Chem Soc Jpn 1995, 68, 1309.

[29] Takeda, Y.; Kawarabayashi, A.; Endo, K.; Yahata, T.; Kudo, Y.; Katsuta, S. Anal Sci 1998, 14, 215.

[30] Kudo, Y.; Usami, J.; Katsuta, S.; Takeda, Y. Talanta 2003, 59, 1213.

[31] Cakir, U.; Cicek, B.; Yildiz, Y. K.; Alkan, M. J Inc Phenom 1999, 34, 153.

[32] Takeda, Y.; Kato, H. Bull Chem Soc Jpn 1979, 52, 1027.

[33] Lindoy, L. F. The Chemistry of Macrocyclic Ligand Complexes; Cambridge University Press: Cambridge, 1989.

[34] Kilic, T.; Dirmenci, T.; Satil, F.; Bilsel, G.; Kocagoz, T.; Altun, M.; Goren, A. C. Chem Nat Comp 2005, 41, 276.

[35] Apak, R.; Güçlü, K.; Özyürek, M.; Karademir, S. E. Microchim Acta 2008, 160, 413.

# Synthesis and Characterization of Novel Color Chemosensors Based on Azo Dyes for Possible Application in Opioid Pharmacology



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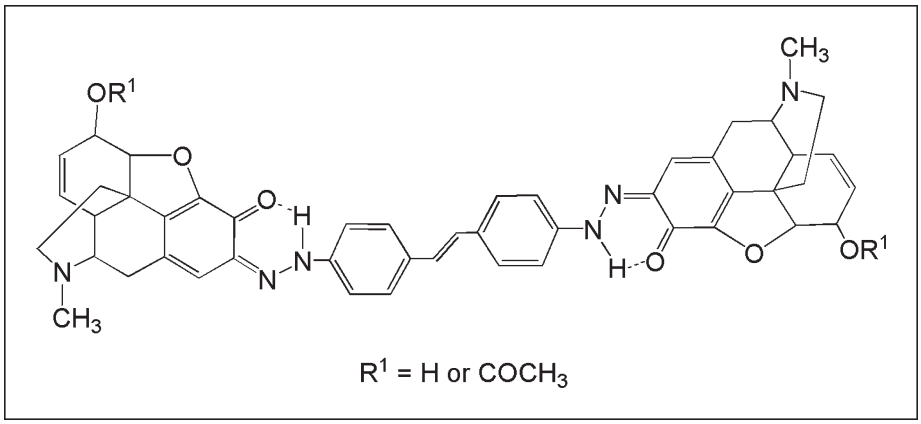


An applicable strategy of chemical labeling of morphine (M) and 6-acetyl morphine (6-AM) using diazonium salts is described. M or 6-AM was coupled with aryl diazoinum salts to give morphine azo dyes. The coupling of the diazotized 4,4′-diaminostilbene with M or 6-AM in ratio 1:2 gave stilbene-based azo dyes containing two M or 6-AM units, respectively. Diazotization of 5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin and subsequent azo coupling of the diazoniun salt with M and with 6-AM was our route to get highly fluorescent morphine dyes. The resulting dyes can exist in two possible tautomeric structures, azo and hydrazone, stabilized to a significant extent by intramolecular H-bonding. It was shown that these dyes exists predominantly or exclusively in their hydrazone form. This conclusion is drawn from the lack of a distinct band in the 380–420 nm region of the absorption spectra (a region in which the long wavelength absorption band for the azo-form is observed), together with results of NMR studies in deuterated DMSO. The tautomeric properties of the compounds were judged by density functional calculations at the B3LYP/6-31G* and B3LYP/6-31G** levels. The analysis of spiked compounds in human urine samples was studied by capillary electrophoresis (CE) with UV-fluorescence photo-diode array detectors.

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## INTRODUCTION

A great amount of attention continues to be devoted to the development of synthetic molecular receptors with the ability to recognize neutral organic species, including abused drugs. The morphine alkaloids comprise a family of structurally related natural products of unique clinical importance in medicine [1]. Morphine is a fascinating compound that has been used as an efficient analgesic and is indispensable in treating pains associated with cancer [2]. Morphine (M) is also found in normal brain, blood, and liver tissue [3]. However, it is strictly controlled by authorities due to its addictive nature. On the other hand, the unusual architecture of M has offered a continuing challenge to the art and science of organic synthesis (Fig. 1) [4,5]. Hence, a number of morphine derivatives have been reported to date [6]. Heroin, which is obtained synthetically from the acetylation of M, has an analgesic potency two to three times that of the parent drug and, due to the two acetyl groups, has better penetration across the blood-brain barrier [7]. Heroin itself is rarely present in detectable quantities in body fluids. The drug hydrolyses rapidly to 6-acetylmorphine (6-AM), which in turn hydrolyses to M. Therefore, heroin consumption can be confirmed by identifying its two primary metabolites [8,9]. In addition, heroin is different from most other opioids in that it has little or no affinity for opioid receptors in the brain. The analgesic effects of the drug are attributed to the combined effect of 6-AM and M [2].

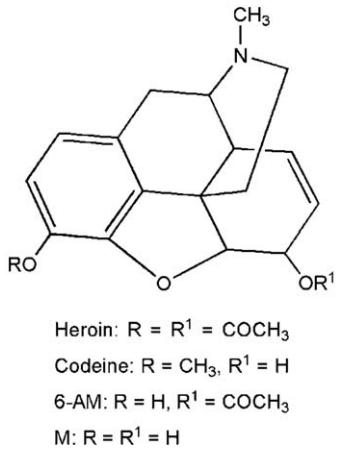



**Figure 1.** Schematic structures of some abused drugs [heroin, codeine, 6-acetylmorphine (6-AM), and morphine (M)].

It is generally accepted that two sites, the basic nitrogen and the phenol moiety, are necessary for analgesic binding to its receptors [10,11]. The phenolic hydroxyl group is recognized as a requisite for the formation of a hydrogen bond with a dipolar site on the receptor and for good antinociceptive activity [11,12]. However, the free hydroxyl group is also a potential site for metabolism, conjugation, and excretion resulting in low oral bioavailability and short duration of action [13,14]. One of the approaches to improve the pharmacological properties of analogues is to modify this phenolic hydroxyl function. Several potent compounds have been synthesized and identified by replacing the hydroxyl moiety of morphinans with other functional groups (amino, carboxamido, 2-aminothiazole) [15,16].

The use of dyes in chemistry, biology, and medicine is growing continuously, with many new applications in the diagnosis and treatment of disease [17–19]. Moreover, azo dyes have been known for over forty years, where they were used for investigations in cancer treatment [20]. Numerous fluorescent probes for monosaccharides based on azo dyes have been described in the literature. Moreover, many abused drugs (*i.e.*, heroin, codine, 6-AM and M) are tertiary amines (Fig. 1) and are not compatible with the most commonly utilized amine reactive fluorescent dyes. These dyes include compounds such as fluorescein isothiocyanate isomer I (FITC) [21], 4-(4,6-dichloro-*s*-triazin-2-ylamino)fluorescein (DTAF) [22], 4-fluoro-7-nitrobenzofurazan (NBD-F) [23], and 3-(4-carboxybenzoyl)-2-quinolinecarboxaldehyde (CBQCA) [24]. Other fluorogenic reagents specifically made for derivatization of the tertiary amine group such as the malonic acid/acetic anhydride system [25] and the aconitic acid method [26] result in a deteriorating effect on the fluorescence of the reaction product. In addition, the products of these reactions are unstable, light sensitive, and give many components that seem to be associated with the reagent blank.

The most important problems for development of a new morphine detector are tedious and time-consuming reaction steps. In an effort to develop novel morphine derivatives that are effective as chemosensors for heroin use at very low concentrations, herein we report fast, economic, and simple approaches to the synthesis of a novel series of highly fluorescence azo-morphine dyes. Compared with the previously reported methods [20–27], the present test produces an intense color which is not affected by the presence of any diluents or adulterants and which is easily adapted to field use. Diaminostilbene and porphyrin related dyes are strongly light absorbing and highly luminescent [28,29]. These dyes are covalently attached to proteins and other biological and nonbiological materials to make these materials fluorescent so that they can be detected. The binding advantage of *trans*-4,4′-bis-diazostilbene or diazoporphyrin over diazobenzene is production of highly fluorescent dyes that can be detected even at very low morphine concentration. The developed method was used for determination of highly diluted M and 6-AM in spiked human urine sample with very high accuracy and precision.

## EXPERIMENTAL

**Materials.** All chemicals and reagents were commercially available and were used as received. Most of solvents were at least of reagent grade and were used without further purification. M, 6-AM, and codeine were obtained from Lipomed Inc. (One Broaway, Cambridge, MA, USA). 5-(*p*-Aminophenyl)-10,15,20-triphenylporphyrin was prepared according to the literature [30]. Analytical thin layer chromatography (TLC) was performed on a glass plates of silica gel 60 $GF_{254}$ (Merck). Visualization was accompanied by UV light (254 nm). Column chromatography was conducted on silica gel 60 (Merck 70–230 mesh). $^{1}H$ NMR and $^{13}C$ NMR spectra were measured on JEOL JNM-AL 300 (300 MHz) and VARIAN UNITY-INOVA 400 (400 MHz) spectrometers. Chemical shifts of $^{1}H$ NMR and $^{13}C$ NMR were expressed in parts per million (ppm, δ units), and coupling constant was expressed in units of Hertz (Hz). Elemental analyses were performed by a Perkin-Elmer 2400 automatic elemental analyzer. All compounds gave elemental analysis within ±0.4%. Electrospray ionization (ESI) mass spectra were recorded on a Shimadzu LCMS-2010 eV spectrometer in $CH_3OH$. The UV–vis data were measured on Shimadzu 3101 PC instrument. The fluorescence (excitation and emission) spectra were determined with Perkin Elmer Lambada 50 PC spectrophotometer: excitation slit width = 5 nm, emission slit width = 5 nm. AP/ACE MDQ CE system coupled with photo-diode array detectors (PAD) supplied from Beckman (Fullerton, CA, USA) was used throughout the experiments. Separation was carried out in a 50.2 cm long × 50 μm (10 cm to the detector, short way). After each

experiment, the capillary was washed with 0.1 mol $dm^{-3}$ sodium hydroxide for 2.0 min, distilled water for 1.0 min, and the separation electrolyte for 2.0 min. Hydrodynamic injection mode was applied for sample loading. 32 Karat version 7.0 supplied from Beckman (Fullerton, CA, USA) was used for controlling the CE system as well as data acquisition and processing.

**General procedure for the synthesis of compounds 1–6.** ***Diazotization.*** A 0–5°C solution of substituted aniline (0.5 mmol) and 1*N* HCl (2 mL) in deionized (DI) water (5 mL) was treated with a 0–5°C solution of $NaNO_2$ (100 mg, 1.5 mmol) in DI water (5 mL) and the diazotization continued for 10 min.

***Coupling.*** The resulting diazonium salt solution was poured into a 0–5°C solution of M or 6-AM (0.5 mmol) in NaOH (50 mg, 1.25 mmol, 5 mL). The mixture was stirred at 0–5°C for another 10 min. The resulting precipitate was filtered off, washed with NaCl, DI water, and dried *in vacuo*. The products were purified by flash column chromatography using hexane and ethylacetate in ratio 2:1 as eluent. Upon storage of the azo coupling products **1–6** at ambient temperature for several months neither change in their UV–vis spectra nor appearance of foreign signals in their $^1$HNMR spectra were observed, which provides evidence of their stability.

***4-(Morphine-2-yl-azo)benzenesulfonic acid (1).*** Yield: 200 mg (87%), mp = 156–158°C, $R_f$ = 0.48 as a red solid; IR (KBr) ν: 3385, 3379 (OH), 1641 (C=C, alkene), 1620 (C=O, hydrazone), 1605 (C=N), 1525 (C=C, aromatic), 1350, 1150 ($SO_2$), 1282, 1091 (C—O—C) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO): δ = 12.75 (br s, 1H, NHO), 7.78 (d, *J* = 7.85 Hz, 2H, aromatic H), 7.56 (d, *J* = 7.85 Hz, 2H, aromatic H), 7.02 (s, 1H, aromatic H), 5.53 (d, 1H, *J* = 9.12 Hz, CH=CH), 5.28 (d, 1H, *J* = 9.12 Hz, CH=CH), 4.76 (d, 1H, *J* = 7.5 Hz), 4.23–4.27 (m, 1H), 3.37–3.32 (m, 1H), 3.01 (d, 1H, *J* = 17.5 Hz), 2.59–2.64 (m, 1H), 2.56 (d, 1H, *J* = 7.05 Hz), 2.42 (dd, 1H, *J* = 5.24 Hz), 2.36 (s, 3H, $NCH_3$), 2.25 (dd, 1H, *J* = 4.2 Hz), 1.96 (td, 1H, *J* = 9.32 Hz, *J* = 5.12 Hz), 1.87 (d, 1H, *J* = 10.54 Hz); $^{13}$C NMR (75 MHz, DMSO) δ = 183.23 (C=O), 156.59, 153.45, 147.23, 139.75, 131.17, 126.5, 42.95 (C), 133.05, 129.89, 128.12, 125.15, 118.23, 117.76, 91.25, 68.45, 59.34, 40.86 (CH), 45.56, 35.05, 21.06 ($CH_2$), 42.69 (N—$CH_3$); MS (ESI), *m*/*z*(%): 469 (100) [$M^+$]; Anal. Calcd. for $C_{23}H_{23}N_3O_6S$ (469.51): C 58.84, H 4.94, N 8.95; found: C 58.81, H 4.89, N 8.92.

***2-(m-Carboxy-phenylazo)morphine (2).*** Yield: 165 mg (76%), mp = 184–186°C, $R_f$ = 0.32 as an orange solid; IR (KBr) ν: 3382, 3375 (OH), 1712 (C=O, carboxylic), 1642 (C=C, alkene), 1618 (C=O, hydrazone), 1595 (C=N), 1521 (C=C, aromatic), 1280, 1087 (C—O—C) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO): δ = 13.25 (br s, 1H, NHO), 7.86–7.45 (m, 4H, aromatic H), 6.85 (s, 1H, aromatic H), 5.57 (d, 1H, *J* = 9.0 Hz, CH=CH), 5.32 (d, 1H, *J* = 9.0 Hz, CH=CH), 4.69 (d, 1H, *J* = 7.42 Hz), 4.2–4.25 (m, 1H), 3.35–3.3 (m, 1H), 3.04 (d, 1H, *J* = 15.9 Hz), 2.54–2.59 (m, 1H), 2.51 (d, 1H, *J* = 7.0 Hz), 2.43 (dd, 1H, *J* = 4.86 Hz), 2.35 (s, 3H, $NCH_3$), 2.25 (dd, 1H, *J* = 4.12 Hz), 1.97 (td, 1H, *J* = 9.67 Hz, *J* = 5.52 Hz), 1.91 (d, 1H, *J* = 10.05 Hz); $^{13}$C NMR (75 MHz, DMSO) δ = 181.83, 177.56 (C=O), 155.69, 145.36, 138.45, 131.65, 126.85, 42.64, (C), 133.21, 126.37, 126.05, 125.87, 125.12, 124.86, 119.45, 118.69, 91.86, 67.75, 58.94, 40.25 (CH), 45.12, 34.68, 21.46 ($CH_2$), 42.85 (N—$CH_3$); (ESI): *m*/*z*(%): 433 (85) [$M^+$]; Anal. Calcd. for $C_{24}H_{23}N_3O_s$ (433.46): C 66.50, H 5.35, N 9.69; found: C 66.42, H 5.29, N 9.61.

***2-(p-Methoxy-phenylazo)morphine (3).*** Yield: 193 mg (92%), mp = 167–169°C, $R_f$ = 0.39 as red solid; IR (KBr) ν: 3382, 3375 (OH), 1635 (C=C, alkene), 1624 (C=O, hydrazone), 1610 (C=N), 1523 (C=C, aromatic), 1287, 1094 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 12.75 (br s, 1H, NHO), 7.79 (d, *J* = 8.12 Hz, 2H, aromatic H), 7.54 (d, *J* = 8.12 Hz, 2H, aromatic H), 6.97 (s, 1H, aromatic H), 5.42 (d, 1H, *J* = 9.25 Hz, CH=CH), 5.25 (d, 1H, *J* = 9.25 Hz, CH=CH), 4.68 (d, 1H, *J* = 7.51 Hz), 4.22–4.25 (m, 1H), 3.41–3.55 (m, 1H), 3.02 (d, 1H, *J* = 17.32 Hz), 2.58–2.65 (m, 1H), 2.57 (d, 1H, *J* = 7.19 Hz), 2.45 (dd, 1H, *J* = 5.35 Hz), 2.36 (s, 3H, $NCH_3$), 2.27 (dd, 1H, *J* = 4.17 Hz), 2.05 (td, 1H, *J* = 9.05 Hz, *J* = 5.6 Hz), 1.92 (d, 1H, *J* = 10.51 Hz); $^{13}$CNMR (75 MHz, DMSO) δ = 183.52 (C=O), 158.45, 156.79, 146.45, 138.95, 131.57, 126.87, 42.45, (C), 132.98, 128.45, 127.96, 125.34, 119.12, 118.07, 91.35, 67.85, 58.96, 40.84 (CH), 45.56, 35.05, 21.06 ($CH_2$), 60.13 (O—$CH_3$), 42.69 (N—$CH_3$). (ESI): *m*/*z*(%) 419 (93) [$M^+$]; Anal. Calcd. for $C_{24}H_{25}N_3O_4$ (419.47): C 68.72, H 6.01, N 10.02; Found: C 68.67, H 6.00, N 10.00.

***2-(p-Nitro-phenylazo)morphine (4).*** Yield: 182 mg (84%), mp = 192–194°C, $R_f$ = 0.41 as a red solid. IR (KBr) ν: 3380, 3375 (OH), 1638 (C=C, alkene), 1620 (C=O, hydrazone), 1600 (C=N), 1520 (C=C, aromatic), 1517, 1334, ($NO_2$), 1282, 1091 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.52 (br s, 1H, NHO), 7.82 (d, *J* = 6.52 Hz, 2H, aromatic H), 7.65 (d, *J* = 6.52 Hz, 2H, aromatic H), 7.05 (s, 1H, aromatic H), 5.62 (d, 1H, *J* = 9.07 Hz, CH=CH), 5.19 (d, 1H, *J* = 9.07 Hz, CH=CH), 4.72 (d, 1H, *J* = 6.95 Hz), 4.37–4.32 (m, 1H), 3.35–3.29 (m, 1H), 3.0 (d, 1H, *J* = 16.98 Hz), 2.55–2.6 (m, 1H), 2.52 (d, 1H, *J* = 7.0 Hz), 2.45 (dd, 1H, *J* = 5.1 Hz), 2.35 (s, 3H, $NCH_3$), 2.24 (dd, 1H, *J* = 4.56 Hz), 1.94 (td, 1H, *J* = 8.79 Hz, *J* = 5.12 Hz), 1.85 (d, 1H, *J* = 10.44 Hz); $^{13}$CNMR (75 MHz, DMSO) δ = 182.54 (C=O), 157.55, 155.05, 147.15, 139.05, 132.02, 126.52, 42.63, (C), 132.85, 128.49, 128.02, 125.65, 119.22, 118.47, 91.05, 67.75, 58.72, 40.79 (CH), 45.34, 34.79, 22.12 ($CH_2$), 42.77 (N—$CH_3$). (ESI): *m*/*z*(%) 434 (91) [$M^+$]; Anal. Calcd. for $C_{23}H_{22}N_4O_s$ (434.44): C 63.59, H 5.10, N 12.90; found: C 63.54, H 5.06, N 12.86.

***4-(6-Acetylmorphine-2-yl-azo)benzenesulfonic acid (5).*** Yield: 230 mg (90%), mp = 145–147°C, $R_f$ = 0.5 as a red solid; IR (KBr) ν: 3382, 3375 (OH), 1722 (C=O, acetyl), 1640 (C=C, alkene), 1619 (C=O, hydrazone), 1602 (C=N), 1521 (C=C, aromatic), 1350, 1150 ($SO_2$), 1285, 1095 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.27 (br s, 1H, NHO), 7.77 (d, *J* = 7.9 Hz, 2H, aromatic H), 7.58 (d, *J* = 7.9 Hz, 2H, aromatic H), 7.0 (s, 1H, aromatic H), 5.52 (d, 1H, *J* = 9.02 Hz, CH=CH), 5.25 (d, 1H, *J* = 9.02 Hz, CH=CH), 4.75 (d, 1H, *J* = 7.32 Hz), 4.25–4.29 (m, 1H), 3.35–3.4 (m, 1H), 3.04 (d, 1H, *J* = 17.56 Hz), 2.59–2.64 (m, 1H), 2.53 (d, 1H, *J* = 7.0 Hz), 2.40 (dd, 1H, *J* = 5.24 Hz), 2.35 (s, 3H, $NCH_3$), 2.26 (dd, 1H, *J* = 4.12 Hz), 2.15 (s, 3H, $COCH_3$), 2.0 (td, 1H, *J* = 8.75 Hz, *J* = 5.25 Hz), 1.9 (d, 1H, *J* = 10.26 Hz); $^{13}$CNMR (75 MHz, DMSO) δ = 181.76, 172.56 (C=O), 157.21, 154.24, 147.05, 138.95, 131.55, 126.65, 42.31, (C), 132.46, 129.44, 128.75, 125.19, 118.25, 117.86, 91.25, 68.45, 59.34, 40.86 (CH), 45.56, 35.05, 22.06 ($CH_2$), 42.69, 21.17 (N—$CH_3$, $COCH_3$). (ESI): *m*/*z*(%) 511 (96) [$M^+$]; Anal. Calcd. for

$C_{25}H_{25}N_3O_7S$ (511.55): C 58.7, H 4.93, N, 8.21; found: C 58.57; H, 4.91; N, 8.15.

***2-(m-Carboxy-phenylazo)-6-acetylmorphine (6).*** Yield: 202 mg (85%), mp = 177–179°C, $R_f$ = 0.35 as an orange solid; IR (KBr) ν: 3377 (OH), 1725 (C=O, acetyl), 1718 (C=O, carboxylic), 1639 (C=C, alkene), 1619 (C=O, hydrazone), 1592 (C=N), 1525 (C=C, aromatic), 1282, 1085 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.39 (br s, 1H, NHO), 7.82–7.5 (m, 4H, aromatic H), 6.89 (s, 1H, aromatic H), 5.55 (d, 1H, *J* = 8.7 Hz, CH=CH), 5.34 (d, 1H, *J* = 8.7 Hz, CH=CH), 4.7 (d, 1H, *J* = 7.75 Hz), 4.24–4.27 (m, 1H), 3.36–3.32 (m, 1H), 3.03 (d, 1H, *J* = 15.35 Hz), 2.55–2.61 (m, 1H), 2.51 (d, 1H, *J* = 7.4 Hz), 2.45 (dd, 1H, *J* = 4.85 Hz), 2.3 (s, 3H, $NCH_3$), 2.25 (dd, 1H, *J* = 4.6 Hz), 2.09 (s, 3H, $CH_3$), 1.93 (td, 1H, *J* = 9.11 Hz, *J* = 5.25 Hz), 1.89 (d, 1H, *J* = 10.29 Hz); $^{13}$CNMR (75 MHz, DMSO) δ = 185.05, 176.98, 172.89 (C=O), 155.43, 145.35, 138.42, 131.62, 126.25, 42.65, (C), 133.27, 126.57, 126.11, 125.23, 125.34, 124.67, 119.49, 118.21, 91.28, 67.45, 58.75, 40.36 (CH), 45.16, 34.59, 21.61 ($CH_2$), 42.85, 21.99 (N—$CH_3$, $COCH_3$); (ESI): *m*/*z*(%): 475 (88) [$M^+$]; Anal. Calcd. for $C_{26}H_{25}N_3O_6$ (475.49): C 65.67, H 5.30, N 8.84; found: C 65.51, H 5.29, N 8.79.

**General procedure for the synthesis of compounds 7 and 8.** These compounds were prepared from M or 6-AM (0.5 mmol) and *trans*, 4,4′-diaminostilbene (407 mg, 1.2 mmol), using the procedure described for **1–6**.

***Trans-4,4′-bis(morphine-2-yl-azo)stilbene (7).*** Yield: 365 mg (91%), mp = 199–201°C, $R_f$ = 0.45 as a red solid; IR (KBr) ν: 3385, 3376 (OH), 1642 (C=C, alkene), 1624 (C=O, hydrazone), 1605 (C=N), 1527 (C=C, aromatic), 1284, 1087 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.45 (br s, 2H, NHO), 7.80 (d, 2H, aromatic H), 7.54 (t, 2H, aromatic H), 7.44 (s, 2H, CH=CH), 4.55 (m, 2H), 4.21–4.26 (m, 2H), 3.38–3.33 (m, 2H), 3.0 (m, 2H), 2.59–2.64 (m, 1H), 2.55 (m, 2H), 2.39 (m, 2H), 2.32 (s, 6H, $NCH_3$), 2.21 (m, 2H), 1.99 (m, 2H), 1.89 (m, 2H); $^{13}$CNMR (75 MHz, DMSO) δ = 182.47 (C=O), 155.98, 146.75, 138.85, 131.27, 126.35, 42.56, (C), 133.12, 129.59, 128.19, 125.16, 118.29, 117.77, 91.45, 68.86, 59.51, 52.43, 40.86 (CH), 45.52, 35.12, 22.12 ($CH_2$), 42.47 (N—$CH_3$); (ESI): *m*/*z*(%) 802 (85) [$M^+$]; Anal. Calcd. for $C_{48}H_{46}N_6O_6$ (802.92): C 71.80, H 5.77, N 10.47; Found: C 71.76, H 5.73, N 10.44.

***Trans-4,4′-bis(6-acetylmorphine-2-yl-azo)stilbene (8).*** Yield: 365 mg (91%), mp = 212–214°C, $R_f$ = 0.52 as a red solid; IR (KBr) ν: 3384, 3377 (OH), 1730 (C=O, acetyl), 1640 (C=C, alkene), 1625 (C=O, hydrazone), 1602 (C=N), 1522 (C=C, aromatic), 1281, 1085 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.49 (br s, 2H, NHO), 7.78 (d, 2H, aromatic H), 7.61 (t, 2H, aromatic H), 7.46 (s, 2H, CH=CH), 4.52 (m, 2H), 4.22–4.27 (m, 2H), 3.4–3.36 (m, 2H), 3.01 (m, 2H), 2.62–2.64 (m, 1H), 2.52 (m, 2H), 2.35 (m, 2H), 2.27 (s, 6H, $NCH_3$), 2.23 (m, 2H), 2.19 (s, 6H, $COCH_3$), 1.97 (m, 2H), 1.86 (m, 2H); $^{13}$CNMR (75 MHz, DMSO) δ = 181.94, 171.67 (C=O), 155.43, 147.05, 139.05, 132.05, 126.63, 42.83, (C), 133.24, 129.69, 128.23, 125.17, 118.23, 117.46, 91.69, 68.57, 59.38, 52.46, 40.82 (CH), 45.62, 35.45, 22.61 ($CH_2$), 42.49 (N—$CH_3$); (ESI): *m*/*z*(%) 886 (90) [$M^+$]; Anal. Calcd. for $C_{52}H_{50}N_6O_8$ (886.99): C 70.41, H 5.68, N 9.47; Found: C 70.39, H 5.67, N 9.45.

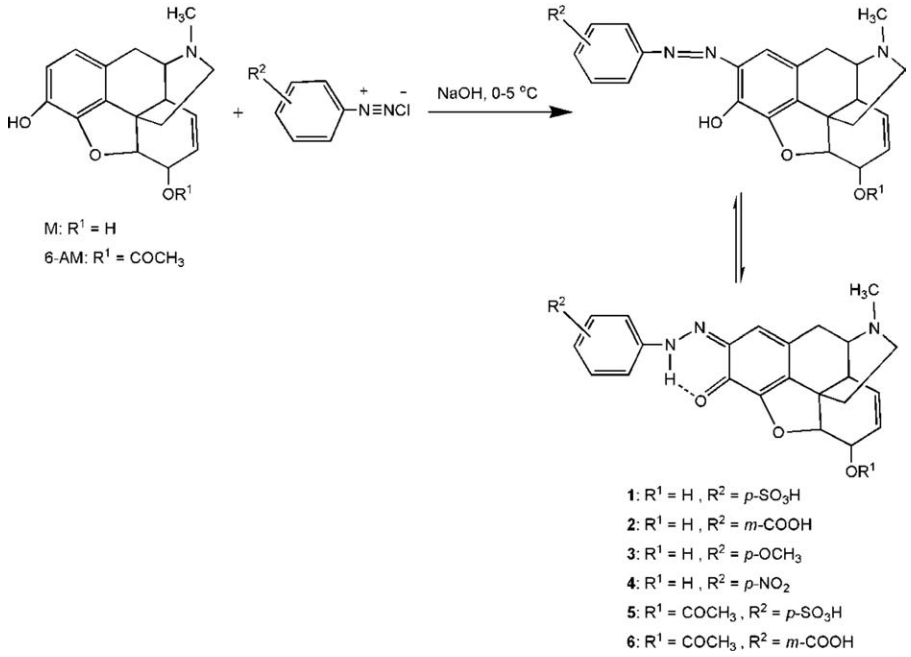
**General procedure for the synthesis of compounds 10 and 11.** A 0–5°C solution of sodium nitrite (0.12 g, 1.74 mmol) in water (2 mL) was added dropwise to a stirred solution of 5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin (785 mg, 1.25 mmol) in 1*N* HCl (5 mL). The mixture was stirred at 5°C for 15 min. A solution of sodium acetate (0.14 g, 1.71 mmol) in water (5 mL) and M or 6-AM (1.11 mmol) in 3% aqueous NaOH (5 mL) were added to the diazonium salt solution. Then, the reaction mixture was stirred at room temperature for 15 min and diluted to 100 mL with water and filtered. The filtrate was neutralized with HCl to pH 7, the porphyrin filtered off, washed with aqueous ammonia solution (10%), then with water, and dried to constant weight at room temperature. For purification, the porphyrin was dissolved in boiling ether (50 mL) and chromatographed on a column (2.5 cm × 60 cm) of silica gel eluting with ether. The elute was evaporated to 5 mL and porphyrin (**10** or **11**) was precipitated with hexane (20 mL).

***5-(Morphine-2-yl-azophenyl)10,15,20-triphenylporphyrin (10).*** Yield: 950 mg, (82%), mp = 230–232°C, $R_f$ = 0.37 as a voilet solid; IR (KBr) ν: 3384, 3377 (OH), 3310 (CH), 2989, 2927 (NH), 1638 (C=C, alkene), 1625 (C=O, hydrazone), 1604(C=N), 1525 (C=C, aromatic), 1280, 1087 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.52 (br s, 2H, NHO), 8.65–8.96 (m, 8H, β-pyrrole), 7.02–8.21 (m, 19H, $H_{arom}$), 5.64 (d, 1H, *J* = 9.05 Hz, CH=CH), 5.2 (d, 1H, *J* = 9.05 Hz, CH=CH), 4.75 (d, 1H, *J* = 7.0 Hz), 4.35–4.25 (m, 1H), 3.35–3.29 (m, 1H), 3.02 (d, 1H, *J* = 17.0 Hz), 2.55–2.6 (m, 1H), 2.52 (d, 1H, *J* = 8.42 Hz), 2.45 (dd, 1H, *J* = 5.5 Hz), 2.35 (s, 3H, $NCH_3$), 2.25 (dd, 1H, *J* = 4.5 Hz), 1.99 (td, 1H, *J* = 8.9 Hz, *J* = 5.3 Hz), 1.92 (d, 1H, *J* = 10.52 Hz), −2.79 (s, 2H, NH); $^{13}$CNMR (75 MHz, DMSO) δ = 181.94 (C=O), 155.43, 153.56, 149.37, 148.82, 147.05, 139.05, 136.92, 135.8, 132.05, 126.63, 42.83, (C), 133.83, 133.24, 130.82, 129.69, 128.37, 128.23, 125.32, 125.17, 118.23, 117.8, 117.46, 115.03, 112.01, 108.75, 91.54, 67.43, 58.78, 52.46, 40.82 (CH), 45.62, 35.45, 22.65 ($CH_2$), 42.52 (N—$CH_3$); (ESI): *m*/*z*(%) 925 (100) [$M^+$]; Anal. Calcd. for $C_{61}H_{47}N_7O_3$ (926.07): C 79.11, H 5.12, N 10.59; Found: C 79.03, H 5.01, N 10.49.

***5-(6-Acetylmorphine-2-yl-azophenyl)10,15,20-triphenylporphyrin (11).*** Yield: 983 mg (85%), mp = 219–221°C, $R_f$ = 0.42 as a voilet solid; IR (KBr) ν: 3384, 3377 (OH), 3310 (CH), 2989, 2927 (NH), 1722 (C=O acetyl), 1638 (C=C, alkene), 1625 (C=O hydrazone), 1604(C=N), 1525 (C=C, aromatic), 1280, 1087 (C—O—C) $cm^{-1}$; $^1$HNMR (300 MHz, DMSO): δ = 13.35 (br s, 2H, NHO), 8.95–8.60 (m, 8H, β-pyrrole), 8.25–6.94 (m, 19H, $H_{arom}$), 6.83 (s, 1H, aromatic H), 5.56 (d, 1H, *J* = 8.5 Hz, CH=CH), 5.37 (d, 1H, *J* = 8.5 Hz, CH=CH), 4.52 (d, 1H, *J* = 7.8 Hz), 4.32–4.27 (m, 1H), 3.38–3.33 (m, 1H), 3.04 (d, 1H, *J* = 15.35 Hz), 2.59–2.64 (m, 1H), 2.52 (d, 1H, *J* = 7.4 Hz), 2.45 (dd, 1H, *J* = 4.85 Hz), 2.32 (s, 3H, $NCH_3$), 2.25 (dd, 1H, *J* = 4.6 Hz), 2.14 (s, 3H, $CH_3$), 1.95 (td, 1H, *J* = 9.11 Hz, *J* = 5.25 Hz), 1.87 (d, 1H, *J* = 10.29 Hz), −2.79 (s, 2H, NH); $^{13}$CNMR (75 MHz, DMSO) δ = 183.67, 172.54 (C=O), 155.45, 154.06, 149.49, 148.85, 147.25, 139.15, 136.87, 135.82, 132.35, 127.75, 42.65, (C), 133.73, 133.26, 130.89, 129.73, 128.25, 128.21, 125.37, 125.36, 118.22, 117.85, 117.29, 115.11, 112.14, 108.76, 91.55, 67.45, 58.77, 52.49, 40.85 (CH), 45.64, 35.46, 22.68 ($CH_2$), 42.22, 23.19 (N—$CH_3$, $COCH_3$); (ESI): *m*/*z*(%) 967 (93) [$M^+$]; Anal. Calcd. for $C_{63}H_{49}N_7O_4$ (968.11): C 78.16, H 5.10, N 10.13; Found: C 78.02, H 5.07, N 10.09.

**Biological studies.** A 500 mg Bond Elut SPE column was used for the extraction. The SPE columns were conditioned by

**Scheme 1**




the sequential passage of 2 × 3 mL of methanol, 2 × 3 mL of water, and 2 × 5 mL of water adjusted to pH 9.5 with $NH_4OH$. Ten millilitres of human urine sample adjusted to pH 9.5 with $NH_4OH$ was vortex, centrifuged, and applied to the SPE columns at a rate of 1.0 mL/min. The columns were washed with 2 × 5 mL of distilled water and left to dry for 10 min. The drugs were eluted with a solution consisting of a single phase mixture of dichloromethane/acetone (50/50) and collected in glass tubes. The elution solvent was evaporated to dryness under a nitrogen stream. The dried residues were then reconstituted in slightly warm water, and derivatization was carried out and then the samples were analyzed using AP/ACE MDQ CE system coupled with photo-diode array detectors (PAD).

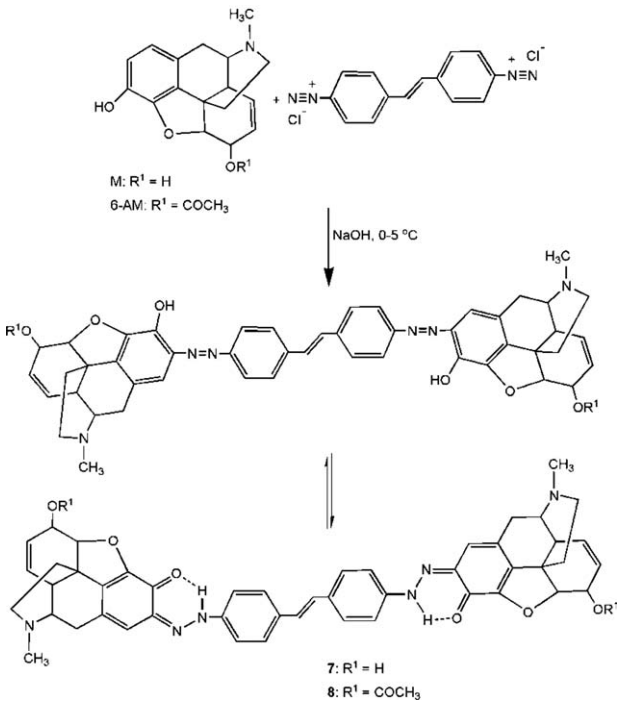
## RESULTS AND DISCUSSION

**Synthesis.** Our straightforward synthesis of morphine azo dyes (**1**–**6**) is outlined in Scheme 1. In a first step, the diazonium ions of aniline derivatives were generated with sodium nitrite in 1*N* HCl. The diazonium ions were then coupled by nucleophilic substitution with the corresponding substrates M or 6-AM. Azo coupling reactions were performed using the diazonium salts of 4-aminosulfonic acid, 3-aminobenzoic acid, 4-methoxyaniline, and 4-nitroaniline to yield 2-(arylazo)morphines **1**–**6**, respectively, (Scheme 1). No reaction was found, however, to occur with codeine under the same reaction conditions.

Synthesis of fluorescent azostilbene morphine dyes was achieved by reaction of *trans*-4,4′-diazostilbene dihydrochloride with M or 6-AM in 1:2 stoichiometric ratio to give stilbene based azo dyes containing two M (**7**) or two 6-AM (**8**) moieties as shown in Scheme 2. The resulting bis-azo dye are belong to the class of direct dyes [31,32]. Furthermore, we have established that *5*-(*p*-aminophenyl)-10,15,20-triphenylporphyrin (**9**) [30] is readily diazotized with sodium nitrite in aqueous mineral acid solution. The diazonium salt obtained is fairly stable; it decomposes significantly at temperature greater than 25 °C. The reaction of porphyrin diazonium salt with M or 6-AM leads to porphyrins containing residues of azo dyes in *meso* position of **10** or **11**, respectively (Scheme 3). The resulting colored compounds were purified by flash column chromatography using hexane/ethyl acetate (2:1) as eluent to produce azo-M (**1**–**4**, **7**, and **10**) and azo-6-AM (**5**, **6**, **8**, and **11**) with excellent yields. Azo coupling reactions of morphines occur predominately ortho to the electron donating hydroxyl group of the morphine aromatic ring. Hence, the inclusion of this design motif in the target dyes avoids potentially difficult separation of isomers.

**Spectroscopic studies.** Overall characterization of dye structures was carried out by elemental analysis, NMR, UV–vis, IR, and mass spectrometry (see experimental section for details). The NMR spectra of compounds **1**–**8**, **10**, and **11** are consistent with proposed structures, showing the expected features with correct integration ratios. Both $^1H$ and $^{13}C$ NMR spectra indicated the appearance of new signals corresponding to the aryl moiety of each azo-compound (Fig. 2). Spectral

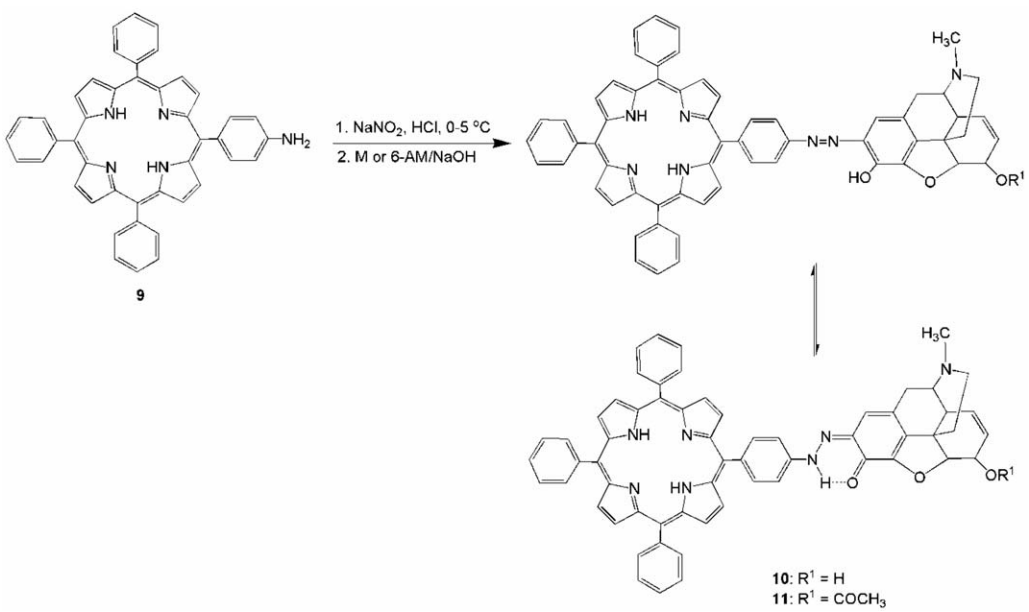
**Scheme 2**




properties of synthesized dyes were affected by intramolecular hydrogen bond between the phenolic hydroxyl group of morphine moiety and the central nitrogen atom of the azo bridge of the azo dye residues. Azo dyes in which the azo group is conjugated with a hydroxyl group can exhibit azo-hydrazone tautomerism, and NMR spectroscopy is established as an effective technique to study tautomer composition [33–35]. The intramolecular hydrogen bond ring is essentially planar and coplanar with its adjacent phenyl ring, which stabilized the hydrazone form. 2-Arylazomorphine derivatives (dyes **1**–**8**, **10**, and **11**) exist predominantly in the hydrazone form via intramolecular hydrogen bonds, which result in the linearity and coplanar conformation of the dyes [28]. The proton peaks involved in hydrogen bonds appear at much lower field than normal proton peak of hydroxyl group and these (12.75–13.52 ppm for dyes **1**–**8**, **10**, and **11**) were confirmed by $^{1}$H NMR. The downfield position of the resonance from the hydrazone proton is attributed to internal hydrogen bonding in which the carbonyl oxygen is hydrogen bonded to this proton [33]. Dyes that occur as the azo tautomer show a $^{13}$C resonance at *ca*. 160 ppm from the carbon attached to the phenolic hydroxyl group, whereas those that occur as the hydrazone tautomer show a resonance at *ca*. 180 ppm for the same carbon atom within a carbonyl group (Fig. 2). Dyes that occur as both tautomers show a single resonance between these limits, due to rapid tautomerisation, with the position determined by the relative concentrations of the two tautomers [34–36]. $^{13}$C NMR spectra from DMSO samples of **1**–**8**, **10**, and **11** confirmed the hydrazone structure by detecting a new carbonyl peak at 181–183 ppm assigned to C3 of M or 6-AM and, thus, morphine dyes **1**–**8**, **10** and **11** are present as the hydrazone tautomer (*ca*. 100%).

According to DFT calculations at the B3LYP/6-31G* level, the hydrazono toutomers of **1**–**8**, **10**, and **11** are

**Scheme 3**



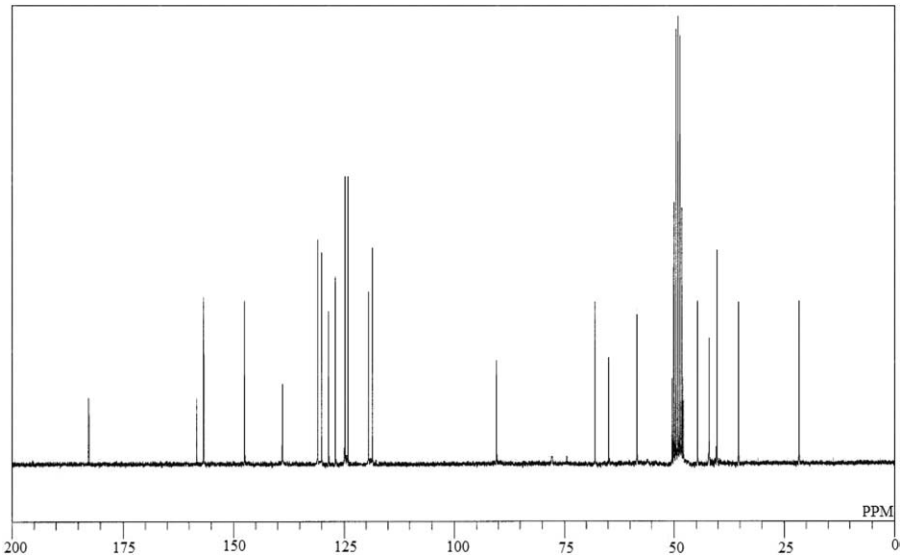



**Figure 2.** $^{13}C$ NMR spectrum of compound **3** in DMSO($d_6$) at 20°C.

favored over the azo toutomers by 2.4–3.6 kcal mole$^{-1}$. As major entropy differences and crystal lattice effects are not to be expected here, these results should secure the hydrazone formulas. Consequently, it can be considered that morphine azo dyes (**1–8**, **10**, and **11**) have such structures as shown in Schemes 1–3.

IR spectra assigned with the aid of the NMR data, provide fingerprints for hydrazone form and hydrogen bonding. The IR spectra of all the resulting colored compounds confirmed the presence of a C═O bond which resonates at 1625–1618 cm$^{-1}$. IR spectrum of compound **4** showed absorption bands at 1517 and 1334 cm$^{-1}$ due to the presence of a $NO_2$ group, whereas the $SO_2$ group of compound **1** and **5** has two vibrational frequencies at 1350 and 1150 cm$^{-1}$. Moreover, the vibrational frequency of aliphatic OH band ν(O─H) of M or the $COCH_3$ band ν(C═O) of 6-AM was not found to be sensitive to the connection of M or 6-AM with the azo derivatives. For compounds **1–4** and **7** ν(O─H) lies in the range of 3385–3375 cm$^{-1}$, and for compounds **5**, **6** and **8** ν(C═O) from 1730 to 1718 cm$^{-1}$, comparable to the frequencies of M ν(O─H) at 3373 cm$^{-1}$, and 6-AM ν(C═O) at 1713 cm$^{-1}$, indicating that the intra bonding of the morphine moiety was not perturbed by substitution on the phenyl ring.

Evidence in support of structures **1–8**, **10**, and **11** is presented by mass spectrometry. The ESI-MS spectra of these compounds in MeOH showed molecular ion peaks ($M^+$) corresponding to the formula of each compound. Mass spectra of all compounds showed molecular ion peaks corresponding to their expected pattern of abundance ranging from 85 to 100% (Fig. 3).

The electronic absorption spectra (EAS) of the investigated morphine dyes **1–8**, **10**, and **11** in ethanolic solutions were studied. There is no visual evidence for a band around 380–420 nm, which could be assigned to the azo form. The compounds comprised two to three bands in the UV region and one band in the visible region (Fig. 4). The band of shortest wavelength appearing in the range 210–255 nm was best ascribed to π–π* transition of the benzenoid system of the compounds. The second band observed in UV region, in the wavelength range 270–285 nm was attributed to π–π* transition within the furan heterocyclic moiety of the compounds. The third band observed in the UV region at 285–290 nm was assigned to n–π* electronic transition

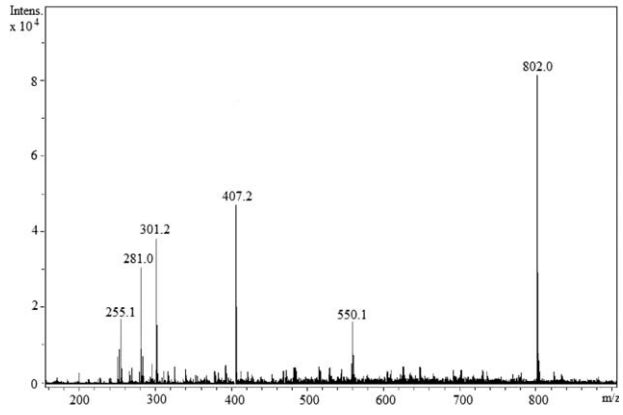



**Figure 3.** ESI-MS of compound **7** in $CH_3OH$.

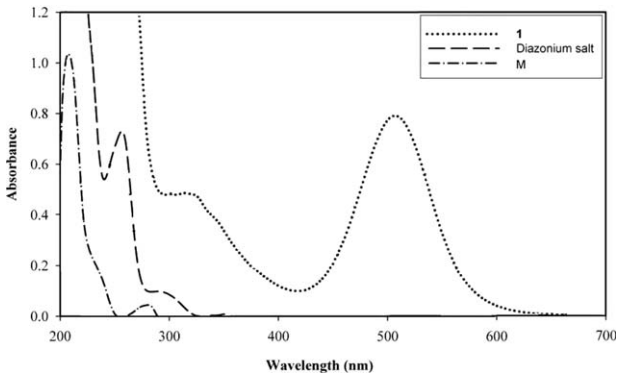



**Figure 4.** Electronic absorption spectra of $2 \times 10^{-5}$ mol dm$^{-3}$ of **1**, diazonium salt of sulfanilic acid and M.

of OH groups. The long wavelength band at about 510 nm corresponds to the hydrazone form [37] (Fig. 4). This band was capable of being assigned to π–π* transition involving the whole electronic system of the compounds with a considerable charge-transfer (CT) character. Such a CT originated mainly from the aryl azo to the morphine moiety, *i.e.*, this band was due to intramolecular CT transition. When analyzing EAS of the porphyrin azo dyes (**10** and **11**), it was difficult to draw an unambiguous conclusion as to whether the π system of the azo dye interacts with the π system of porphyrin ring. The Soret band of tetraphenyporphyrin ($\lambda_{max} \sim$ 400 nm; $\varepsilon \sim 4.75 \times 10^5$ dm$^3$ mol$^{-1}$ cm$^{-1}$) is found alongside with the broad absorption band of azo dye residue ($\lambda_{max} \sim$ 590 nm; $\varepsilon \sim 3.35 \times 10^4$ dm$^3$ mol$^{-1}$ cm$^{-1}$), which does not permit a confident judgment to be made on whether transfer of π electron density from the azo dye residue to the porphyrin ring has taken place. However, the sharp reduction in intensity of the Soret band and the growth in intensity of the electronic transition bands and also their bathochromic shift indicate the existence of such interactions.

The compounds (**1**–**8**) exhibited emission fluorescence peak even at very low concentration (5–8 $\times 10^{-9}$ mol dm$^{-3}$) in aqueous solution as indicated by capillary electrophoresis (CE) with UV-fluorescence photo diode-array detectors. However, compounds **10** and **11** showed highly intense fluorescence peaks at 665 and 670 nm, respectively. The synthesis of **10** and **11** will provide new insight into the role of morphine determination using simple and fast chemistry as well as highly sensitive techniques [*e.g.*, CE with laser induced fluorescence detector (LIF)].

**Biology.** The determination of M in biological samples has become almost a routine assay in many toxicology laboratories owing to the spread of the abuse of

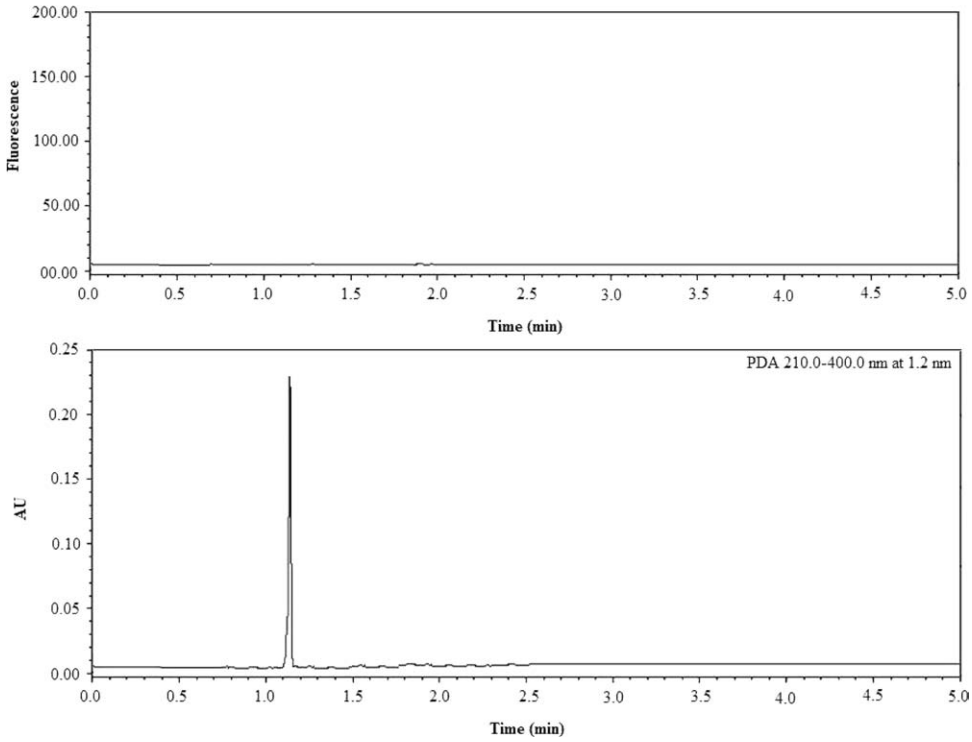



**Figure 5.** Electropherograms of $5 \times 10^{-6}$ mol dm$^{-3}$ diazonium salt of sulfanilic acid in water under the optimized conditions: 10.0 s injection time, applied voltage 25 kV, 25°C, 100 mmol dm$^{-3}$ borate electrolyte concentration, and pH 9.0.

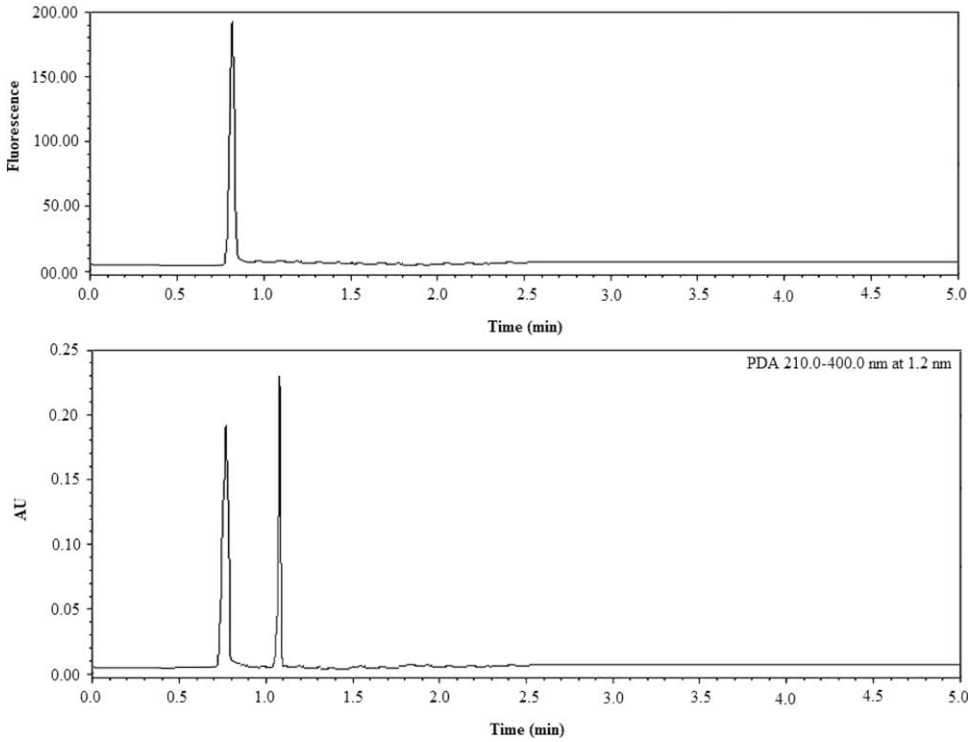



**Figure 6.** Electropherograms of human urine sample spiked with $5 \times 10^{-9}$ mol dm$^{-3}$ of M coupled with $5 \times 10^{-6}$ mol dm$^{-3}$ diazonium salt of sulfanilic acid under the optimized conditions: 10.0 s injection time, applied voltage 25 kV, 25°C, 100 mmol dm$^{-3}$ borate electrolyte concentration, and pH 9.0.

heroin, which is mainly biotransformed into M. In this experiment, the coupling reaction of diazonium salt of sulfanilic acid was carried out with drug-free urine sample and with urine sample spiked with M and 6-AM. No remarkable change was observed for the drug-free urine sample as indicated by CE (data not shown). For urine sample spiked with the M, a deep red color appeared at once which was measured by CE, giving two peaks after 45 s and 65 s corresponding to azo-M (**1**) and diazonium salt of sulfanilic acid, respectively, (Figs. 4 and 5). The extraction recoveries were found to be >99.5% and RSD values of the recovery did not exceed 0.92% indicating good repeatability of the adopted method.

## CONCLUSIONS

A number of M and 6-AM azo dyes were synthesized and the possibility of using these dyes as color chemosensors of abused drugs is reported. The synthesis starts from commercially available aniline derivatives and can be completed in one step with an overall yield of 76–92%. *Trans*-4,4′-diaminostilbene or 5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin in azo dye reaction gave highly fluorescent morphine dyes which could be easily detected at very low concentrations using CE techniques. It is found that between the phenolic OH and the central N atom intramolecular proton transfer exists with the hydrazone form being major component. The compounds existed in hydrazone forms exclusively, being stabilized by the intramolecular hydrogen bonds. The resulting azo compounds are highly fluorescent in ethanol and water. Low detection limit was obtained ranging from 5–8 nmol dm$^{-3}$ for M or 6-AM coupled with freshly prepared diazonium salts. Consequently, this method is characterized by simple, rapid, and economic determination of abused drugs in forensic cases as an initial test and clinical analysis to prevent overdose-induced toxicity.

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### REFERENCES AND NOTES

[1] Przewlocki, R.; Przewlocka, B. Eur J Pharmacol 2001, 429, 79.

[2] Levi P. E. In Modern Toxicology; Elsevier Science Publishing Co.: Inc. Connecticut, 1997; pp 222–274.

[3] Benyhe, S. Life Sci 1994, 55, 969.
[4] Nagata, H.; Miyazawa, N.; Ogasawara, K. Chem Commun 2001, 1094.
[5] Parker, K. A.; Fokas, D. J Org Chem 1994, 59, 3933.
[6] Li, Y.; Chase, A. R.; Slivka, P. F.; Baggett, C. T.; Zhao, T. X.; Yin, H. Bioconjugate Chem 2008, 19, 2585.
[7] Kerrigan, S.; Goldberger, B. A. In Principles of Forensic Toxicology; Levine, B., Ed.; American Association for Clinical Chemistry: Inc. Washington, DC, 2003; pp 187–205.
[8] Fernandez, P.; Morales, L.; Vazquez, C. A.; Bermejo, M.; Tabernero, M. J. Forensic Sci Int 2006, 161, 31.
[9] Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. Org Lett 2006, 8, 5311.
[10] Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. J Med Chem 1978, 21, 153.
[11] Portoghese, P. S. J Med Chem 1965, 8, 609.
[12] Katsuura, K.; Yamaguchi, K.; Sakai, S.; Mitsuhashi, K. Chem Pharm Bull 1983, 31, 1518.
[13] Aldrich, J. V.; Vigil-Cruz, S. C. In Burger's Medicinal Chemistry and Drug Discovery; Abraham, D., Ed.; John Wiley: New York, 2003; pp 329–481.
[14] Hori, M.; Iwamura, T.; Morita, T.; Imai, E.; Oji, H.; Kataoka, T.; Shimizu, H.; Ban, M.; Nozaki, M.; Niwa, M.; Fujimura, H. Chem Pharm Bull 1989, 37, 2222.
[15] Zhang, A.; Xiong, W.; Bidlack, J. M.; Hilbert, J. E.; Knapp, B. I.; Wentland, M. P.; Neumeyer, J. L. J Med Chem 2004, 47, 165.
[16] Zhang, A.; Xiong, W.; Hilbert, J. E.; DeVita, E. K.; Bidlack, J. M.; Neumeyer, J. L. J Med Chem 2004, 47, 1886.
[17] Moura, J. C. V. P. In Non-Antibiotics; Chakrabarty, A. N., Molnar J., Eds.; NISCOM: New Delhi, 1998; pp 327–356.
[18] Altenberg-Greulich, B.; Vriend, G. J Mol Struct 2001, 598, 1.
[19] Nelson, P. E. J Chromatogr 1984, 290, 59.
[20] Ward, C. J.; Patel, P.; James, T. D. J Chem Soc Perkin Trans 1 2002, 462.
[21] Underberg, W. J. M.; Waterval, J. C. M. Electrophoresis 2002, 23, 3922.
[22] Hu, S.; Li, P. C. H. J Chromatogr A 2000, 876, 183.
[23] Miyano, H.; Toyo'oka, T.; Imai, K. Anal Chim Acta 1985, 170, 81.
[24] Liu, J.; Hsieh, Y.-Z.; Wiesler, D.; Novotny, M. Anal Chem 1991, 63, 408.
[25] Rama Rao, N. V.; Tandon, S. N. Anal Lett 1978, 6, 477.
[26] Groth, A. B.; Wallerberg, G. Acta Chem Scand 1966, 20, 2628.
[27] Alnajjar, A. O.; El-Zaria, M. E. Eur J Med Chem 2008, 43, 357.
[28] Abbott, L. C.; Batchelor, S. N.; Jansen, L.; Oakes, J.; Smith, J. R. L.; Moore, J. N. New J Chem 2004, 28, 815.
[29] Syrbu, S. A.; Semeikin, A. S.; Syrbu, T. V. Chem Heterocycl Comp 1996, 32, 897.
[30] Syrbu, S. A.; Semeikin, A. S.; Syrbu, T. V. Chem Heterocycl Comp 1996, 32, 573.
[31] Shore J. Colorants and Auxiliaries; Society of Dyers and Colorists: Bradford, 1990; Vol 1, pp 316–321.
[32] Hunger K. Industrial Dyes; Wiley-VCH: Weinheim, 2003; pp 20–35.
[33] Oakes, J.; Gratton, P.; Clark, R.; Wilkes, I. J Chem Soc Perkin Trans 2 1998, 2569.
[34] Cross, W. I.; Flower, K. R.; Pritchard, R. G. J Chem Res (S) 1999, 178.
[35] Lyčka, A. Dyes Pigm 1999, 43, 27.
[36] Lyčka, A.; Vrba, Z.; Vrba, M. Dyes Pigm 2000, 47, 45.
[37] Antonov, L.; Stoyanov, S. Dyes Pigm 1995, 28, 31.

# Cynogen Bromide and Ethylacetoacetate in Heterocyclization: Novel Synthesis of Tetracyclic Derivative of 3-Aryl Quinazolinones



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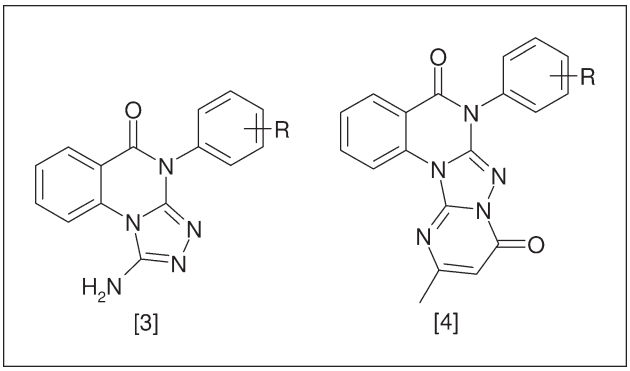


In this work, tricyclic 1-amino-4-(substituted phenyl)[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one **3** was synthesized by treatment of 2-hydrazinyl-3-(substituted phenyl)quinazolin-4(3*H*)-one **2** with cyanogen bromide, which on cyclization with ethylacetoacetate to get the targeted fused tetracyclic derivatives of quinazoli-4(3H)one **4**. The synthesized compounds have been characterized using IR and $^1$H NMR, mass spectral data together with elemental analysis.

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## INTRODUCTION

Quinazoline derivatives have attracted considerable attention due to their significant biological activities [1,2], especially antifungal [3,4], insecticidal [5], antihistaminic [6], anti-inflammatory [7], antibacterial [8], anticonvulsant [9,10], antithrombotic [11], antitubercular [12], and antitumor [13]. In this article, we report a new route for the synthesis of triazolo and tetracyclic derivatives of quinazolinone.

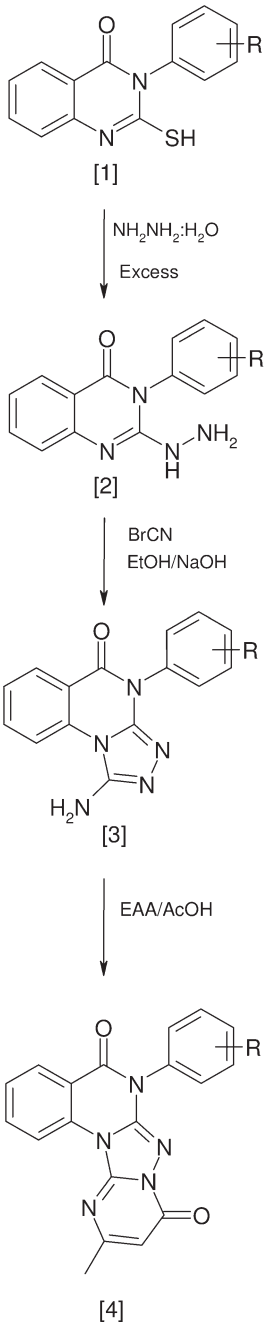
## RESULT AND DISCUSSION

The new triazolo and tetracyclic derivatives of quinazolinone were prepared following the reaction sequences depicted in Scheme 1 and supported mechanism in Scheme 2. The starting compound **1** was prepared by sequential treatment of anthranilic acid with thiocarbamate salts of substituted aniline and carbon disulphide according to the reported method [14]. The appearance of broad band at 3330–3110 cm$^{-1}$ in IR spectrum and a singlet displayed at δ, 10–11 ppm in the PMR spectrum due to —SH supports their formation. Compounds **1a–g** were heated with excess hydrazine hydrate to form 2-hydrazino derivatives **2a–g** in good yield [15]; the formation of which has been explained by the appearance of IR band at 3390–3300 cm$^{-1}$ due to —NHNH$_2$ and disappearance of singlet displayed at δ, 10–11 ppm due to —SH and two additional singlets appeared between δ, 9–11 and δ, 2–6 ppm due to —NH and —NH$_2$ protons, respectively, in their PMR spectra. The condensation of **2** with cyanogens bromide in absolute alcohol gave the corresponding desired tricyclic amino triazoles **3a–g**; the formation of which was confirmed by the observation of a broad IR band at 3420–3000 cm$^{-1}$ and singlet between δ, 3–6 ppm due to —NH$_2$ protons in their PMR spectrum. The compounds **3a–g** were cyclocondensed with ethylacetoacetate to get the targeted tetracyclic compounds **4a–g**. The formation of **4** has been established by the disappearance of singlet between δ, 3–6 due to —NH$_2$ protons and appearance of additional singlets due to Ar—CH$_3$ and =CH in their PMR spectrum.

## EXPERIMENTAL

All melting points reported are incorrect and were determined by open capillary method. All chemicals used were of A.R. grade and have been used without further purification. IR spectra (in KBr, cm$^{-1}$) were recorded on a Perkin-Elmer 783 (FTIR) spectrophotometer. $^1$H NMR spectra recorded in

**Scheme 1**




$CDCl_3$/DMSO-$d_6$ were scanned on a Bruker A-300 F-NMR spectrometer (Table 1). TMS was used as an internal standard with chemical shifts δ in ppm from down field to up field. Mass spectra were analyzed by EI technique on Shimadzu QP 2010 PLUS GC-MS system. The purity of products, in addition to the elemental analysis (Table 2), was checked by TLC.

**3-(4-Methoxyphenyl)-2-sulfanylquinazolin-4(3*H*)-one (1).** These compounds were prepared according to the reported method [14].

**2-Hydrazinyl-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one (2a).** A compound **la** (4.824 gm, 0.018 mol) was refluxed with 5 mL hydrazine hydrate in ethanol (15 mL) with constant stirring at 100°C for about 1.5 h, then cooled and thus the solid obtained was recrystallized from ethanol to furnish 2a [15], yield, 4.118 gm (86%), m.p. 207°C, IR: 3386–3328, 1664 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ (ppm), 2.65 (s, 3H, Ar—$CH_3$), 6.25(s, 2H, —$NH_2$), 6.9–8.1 (m, 8H, Ar—H), 10.9 (s, 1H, br, —NH); ms: m/z 282(12), 266(26), 251(45), 175(100), 107(55), 31(10). *Anal. Calcd.* for $C_{15}H_{14}O_2N_4$ (266): C, 63.82%; H, 5.00%; N, 19.85%. Found: C, 63.89%; H, 5.04%; N, 19.81%.

**1-Amino-4-(4-methoxyphenyl)[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one (3a).** A compound **2a** (5.054 gm, 0.019 mole) in ethanolic NaOH (50 mL) and cyanogen bromide (1 $cm^3$, 0.019 mole) were stirred for 3 h at room temperature. After neutralization of it with 10% sodium bicarbonate, the solid obtained was filtered and further recrystallized from ethanol to give **3a**, yield, 4.423 gm (80%), m.p. 270°C. IR: 3420–3010, 1685, 1615 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ (ppm), 2.56 (s, 3H, Ar—$CH_3$), 5.62 (s, 2H, —$NH_2$), 7.1–8.2 (m, 8H, Ar—H); ms: m/z 307(50), 291(20), 276(62), 200(100), 107(72), 31(16). *Anal. Calcd.* for $C_{16}H_{13}ON_5$ (291): C, 62.53%; H, 4.26%; N, 22.79%. Found: C, 62.61%; H, 4.32%; N, 22.71%.

**Scheme 2**

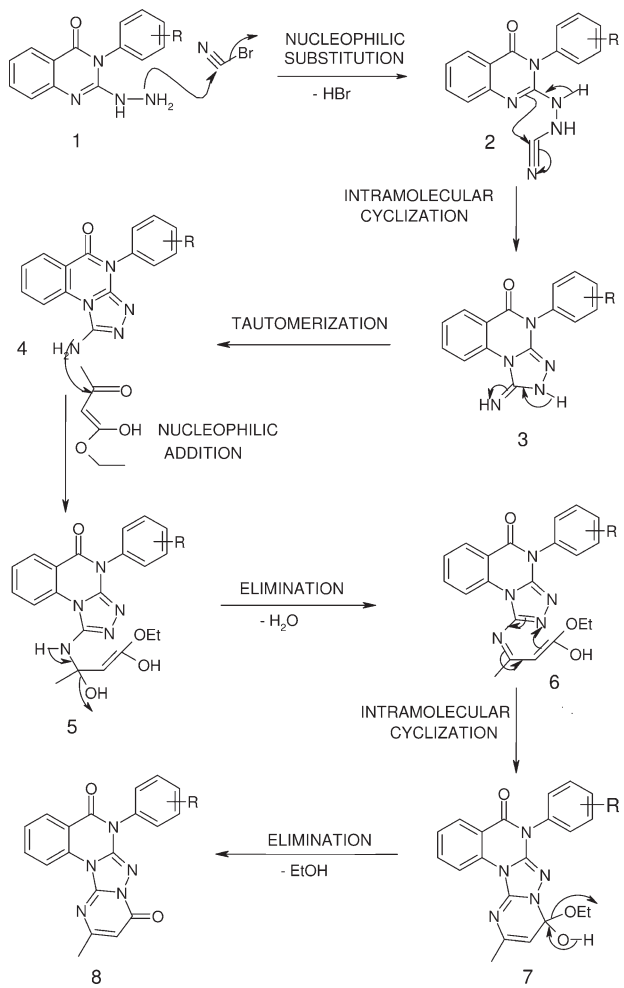


**Table 1**

Spectral characterization data of compounds **2**, **3**, and **4**.

| Compound | IR(ν,$cm^{-1}$) KBr | $H^1$ NMR ($CDCl_3$/DMSO-$d_6$) δ(ppm) |
|---|---|---|
| **2a** | 3386–3328 (—$HNNH_2$), 1660 (cyclic amido C=O), 1620 (C=N) | 2.65 (s, 3H, Ar—$OCH_3$), 5.96(s, 2H, —$NH_2$), 6.9–8.1 (m, 8H, Ar—H), 10.9 (s(br), 1H, —NH) |
| **2b** | 3372–3320 (—$HNNH_2$), 1654 (cyclic amido C=O), 1621 (C=N) | 2.58 (s, 3H, Ar—$CH_3$), 2.95(s, 2H, —$NH_2$), 7.0–8.2 (m, 8H, Ar—H), 10.15 (s(br),1H, —NH) |
| **2c** | 3381–3319 (—$HNNH_2$), 1670 (cyclic amido C=O), 1625 (C=N) | 2.62 (s, 3H, Ar—$CH_3$), 3.74 (s, 2H, —$NH_2$), 6.9–8.1 (m, 8H, Ar—H), 11.00 (s(br),1H, —NH) |
| **2d** | 3380–3332 (—$HNNH_2$), 1671 (cyclic amido C=O), 1622 (C=N) | 2.61 (s, 3H, Ar—$CH_3$), 5.05 (s, 2H, —$NH_2$), 7.2–8.4 (m, 8H, Ar—H), 11.02 (s(br),1H, —NH) |
| **2e** | 3390–3331 (—$HNNH_2$), 1664 (cyclic amido C=O), 1615 (C=N) | 6.00 (s, 2H, —$NH_2$), 6.8–8.0 (m, 8H, Ar—H), 9.85 (s(br),1H, —NH) |
| **2f** | 3376–3315 (—$HNNH_2$), 1669 (cyclic amido C=O), 1630 (C=N) | 5.14(s, 2H, —$NH_2$), 7.0–8.3 (m, 8H, Ar—H), 9.51 (s(br),1H, —NH) |
| **2g** | 3388–3330 (—$HNNH_2$), 1658 (cyclic amido C=O), 1628 (C=N) | 2.86 (s, 2H, —$NH_2$), 6.9–8.0 (m, 8H, Ar—H), 10.79 (s(br),1H, —NH) |
| **3a** | 3400–3100 (—$NH_2$), 1685 (cyclic amido C=O ), 1615 (C=N) | 2.56 (s, 3H, Ar—$OCH_3$), 5.62 (s, 2H, —$NH_2$), 7.1–8.2 (m, 8H, Ar—H) |
| **3b** | 3410–3050 (—$NH_2$), 1690 (cyclic amido C=O ), 1619 (C=N) | 2.51 (s, 3H, Ar—$CH_3$), 3.72 (s, 2H, —$NH_2$), 7.0–8.1 (m, 8H, Ar—H) |
| **3c** | 3390–3000 (—$NH_2$), 1684 (cyclic amido C=O ), 1622 (C=N) | 2.50 (s, 3H, Ar—$CH_3$), 3.91 (s, 2H, —$NH_2$), 7.2–8.2 (m, 8H, Ar—H) |
| **3d** | 3416–3010 (—$NH_2$), 1681 (cyclic amido C=O ), 1615 (C=N) | 2.55 (s, 3H, Ar—$CH_3$), 4.22 (s, 2H, —$NH_2$), 7.1–8.0 (m, 8H, Ar—H) |
| **3e** | 3395–3012 (—$NH_2$), 1689 (cyclic amido C=O ), 1630 (C=N) | 4.80 (s, 2H, —$NH_2$), 6.8–8.0 (m, 8H, Ar—H) |
| **3f** | 3415–3090 (—$NH_2$), 1685 (cyclic amido C=O ), 1625 (C=N) | 6.00 (s, 2H, —$NH_2$), 7.1–8.3 (m, 8H, Ar—H) |
| **3g** | 3400–3105 (—$NH_2$), 1687 (cyclic amido C=O ), 1617 (C=N) | 5.35 (s, 2H, —$NH_2$), 7.0–8.3 (m, 8H, Ar—H) |
| **4a** | 1725–1690 broad and 1662 (cyclic amido C=O), 1626 (C=N) | 2.44 (3H, s, Ar—$OCH_3$), 2.49 (s, 3H, =C—$CH_3$), 6.21 (1H, s, =CH), 7.2–8.4 (8H, m, Ar—H) |
| **4b** | 1720–1691 broad and 1668 (cyclic amido C=O), 1618 (C=N) | 2.51 (s, 3H, Ar—$CH_3$), 2.49 (s, 3H, =C—$CH_3$), 6.32 (s, 1H, =CH), 7.0—8.2 (m, 8H, Ar—H) |
| **4c** | 1722–1693 broad and 1665 (cyclic amido C=O), 1615 (C=N) | 2.38 (s, 3H, Ar—$CH_3$), 2.58 (s, 3H, =C—$CH_3$), 6.65 (s, 1H, =CH), 7.1–8.3 (m, 8H, Ar—H) |
| **4d** | 1709–1696 broad and 1670 (cyclic amido C=O), 1620 (C=N) | 2.40 (s, 3H, Ar—$CH_3$), 2.39 (s, 3H, =C—$CH_3$), 6.43 (s, 1H, =CH), 7.0–8.5 (m, 8H, Ar—H) |
| **4e** | 1720–1684 broad and 1667 (cyclic amido C=O), 1622 (C=N) | 2.45 (s, 3H, =C—$CH_3$), 6.22 (s, 1H, =CH), 7.2–8.2 (m, 8H, Ar—H) |
| **4f** | 1730–1700 broad and 1675 (cyclic amido C=O), 1632 (C=N) | 2.61 (s, 3H, =C—$CH_3$), 6.51 (s, 1H, =CH), 7.1–8.3 (m, 8H, Ar—H) |
| **4g** | 1728–1697 broad and 1668 (cyclic amido C=O), 1625 (C=N) | 2.51 (s, 3H, =C—$CH_3$), 6.40 (1H, =CH), 7.0–8.1 (m, 8H, Ar—H) |

**Table 2**

Characterization data of compounds **2**, **3**, and **4**.

| Compound | R groups | m.p. (°C) | Yield (%) | Molecular formula | Calcd (%) (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **2b** | *o*-$CH_3$ | 209 | 86 | $C_{15}H_{14}ON_4$ | 67.65 (67.59) | 5.30 (5.38) | 21.04 (21.10) |
| **2c** | *m*-$CH_3$ | 211 | 86 | $C_{15}H_{14}ON_4$ | 67.65 (67.58) | 5.30 (5.25) | 21.04 (21.12) |
| **2d** | *p*-$CH_3$ | 205 | 76 | $C_{15}H_{14}ON_4$ | 67.65 (67.72) | 5.30 (5.35) | 21.04 (21.09) |
| **2e** | *p*-Cl | 218 | 82 | $C_{14}H_{11}ON_4Cl$ | 58.65 (58.58) | 3.87 (4.95) | 19.54 (19.47) |
| **2f** | *m*-Cl | 222 | 82 | $C_{14}H_{11}ON_4Cl$ | 58.65 (58.55) | 3.87 (4.80) | 19.54 (19.60) |
| **2g** | *p*-Br | 196 | 83 | $C_{14}H_{11}ON_4Br$ | 50.78 (50.62) | 3.35 (3.40) | 16.92 (16.86) |
| **3b** | *o*-$CH_3$ | 269 | 78 | $C_{16}H_{13}ON_5$ | 65.97 (65.91) | 4.50 (4.58) | 24.04 (24.16) |
| **3c** | *m*-$CH_3$ | 272 | 68 | $C_{16}H_{13}ON_5$ | 65.97 (66.06) | 4.50 (4.44) | 24.04 (24.12) |
| **3d** | *p*-$CH_3$ | 265 | 72 | $C_{16}H_{13}ON_5$ | 65.97 (65.98) | 4.50 (4.49) | 24.04 (23.99) |
| **3e** | *p*-Cl | 278 | 70 | $C_{15}H_{10}ON_5Cl$ | 57.80 (57.73) | 3.23 (3.12) | 22.47 (22.38) |
| **3f** | *m*-Cl | 281 | 69 | $C_{15}H_{10}ON_5Cl$ | 57.80 (57.71) | 3.23 (3.11) | 22.47 (22.51) |
| **3g** | *p*-Br | 276 | 73 | $C_{15}H_{10}ON_5Br$ | 50.58 (50.65) | 2.83 (2.91) | 19.66 (19.51) |
| **4b** | *o*-$CH_3$ | 308 | 70 | $C_{20}H_{15}O_2N_5$ | 67.22 (67.16) | 4.23 (4.11) | 19.60 (19.52) |
| **4c** | *m*-$CH_3$ | 307 | 68 | $C_{20}H_{15}O_2N_5$ | 67.22 (67.11) | 4.23 (4.18) | 19.60 (19.69) |
| **4d** | *p*-$CH_3$ | 302 | 69 | $C_{20}H_{15}O_2N_5$ | 67.22 (67.27) | 4.23 (4.22) | 19.60 (19.69) |
| **4e** | *p*-Cl | 312 | 73 | $C_{19}H_{12}O_2N_5Cl$ | 60.41 (60.36) | 3.20 (3.14) | 18.54 (18.48) |
| **4f** | *m*-Cl | 310 | 70 | $C_{19}H_{12}O_2N_5Cl$ | 60.41 (60.50) | 3.20 (3.12) | 18.54 (18.48) |
| **4g** | *p*-Br | 314 | 61 | $C_{19}H_{12}O_2N_5Br$ | 54.04 (54.11) | 2.86 (2.77) | 16.59 (16.64) |

**Fused tetracyclic quinazolin-4(3H)one (4a).** A mixture of **3a** (2.91 gm, 0.01 mole), ethylacetoacetate (12.7 $cm^3$, 0.01 mole) and glacial acetic acid (20 mL) was refluxed for 4 h. The solution was concentrated, cooled, and the crude product obtained was recrystallized from chloroform:*n*-hexane (50% v/v) mixture, yield, 2.570 gm (72%), m.p. 310°C. IR: 1725–1690 broad, 1662 $cm^{-1}$, 1625. $^1$H NMR (DMSO-$d_6$) δ (ppm): 2.44 (s, 3H, Ar—$CH_3$), 2.47 (s, 3H, Ar—$CH_3$), 6.21 (s, 1H, =CH), 7.2–8.4 (m, 8H, Ar—H); ms: m/z 373(45), 342(55), 266(100), 107(35), 31(15). *Anal. Calcd.* for $C_{20}H_{15}O_2N_5$ (357): C, 64.34%; H, 4.05%; N, 18.76%. Found: C, 64.27%; H, 4.11%; N, 18.79%.

## REFERENCES AND NOTES

[1] Ammar, Y. A.; El-Sharief, A. M. Sh.; Zahran, M. A.; Ali, A. H.; El-Gaby, M. S. A. Molecules 2001, 6, 267.

[2] El-Sharief, A. M. Sh.; Ammar, Y. A.; Zahram, M. A.; Ali, A. H. J Chem Res 2002, 5, 205.

[3] Alagarsamy, V.; Giridhar, R.; Yadav, M. R.; Revati, R.; Ruckmani, K.; Chercq, E. D. Indian J Pharm Sci 2006, 68, 532.

[4] Ghorab, M. M. Farmaco 2000, 55, 249.

[5] Singh, T.; Sharma, S.; Kishore, V.; Shrivastava, K. A. Indian J Chem 2006, B45, 2558.

[6] Raju, M. B.; Singh, S. D.; Raghu, R. R. A.; Rajan, K. S. Indian J Pharm Sci 2007, 69, 853.

[7] Yadav, M. R.; Shirude, S. T.; Parmar, A.; Balaraman, R.; Giridhar, R. J Heterocycl Compd 2006, 42, 1038.

[8] Alagarsamy, V.; Pathak, U. S.; Goyal, R. K. Indian J Pharm Sci 2000, 62, 63.

[9] Ghany, A. E. A.; Hemeda, A. W. M. Acta Pharm 2003, 53, 127.

[10] El-Helby, A. G. A. Acta Pharm 2003, 53, 127.

[11] Demer, J. P. J Heterocycl Chem 1989, 26, 1535.

[12] Kunes, J. Farmaco 2001, 55, 725.

[13] Bradly, D. S. Tetrahedron Lett 2001, 42, 1851.

[14] Husain, M. I.; Shrivastava, G. C.; Dua, P. R. Indian J Chem 1982, B21, 381.

[15] Salih N. A. Turk J Chem 2008, 32, 229.

# Transformations of 2-Aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines, Cycloadducts of the $BiCl_3$-Catalyzed Three-Component Povarov Reaction: Oxidation and Reduction Processes Towards New Potentially Bioactive 2-Arylquinoline Derivatives

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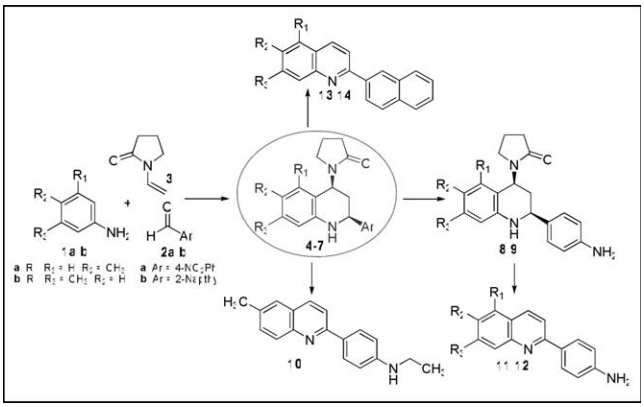

Synthesis and spectral characterization of new series of 2-aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines and their aromatic analogs, 2-arylquinolines are reported. It was found that substituted tetrahydroquinoline precursors are easily prepared using $BiCl_3$-catalyzed three-component Povarov reaction between 4-nitrobenzaldehyde or 2-naphtylcarboxyaldehyde, anilines and *N*-vinylpyrrolidin-2-one, and could be transformed *via* oxidation and reduction processes into potentially bioactive 2-arylquinoline derivatives, unsubstituted at the C-4 position. The all set of (tetrahydro)quinolines were characterized by IR, $^1H$ and $^{13}C$-NMR spectroscopy.

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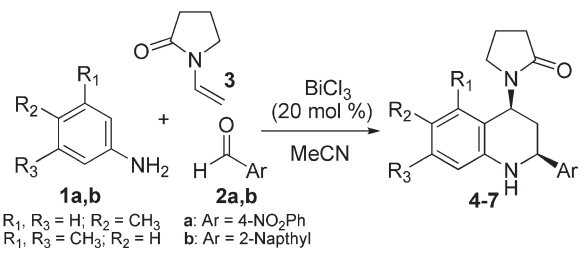
## INTRODUCTION

Quinoline and tetrahydroquinoline structures are essential feature of many natural products. These heterocycles play a key role in heterocyclic and medicinal chemistry. Their syntheses by various methodologies have been published extensively [1–4]. Polyfunctionalized tetrahydroquinolines (THQs) are molecules of great interest in organic synthesis because many natural products present this system in their structure, and these compounds exhibit diverse biological activities [5–9]. Apart from their marked bioactivities, THQs are also important and reliable precursors in quinoline preparation, another group of heterocyclic molecules that has a great number of pharmacological properties [10]. However, general syntheses of functionalized quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions are less common [11], and often suffer from harsh reaction conditions, expensive reagents, or both. Moreover, the number of these commercially available reagents is exceedingly small that limits the preparation of quinolines substituted on the quinoline aryl moiety.

For these reasons, the synthesis of new THQs is still of great interest. An efficient route for the preparation of THQs is the acid-catalyzed Povarov reaction that is classified as imino Diels-Alder cycloaddition [11,12]. Moreover, this methodology that permits the condensation of anilines, aldehydes, and electron-rich alkenes using acidic catalysts under mild conditions to afford new tetrahydroquinolines, can overcome synthetic limitations for the construction of functionalized quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions and are useful tool for the generation of quinoline derivatives with several degrees of structural diversity. Then, appropriate choice of aldehydes and alkenes in this cycloaddition reaction

**Scheme 1**




provides a facile entry to heterocyclic systems which is an essential moiety in many active pharmaceuticals.

As a part of our research program on the *N*-aryl imines towards the synthesis of bioactive substituted tetrahydroquinolines and quinolines, we are pursuing investigations on the synthesis of small drug-like (tetrahydro)quinoline molecules containing C-2 aryl fragment, those synthesis could be accomplished *via* cycloaddition reactions. We now want to report simple preparation of new 2-aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines using $BiCl_3$-catalyzed three component Povarov reaction between 4-nitrobenzaldehyde or 2-naphtylcarboxyaldehyde, anilines and *N*-vinylpyrrolidin-2-one (NVP), and their transformations into potentially bioactive 2-arylquinoline derivatives, unsubstituted at the C-4 position.

## RESULTS AND DISCUSSION

Planning synthesis of new 2-arylquinoline derivatives, we paid attention the following considerations: (i) *N*-vinylpyrrolidin-2-one (NVP) is very active electron-rich alkene in this reaction [13–16] and it is an available, stable, and cheap reagent. Moreover, 2-oxopyrrolidinyl moiety on the tetrahydroquinoline ring could be easily removed; (ii) 4-nitrobenzaldehyde could provide 4-aminophenyl fragment, those synthetic utilization to construct *N*-heterocycles is well recognized; (iii) 2-naphtylcarboxyaldehyde was chosen for the preparation of new 2-naphtylquinolines, aromatic planar molecules, and interesting models in biological tests (anticancer activity).

So, using $BiCl_3$-catalyzed (20 mol %) three component Povarov reaction between anilines **1a,b**, aldehydes **2a,b** and NVP **3** in MeCN, a new series of the functionalised THQs **4–7** was easily prepared in excellent yields (Scheme 1).

Structural elucidation of obtained solid substances (Table 1) was started with IR analysis that indicated at the presence of characteristic intensive bands in zone 3394, 3271, and 1666 $cm^{-1}$ (NH and C=O for all comp. **4–7**), and also 1512 and 1342 $cm^{-1}$ ($NO_2$ for comp. **4,5**). From their spectral analyses ($^1$H-, $^{13}$C-NMR and COSY), it was found that the *cis*-diastereoisomer was prevalent in all of the cases studied. For example, from $^1$H-NMR spectrum of comp. **4**, it could clearly observed two doublets of doublets at 5.69 ppm ($J_{3,4}$ = 11.1 and 6.4 Hz) and 4.65 ppm ($J_{2,3}$ = 10.7 and 3.1 Hz) that correspond to the THQ protons 4-H and 2-H, respectively.

The large vicinal coupling confirmed strongly axial–axial dispositions of the THQ protons 4-H and 2-H and, consequently, the substituents at C-4 and C-2 should have an equatorial disposition that indicates at a *cis* configuration of the THQ ring.

Having stable solid THQ derivatives in our hands, we realized some simple chemical transformations, which resulted in the efficient preparation of quinoline molecules **10–14** (Scheme 2). First, to obtain new 2-(4-aminophenyl)-THQs **8,9**, we analysed reduction process of nitro derivatives **4,5** under different reaction conditions. The conventional hydrogenation process [$H_2$/Pd-C (10%)/MeOH] always gave in moderate yields the desired products, contaminated with side-products. The change of solvent nature (MeOH → MeOH/$CH_2Cl_2$) in $H_2$/Pd-C hydrogenation reaction (method **A**) did not improve this situation. Thus, we addressed to another reduction reaction that uses $NaBH_4$ and $NiCl_2$ in MeOH/$CH_2Cl_2$ (method **B**) that resulted an efficient and selective system, which satisfied to our plans. Under these reaction conditions, it was possible to prepare desired *cis*-2-(4-aminophenyl)-THQs **8,9** in good yields. However, it should be noted that among different attempts to find ideal conditions for hydrogenation process of comp. **4** we tested also a $H_2$/Pd-C/MeCN-MeOH system (method **C**) that allowed obtaining an unexpected quinoline product **10**. This formation could be assumed as a result of subsequent three processes: (1)

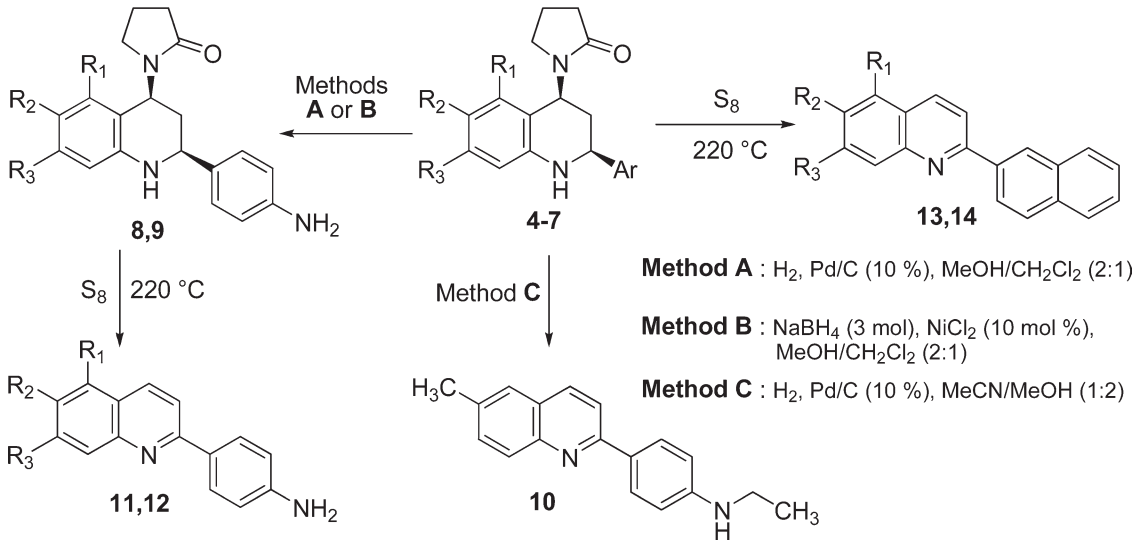
**Table 1**

Tetrahydroquinolines **4–9** and quinolines **10–14** prepared by imino Diels-Alder reaction.

| Comp. | $R_1$ | $R_2$ | $R_3$ | Ar | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| **4** | H | Me | H | 4-$NO_2$Ph | 222–223 | 95 |
| **5** | Me | H | Me | 4-$NO_2$Ph | 239–240 | 98 |
| **6** | H | Me | H | 2-Naphtyl | 214–215 | 72 |
| **7** | Me | H | Me | 2-Naphtyl | 182–183 | 90 |
| **8** | H | Me | H | 4-$NH_2$Ph | 233–234 | 95[a] (54)[b] |
| **9** | Me | H | Me | 4-$NH_2$Ph | 183–185 | 97[a] |
| **10** | H | Me | H | 4-NHEtPh | 149–151 | 47[c] |
| **11** | H | Me | H | 4-$NH_2$Ph | 178–179 | 89[a] |
| **12** | Me | H | Me | 4-$NH_2$Ph | 115–116 | 73[a] |
| **13** | H | Me | H | 2-Naphtyl | 160–161 | 87 |
| **14** | Me | H | Me | 2-Naphtyl | 86–87 | 73 |

[a] Obtained by method **B**.
[b] Obtained by method **A**.
[c] Obtained by method **C**.

**Scheme 2**




ring aromatization reaction with pyrrolidine fragment elimination, (2) nitro group reduction into amine function, (3) N-ethylation of amine group to give *N*-ethylamino derivative **10** (Scheme 2). Its quinoline structure was strongly confirmed by $^1$H-, $^{13}$C-NMR spectra and 2D NMR spectroscopy.

Other quinoline derivatives **11–14** were easily prepared from the respective tetrahydroquinolines by use of their rapid fusion with elemental sulfur following our developed protocol [17]. These quinoline molecules are stable, yellowish substances that were purified by means of a short chromatographic column (Table 1).

Finally, the obtained THQs **6–9** were subjected into oxidation process using our rapid fusion-sulfur protocol to prepare new corresponding2-(4-aminophenyl)quinolines **11,12** and 2-(2-naphtyl)quinolines **13,14**. This aromatization reaction was achieved by its fusion with elemental sulfur at 220–240°C in 5–10 min. All new compounds were directly isolated without previous extraction using flash column chromatographic and were completely identified using NMR spectroscopy.

In conclusion, we reported the efficient synthesis of new series of 2-aryl-4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines and their aromatic analogs, 2-arylquinolines, unsubstituted at the C-4 position. These potentially bioactive 2-(aryl)quinoline derivatives could be important models in antioxidant, antiparasitic or/and anticancer studies [18].

## EXPERIMENTAL

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Lumex Infralum FT-02 spectrophotometer in KBr. $^1$H, $^{13}$C-NMR spectra were recorded on Bruker AM-400 spectrometer. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for protons). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; td, triplet of doublets; q, quartet; sp, septet; m, multiplet; b, broad. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS Chemstation Data system was used for ms identification at 70 EV using a 60 m capillary column coated with HP-5 [5%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin–Elmer 2400 Series II analyzer and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminium sheet.

**General procedure for the imino Diels-Alder reaction of anilines, aldehydes and NVP.** To a solution of the appropriate aniline (1.00 mmol) and aldehyde (1 mmol) in anhydrous $CH_3CN$ (20 mL) under $N_2$ atmosphere, was added 20 mol % $BiCl_3$ (0.57 mmol) and *N*-vinylpyrrolidone (1.2 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with a solution of $Na_2CO_3$. The organic layer was separated, and dried with $Na_2SO_4$. The organic solvent was removed *in vacuo* and the product purified with chromatography column (hexane/ethyl acetate).

***1-[6-Methyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (4).*** The compound **4** was obtained in 95% yield, yellow solid, m.p. 222–223°C. IR (potassium bromide): ν 3394, 2947, 2916, 1666, 1620 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.20 (2H, d, $J$ = 8.7 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 7.61 (2H, d, $J$ = 8.7 Hz, 2-$H_{Ar}$ and 6-$H_{Ar}$), 6.90 (1H, dd, $J$ = 8.0, 1.7 Hz, 7-$H_{THQ}$), 6.68 (1H, s, 5-$H_{THQ}$), 6.57 (1H, d, $J$ = 8.1 Hz, 8-$H_{THQ}$), 5.69 (1H, dd, $J$ = 11.1, 6.4 Hz, 4-$H_{aTHQ}$), 4.65 (1H, dd, $J$ = 10.7, 3.1 Hz, 2-$H_{aTHQ}$), 4.03 (1H, br.s, N—H), 3.21 (2H, t, $J$ = 6.9 Hz, 5-$H_{Pyrr}$), 2.59–2.41 (2H, m, 3-$H_{Pyrr}$), 2.23 (3H, s, 6-$Me_{THQ}$), 2.13–1.99 (4H, m, 4-$H_{Pyrr}$ and 3-$H_{THQ}$). $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 175.8, 150.6, 147.4, 142.9, 129.0, 128.1, 127.3 (2C), 126.9, 123.9 (2C), 118.8, 115.4, 56.0, 48.1, 42.2, 35.3, 31.3, 20.5, 18.1. gc-ms $t_R$: 44.57 min,

*m*/*z*: 351 (molecular ion). *Anal*. *Calcd*. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.40; H, 5.99; N, 11.97.

***1-[5,7-Dimethyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (5).*** The compound **5** was obtained in 98% yield, yellow solid, m.p. 239–240°C. IR (potassium bromide): ν 3271, 2972, 2916, 2854, 1666 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.21 (2H, d, $J$ = 8.7 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 7.62 (2H, d, $J$ = 8.6 Hz, 2-$H_{Ar}$ and 6-$H_{Ar}$), 6.47 (1H, s, 6-H), 6.37 (1H, s, 8-$H_{THQ}$), 5.57 (1H, t, $J$ = 8.5 Hz, 4-$H_{aTHQ}$), 4.48 (2H, dd, $J$ = 10.6, 2.5 Hz, 2-$H_{aTHQ}$), 3.97 (1H, br.s, N—H), 3.08 (1H, ddd, $J$ = 9.7, 8.7, 5.4 Hz, 5-$H_{ePyrr}$), 2.82 (1H, ddd, $J$ = 9.9, 8.4, 6.0 Hz, 5-$H_{aTHQ}$), 2.43-2.27 (3H, m, 3-$H_{Pyrr}$ and 3-$H_{eTHQ}$), 2.23 (3H, s, 5-$Me_{THQ}$), 2.10 (1H, t, $J$ = 12.0 Hz, 3-$H_{aTHQ}$), 2.06 (3H, s, 7-$Me_{THQ}$), 1.94-1.72 (2H, m, 4-$H_{Pyrr}$). $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 174.5, 150.5, 147.3, 146.7, 138.3, 138.2, 127.2 (2C), 123.9 (2C), 122.8, 114.9, 114.3, 55.4, 46.5, 42.4, 36.3, 31.0, 21.0, 19.3, 17.8. gc-ms $t_R$: 49.65 min, *m*/*z*: 365 (molecular ion). *Anal*. *Calcd*. for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.01; H, 6.35; N, 11.48.

***1-(6-Methyl-2-(2-naphtyl)-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one (6).*** The compound **6** was obtained in 72% yield, white solid, m.p. 214–215°C. IR (potassium bromide): ν 3332, 3055, 3024, 2954, 2916 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 7.88 (1H, s, 1-$H_{Napht}$), 7.85-7.82 (3H, m, 4-$H_{Napht}$, 5-$H_{Napht}$ and 8-$H_{Napht}$), 7.52-7.50 (1H, m, 3-$H_{Napht}$), 7.49-7.45 (2H, m, 6-$H_{Napht}$ and 7-$H_{Napht}$), 6.89 (1H, d, $J$ = 7.9 Hz, 8-$H_{THQ}$), 6.70 (1H, s, 5-$H_{THQ}$), 6.55 (1H, d, $J$ = 8.0 Hz, 7-$H_{THQ}$), 5,74 (1H, t, $J$ = 8.9, 4-$H_{aTHQ}$), 4.71 (1H, t, $J$ = 6.9 Hz, 2-$H_{aTHQ}$), 3.99 (1H, br.s, N—H), 3.28-3.18 (2H, m, 5-$H_{Pyrr}$), 2.50-2.42 (2H, m, 3-$H_{Pyrr}$), 2.24 (3H, s, 6-$Me_{THQ}$), 2.18-2.14 (2H, m, 3-$H_{THQ}$), 2.04-1.97 (2H, m, 4-$H_{Pyrr}$). $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 175.8, 143.6, 140.6, 133.4, 133.1, 128.9, 128.5, 127.8, 127.7, 127.5, 127.1, 126.2, 125.9, 125.0, 124.6, 119.0, 115.2, 56.6, 48.5, 42.3, 35.4, 31.4, 20.6, 18.2. gc-ms $t_R$: 55.83 min, *m*/*z*: 356 (molecular ion). *Anal*. *Calcd*. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.84; H, 6.78; N, 7.84.

***1-[5,7-Dimethyl-2-(2-naphtyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (7).*** The compound **7** was obtained in 90% yield, white solid, m.p. 182–183°C. IR (potassium bromide): ν 3332, 3047, 3016, 2978, 2924 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 7.87 (1H, s, 1-$H_{Napht}$), 7.84-7.81 (3H, m, 4-$H_{Napht}$, 5-$H_{Napht}$ and 8-$H_{Napht}$), 7.51-7.50 (1H, m, 3-$H_{Napht}$), 7.48-7.45 (2H, m, 6-$H_{Napht}$ and 7-$H_{Napht}$), 6.44 (1H, s, 6-$H_{THQ}$), 6.36 (1H, s, 8-$H_{THQ}$), 5.62 (1H, t, $J$ = 8.5 Hz, 4-$H_{aTHQ}$), 4.50 (1H, d, $J$ = 10.6 Hz, 2-$H_{aTHQ}$), 4.01 (1H, br.s, N—H), 3.16-3.10 (1H, m, 5-$H_{ePyrr}$), 2.85-2.70 (1H, m, 5-$H_{aPyrr}$), 2.46-2.26 (3H, m, 3-$H_{Pyrr}$ and, 3-$H_{eTHQ}$), 2.23 (3H, s, 7-$Me_{THQ}$), 2.19-2.14 (1H, m, 3-$H_{aTHQ}$), 2.08 (3H, s, 5-$Me_{THQ}$), 1.92-1.97 (2H, m, 4-$H_{Pyrr}$). $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 174.4, 147.5, 140.4, 138.3, 138.0, 133.4, 133.0, 128.4, 127.8, 127.6, 126.2, 125.9, 124.8, 124.6, 122.3, 115.1, 114.1, 55.9, 46.8, 42.4, 36.4, 31.1, 21.0, 19.4, 17.8. gc-ms $t_R$: 54.14 min, *m*/*z*: 370 (molecular ion). *Anal*. *Calcd*. for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 81.06; H, 7.03; N, 7.54.

**General procedure for the hydrogenation with $H_2$/Pd/C (method A).** To a solution of nitro derivative (**4**) (2.85 mmol) in MeOH:$CH_2Cl_2$ (2:1) was added Pd/C (10% p/p). Molecular hydrogen was injected to the system; the reaction mixture was stirred at room temperature for 24 h. The organic layer was filtered in a chromatographic column (silica gel), the solvent was removed *in vacuo* and the product was purified with chromatography column (hexane/ethyl acetate).

***1-[6-Methyl-2-(4-aminophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (8).*** The compound (**8**) was obtained in 54% yield, yellow solid, m.p. 233–234°C. IR (potassium bromide): ν 3440, 3379, 3356, 3240, 2947, 2916, 1666 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.28 (1H, d, $J$ = 8.4 Hz, 2-$H_{Ar}$), 8.18 (1H, d, $J$ = 8.3 Hz, 6-$H_{Ar}$), 7.70 (2H, dd, $J$ = 11.5, 8.7 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 6.90 (1H, bt, $J$ = 5.5 Hz, 7-$H_{THQ}$), 6.69 (1H, s, 5-$H_{THQ}$), 6.55 (1H, t, $J$ = 6.9 Hz, 8-$H_{THQ}$), 5.71 (1H, dd, $J$ = 10.2, 6.9 Hz, 4-$H_{aTHQ}$), 4.62 (1H, ddd, $J$ = 12.0, 10.6, 3.4 Hz, 2-$H_{aTHQ}$), 3.96 (1H, s, $NH_2$), 3.20 (2H, d, $J$ = 5.9 Hz, 5-$H_{Pyrr}$), 2.59-2.43 (2H, m, 3-$H_{Pyrr}$), 2.23 (3H, s, 6-$Me_{THQ}$), 2.12-1.01 (4H, m, 3-$H_{THQ}$ and 4-$H_{Pyrr}$) ppm. gc-ms $t_R$: 25.34 min, *m*/*z*: 321 (molecular ion). *Anal*. *Calcd*. for $C_{20}H_{23}N_3O$ C, 74.74; H, 7.21; N, 13.07. Found: C, 74.75; H, 7.20; N, 13.05.

**General procedure for reduction reaction with $NiCl_2$/$NaBH_4$ (method B).** To a mixture of nitro derivatives (**4**,**5**) (2.85 mmol) and nickel chloride (II) (0.28 mmol) in MeOH:$CH_2Cl_2$ (2:1), $NaBH_4$ (8.55 mmol) was added in small portions, keeping reaction system at 0°C. The reaction was stirred by 1 hour at room temperature and the organic layer was filtered and washed (methanol and distilled water), extracted with $CH_2Cl_2$ (3 × 10 mL) and dried under $Na_2SO_4$.

***1-[6-Methyl-2-(4-aminophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (8).*** The compound (**8**) was obtained in 95% yield. Their physicochemical parameters were identical to product (**8**) obtained by method **A**.

***1-[5,7-Dimethyl-2-(4-aminophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (9).*** The compound (**9**) was obtained in 97% yield, yellow solid, m.p. 255–258°C. IR (potassium bromide): ν 3440, 2916, 1666, 1620, 1589 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.29 (1H, d, $J$ = 8.2 Hz, 2-$H_{Ar}$), 8.18 (1H, d, $J$ = 8.1 Hz, 6-$H_{Ar}$), 7.55 (2H, d, $J$ = 8.9 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 6.45 (1H, s, 6-$H_{THQ}$), 6.36 (1H, m, 8-$H_{THQ}$), 5.58 (1H, t, $J$ = 8.5 Hz, 4-$H_{aTHQ}$), 4.42 (1H, t, $J$ = 12.1 Hz, 2-$H_{aTHQ}$), 3.97 (2H, br.s, $NH_2$), 3.11 (1H, dd, $J$ = 14.1, 8.5 Hz, 5-$H_{ePyrr}$), 2.82 (1H, dd, $J$ = 15.3, 7.8 Hz, 5-$H_{aPyrr}$), 2.41-2.31 (3H, m, 3-$H_{Pyrr}$ and 3-$H_{eTHQ}$), 2.22 (3H, s, 5-$Me_{THQ}$), 2.11 (1H, t, $J$ = 12.0 Hz, 3-$H_{aTHQ}$), 2.07 (3H, s, 7-$Me_{THQ}$), 1.85 (2H, dd, $J$ = 13.8, 6.0 Hz, 4-$H_{Pyrr}$) ppm. gc-ms $t_R$: 26.62 min, *m*/*z*: 335 (molecular ion). *Anal*. *Calcd*. for $C_{21}H_{25}N_3O$ C, 75.19; H, 7.51; N, 12.53. Found: C, 75.18; H, 7.50; N, 12.55.

**General procedure for the hydrogenation with $H_2$/Pd/C (method C).** To a solution of nitro derivative (**4**) (2.85 mmol) in MeOH/MeCN (2:1) was added Pd/C (10% p/p). Molecular hydrogen was injected to the system; the reaction mixture was stirred at room temperature for 24 h. The organic layer was filtered in a chromatographic column (silica gel), the solvent was removed *in vacuo* and the product was purified with chromatography column (hexane/ethyl acetate).

***2-(4-N-Ethylaminophenyl)-6-methylquinoline (10)*** The compound (**10**) was obtained in 46% yield, yellow solid, m.p. 149–151°C. IR (potassium bromide): ν 3394, 2961, 2916, 2854, 1605 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.02 (2H, d, $J$ = 8.6 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 8.00 (1H, d, $J$ = 8.1 Hz, 8-$H_{Qu}$), 7,99 (1H, d, $J$ = 8.6 Hz, 3-$H_{Qu}$), 7.74 (1H, d, $J$ = 8.7 Hz, 4-$H_{Qu}$), 7.50 (1H, s, 5-$H_{Qu}$), 7.49 (1H, d, $J$ = 8.5 Hz, 7-$H_{Qu}$), 6.69 (2H, d, $J$ = 8.7 Hz, 2-$H_{Ar}$ and 6-$H_{Ar}$), 3.79 (1H, br.s, N—H), 3.21 (2H, q, $J$ = 7.1 Hz, —$CH_2$Me$_{Ar}$), 2.50 (3H, s, 6-$Me_{Qu}$), 1.26 (3H, t, $J$ = 7.1 Hz, —$CH_2Me_{Ar}$) ppm. $^{13}$C-

NMR ($CDCl_3$, 100 MHz): δ 156.5, 149.4, 146.8, 135.6, 135.0, 131.5, 129.0, 128.5 (2C), 128.4, 126.6, 126.3, 118.2, 112.6 (2C), 38.2, 21.5, 14.7, ppm. gc-ms $t_R$: 26,50 min, *m*/*z*: 262 (molecular ion). *Anal*. *Calcd*. for $C_{18}H_{18}N_2$ C, 82.41; H, 6.92; N, 10.68. Found: C, 82.40; H, 6.93; N, 10.69.

**General procedure for the aromatization with sulfur.** The 2-(aminophenyl) and 2-(nitroaryl) substituted tetrahydroquinolines (**4**-**7**) were heated quickly (10–15 min) in the presence of elemental sulfur ($S_8$) to 220–230°C. The reaction mixture was adsorbed under silica gel and separated by chromatography column to afford the 2-arylquinolines.

***2-(4-Aminophenyl)-6-methylquinoline (11).*** The compound (**11**) was obtained in 89% yield, yellow solid, m.p. 178–179°C. IR (potassium bromide): ν 3386, 3301, 3193, 3055, 3023 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.03 (1H, d, $J$ = 8.7 Hz, 4-$H_{Qu}$), 8.01 (3H, dt, $J$ = 8.6, 2.0 Hz, 2-$H_{Ar}$ and 6-$H_{Ar}$), 7.92 (1H, dd, $J$ = 8.8, 1.3 Hz, 8-$H_{Qu}$)7.76 (1H, d, $J$ = 8.6 Hz, 3-$H_{Qu}$), 7.53 (1H, s, 5-$H_{Qu}$), 7.52 (1H, dd, $J$ = 8.8, 1.3 Hz, 7-$H_{Qu}$), 6.80 (2H, dt, $J$ = 8.6, 2.0 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 3.85 (2H, br.s, $NH_2$), 2.53 (3H, s, 6-$Me_{Qu}$) ppm. $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 156.4, 147.6, 146.9, 135.8, 135.3, 131.6, 130.1, 129.1, 128.6 (2C), 126.8, 126.3, 118.3, 115.1 (2C), 21.5 ppm. gc-ms $t_R$: 25.13 min, *m*/*z*: 234 (molecular ion). *Anal*. *Calcd*. for $C_{16}H_{14}N_2$ C, 82.02; H, 6.02; N, 11.96. Found: C, 82.00; H, 6.03; N, 11.97.

***2-(4-Aminophenyl)-5,7-dimethylquinoline (12).*** The compound (**12**) was obtained in 73% yield, yellow solid, m.p. 115–116°C. IR (potassium bromide): ν 3433, 3317, 3201, 3032, 2962 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.23 (1H, d, $J$ = 8.9 Hz, 3-$H_{Qu}$), 8.01 (2H, d, $J$ = 8.5 Hz, 2-$H_{Ar}$ and 6-$H_{Ar}$), 7.75 (1H, s, 8-$H_{Qu}$), 7.73 (1H, d, $J$ = 8.9 Hz, 4-$H_{Qu}$), 7.13 (1H, s, 6-$H_{Qu}$), 6.79 (2H, d, $J$ = 8.5 Hz, 3-$H_{Ar}$ and 5-$H_{Ar}$), 3.85 (2H, br.s, $NH_2$), 2.63 (3H, s, 7-$Me_{Qu}$), 2.50 (3H, s, 5-$Me_{Qu}$) ppm. $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 156.6, 148.8, 147.6, 139.2, 133.8, 132.6, 130.0, 128.6 (2C), 128.5, 126.7, 124.1, 117.0, 115.1 (2C), 21.8, 18.4 ppm. gc-ms $t_R$: 26.94 min, *m*/*z*: 248 (molecular ion). *Anal*. *Calcd*. for $C_{17}H_{16}N_2$ C, 82.22; H, 6.49; N, 11.28. Found: C, 82.23; H, 6.51; N, 11.30.

***6-Methyl-2-(2-napthyl)quinoline (13).*** The compound (**13**) was obtained in 87% yield, white solid, m.p. 160–161°C. IR (KBr): ν 3055, 3008, 2916, 2854, 1589 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.58 (1H, s, 1-$H_{Napht}$), 8.35 (1H, d, $J$ = 8.5 Hz, 4-$H_{Napht}$), 8.12-8.00 (2H, m, 3-$H_{Qu}$ and 8-$H_{Qu}$), 7.99-7.95 (3H, m, 4-H, 3-$H_{Napht}$, 8-$H_{Napht}$), 7.89-7.56 (1H, m, 5-$H_{Napht}$), 7.58 (1H, s, 5-$H_{Qu}$), 7.58-7.56 (1H, m, 7-$H_{Qu}$), 7.53-7.49 (2H, m, 6-$H_{Qu}$ and 7-$H_{Napht}$), 2.54 (3H, s, 6-$Me_{Qu}$) ppm. $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ156.2, 146.9, 137.0, 136.2, 136.1, 133.7, 133.5, 131.9, 129.4, 128.8, 128.5, 127.7, 127.2, 126.9, 126.5, 126.3, 126.2, 125.0, 119.1, 21.6 ppm. gc-ms $t_R$: 27.02 min, *m*/*z*: 269 (molecular ion). *Anal*. *Calcd*. for $C_{20}H_{15}N$ C, 89.19; H, 5.61; N, 5.20. Found: C, 89.20; H, 5.62; N, 5.21.

***5,7-Dimethyl-2-(2-napthyl)quinoline (14).*** The compound (**14**) was obtained in 73% yield, white solid, m.p. 86–87°C. IR (KBr): ν 3055, 2970, 2900, 2854, 1620 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 8.58 (1H, s, 1-$H_{Napht}$), 8.34 (1H, dd, $J$ = 8.7, 1.5 Hz, 4-$H_{Napht}$), 8.28 (1H, d, $J$ = 8.7 Hz, 3-$H_{Qu}$), 7.97-7.94 (1H, m, 8-$H_{Napht}$), 7.95 (1H, d, $J$ = 8.5 Hz, 3-$H_{Napht}$), 7.91 (1H, d, $J$ = 8.7 Hz, 4-$H_{Qu}$), 7.88–7.85 (1H, m, 5-$H_{Napht}$), 7.85 (1H, s, 8-$H_{Qu}$), 7.50 (2H, dd, $J$ = 6.2, 3.2 Hz, 6-$H_{Napht}$ and 7-$H_{Napht}$), 7.17 (1H, s, 6-$H_{Qu}$), 2.63 (3H, s, 7-$Me_{Qu}$), 2.52 (3H, s, 5-$Me_{Qu}$) ppm. $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 156.5, 148.9, 139.5, 137.0, 133.9, 133.8, 133.5, 132.9, 129.1, 128.8, 128.4, 127.7, 127.0, 126.9, 126.5, 126.2, 125.0, 124.6, 117.8, 21.8, 18.5 ppm. gc-ms $t_R$: 29.02 min, *m*/*z*: 283 (molecular ion). *Anal*. *Calcd*. for $C_{21}H_{17}N$ C, 89.01; H, 6.05; N, 4.94. Found: C, 89.02; H, 6.04; N, 4.93.

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## REFERENCES AND NOTES

[1] Jones, G. In Pyridines and Their Benzo Derivatives; Katritzky, A., Eds.; Pergamon Press: Oxford, 1984, Vol. 2, pp 395–510.

[2] Katrizky, A. R.; Rachwal, S.; Rachwal, B. Tetrahedron 1996, 52, 15031.

[3] Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. J. Heterocycl Chem 1998, 35, 761.

[4] Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. Curr Org Chem 2005, 9, 141.

[5] Kouznetsov, V.; Vargas, L.; Leal, S.; Mora, U.; Coronado, C.; Meléndez, C.; Romero, A.; Escobar, P. Lett Drug Des Discov 2007, 4, 293.

[6] Meléndez, C.; Kouznetsov, V.; Sortino, M.; Álvarez, S.; Zacchino, S. Bioorg Med Chem 2008, 16, 7908.

[7] Vargas, L.; Castelli, M.; Kouznetsov, V.; Urbina, J.; López, S.; Sortino, M.; Enriz, R.; Ribas, J.; Zacchino, S. Bioorg Med Chem 2003, 11, 1531.

[8] Nandhakumar, R.; Suresh, T.; Calistus, A.; Rajesh, K.; Mohan, P. Eur J Med Chem 2007, 42, 1.

[9] Bekhit, A.; El-Sayed, O.; Aboulmagd, E.; Park, J. Eur J Med Chem 2004, 39, 249.

[10] Kariba, R.; Houghton, P.; Yenesew, A. J Nat Prod 2002, 65, 566.

[11] Katrizky, A. R.; Rachwal, B.; Rachwal, S. J Org Chem 1995, 60, 3993.

[12] Kouznetsov, V. V. Tetrahedron 2009, 65, 2721.

[13] Povarov, L.S. Russ Chem Rev 1967, 36, 656.

[14] Zhang, W.; Guo, Y.; Liu, Z.; Jin, X.; Yang, L.; Liu, Z.-L. Tetrahedron 2005, 61, 1325.

[15] Han, B.; Jia, X.-D.; Jin, X.-L.; Zhou, Y.-L.; Yang, L.; Liu, Z.-L.; Yu, W. Tetrahedron Lett 2006, 47, 3545.

[16] Srinivasa, A.; Mahadevan, K. M.; Hulikal, V. Monatsh Chem 2008, 139, 255.

[17] Kouznetsov, V.; Mora U. Lett Org Chem 2006, 3, 699.

[18] Antiparasitic and cytotoxic activities for this new series of compounds will be published in due course.

# Dibromination of 5-Pyrazolones and 5-Hydroxypyrazoles *via* Dibromoisocyanuric Acid



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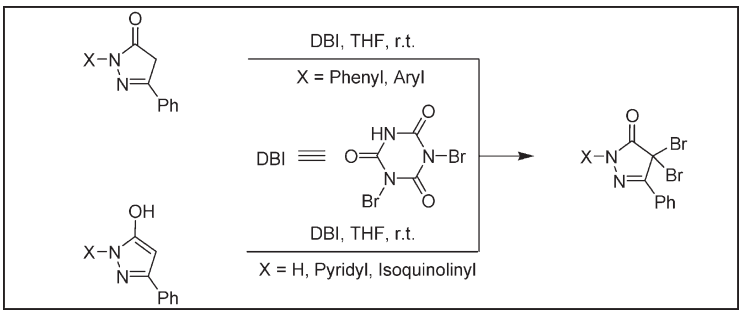


A safe and efficient method was developed for the dibromination of pyrazolones and 5-hydroxypyrazoles by use of dibromoisocyanuric acid (DBI). The reaction gave the corresponding dibrominated pyrazolones in excellent yields (≥91%).

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## INTRODUCTION

Halogenated pyrazolone compounds attracted attentions for some of them displaying interesting biological activities [1]. Among the compounds, 4,4-dibromo-5-pyrazolone have been reported as fungicides against *Helminthosporium oryzae* [2], α-glucosidase inhibitors, and used for the treatment of tumor metastasis, AIDS, diabetes, hyperlipidemia, autoimmune disease, allergy, and rejection in organ transplant [3]. They are also useful synthetic intermediates for the preparation of diazo-dyes [4], and fused- [5] and spiro-hetercyclic compounds [6].

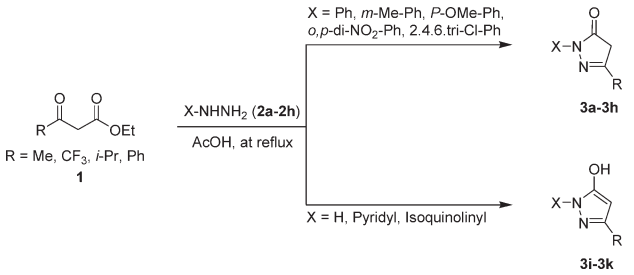
Traditional method for the synthesis of brominated pyrazolone is the use of $Br_2$ in acetic acid [7]. However, harsher conditions and manipulations with care are required. Use of the mild brominating reagent *N*-bromosuccinimide (NBS) [8b] or 1,3-dibromo-5,5-dimethylhydantoin [8c] does not also provide the corresponding dibrominated products in satisfactory yields as the monobrominated and coupling by-products were accompanied to form. As a mild brominating agent, dibromoisocyanuric acid (DBI) has been reported to brominates primary amides [9] and *N*,*N*-dimethylanilines [10]. For the structural similarity of the substrates, it is possible to extend the reagent to pyrazolones. Herein, we report an efficient method for the dibromination of pyrazolones and 5-hydroxypyrazoles by using DBI. A series of 4,4-dibromo-5-pyrazolones could be obtained in excellent yields (≥91%) by this method. Comparison with the use of NBS as the brominating agent, we found the use of DBI toward pyrazolones was more efficient.

## RESULTS AND DISCUSSION

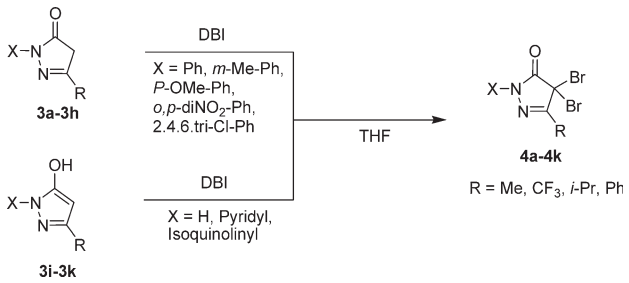
5-Pyrazolones were prepared as the substrates for the investigation of dibromination by DBI through tandem condensation and thermal cyclization following the reported procedure [11]. α-Keto esters **1** were heated at reflux in AcOH with equal equivalent of arylhydrazines **2a**–**2h** possessing various substituents including *m*-Me, *p*-OMe, *o*, *p*-di-$NO_2$, and 2,4,6,-trichloro at the phenyl ring for 4.0 h. The corresponding 5-pyrazolones (keto form) were obtained in good to excellent yields (>75%, see Scheme 1 and Chart 1) [11]. Use of hydrazine, and pyridyl and isoquinolinyl hydrazines as the starting material provided the corresponding 5-hydroxypyrazoles **3i**–**3k** (enol form) in >86% yields (see Scheme 1, and Chart 1). The experiment results were consistent with the literature reported [12].

To search an efficient and reproducible procedure, we carried out a model study by treating 5-pyrazolone (**3a**)

**Scheme 1**




**Scheme 2**




with DBI [13] in THF at room temperature for 30 min (see Chart 1 and Scheme 2). The reaction afforded the desired 4,4-dibromo-5-pyrazolone (**4a)** in 95% yield. Compound **4a** was fully characterized by spectroscopic method and the results were consistent with the reported data from literature [14]. In a control experiment by reacting **3a** with NBS, the reaction was less efficient which provided **4a** in 78% yield.

By using the newly developed method shown in Scheme 2, we successful applied this synthetic strategy to 5-pyrazolones **3b–3h** with *N*-substituted group, including *m*-Me, *p*-OMe, *o*,*p*-di-$NO_2$, and 2,4,6-trichloro. The corresponding products **4b–4h** were obtained in the ≥91% yields (see Table 1). This synthetic strategy is applicable to 5-hydroxypyrazole (enol form of 5-pyrazolone) that bear *N*-substituted group, such as H, pyridyl, and isoquinolinyl (**3i–3k**). The desired compounds **4i–4k** were afforded in 91–95% yields and fully characterized by spectroscopic methods. For example, compound **4k** possessed characterization absorptions at δ 42.5 ppm for O=C—$^{13}C(Br)_2$ in pyrazolone ring and IR absorptions showed peaks at 1751 $cm^{-1}$ for stretching of the —C=O group.

We proposed a plausible mechanism for the dibromination of 5-pyrazolones by use of DBI as shown in Scheme 3. When 5-hydroxypyrazoles **3a–3h** were treated with DBI, the compounds favored the enol form in the acidic condition and underwent the smoothly nucleophilic substitution reaction to generate the corresponding mono-bromo-5-pyrazolone intermediates **6** with *N*-monobromoisocyanuric acid **5**. Application of 5-hydroxy-3-phenyl-1*H*-pyrazole (**3i**), 5-hydroxy-3-phenyl-1-(pyrid-2-yl)-1*H*-pyrazole (**3j**), and 5-hydroxy-3-phenyl-1-(3-isoquinolinyl)-1*H*-pyrazole (**3k**) as the model demonstrated that the enol species could also proceeded the nucleophilic substitution in the same reaction condition. For the further conjunction conversion, mono-bromo-5-pyrazolones **6** were converted to the mono-bromo-5-hydroxypyrazoles **7** under the reaction mixture. Finally, mono-bromo-5-hydroxypyrazole intermediates **7** consequential trapped the secondary equivalent bromine from the *N*-monobromoisocyanuric acid **5** to generate final dibrominated products **4a–4k** and cyanuric acid **8**. Cyanuiric acid **8** can be isolated by column chromatography and identified by IR and $^{13}C$ NMR spectroscopic methods to demonstrate the plausible mechanism.

In conclusion, we have successfully developed a dibrominating method for the conversion of the keto form pyrazolone and the enol form 5-hydroxypyrazole substrates by use of DBI as the reagent. The reaction provided 4,4-dibromo-pyrazolones **4a–4k** in excellent yields (≥91%). This newly developed bromination method was a safe and efficient would be useful in the large-scale preparation of the dibrominated pyrazolones.

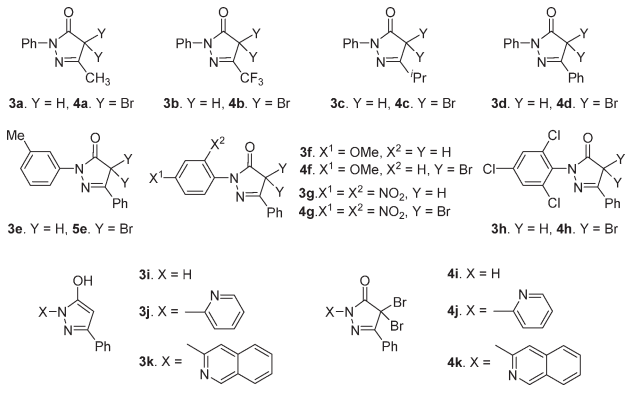


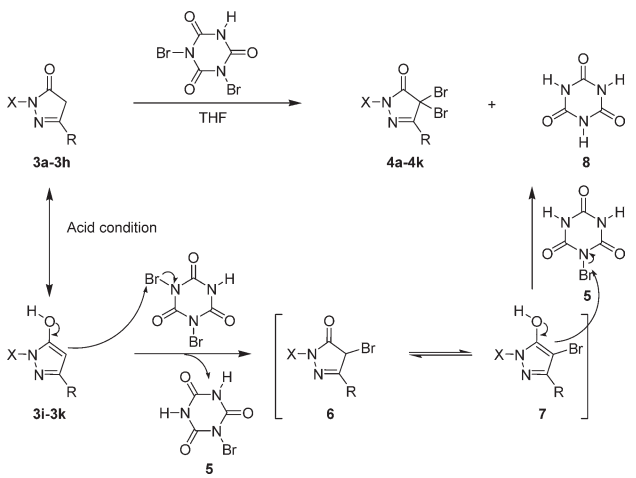

**Chart 1**

**Table 1**

The results of bromination by using dibromoisocyanuric acid (DBI).

| 5-Pyrazolones (**3a–3h**) or 5-hydroxypyrazoles (**3i–3k**) | | | Dibromination (**4a–4k**) | |
|---|---|---|---|---|
| Compounds | X | R | Products | Yields (%) |
| **3a** | Ph | Me | **4a** | 95 |
| **3b** | Ph | $CF_3$ | **4b** | 94 |
| **3c** | Ph | *i*-Pr | **4c** | 98 |
| **3d** | Ph | Ph | **4d** | 96 |
| **3e** | *m*-Me-Ph | Ph | **4e** | 94 |
| **3f** | *p*-OMe-Ph | Ph | **4f** | 93 |
| **3g** | *o*,*p*-*di*-$NO_2$-Ph | Ph | **4g** | 97 |
| **3h** | 2,4,6,-*tri*-Chloro-Ph | Ph | **4h** | 92 |
| **3i** | H | Ph | **4i** | 93 |
| **3j** | Pyridyl | Ph | **4j** | 95 |
| **3k** | Isoquinolinyl | Ph | **4k** | 91 |

**Scheme 3**




## EXPERIMENTAL

**General procedure.** All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Dichloromethane, ethyl acetate, hexanes, and methanol were purchased from Mallinckrodt Chemical Co. Dry tetrahydrofuran (reagent grade) was used. The following compounds were purchased from Acoros Chemical Co: *o*-tolyhydrazine hydrochoide, *tert*-butyl acetoacetate, ethyl isobutylacetate, phenylhydrazine 4-methoxyphenylhydrazine hydrochloride, and 2,4-dinitrophenyl hydrazine. 2,4,6-Trichlorophenyl hydrazine, 2-hydrazinopyridine, and isonicotinic acid hydrazide were purchased from TCI Chemical Co. Ethyl trifluoroacetoacetate and *tert*-butyl acietoacetate from Alfa Chemical Co. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FTIR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm−1 absortion. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of $CDCl_3$, $CH_3OD$, and *d6*-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by used of $CDCl_3$, $CH_3OD$, and *d6*-DMSO as solvent. Carbon-13 chemical shifts are referenced to the center of the CDCl3 triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

**Standard procedure for dibromination to prepare 4,4-dibromo-5-pyrazolone derivatives 4a–4k.** To a solution of pyrazolones **3a–3h** or 5-hydroxypyrazoles **3i–3k** (1.0 equiv) in THF (20 mL) was added DBI (2.1 equiv). The reaction mixture was stirred at room temperature for ∼1 h. The solution was concentrated under reduced pressure and the resultant oil was redissolved in $CH_2Cl_2$ (50 mL). The solution was washed with $H_2O$ (20 mL × 2), brine (20 mL × 2), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc in hexanes as eluant) to give 4,4-dibromo-5-pyrazolones **4a–4k** as solids in 91–98% yields.

***4,4-Dibromo-3-methyl-1-phenyl-2-pyrazolin-5-one (4a).*** To a solution of pyrazolones **3a** (20 g, 0.114 mol, 1.0 equiv) in THF (150 mL) was added DBI (69.2 g, 0.242 mol, 2.1 equiv). The reaction mixture was stirred at room temperature for ∼1 h. The solution was concentrated under reduced pressure and the resultant oil was redissolved in $CH_2Cl_2$ (200 mL). The solution was washed with $H_2O$ (80 mL × 2), brine (80 mL × 2), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc in hexanes as eluant) to give 4,4-dibromo-5-pyrazolones **4a** as solids in 95 % yields. mp 80–82°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 2.42 (s, 3 H, $CH_3$), 7.21 (d, 1 H, $J$ = 2.6 Hz, ArH), 7.39 (dd, 2 H, $J$ = 7.4, 2.6 Hz, ArH), 7.84 (d, 2 H, $J$ = 7.4 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 20.0, 41.7, 118.9, 125.0, 128.8, 138.1, 159.9, 170.6; IR (KBr) 3199 (m), 2960 (m), 1706 (s, C=O), 1508 (s, C=N), 1348 (m), 1227 (m), 972 (m), 754 (m) $cm^{-1}$; EIMS m/z (relative intensity) 362 (M + 2, 7), 360 ($M^+$, 14), 358 (M – 2, 7), 281 (84), 279 (84), 265 (3), 201 (20), 200 (13), 184 (3), 171 (4), 131 (3), 105 (11), 95 (7), 92 (4), 77 (100), 65 (8), 51 (13). Anal. Calcd for $C_{10}H_8Br_2N_2O$; C: 36.18; H: 2.43; N: 8.44, Found: C: 36.22; H: 2.47; N: 8.46.

***4,4-Dibromo-1-phenyl-3-trifluoro-2-pyrazolin-5-one (4b).*** mp 119–121°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.24–7.52 (m, 3 H, ArH), 7.81 (d, 2 H, $J$ = 7.8 Hz, ArH); IR (KBr) 3391 (s), 3184 (m), 1631 (s, C=O), 1576 (s, C=N), 1404 (m), 1113 (m), 773 (m), 704 (m), 633 (m) $cm^{-1}$. Anal. Calcd for $C_{10}H_5Br_2F_3N_2O$; C: 31.12; H: 1.31; N: 7.26, Found: C: 31.46; H: 1.65; N: 6.94.

***4,4-Dibromo-3-isopropyl-1-phenyl-2-pyrazolin-5-one (4c).*** mp 77–79°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 1.44 (d, 6 H, $J$ = 7.2 Hz, 2 × $CH_3$), 3.06 (m, 1 H, $CHMe_2$), 7.23 (d, 1 H, $J$ = 7.9 Hz, ArH), 7.41 (dd, 2 H, $J$ = 7.9, 3.2 Hz, ArH), 7.86 (d, 2 H, $J$ = 3.2 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 22.2 (2 × $CH_3$), 28.6, 45.8, 118.8 (2 × CH), 125.9, 129.0 (2 × CH), 137.1, 163.1, 165.0; IR (KBr) 3193 (m), 2935 (m), 1717 (s, C=O), 1575 (s, C=N), 1489 (m), 1283 (m), 979 (m), 802 (m), 763 (m) $cm^{-1}$; EIMS *m/z* (relative intensity) 359 (M+2, 4), 358 ($M^+$, 8), 357 (M–2, 4), 344 (9), 315 (4), 278 (6), 254 (8), 253 (14), 252 (8), 201 (9), 184 (5), 174 (28), 173 (32), 171 (4), 145 (3), 130 (6), 119 (4), 105 (19), 91 (32), 78 (10), 77 (100), 67 (11), 64 (10), 51 (24). Anal. Calcd for $C_{12}H_{12}Br_2N_2O$; C: 40.03; H: 3.36; N: 7.78, Found: C: 40.06; H: 3.32; N: 7.81.

***4,4-Dibromo-1,3-diphenyl-2-pyrazolin-5-one (4d).*** mp 128–130°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.27 (d, 1 H, $J$ = 7.6 Hz, ArH), 7.42–7.54 (m, 5 H, ArH), 7.99 (d, 2 H, $J$ = 7.8 Hz, ArH), 8.23 (d, 2 H, $J$ = 7.8 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 42.7, 119.1 (2 × CH), 126.4, 127.2 (2 × CH), 128.9 (2 × CH), 129.2 (2 × CH), 131.7, 137.0, 137.1, 153.5, 165.7; IR (KBr) 3391 (s), 3184 (m), 1632 (s, C=O), 1575 (s, C=N), 1404 (m),1112 (m), 773 (m), 704 (m) $cm^{-1}$; EIMS *m/z* (relative intensity) 397 (M+2, 18), 395 ($M^+$, 30), 393 (M–2, 18), 338 (14), 315 (45), 263 (9), 219 (66), 241 (15), 165 (19), 154 (39), 119 (52), 95 (93), 69 (99), 55 (100); HRMS calcd for $C_{15}H_{10}Br_2N_2O$ 391.9160, found 391.9157. Anal. Calcd for $C_{15}H_{10}Br_2N_2O$; C: 45.72; H: 2.56; N: 7.11, Found: C: 45.76; H: 2.59; N: 7.15.

***4,4-Dibromo-1-(2-methyl)-phenyl-3-phenyl-2-pyrazolin-5-one (4e).*** mp 104–106°C; $^1$H NMR ($CD_3OD$, 200 MHz) δ 2.23 (s, 3 H, $CH_3$), 7.47–7.52 (m, 7 H, ArH), 7.96–8.01 (m, 2 H, ArH); $^{13}$C NMR ($CD_3OD$, 50 MHz) δ 16.0, 126.1 (2 × CH), 127.0, 127.6, 128.0, 128.5, 129.0 (2 × CH), 130.6, 131.0, 131.1, 132.5, 136.6, 149.8, 157.5; IR (KBr) 3198 (s), 2959 (m), 1717 (s, C=O), 1542 (s, C=N), 1319 (m), 1194 (m), 980 (m), 761 (m) cm$^{-1}$; MS *m*/*z* (relative intensity) 410 (M + 2, 6), 408 ($M^+$, 12), 406 (M – 2, 6), 365 (2), 327 (74), 311 (3), 283 (7), 249 (53), 219 (10), 191 (6), 171 (6), 145 (12), 129 (36), 105 (24), 91 (100), 65 (26), 51 (16). Anal. Calcd for $C_{16}H_{12}Br_2N_2O$; C: 47.09; H: 2.96; N: 6.86, Found: C: 47.13; H: 2.92; N: 6.90.

***4,4-Dibromo-1-(4-methoxy)-phenyl-3-phenyl-2-pyrazolin-5-one (4f).*** mp 108–110°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3 H, $CH_3$), 6.97 (d, 2 H, $J$ = 7.2 Hz, ArH), 7.48–7.51 (m, 3 H, ArH), 7.85 (d, 2 H, $J$ = 7.2 Hz, ArH), 8.19 (d, 2 H, $J$ = 7.8 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 42.6, 55.6, 114.2 (2 × CH), 121.0 (2 × CH), 127.1 (2 × CH), 127.3, 128.8 (2 × CH), 130.2, 131.5, 153.4, 157.9, 165.4; IR (KBr) 3194 (s), 2959 (m), 1717 (s, C=O), 1508 (s, C=N), 1251 (m), 1006 (m) cm$^{-1}$; MS *m*/*z* (relative intensity) 427 (M+2, 2), 425 ($M^+$, 4), 423 (M–2, 2), 345 (99), 343 (97), 266 (82), 265 (53), 235 (14), 221 (17), 209 (6), 162 (8), 160 (15), 158 (8), 135 (48), 129 (39), 121 (30), 107 (100), 102 (17), 92 (38), 77 (66), 64 (19). Anal. Calcd for $C_{16}H_{12}Br_2N_2O_2$; C: 45.31; H: 2.85; N: 6.61, Found: C: 45.27; H: 2.89; N: 6.57.

***4,4-Dibromo-1-(2,4-dinitro)-phenyl-3-phenyl-2-pyrazolin-5-one (4g).*** mp 182–184°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.22–7.28 (m, 1 H, ArH), 7.45–7.52 (m, 2 H, ArH), 7.86 (dd, 1 H, $J$ = 7.8, 3.7 Hz, ArH), 7.97 (d, 1 H, $J$ = 7.8 Hz, ArH), 8.22–8.27 (m, 2 H, ArH), 8.61 (d, 1 H, $J$ = 3.7 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 38.4, 121.2, 124.9, 126.3 (2 × CH), 127.5, 129.2 (2 × CH), 129.8, 131.7, 134.3, 141.9, 144.6, 157.2, 169.9; IR (KBr) 3195 (m), 2926 (s), 1749 (s, C=O), 1510 (s, C=N), 1339 (m), 1169 (m), 1079 (m), 892 (m), 685 (m) cm$^{-1}$; EIMS *m*/*z* (relative intensity) 486 (M+2, 9), 484 ($M^+$, 17), 482 (M–2, 9), 405 (98), 325 (89), 279 (11), 205 (17), 147 (19), 129 (100), 103 (88), 93 (29), 77 (80), 63 (22-), 51 (31); HRMS calcd for $C_{15}H_8Br_2N_4O_5$ 481.8861, found 481.8857. Anal. Calcd for $C_{15}H_8Br_2N_4O_5$; C: 37.22; H: 1.67; N: 11.57, Found: C: 37.26; H: 1.71; N: 11.61.

***4,4-Dibromo-1-(2,4,6-trichloro)-phenyl-3-phenyl-2-pyrazolin-5-one (4h).*** mp 90–91°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.46–7.52 (m, 5 H, ArH), 8.11–8.16 (m, 2 H, ArH); IR (KBr) 3198 (m), 1749 (s, C=O), 1557 (s, C=N), 1470 (m), 1183 (m), 1064 (m), 815 (m) cm$^{-1}$; EIMS *m*/*z* (relative intensity) 502 (M + 2, 4), 500 ($M^+$, 8), 498 (M – 2, 4), 419 (67), 416 (100), 391 (14), 389 (21), 387 (11), 339 (46), 303 (20), 273 (21), 221 (4), 207 (27), 179 (57), 158 (29), 129 (63), 103 (68), 75 (33), 51 (25). Anal. Calcd for $C_{15}H_7Br_2Cl_3N_2O$; C: 36.22; H: 1.42; N: 5.63, Found: C: 36.45; H: 1.56; N: 5.31.

***4,4-Dibromo-3-phenyl-2-pyrazolin-5-one (4i).*** mp 147–149°C; $^1$H NMR (DMSO-$d_6$, 200 MHz) δ 7.49–7.54 (m, 3 H, ArH), 8.11–8.16 (m, 2 H, ArH); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) δ 40.5, 126.3 (2 × CH), 127.9, 128.3 (2 × CH), 130.7, 154.3, 170.5; IR (KBr) 3156 (m), 1742 (s, C=O), 1541 (m, C=N), 1271 (m), 865 (m), 742 (m), 692 (m) cm$^{-1}$; EIMS m/z (relative intensity) 320 (M + 2, 8), 318 ($M^+$, 16), 316 (M – 2, 8), 240 (61), 209 (7), 182 (13), 160 (41), 129 (100), 102 (86), 77 (44), 75 (46), 63 (12), 51 (39). Anal. Calcd for $C_9H_6Br_2N_2O$; C: 34.00; H: 1.90; N: 8.81, Found: C: 33.97; H: 1.94; N: 8.78.

***4,4-Dibromo-3-phenyl-1-(pyrid-2-yl)-2-pyrazolin-5-one (4j).*** mp 180–182°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.16–7.27 (m, 1 H, ArH), 7.43–7.50 (m, 3 H, ArH), 7.79–7.87 (m, 1 H, ArH), 7.90–7.99 (m, 1 H, ArH), 8.21–8.26 (m, 2 H, ArH), 8.55–8.58 (m, 1 H, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 42.4, 114.9, 122.0, 127.0, 127.5 (2 × CH), 127.8, 128.7 (2 × CH), 131.8, 138.5, 148.9, 154.2, 165.9; IR (KBr) 3200 (s), 2929 (m), 1718 (s, C=O), 1558 (s, C=N), 1409 (m), 1311 (m), 1268 (m), 974 (m), 864 (m), 828 (m), 812 (m), 739 (m), 690 (m) cm$^{-1}$; EIMS *m*/*z* (relative intensity) 395 ($M^+$, 2), 320 (8), 318 (16), 316 (8), 237 (46), 209 (7), 182 (12), 160 (12), 129 (100), 102 (69), 75 (32), 51 (21); HRMS calcd for $C_{14}H_9Br_2N_3O$ 392.9112, found 392.9109.

***4,4-Dibromo-3-phenyl-1-(3-isoquinolinyl)-2-pyrazolin-5-one (4k).*** mp 131–133°C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.38–7.58 (m, 5 H, ArH) 7.70–7.85 (m, 3 H, ArH) 8.09–8.16 (m, 1 H, ArH) 8.27–8.34 (m, 2 H, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 42.5, 113.7, 126.7, 126.9, 127.1, 127.5, 127.6 (2 × CH), 128.7 (2 × CH), 129.1, 130.4, 131.9, 138.9, 146.8, 148.0, 154.3, 166.2; IR (KBr) 3045 (m), 2884 (m), 1751 (s, C=O), 1645 (m, C=N), 1503 (m), 1429 (m), 1383 (m), 1290 (m), 899 (m), 823 (m), 686 (m) cm$^{-1}$. Anal. Calcd for $C_{18}H_{11}Br_2N_3O$; C: 48.57; H: 2.49; N: 9.44, Found: C: 48.24; H: 2.64; N: 9.31.

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## REFERENCES AND NOTES

[1] Kakiuchi, Y.; Sasaki, N.; Satoh-Masuoka, M.; Murofushi, H.; Murakami-Murofushi, K. Biochem Biophys Res Commun 2004, 320, 1351.

[2] Sarojbasinidas, A. N.; Mishra, C. R.; Mittra, A. S. J Indian Chem Soc 1977, LIV, 485.

[3] Fuminori, K.; Hirohiko, K. Jpn. Pat.45588, 1998.

[4] Kirscuke, K.; Luize, G.; Schmttz, E. J Park Chem 1984, 326, 367.

[5] Chande, M. S.; Bhandari, J. D.; Joshi, V. R. Indian J Chem B 1993, 32B, 1218.

[6] El-Saraf, G. A.; El-Sayed, A. M. Heteroat Chem 2003, 14, 211.

[7] (a) Karci, F.; Ertan, N. Dyes Pigments 2002, 55, 99; (b) Ho, Y. W. Dyes Pigments 2004, 64, 223.

[8] (a) Ahmed, S. A.; Award, D. M. A.; Abdel-Wahab, Aboel-Mahab, A. Chem Commun 2002, 1, 84; (b) Edward, M. K.; Dov, F.; Marcia, B. S.; Israel, G. J Org Chem 1982, 47, 214; (c) Spitulnik, M. J. Synthesis 1985, 47, 299.

[9] Demko, Z. P.; Bartsch, M.; Sharpless, K. B. Org Lett 2000, 15, 2221.

[10] Rossevear, J.; Wishire, J. F. K. Aust J Chem 1972, 30, 1561.

[11] (a) Wang, X.-j.; Tan, J.; Grozinger, K. Tetrahedron Lett 2000, 41, 4713; (b) DeRuiter, J.; Carter, D. A.; Arledge, W. S.; Sullivan, P. J. J Heterocycl Chem 1987, 24, 149; (c) Brana, M. F.; Gradillas, A.; Ovalles, A. G.; López, B.; Acero, N.; Llinares, F.; Mingarro, D. M. Bioorg Med Chem 2006, 14, 9.

[12] (a) McFerrin, C. A.; Hammer, R. P.; Fronczek, F. R.; Watkins, S. F. Acta Cryst 2006, E62, 2518; (b) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. J Med Chem 2007, 50, 5053; (c) Mojtahedi, M. M.; Javadpour, M. Abaee, M. S. Utrason SonoChem 2008, 15, 828; (d) Basaif, S. A.; Hassan, M. A.; Gobouri, A. A. Dyes Pigments 2007, 72, 387.

[13] Gottardi, W. Monatsh Chem 1975, 106, 611.

[14] Kirscuke, K.; Luize, G.; Schmttz, E. J Park Chem 1984, 326, 367.

# Synthesis of Trispiro[oxindole-pyrrolidine]-cyclopentanone-isoxazolines by 1,3-Dipolar Cycloaddition



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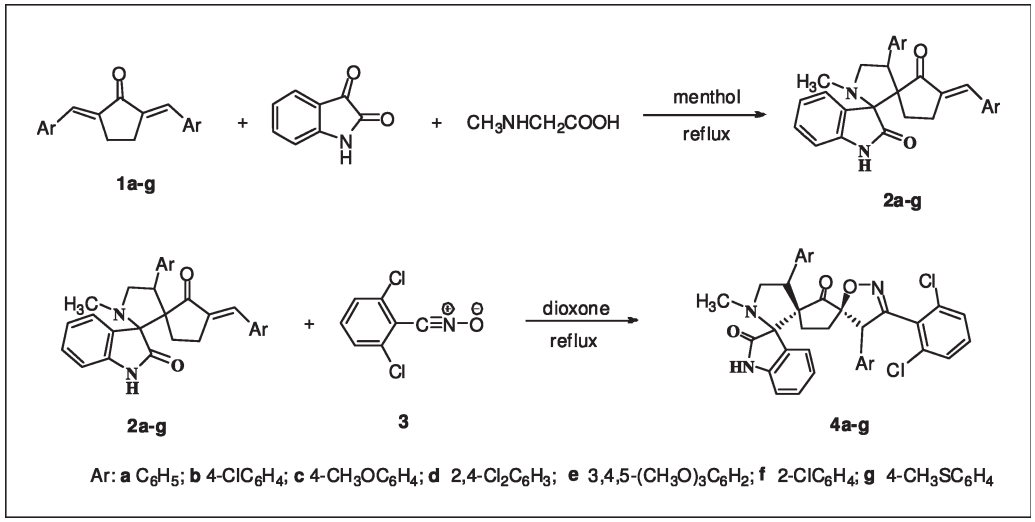


The 1,3-dipolar cycloaddition of an azomethine ylide generated by a decarboxylative route from sarcosine and isatin to 2,5-bis(arylmethylidene)-cyclopentanones afforded novel dispiro oxindole/pyrrolidines in moderate yields. Further cycloaddition of these dispiro oxindole/pyrrolidines with nitrile oxide afforded trispiro[oxindole-pyrrolidine]-cyclopentanone-isoxazolines in moderate yields with high regio- and stereoselectivity.

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## INTRODUCTION

Spiro-compounds are an important class of organic compounds based on their biological activities [1], which are motifs in many pharmacologically important alkaloids, as typified by rhyncophylline, corynoxeine, mitraphylline, horsifiline, and spirotryprostatins [2]. Therefore, the synthesis of spiro-compounds has recently attracted the interest of organic chemists.

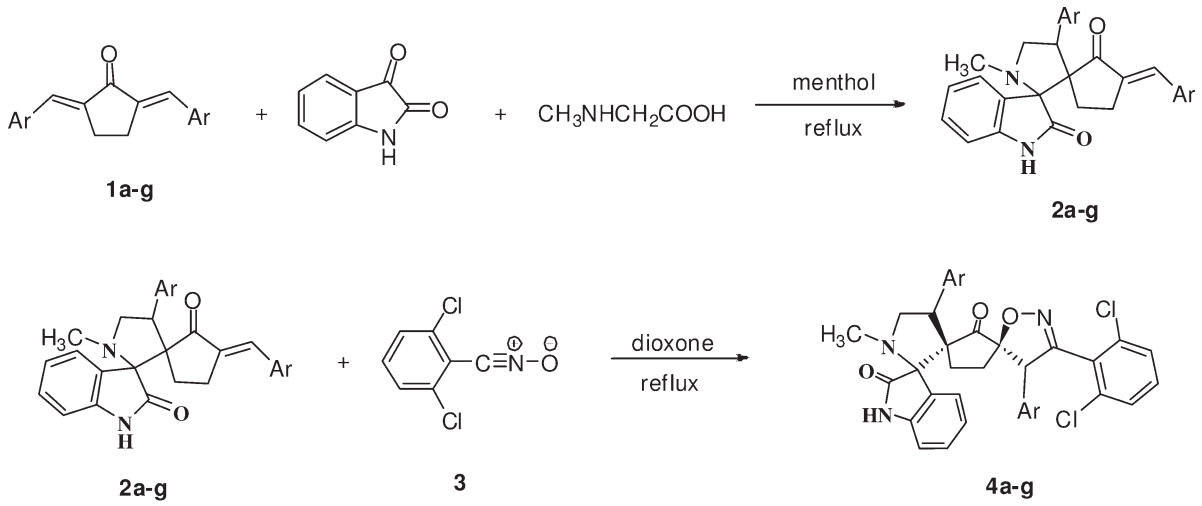
On the other hand, one of the most widely used methods for the synthesis of these compounds is via the intermolecular 1,3-dipolar cycloaddition reaction to exocyclic double bonds [3,4]. Therefore, the substrate with two exocyclic double bonds could be transformed to different spiro-groups by appropriate methods. Kumar and Perumal [5] used 1-methyl-3,5-bis[(E)-arylmethylidene]-tetrahydro-4(1H)-pyridinones through a tandem sequence comprising nitrile oxide cycloaddition to obtain cycloreversion mono-spiro-isoxazoline compounds other than the presumed tri-spiro product.

In the present work, we report the results of a tandem azomethine ylide/nitrile oxide cycloaddition of 2,5-bis(arylmethylidene)-cyclopentanone to obtain trispiro-[oxindole-pyrrolidine]-cyclopentanone-isoxazoline compound **4** (Scheme 1).

## RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition of the azomethine ylide generated *in situ* from isatin and sarcosine to 2,5-bis(arylmethylidene)-cyclopentanone (**1a–g**) afforded novel dispiroheterocycles (**2a–g**) in moderate to good yields (80–85%) (Scheme 1). This cycloaddition reaction proceeded with high stereo- and regioselectivity to afford only one isomer, which was evidenced from TLC and $^1$H-NMR of the crude reaction mixture. The $^1$H-NMR spectrum of **2a** demonstrated the presence of four multiplet of cyclopentanone $CH_2$ at δ 1.23–1.30, 2.12–2.16, 2.17–2.21, 2.35–2.40: one doublet of doublets at δ 4.37

**Scheme 1**




Ar: **a** $C_6H_5$; **b** 4-$ClC_6H_4$; **c** 4-$CH_3OC_6H_4$; **d** 2,4-$Cl_2C_6H_3$; **e** 3,4,5-$(CH_3O)_3C_6H_2$; **f** 2-$ClC_6H_4$; **g** 4-$CH_3SC_6H_4$

and two triplets at δ 3.60, 3.99 assigned as pyrrolidine protons, and two singlets at δ 2.25 and 8.31 assignable to the —$NCH_3$ and —NH, respectively. The $^{13}$C-NMR spectrum of **2a** demonstrated the presence of two spiro carbons at δ 65.61 and 77.73, two carbonyl carbons at δ 178.99 and 206.90.

The dispiroheterocycles **2** were reacted subsequently with nitrile oxide (Scheme 1) and tri-spiroheterocycles **3** were obtained in 70–85% yields. The stereo- and regioselectivity of this cycloaddition reaction was evidenced from TLC and $^1$H-NMR of the crude reaction mixture. The structures of **4a–g** were confirmed by IR, NMR, elemental analyses together with X-ray. For example, the IR spectrum of **4a** exhibited two carbonyl peaks locating at 1746.7 and 1709.8 $cm^{-1}$, which was assigned to the carbonyl group in cyclopentanone ring and the carbonyl group of lactam, respectively. What is more, the mass spectrum of **4a** showed a molecular ion peak at *m/z* 623 (M+1), which confirmed the addition of **3** to the exocyclic double bonds of **2a**.

The $^1$H-NMR spectrum of **4a** revealed a singlet at δ 2.15 resulting from N—CH3, four multiplets in the range of δ 0.99–1.02, 1.37–1.40, 1.53–1.55, and 1.66–1.70 resulting from the C**H**$_2$ in cyclopentanone ring, a triplet at δ 4.20 for C**H** and two triplets at δ 3.55 and 3.97 for C**H**$_2$ in pyrrole ring and a characterize singlet at δ 4.69 for PhC**H**. The $^{13}$C-NMR spectrum of the product **4a** exhibited the presence of methyl carbon at δ 34.8; two **C**$H_2$ in cyclopentanone ring at δ 28.6 and 28.8; three spiro carbons at δ 92.4, 77.4, and 65.5; N—**C**$H_2$ at δ 59.4; benzylic carbons at δ 58.2 and 51.6, respectively; and carbonyl carbons at δ 177.7 and 213.4. Further, the structure of the product was confirmed by X-ray diffraction analysis of **4a** [6] (Fig. 1).

## EXPERIMENTAL

**1** [7] and **3** [8] were prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for $^1$H, and 125 MHz for $^{13}$C. TMS was used as an internal reference for $^1$H and $^{13}$C chemical shifts. $CDCl_3$ was as solvent. Elemental analysis was measured by an Elementar analyzer (varioELII). MS was measured by a Finnigan LCQ Advantage MAX mass spectrometer; IR spectra were recorded on Perkin-Elmer spectrometer. Melting points were measured by a Yanaco MP500 melting points apparatus and uncorrected.

**General procedure for the synthesis of spirooxindoles (2a–g).** A solution of isatin (1mmol), sarcosine (1mmol), and 2,5-diarylidene-cyclopentanone **1** (1mmol) in methanol (30 mL) was refluxed overnight. Completion of the reaction was evidenced by TLC analysis. The solvent was removed *in vacuo*. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate (v/v 5:1) as eluent to afford the corresponding **2**.

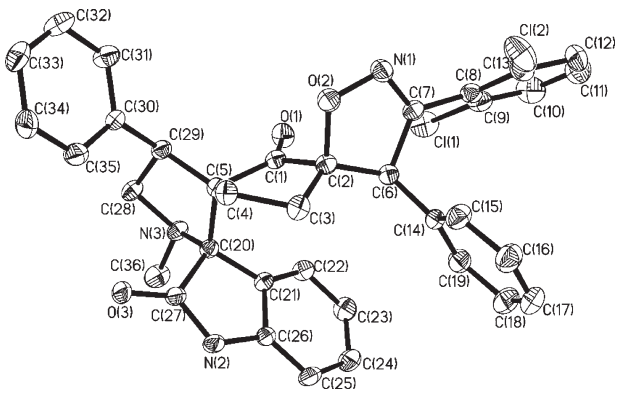



**Figure 1.** ORTEP diagram of **4a** (H atoms have been omitted for clarity).

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-benzylidenecyclopentanone-4-phenyl-pyrrolidine (2a).*** White solid, yield 85%; mp: 206–208°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.23–1.30 (m, 1H), 2.12–2.16 (m, 1H), 2.17–2.21 (m, 1H), 2.25 (s, 3H), 2.35–2.40 (m, 1H), 3.60 (t, $J$ = 8.0 Hz, 1H), 3.99 (t, $J$ = 10.0 Hz, 1H), 4.37 (dd, $J$ = 8.0, 10.0 Hz, 1H), 6.79–6.84 (m, 1H), 6.91 (t, $J$ = 7.5 Hz, 1H), 7.10–7.13 (m, 1H), 7.18–7.20 (m, 3H), 7.22–7.27 (m, 5H), 7.31 (t, $J$ = 8.0 Hz, 2H), 7.53 (d, $J$ = 6.5 Hz, 2H), 8.31 (s, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 26.21, 30.70, 35.00, 49.15, 59.95, 65.61, 77.73, 109.21, 122.96, 125.99, 126.88, 127.78, 128.34, 128.48, 129.19, 129.38, 130.18, 130.38, 133.53, 135.37, 135.52, 139.59, 141.32, 178.99, 206.90; IR (KBr) $v$: 1721.4, 1704.3 cm$^{-1}$; MS(ESI) $m/z$: 435 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{26}N_2O_2$: C 80.16, H 6.03, N 6.45; found C 80.06, H 6.17, N 6.49.

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(4-chloro)benzylidenecyclopentanone-4-(4-chloro)phenyl-pyrrolidine (2b).*** White solid, yield 85%; mp: 224–226°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.20–1.27 (m, 1H), 2.08–2.14 (m, 1H), 2.20 (s, 3H), 2.19–2.22 (m, 1H), 2.33–2.38 (m, 1H), 3.58 (t, $J$ = 8.5 Hz, 1H), 3.92 (t, $J$ = 9.5 Hz, 1H), 4.31 (dd, $J$ = 8.5, 9.5 Hz, 1H), 6.77 (d, $J$ = 7.5 Hz, 1H), 6.89 (t, $J$ = 7.5 Hz, 1H), 7.11–7.14(m, 4H), 7.19–7.21 (m, 1H), 7.23–7.28 (m, 4H), 7.45 (d, $J$ = 8.0 Hz, 2H), 8.14 (bs, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 26.11, 30.62, 34.92, 48.40, 59.99, 65.43, 77.52, 109.26, 122.99, 125.72, 127.70, 128.50, 128.82, 129.51, 131.29, 131.72, 132.33, 132.74, 133.71, 135.25, 135.72, 138.07, 141.24, 178.44, 206.48; IR (KBr) $v$: 1720.5, 1708.1 cm$^{-1}$; MS(ESI) $m/z$: 503 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{24}Cl_2N_2O_2$: C 69.19, H 4.81, N 5.56; found C 69.37, H 4.92, N 5.48.

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(4-methoxy)-benzylidenecyclopentanone-4-(4-methoxy)phenyl-pyrrolidine (2c).*** White solid, yield 83%; mp: 188–190°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.24–1.35 (m, 1H), 2.06–2.17 (m, 2H), 2.20 (s, 3H), 2.31–2.36 (m, 1H), 3.56 (t, $J$ = 8.5 Hz, 1H), 3.78 (s, 6H), 3.93 (t, $J$ = 9.5 Hz, 1H), 4.29 (t, $J$ = 9.0 Hz, 1H), 6.74 (d, $J$ = 7.5 Hz, 1H), 6.79 (d, $J$ = 8.5 Hz, 2H), 6.84 (d, $J$ = 8.5 Hz, 2H), 6.89 (t, $J$ = 7.5 Hz, 1H), 7.09 (t, $J$ = 7.5 Hz, 2H), 7.17–7.22 (m, 3H), 7.43 (d, $J$ = 7.5 Hz, 2H), 7.96 (bs, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 26.3, 30.6, 35.1, 48.5, 55.2, 55.3, 60.2, 65.5, 77.87, 109.3, 113.7, 114.1, 114.3, 122.9, 126.1, 127.8, 128.1, 129.3, 131.4, 131.7, 132.1, 132.6, 133.2, 133.5, 141.6, 158.5, 160.5, 179.2, 207.1; IR (KBr) $v$: 1718.6, 1704.7 cm$^{-1}$; MS(ESI) $m/z$: 495 $[M+H]^+$. Anal. Calcd. for $C_{31}H_{30}N_2O_4$: C 75.28, H 6.11, N 5.66; found C 75.34, H 6.21, N 5.45.

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(2,4-dichloro)-benzylidenecyclopentanone-4-(2,4-dichloro)phenyl-pyrrolidine (2d).*** White solid, yield 80%; mp: 239–241°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.16–1.18 (m, 1H), 1.99–2.05 (m, 2H), 2.20 (s, 3H), 2.23–2.26 (m, 1H), 3.59 (t, $J$ = 8.5 Hz, 1H), 3.96 (t, $J$ = 9.0 Hz, 1H), 4.87 (t, $J$ = 9.0 Hz, 1H), 6.77–6.80 (m, 2H), 6.92 (t, $J$ = 7.5 Hz, 1H), 7.06–7.09 (m, 1H), 7.14–7.18 (m, 2H), 7.27–7.30 (m, 1H), 7.33–7.36 (m, 2H), 7.52 (s, 1H), 7.83 (s, 1H), 8.03 (d, $J$ = 9.0 Hz, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 25.93, 30.28, 34.96, 43.09, 58.70, 64.68, 77.49, 109.26, 123.26, 125.32, 126.79, 127.27, 127.93, 128.75, 128.84, 129.57, 129.74, 130.23, 132.29, 132.36, 133.01, 135.18, 135.96, 136.24, 136.36, 137.79, 141.28, 178.07, 204.96; IR (KBr) $v$: 1716.6, 1685.9 cm$^{-1}$; MS(ESI) $m/z$: 571 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{22}Cl_4N_2O_2$: C 60.86, H 3.87, N 4.89; found C 60.97, H 3.81, N 4.99.

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(3,4,5-trimethoxy)benzylidenecyclopentanone-4-(3,4,5-trimethoxy)phenyl-pyrrolidine (2e).*** White solid, yield 82%; mp: 222–224°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.26–1.38 (m, 1H), 2.05–2.14 (m, 1H), 2.20 (s, 3H), 2.21–2.25 (m, 1H), 2.45–2.50 (m, 1H), 3.63 (t, $J$ = 8.5 Hz, 1H), 3.78 (s, 6H), 3.84 (s, 6H), 3.87 (s, 6H), 3.96 (t, $J$ = 9.0 Hz, 1H), 4.26 (dd, $J$ = 8.5, 9.0 Hz, 1H), 6.46 (s, 2H), 6.77–6.92 (m, 4H), 7.11–7.18 (m, 2H), 7.23 (s, 1H), 8.44 (bs,1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 26.16, 30.66, 34.98, 49.61, 56.06, 60.21, 60.45, 60.80, 60.90, 65.52, 77.69, 107.18, 107.61, 109.18, 122.84, 125.76, 127.64, 129.44, 130.84, 133.97, 134.64, 135.53, 163.50, 139.33, 141.55, 152.94, 152.99, 178.54, 207.10; IR (KBr) $v$: 1715.8, 1692.3 cm$^{-1}$; MS(ESI) $m/z$: 615 $[M+H]^+$. Anal. Calcd. for $C_{35}H_{38}N_2O_8$: C 68.39, H 6.23, N 4.56; found C 68.54, H 6.32, N 4.71.

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(2-chloro)benzylidenecyclopentanone-4-(2-chloro)phenyl-pyrrolidine (2f).*** White solid, yield 85%; mp: 234–236°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.16–1.23 (m, 1H), 1.99–2.06 (m, 2H), 2.22 (s, 3H), 2.24–2.29 (m, 1H), 3.60 (t, $J$ = 8.5 Hz, 1H), 4.05 (t, $J$ = 9.0 Hz, 1H), 4.94 (t, $J$ = 9.0 Hz, 1H), 6.79–6.81 (m, 1H), 6.86–6.87 (m, 1H), 6.93–6.96 (m, 1H), 7.06–7.09 (m, 1H), 7.14–7.20 (m, 4H), 7.26–7.34 (m, 3H), 7.60 (s, 1H), 8.09 (d, $J$ = 7.5 Hz, 1H), 8.19 (s, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 25.97, 30.32, 35.04, 43.61, 58.68, 64.81, 77.67, 109.24, 123.23, 125.55, 126.28, 126.87, 127.93, 128.00, 129.16, 129.45, 129.65, 129.77, 129.81, 129.87, 131.37, 133.85, 135.51, 135.86, 137.31, 137.64, 141.42, 178.48, 205.36; IR (KBr) $v$: 1715.7, 1702.5 cm$^{-1}$; MS(ESI) $m/z$: 503 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{24}Cl_2N_2O_2$: C 69.19, H 4.81, N 5.56; found C 69.06, H 5.02, N 5.78.

***1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(4-methylsulfanyl)benzylidenecyclopentanone-4-(4-methylsulfanyl)phenyl-pyrrolidine (2g).*** White solid, yield 85%; mp: 203–204°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.26–1.33 (m, 1H), 2.08–2.14 (m, 1H), 2.20 (s, 3H), 2.18–2.22 (m, 1H), 2.32–2.37 (m, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 3.57 (t, $J$ = 8.5 Hz, 1H), 3.95 (t, $J$ = 9.5, Hz, 1H), 4.31 (dd, $J$ = 8.5, 9.5 Hz, 1H), 6.79 (d, $J$ = 7.5 Hz, 1H), 6.88 (t, $J$ = 7.5 Hz, 1H), 7.08–7.13 (m, 4H), 7.16–7.20 (m, 3H), 7.26–7.28 (m, 1H), 7.45 (d, $J$ = 8.0 Hz, 2H), 7.52 (d, $J$ = 8.5 Hz, 1H), 8.57 (bs, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 15.03, 15.87, 26.31, 30.64, 35.02, 48.71, 59.96, 65.54, 77.73, 109.30, 122.91, 125.59, 125.86, 125.95, 126.55, 127.75, 129.40, 130.62, 130.88, 131.14, 131.80, 132.35, 133.20, 133.40, 134.55, 136.54, 136.61, 136.78, 140.99, 141.16, 141.45, 178.82, 206.82; IR (KBr) $v$: 1719.4, 1702.3 cm$^{-1}$; MS(ESI) $m/z$: 527 $[M+H]^+$. Anal. Calcd. for $C_{31}H_{30}N_2O_2S_2$: C 70.69, H 5.74, N 5.32; found C 70.53, H 5.47, N 5.50.

**General procedure for the synthesis of trispiro[oxindole-pyrrolidine]-cyclopentanone-isoxazoline (4a–g).** A solution of **2** (1mmol), **3** (1mmol) in dioxane (30 mL) was refluxed overnight. Completion of the reaction was evidenced by TLC analysis. The solvent was removed *in vacuo*. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate (v/v 5:1) as eluent to afford the corresponding **4**.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-diphenyl-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4a).*** White solid, yield

83%; mp: 250–251°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 0.99–1.02 (m, 1H), 1.37–1.40 (m, 1H), 1.53–1.55 (m, 1H), 1.66–1.70 (m, 1H), 2.15 (s, 3H), 3.55 (t, $J$ = 9.0 Hz, 1H), 3.97 (t, $J$ = 9.0 Hz, 1H), 4.20 (t, $J$ = 8.0 Hz, 1H), 4.69 (s, 1H), 6.54–6.55 (m, 2H), 6.77 (d, $J$ = 8.0 Hz, 1H), 6.99–7.02 (m, 2H), 7.04–7.07 (m, 1H), 7.10–7.13 (m, 1H), 7.22–7.25 (m, 4H), 7.32–7.38 (m, 4H), 7.49 (d, $J$ = 7.5Hz, 2H), 7.74 (br, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 28.59, 28.82, 34.80, 51.58, 58.17, 59.44, 65.46, 77.42, 92.37, 109.75, 123.43, 126.90, 127.06, 127.24, 128.01, 128.08, 128.35, 128.51, 128.74, 128.78, 129.46, 129.89, 130.29, 130.80, 132.73, 135.74, 138.18, 142.09, 155.16, 177.69, 213.37; IR (KBr) $v$: 1746.7, 1709.8 cm$^{-1}$; ESI MS $m/z$: 623 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{29}Cl_2N_3O_3$: C 69.46, H 4.70, N 6.75; found C 69.32, H 4.59, N 6.91.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(4-chlorophenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4b).*** White solid, yield 85%; mp: 203–206°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 0.97–0.99 (m, 1H), 1.46–1.54 (m, 2H), 1.77–1.84 (m, 1H), 2.12 (s, 3H), 3.54 (t, $J$ = 8.5 Hz, 1H), 3.90 (t, $J$ = 9.5 Hz, 1H), 4.18 (t, $J$ = 9.0 Hz, 1H), 4.71 (s, 1H), 6.51–6.52 (m, 2H), 6.77–6.78 (m, 1H), 7.00–7.02 (m, 2H), 7.15–7.17 (m, 1H), 7.23–7.30 (m, 6H), 7.33–7.35 (m, 1H), 7.42–7.43 (m, 2H), 8.01 (br, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 28.75, 29.18, 34.67, 50.65, 57.33, 59.46, 65.48, 92.04, 109.97, 123.34, 126.67, 126.75, 128.31, 128.50, 128.67, 128.86, 129.96, 130.70, 131.04, 131.24, 131.56, 133.07, 134.14, 135.62, 136.81, 142.17, 155.00, 177.76, 212.72; IR (KBr) $v$: 1739.8, 1717.7 cm$^{-1}$; MS(ESI) $m/z$: 691 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{27}Cl_4N_3O_3$: C 62.53, H 3.94, N 6.08; found C 62.47, H 3.98, N 6.16.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(4-methoxyphenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4c).*** White solid, yield 80%; mp: 175–177°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.09–1.09 (m, 1H), 1.35–1.38 (m, 1H), 1.55–1.63 (m, 2H), 2.13 (s, 3H), 3.52 (t, $J$ = 8.5 Hz, 1H), 3.65 (s, 3H), 3.79 (s, 3H), 3.90 (t, $J$ = 9.5 Hz, 1H), 4.15 (t, $J$ = 9.0 Hz, 1H), 4.63 (s, 1H), 6.46–6.54 (m, 4H), 6.80–6.82 (m, 1H), 6.86–6.87 (m, 2H), 7.11–7.12 (m, 1H), 7.21–7.26 (m, 3H), 7.34–7.37 (m, 2H), 7.41–7.43 (m, 2H), 8.30 (s, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 28.46, 28.52, 34.77, 51.00, 55.01, 55.22, 57.59, 59.56, 65.26, 77.51, 92.33, 109.85, 113.30, 113.80, 123.36, 124.55, 126.86, 127.12, 128.63, 128.73, 129.81, 130.13, 130.64, 130.74, 131.28, 135.67, 142.23, 155.22, 158.69, 159.18, 178.15, 213.82; IR (KBr) $v$: 1743.5, 1717.1 cm$^{-1}$; MS(ESI) $m/z$: 683 $[M+H]^+$. Anal. Calcd. for $C_{38}H_{33}Cl_2N_3O_5$: C 66.86, H 4.87, N 6.16; found C 67.01, H 4.78, N 6.27.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(2,4-dichlorophenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4d).*** White solid, yield 76%; mp: 188–190°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.09–1.14 (m, 1H), 1.42–1.45 (m, 1H), 1.55–1.58 (m, 1H), 1.70–1.73 (m, 1H), 2.15 (s, 3H), 3.54 (t, $J$ = 8.5 Hz, 1H), 3.84 (t, $J$ = 8.5 Hz, 1H), 4.72 (t, $J$ = 9.0 Hz, 1H), 5.26 (s, 1H), 6.76 (d, $J$ = 7.5 Hz, 1H), 7.04–7.13 (m, 4H), 7.20–7.24 (m, 5H), 7.28–7.30 (m, 1H), 7.41–7.42 (m, 2H), 8.03 (br, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 27.33, 27.82, 34.82, 47.06, 52.66, 59.65, 62.72, 77.92, 92.84, 109.74, 124.12, 125.81, 126.38, 126.97, 127.15, 128.66, 128.75, 129.00, 129.13, 129.19, 129.22, 129.85, 131.19, 132.89, 132.96, 133.54, 134.36, 134.42, 143.82, 135.89, 136.80, 142.15, 154.93, 177.78, 211.60; IR (KBr) $v$: 1750.7, 1717.8 cm$^{-1}$; MS(ESI) $m/z$: 760 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{25}Cl_6N_3O_3$: C 56.87, H 3.31, N 5.53; found C 56.84, H 3.17, N 5.40.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(3,4,5-trimethoxyphenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4e).*** White solid, yield 70%; mp: 206–208°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.12–1.17 (m, 1H), 1.55–1.60 (m, 1H), 1.68–1.71 (m, 1H), 1.83–1.88 (m, 1H), 2.15 (s, 3H), 3.57 (t, $J$ = 8.5 Hz, 1H), 3.70 (s, 6H), 3.72 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 3.94 (t, $J$ = 9.5 Hz, 1H), 4.13 (t, $J$ = 9.5 Hz, 1H), 4.61 (s, 1H), 6.78 (d, $J$ = 7.5 Hz, 2H), 7.15–7.21 (m, 4H), 7.28–7.30 (m, 3H), 7.35 (d, $J$ = 7.5 Hz, 2H), 8.19 (br, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 28.26, 28.98, 34.74, 52.06, 56.12, 56.22, 57.91, 59.52, 60.65, 60.80, 65.35, 92.50, 106.64, 109.86, 123.01, 126.88, 128.36, 128.54, 129.00, 129.71, 130.98, 134.08, 135.69, 136.78, 137.78, 142.46, 152.78, 153.05, 155.65, 177.65, 213.16; IR (KBr) $v$: 1742.0, 1713.1 cm$^{-1}$; MS(ESI) $m/z$: 803 $[M+H]^+$. Anal. Calcd. for $C_{42}H_{41}Cl_2N_3O_9$: C 62.84, H 5.15, N 5.23; found C 62.94, H 5.28, N 5.15.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(2-chlorophenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4f).*** White solid, yield 70%; mp: 195–196°C; $^1$H-NMR (DMSO-$d_6$, 500 MHz): δ 1.03–1.07 (m, 1H), 1.27–1.32 (m, 1H), 1.36–1.39 (m, 1H), 1.62–1.64 (m, 1H), 2.01 (s, 3H), 3.39 (t, $J$ = 9.0 Hz, 1H), 3.74 (t, $J$ = 9.0 Hz, 1H), 4.50 (t, $J$ = 9.0 Hz, 1H), 5.20 (s, 1H), 6.75 (d, $J$ = 8.0 Hz, 1H), 7.02 (t, $J$ = 8.0 Hz, 1H), 7.17–7.25 (m, 6H), 7.36–7.41 (m, 2H), 7.42–7.45 (m, 3H), 7.47–7.49 (m, 1H), 8.07–8.08 (m, 1H), 10.72 (s, 1H); $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) δ: 26.46, 27.13, 34.10, 47.13, 52.75, 59.07, 61.85, 77.08, 92.66, 109.64, 122.63, 125.42, 125.62, 126.95, 127.12, 128.00, 128.98, 129.02, 129.11, 129.38, 129.41, 129.65, 130.24, 131.95, 131.99, 132.42, 132.71, 134.74, 135.20, 143.81, 154.01, 176.97, 212.13; IR (KBr) $v$: 1746.3, 1701.1 cm$^{-1}$; MS(ESI) $m/z$: 691 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{27}Cl_4N_3O_3$: C 62.53, H 3.94, N 6.08; found C 62.62, H 4.02, N 6.01.

***3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(4-methylsulfanylphenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4g).*** White solid, yield 74%; mp: 195–196°C; $^1$H-NMR ($CDCl_3$, 500 MHz): δ 1.01–1.06 (m, 1H), 1.42–1.46 (m, 1H), 1.53–1.60 (m, 1H), 1.72–1.77 (m, 1H), 2.14 (s, 3H), 2.37 (s, 3H), 2.47 (s, 3H), 3.52 (t, $J$ = 8.5 Hz, 1H), 3.92 (t, $J$ = 9.5 Hz, 1H), 4.17 (t, $J$ = 8.0 Hz, 1H), 4.66 (s, 1H), 6.46–6.48 (m, 2H), 6.75–6.76 (m, 1H), 6.87–6.88 (m, 2H), 7.11–7.14 (m, 1H), 7.21–7.24 (m, 5H), 7.33–7.35 (m, 2H), 7.41 (d, $J$ = 8.0 Hz, 2H), 7.52 (br, 1H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ: 15.07, 15.83, 28.61, 29.07, 34.76, 51.05, 57.64, 59.38, 65.44, 77.41, 92.26, 109.96, 123.38, 125.36, 126.65, 126.85, 126.96, 128.59, 128.83, 129.13, 129.83, 129.91, 130.71, 130.89, 135.08, 135.70, 137.22, 138.74, 142.25, 155.13, 178.06, 213.29; IR (KBr) $v$: 1732.6, 1713.1 cm$^{-1}$; MS(ESI) $m/z$: 715 $[M+H]^+$. Anal. Calcd. for $C_{38}H_{33}Cl_2N_3O_3S_2$: C 63.86, H 4.65, N 5.88; found C 63.65, H 4.56, N 6.04.

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## REFERENCES AND NOTES

[1] (a) Hedin, P. A. J Agric Food Chem 1982, 30, 201; (b) Winfred, G. B.; Rutger, M.; Fieseler, F. J Org Chem 2000, 65, 8317; (c) Metwally, K. A.; Dukat, M. J Med Chem 1998, 41, 5084; (d) Suenaga, K.; Araki, K.; Sengoku, T. Org Lett 2001, 3, 527; (e) Barbara, C. M.; Potts, D.; John, F. J Am Chem Soc 1991, 113, 6321; (f) Nicholas, G. M.; Eckman, L. L.; Newton, G. L. Bioorg Med Chem 2003, 11, 601; (g) Patrizia, C.; Carmela, D.; Ernesto, F. J Nat Prod 1999, 62, 590.

[2] (a) Sebahar, P. R.; Williams, R. M. J Am Chem Soc 2000, 122, 5666; (b) Marti, C.; Carreira, E. M. Eur J Org Chem 2003, 2209; (c) Hiromitsu, T.; Yuhshin, T.; Mariko, K. J Org Chem 1994, 59, 4381.

[3] Caramella, P.; Grunanger, P. 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 291.

[4] Sridhar, G.; Gunasundari, T.; Raghunathan, R. Tetrahedron Lett 2007, 48, 319.

[5] Kumar, R. R.; Perumal, S. Tetrahedron 2007, 63, 12220.

[6] Li, X. F.; Feng, Y. Q.; Gao, B.; Li, N. Acta Crystallogr Sect E 2003, 59, 1659.

[7] Huitric, A. C.; Kumler, W. D. J Am Chem Soc 1956, 78, 614.

[8] Grundamann, C.; Dean, J. M. J Org Chem 1965, 30, 2810.

# Promising Antimicrobial Agents: Synthetic Approaches to Novel Tricyclic and Tetracyclic Pyrimidinones with Antimicrobial Properties

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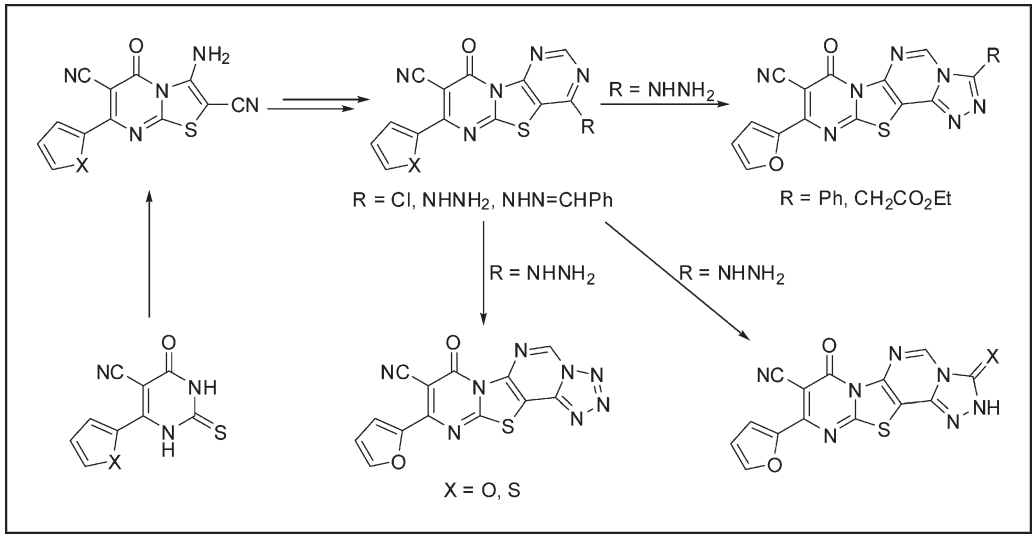


New tricyclic pyrimidinone derivatives were obtained from the corresponding thiazolopyrimidinone or hydrazino systems. The annelation of tricyclic hydrazino compound with 1,2,4-triazole and tetrazole moieties gave novel tetracyclic condensed pyrimidinones. The investigation of the antimicrobial properties of tricyclic and tetracyclic pyrimidinones, by agar-well diffusion assay, was carried out against six pathogenic bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella spp*, and *Salmonella typhyrium*) and four pathogenic fungi (*Aspergillus flavus*, *Aspergillus niger*, *Aspergillus fumigatus*, and *Trichderma horozianum*). Most of the compounds tested exhibited some degree of antimicrobial activity against microorganisms. Among these compounds, 4-benzylidenhydrazino-8-cyano-7-(furan-2-yl)thiazolo[3,2-*a*:4,5-*d*']dipyrimidin-9-one (**12**) showed the most favorable antibacterial activity, while compound **17** showed the highest effect on fungi. Interestingly, tetrazole derivative **19** displayed a remarkable effect on fungi much more than the corresponding 3-substituted triazole derivatives on the one hand, whereas the lowest effect on bacteria on the other.

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## INTRODUCTION

Pyrimidine and its derivatives are ubiquitous in nature. As such, the pyrimidine subunit has found widespread applications in therapeutically active compounds. Most importantly, pyrimidine bases are fundamental constituents of the building blocks of DNA and RNA and hence play a significant role in biochemical vital processes for human beings and animals [1,2]. Various analogs of thiopyrimidinones display antibacterial, antifungal, antiviral [3–5], and antileishmanial activities [3,6], whereas some derivatives of dihydropyrimidine (DHPM) have interesting biological properties such as antimicrobial [7], antiviral [8], and anticancer [9] activities and moreover are found to be useful in the treatment of benign prostatic hyperplasia [10]. More recently, these partly reduced DHPMs have emerged as anti-inflammatory agents [11]. Very recently, *S*-alkylpyrimidines possessing antifungal and antibacterial activities have been also reported in the literature [12]. Some time ago, a series of chloropyrimidines were identified as a new class of antimicrobial agents [13]. Also,

numerous nucleosides containing 1-substituted pyrimidines have found utility as anticancer and antiviral chemotherapeutic agents [8,14,15]. It should be kept in mind that thiazoles have occupied a unique place and have remarkably contributed to biological and medicinal chemistry [16–18]. Such medicines as sulfathiazole, phthalylsulfathiazole and related compounds are widely used in medical practice [19]. The thiazole ring unit is a useful structural component of natural compounds, *e.g*., Vitamin B1 (thiamine), penicillin, and carboxylase [19,20]. The 2-aminothiazole ring system has been employed in the preparation of a number of important drugs required for treatment of hypertension [21], inflammation [22], bacterial [23], and HIV infections [24]. Furthermore, aminothiazoles are well known for their antifungal [25], antimicrobial [26–28], antiviral [29], anti-inflammatory, and antioxidant [30] applications and also have been utilized for the treatment of both breast and prostate cancer [31,32], as a novel class of adenosine receptor antagonists [33,34] and in the development of cyclin-dependent kinase (CDK) inhibitors [35]. Moreover, some of the thiazole analogues are used as fungicides, inhibiting *in vivo* the growth of *Xanthomonas* and as an ingredient of herbicides or an schistosomicidal and anthelmintic drugs [36]. Literature survey reveals that triazole-containing substances are also well known for their diverse pharmaceutical activities including antimicrobial [37], insecticidal [38], antitumor [37,39], and anticonvulsant [40] effects, and moreover, triazolopyrimidines have recently been identified as adenosine $A_3$ receptor antagonists [41]. Interestingly, the fused tetrazoles have been found to exhibit similar biological properties to those of their corresponding triazole analogs [42].

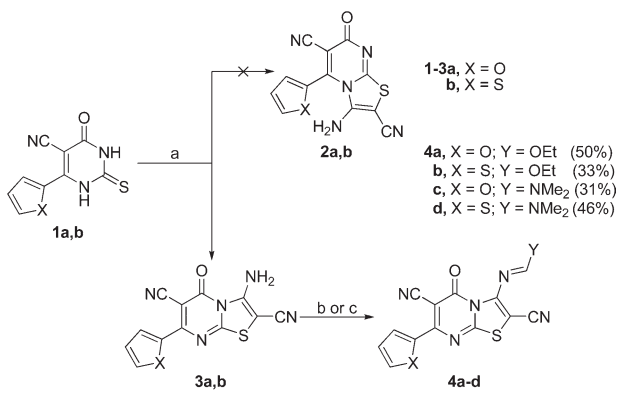
On the basis of the above data and continuing our studies on condensed heterocycles as a part of a chemotherapeutic research program [43–45], it was envisaged that the combined effect of all the above pharmacophores could result in interesting chemotherapeutic activity. Therefore, the goal of the present work was to synthesize substances containing a fused pyrimidine-thiazole scaffold as part of a tricyclic framework **8**, **10–12** and tetracyclic compounds of the same tricyclic structure with a heterocycle anellated to the pyrimidine ring **13**, **16–19** and to screen for their antibacterial and antifungal activities.

## RESULTS AND DISCUSSION

Treatment of the 2-thioxopyrimidines **1a**,**b** [4,46] with bromomalononitrile, in ethanol containing potassium hydroxide, provided bicyclic products. Principally, there are three possible cyclization sites, *i.e*., either at *N*-3 or *N*-1 or partial cyclization at both, depending on the mode of cyclization. In practice, these reactions led to, in each case, the formation of only one isolable product as evidenced by TLC analysis. The structure of the isolated products was considered to be 5-one structure **3** rather than the related isomeric 7-one structure **2** based on the fact that the *N*-3 nitrogen atom of the pyrimidine ring in 2-thiouracil analogues has higher nucleophilic character when compared with *N*-1 atom, and hence, *N*-3 nitrogen is more reactive towards electrophiles than the *N*-1 position, which is part of a push-pull system with the cyano group in the 5-position of the pyrimidine ring. Therefore, the *N*-3 and not the *N*-1 always participates in the cyclization processes as clearly indicated from literature reports [4,47–52]. The IR and $^{13}C$ NMR spectra provide further evidence for the proposed structure by comparison of these spectra with those of similar annelated pyrimidinones. The IR spectra of the products isolated from the studied reactions showed among its peaks those for carbonyl carbon of the pyrimidinone ring at ν 1692 and 1690 $cm^{-1}$, respectively. This high frequency absorption is in favor of structure **3** [47,51,52]. Literature reports [47,53] have shown that the chemical shift for the carbonyl carbon in pyrimidin-4-one derivatives is markedly affected by the nature of the adjacent nitrogen (*N*-3) (pyrrole type in our structure **3** and pyridine type as in structure **2**). For instance, the $^{13}C$ NMR spectrum of compound **3a**, as a typical example, displayed the signal of the carbonyl carbon residue at δ 160.8 ppm. Such an upfield chemical shift value is in agreement with pyrimidin-5-one **3** rather than with pyrimidin-7-one **2**, for which carbonyl stretching frequencies would be expected to appear in the region ν 1640–1660 $cm^{-1}$, and the cyclic carbonyl groups would be expected to resonate in the lower field region ($\delta_C \sim 170$ ppm) as reported by Shawali *et al*. [47]. Consequently, it is reasonable to conclude that the studied reactions are completely regioselective and the structure of the isolated products is pyrimidin-5-one **3**; the alternative cyclization mode to the respective 7-one **2** is therefore discarded. Condensation of 3-amino-2-cyanothiazolopyrimidines **3a**,**b** with triethyl orthoformate gave the corresponding imino ethers **4a**,**b** while with dimethylformamide dimethylacetal (DMFDMA), the amidines **4c**,**d** were obtained (Scheme 1).

Closure of a second pyrimidine ring of the thiazolodipyrimidine ring system was carried out by heating *N*-ethoxymethylene derivative **4a** at reflux in an alcoholic solution of hydrazine hydrate (Scheme 2) to yield a reaction product of molecular formula $C_{13}H_7N_7O_2S$, which corresponded to the addition of the hydrazine to **4a** and the loss of one molecule of ethanol. The IR spectrum of the reaction product was characterized by the absence of one absorption for the cyano group and the presence of an absorption band in the region ν 3382–3200 $cm^{-1}$ due to the hydrazino moiety in

**Scheme 1.** Synthetic pathway of thiazolopyrimidines **3**, **4**.

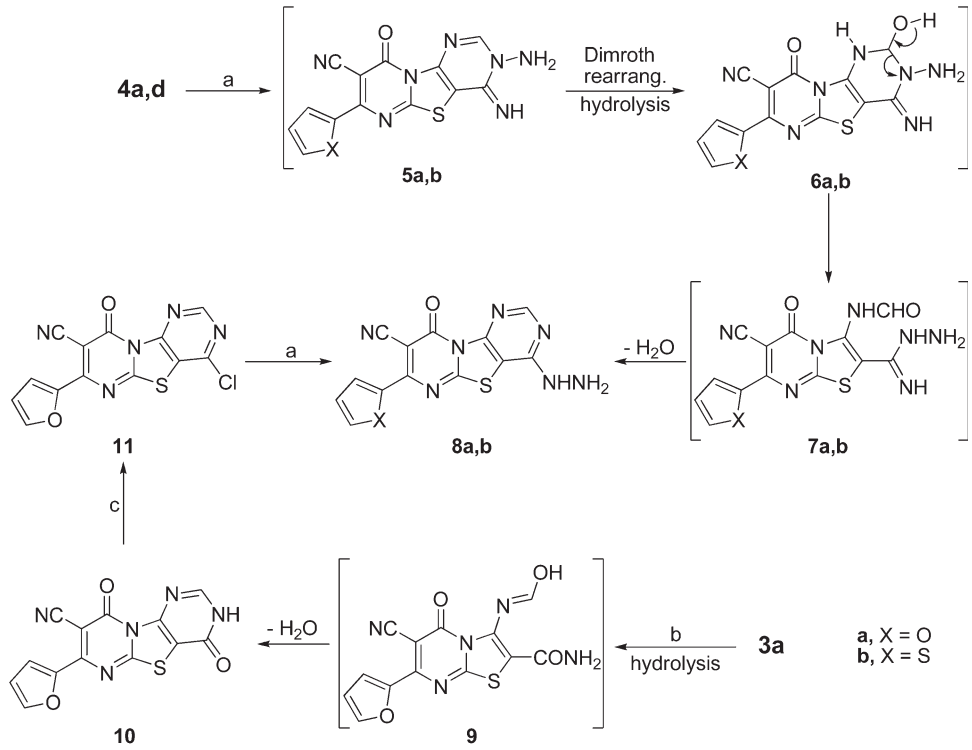



*Reagents and conditions:* (a) $BrCH(CN)_2$, KOH. EtOH, r.t. (41-45%); (b) $HC(OEt)_3$, reflux (33-50%); (c) $(MeO)_2CHNMe_2$, xylene, reflux (31-46%)
r.t.= room temperature

addition to a single cyano group at ν 2219 $cm^{-1}$ and carbonyl function at ν 1697 $cm^{-1}$. The $^1H$ NMR spectrum of that product indicated the disappearance of the resonance signals from protons of the ethyl unit and the appearance of signals from the hydrazino moiety and a pyrimidine methine in their proper positions, besides the expected furyl resonances. Accordingly, this compound could be formulated as the tricyclic hydrazino derivative **8a**, formed most likely *via* a Dimroth-type rearrangement [54–56] of the initial cyclization product **5a**. The $^{13}C$ NMR spectrum of the isolated product was also in accordance with the proposed structure (see Experimental section). The pathway of this reaction, as illustrated in Scheme 2, may involve, first, the anticipated formation of imino compound **5a** followed by subsequent covalent hydration under the applied reaction conditions to afford the 2-hydroxy intermediate **6a**. Then, the pyrimidine ring opens and forms the formyl intermediate **7a**, which undergoes spontaneous heteroannelation with the more nucleophilic imino group to give the rearranged hydrazino compound **8a** (Scheme 2). A similar treatment of amidine **4d** with hydrazine hydrate resulted in the formation of the Dimroth rearrangement product **8b**. Intermediacy of **5b**, **6b**, and **7b** are most likely. It is worth mentioning that the latter products of the reaction of **4a**,**d** with hydrazine hydrate were recovered completely unchanged when subjected to conditions leading to hydrolysis of the imino group to carbonyl function, thus supporting the Dimroth rearrangement of **5a**,**b** to **8a**,**b** (Scheme 2).

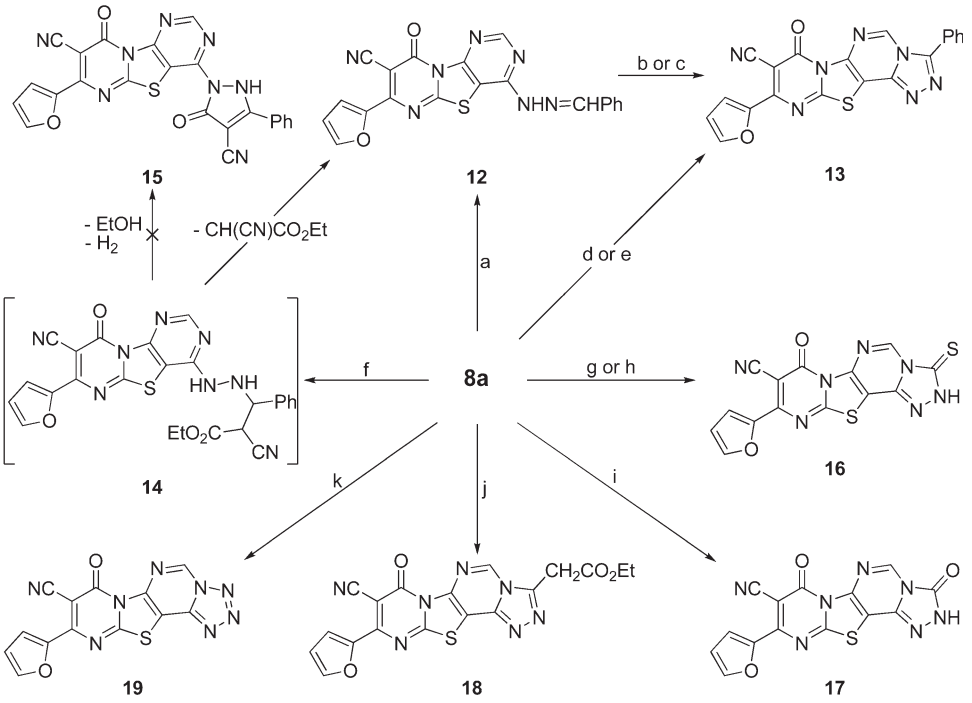
Nevertheless, a proof of structure **8** was accomplished by using an alternative synthetic route involving the cycliztion of aminonitrile **3a** with formic acid to give the dione **10** through the intermediate formation of carboxamide **9**. A further reaction of **10** with phosphorus

**Scheme 2.** Synthetic pathway of thiazolodipyrimidines **8**, **10**, **11**.




*Reagents and conditions:* (a) $N_2H_4.H_2O$, abs. EtOH, reflux (32-61%); (b) $HCO_2H$, reflux (56%); (c) $POCl_3$, reflux (77%)

**Scheme 3.** Synthetic pathway of tetracyclic pyrimidinones **13**, **16–19**.




*Reagents and conditions:* (a) PhCHO, abs. EtOH, pip., reflux (40%); (b) $PhNO_2$, reflux (72%); (c) $FeCl_3$, EtOH, reflux (63%); (d) $PhCO_2H$, $POCl_3$, reflux (59%); (e) PhCOCl, reflux (62%); (f) $PhCH{=}C(CN)CO_2Et$, EtOH, pip., reflux (53%); (g) PhNCS, NaOEt, reflux (75%); (h) $CS_2$, py., reflux (64%); (i) $ClCO_2Et$, py., reflux (89%); (j) $CH_2(CO_2Et)_2$, reflux (69%); (k) gl. AcOH, HCl, $NaNO_2$, 0-5 °C (60%)

oxychloride produced the respective chloro derivative **11**, hydrazinolysis of which led to the hydrazino compound **8a** (61% yield), whose spectral characteristics were completely coincident with the previously isolated sample (Scheme 2).

Treatment of **8a** with benzaldehyde, in boiling absolute ethanol in the presence of piperidine furnished the corresponding acyclic condensation product **12**. Oxidative cyclodehydrogenation of Schiff's base **12** by boiling in nitrobenzene or by treatment with ethanolic iron(III) chloride solution led to, in every case, a single product for which the tetracyclic-condensed structure **13** was established on the basis of its analytical and spectroscopic data. The absence of the methine proton of the hydrazone **12** in the $^1$H NMR spectrum of **13** confirmed the structure. It is interesting to note that the same product **13** could be also obtained directly from cyclocondensation of the hydrazino derivative **8a** with benzoic acid in boiling phosphorus oxychloride. This fact was supported by heating compound **8a** at reflux in an excess of benzoyl chloride, wherein compound **13** was also isolated.

It is remarkable to report here that an unexpected reaction took place on reacting **8a** with ethyl benzylidenecyanoacetate in the presence of piperidine in an attempt to obtain the pyrazolyl derivative **15**. To our surprise, this reaction did not give the desired **15** and instead the Schiff's base **12** was isolated as indicated from TLC analysis, mp, mixed mp, and IR data of the reaction product. This result can be explained by assuming the formation of Michael adduct **14** as a first step. Subsequent ethyl cyanoacetate elimination leads eventually to the final benzylidene derivative **12**, what is in agreement with a previous literature report [37].

Another new tetracyclic pyrimidinone derivative **16** was synthesized from the hydrazino compound **8a** by reaction with one carbon inserting agents. Thus, interaction of **8a** with phenyl isothiocyanate in ethanolic sodium ethoxide solution gave the target **16** (Scheme 3). This reaction is assumed to proceed most likely with *in situ* evolution of aniline. In support of this hypothesis, the desired **16** was also obtained by an independent route involving the reaction of **8a** with carbon disulfide at reflux in pyridine, leading to a reaction product that was identical to **16** obtained by the prescribed method according to TLC analysis, mp, mixed mp, and IR data.

The hydrazino derivative **8a** proved to be a useful precursor for the synthesis of other tetracyclic pyrimidinones. Thus, reaction of **8a** with an excess of ethyl chloroformate, at reflux in pyridine, led to the triazolone

**Table 1**

Mean diameter of inhibition zone (mm) as a criterion of antibacterial activity for selected tricyclic and tetracyclic derivatives.

| Compd. | Test bacterial isolate | | | | | |
|---|---|---|---|---|---|---|
| | *S. aureus* | *Klep. spp* | *S. typhy.* | *B. cereus* | *E. coli* | *P. aeruginosa* |
| **8a** | 2.9 ± 0.2 | 1.7 ± 0.2 | 1.4 ± 0.2 | 1.7 ± 0.2 | 0.0 | 0.0 |
| **10** | 1.9 ± 0.2 | 1.7 ± 0.2 | 0.0 | 1.4 ± 0.2 | 1.7 ± 0.2 | 0.0 |
| **11** | 1.7 ± 0.1 | 1.4 ± 0.2 | 1.3 ± 0.2 | 1.4 ± 0.1 | 1.5 ± 0.2 | 1.4 ± 0.2 |
| **12** | 1.4 ± 0.2 | 1.6 ± 0.2 | 1.3 ± 0.2 | 1.9 ± 0.2 | 1.5 ± 0.2 | 1.7 ± 0.2 |
| **13** | 1.7 ± 0.2 | 1.5 ± 0.2 | 0.0 | 1.8 ± 0.2 | 0.0 | 0.0 |
| **16** | 1.6 ± 0.2 | 1.6 ± 0.2 | 0.0 | 1.8 ± 0.2 | 0.0 | 0.0 |
| **17** | 1.4 ± 0.1 | 1.8 ± 0.2 | 0.0 | 2.1 ± 0.2 | 1.7 ± 0.2 | 2 |
| **18** | 1.5 ± 0.2 | 1.6 ± 0.2 | 0.0 | 1.8 ± 0.2 | 0.0 | 0.0 |
| **19** | 1.7 ± 0.2 | 1.5 ± 0.2 | 0.0 | 1.5 ± 0.2 | 0.0 | 0.0 |
| Standard[a] | 1.4 ± 0.1 | 1.3 ± 0.1 | 1.4 ± 0.2 | 1.2 ± 0.1 | 1.2 ± 0.2 | 1.3 ± 0.2 |

[a] Standard for bacteria: Oxacillin 1 mg/mL.

analogue **17**, while with diethyl malonate, the ethyl ester **18** was isolated in acceptable yield. Elucidation of structure for the latter products was established on the basis of elemental and spectroscopic analyses in each case (see Experimental section).

As an extension to this synthetic route, treatment of compound **8a** with sodium nitrite resulted in the formation of a similar product with annelated tetrazole ring **19**, formed most likely *via* diazotization, by the action of *in situ* generated nitrous acid on **8a**, followed by self-condensation. A similar diazotization of hydrazinopyrimidines with sodium nitrite has been reported previously [42,49,54].

**Antimicrobial evaluation.** As shown by the results in Tables 1 and 2, the majority of the new tricyclic and tetracyclic compounds tested displayed *in vitro* antibacterial and antifungal activities. In general, the chemical structure of the whole molecule, comprising the nature of the heterocyclic system as well as the type of the substituted function present in the heterocyclic ring structure, has a pronounced effect on antimicrobial activity. In particular, it has been found that antimicrobial activity was highly dependent on the type of substituent at the 4-position of pyrimidine ring in the tricyclic core (compounds **8a** and **10–12**, respectively). The most toxic compound to the test bacterial isolates was that containing a benzylidenhydrazino moiety at position 4 of pyrimidine ring in the tricyclic ring system (compound **12**) as compared with the other 4-substituted analogues (compounds **8a**, **10**, and **11**). Replacement of the benzylidenhydrazino moiety by a chlorine atom diminished slightly the activity of **11**; however, 4-chloro analog **11** exhibited more pronounced antibacterial activity than the corresponding 4-hydrazino **8a** or 4-oxo **10** derivatives. Fusion of 3-substituted 1,2,4-triazoles with the parent thiazolodipyrimidine structure (compounds **13** and **16–18**) led in general to a decrease in antibacterial activity relative to the corresponding tricyclic products. However, the antifungal activity of tetracyclic triazole derivative **17** was found to be the highest. This was followed by the tetrazole derivative **19**, which displayed a remarkable effect on fungi much more than the other 3-substituted triazole derivatives (compounds **13**, **16**, and **18**). Despite promising *in vitro* antifungal activity of **19**, only poor activity was found against test bacterial isolates (*Staphylococcus aureus*, *Klebsiella spp*, and *Bacillus cereus*).

## CONCLUSION

New heterocyclic motifs were obtained from the reaction of aminonitriles **3a**,**b** and hydrazino compound **8a** with several commercially available reactants. All the tricyclic and tetracyclic compounds described in this work retain a thiazolodipyrimidinone core, while a fourth fused heterocyclic nucleus (triazole or tetrazole)

**Table 2**

Mean diameter of inhibition zone (mm) as a criterion of antifungal activity for selected tricyclic and tetracyclic derivatives.

| Compd. | Test fungal isolate | | | |
|---|---|---|---|---|
| | *A. niger* | *A. flavus* | *A. fumigatus* | *T. horozianum* |
| **8a** | 2.6 ± 0.2 | 2.4 ± 0.2 | 1.7 ± 0.2 | 2 |
| **10** | 2.5 ± 0.2 | 2.8 ± 0.4 | 0.0 | 2.4 ± 0.4 |
| **11** | 2.4 ± 0.2 | 2.2 ± 0.2 | 1.6 ± 0.2 | 2.4 ± 0.4 |
| **12** | 2 | 3 ± 0.4 | 0.0 | 2.2 ± 0.2 |
| **13** | 2.1 ± 0.2 | 2.6 ± 0.4 | 0.0 | 2.5 ± 0.2 |
| **16** | 2.5 ± 0.2 | 2.5 ± 0.2 | 1.6 ± 0.2 | 2.5 ± 0.2 |
| **17** | 3.1 ± 0.2 | 3.2 ± 0.2 | 2.8 ± 0.4 | 2.9 ± 0.4 |
| **18** | 2.5 ± 0.2 | 2.6 ± 0.2 | 0.0 | 1.8 ± 0.2 |
| **19** | 2.4 ± 0.2 | 2.5 ± 0.2 | 1.8 ± 0.2 | 2.5 ± 0.2 |
| Standard[a] | 2.6 ± 0.2 | 2.8 ± 0.1 | 2.8 ± 0.1 | 2.4 ± 0.2 |

[a] Standard for fungi: Mycostatine 1 mg/mL.

was constructed by cyclocondensation reactions of tricyclic hydrazino compound **8a** with various chemical reagents. The biological potential of all the fused pyrimidinone derivatives was further investigated by screening for their antimicrobial activity. The test compounds displayed different levels of antibacterial and antifungal activities, with the assays carried out on six pathogenic bacteria and four pathogenic fungi. The most potent compounds against test bacterial and fungal isolates were 4-benzylidenhydrazino compound **12** and dione derivative **17**, respectively. Further studies on structure–activity relationships (SAR) combined with molecular modeling approaches of these condensed heterocyclic derivatives are currently underway, and the results of this research will be reported in due course. We believe that research in this direction should be encouraged in order to broaden the applicability of these new heterocyclic frameworks to serving as leads for designing novel chemotherapeutic agents.

## EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer in DMSO-$d_6$ as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. EI mass spectra were recorded on a Shimadzu GC MS-QP 1000 EI mass spectrometer at 70 eV. Compounds **1a**,**b** were prepared according to known methods [4,46].

**General procedure for the preparation of 7-substituted-3-amino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitriles (3a,b).** To a warm ethanolic potassium hydroxide solution [prepared by dissolving potassium hydroxide (0.005 mol) in ethanol (30 mL)] of either pyrimidinethione **1a** or **1b** (0.005 mol), bromomalononitrile (0.005 mol) was added portionwise with stirring. The reaction content was then left overnight at room temperature, whereby the solid product so precipitated upon dilution with water was filtered off, dried, and recrystallized from the appropriate solvents to give the title compounds **3a** (0.64 g; 45%) and **3b** (0.61 g; 41%), respectively.

**3-Amino-7-(2-furyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitrile (3a).** This compound was obtained as a yellow solid (DMF/$H_2O$), mp 267–268°C; IR (ν/$cm^{-1}$): 3380, 3272 ($NH_2$), 2221, 2202 (2CN), 1692 (CO); $^1$H NMR (δ ppm): 6.74 (dd, 1H, $J$ = 1.6, 3.7 Hz, furan H-4), 7.31 (d, 1H, $J$ = 3.7 Hz, furan H-3), 7.90 (d, 1H, $J$ = 1.6 Hz, furan H-5), 8.48 (s, 2H, $NH_2$, $D_2O$-exchangeable); $^{13}$C NMR (δ ppm): 79.9, 98.5 (C-2, C-6), 111.2, 112.1 (furan C-3,4), 116.8 (CN), 118.0 (CN), 144.2 (furan C-5), 155.0 (furan C-2), 158.5, 159.0 (C-8a, C-3), 160.8 (CO), 167.9 (C-7); *Anal*. Calcd. for $C_{12}H_5N_5O_2S$ (283.270): C, 50.88; H, 1.78; N, 24.72; S, 11.32. Found: C, 50.59; H, 1.60; N, 24.51; S, 11.09.

**3-Amino-5-oxo-7-(2-thienyl)-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitrile (3b).** This compound was obtained as a yellowish white solid (DMF), mp 251-252 °C; IR (ν/$cm^{-1}$): 3374, 3260 ($NH_2$), 2218, 2202 (2CN), 1690 (CO); $^1$H NMR (δ ppm): 7.05 (dd, 1H, $J$ = 3.5, 4.9 Hz, thiophene H-4), 7.89 (d, 1H, $J$ = 3.5 Hz, thiophene H-3), 8.04 (d, 1H, $J$ = 4.9 Hz, thiophene H-5), 8.72 (s, 2H, $NH_2$, $D_2O$-exchangeable); Anal. Calcd. for $C_{12}H_5N_5OS_2$ (299.337): C, 48.15; H, 1.68; N, 23.40; S, 21.42. Found: C, 47.87; H, 1.53; N, 23.31; S, 21.15.

**General procedure for the preparation of 7-substituted-3-(ethoxymethylene)amino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitriles (4a,b).** A mixture of either **3a** or **3b** (0.005 mol) and triethyl orthoformate (10 mL) was heated at reflux for 10 h. After distillation of the ortho ester, the viscous mass was treated with ether or petroleum ether (3 mL). The precipitated crystals of products **4a**,**b** were collected by filtration and recrystallized from the proper solvents to give the imino ethers **4a** (0.85 g; 50%) and **4b** (0.59 g; 33%), respectively.

**3-(Ethoxymethylene)amino-7-(2-furyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitrile (4a).** This compound was obtained as a pale brown solid (EtOH/$H_2O$), mp 214°C; IR (ν/$cm^{-1}$): 2225, 2216 (2CN), 1700 (CO), 1621 (C=N); $^1$H NMR (δ ppm): 1.41 (t, 3H, $J$ = 7.3 Hz, $CH_3$ ethoxy), 4.43 (q, 2H, $J$ = 7.3 Hz, $OCH_2$), 6.68 (dd, 1H, $J$ = 1.6, 3.8 Hz, furan H-4), 7.35 (d, 1H, $J$ = 3.8 Hz, furan H-3), 7.85 (d, 1H, $J$ = 1.6 Hz, furan H-5), 8.36 (s, 1H, methylenic CH); MS: $m/z$ (%) = 339 ($M^+$, 18%); Anal. Calcd. for $C_{15}H_9N_5O_3S$ (339.334): C, 53.09; H, 2.67; N, 20.64; S, 9.45. Found: C, 52.93; H, 2.51; N, 20.37; S, 9.30.

**3-(Ethoxymethylene)amino-5-oxo-7-(2-thienyl)-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitrile (4b).** This compound was obtained as a golden yellow solid (EtOH), mp 201–202°C; IR (ν/$cm^{-1}$): 2221, 2215 (2CN), 1704 (CO), 1621 (C=N); $^1$H NMR (δ ppm): 1.39 (t, 3H, $J$ = 7.4 Hz, ethoxy $CH_3$), 4.45 (q, 2H, $J$ = 7.4 Hz, $OCH_2$), 7.24 (dd, 1H, $J$ = 3.7, 4.8 Hz, thiophene H-4), 7.95 (d, 1H, $J$ = 3.7 Hz, thiophene H-3), 8.10 (d, 1H, $J$ = 4.8 Hz, thiophene H-5), 8.36 (s, 1H, methylenic CH); Anal. Calcd. for $C_{15}H_9N_5O_2S_2$ (355.390): C, 50.69; H, 2.55; N, 19.71; S, 18.04. Found: C, 50.47; H, 2.43; N, 19.49; S, 17.86.

**General procedure for the preparation of 7-substituted-3-(dimethylaminomethylenamino)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitriles (4c,d).** To a solution of either **3a** or **3b** (0.005 mol), in dry xylene (30 mL), DMFDMA (0.006 mol) was added and the reaction content was then heated under reflux for 6 h. The reaction mixture was cooled and triturated with petroleum ether (40–60). The solid product obtained was filtered off, dried and recrystallized from the appropriate solvents to give the amidines **4c** (0.52 g; 31%) and **4d** (0.82 g; 46%), respectively.

**3-(Dimethylaminomethylenamino)-7-(2-furyl)-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitrile (4c).** This compound was obtained as an orange solid (EtOH), mp 239–241°C; IR (ν/$cm^{-1}$): 2225, 2214 (2CN), 1700 (CO), 1618 (C=N); $^1$H NMR (δ ppm): 3.05, 3.14 (2s, 6H, $NMe_2$), 6.85–7.17 (m, 2H, furan H-3,4), 7.83 (d, 1H, $J$ = 1.9 Hz, furan H-5), 8.23 (s, 1H, methylenic CH); Anal. Calcd. for $C_{15}H_{10}N_6O_2S$ (338.340): C, 53.25; H, 2.98; N, 24.84; S, 9.48. Found: C, 52.99; H, 2.81; N, 24.57; S, 9.20.

**3-(Dimethylaminomethylenamino)-5-oxo-7-(2-thienyl)-5*H*-thiazolo[3,2-*a*]pyrimidine-2,6-dicarbonitrile (4d).** This compound was obtained as a brown solid (1,4-dioxane), mp 232–233°C; IR (ν/$cm^{-1}$): 2220, 2212 (2CN), 1695 (CO), 1617 (C=N); $^1$H NMR (δ ppm): 2.89, 2.99 (2s, 6H, $NMe_2$), 7.30 (dd, 1H, $J$ = 3.9, 5.2 Hz, thiophene H-4), 7.81 (d, 1H, $J$ = 3.9

Hz, thiophene H-3), 7.97 (d, 1H, $J$ = 5.2 Hz, thiophene H-5), 8.12 (s, 1H, methylenic CH); Anal. Calcd. for $C_{15}H_{10}N_6OS_2$ (354.417): C, 50.83; H, 2.84; N, 23.71; S, 18.09; Found: C, 50.55; H, 2.72; N, 23.46; S, 17.91.

**General procedure for the preparation of 7-substituted-8-cyano-4-hydrazinothiazolo[3,2-*a*:4,5-*d*′]dipyrimidin-9-ones (8a,b).** ***Method A for compounds 8a,b.*** A mixture of either **4a** or **4d** (0.005 mol), hydrazine hydrate (0.05 mol, 2.5 mL) and absolute ethanol (12 mL) was refluxed for 5 h. The precipitates formed after cooling overnight were collected by filtration, washed with cold alcohol, and recrystallized from the proper solvents to give the hydrazino compounds **8a** (0.89 g; 55%) and **8b** (0.55 g; 32%), respectively.

*8-Cyano-7-(2-furyl)-4-hydrazinothiazolo[3,2-a:4,5-d′]dipyrimidin-9-one (8a).* This compound was obtained as a light brown solid (EtOH), mp 246–247°C; IR (ν/cm$^{-1}$): 3382–3200 (NH, $NH_2$), 2219 (CN), 1697 (CO); $^1$H NMR (δ ppm): 4.76 (s, br, 2H, $NH_2$, $D_2O$-exchangeable), 6.69 (dd, 1H, $J$ = 1.6, 3.7 Hz, furan H-4), 7.25 (d, 1H, $J$ = 3.7 Hz, furan H-3), 7.81 (d, 1H, $J$ = 1.6 Hz, furan H-5), 7.95 (s, 1H, pyrimidine H-2), 10.15 (s, br, 1H, NH, $D_2O$-exchangeable); $^{13}$C NMR (δ ppm): 95.3, 99.0, 111.5, 112.2 (furan C-3,4), 117.1 (CN), 143.5 (furan C-5), 155.2 (furan C-2), 157.4, 158.0, 158.5, 159.6, 161.4 (CO), 167.8 (C-7); *Anal*. Calcd. for $C_{13}H_7N_7O_2S$ (325.311): C, 48.00; H, 2.17; N, 30.14; S, 9.86. Found: C, 47.73; H, 1.99; N, 29.88; S, 9.72.

*8-Cyano-4-hydrazino-7-(2-thienyl)thiazolo[3,2-a:4,5-d′]dipyrimidin-9-one (8b).* This compound was obtained as canary yellow crystals (MeOH), mp 261°C; IR (ν/cm$^{-1}$): 3370–3208 (NH, $NH_2$), 2219 (CN), 1702 (CO); $^1$H NMR (δ ppm): 4.95 (s, br, 2H, $NH_2$, $D_2O$-exchangeable), 7.16 (dd, 1H, $J$ = 4.3, 4.8 Hz, thiophene H-4), 7.88–7.92 (m, 2H, thiophene H-3, pyrimidine H-2), 8.06 (d, 1H, $J$ = 4.8 Hz, thiophene H-5), 10.54 (s, br, 1H, NH, $D_2O$-exchangeable); MS: $m/z$ (%) = 341 ($M^+$, 26%); Anal. Calcd. for $C_{13}H_7N_7OS_2$ (341.378): C, 45.74; H, 2.07; N, 28.72; S, 18.79. Found: C, 45.60; H, 1.92; N, 28.46; S, 18.51.

***Method B for compound 8a.*** Chloro compound **11** (0.002 mol) was mixed with hydrazine hydrate (0.006 mol), in absolute ethanol (20 mL). The mixture was stirred under reflux for 3 h. The precipitate formed during reflux was collected by filtration and found, after recrystallization from EtOH, identical in all respects to that obtained from method A (61% yield).

**8-Cyano-7-(2-furyl)-4,9-dioxo-3,4-dihydro-9*H*-thiazolo[3,2-*a*:4,5-*d*′]dipyrimidine (10).** Compound **3a** (0.003 mol) was heated under reflux in formic acid (10 mL) for 7 h. The reaction mixture was then diluted with cold water and allowed to stand overnight. The resulting precipitate was filtered off, washed with ethanol (20 mL), dried, and recrystallized from DMF/EtOH (2:1) as reddish brown crystals (0.52 g; 56%), mp 256–257°C; IR (ν/cm$^{-1}$): 3157 (NH), 2221 (CN), 1697, 1670 (2CO); $^1$H NMR (δ ppm): 6.64 (dd, 1H, $J$ = 1.7, 4.0 Hz, furan H-4), 7.33 (d, 1H, $J$ = 4.0 Hz, furan H-3), 7.76 (d, 1H, $J$ = 1.7 Hz, furan H-5), 8.01 (s, 1H, pyrimidine H-2), 12.52 (s, br, 1H, NH, $D_2O$-exchangeable); Anal. Calcd. for $C_{13}H_5N_5O_3S$ (311.280): C, 50.16; H, 1.62; N, 22.50; S, 10.30. Found: C, 49.87; H, 1.54; N, 22.42; S, 10.13.

**4-Chloro-8-cyano7-(2-furyl)thiazolo[3,2-*a*:4,5-*d*′]dipyrimidin-9-one (11).** A suspension of compound **10** (0.002 mol) in phosphorus oxychloride (30 mL) was refluxed with stirring for 5 h and then left aside to cool to room temperature overnight under stirring. Excess reagent was removed under reduced pressure. The residue was poured to ice/water with stirring and the precipitate was filtered off, dried, and recrystallized from acetone to give the chloro compound **11** as a dark brown solid (0.51 g; 77%), mp > 300°C; IR (ν/cm$^{-1}$): 2223 (CN), 1699 (CO); $^1$H NMR (δ ppm): 6.72 (dd, 1H, $J$ = 1.8, 3.9 Hz, furan H-4), 7.31 (d, 1H, $J$ = 3.9 Hz, furan H-3), 7.84 (d, 1H, $J$ = 1.8 Hz, furan H-5), 8.45 (s, 1H, pyrimidine H-2); Anal. Calcd. for $C_{13}H_4ClN_5O_2S$ (329.726): C, 47.35; H, 1.22; Cl, 10.75; N, 21.24; S, 9.72. Found: C, 47.09; H, 1.10; Cl, 10.62; N, 20.98; S, 9.56.

**4-Benzylidenhydrazino-8-cyano-7-(2-furyl)thiazolo[3,2-*a*:4,5-*d*′]dipyrimidin-9-one (12).** ***Method A.*** Compound **8a** (0.005 mol) was dissolved in absolute ethanol (20 mL), then benzaldehyde (0.006 mol) and piperidine (0.5 mL) were added. The reaction mixture was heated at reflux for 1.5 h. On cooling, the deposited solid product was filtered off and dried. Recrystallization from EtOH gave yellow crystals of the title compound **12** (0.83 g; 40%), mp 261–262°C; IR (ν/cm$^{-1}$): 3330 (NH), 3080 (arom. CH), 2223 (CN), 1698 (CO), 1626 (C=N); $^1$H NMR (δ ppm): 6.71–6.76 (m, 1H, furan H-4), 7.42–7.76 (m, 6H, furan H-3, Ph), 7.86 (d, 1H, $J$ = 2.0 Hz, furan H-5), 7.95 (s, 1H, pyrimidine H-2), 8.49 (s, 1H, CH=N), 11.92 (s, 1H, NH, $D_2O$-exchangeable); *Anal*. Calcd. for $C_{20}H_{11}N_7O_2S$ (413.419): C, 58.11; H, 2.68; N, 23.72; S, 7.76. Found: C, 57.86; H, 2.52; N, 23.50; S, 7.49.

***Method B.*** To a solution of **8a** (0.002 mol) and few drops of piperidine (0.5 mL) in ethanol (10 mL), ethyl benzylidenecyanoacetate (0.002 mol) was added. The reaction content was heated under reflux for 3 h. After cooling, the obtained crystalline product was collected by filtration, washed several times with water, and dried. Recrystallization from EtOH gave, upon air drying, a yellow product (0.44 g; 53%) identical in all aspects (mp, mixed mp, and IR data) to that described in method A.

**9-Cyano-10-(2-furyl)-3-phenylpyrimido[2′,1′:2,3]thiazolo[5,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-8-one (13).** ***Method A.*** Compound **12** (0.002 mol) was heated at reflux in nitrobenzene (10 mL) for 1 h. The final mixture was concentrated and the product deposited after cooling was recrystallized from dilute acetic acid to give the 3-phenyl derivative **13** as a brown solid (0.59 g; 72%), mp > 300°C; IR (ν/cm$^{-1}$): 3064 (arom. CH), 2220 (CN), 1697 (CO); $^1$H NMR (δ ppm): 6.75 (dd, 1H, $J$ = 1.7, 3.8 Hz, furan H-4), 7.34–7.79 (m, 6H, furan H-3, Ph), 7.89 (d, 1H, $J$ = 1.7 Hz, furan H-5), 8.30 (s, 1H, pyrimidine H-5); Anal. Calcd. for $C_{20}H_9N_7O_2S$ (411.404): C, 58.39; H, 2.21; N, 23.83; S, 7.79. Found: C, 58.21; H, 2.08; N, 23.56; S, 7.80.

***Method B.*** To a solution of **12** (0.0025 mol) in ethanol (50 mL), ethanolic iron(III) chloride solution [prepared by dissolving iron(III) chloride (0.005 mol) in ethanol (10 mL)] was added portionwise while stirring. The reaction content was then boiled for 15 min and left at room temperature overnight. The solid product that separated out was collected by filtration and recrystallized from dilute acetic acid to give a tetracyclic product (0.65 g; 63%) that was found to be identical in all aspects (mp, mixed mp, and IR data) to the product prepared by method A.

***Method C.*** A mixture of **8a** (0.002 mol) and benzoic acid (0.004 mol) was refluxed with phosphorus oxychloride (10 mL) for 30 min. Excess phosphorus oxychloride was distilled off under reduced pressure. The residue was triturated with dilute sodium hydroxide solution to remove the unreacted material. The solid residue was recrystallized from dilute acetic acid to give a solid product (0.49 g; 59%). Again, this product was identified as **13**.

***Method D.*** A mixture of **8a** (0.002 mol) and benzoyl chloride (10 mL) was refluxed for 4 h. The excess of benzoyl chloride was extracted with benzene and the residue was

recrystallized from dilute acetic acid to give a solid product (0.51 g; 62%). The material proved to be **13**.

**9-Cyano-10-(2-furyl)-3-thioxo-2,3-dihydropyrimido[2′,1′:2,3]thiazolo[5,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-8-one (16).** ***Method A.*** To a solution of **8a** (0.002 mol) in ethanolic sodium ethoxide [prepared by dissolving sodium metal (0.002 mol) in absolute ethanol (25 mL)], phenyl isothiocyanate (0.002 mol) was added dropwise. The mixture was refluxed with stirring for 10 h and then left to cool to room temperature overnight under stirring. The reaction mixture was then poured onto iced water and neutralized with dilute hydrochloric acid. The resulting precipitate was collected by filtration, washed several times with water and recrystallized from DMF to give pale brown crystals of the thione derivative **16** (0.55 g; 75%), mp 285–288°C; IR (ν/cm$^{-1}$): 3305–3110 (NH), 2225 (CN), 1700 (CO), 1395 (C=S); $^1$H NMR (δ ppm): 6.64 (dd, 1H, $J$ = 1.6, 3.7 Hz, furan H-4), 7.26 (d, 1H, $J$ = 3.7 Hz, furan H-3), 7.80 (d, 1H, $J$ = 1.6 Hz, furan H-5), 8.40 (s, 1H, pyrimidine H-5), 9.55 (s, 1H, NH, $D_2O$-exchangeable); Anal. Calcd. for $C_{14}H_5N_7O_2S_2$ (367.372): C, 45.77; H, 1.37; N, 26.69; S, 17.46. Found: C, 45.60; H, 1.27; N, 26.39; S, 17.36.

***Method B.*** A mixture of compound **8a** (0.002 mol) and carbon disulfide (0.02 mol) in dry pyridine (10 mL) was heated under reflux for 6 h. The precipitated crystals were filtered off, dried, and recrystallized from DMF to produce the thione derivative **16** (0.47 g; 64%). Mixed melting points with a sample of **16** prepared from phenyl isothiocyanate according to method A showed no depression. The spectral data of compound **16** obtained from both sources were superimposable.

**9-Cyano-10-(2-furyl)-3,8-dioxo-2,3-dihydro-8*H*-pyrimido[2′,1′:2,3]thiazolo[5,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (17).** To a mixture of dry pyridine (10 mL) and **8a** (0.0012 mol) was carefully added ethyl chloroformate (1 mL, 0.01 mol) and the mixture was refluxed for 48 h. After cooling, the reaction mixture was poured onto iced water containing a few drops of hydrochloric acid. The solid that separated out was filtered off, washed with water several times, dried, and then recrystallized from EtOH to give the dione derivative **17** as a yellow solid (0.38 g; 89%), mp > 300°C; IR (ν/cm$^{-1}$): 3300 (NH), 2221 (CN), 1702, 1680 (2CO); $^1$H NMR (δ ppm): 6.88–7.15 (m, 2H, furan H-3,4), 7.78 (d, 1H, $J$ = 2.0 Hz, furan H-5), 8.11 (s, 1H, pyrimidine H-5), 10.92 (s, br, 1H, NH, $D_2O$-exchangeable); MS: $m/z$ (%) = 351 ($M^+$, 16%); Anal. Calcd. for $C_{14}H_5N_7O_3S$ (351.305): C, 47.87; H, 1.43; N, 27.91; S, 9.13. Found: C, 47.58; H, 1.33; N, 27.74; S, 8.96.

**Ethyl {9-cyano-10-(2-furyl)-8-oxo-8*H*-pyrimido[2′,1′:2,3]thiazolo[5,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-3-yl}acetate (18).** A suspension of compound **8a** (0.002 mol) in diethyl malonate (10 mL) was gently heated under reflux for 10 h. The reaction mixture was triturated with ethanol (15 mL) and then allowed to cool. The formed precipitate was collected by filtration and purified by recrystallization from 1,4-dioxane to give light brown crystals of the ethyl ester **18** (0.58 g; 69%), mp 209–210°C; IR (ν/cm$^{-1}$): 2960, 2835 (aliph. CH), 2223 (CN), 1730, 1698 (2CO); $^1$H NMR (δ ppm): 1.25 (t, 3H, $J$ = 7.2 Hz, ester Me), 4.20 (q, 2H, $J$ = 7.2 Hz, ester $CH_2$), 5.11 (s, 2H, $CH_2CO$), 6.90–7.19 (m, 2H, furan H-3,4), 7.75 (d, 1H, $J$ = 1.9 Hz, furan H-5), 8.70 (s, 1H, pyrimidine H-5); $^{13}$C NMR (δ ppm): 14.0 (ester Me), 34.5 ($CH_2$), 60.7 (ester $CH_2$), 98.7 (C-9), 111.4, 112.5 (furan C-3,4), 118.3 (CN), 133.1, 138.5, 143.8 (furan C-5), 148.0, 155.6 (furan C-2), 156.3, 158.4, 160.1, 161.6 (ring CO), 166.9, 168.0 (ester CO, C-10); Anal. Calcd. for $C_{18}H_{11}N_7O_4S$ (421.395): C, 51.30; H, 2.63; N, 23.27; S, 7.61. Found: C, 51.06; H, 2.49; N, 22.99; S, 7.50.

**9-Cyano-10-(2-furyl)pyrimido[2′,1′:2,3]thiazolo[5,4-*e*]tetrazolo[1,5-*c*]pyrimidin-8-one (19).** Compound **8a** (0.003 mol) was dissolved in glacial acetic acid (15 mL) containing concentrated hydrochloric acid (1.5 mL), a small amount of insoluble material was filtered off, then the liquid was cooled in ice bath at 0–5°C. The mixture was stirred at this temperature and treated gradually with a cold saturated solution of sodium nitrite [1g of sodium nitrite (0.015 mol) in water (10 mL)] over a period of 15 min. The mixture was kept in ice bath at 0–5°C with continuous stirring for further 2 h, then it was left to stand overnight at room temperature and diluted with water, whereon precipitation took place. The solid thus formed was isolated by filtration, washed abundantly with cold water, recrystallized from aqueous DMF, and air dried to give the fused tetrazole derivative **19** as a yellow solid (0.58 g; 60%), mp 221–222°C; IR (ν/cm$^{-1}$): 2218 (CN), 1701 (CO); $^1$H NMR (δ ppm): 6.75 (dd, 1H, $J$ = 1.8, 4.0 Hz, furan H-4), 7.30 (d, 1H, $J$ = 4.0 Hz, furan H-3), 7.84 (d, 1H, $J$ = 1.8 Hz, furan H-5), 9.80 (s, 1H, pyrimidine H-5); MS: $m/z$ (%) = 336 ($M^+$, 22%); Anal. Calcd. for $C_{13}H_4N_8O_2S$ (336.288): C, 46.43; H, 1.20; N, 33.32; S, 9.53. Found: C, 46.25; H, 1.12; N, 33.07; S, 9.41.

**Antimicrobial activity.** The preliminary antimicrobial activity of the synthesized tricyclic and tetracyclic derivatives was evaluated *in vitro* by means of the agar-well diffusion assay. The assay was carried out according to the method of Hufford *et al*. [57] with some modifications. A total of 10 test microorganisms were used for the current antimicrobial activity studies: two gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*), four gram negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhyrium*, and *Klebsiella spp*), and four fungi (*Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Trichoderma horozianum*). The culture media used were Nutrient agar for bacteria and Czapek's agar (Difco) for fungi. Twenty-five milliliters of the specified molten agar (45°C) was aseptically mixed with either 100 μL of a bacterial suspension or 1 mL of a fungal suspension and poured into 15 mm sterile Petri dishes. For the preparation of the inocula colonies of bacteria were suspended in nutrient broth incubated overnight and fungi were suspended in sterile saline solution (NaCl, 0.85%), respectively. Once the agar was hardened, 9-mm wells were bored using a sterile cork borer. One hundred milliliters of the DMF extract (2 μm) were placed into the wells and the plates were incubated for 24 h at 37°C for the bacteria and 24–72 h at 28°C for the fungi. The antimicrobial activity was measured as the diameter (mm) of clear zone of growth inhibition. Solvent controls (DMF) were included in every experiment as negative controls. DMF was used for dissolving the crude extracts and gave negative results, confirming that it did not influence on antimicrobial activity observed for the compounds tested.

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## REFERENCES AND NOTES


[1] Borisenko, V. E.; Krekov, S. A.; Fomenko, M. Y.; Koll, A.; Lipkovski, P. J Mol Struct 2008, 882, 9.

[2] Padhy, A. K.; Bardhan, M.; Panda, C. S. Indian J Chem 2003, 42B, 910.

[3] Balalaie, S.; Bararjanian, M.; Rominger, F. J Heterocycl Chem 2006, 43, 821.

[4] Ram, V. J.; Vanden Berghe, D. A.; Vlietinck, A. J. Liebigs Ann Chem 1987, 9, 797.

[5] Ram, V. J.; Vanden Berghe, D. A.; Vlietinck, A. J. J Heterocycl Chem 1984, 21, 1307.

[6] Ram, V. J.; Goal, A.; Nath, M.; Srivastava, P. Bioorg Med Chem Lett 1994, 4, 2653.

[7] Gossnitzer, E.; Feierl, G.; Wagner, U. Eur J Pharm Sci 2002, 15, 49.

[8] Kumar, R.; Nath, M.; Tyrrell, D. L. J. J Med Chem 2002, 45, 2032.

[9] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[10] Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. J Med Chem 2000, 43, 2703.

[11] Bahekar, S. S.; Shinde, D. B. Bioorg Med Chem Lett 2004, 14, 1733.

[12] Al-Omran, F. A.; El-Khair, A. A. J Heterocycl Chem 2008, 45, 1057.

[13] Agarwal, N.; Srivastava, P.; Raghuwanshi, S. K.; Upadhyay, D. N.; Sinha, S.; Shukla, P. K.; Ram, V. J. Bioorg Med Chem 2002, 10, 869.

[14] Al-Soud, Y. A.; Al-Masoudi, N. A. Arch Pharm Pharm Med Chem 1999, 332, 143.

[15] Pomeisl, K.; Holy, A.; Votruba, I. Nucleic Acids Symp Ser 2008, 657.

[16] Das, B.; Reddy, V. S.; Ramu, R. J Mol Catal A: Chem 2006, 252, 235.

[17] Kodomari, M.; Aoyama, T.; Suzuki, Y. Tetrahedron Lett 2002, 43, 1717.

[18] Kaupp, G.; Amer, F. A.; Metwally, M. A.; Abdel-latif, E. J Heterocycl Chem 2003, 40, 963.

[19] Sadigova, S. E.; Magerramov, A. M.; Allakhverdiev, M. A.; Alieva, R. A.; Chyragov, F. M.; Vekilova, T. M. Zhurnal Obshchei Khimii 2003, 73, 2043 (in Russian); Russ J General Chem (Engl. Transl.) 2003, 73, 1932.

[20] Zbarskii, B. I.; Ivanov, I. I.; Mardashev, S. R. Biologicheskaya Khimiya (Biological Chemistry); Leningrad: Meditsina, 1972; p 171; Chem Abstr 1973, 78, 132816r.

[21] Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J Med Chem 1992, 35, 2562.

[22] Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. J Med Chem 1988, 31, 1719.

[23] Tsuji, K.; Ishikawa, H. Bioorg Med Chem Lett 1994, 4, 1601.

[24] Venkatachalam, T. K.; Sudbeck, E. A.; Mao, C.; Uckun, F. M. Bioorg Med Chem Lett 2001, 11, 523.

[25] Liu, H.-L.; Li, Z.; Anthonsen, T. Molecules 2000, 5, 1055.

[26] Morales-Bonilla, P.; Pérez-Cardena, A.; Quintero-Mármol, E.; Arias-Téllez, J. L.; Mena-Rejón, G. J. Heteroat Chem 2006, 17, 254.

[27] Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F.-U. J Med Chem 2001, 44, 619.

[28] Pandeya, S. N.; Sriram, D.; Nath, G.; DeClercq, E. Eur J Pharm Sci 1999, 9, 25.

[29] Simoneau, B. Chimia 1999, 53, 297.

[30] Geronikaki, A.; Hadjipavlou-Litina, D.; Chatziopoulos, C.; Soloupis, G. Molecules 2003, 8, 472.

[31] Wilson, K. J.; Illig, C. R.; Subasinghe, N.; Hoffman, J. B.; Rudolph, M. J.; Soll, R.; Molloy, C. J.; Bone, R.; Green, D.; Randall, T.; Zhang, M.; Lewandowski, F. A.; Zhou, Z.; Sharp, C.; Maguire, D.; Grasberger, B.; DesJarlais, R. L.; Spurlino, J. Bioorg Med Chem Lett 2001, 11, 915.

[32] Gorczynski, M. J.; Leal, R. M.; Mooberry, S. L.; Bushweller, J. H.; Brown, M. L. Bioorg Med Chem 2004, 12, 1029.

[33] Borghini, A.; Pietra, D.; Domenichelli, P.; Bianucci, A. M. Bioorg Med Chem 2005, 13, 5330.

[34] Bhattacharya, P.; Leonard, J. T.; Roy, K. Bioorg Med Chem 2005, 13, 1159.

[35] Kabalka, G. W.; Mereddy, A. R. Tetrahedron Lett 2006, 47, 5171.

[36] Metzger, J. V. In Comprehensive Heterocyclic Chemistry 1; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol 6, p 328.

[37] El-Hawash, S. A. M.; Habib, N. S.; Kassem, M. A. Arch Pharm Chem Life Sci 2006, 339, 564.

[38] Luo, Y.-P.; Lin, L.; Yang, G.-F. J Heterocycl Chem 2007, 44, 937.

[39] Abou El Ella, D. A.; Ghorab, M. M.; Noaman, E.; Heiba, H. I.; Khalil, A. I. Bioorg Med Chem 2008, 16, 2391.

[40] Küçükgüzel, I.; Küçükgüzel, Ş. G.; Rollas, S.; Ötük-Saniş, G.; Özdemir, O.; Bayrak, İ.; Altuğ, T.; Stables, J. P. IL Farmaco 2004, 59, 893.

[41] Baraldi, P. G.; Cacciari, B.; Moro, S.; Spalluto, G.; Pastorin, G.; Ros, T. D.; Klotz, K.-N.; Varani, K.; Gessi, S.; Borea, P. A. J Med Chem 2002, 45, 770.

[42] Lockhart, C. C.; Sowell, J. W., Sr. J Heterocycl Chem 1996, 33, 659.

[43] Gaber, H. M.; Bagley, M. C. ChemMedChem 2009, 4, 1043.

[44] Filichev, V. V.; Gaber, H.; Olsen, T. R.; Jørgensen, P. T.; Jessen, C. H.; Pedersen, E. B. Eur J Org Chem 2006, 3960.

[45] Gaber, H. M.; Elgemeie, G. E. H.; Ouf, S. A.; Sherif, S. M. Heteroat Chem 2005, 16, 298.

[46] Abdou, I. M.; Attia, A. M.; Strekowski, L. Nucleosides Nucleotides Nucleic Acids 2002, 21, 15.

[47] Shawali, A. S.; Abbas, I. M.; Mahran, A. M. J Iranian Chem Soc 2004, 1, 33.

[48] Geies, A. A. Collect Czech Chem Commun 1992, 57, 1565.

[49] El-Dean, A. M. K. Monatsh Chem 1998, 129, 523

[50] Abdel-Fattah, A. M.; Sherif, S. M.; El-Reedy, A. M.; Gad-Alla, S. A. Phosphorus, Sulfur and Silicon 1992, 70, 67.

[51] Manhi, F. M.; Abdel-Fattah, A. M. Egypt J Pharm Sci 1992, 33, 825.

[52] Khodair, A. I.; Ibrahim, E. E.; Al Ashry, E. S. H. Nucleosides Nucleotides 1997, 16, 433.

[53] Reiter, J.; Pongó, L.; Dyortsák, P. Tetrahedron 1987, 43, 2497.

[54] Oganisyan, A. Sh.; Noravyan, A. S.; Grigoryan, M. Zh. Chem Heterocycl Compds 2004, 40, 75.

[55] Oliveira-Campos, A. M. F.; Salaheldin, A. M.; Rodrigues, L. M. Arkivoc 2007, XVI, 92.

[56] Bakhite, E. A.; Abdel-Rahman, A. E.; Al-Taifi, E. A. J Chem Res 2005, 11, 147.

[57] Hufford, C. D.; Funderburk, J. M.; Morgan, J. M.; Robertson, L. W. J Pharm Sci 1975, 64, 789.

# The Reaction of 3,4-Dihydro-2H-Pyran with Oxalyl Chloride: Formation and Crystal Structure Analysis of an Unexpected Bicyclic Product



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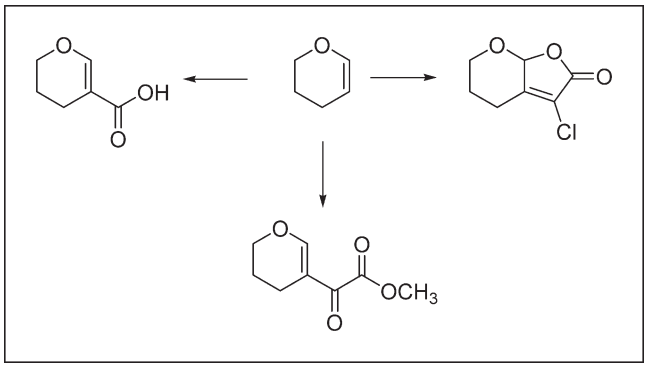


3,4-Dihydro-2-H-pyran and oxalyl chloride react, depending on the conditions, to keto esters, a pyran-3-carboxylic acid or derivatives thereof, or to an hitherto unknown bicyclic acetal containing a vinyl chloride moiety. The structure of the latter product has been unambiguously elucidated by single-crystal X-ray structure analysis. A mechanism for its formation is proposed.

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## INTRODUCTION

Despite their structural simplicity, tetrahydropyran-3-carboxylic acid and its esters display interesting biological activities as attractants for cockroaches [1–3]. One approach toward these compounds proceeds via hydrogenation of dihydropyran-3-carboxylic acid derivatives **3**, which are in turn available by trichloroacetoxylation of dihydropyran (**1**) and subsequent methanolysis or basic hydrolysis of the intermediate trichloromethyl ketones **2**, as outlined in Scheme 1 [4–6]. A Cobalt-catalyzed methoxycarbonylation of vinyl bromides has also been investigated, but is less commonly used [7].

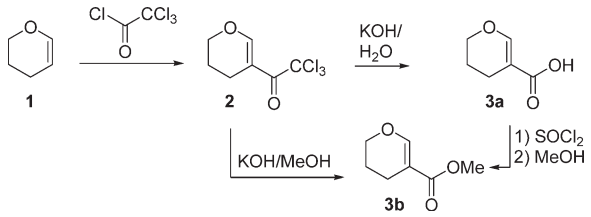
5,6-Dihydro-4*H*-pyran-3-carboxylic acid (**3a**) has also been used as an intermediate in the synthesis of pharmacologically active heterocycles, for example, pyrimidines with activity against cancer [8], anti-inflammatory peptide conjugates [9,10], or fungicides [11]. The corresponding carboxaldehyde is a useful intermediate in the synthesis of renin inhibitors [12] and anti-inflammatory agents [13].

In light of the relevance of dihydropyran-3-carboxylic acid and its derivatives, in particular for the synthesis of heterocycles, we investigated the route described in Scheme 1 in detail. While the carboxylic acid **3a** is indeed conveniently accessible via basic hydrolysis of the trichloromethyl ketone **2**, less satisfactory results were obtained for the methanolysis. However, the ester **3b** is more conveniently synthesized by converting **3a** to its chloride, which is subsequently treated with methanol. We thought that the strongly basic conditions used for the conversion of **2** to **3a** and the additional steps required to obtain the ester **3b** are disadvantageous and therefore sought for a more straightforward alternative.

## RESULTS AND DISCUSSION

The reaction of alkyl vinyl ethers with oxalyl chloride was investigated by Effenberger. Thus, by adjusting the appropriate stoichiometry, symmetrical 1,2-diketones were synthesized in good yields [14]. Later, Tietze *et al.* demonstrated that the intermediate α-keto acid chlorides undergo a clean decarbonylation at temperatures above 100°C to give acyclic *E*-3-alkoxy acryloyl chlorides [15], which are useful intermediates in the synthesis of heterocycles [16]. This approach should also be applicable to dihydropyran-3-carboxylic acid (**3a**) and its derivatives, with dihydropyran (**1**). In contrast to the established two- to four-step route depicted in Scheme 1, this

**Scheme 1.** Established routes to tetra- and dihydropyran-3-carboxylic acids.




synthesis might potentially be conducted as a one-pot reaction. A literature search revealed that the reaction of dihydropyran (**1**) with oxalyl chloride followed by treatment with methanol gives exclusively the α-keto ester **4**, which was used as a substrate in hetero-Diels-Alder reactions [17,18]. However, this transformation was not documented in full detail in the literature, and we therefore decided to start at this point. We could indeed obtain **4** in fair yield if **1** was treated with 1.5 equivalents of oxalyl chloride at low-temperature, followed by the addition of methanol. Next, we tried to synthesize methyl ester **3b** by inducing a decarbonylation before methanolysis. To this end, the reaction mixture was heated to 120°C, after the addition of the oxalyl chloride. To our surprise, the desired ester **3b** was only obtained as a minor product. The major product showed an $M^+$ signal at $m/z = 174$, with the characteristic isotopic pattern for compounds with one chlorine atom. In the IR spectrum absorptions at 1793 $cm^{-1}$ and 1771 $cm^{-1}$ suggested the presence of a lactone moiety. On the basis of the information gathered from NMR- and mass spectra, a molecular formula of $C_7H_7O_3Cl$ was deduced. From the $^1$H-NMR spectra, it became obvious that the six-membered oxacycle was still intact and that the protons of the $CH_2$-groups are no longer chemically equivalent, but are diastereotopic. This is indicative for the formation of a new stereogenic center in the course of the reaction. In the $^{13}$C-NMR-spectrum two signals arising from quaternary olefinic carbon atoms at 166 ppm and 118 ppm, and a signal at 98 ppm were observed. The latter was interpreted as a cyclic acetal carbon. The proton that is attached to this carbon atom was observed at 5.59 ppm as a singlet. Notably, no methanol was incorporated in the molecule. From this information, we tentatively assigned the bicyclic structure **5** to the new compound (Scheme 2).

**Scheme 2.** Formation of α-keto ester **4** and the unexpected bicyclic acetal product **5** from dihydropyran.

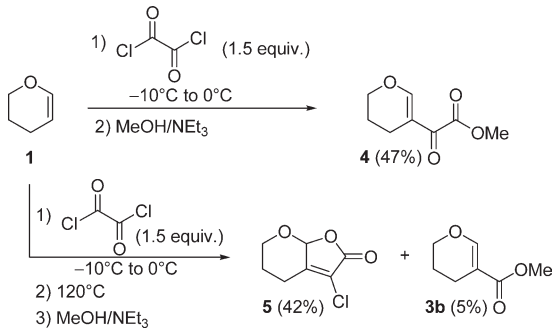



**Table 1**

Selected bond lengths (Å) and bond angles (°) for **5**.

| | | | |
|---|---|---|---|
| Cl1A–C2A | 1.704(2) | Cl1B–C2B | 1.709(2) |
| O1A–C1A | 1.362(3) | O1B–C1B | 1.362(3) |
| O1A–C7A | 1.433(3) | O1B–C7B | 1.425(3) |
| O2A–C1A | 1.201(3) | O2B–C1B | 1.197(3) |
| O3A–C6A | 1.450(4) | O3B–C6B | 1.456(3) |
| O3A–C7A | 1.396(3) | O3B–C7B | 1.391(3) |
| C3A–C7A | 1.492(3) | C3B–C7B | 1.501(3) |
| C2A–C3A | 1.320(4) | C2B–C3B | 1.314(4) |
| Cl1A–C2A–C1A | 120.62(19) | Cl1B–C2B–C1B | 120.77(19) |
| O1A–C1A–O2A | 122.2(2) | O1B–C1B–O2B | 121.8(2) |
| O1A–C1A–C2A | 107.6(2) | O1B–C1B–C2B | 107.8(2) |
| C1A–C2A–C3A | 110.1(2) | C1B–C2B–C3B | 110.0(2) |
| C2A–C3A–C4A | 134.6(2) | C2B–C3B–C4B | 135.7(2) |
| C6A–O3A–C7A | 109.1(2) | C6B–O3B–C7B | 108.7(2) |
| O1A–C7A–C3A | 105.9(2) | O1B–C7B–C3B | 105.62(19) |

Unambiguous proof for this structural assignment came from a single crystal X-ray structure analysis. Compound **5** has the structure of a bicyclic acetal. One chlorine atom is attached to a C-C-double bond, which is in conjugation to the carbonyl group. As the compound crystallizes in the centrosymmetric space group $P\bar{1}$, both enantiomers are found in the cell. Two molecules are present in the asymmetric unit, which are symmetry independent and therefore show slight differences in their structural parameters. Representative bond lengths and angles for both symmetry independent molecules (denoted as A and B) are listed in Table 1. A representation of both symmetry-independent molecules is given in Figure 1.

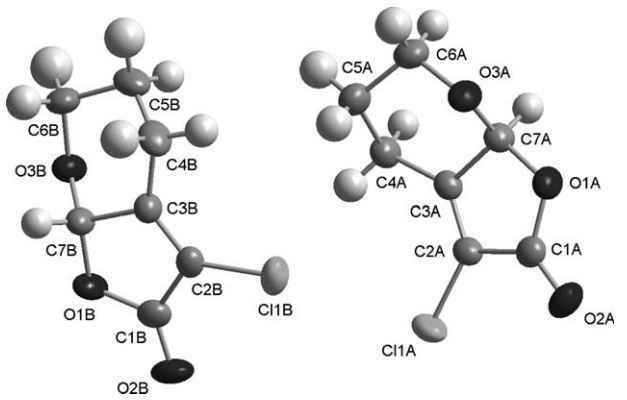



**Figure 1.** Molecular structure of compound **5** with thermal ellipsoids drawn at the 50% probability level.

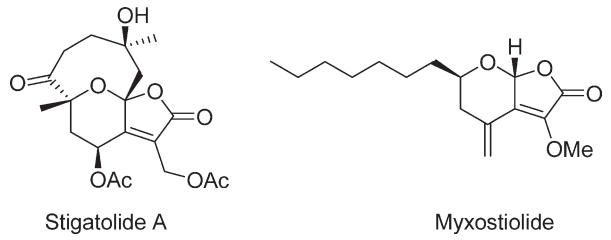
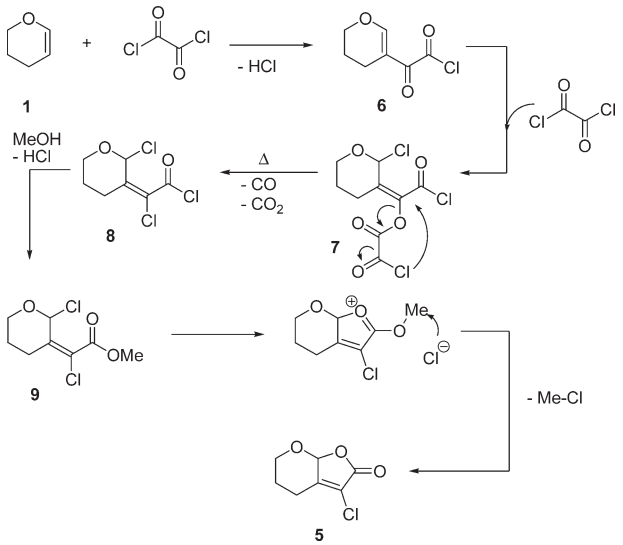



**Figure 2.** Structures of spicatolide A and myxostiliolide.

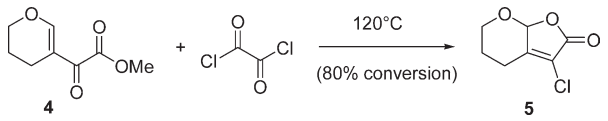
A literature search revealed, that there is ample precedence for bicyclic saturated γ-butyrolactones annellated to six-membered oxacycles. In most cases, these products result from an addition of 1,3-dicarbonyl compounds to cyclic enol ethers via a radical pathway [19–25]. In contrast, only comparatively few 3,4-unsaturated bicyclic γ-butyrolactones such as **5** have been described in the literature. Interestingly, this structural pattern is found in some biologically active natural products such as the anti-inflammatory germacranolide spicatolide A [26] or the plant-growth regulator myxostiliolide (Fig. 2) [27].

Elucidation of the mechanism for the formation of **5** is hampered by a lack of isolable intermediates. We propose the following tentative mechanism: in the first step, oxalyl chloride will most likely attack at carbon atom C3 to give the α-keto acid chloride **6**. We assume that now excess oxalyl chloride reacts with one carbonyl oxygen of **6** to give the intermediate vinyl ester **7**. Upon heating, **7** undergoes a fragmentation to CO, $CO_2$, and a vinyl chloride **8**, which is eventually trapped by methanol in the presence of pyridine. Most likely, the sequence is terminated by demethylation of the methyl ester **9** with a chloride ion and intramolecular nucleophilic attack of the carboxylate at the anomeric carbon, resulting in the product **5** (Scheme 3).

**Scheme 3.** Mechanistic proposal for the formation of the unexpected bicyclic acetal **5**.



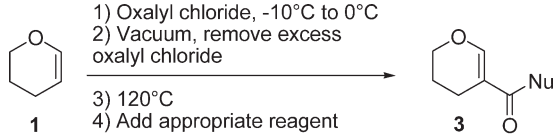

**Scheme 4.** Formation of bicyclic product **5** from keto ester **4**.




It should be noted that the crucial step of this sequence, the formation of the vinyl chloride moiety from a ketone, is not without precedence. A somewhat related reaction was reported for 7-keto steroids, which react with oxalyl chloride in refluxing toluene to vinylic 7-chloro steroids [28]. We do not have definite evidence that the individual steps leading to the formation of **5** indeed proceed in this order. It is, however, quite unlikely that the chlorination of the ketone moiety occurs after methanolysis of the acid chloride, because a considerable amount of the oxalyl chloride would also be destroyed. Strong support for the final demethylation step proposed by us comes from an experiment, in which pure keto ester **4** was treated with oxalyl chloride. After heating the mixture to 120°C, an 80% conversion to the expected bicyclic product **5** was observed by NMR-spectroscopy of the crude reaction mixture. The only other component that could be detected was unreacted starting material **4** (Scheme 4).

From the results discussed above, we concluded that the selective formation of the desired dihydropyran-3-carboxylic acid derivatives **3** requires careful removal of excess oxalyl chloride before the reaction mixture is heated to induce the decarbonylation. This was achieved by applying vacuum at moderately high-temperatures before the mixture is heated to 120°C to induce the decarbonylation. After completion of the decarbonylation step, different nucleophiles were added to obtain the desired derivatives **3**. Thus, with an aqueous solution of $Na_2CO_3$ the carboxylic acid **3a** was obtained, whereas addition of methanol and pyridine gave the ester **3b**. By using diisopropyl amine as a nucleophile,

**Scheme 5.** Synthesis of dihydropyran-3-carboxylic acid derivatives **3** via decarbonylation of α-keto acid chlorides.




| No | Nu | Reagent | Yield |
|---|---|---|---|
| **3a** | -OH | $Na_2CO_3$ (aq) | 78% |
| **3b** | -OMe | MeOH/pyridine | 64% |
| **3c** | $-N(Pr^i)_2$ | $HN(Pr^i)_2/NEt_3$ | 96% |

the expected amide **3c** was obtained in nearly quantitative yield (Scheme 5).

## CONCLUSION

The reaction of oxalyl chloride with dihydropyran, followed by thermal decarbonylation and trapping with an appropriate nucleophile, is a useful alternative synthesis of dihydropyran-3-carboxylic acid derivatives. An unexpected reaction pathway was observed in the course of this synthesis, leading to an interesting bicyclic vinyl chloride. The structure of this product was unambiguously elucidated by X-ray crystal structure analysis.

## EXPERIMENTAL

All reactions were run under an atmosphere of dry nitrogen in dried glassware. Commercial reagents were used as received. Methanol was obtained dried and degassed in a septum bottle under argon and used as received. $^1$H-NMR-spectra were obtained at 300 MHz in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard. Coupling constants are given in Hz. $^{13}$C-NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ ($\delta = 77.0$ ppm) as an internal standard. IR spectra were recorded as films on NaCl or KBr plates or as KBr-discs. The peak intensities are defined as strong (s), medium (m), or weak (w). Mass spectra were obtained at 70 eV.

**Methyl 2-(5,6-dihydro-4H-pyran-3-yl)-2-oxoacetate (4).** Oxalyl chloride (2.20 mL, 24.9 mmol) was cooled to −10°C. 3,4-Dihydro-2*H*-pyran (**1**, 1.50 mL, 16.6 mmol) was slowly added, and the mixture was warmed to ambient temperature. Stirring at ambient temperature was continued for 12 h, and the mixture was then recooled to 0°C. Triethyl amine (4.60 mL, 33.2 mmol) followed by methanol (1.40 mL, 33.2 mmol) were slowly added. Water was added to the reaction mixture, which was then extracted with dichloromethane, dried with $Na_2SO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity) to give the title compound **4** (1.32 g, 47%) as a colourless oil. Analytical data match those reported in the literature [29]. $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H, H-2), 4.14 (t, 2H, $J = 5.2$ Hz, H-6), 3.83 (s, 3H, OMe), 2.28 (t, 2H, $J = 6.2$ Hz, H-4), 1.87 (m, 2H, H-5); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 184.3 (O=*C*—COOMe), 163.9 (*C*OOMe), 163.4 (C-2), 114.1 (C-3), 67.8 (C-6), 52.4 (OMe), 20.5, 17.4 (C-4, C-5); IR: 1731 (s), 1653 (m), 1599 (s), 1172 (s) cm$^{-1}$; MS (EI): *m*/*z* 170 ($M^+$), 111 ($M^+$-$CO_2$Me), 83.

**3-Chloro-5,6-dihydro-4*H*-furo[2,3-b]pyran-2-(7a*H*)-one (5).** Oxalyl chloride (2.00 mL, 23.2 mmol) was cooled to −10°C. 3,4-Dihydro-2*H*-pyran (**1**, 1.40 mL, 15.5 mmol) was slowly added, and the mixture was warmed to ambient temperature. Stirring at ambient temperature was continued for 12 h. The solution was then heated to 120°C for 0.5 h, cooled to ambient temperature, and then to 0°C. Pyridine (1.30 mL) and methanol (0.7 mL) were added and stirring was continued at ambient temperature for 2 h. All volatiles were removed in vacuo, and the residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity). The title compound **5** (1.11 g, 42%) was obtained as a colourless solid, mp 49°C. $^1$H-NMR (300 MHz, $CDCl_3$): δ 5.58 (s, 1H, H-7a), 4.10 (dddm, 1H, $J = 1.9$, 4.1, 12.2 Hz, H-6), 3.76 (dt, 1H, $J = 2.4$, 12.2 Hz, H-6), 2.98 (dm, 1H, $J = 14.5$ Hz, H-4), 2.47 (ddm, 1H, $J = 6.4$, 14.5 Hz, H-4), 1.95 (m, 1H, H-5), 1.77 (ddm, 1H, $J = 4.8$, 12.4 Hz, H-5); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 165.6 (C-2), 156.5 (C-3a), 118.4 (C-3), 98.1 (C-7a), 65.3 (C-6), 25.7, 23.9 (C-4, C-5); IR: 1793, 1771, 1086, 990 cm$^{-1}$; MS: *m*/*z* 176/174 ($M^+$), 145/147; Anal. calcd. for $C_7H_7ClO_3$: C, 48.2; H, 4.0. Found: C, 47.9; H, 4.1.

**Single crystal X-ray structure determination of 5.** Suitable crystals were obtained by dissolving a sample of **5** in dichloromethane and slowly evaporating the solvent at 4°C in an open vessel. Single-crystal diffraction data were measured at 210 K on an imaging plate diffraction system IPDS-II (Stoe) using graphite-monochromated Mo-$K_\alpha$ radiation ($\lambda = 0.71073$ Å). One hundred eighty frames were collected with ω scan widths of 0.5° and 3 min exposure times. The data were corrected by a spherical absorption correction using the program X-Area [30] as well as for Lorentz, polarization and extinction effects. Crystal data: $C_7H_7ClO_3$, $M_r = 174.58$, space group $P\bar{1}$, $a = 8.4324(16)$ Å, $b = 8.6447(17)$ Å, $c = 10.8716(19)$ Å, $\alpha = 77.477(15)°$, $\beta = 78.056(15)°$, $\gamma = 76.460(15)°$, $V = 741.9(2)$ Å$^3$, $Z = 4$, $d_{calc} = 1.563$ g·cm$^{-3}$, colorless block, 0.55 × 0.31 × 0.19 mm, $\mu = 0.464$ mm$^{-1}$, 4819 total reflections ($2\theta_{max} = 50.00°$), 2452 independent ($R_{int} = 0.0571$), 1854 observed [$I < 2\sigma(I)$], 256 parameters. Final $R1$ [$I < 2\sigma(I)$] = 0.0393, $wR2$ (all data) = 0.0947, $S = 0.955$, largest difference peak and hole 0.272 and −0.220 e·Å$^3$. The structure was solved by direct methods using the SHELXS-97 [31] program and refined by full-matrix least-squares of $F^2$ using the program SHELXL-97 [32]. All nonhydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were located in a difference Fourier map. CCDC 755365 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**5,6-Dihydro-4H-pyran-3-carboxylic acid (3a).** Oxalyl chloride (3.60 mL, 41.5 mmol) was cooled to 0°C, and 3,4-dihydro-2*H*-pyran (**1**, 2.50 mL, 27.7 mmol) was added. The solution was slowly warmed to ambient temperature and stirring was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo (10 mbar) at 30°C. The mixture was then heated to 120°C for 0.5 h, cooled to ambient temperature, and poured into an ice-cold aqueous solution of $Na_2CO_3$. The alkaline solution was extracted with dichloromethane, and then acidified with hydrochloric acid (6 M). The aqueous layer was extracted with dichloromethane, and the organic solution was dried with $MgSO_4$, filtered, and evaporated to yield the title compound **3a** (2.76 g, 78%) as a colourless solid, mp 72–74°C. Analytical data match those reported in the literature [5]. $^1$H-NMR (300 MHz, $CDCl_3$): δ 10.42 (bs, 1H, COOH), 7.69 (s, 1H, H-2), 4.07 (t, 2H, $J = 5.2$ Hz, H-6), 2.23 (dt, 2H, $J = 6.5$, 1.2 Hz, H-4), 1.86 (m, 2H, H-5); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 173.4 (C=O), 157.4 (C-2), 105.1 (C-3), 66.8 (C-6), 20.9, 18.8 (C-4-5); IR: 1661 (s), 1623 (s), 1431 (s), 1175 (s) cm$^{-1}$; MS (EI): *m*/*z* 128 ($M^+$), 83 ($M^+$-$CO_2$H), 55; Anal. calcd. for $C_6H_8O_3$: C, 56.3; H, 6.3. Found: C, 56.3; H, 6.2.

**Methyl 5,6-dihydro-4H-pyran-3-carboxylate (3b).** Oxalyl chloride (3.60 mL, 41.5 mmol) was cooled to 0°C, and 3,4-dihydro-2H-pyran (**1**, 2.50 mL, 27.7 mmol) was added. The solution was slowly warmed to ambient temperature and stirring

was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo (10 mbar) at 30°C. The mixture was then heated to 120°C for 0.5 h, and subsequently cooled to ambient temperature. A mixture of methanol (2.60 mL, 64.2 mmol) and pyridine (5.00 mL) was added, and the solution was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity) to give the title compound **3b** (2.52 g, 64%) as a colourless liquid. The compound was found to be sufficiently pure by $^1$H-NMR spectroscopy, although repeated attempts to obtain microanalytical data within the usual limits were unsuccessful. Analytical data match those reported in the literature [6]. $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.52 (s, 1H, H-2), 3.99 (t, 2H, $J$ = 5.3 Hz, H-6), 3.65 (s, 3H, OMe), 2.21 (t, 2H, $J$ = 6.4 Hz, H-4), 1.82 (m, 2H, H-5); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 168.1 (C=O), 155.3 (C-2), 105.7 (C-3), 66.5 (C-6), 50.9 (OMe), 21.0, 19.1 (C-4-5); IR: 1700 (s), 1628 (s), 1261 (s), 1171 (s) cm$^{-1}$; MS: $m/z$ 142 ($M^+$), 111 ($M^+$-OMe), 83 ($M^+$-$CO_2$Me), 55.

***N*,*N*-Diisopropyl-5,6-dihydro-4H-pyran-3-carboxamide (3c).** Oxalyl chloride (1.40 mL, 16.6 mmol) was cooled to 0°C, and 3,4-dihydro-2H-pyran (**1**, 1.00 mL, 11.0 mmol) was added. The solution was slowly warmed to ambient temperature and stirring was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo (10 mbar) at 30°C. The mixture was then heated to 120°C for 0.5 h, and subsequently cooled to ambient temperature. A mixture of diisopropyl amine (3.00 mL, 21.2 mmol) and triethyl amine (3.00 mL) was added, and the solution was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity) to give the title compound **3c** (2.25 g, 96%) as a highly viscous oil. The compound was found to be sufficiently pure by $^1$H-NMR spectroscopy. Repeated attempts to purify the compound by crytallization were unsuccessful. $^1$H-NMR (300 MHz, $CDCl_3$): δ 6.46 (s, 1H, H-2), 3.88 (t, 2H, $J$ = 5.1 Hz, H-6), 3.73 (sept, 2H, $J$ = 6.8 Hz, C*H*-$Me_2$), 2.12 (t, 2H, $J$ = 6.2 Hz, H-4), 1.79 (m, 2H, H-5), 1.16 (d, 12 H, $J$ = 6.8 Hz, Me); $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 170.3 (C=O), 143.6 (C-2), 111.3 (C-3), 65.3 (C-6), 47.8 (2*C*H-$Me_2$), 21.5, 21.1 (C-4-5), 20.8 (4*Me); IR: 1612 (s), 1434 (s), 1157 (s)1029 (s) cm$^{-1}$; MS: $m/z$ 211 ($M^+$), 111 [$M^+$-CO($NPr^i$)$_2$].

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## REFERENCES AND NOTES

[1] Pandey, K. S.; Shriprakash; Pandey, M.; Rao, K. M.; Vaidyanathaswamy, R. Biosci Biotechnol Biochem 1994, 58, 1879.

[2] Pandey, K. S.; Shriprakash; Rao, K. M.; Vaidyanathaswamy, R. Biosci Biotechnol Biochem 1994, 58, 647.

[3] Szori, K.; Szollosi, G.; Bartok, M. N. J Chem 2008, 32, 1354.

[4] Trost, B. M.; Balkovec, J. M.; Mao, M. K. T. J Am Chem Soc 1986, 108, 4974.

[5] Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. Synthesis 1986, 1016.

[6] Madruga, C. D. C.; Clerici, E.; Marcos, A. P.; Zanatta, N. J Heterocycl Chem 1995, 32, 735.

[7] Marchal, J.; Bodiguel, J.; Fort, Y.; Caubere, P. J Org Chem 1995, 60, 8336.

[8] Finlay, M. R. V. Astrazeneca Patent WO 2009007749, 2009.

[9] Piccariello, T. New River Pharmaceuticals Inc. Patent WO 2003034980, 2003.

[10] Piccariello, T.; Kirk, R.; Olon, L. P. New River Pharmaceuticals Inc., WO 2003101476, 2003.

[11] Plowman, R. E. Imperial Chemical Industries Ltd., DE 2245511, 1973.

[12] Spoors, P. G.; Kallander, L. S.; Claremon, D. A. Vitae Pharmaceuticals Inc., WO 2009038719, 2009.

[13] Bharate, S. B.; Mahajan, T. R.; Gole, Y. R.; Nambiar, M.; Matan, T. T.; Kulkarni-Almeida, A.; Balachandran, S.; Junjappa, H.; Balakrishnan, A.; Vishwakarma, R. A. Bioorg Med Chem 2008, 16, 7167.

[14] Effenberger, F. Chem Ber 1965, 98, 2260.

[15] Tietze, L. F.; Schneider, C.; Pretor, M. Synthesis 1993, 1079.

[16] Fernández, F.; García-Mera, X.; Morales, M.; Rodríguez-Borges, J. Synthesis 2001, 239.

[17] Gaulon, C.; Gizecki, P.; Dhal, R.; Dujardin, G. Synlett 2002, 952.

[18] Vu, N. Q.; Grée, D.; Grée, R.; Brown, E.; Dujardin, G. Tetrahedron Lett 2003, 44, 6425.

[19] Baciocchi, E.; Casu, A.; Ruzziconi, R. Synlett 1990, 679.

[20] Nair, V.; Mathew, J. J Chem Soc Perkin Trans 1 1995, 187.

[21] Linker, T.; Hartmann, K.; Sommermann, T.; Scheutzow, D.; Ruckdeschel, E. Angew Chem Int Ed Engl 1996, 35, 1730.

[22] Linker, T.; Sommermann, T.; Kahlenberg, F. J Am Chem Soc 1997, 119, 9377.

[23] Mellor, J. M.; Mohammed, S. Tetrahedron 1993, 49, 7557.

[24] Roy, S. C.; Mandal, P. K. Tetrahedron 1996, 52, 12495.

[25] Schmidt, B.; Wildemann, H. Eur J Org Chem 2000, 3145.

[26] Ragasa, C. Y.; Padolina, W. G.; Yamauchi, T.; Otsuka, H.; Yamasaki, K.; Satoh, T. Phytochemistry 1993, 33, 627.

[27] Kimura, Y.; Shimada, A.; Kusano, M.; Yoshii, K.; Morita, A.; Nishibe, M.; Fujioka, S.; Kawano, T. J Nat Prod 2002, 65, 621.

[28] Guthrie, R. W.; Boris, A.; Mennona, F. A.; Mullin, J. G.; Kierstead, R. W. J Med Chem 1973, 16, 65.

[29] Lamarque, L.; Méou, A.; Brun, P.; Chauvet, F. Spectrosc Lett 1996, 29, 159.

[30] X-Area, Stoe and Cie; Darmstadt, Germany, 2004.

[31] Sheldrick, G. M. SHELXS-97, Program for the Crystal Structure Solution; University of Göttingen, Germany, 1997.

[32] Sheldrick, G. M. SHELXL-97, Program for the Crystal Structure Refinement; University of Göttingen, Germany, 1997.

# Ester- and Ketone-Substituted (±)-1-Alkyl-6-nitro-1,2,3,4-tetrahydroquinolines by a Tandem $S_NAr$-Michael Reaction



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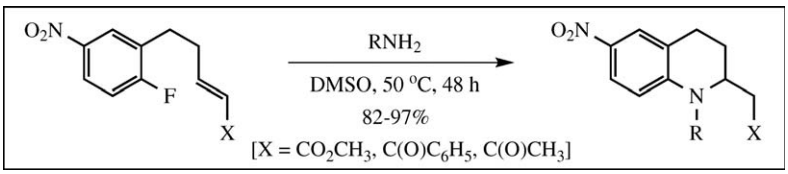


A synthesis of ester- and ketone-substituted (±)-1-alkyl-6-nitro-1,2,3,4-tetrahydroquinolines has been developed from 2-pentenoates and 2-penten-1-ones substituted at C5 by a 2-fluoro-5-nitrophenyl group. The cyclization involves an $S_NAr$ reaction followed by a Michael addition that occurs *exo* to the final ring. A previously reported version of this annulation proceeded by an initial *endo* Michael addition (acceptor became part of the final ring) followed by an $S_NAr$ ring closure. The current reactions proceed in 82–97% yields in DMSO using primary amines that are unbranched at the α carbon. The synthesis of the reaction substrates as well as process optimization, mechanistic studies to elucidate the reaction chronology and comparisons with the *endo* Michael variant are presented.

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## INTRODUCTION

We recently described the use of a tandem Michael-$S_NAr$ reaction sequence for the preparation of 1-alkyl-2,3-dihydro-1(4*H*)-quinolinones [2]. In that initial report, the Michael reaction occurred *via* an *endo* pathway such that the acceptor moiety became part of the final ring [3]. In the current project, we have employed a similar process to prepare ester- and ketone-substituted (±)-1-alkyl-6-nitro-1,2,3,4-tetrahydroquinolines [4,5], but the Michael reaction occurs *exo* to the final ring. These strategies offer efficient and potentially valuable routes to new members of this important family of heterocycles.

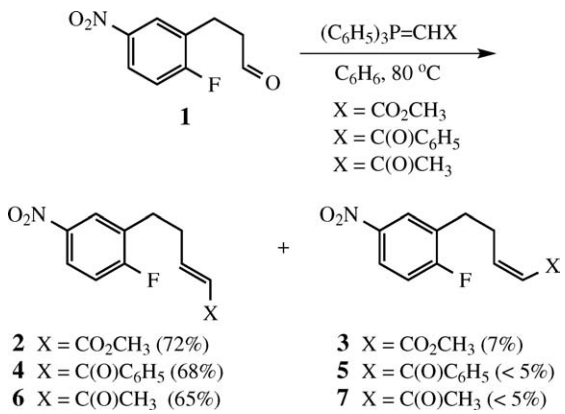
Tetrahydroquinolines are widely distributed in nature [6] and comprise the core structure in numerous pharmaceutical agents [7,8]. Specifically, tetrahydroquinoline-2-acetic esters have been used in the synthesis of 9-azasteroid antimycotic agents [7a], pyrrolobenzodiazepine antitumor antibiotics [7b], and quinoxalinediones for limiting neuronal damage in stroke and heart attack victims [8]. Efficient access to new tetrahydroquinoline derivatives bearing alternative substitution patterns could potentially yield new drugs with improved bioactivities.

## RESULTS AND DISCUSSION

The synthesis of our cyclization substrates is shown in Scheme 1. Treatment of 3-(2-fluoro-5-nitrophenyl)propanal (**1**) [5e,f] with (carbomethoxymethylene)triphenylphosphorane in benzene at reflux for 12 h gave methyl (*E*)-5-(2-fluoro-5-nitrophenyl)-2-pentenoate (**2**) in 72% yield and its double bond isomer **3** in 7% yield following purification. The unsaturated ketones **4** and **6** were formed in 68 and 65% yields, respectively, almost exclusively as the *E* isomers by reacting **1** with (benzoylmethylene)triphenylphosphorane and (acetylmethylene)-triphenylphosphorane.

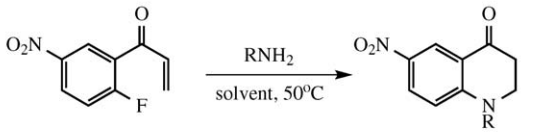
Our cyclization study sought to demonstrate the feasibility of preparing 1-alkyl-6-nitro-1,2,3,4-tetrahydroquinolines from substrates **2**, **4**, and **6** and primary amines by a tandem sequence involving the Michael and $S_NAr$ reactions. In contrast to our earlier report [2], where Michael addition occurred to an acceptor that became

**Scheme 1.** Synthesis of the cyclization substrates.

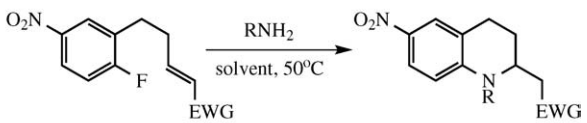


**Scheme 2.** Endo and Exo cyclization.

A. *Endo*: Michael acceptor becomes part of the developing ring [2]




B. *Exo*: Michael acceptor remains outside of ring



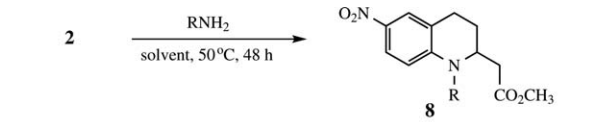

EWG = electron withdrawing group

part of the final ring (*endo* addition), the current reaction requires addition to an acceptor that remains *exo* to the ring [3] (Scheme 2). The success of this process would dramatically expand the scope of this annulation method.

We began our study by reacting unsaturated ester **2** with a series of primary amines in *N*,*N*-dimethylformamide (DMF) at 50°C. This protocol had proven successful in earlier reactions of this type. The reaction proceeded in reasonable yields of 64–81%, but the product was always accompanied by 5–10% of recovered starting material along with 2–4% of a product resulting from amine exchange with the solvent [9] and substitution of dimethylamine on the activated aromatic ring. In most cases, this substitution product was readily removed by preparative thin layer chromatography, but we sought a method that would provide the tetrahydroquinoline without this contaminant. Further experimentation showed that dimethyl sulfoxide (DMSO) was a superior solvent for this reaction and gave higher yields of the heterocycle without the dimethylamine substitution product [10].

The reaction is run by dissolving 1.00 eq of the ketone in DMSO, then adding 1.25 eq of the amine and stirring at 50°C for 48 h. Optimum yields are obtained when one additional 0.10-eq portion of the amine is added to the reaction after the first 24 h. The amine must be primary since it must react at two sites within the molecule. A major limitation of the current process is its sensitivity to steric hindrance near the nitrogen. Amines with branching at the α carbon gave tetrahydroquinolines in lower yields along with numerous other products [11]. Higher temperatures and longer reaction times in these cases yielded complex mixtures that could not be separated.

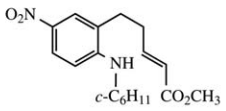
The results of our current study with ester **2** are summarized in Figure 1 and show the comparison of yields obtained in DMF and DMSO. Reaction of **2** with unbranched primary amines gave the target tetrahydroquinolines **8a-d** in 64–81% yields in DMF and in 82–93% yield in DMSO. Using the optimized conditions in DMSO, more hindered amines, such as cyclohexylamine, gave tetrahydroquinoline **8e** in significantly lower yield (48%), with the remainder being $S_NAr$ product **9** (23%) and recovered **2** (5%).




**8**

| R | DMF Yield of **8** (%)[a,b] | DMSO Yield of **8** (%)[a,b] |
|---|---|---|
| Unbranched | | |
| **a** $C_6H_5CH_2$ | 72 | 88 |
| **b** $C_6H_5CH_2CH_2$ | 81 | 84 |
| **c** *n*-$C_6H_{13}$ | 79 | 93 |
| **d** $(CH_3)_2CHCH_2$ | 75 | 82 |
| Branched | | |
| **e** *c*-$C_6H_{11}$ | 11[c] | 48[c] |

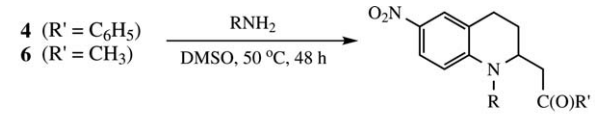
[a]Each reaction also gave 5-10% of recovered starting material.
[b]These reactions also gave 2–4% of a product arising from amine exchange with solvent and substitution of dimethylamine on the aromatic ring.
[c]Compound **9** was also isolated.




**9**

**Figure 1.** Cyclization of **2** and solvent study.

Further cyclization results with ketones **4** and **6** are shown in Figure 2. Using our standard protocol in DMSO solvent, the annulation with ketones proceeded somewhat better than for the ester substrate, giving the products in 88–97% yield. Again, the yields dropped precipitously when the amine was branched at the α carbon.



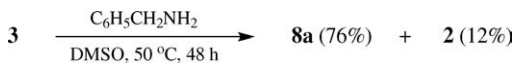

**10** (R' = $C_6H_5$)
**11** (R' = $CH_3$)

| R | R' = $C_6H_5$ Yield of **10** (%) | R' = $CH_3$ Yield of **11** (%) |
|---|---|---|
| Unbranched | | |
| **a** $C_6H_5CH_2$ | 94 | 93 |
| **b** $C_6H_5CH_2CH_2$ | 95 | 96 |
| **c** *n*-$C_6H_{13}$ | 97 | 92 |
| **d** $(CH_3)_2CHCH_2$ | 88 | 93 |
| Branched | | |
| **e** *c*-$C_6H_{11}$ | 36[a] | 37[a] |

[a]Major product from a complex reaction mixture.

**Figure 2.** Cyclization of ketones **4** and **6**.

**Scheme 3.** Cyclization of *Z* substrate **3**.

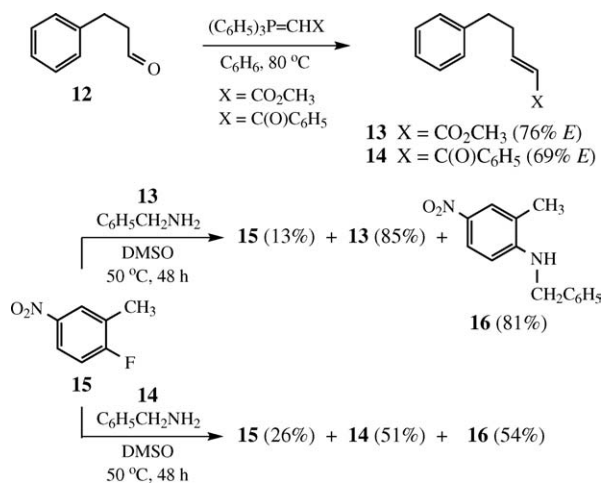



Finally, in an additional experiment, reaction of benzylamine with the *Z* substrate **3** in DMSO was attempted (Scheme 3). This reaction proceeded to give tetrahydroquinoline **8a** in slightly lower yield (76%) than that isolated from the corresponding *E* substrate **2** (88%). Interestingly, the unsaturated ester recovered from this reaction (12%) proved to be **2** rather than **3**. This observation provides experimental evidence for the reversibility of the Michael addition under the reaction conditions used [12].

The isolation of the $S_NAr$ product from the reaction of cyclohexylamine with the unsaturated ester substrates suggests that the $S_NAr$ reaction initiates the current annulation sequence [12]. The reaction chronology is less clear in the case of the ketones. Ketones are better Michael acceptors [13], but are also susceptible to other condensative processes. Thus, cyclohexylamine gave a much more complex product mixture in reactions with these substrates and it was not possible to identify the other products.

In an effort to elucidate the reaction chronology, competitive reaction studies were carried out (Scheme 4) using unsaturated ester **13** and ketone **14**, prepared from 3-phenylpropanal (**12**). These substrates lack the aromatic substitution necessary for the $S_NAr$ reaction [10], and thus, can only undergo a Michael addition. If these are reacted with benzylamine in the presence of 2-fluoro-5-nitrotoluene (**15**), it should be possible to observe whether the Michael addition or the $S_NAr$ process occurs faster in compounds having reactive environments similar to those found in our annulation substrates. Thus, in separate experiments, **13** and **14** were heated at 50°C with **15** and benzylamine in DMSO for 48 h. In each case, workup resulted in isolation of the $S_NAr$ product, *N*-benzyl-2-methyl-4-nitroaniline (**16**), with none of the Michael product detected. The mass balance in the reaction of ester **13** was high, while the more reactive ketone **14** gave a lower return of **16** and unreacted material. Thus, it seems clear that the $S_NAr$ reaction initiates the annulation process for the ester, but the scenario is less certain for the ketone. Though we did not detect the product from conjugate addition of benzylamine to **14**, a reverse Michael reaction [13] from such an adduct followed by reaction of the free amine with **15** could deliver the observed $S_NAr$ product **16**.

**Scheme 4.** Synthesis of **13** and **14** and their competitive reactions with benzylamine in the presence of **15**.




## CONCLUSION

We have developed an approach to the synthesis of (±)-1-alkyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetates based on a tandem Michael-$S_NAr$ reaction. The reaction gives high yields in many cases but is sensitive to steric hindrance, with branching at the α carbon of the amine dramatically lowering the yield. Observations from the study suggest that the $S_NAr$ reaction initiates the annulation sequence, and this is supported by a competitive reaction study. However, because the Michael reaction is reversible, our study does not provide incontrovertible proof of this assertion. The current study broadens the scope of tandem reactions involving the $S_NAr$ and Michael reactions to include cyclizations that involve an *exo* Michael process.

## EXPERIMENTAL

All reactions were run under dry nitrogen. Anhydrous *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were purchased commercially and syringed into reactions where they were used. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed by one of the following methods: (1) flash column chromatography [14] on silica gel (grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20 cm × 20 cm silica gel GF plates (Analtech 02015). Band elution for all chromatographic methods was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks. $^1H$ and $^{13}C$ NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (*J*) are given in Hz. Unless otherwise indicated, mass spectra (electron impact/direct probe) were obtained at 70 eV.

**General procedure for Wittig olefination: Methyl (*E*)-5-(2-fluoro-5-nitrophenyl)-2-pentenoate (2) and methyl (*Z*)-5-(2-fluoro-5-nitrophenyl)-2-pentenoate (3).** A 100 mL benzene solution of 1.00 g (5.08 mmol) of 3-(2-fluoro-5-nitrophenyl)propanal (**1**) [5e,f] and 3.35 g (10.0 mmol) of (methoxycarbonylmethylene)triphenylphosphorane was heated under reflux for 12

h, then cooled and concentrated under vacuum. Flash chromatography of the resulting material on a 30 cm × 2.5 cm column eluted with 5% ether in hexanes gave two bands: band 1, 0.09 g (7%) of **3** as a light yellow solid, mp 58–60°C; band 2, 0.92 g (72%) of **2** as a light yellow oil. The spectral data for **2** were: IR: 1714, 1655, 1521, 1350, 1244 $cm^{-1}$; $^1H$ NMR: δ 8.14 (m, 2H), 7.18 (t, 1H, $J$ = 9.0), 6.97 (dt, 1H, $J$ = 15.9, 6.6), 5.87 (dt, 1H, $J$ = 15.9, 1.1), 3.73 (s, 3H), 2.90 (t, 2H, $J$ = 7.5), 2.58 (q, 2H, $J$ = 7.5); $^{13}C$ NMR: δ 166.6, 164.6 (d, $J$ = 256.5), 146.4, 144.3, 129.4 (d, $J$ = 18.8), 126.2 (d, $J$ = 6.9), 124.2 (d, $J$ = 10.3), 122.4, 116.3 (d, $J$ = 25.2), 51.1, 31.8, 27.5. *Anal*. Calcd for $C_{12}H_{12}FNO_4$: C, 56.92; H, 4.74; N, 5.53. Found: C, 56.98; H, 4.75; N, 5.51.

The spectral data for **3** were: IR: 1722, 1649, 1527, 1348, 1245 $cm^{-1}$; $^1H$ NMR: δ 8.17 (dd, 1H, $J$ = 6.0, 2.7), 8.12 (ddd, 1H, $J$ = 8.8, 7.1, 2.7), 7.17 (t, 1H, $J$ = 8.8), 6.24 (dt, 1H, $J$ = 11.3, 7.1), 5.85 (d, 1H, $J$ = 11.3), 3.70 (s, 3H), 3.04 (q, 2H, $J$ = 7.7), 2.89 (t, 2H, $J$ = 7.7); $^{13}C$ NMR: δ 166.4, 164.4 (d, $J$ = 255.9), 143.7, 144.2, 129.8 (d, $J$ = 17.8), 126.4 (d, $J$ = 6.7), 123.9 (d, $J$ = 10.0), 121.0, 116.1 (d, $J$ = 25.2), 51.2, 29.7, 27.8. *Anal*. Calcd for $C_{12}H_{12}FNO_4$: C, 56.92; H, 4.74; N, 5.53. Found: C, 57.01; H, 4.77; N, 5.48.

**(*E*)-5-(2-Fluoro-5-nitrophenyl)-1-phenyl-2-penten-1-one (4).** This compound was prepared as above from 1.00 g (5.08 mmol) of **1** and 3.80 g (10.0 mmol) of (benzoylmethylene)triphenylphosphorane. Purification by flash chromatography of a 30 cm × 2.5 cm column eluted with 5–15% ether in hexanes afforded 1.03 g (68%) of **4** as a light yellow solid, mp 85–86°C. IR: 1670, 1623, 1528, 1350, 1244 $cm^{-1}$; $^1H$ NMR: δ 8.17 (m, 2H), 7.90 (d, 2H, $J$ = 7.1), 7.57 (t, 1H, $J$ = 7.1), 7.47 (t, 2H, $J$ = 7.7), 7.19 (t, 1H, $J$ = 8.8), 7.05 (dt, 1H, $J$ = 15.4, 6.6), 6.92 (d, 1H, $J$ = 15.4), 2.98 (t, 2H, $J$ = 7.7), 2.69 (dt, 2H, $J$ = 7.7, 6.9); $^{13}C$ NMR: δ 190.4, 164.6 (d, $J$ = 256.8), 146.4, 144.2, 137.6, 132.9, 129.5 (d, $J$ = 18.3), 128.6 128.5, 127.1, 126.3 (d, $J$ = 6.9), 124.2 (d, $J$ = 10.3), 116.4 (d, $J$ = 25.2), 32.5, 27.7. *Anal*. Calcd for $C_{17}H_{14}FNO_3$: C, 68.23; H, 4.68; N, 4.68. Found: C, 68.27; H, 4.71; N, 4.61. A small amount of **5**, contaminated with **4**, was isolated, but not used.

**(*E*)-6-(2-Fluoro-5-nitrophenyl)-3-hexen-2-one (6).** This compound was prepared as above from 1.00 g (5.08 mmol) of **1** and 3.18 g (10.0 mmol) of (acetylmethylene)triphenylphosphorane. Purification by flash chromatography on a 30 cm × 2.5 cm column eluted with 5–10% ether in hexanes afforded 0.78 g (65%) of **6** as a light yellow oil. IR: 1675, 1630, 1528, 1351, 1248 $cm^{-1}$; $^1H$ NMR: δ 8.14 (m, 2H), 7.20 (t, 1H, $J$ = 9.3), 6.81 (dt, 1H, $J$ = 15.9, 7.1), 6.10 (d, 1H, $J$ = 15.9), 2.93 (t, 2H, $J$ = 7.7), 2.60 (q, 2H, $J$ = 7.1), 2.26 (s, 3H); $^{13}C$ NMR: δ 198.1, 164.5 (d, $J$ = 256.5), 145.0, 144.2, 132.2, 129.3 (d, $J$ = 18.0), 126.2 (d, $J$ = 6.9), 124.2 (d, $J$ = 10.3), 116.3 (d, $J$ = 25.2), 32.1, 27.5, 27.0. *Anal*. Calcd for $C_{12}H_{12}FNO_3$: C, 60.76; H, 5.06; N, 5.91. Found: C, 60.69; H, 5.04; N, 5.94. A small amount of **7**, contaminated with **6**, was isolated, but not used.

**General procedure for the tandem $S_NAr$-Michael reaction: Methyl (±)-1-benzyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8a).** To a solution of 61 mg (0.24 mmol) of **2** in 2 mL of anhydrous DMSO was added 32 mg (0.033 mL, 0.30 mmol) of benzylamine. The reaction was stirred at 50°C for 48 h; one additional 0.10 mmol portion (0.011 mL) of the amine was added to the reaction after the first 24 h. The reaction was cooled and added to 20 mL of aqueous NaCl and extracted with 20 mL of ether (3×). The combined ether layers were washed with 20 mL of aqueous NaCl (1×), dried ($MgSO_4$) and concentrated under vacuum to give a yellow oil. Preparative thin layer chromatography on a 20 cm × 20 cm plate eluted with 20% ethyl acetate in hexanes afforded two major bands: band 1, 5 mg (8%) of recovered starting material; band 2, 72 mg (88%) of **8a** as a yellow solid, mp 135–138°C. IR: 1734, 1510, 1321 $cm^{-1}$; $^1H$ NMR: δ 7.94 (s, 1H), 7.86 (d, 1H, $J$ = 9.3), 7.38–7.23 (complex, 3H), 7.16 (d, 2H, $J$ = 7.1), 6.40 (d, 1H, $J$ = 9.3), 4.72 (d, 1H, $J$ = 17.3), 4.62 (d, 1H, $J$ = 17.3), 4.09 (apparent sextet, 1H, $J$ = 4.2), 3.67 (s, 3H), 3.03–2.80 (complex, 2H), 2.70 (dd, 1H, $J$ = 15.4, 4.9), 2.57 (dd, 1H, $J$ = 15.4, 8.8), 2.06 (m, 2H); $^{13}C$ NMR: δ 171.3, 149.1, 137.1, 136.4, 128.9, 127.4, 126.0, 125.2, 124.3, 120.5, 110.6, 55.4, 53.8, 51.9, 37.8, 24.6, 23.1; ms: $m/z$ 249 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.06; H, 5.88; N, 8.24. Found: C, 67.09; H, 5.91; N, 8.20.

For reactions run in DMF, 2 mL of dry DMF was substituted for DMSO. The yields are given in Figure 1. These reactions all gave 5–10% of recovered substrate as well as 2–4% of a product resulting from amine exchange with the solvent and substitution of dimethylamine on the aromatic ring. This product was identified by $^1H$ NMR, but could not be isolated in pure form.

**Tandem $S_NAr$-Michael reaction using the *Z* substrate: Methyl (±)-1-benzyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8a).** This same procedure was carried out using 50 mg (0.20 mmol) of **3** and a total of 28 mg (0.029 mL, 0.27 mmol) of benzylamine in 2 mL of anhydrous DMSO to give 52 mg (76%) of **8a** along with 6 mg (12%) of **2**. The spectral data for these two materials matched those given above.

**Methyl (±)-1-(2-phenylethyl)-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8b).** This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 48 mg (0.050 mL, 0.40 mmol) of phenethylamine. Purification by preparative thin layer chromatography eluted with 20% ethyl acetate in hexanes gave 71 mg (84%) of **8b** as a yellow oil. IR: 1734, 1510, 1322 $cm^{-1}$; $^1H$ NMR: δ 8.02 (dd, 1H, $J$ = 9.3, 2.7), 7.93 (d, 1H, $J$ = 2.2), 7.38–7.22 (complex, 3H), 7.19 (d, 2H, $J$ = 7.2), 6.62 (d, 1H, $J$ = 9.3), 3.80 (ddd, 1H, $J$ = 14.8, 7.7, 4.9), 3.73 (obscured m, 1H), 3.70 (s, 3H), 3.47 (dt, 1H, $J$ = 14.8, 8.2), 3.02–2.68 (complex, 4H), 2.55 (dd, 1H, $J$ = 15.4, 5.5), 2.42 (dd, 1H, $J$ = 15.4, 8.8), 1.83 (dm, 1H, $J$ = 13.8), 1.66 (m, 1H); $^{13}C$ NMR: δ 171.5, 148.4, 138.2, 136.7, 128.75, 128.70, 126.8, 125.5, 124.5, 120.4, 109.5, 55.2, 51.9 (2C), 37.5, 33.0, 24.2, 22.9; ms: $m/z$ 263 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.80; H, 6.21; N, 7.91. Found: C, 67.84; H, 6.24; N, 7.79.

**Methyl (±)-1-hexyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8c).** This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 40 mg (0.053 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 75 mg (93%) of **8c** as a yellow oil. IR: 1736, 1510, 1321 $cm^{-1}$; $^1H$ NMR: δ 7.97 (dd, 1H, $J$ = 9.2, 2.7), 7.90 (d, 1H, $J$ = 2.2), 6.49 (d, 1H, $J$ = 9.2), 3.96 (m, 1H), 3.72 (s, 3H), 3.51 (ddd, 1H, $J$ = 14.8, 8.2, 5.5), 3.20 (dt, 1H, $J$ = 14.8, 8.2), 2.94–2.70 (complex, 2H), 2.62 (dd, 1H, $J$ = 15.4, 4.9), 2.48 (dd, 1H, $J$ = 15.4, 8.8), 1.98 (dm, 1H, $J$ = 13.7), 1.87 (m, 1H), 1.62 (m, 2H), 1.33 (m, 6H), 0.90 (distorted t, 3H, $J$ = 6.6); $^{13}C$ NMR: δ 171.5, 148.8, 136.3, 125.4, 124.5, 120.2, 109.5, 54.8, 51.9,

50.3, 37.5, 31.5, 26.8, 26.6, 24.4, 22.9, 22.6, 14.0; ms: *m/z* 263 ($M^+$-$C_5H_{11}$). *Anal*. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.67; H, 7.78; N, 8.38. Found: C, 64.78; H, 7.82; N, 8.29.

**Methyl (±)-1-isobutyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8d).** This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 29 mg (0.040 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 60 mg (82%) of **8d** as a yellow oil. IR: 1735, 1510, 1321 $cm^{-1}$; $^1H$ NMR δ 7.95 (dd, 1H, $J$ = 9.3, 2.7), 7.92 (s, 1H), 6.48 (d, 1H, $J$ = 9.3), 3.96 (apparent sextet, 1H, $J$ = 4.4), 3.72 (s, 3H), 3.50 (dd, 1H, $J$ = 14.3, 4.9), 3.00–2.75 (complex, 3H), 2.58 (dd, 1H, $J$ = 15.4, 5.5), 2.45 (dd, 1H, $J$ = 15.4, 8.8), 2.12 (m, 1H), 1.99 (m, 2H), 0.97 (d, 3H, $J$ = 6.6), 0.95 (d, 3H, $J$ = 6.6); $^{13}C$ NMR δ 171.6, 149.0, 136.5, 125.6, 124.2, 119.9, 110.0, 57.8, 55.7, 52.0, 36.6, 26.6, 24.0, 22.7, 20.1; ms: *m/z* 263 ($M^+$-$C_3H_7$). *Anal*. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.75; H, 7.19; N, 9.15. Found: C, 62.84; H, 7.22; N, 9.09.

**Methyl (±)-1-cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8e).** This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 39 mg (0.046 mL, 0.40 mmol) of cyclohexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 38 mg (48%) of **8e** as a yellow solid, mp 94–96°C. IR: 1734, 1510, 1321 $cm^{-1}$; $^1H$ NMR: δ 7.96 (dd, 1H, $J$ = 9.3, 2.7), 7.93 (s, 1H), 6.68 (d, 1H, $J$ = 9.3), 4.19 (m, 1H), 3.71 (overlapping m, 1H and s, 3H), 3.00–2.72 (complex, 3H), 2.53 (dd, 1H, $J$ = 15.4, 9.3), 2.45 (dd, 1H, $J$ = 15.4, 4.9), 1.95 (m, 5H), 1.74 (m, 3H), 1.58 (m, 1H), 1.40 m, 1H), 1.22 (m, 1H); $^{13}C$ NMR: δ 171.5, 149.5, 136.5, 126.0, 124.1, 120.8, 111.1, 59.0, 51.9, 47.5, 38.4, 31.0, 30.3, 26.1 (2C), 25.5, 24.2, 22.8; MS: *m/z* 332 ($M^+$). *Anal*. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.06; H, 7.23; N, 8.43. Found: C, 64.97; H, 7.19; N, 8.45.

This reaction also afforded 3 mg (5%) of recovered **2** as a light yellow oil and 18 mg (23%) of methyl (*E*)-5-(2-cyclohexylamino-5-nitrophenyl)-2-pentenoate (**9**) as a yellow oil. The spectral data for **9** were: IR: 3397, 1721, 1657, 1532, 1314 $cm^{-1}$; $^1H$ NMR: δ 8.05 (dd, 1H, $J$ = 9.3, 2.7), 7.95 (d, 1H, $J$ = 2.2), 7.02 (dm, 1H, $J$ = 15.4), 6.59 (d, 1H, $J$ = 9.3), 5.92 (d, 1H, $J$ = 15.4), 4.21 (br d, 1H, $J$ = 6.0), 3.74 (s, 3H), 3.43 (m, 1H), 2.59 (apparent 2s, 4H), 2.05 (m, 2H), 1.80 (m, 2H), 1.70 (m, 1H), 1.44 (m, 2H), 1.26 (m, 3H); $^{13}C$ NMR: δ 166.6, 149.9, 147.0, 137.2, 124.9 (2C), 122.9, 122.2, 108.8, 51.6, 51.5, 33.0, 30.3, 28.9, 25.6, 24.7; ms (30 eV): *m/z* 332 ($M^+$). *Anal*. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.06; H, 7.23; N, 8.43. Found: C, 65.12; H, 7.25; N, 8.37.

**(±)-2-(1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10a).** This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 43 mg (0.043 mL, 0.40 mmol) of benzylamine. Purification by preparative thin layer chromatography eluted with 25% ethyl acetate in hexanes gave 87 mg (94%) of **10a** as a yellow oil. IR: 1681, 1510, 1328 $cm^{-1}$; $^1H$ NMR: δ 7.90 (m, 4H), 7.59 (t, 1H, $J$ = 7.7), 7.46 (t, 2H, $J$ = 7.7), 7.36-7.24 (complex, 4H), 7.18 (d, 1H, $J$ = 7.1), 6.42 (d, 1H, $J$ = 9.3), 4.71 (d, 1H, $J$ = 17.0), 4.64 (d, 1H, $J$ = 17.0), 4.38 (m, 1H), 3.28 (d, 2H, $J$ = 6.0), 2.93 (m, 2H), 2.09 (m, 2H); $^{13}C$ NMR: δ 197.8, 149.4, 136.9, 136.6, 136.5, 133.6, 128.9, 128.8, 128.0, 127.4, 126.1, 125.3, 124.4, 120.4, 110.5, 54.7, 53.9, 41.5, 24.8, 23.3. ms: *m/z* 295 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.61; H, 5.70; N, 7.25. Found: C, 74.74; H, 5.73; N, 7.14.

**(±)-2-(6-Nitro-1-phenethyl-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10b).** This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 48 mg (0.050 mL, 0.40 mmol) of phenethylamine. Purification by preparative thin layer chromatography eluted with 20% ethyl acetate in hexanes gave 91 mg (95%) of **10b** as a yellow oil. IR 1681, 1510, 1327 $cm^{-1}$; $^1H$ NMR: δ 8.02 (dd, 1H, $J$ = 9.3, 2.7), 7.94 (d, 1H, $J$ = 2.7), 7.90 (d, 2H, $J$ = 8.0), 7.59 (t, 1H, $J$ = 7.7), 7.46 (t, 2H, $J$ = 7.7), 7.36-7.21 (complex, 4H), 7.19 (d, 1H, $J$ = 7.4), 6.61 (d, 1H, $J$ = 9.3), 4.05 (m, 1H), 3.78 (ddd, 1H, $J$ = 14.3, 8.2, 5.5), 3.49 (dt, 1H, $J$ = 14.8, 8.2), 3.12 (m, 2H), 3.05–2.70 (complex, 4H), 1.87 (dm, 1H, $J$ = 13.2), 1.72 (m, 1H); $^{13}C$ NMR: δ 198.0, 148.7, 138.3, 136.6, 136.5, 133.6, 128.8 (2C), 128.7, 128.0, 126.7, 125.6, 124.5, 120.4, 109.5, 54.5, 52.0, 41.5, 33.0, 24.5, 23.1; ms: *m/z* 309 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{25}H_{24}N_2O_3$: C, 75.00; H, 6.00; N, 7.00. Found: C, 75.16; H, 6.05; N, 6.93.

**(±)-2-(1-Hexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10c).** This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 40 mg (0.053 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 88 mg (97%) of **10c** as a yellow oil. IR: 1682, 1510, 1328 $cm^{-1}$; $^1H$ NMR: δ 7.95 (m, 4H), 7.60 (t, 1H, $J$ = 7.7), 7.48 (t, 2H, $J$ = 7.7), 6.49 (d, 1H, $J$ = 8.8), 4.27 (m, 1H), 3.51 (ddd, 1H, $J$ = 14.3, 8.8, 5.5), 3.20 (d, 2H, $J$ = 7.1), 3.20 (obscured m, 1H), 2.84 (m, 2H), 2.03 (dm, 1H, $J$ = 11.0), 1.91 (m, 1H), 1.62 (m, 2H), 1.32 (complex, 6H), 0.89 (distorted t, 3H, $J$ = 6.6); $^{13}C$ NMR: δ 198.1, 149.1, 136.7, 136.2, 133.6, 128.8, 128.0, 125.5, 124.5, 120.0, 109.4, 54.2, 50.4, 41.3, 31.5, 26.8, 26.6, 24.6, 23.1, 22.5, 13.9; ms: *m/z* 309 ($M^+$-$C_5H_{11}$). *Anal*. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.63; H, 7.37; N, 7.37. Found: C, 72.58; H, 7.34; N, 7.39.

**(±)-2-(1-Isobutyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10d).** This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 29 mg (0.040 mL, 0.40 mmol) of isobutylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 74 mg (88%) of **10d** as a yellow oil. IR: 1681, 1510, 1324 $cm^{-1}$; $^1H$ NMR: δ 7.93 (m, 4H), 7.60 (t, 1H, $J$ = 7.7), 7.47 (t, 2H, $J$ = 7.7), 6.48 (d, 1H, $J$ = 8.8), 4.25 (m, 1H), 3.47 (dd, 1H, $J$ = 14.8, 4.9), 3.17 (d, 2H, $J$ = 7.1), 3.00–2.75 (complex, 3H), 2.12 (m, 1H), 2.04 (m, 2H), 0.99 (d, 3H, $J$ = 6.6), 0.94 (d, 3H, $J$ = 6.6); $^{13}C$ NMR: δ 198.2, 149.3, 136.7, 136.3, 133.6, 128.8, 128.0, 125.7, 124.3, 119.8, 110.0, 57.9, 55.1, 40.4, 26.6, 24.2, 22.9, 20.1 (2C); ms: *m/z* 309 ($M^+$-$C_3H_7$). *Anal*. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.59; H, 6.82; N, 7.95. Found: C, 71.77; H, 6.85; N, 7.89.

**(±)-2-(1-Cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10e).** This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 39 mg (0.046 mL, 0.40 mmol) of cyclohexylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 32 mg (36%) of **10e** as a yellow oil. IR 1679, 1503, 1324 $cm^{-1}$; $^1H$ NMR: δ 7.98 (dd, 1H, $J$ = 9.3, 2.7), 7.93 (obscured signal, 1H), 7.92 (d, 2H, $J$ = 7.1), 7.60 (t, 1H, $J$ = 7.1), 7.47 (t, 2H, $J$ = 7.7), 6.71 (d, 1H, $J$ = 9.3), 4.50 (m, 1H), 3.74 (tt, 1H, $J$ = 11.5, 3.3), 3.31 (dd, 1H, $J$ = 17.6, 9.3), 2.97 (dd, 1H, $J$ = 17.6, 3.3), 2.81 (m, 3H), 2.04 (dm, 1H, $J$ = 13.2), 1.90 (m, 3H), 1.85–1.50 (complex, 4H), 1.39 (m, 2H), 1.20 (tt, 1H, $J$ = 13.2, 3.3); $^{13}C$ NMR: δ 198.0, 149.9, 136.8,

136.4, 133.6, 128.8, 128.6, 128.5, 128.0, 126.1, 124.2, 120.6, 111.1, 59.1, 46.8, 42.1, 31.1, 30.3, 26.1 (2C), 25.4, 24.3, 23.0; ms: *m*/*z* 378 ($M^+$). *Anal*. Calcd for $C_{23}H_{26}N_2O_3$: C, 73.02; H, 6.88; N, 7.41. Found: C, 73.12; H, 6.92; N, 7.34. No other products could be isolated from this reaction in pure form.

**(±)-1-(1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)propan-2-one (11a).** This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 43 mg (0.043 mL, 0.40 mmol) of benzylamine. Purification by preparative thin layer chromatography eluted with 20% ethyl acetate in hexanes gave 72 mg (92%) of **11a** as a yellow oil. IR: 1714, 1511, 1320 $cm^{-1}$; $^1H$ NMR: δ 7.93 (d, 1H, *J* = 2.7), 7.85 (dd, 1H, *J* = 9.3, 2.7), 7.38–7.22 (complex, 3H), 7.15 (d, 2H, *J* = 7.1), 6.40 (d, 1H, *J* = 9.3), 4.66 (d, 1H, *J* = 17.6), 4.61 (d, 1H, *J* = 17.6), 4.18 (sextet, 1H, *J* = 3.8), 2.86 (m, 2H), 2.80 (dd, 1H, *J* = 17.6, 4.9), 2.72 (dd, 1H, *J* = 17.6, 7.7), 2.13 (s, 3H), 2.00 (m, 2H); $^{13}C$ NMR: δ 206.2, 149.4, 136.9, 136.5, 128.9, 127.4, 126.1, 125.2, 124.4, 120.4, 110.5, 53.9, 53.8, 46.9, 30.8, 24.9, 23.3; ms: *m*/*z* 233 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 11.57, Found: C, 70.33; H, 6.14; N, 11.64.

**(±)-1-(6-Nitro-1-phenethyl-1,2,3,4-tetrahydroquinolin-2-yl) propan-2-one (11b).** This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 48 mg (0.050 mL, 0.40 mmol) of phenethylamine. Purification by preparative thin layer chromatography eluted with 15% ethyl acetate in hexanes gave 78 mg (96%) of **11b** as a yellow oil. IR: 1714, 1514, 1318 $cm^{-1}$; $^1H$ NMR: δ 8.01 (dd, 1H, *J* = 9.3, 2.7), 7.91 (d, 1H, *J* = 2.7), 7.37–7.22 (complex, 3H), 7.19 (d, 2H, *J* = 7.1), 6.60 (d, 1H, *J* = 9.3), 3.85 (m, 1H), 3.80 (ddd, 1H, *J* = 14.3, 8.8, 5.5), 3.46 (dt, 1H, *J* = 14.2, 7.7), 2.90 (m, 2H), 2.74 (m, 2H), 2.66 (dd, 1H, *J* = 17.6, 4.9), 2.58 (dd, 1H, *J* = 17.6, 7.1), 2.14 (s, 3H), 1.79 (dm, 1H, *J* = 13.2), 1.66 (m, 1H); $^{13}C$ NMR: δ 206.5, 148.7, 138.3, 136.4, 128.74, 128.66, 126.7, 125.5, 124.5, 120.3, 109.4, 53.5, 51.9, 46.7, 32.9, 30.9, 24.4, 23.0; ms: *m*/*z* 247 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{20}H_{22}N_2O_3$: C, 71.01; H, 6.51; N, 8.28. Found: C, 71.09; H, 6.55; N, 8.22.

**(±)-1-(1-Hexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)propan-2-one (11c).** This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 40 mg (0.053 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 70 mg (92%) of **11c** as a yellow oil. IR: 1714, 1510, 1315 $cm^{-1}$; $^1H$ NMR: δ 7.97 (dd, 1H, *J* = 9.3, 2.7), 7.90 (d, 1H, *J* = 2.7), 6.48 (d, 1H, *J* = 9.3), 4.05 (m, 1H), 3.49 (ddd, 1H, *J* = 14.8, 8.8, 5.5), 3.16 (ddd, 1H, *J* = 14.8, 8.8, 5.5), 2.78 (m, 2H), 2.68 (m, 2H), 2.19 (s, 3H), 1.90 (m, 2H), 1.59 (m, 2H), 1.41–1.23 (complex, 6H), 0.90 (distorted t, 3H, *J* = 6.6); $^{13}C$ NMR: δ 206.5, 149.0, 136.2, 125.5, 124.5, 120.0, 109.4, 53.3, 50.3, 46.6, 31.5, 31.0, 26.8, 26.6, 24.6, 23.1, 22.6, 14.0; ms: *m*/*z* 247 ($M^+$-$C_5H_{11}$). *Anal*. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.92; H, 8.18; N, 8.81. Found: C, 67.99; H, 8.24; N, 8.76.

**(±)-1-(1-Isobutyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)propan-2-one (11d).** This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 29 mg (0.040 mL, 0.40 mmol) of isobutylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 65 mg (93%) of **11d** as a yellow oil. IR: 1718, 1510, 1318 $cm^{-1}$; $^1H$ NMR: δ 7.94 (dd, 1H, *J* = 9.3, 2.7), 7.91 (br s, 1H), 6.47 (d, 1H, *J* = 9.3), 4.04 (septet, 1H, *J* = 3.3), 3.47 (dd, 1H, *J* = 14.3, 4.9), 2.81 (m, 3H), 2.65 (d, 2H, *J* = 6.6), 2.18 (s, 3H), 2.10 (m, 1H), 1.95 (m, 2H), 0.97 (d, 3H, *J* = 6.6), 0.94 (d, 3H, *J* = 6.6); $^{13}C$ NMR: δ 206.6, 149.3, 136.3, 125.3, 124.3, 119.7, 109.9, 57.7, 54.2, 45.6, 31.0, 26.6, 24.1, 22.9, 20.1 (2C); ms: *m*/*z* 247 ($M^+$-$C_3H_7$). *Anal*. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.21; H, 7.59; N, 9.66. Found: C, 66.26; H, 7.61; N, 9.58.

**(±)-1-(1-Cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl) propan-2-one (11e).** This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 39 mg (0.046 mL, 0.40 mmol) of cyclohexylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 28 mg (37%) of **11e** as a yellow solid, mp 117–120°C. IR: 1714, 1509, 1321 $cm^{-1}$; $^1H$ NMR: δ 7.96 (dd, 1H, *J* = 9.3, 2.7), 7.91 (br s, 1H), 6.67 (d, 1H, *J* = 9.3), 4.27 (m, 1H), 3.70 (tt, 1H, *J* = 11.5, 3.3), 2.84–2.67 (complex, 4H), 2.52 (dd, 1H, *J* = 7.1, 3.3), 2.16 (s, 3H), 2.01–1.81 (complex, 4H), 1.80–1.54 (complex, 4H), 1.40 (m, 2H), 1.25 (tt, 1H, *J* = 13.2, 3.3); $^{13}C$ NMR: δ 206.5, 149.8, 136.3, 126.0, 124.1, 120.5, 111.0, 59.0, 47.4, 46.1, 31.1, 30.3, 26.1, 25.4, 24.3, 22.9; ms: *m*/*z* 316 ($M^+$). *Anal*. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.44; H, 7.64; N, 8.77. No other products could be isolated from this reaction in pure form.

**Methyl (*E*)-5-phenyl-2-pentenoate (13).** This compound was prepared as described for **2** using 1.00 g (7.46 mmol) of **12** and 3.73 g (11.2 mmol) of (methoxycarbonylmethylene)triphenylphosphorane in benzene. Flash chromatography on a 30 cm × 2.5 cm column eluted with 5–10% ether in hexanes gave 1.07 g (76%) of **13** as a colorless oil [15]. IR: 1729, 1659 $cm^{-1}$; $^1H$ NMR: δ 7.29 (m, 2H), 7.19 (m, 3H), 7.01 (dt, 1H, *J* = 15.4, 7.1), 5.85 (dt, 1H, *J* = 15.4, 1.6), 3.72 (s, 3 H), 2.77 (t, 2H, *J* = 7.1), 2.51 (q, 2H, *J* = 7.1); $^{13}C$ NMR: δ 166.9, 148.3, 140.7, 128.4, 128.3, 126.1, 121.4, 51.4, 34.3, 33.9; ms (30 eV): *m*/*z* 190 ($M^+$). *Anal*. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.37. Found: C, 75.90; H, 7.41.

**(*E*)-1,5-Diphenyl-2-penten-1-one (14).** This compound was prepared as described for **2a** from 1.00 g (7.46 mmol) of **12** and (11.2 mmol) of (benzoylmethylene)triphenylphosphorane. Flash chromatography on a 30 cm × 2.5 cm column eluted with 8–12% ether in hexanes gave 1.21 g (69%) of **14** as a yellow oil [15]. IR 1670, 1623 $cm^{-1}$; $^1H$ NMR: δ 7.87 (d, 2H, *J* = 7.4), 7.54 (t, 1H, *J* = 7.4), 7.44 (t, 2H, *J* = 7.4), 7.30 (t, 2H, *J* = 7.4), 7.22 (m, 3H), 7.08 (dt, 1H, *J* = 15.4, 7.1), 6.86 (d, 1H, *J* = 15.4), 2.85 (t, 2H, *J* = 7.1), 2.64 (q, 2H, *J* = 7.1); $^{13}C$ NMR: δ 190.8, 148.4, 140.7, 137.8, 132.6, 128.5, 128.4 (2C), 128.3, 126.5, 126.1, 34.47, 34.44; ms (30 eV): *m*/*z* 236 ($M^+$). *Anal*. Calcd for $C_{17}H_{16}O$: C, 86.44; H, 6.78. Found: C, 86.37; H, 6.74.

**Control experiment: Competitive reaction of benzylamine with 13 and 15.** A mixture of 95 mg (0.50 mmol) of **13**, 75 mg (0.50 mmol) of **15** and 54 mg (0.055 mL, 0.50 mmol) of benzylamine in 3 mL of anhydrous DMSO was heated at 50°C for 48 h. The mixture was cooled, worked up with aqueous NaCl and purified by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes to give three major bands: band 1, 10 mg (13%) of recovered **15**; band 2: 81 mg (85%) of recovered **13**; band 3, 92 mg (81%) of *N*-benzyl-2-methyl-4-nitroaniline (**16**) as a yellow solid, mp 99–100°C. The spectral data for **16** were: IR: 3417, 1531, 1328 $cm^{-1}$; $^1H$ NMR: δ 8.00 (dd, 1H, *J* = 8.2, 2.2), 7.99 (s, 1H), 7.42–7.30 (complex, 5H), 6.54 (d, 1H, *J* = 8.2), 4.66 (br s, 1H), 4.48 (d, 2H, *J* = 4.9), 2.21 (s, 3H); $^{13}C$ NMR: δ 151.3,

137.4, 134.8, 129.0, 127.8, 127.3, 126.0, 124.6, 121.2, 108.3, 47.8, 17.3; ms: *m*/*z* 151 ($M^+$-$C_7H_7$). *Anal*. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.79; N, 11.57. Found: C, 69.45; H, 5.79; N, 11.52.

**Control experiment: Competitive reaction of benzylamine with 14 and 15.** A mixture of 118 mg (0.50 mmol) of **14**, 75 mg (0.50 mmol) of **15** and 54 mg (0.055 mL, 0.50 mmol) of benzylamine was reacted, worked up and purified as above to give: band 1, 20 mg (26%) of recovered **15**; band 2: 60 mg (51%) of recovered **14**; band 3, 61 mg (54%) of **16**. This reaction mixture was more complex due to the greater reactivity of the ketone, but none of the conjugate addition product was detected.

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## REFERENCES AND NOTES

[1] Undergraduate Research Participant, 2008–2010.

[2] Bunce, R. A.; Nago, T. J Heterocycl Chem 2009, 46, 623.

[3] Baldwin, J. E. J Chem Soc Chem Commun 1976, 734.

[4] For a previous synthesis of 1,2,3,4-tetrahydroquinoline-2-acetic esters, see Bunce, R. A., Herron, D. M.; Ackerman, M. L. J Org Chem 2000, 65, 2847.

[5] For our previous approaches to 1,2,3,4-tetrahydroquinolines, see (a) Bunce, R. A.; Herron, D. M.; Johnson, L. B.; Kotturi, K. V. J Org Chem 2001, 66, 2822; (b) Bunce, R. A.; Herron, D. M.; Lewis, J. R.; Kotturi, S. V.; Holt, E. M. J Heterocycl Chem 2003, 40, 101; (c) Bunce, R. A.; Schammerhorn, J. E.; Slaughter, L. M. J Heterocycl Chem 2006, 43, 1505; (d) Bunce, R. A.; Schammerhorn, J. E.; Slaughter, L. M. J Heterocycl Chem 2007, 44, 1051; (e) Bunce, R. A.; Nago, T.; Sonobe, N. J Heterocycl Chem 2007, 44, 1059; (f) Bunce, R. A.; Nago, T.; Sonobe, N.; Slaughter, L. M. J Heterocycl Chem 2008, 45, 551; (g) Bunce, R. A.; Nago, T. J Heterocycl Chem 2008, 45, 1155.

[6] (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. Tetrahedron 1996, 52, 15031; (b) Michael, J. P. Nat Prod Rep 1997, 14, 605; (c) Gallou-Dagommer, I.; Gastaud, P.; RajanBabu, T. V. Org Lett 2001, 3, 2053.

[7] For examples using 1,2,3,4-tetrahydroquinoline-2-acetic esters, see (a) Jones, G.; Wood, J. Tetrahedron 1965, 21, 2961; (b) Perron, J.; Joseph, B.; Mérour, J.-Y. Eur J Org Chem 2004, 4606.

[8] (a) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. J Med Chem 1994, 37, 3956; (b) Nagata, R.; Kodo, T.; Yamaguchi, H.; Tanno, N. Bioorg Med Chem Lett 1995, 5, 1533; (c) Katayama, S. Ae, N.; Nagata, R. Tetrahedron: Asymmetry 1998, 9, 4295.

[9] Amine exchange in amides is usually catalyzed by metal oxides, see Takahashi, K.; Shibagaki, M.; Mastushita, H. Agric Biol Chem 1988, 52, 853.

[10] Paradisi, C. In Comprehensive Organic Synthesis. Selectivity, Strategy and Efficiency in Modern Organic Chemistry; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon Press: New York, NY; Vol 4, pp 423–450.

[11] Other amines singly branched at the α-carbon were not explored since cyclohexylamine is a relatively unhindered case. Aniline and *tert*-butylamine gave none of the ring-closed product.

[12] In our earlier work, which focused on unhindered substrates that close by an *endo* process, evidence suggested that the Michael addition initiated the annulation sequence (see Ref 2). Subsequent experiments, however, have shown that increased substitution on the β-carbon of the Michael acceptors results in a reversal of the steps in this reaction. The results of this study will be reported in due course.

[13] (a) Bergmann, E. D.; Ginsberg, D.; Pappo, R. Org React 1959, 10, 179; (b) Bunce, R. A.; Pierce, J. D. Tetrahedron Lett 1986, 27, 5583.

[14] Still, W. C.; Kahn, M.; Mitra, A. J Org Chem 1978, 43, 2923.

[15] The *Z* isomer was also produced (<5% mixed with the *E* isomer), but it was not used.

# Synthesis of New Sulfur-Linked 1,2,4-Triazolothienopyrimidine and 1,2,4-Triazolopyrazolopyrimidine Derivatives Containing Fused Heterocyclic Pyrimidines



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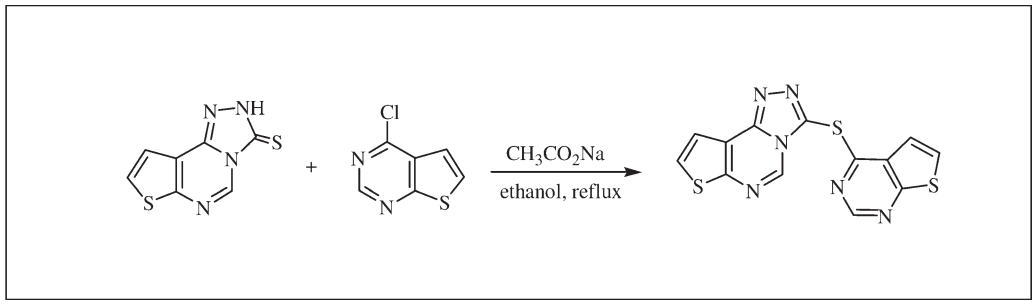


A series of novel *bis*-heterocyclic compounds **12–20** were synthesized by integrating fused heterocyclic pyrimidines, such as thienopyrimidine and pyrazolopyrimidine into the scaffold of thienotriazolopyrimidines, and pyrazolotriazolopyrimidines through a sulfur-linkage.

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## INTRODUCTION

The chemistry of heterocycles containing pyrimidine moiety have attracted considerable interest for many years because of their diverse biological activities, such as anti-inflammatory, anti-HIV-1, antimicrobial, and antitumor activities [1–4]. Some fused heterocyclic pyrimidines have acquired much importance because of their wide range of biological applications.

For instance, pyrazolopyrimidine **1** was as shown in Figure 1 investigated as antifungal and antibacterial agents [5], and other similar pyrazolopyrimidines were also reported to possess inhibitory activities of the insulin-like growth factor receptor (IGF-IR) and human cyclin-dependent kinase 2 [6,7]. Various triazolopyrimidine derivatives were known as dual thrombin/factor Xa inhibitors, human adenosine $A_{2A}$ receptor ligands, and herbicides [8–10]. Also, new thienopyrimidine derivatives have been identified as potent inhibitors of VEGF receptor-2 kinase and selective and potent ligands for the 5-$HT_3$ receptor [11,12]. Furthermore, it has been noticed that introduction of an additional ring to the fused heterocyclic pyrimidines tends to exert profound influence in conferring new biological activities in these molecules. Recently, thienotriazolopyrimidine **2** and pyrazolotriazolopyrimidine **3** derivatives as tricyclic heterocyclic compounds (five-six-five ring systems) have been explored for adenosine $A_1/A_{2A}$ or $A_{2A}/A_3$ receptor antagonists [13,14].

Starting from using the thienotriazolopyrimidine derivatives **4** and **5** which have been recently reported from our laboratories [15] and in continuation to our works for biologically active heterocyclic compounds [16] we now report the synthesis of new *bis*-heterocyclic compounds **12–20** prepared by integrating fused heterocyclic pyrimidines, such as thienopyrimidines and pyrazolopyrimidines into the scaffold of thienotriazolopyrimidines and pyrazolotriazolopyrimidines through a sulfur-linkage in the hope of obtaining compounds of diverse pharmaceutical activities.

## RESULTS AND DISCUSSION

For the synthesis of key intermediates **9**, **10**, and **11**, 2-aminothiophene-3-carbonitrile and 3-aminothiophene-2-carboxamide as starting materials were obtained, respectively, according to the modified Gewald method [17]. 5-Amino-1-phenyl-1*H*-pyrazole-4-carbonitrile was also prepared by the reaction of phenylhydrazine with ethoxymethylenemalonitrile in refluxing ethanol [18]. Compounds **6** and **8** were obtained from the reaction of starting materials with triethyl orthoformate and subsequent cyclization with hydrazine. Condensation of 3-aminothiophene-2-carboxamide with aqueous formic acid and subsequent treatment with $POCl_3$ and hydrazine gave **7**, as shown Scheme 1 [15]. Electrophilic attack of $CS_2$ in the presence of ethanolic KOH on the hydrazines **6**, **7**, and **8** gave via further intramolecular cyclization and elimination of $H_2S$ fused 1,2,4-triazolopyrimidine-3-thiones **9–11**, respectively, which exhibit a

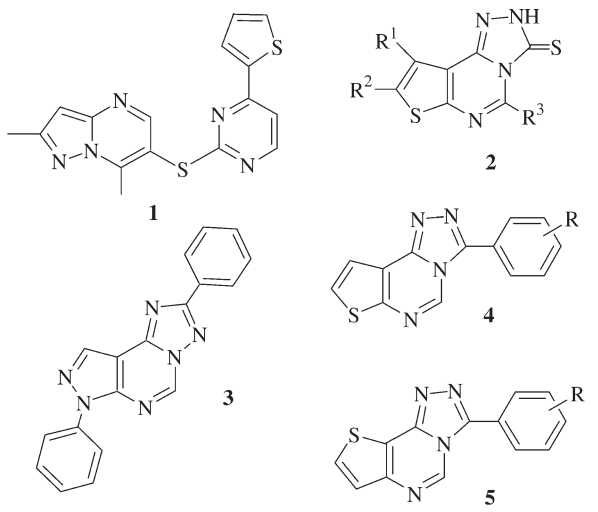


**Figure 1.** Compounds **1–5**.

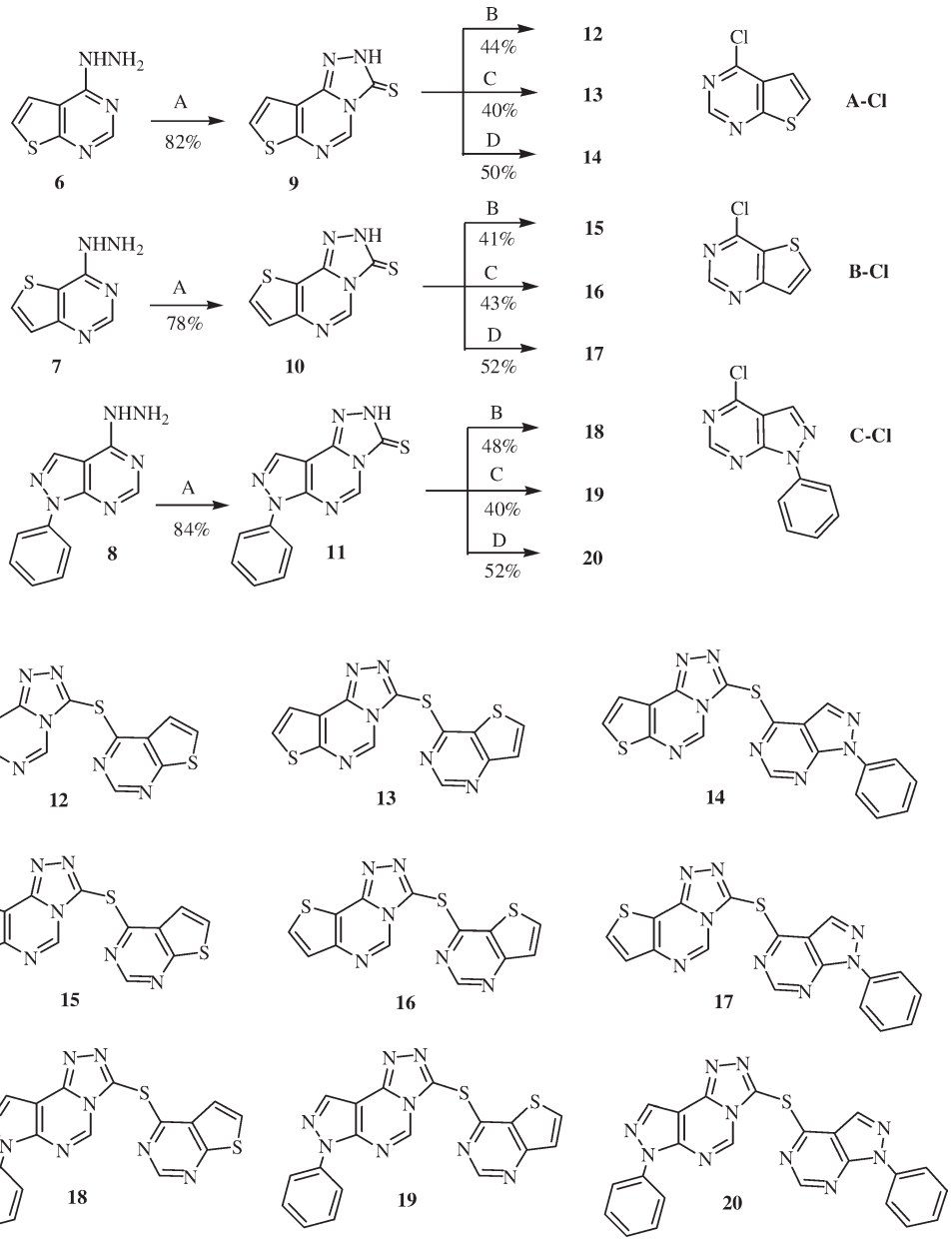
thione-thiol equilibrium. The structure of these compounds was confirmed by elemental analysis, $^1$H-NMR and IR spectra. The IR spectra showed characteristic peaks at 1200 (weak) and 3190 cm$^{-1}$ for the C=S and NH groups, respectively. The disappearance of the primary amino protons and the appearance of the secondary amino signal near at δ 14.0 in $^1$H-NMR spectrum indicated the thione tautomer of cyclization products. The mass spectral data of **9** and **10**, for instance, showed a molecular ion peak at m/z 208, and also showed ion at m/z 135 which could be attributed to the loss of N—NH—C=S from the molecular ion.

The compounds **12–20** were prepared as shown Scheme 2 in moderate yield by treatment of fused 1,2,4-triazolopyrimidine-3-thiones **9–11** with chlorothienopyrimidines (**A-Cl** and **B-Cl**) or chlorophenylpyrazolopyrimidine (**C-Cl**) in refluxing ethanol containing sodium acetate. The structures of **12–20** were established on the basis of their spectral data and elemental analysis. The IR spectra of these compounds exhibited absorption bands in the region of 1630–1490 cm$^{-1}$ for aromatic C=C, C=N stretching vibrations, and disappearance of NH and C=S stretching signals of cyclic thiourea. The $^1$H-NMR spectra of 3-(thieno[2,3-*d*]pyrimidin-4-ylthio)-thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine **(12)**, for example, showed four doublet signals because of protons of two thiophenes, and two singlet signals attributed to protons of two pyrimidine rings. Thus, one pair of doublet signals at δ 8.11 and 7.85 corresponded to thiophene protons (H-8 and H-9) of thieno[3,2-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine ring, and the other one at δ 8.03 and 7.50 attributed to thiophene protons (H-5′ and H-6′) of thieno[2,3-*d*]pyrimidine ring. Two singlets at δ 9.77 and 8.81 were observed for pyrimidine proton (H-5) of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine ring, and pyrimidine proton (H-2′) of thieno[2,3-*d*]pyrimidine ring, respectively. The mass spectrum of **12** revealed m/z = 342 corresponding the molecular formula, $C_{13}H_6N_6S_3$. The ions at 208, 135 were fragments obtained from cleavage of sulfide bond of **12**. The more deshielded α proton (H-6′) of thiophene of thieno [3,2-*d*]pyrimidine ring in 3-(thieno[3,2-*d*]pyrimidin-4-ylthio)thieno[3,2-*e*][1,2,4]tri-azolo[4,3-*c*]pyrimidine **(13)** appeared as a doublet at δ 8.43, whereas the β proton (H-7′) was found to appear at δ 7.68 in little higher field as a doublet when compared with **12**. The mass fragmentation pattern of **13** was in agreement with the pattern of **12**, giving a molecular ion peak at 341. The $^1$H-NMR of 3-(1-phenyl-1*H*-pyrazolo [3,4-*d*]pyrimidin-4-ylthio)thieno[3,2-*e*][1,2,4]triazolo [4,3-*c*]pyrimidine **(14)** displayed two singlets at δ 8.75 and 8.65, respectively for pyrimidine (H-6′) and pyrazole protons (H-3′) of phenylpyrazolopyrimidine ring. Multiplets responsible for phenyl ring appeared at δ 8.15, 7.54, and 7.71 as a doublet and two triplets, and the proton resonance of the thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine ring was observed as two doublets at δ 8.19 and 8.00 for thiophene (H-8 and H-9) and as a singlet at δ 9.34 for pyrimidine (H-5), respectively. The mass spectrum of **14** revealed m/z = 402 corresponding the molecular formula, $C_{18}H_{10}N_8S_2$. The ions at 228, 208, and 195 were fragments due to cleavage of sulfide bond of **14**.

The $^1$H-NMR spectra of **15–16** and **17** showed patterns similar to those of corresponding **12–13** and **14**. It is noteworthy that the chemical shifts of thiophene and pyrimidine protons for thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine ring were changed at δ 9.78–7.69 in higher field or in more downfield because of sulfur-linked fused heterocycles, such as thienopyrimidines or pyrazolo-

**Scheme 1.** Reagent and conditions: A: $HC(OEt)_3$, reflux; B: $NH_2NH_2$-$H_2O$, reflux; C: HCOOH, reflux; D: (i) $POCl_3$, reflux, (ii) $NH_2NH_2$-$H_2O$, reflux; E: $HC(OEt)_3$, reflux; F: $NH_2NH_2$-$H_2O$, reflux.

**Scheme 2.** Reagents and conditions: A: $CS_2$/KOH, ethanol, reflux; B: **A-Cl**, $CH_3CO_2Na$, ethanol, reflux; C: **B-Cl**, $CH_3CO_2Na$, ethanol, reflux; D:**C-Cl**, $CH_3CO_2Na$, ethanol, reflux.




pyrimidine. The mass spectra of **15–16** and **17** revealed the very similar fragmentations compared with corresponding **12–13** and **14** having the same molecular formulas, respectively.

The compounds **18–19** were also characterized by $^1$H-NMR spectra, which exhibited three singlets at δ 9.79–8.56 and two doublets at δ 8.45–7.45 for fused heterocycles and multiplet signals at δ 8.15–7.47 for phenyl ring, like patterns of **14** and **17**. The $^1$H-NMR spectrum of **20** containing two phenylpyrazolopyrimidine moieties showed four singlets for pyrimidine and pyrazole protons of two rings. The signals attributed to pyrimidine (H-5) and pyrazole protons (H-9) of phenylpyrazolo triazolopyrimidine ring were observed at δ 8.84 and 8.32, whereas the similar signals attributed to pyrimidine (H-6′) and pyrazole protons (H-3′) of phenylpyrazolopyrimidine ring were observed δ 8.68 and 8.58, respectively. Data from the elemental analysis and molecular ion recorded in the mass spectrum further confirmed the assign structure.

The compounds **12–20** were examined preliminarily for the antibacterial activity *in vitro* against *Escherichia coli* and were found to be slightly less active than that of compound **1**. They are under evaluation for other

biological activities and the results will be published elsewhere.

In conclusion, we have reported the synthesis of new sulfur-linked *bis*-heterocyclic compounds **12–20** with potential biological activities.

## EXPERIMENTAL

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions were checked on thin-layer chromatograpohy of Merck Kieselgel $60F_{254}$ and purified by column chromatography Merck silica gel (70–230 mesh). The $^1$H-NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (300 MHz) with $Me_4Si$ as internal standard and chemical shifts are given in ppm (δ). IR spectra were recorded using a JASCO FT/IR-200 spectrophotometer. Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

**General procedure for the preparation of fused 1,2,4- triazolopyrimidine-3-thione derivatives (9–11).** A solution of potassium hydroxide (10 mmol) and $CS_2$ (2 mL) in ethanol (30 mL) was added dropwise to a solution of appropriate thienopyrimidinyl hydrazine or pyrazolopyrimidinyl hydrazine **6-8** (20 mmole) in ethanol (20 mL). The reaction mixture was then refluxed for 8 hours. After cooling and evaporation of the solvent, the residue was dissolved in water and acidified by adding 10% HCl. The solid product was purified by recrystallization from ethanol.

***Thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine-3(2H)-thione(9).*** Yield 82%, mp 220–222°C; IR (KBr) 3190, 1200 $cm^{-1}$, $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 14.0 (s, 1H, NH), 9.44 (s, 1H, H-5), 8.12 (d, $J$ = 5.8 Hz, 1H, H-8), 7.58 (d, $J$ = 5.8 Hz, 1H, H-9), ms: m/z (%) 208 ($M^+$ , 95) 181 (29), 162 (42), 135 (100), 84 (23). *Anal*. Calcd. for $C_7H_4N_4S_2$: C, 40.37; H, 1.94, N, 26.90. Found: C, 40.50; H, 1.82; N, 27.01.

***Thieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine-3(2H)-thione (10).*** Yield 78%, mp 212–213°C; IR (KBr) 3150, 1210 $cm^{-1}$, $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 13.8 (s, 1H, NH), 8.84 (s, 1H, pyrimidine), 7.90 (d, $J$ = 5.8 Hz, 1H, thiophene proton), 7.49 (d, $J$ = 5.8 Hz, 1H, thiophene proton), ms: m/z (%) 208 ($M^+$, 60), 176 (61), 162 (15), 135 (34), 84 (99). *Anal*. Calcd. for $C_7H_4N_4S_2$: C, 40.37; H, 1.94, N, 26.90. Found: C, 40.44; H, 1.99; N, 26.76.

***7-Phenyl-2H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimi-dine-3(7H)-thione (11).*** Yield 84%, mp 259–261°C; IR (KBr) 3190, 1210 $cm^{-1}$, $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 14.2 (s, 1H, NH), 9.47 (s, 1H, pyrimidine), 8.52 (s, 1H, pyrazole), 8.07 (d, $J$ = 7.8 Hz, 2H, phenyl), 7.64 (t, 2H, phenyl), 7.46 (t, 1H, phenyl), ms: m/z (%) 268 ($M^+$, 100), 222 (15), 195 (12), 84 (15). *Anal*. Calcd. for $C_{12}H_8N_6S$: C, 53.72; H, 3.01, N, 31.32. Found: C, 53.84; H, 2.88; N, 31.44.

**General procedure for the preparation of sulfur-linked bis-heterocyclic compounds (12–20).** A suspension of anhydrous sodium acetate (15 mmol), chlorothienopyrimidine (**A-Cl** or **B-Cl**) or chlorophenylpyrazolopyrimidine (**C-Cl**) (10 mmol) and the appropriate fused 1,2,4-triazolopyrimidine-3-thione **9-11** (10 mmol) in ethanol (30 mL) was refluxed for 6–8 h. After cooling, the solid products formed were filtered, washed with water and recrystallized from ethanol.

***3-(Thieno[2,3-d]pyrimidin-4-ylthio)thieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (12).*** Yield 44%, mp 253–255°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.77 (s, 1H, H-5), 8.81 (s, 1H, H-2′), 8.11 and 7.85 (d and d, $J$ = 5.8 Hz, 2H, H-8 and H-9), 8.03 and 7.50 (d and d, $J$ = 5.8 Hz, 2H, H-5′ and H-6′), ms: m/z (%) 342 ($M^+$, 99), 284 (9), 208 (12), 162 (5), 135 (22). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.51; H, 1.89; N, 24.37.

***3-(Thieno[3,2-d]pyrimidin-4-ylthio)thieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (13).*** Yield 40%, mp 213–215°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.77 (s, 1H, H-5), 8.99 (s, 1H, H-2′), 8.43 and 7.68 (d and d, $J$ = 5.8 Hz, 2H, H-6′ and H-7′), 8.12 and 7.84 (d and d, $J$ = 5.8 Hz, 2H, H-8 and H-9), ms: m/z (%) 342 ($M^+$, 100), 284 (5), 208 (42), 162 (15), 135 (31). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.48; H, 1.85; N, 24.43.

***3-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)thieno [3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (14).*** Yield 50%, mp 244–246°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.34 (s, 1H, H-5), 8.75 (s, 1H, H-6′), 8.65 (s, 1H, H-3′), 8.19 and 8.00 (d and d, $J$ = 5.8 Hz, 2H, H-8 and H-9), 8.15 (d, $J$ = 7.8 Hz, 2H, phenyl), 7.54 (t, 2H, phenyl), 7.41 (t, 1H, phenyl), ms: m/z (%) 402 ($M^+$, 100), 374 (10), 344 (11), 228 (8), 208 (5). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.88; H, 2.59; N, 27.63.

***3-(Thieno[2,3-d]pyrimidin-4-ylthio)thieno[2,3-e][1,2,4] triazolo[4,3-c]pyrimidine (15).*** Yield 41%, mp 234–236°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.32 (s, 1H, H-5), 8.78 (s, 1H, H-2′), 7.94 and 7.69 (d and d, $J$ = 5.8 Hz, 2H, H-8 and H-7), 7.62 and 7.44 (d and d, $J$ = 5.8 Hz, 2H, H-6′ and H-5′), ms: m/z (%) 342 ($M^+$, 95), 284 (10), 208 (12), 162 (10), 135 (15). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.49; H, 1.85; N, 24.66.

***3-(Thieno[3,2-d]pyrimidin-4-ylthio)thieno[2,3-e][1,2,4] triazolo[4,3-c]pyrimidine (16).*** Yield 43%, mp 228–230°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.78 (s, 1H, H-5), 9.00 (s, 1H, H-2′), 8.46 and 7.69 (d and d, $J$ = 5.8 Hz, 2H, H-6′ and H-7′), 8.37 and 7.78 (d and d, $J$ = 5.8 Hz, 2H, H-8 and H-7), ms: m/z (%) 342 ($M^+$, 100), 298 (26), 284 (8), 208 (7), 168 (2), 135 (3). *Anal*. Calcd. for $C_{13}H_6N_6S_3$: C, 45.60; H, 1.77, N, 24.54. Found: C, 45.44; H, 1.90; N, 24.70.

***3-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)thieno [2,3-e][1,2,4]triazolo[4,3-c]pyrimidine (17).*** Yield 52%, mp 183–185°C; $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 8.91 (s, 1H, H-5), 8.58 (s, 1H, H-6′), 8.28 (s, 1H, H-3′), 7.91 and 7.69 (d and d, $J$ = 5.8 Hz, 2H, H-8 and H-7), 8.17 (d, $J$ = 7.8 Hz, 2H, phenyl), 7.56 (t, 2H, phenyl), 7.40 (t, 1H, phenyl), ms: m/z (%) 402 ($M^+$, 100), 358 (32), 228 (12), 208 (25), 195 (18), 135 (45), 77 (24). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.60; H, 2.61; N, 27.90.

***4-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c] pyrimidin-3-ylthio)thieno[2,3-d]pyrimidine (18).*** Yield 48%, mp 285–287°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.23 (s, 1H, H-5), 8.79 (s, 1H, H-2′), 8.56 (s, 1H, H-9), 7.70 and 7.45 (d and d, $J$ = 5.8 Hz, 2H, H-6′ and H-5′), 8.15 (d, $J$ = 7.8 Hz, 2H, phenyl), 7.60 (t, 2H, phenyl), 7.47 (t, 1H, phenyl), ms: m/z (%) 402 ($M^+$, 100), 374 (19), 268 (30), 222 (14), 195 (12), 135 (31), 77 (18). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.80; H, 2.64; N, 27.62.

***4-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c] pyrimidin-3-ylthio)thieno[3,2-d]pyrimidine (19).*** Yield 40%, mp 230–232°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 9.79 (s, 1H, H-5), 9.02 (s, 1H, H-2′), 8.79 (s, 1H, H-9), 8.45 and 7.69 (d and d, $J$ = 5.8 Hz, 2H, H-6′ and H-7′), 8.10 (d, $J$ = 7.8 Hz, 2H, phenyl), 7.65 (t, 2H, phenyl), 7.50 (t, 1H, phenyl), ms: m/z (%) 402 ($M^+$, 100), 374 (18), 268 (26), 222 (28), 195 (18), 168 (12), 135 (84), 77 (43). *Anal*. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50, N, 27.84. Found: C, 53.88; H, 2.40; N, 27.69.

***7-Phenyl-3-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)-7H-pyrazolo[4,3-e][1,2,4]triaqzolo[4,3-c]pyrimidine (20).*** Yield 52%, mp 297–299°C (from ethanol); $^1$H-NMR (dimethyl sulfoxide-$d_6$): δ 8.84 (s, 1H, H-5), 8.68 (s, 1H, H-6′), 8.58 (s, 1H, H-3′), 8.32 (s, 1H, H-9), 8.17 (d, $J$ = 7.8 Hz, 2H, phenyl), 8.14 (d, $J$ = 7.8 Hz, 2H, phenyl) 7.60–7.53 (m, 4H, phenyl), 7.47–7.37 (m, 2H, phenyl), ms: m/z (%) 462 ($M^+$, 100), 434 (18), 404 (13), 268 (17), 228 (24), 195 (18), 168 (19), 141 (13), 77 (3). *Anal*. Calcd. for $C_{23}H_{14}N_{10}S$: C, 59.73; H, 3.05, N, 30.29 Found: C, 59.85; H, 2.91; N, 30.40.

## REFERENCES AND NOTES

[1] Gavrilov, M. Y.; Mardanova, I. G.; Kolla, V. E.; Konshin, M. E. Pharm Chem J 1988, 22, 554.

[2] Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; Balzarini, J.; De Clereq, E. J Med Chem 1991, 34, 349.

[3] Darias, V.; Abdallah, S. S.; Tello, M. L.; Delgada, L. D.; Vega, S. Arch Pharm 1994, 327, 779.

[4] Cordeu, L.; Cubedo, E.; Bandrés, E.; Rebollo, A.; Sáenz, X.; Chozas, H.; Victoria Domínguez, M.; Echeverría, M.; Mendivil, B.; Sanmartin, C.; Palop, J. A.; Font, M.; García-Foncillas, J. Bioorg Med Chem 2007, 15, 1659.

[5] Al-Omran, F. A.; El-Khair, A. A. J Heterocycl Chem 2008, 43, 595.

[6] Hubbard, R. D.; Bamaung, N. Y.; Palazzo, F.; Zhang, Q.; Kovar, P.; Osterling, D. J.; Hu, X.; Wilsbacher, J. L.; Johnson, E. F.; Bouska, J.; Wang, J.; Bell, R. L.; Davidsen, S. K.; Sheppard, G. S. Bioorg Med Chem Lett 2007, 17, 5406.

[7] Williamson, D. S.; Parratt, M. J.; Bower, J. F.; Moore, J. D.; Richardson, C. M.; Dokurno, P.; Cansfield, A. D.; Francis, G. L.; Hebdon, R. J.; Howes, R.; Jackson, Philip S.; Lockie, A. M.; Murray, J. B.; Nunns, C. L.; Powles, J.; Robertson, A.; Surgenor, A. E.; Torrance, C. J. Bioorg Med Chem Lett 2005, 15, 863.

[8] Deng, J. Z.; McMasters, D. R.; Rabbat, P. M. A.; Williams, P. D.; Coburn, C. A.; Yan, Y.; Kuo, L. C.; Lewis, S. D.; . Lucas, B. J.; Krueger, J. A.; Strulovici, B.; Vacca, J. P.; Lylea, T. A.; Burgey, C. S. Bioorg Med Chem Lett 2005, 15, 4411.

[9] Yao, G.; Haque, S.; Sha, Li.; Kumaravel, G.; Wang, J.; Engber, T. M.; Whalley, E. T.; Conlon, P. R.; Chang, H.; Kiesman, W. F.; Petter, R. C. Bioorg Med Chem Lett 2005, 15, 511.

[10] Johnson, T. C.; Martin, T. P.; Mann, R. K.; Pobanz, M. A. Bioorg Med Chem 2009, 17, 4230.

[11] Munchhof, M. J.; Beebe, J. S.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Higdon, R. C.; Hillerman, S. M.; Soderstrom, C. I.; Knauth, E. A.; Marx, M. A.; Rossi, A. M. K.; Sobolov, S. B.; Sun, J. Bioorg Med Chem Lett 2004, 14, 21.

[12] Modica, M.; Romeo, G.; Materia, L.; Russo, F.; Cagnotto, A.; Mennini, T.; Gáspár, R.; Falkay, G.; Fülöp, F. Bioorg Med Chem 2004, 12, 3891.

[13] Prasad, M. R.; Rao, A. R.; Rao, P. S.; Rajan, K. S.; Meena, S.; Madhavi, K. Eur J Med Chem 2008, 43, 614.

[14] Baraldi, P. G.; El-Kasher, H.; Farghaly, A.-R.; Venelle, P.; Fruttarolo, F. Tetrahedron 2004, 60, 5093.

[15] Jo, B. S.; Son, H. Y.; Song, Y.-H. Heterocycles 2008, 75, 3091.

[16] (a) Lee, H. M.; Song, Y.-H.. Bull Korean Chem Soc 2010, 31, 185; (b) Jo, B. S.; Song, Y.-H.; Syn Commun 2009, 39, 4407; (c) Song, Y.-H.; Jo, B. S. J Heterocycl Chem 2009, 46, 1132; (d) Song, Y.-H.; Jo, B. S. Bull Korean Chem Soc 2009, 30, 969; (e) Song, Y.-H.; Jo, B. S.; Lee, H. M. Heterocycl Commun 2009, 15, 203; (f) Lee, H. M.; Song, Y.-H. J Kor Chem Soc 2009, 53, 387; (g) Kim, K. H.; Song, Y.-H. Heterocycl Commun 2008, 14, 405; (h) Song, Y.-H.; Seo, J. J Heterocycl Chem 2007, 44, 1439; (i) Song, Y.-H. Heterocycl Commun 2007, 13, 33.

[17] Gewald, K. Chem Ber 1965, 98, 3571.

[18] Peat, A. J.; Boucheron, J. A.; Dickerson, S. H.; Garrido, D.; Mills, W.; Peckham, J.; Preugschat, F.; Smalley, T.; Schweiker, S. L.; Wilson, J. R.; Wang, T. Y.; Zhou, H. Q.; Thomson, S. A. Bioorg Med Chem Lett 2004, 14, 2121.

# Synthesis of Novel and Biologically Potent Heteropolycyclics Containing Bridge Head Nitrogen



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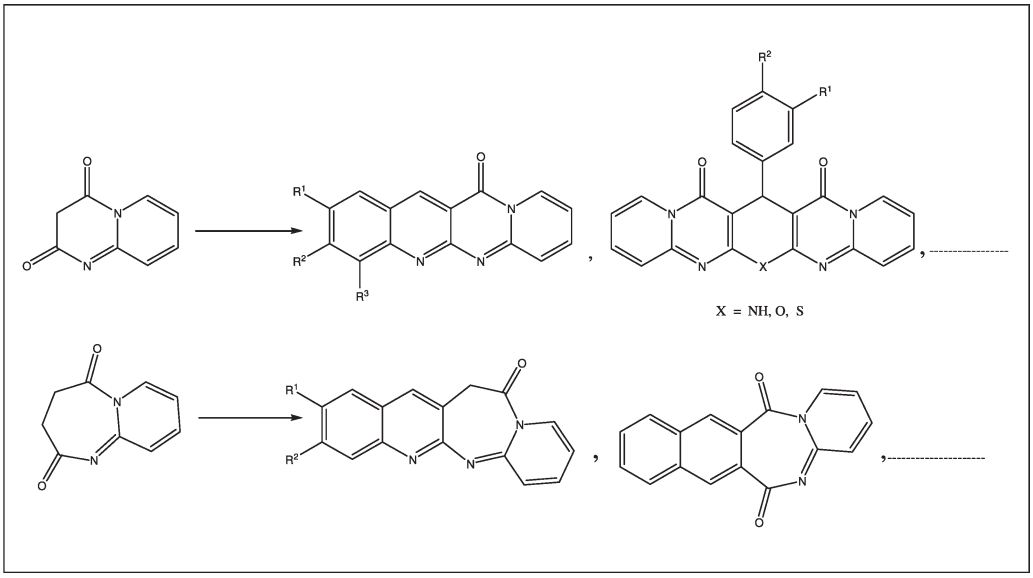


A facile one pot synthesis of 2,3,4,5-tetrahydropyrido [1,2-*a*] [1,3] diazepine-2,5-dione **2** and 3,4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione **3** has been achieved. Condensation of **3** with *o*-aminobenzaldehydes produced the linear product **4** and not the angular one **5**. Cyclocondensation of **3** with 1,5-diketones afforded a tricyclic linear system **6**, a bis assembly system **7** and two novel heterotetracyclic nitrogen bridged linear systems **8** and **10**. Condensation of *o*-aminobenzaldehydes with **2** produced a novel linear system **12** and a new doubly fused hexacyclic system **11**. Cyclodehydration of **2** with 1,2-dicarbaldehydes produced **1**, **13**, and a new heterotetracyclic nitrogen bridged system **14**. Condensation of **3** with aromatic aldehydes in presence of ethylene glycol as solvent without the use of catalyst generated the doubly nitrogen bridged linear pentacyclic systems **15–17**. The synthesized compounds have been adequately characterized and screened for bronchodilatory and antimicrobial activities with promising results.

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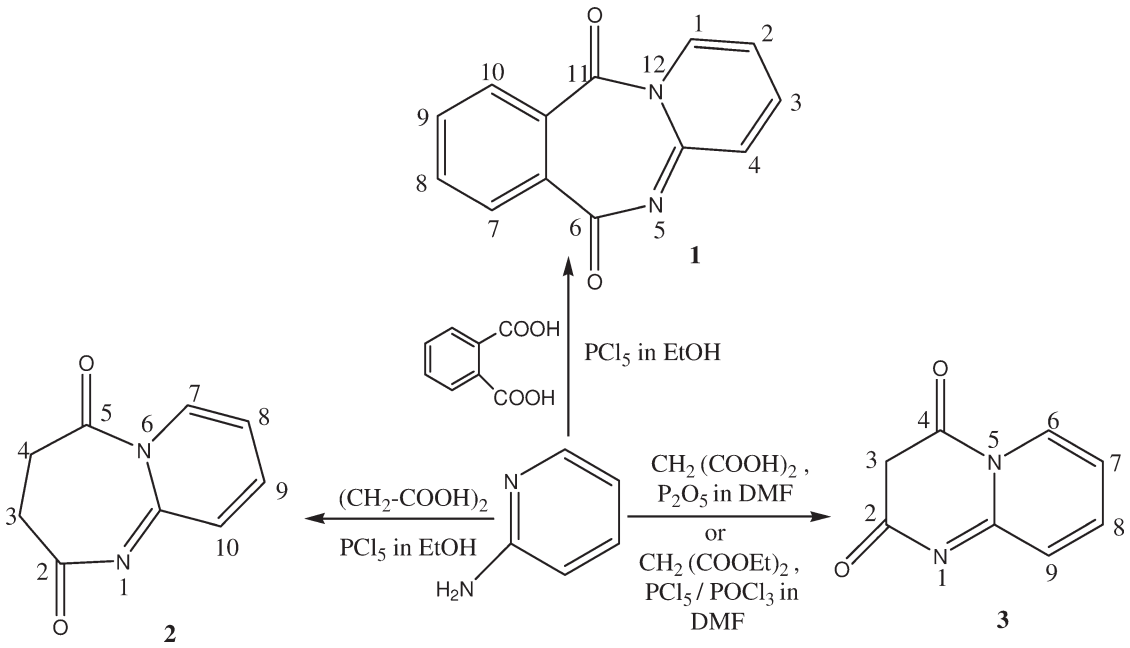
## INTRODUCTION

Diazepines and benzodiazepines are known to exhibit a wide variety of biological activities such as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic activity [1–3]. Some of the benzodiazepine derivatives particularly 7-(*p*-methoxyphenyl)-8-phenoxy-1, 5-benzo-3-azanonem (1,5-BDZ-OMe) and 7-phenyl-8-phenoxy-1,5-benzo-3-azanonem (1,5-BDZ-H) possess hypnotic activity [4]. Pyrrolo [2,1-*c*] [1,4] benzodiazepines such as anthramycin and DC-81 are well-known antitumor antibiotics (PBDS) derived from streptomyces species [5].

Compounds possessing quinazoline and quinazolinone nuclei show potent biological activities including bronchodilatory, anticancer, anticonvulsant, antibacterial, anti-HIV properties [6,7], anthelmintic [8], antiparkinsonium [9], antitubercular [10], hypoglycemic [11], antiviral [12], anticoagulant [13], antifibrillatory [14], cardiac stimulant [15], CNS depressant [16], neuroleptic [17], and hypnotic [18]. Vasicine and vasicinone, the two known alkaloids and a synthetic compound 7,8,9,10-tetrahydroazepino [2,1-*b*] quinazolin-12(6*H*)-one (RLX) all bearing quinazoline moiety have been evaluated as potent bronchodilatory and oxytocic agents [19–22]. The latter compound has been found to be six times more potent than aminophylline [23].

Quinoline and its derivatives are known for their antimalarial and therapeutic properties. A number of quinoline derivatives are known to possess antitumour, antibacterial, antifungal, hypotensive, anti-HIV, analgesic,

**Scheme 1**



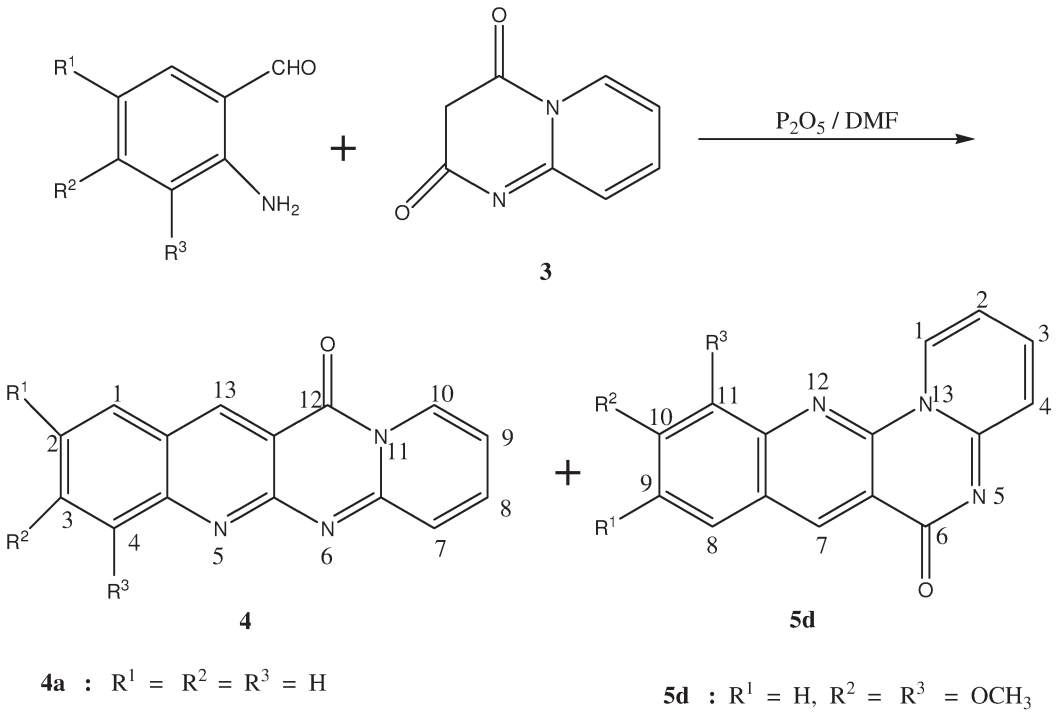

anti-Leishmanial, and anti-inflammatory activities [24]. In addition, the synthesis of pyrido [1,2-*a*] pyrimidin-4-ones provided a wide spectrum of biological activities [25–31] such as tranquilizer, antiallergic, antiulcerative, antiasthmetic and bronchodilatory activity, analgesic activity, and human platelet aggregation inhibitory properties. Biologically active evaluations of these constituent moieties in the recent years encouraged us to generate the novel condensed heteropolycyclic systems containing bridge head nitrogen atom, most of them hitherto unknown in literature and comprising of one or more than one of these moieties. Such novel systems might expectedly prove to be the potent therapeutic agents in near future.

## RESULTS AND DISCUSSION

In this work, 6*H*,11*H*-pyrido[1,2-*b*][2,4]benzodiazepine-6,11-dione **1** and 2,3,4,5-tetrahydropyrido[1,2-*a*] [1,3]diazepine-2,5-dione **2** were designed and generated by the condensation of 2-aminopyridine with phthalic acid and succinic acid, respectively, both in presence of $PCl_5$ in ethanol. An active methylene heterocycle, 3,4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione **3** was produced by the condensation of 2-aminopyridine either with malonic acid in presence of anhydrous $P_2O_5$ in DMF or with diethyl malonate in the presence of $PCl_5$/ $POCl_3$ in DMF (Scheme 1). Compound **3** has been known in literature, having been prepared through other approaches [32–34]. Literature m.p, analytical data, and spectral data confirmed the structure assigned to it in this study. Presence of peculiar bands between 1590 to 1600 $cm^{-1}$ and 1675 to 1710 $cm^{-1}$ in IR spectra of compounds **1** and **2** favored the presence of C=N and CON< (tertiary amide) functionalities. Presence of signal of aromatic protons only for compound **1**, a downfield multiplet due to two methylene groups around δ 2.35 to 2.43 ppm for compound **2**, and the absence of any $D_2O$ exchangable proton in $^1H$ NMR spectra of either of these two compounds confirmed the heterocyclisation and their structures unambigously.

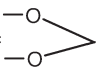
The active methylene compound **3** was put to Knoevenagel condensation with some *o*-aminobenzaldehydes followed by subsequent heterocyclodehydration affording a single product (**4a–c**) and in one case affording the main product **4d** associated with another very minor product (TLC). The compounds **4a–d** have been characterized as 12*H*-pyrido [1′,2′:1,2] pyrimido [4,5-*b*] quinolin-12-ones belonging to a linear ''ortho fused'' system. The minor product which could not be separated from **4d** might be the angular product, 6*H*-pyrido [1′, 2′:1, 2] pyrimido [4,5-*b*] quinolin-6-one **5d** (Scheme 2). The literature report [35] regarding compound **4a** confirmed its structure by comparing m.p, analytical, and spectral data of **4a** of this study with that known in literature. The appearance of peaks of methylenedioxy protons at δ 6.10 ppm in **4c**, two methoxyl group protons at δ 3.70 and 3.75 ppm in compound **4b**, and two methoxyl group protons at δ 3.72 and δ 3.78 ppm for compound **4d** in $^1H$ NMR spectra confirmed their structures unequivocally. Other signals in $^1H$ NMR spectra of **4b–d** were almost identical with those for compound **4a**.

**Scheme 2**




**4a** : $R^1 = R^2 = R^3 = H$

**4b** : $R^1 = R^2 = OCH_3$ ; $R^3 = H$

**4c** : $R^1 + R^2 =$  ; $R^3 = H$

**4d** : $R^1 = H$, $R^2 = R^3 = OCH_3$

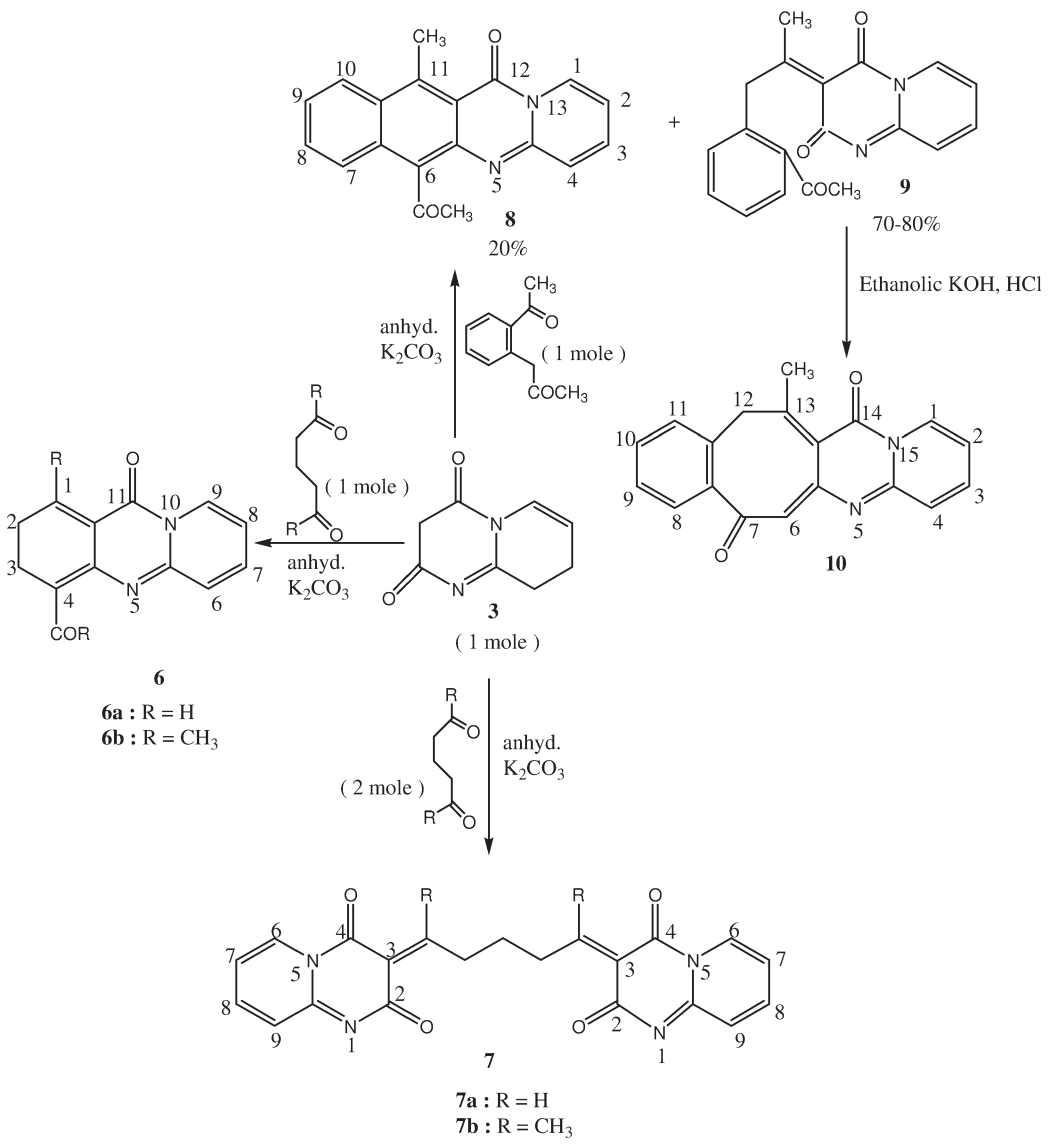
**5d** : $R^1 = H$, $R^2 = R^3 = OCH_3$

Working on the similar route of synthesis, cyclocondensation of **3** with 1,5-dicarbonyl compounds like glutaraldehyde and heptane-2,6-dione in the mole ratio of 1:1 and 1:2 in presence of anhydrous $K_2CO_3$ was carried producing two entirely different product systems, a quinazoline based linearly fused tricyclic system, 4-acyl-2,3-dihydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one **6a–b**, and a bis heterocyclic ring assembly system, 1,5-bis (2,4-dioxo-3,4-dihyro-2*H*-pyrido [1,2-*a*] pyrimidin-3-ylidine) pentane **7a–b**, respectively, in each case. The compound **6a** obtained from 1:1 condensation showed a characteristic downfield singlet at δ 9.96 ppm due to proton of CHO at C-4, a downfield triplet at δ 5.70 ppm due to ethylenic proton at position 1, and a multiplet at δ 1.7 to 1.85 ppm due to four methylenic protons besides four aromatic protons as multiplet in its $^1$H NMR spectrum. The compound **6b** had two prominent singlets of three protons each at δ 2.43 and 2.15 ppm due to $COCH_3$ and $CH_3$ protons, respectively. The appearance of a multiplet due to six protons of three methylene groups and a triplet due to two ethylenic protons in the acyclic portion confirmed unequivocally the structure of **7a**. Similarly, 6-aceto-12*H*-11-methylbenzo [*g*] pyrido[2,1-*b*]quinazolin-12-one **8** and 12*H,14H*-13-methylbenzo [5,6] [8] annuleno [1,2-*d*] pyrido [1,2-*a*] pyrimidine-7,14-dione **10** were also generated from compound **3**, the latter through the intermediacy of **9** (Scheme 3).

Under slightly different conditions, a highly hybrid quinoline-based doubly fused hexacyclic system, tetrasubstituted pyrido[1′,2′:1,2]quino [3″,2″:6,7][1,3] diazepino[4,5-*b*] quinoline **11** and a novel linear disubstituted system, pyrido[1′,2′:1,2] [1:3] diazepino[4,5-*b*]quinolin-12(13*H*)-one **12** were generated from **2** whose characterization was done as usual (details in experimental part). Again, cyclodehydration of **2** with malealdehyde and succinaldehyde produced **1** and its dihydro analogue **13**, respectively, and the condensation between **2** and phthalaldehyde produced a new heterotetracyclic system 6*H*,13*H*-pyrido[1,2-*a*]naphtho[2,3-*e*] [1,3] diazepine-6,13-dione **14** (Scheme 4).

In extension of our earlier work [36,37], it was thought worthwhile to study the condensation of active methylene compound **3** with aromatic aldehydes in ethylene glycol as solvent without the use of catalyst. Knoevenagel condensation, Michael addition, and cyclodehydration took place simulataneously resulting in the formation of a novel linear and heteropentacyclic system **16** containing a central pyran ring. The

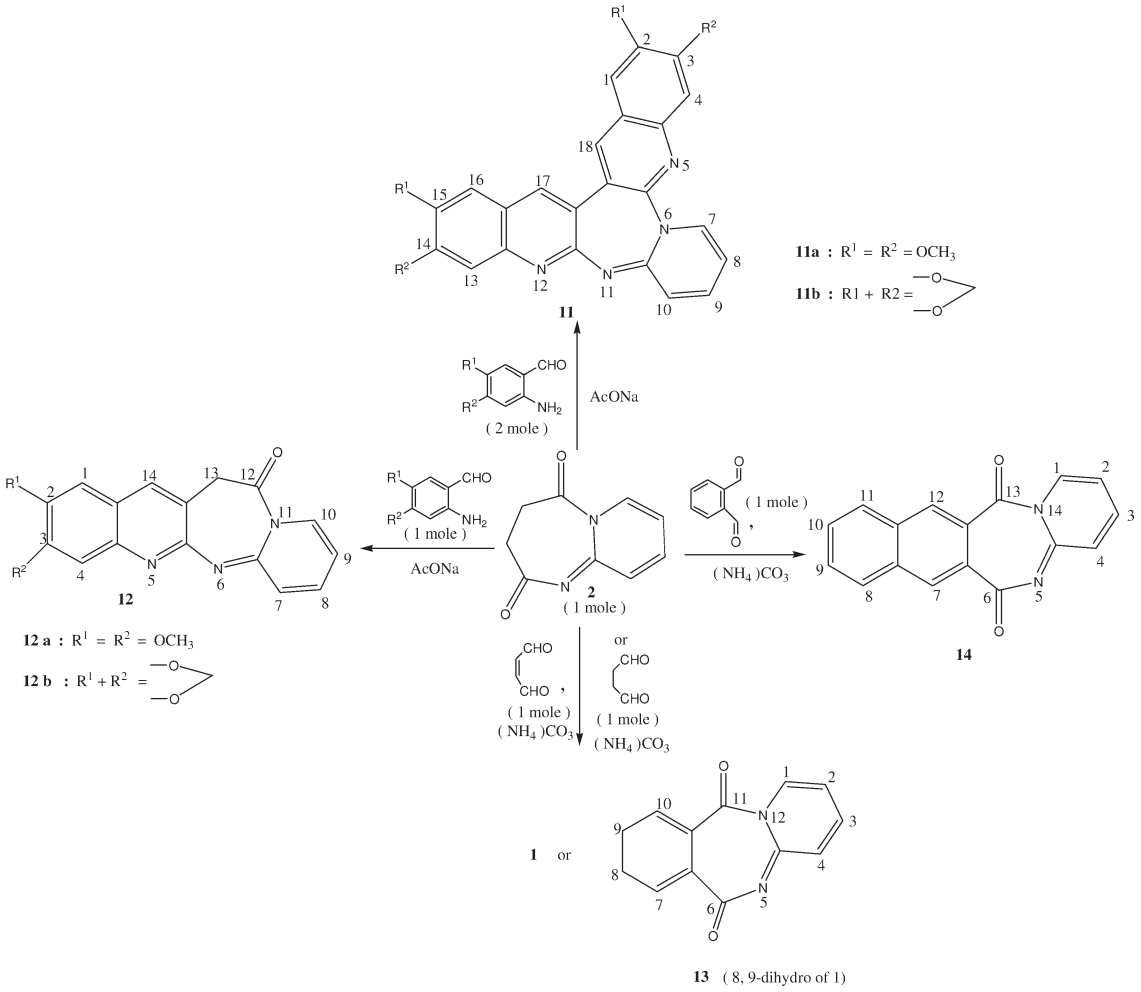
**Scheme 3**




intermediates could not be isolated but the second intermediate after the two transformations seemed to be more interesting for exploitation in the ring closure heterocyclising reaction. Hence, compound **3** was treated with different aromatic aldehydes in ethylene glycol producing compound **16** and refluxed in DMF in presence of ammonium acetate, $P_2O_5$ and $P_2S_5$ giving similar results in each case producing three novel linear heteropentacyclic systems **15**, **16**, and **17** with pyridine, pyran, and thiopyran central ring, respectively (Scheme 5). The characterization has been made for these systems on the basis of elemental analysis and spectral studies. The present exposition has twofold importance, firstly the study of the versatility and reactions of compound **3** and **2** with different aldehydes under different conditions resulting in generation of various novel-fused heterocyclic systems most of which are hitherto unknown in literature and secondly the study of physiological nature of these systems.

**Pharmacology.** On preliminary pharmacological investigations, the compounds **4a–d**, **6a–b**, **8**, **11a–b**, and **12a–b** have been found to be promising bronchodilatory and oxytocic agents having activities comparable to those of alkaloid vasicine and its natural and synthetic analogues. The detailed study of the evaluation of these biological activities is under active exploration from our research laboratory. The drugs employed in this study are 7,8,9,10-tetrahydroazepino [2,1-*b*] quinazolin-12(6*H*)-one; Aminophyllin injection I.P (Burroughs Welcome & Co.); Histamine diphosphate (Sigma); Adrenaline tartarate (IP); Propanolol HCl (ICI); 5-hydroxytryptamine; and Egg albumin (BDH).

**Scheme 4**



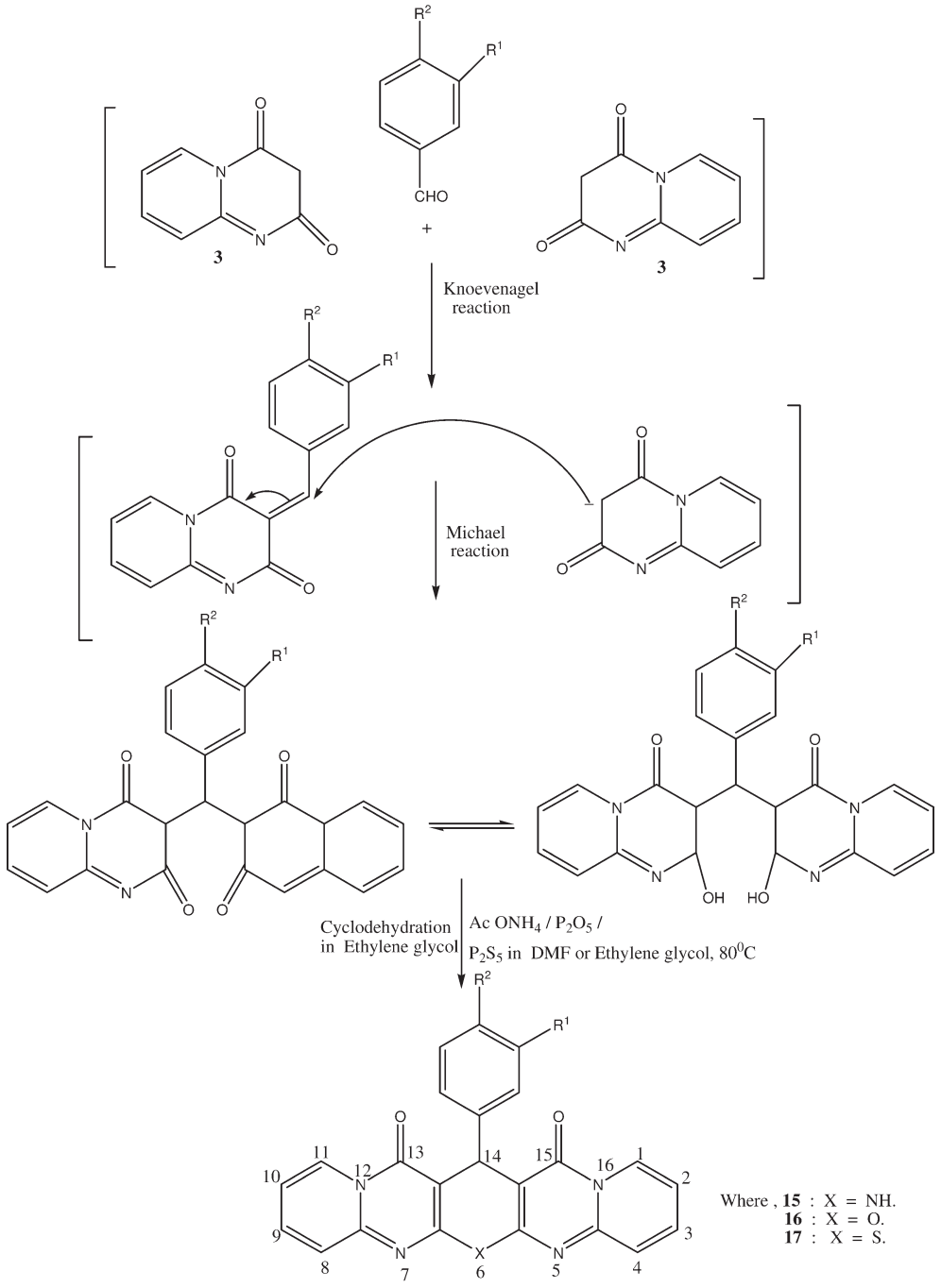

The comparative SAR of various compounds [38] and the results of other details regarding these activities are being currently determined. The compounds **4a–d**, **6a–b**, **8**, **11a–b**, and **12a** have been found to be weakly to moderately active antimicrobial agents. Compounds **4a–d**, **6a–b**, **11a–b**, and **12a** have been found to be highly promising, as regards ''Tracheal smooth muscle activity'' and ''Antitussive activity.''

**Antimicrobial activity.** The compounds **3**, **7a–b**, **15a–d**, and **4a–d** have been screened for their antifungal activity against Aspergillus, Penicillium, and Cladosporium species. For antibacterial activity, these compounds have been screened against *E.coli*, *Bacillus subtilis*, and *Bacillus cereus*. Both the activities were evaluated at the same concentration of 1000 μg and through well diffusion technique. The standard antifungal agent fluconazole and the antibacterial agent norfloxacin were also screened under similar conditions for a comparative study. The inhibition zones formed were measured in mm and are listed in (Table 1).

**Broncodilatory activity**

***Tracheal smooth muscle activity.*** Preparation of tissue was similar to that described by Castillow and de Beer [39] except that the tracheal ring was opened by severing the cartilage. Guineapigs (350–500 g) of either sex were sacrificed by a blow to the head and the tracheae rapidly excised. The tracheal chain was prepared and suspended in a 20 mL tissue bath containing Krebs-henselet solution (KHS) continuously aerated with 95% $O_2$ and 5% $CO_2$ and maintained at 37°. The composition (mM) of (KHS) was NaCl 118, KCl 4.7, $MgSO_4 \cdot 7H_2O$ 1.2, $CaCl_2$ 2.2, $KH_2PO_4$ 1.2, $NaHCO_3$ 24.9, and (+)-glucose 11.1. The responses were recorded isotonically on a kymograph. The tissue was adjusted to an initial tension of 1.5 g and allowed to equilibrate (60–90) min. Relaxation effect of the drug was studied on tracheal chain precontracted with histamine diphosphate ($1 \times 10^{-6}$ g/mL) or acetylcholine chloride ($1 \times 10^{-6}$ g/mL). The test drugs were added 8 min after the tonic contraction reached plateau. The responses were calculated as percent to relaxing of

**Scheme 5**




**15a, 16a, 17a :** $R^1$ = H, $R^2$ = $OCH_3$ **15b, 16b, 17b :** $R^1$ = H, $R^2$ = $CH_3$

**15c, 16c, 17c :** $R^1$ = $R^2$ = $OCH_3$ **15d, 16d, 17d :** $R^1 + R^2$ =

precontracted muscle back to base line tension (10% relaxation). If there was relaxation to muscle slightly below the base line, it was also taken as 100% relaxation.

***Antitussive activity.*** Kobayshi's [40] method was used in this study. Guineapigs (300–400 g) were aneasthetised by I/P urethane (6.5 mL/kg; 25%) and fixed in

**Table 1**

Antimicrobial activity of compounds **3**, **7a–b**, **15a–d**, and **4a–d**.

| | Antibacterial activity | | | Antifungal activity | | |
|---|---|---|---|---|---|---|
| Compd. No | *E. coli* | *B. subtilis* | *B. cereus* | *A. niger* | *P. species* | *C. species* |
| **3** | 14 | 12 | 17 | 17 | 13 | 16 |
| **7a** | 15 | 13 | 16 | 14 | 12 | 17 |
| **7b** | 17 | 11 | 18 | 18 | 16 | 17 |
| **15a** | 20 | 22 | 19 | 19 | 18 | 20 |
| **15b** | 19 | 23 | 23 | 21 | 22 | 23 |
| **15c** | 20 | 19 | 23 | 23 | 24 | 24 |
| **15d** | 20 | 18 | 21 | 20 | 19 | 20 |
| **4a** | 19 | 17 | 14 | 17 | 18 | 19 |
| **4b** | 18 | 16 | 16 | 19 | 18 | 19 |
| **4c** | 20 | 19 | 18 | 20 | 17 | 17 |
| **4d** | 21 | 19 | 17 | 17 | 21 | 20 |
| **NR** | 28 | 26 | 28 | – | – | – |
| **Flu** | – | – | – | 32 | 25 | 23 |

Note: 10 mm, inactive; 11–15 mm, weakly active; 16–22 mm, moderately active; 22–25 mm, highly active.
NR, norfloxacin; Flu, fluconazole.

dorsal position. The trachea was exposed and a small incision made at a distance of 1.5 cm from the clavicle. A fine and very thin polythene tube was inserted into the incision as deep as 3 cm to give the stimulus. The stimulus was applied two times before and 15, 30, 45, 60, 90 and 120 min after the drug administration by oral route. If no coughing occurred in two or more out of five trails after drug administration, the drug was estimated as effective percent inhibition was recorded. Results are shown in (Table 2) as follows:

## EXPERIMENTAL

**General.** Melting points were measured in open capillaries on perfit melting point apparatus and are uncorrected. IR spectra on KBr were recorded on Brucker—4800 infrared spectrometer. NMR and EIMS/HRMS spectra were recorded on Brucker AC-400 (400 MHz and 100 MHz) and JEOL D-300 mass spectrometer, respectively. Elemental analysis was carried out on simple CHNS analyzer (CHNS-932, LECO Corporation, USA). $^{1}H$ and $^{13}C$ chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as internal standard. All experiments were performed in oven dried glass

**Table 2**

Bronchodilatory and antitussive activities[a] of compounds **4a–d**, **6a–b**, **8**, **11a–b**, and **12a–b**.

| | *In vitro* guinea pig trachea % relaxation | | | Antitussive activity (guinea pig) | |
|---|---|---|---|---|---|
| Compd. | Histamine | Acetylcholine | Concn (μ/mL) | % cough inhibition | Dose (mg/kg) |
| **4a** | 60 | – | – | – | 10 |
| **4b** | 80 | 70 | 30 | 80[b] | 10 |
| **4c** | 60–80 | 40–50 | 9 | 60[b] | 10 |
| | 70–90 | 70–80 | 20 | 80[b] | |
| | 90 | 80–90 | 40 | 80[b] | |
| **4d** | 80 | – | 40 | 100[b] | 10 |
| **6a** | 80 | 80–85 | 9 | 100[c] | 10 |
| **6b** | – | 60 | 70 | 80[c] | 10 |
| **8** | 80 | 80–15 | 30 | 60[c] | 10 |
| **11a** | 40–50 | 40–50 | 30 | 100[d] | 10 |
| **1b** | 50–60 | 50–60 | 40 | 100[d] | 10 |
| **12a** | 40–50 | 40–50 | 30 | 100[e] | 10 |
| **Bromhexine hydrochloride** | | | | 40–80[e] | 2 |
| | | | | 100[e] | 4 |

[a] Minimium of four experiments for each group.
[b] Onset of action after 45 min and duration of 3 h.
[c] Onset of action after 45 min and duration >3 h.
[d] Onset of action after 30 min and duration >3 h .
[e] Onset of action after 15 min and duration >3 h.

apparatus. SISCO silica was used as adsorbent for TLC (0.5 mm thick plates) and TLC plates were eluted with 1:9 ratios of ethyl acetate and *n*-hexane. The column chromatography was performed over silica gel (60–120 mesh) with graded solvent systems of ethyl acetate-pet ether (60–80).

**General procedure for the synthesis of 1–3.** A mixture of 2-aminopyridine (0.01 mole) and appropriate dibasic acid/ester (0.01 mole) was initially grinded for about 20 min and then fused or refluxed as such for about 1 h without any solvent in a round bottom flask and finally refluxed on water bath in presence of 15 mL of ethanol and $PCl_5$ or at 150–160°C in presence of anhydrous $POCl_3/PCl_5$ in 20 mL of DMF or $P_2O_5$ in 20 mL of DMF. After the reaction time (TLC), the solvent was evaporated under reduced pressure and 100 mL of $H_2O$ was added. The precipitates obtained were filtered, dried, and then crystallized from hot ethanol to generate pure 1–**3**.

***6H,11H-Pyrido [1,2-b] [2,4]benzodiazepine-6,11-dione (1).*** It was obtained from phthalic acid (8.30 g, 0.01 mole) and 2-aminopyridine (4.70 g, 0.01 mole) as colorless solid; m.p.150–152°C ; yield 78%; IR (KBr) ν/cm$^{-1}$: 1320–1325 (C—N), 1600 (C=N), 1610–1620 (C=C), 1675 (C=O); MS: m/z = 224 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.01–7.81 (m, 8H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 110.2, 114.0, 125.4, 126.8, 128.7, 130.4, 132.4, 133.7, 135.1, 136.1, 154.1, 158.9, 162.8. Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.5; N, 12.5. Found: C, 68.9; H, 3.3; N, 12.1.

***2,3,4,5-Tetrahydrohyropyrido [1,2-a] [1,3] diazepine-2,5-dione (2).*** It was obtained from succinic acid (5.90 g, 0.01 mole) and 2-aminopyridine (4.70 g, 0.01 mole); m.p. 102–104°C; yield 72%; IR (KBr) ν/cm$^{-1}$: 1305–1320 (C—N), 1594 (C=N), 1685–1710 (C=O); MS: m/z = 176 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 2.35–2.43 (m, 4H, 2×$CH_2$), 7.2–7.6 (m, 4H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δppm) = 25.7, 31.2, 110.4, 115.5, 120.3, 124.5, 162.9, 165. 8, 180.7. Anal. Calcd for $C_9H_8N_2O_2$. C, 61.3; H, 4.5; N, 15.9. Found: C, 58.2; H, 4.4; N, 15.4.

***3,4-Dihydro-2H-pyrido [1,2-a] pyrimidine-2,4-dione (3).*** Crystallized from DMF, m.p. 301–303°C, (literature m.p. 296–298°C [32]; 295–298°C [33]; 305–308°C [34]).The observed analytical and spectral data were found in complete conformity with the literature values.

**General procedure for the synthesis of 4.** Dissolved (0.01 mole) of substituted *o*-aminobenzaldehyde in 40 mL of hot rectified spirit and added to it a solution of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione (0.01 mole) **3** in 25 mL of rectified spirit and 0.02 mole of fused anhydrous sodium acetate. Swirled to mix and set aside for 5–6 h and finally refluxed the mixture for an hour. Distilled off the ethanol and added 100 mL of $H_2O$. Filtered, washed, the crystalline product with water twice and with a little cold ethanol and crystallized from about 100 mL of hot rectified spirit to obtain the pure and dry product 4.

***12H-Pyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4a).*** Crystallized from butanone, m.p. 272–273°C. The observed and literature [35] analytical and spectral data were in complete agreement with each other, thus conforming the structure of the synthesized compound.

***12H-2,3-Dimethoxypyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4b).*** It was obtained from 6-aminoveratraldehyde (1.81 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 246–248°C; yield 67%; IR (KBr) ν/cm$^{-1}$: 1320–1330 (C—N), 1590 (C=N), 1692 (C=O); MS: m/z = 307 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 7.10–7.90 (m, 7H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 56.0, 56.3, 110.1, 120.3, 121.4, 122.7, 123.6, 128.9, 130.1, 140.2, 145.7, 158.2, 159.4, 164.3, 165.6, 169.8, 189.0. Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.2; N, 13.6. Found: C, 66.41; H, 4.0; N, 13.8.

***12H-[1,3]Dioxolo[4,5-g]pyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4c).*** It was obtained from 6-aminopiperonal (1.65 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 190–192°C; yield 64%; IR (KBr) ν/cm$^{-1}$: 1305–1320 (C—N), 1620 (C=N), 1690 (C=O); MS: m/z = 291 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 6.10 (s, 2H, $CH_2O_2$), 7.20–7.92 (m, 7H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$) : δ (ppm) = 90.5, 108.0, 108.3, 110.1, 114.6, 120.2, 124.1, 124.8, 136.6, 137.1, 140.2, 151.2, 155.3, 162.3, 163.5, 165.4. Anal. Calcd. for $C_{16}H_9N_3O_3$: C, 65.97; H, 3.0; N, 14.4. Found: C, 64.12; H, 2.9; N, 14.7.

***12H-3,4-Dimethoxypyrido[1′,2′:1,2]pyrimido[4,5-b]quinolin-12-one (4d).*** It was obtained from 2-aminoveratraldehyde (1.81 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 242–244°C; yield 68%; IR (KBr) ν/cm$^{-1}$: 1320–1330 (C—N), 1590 (C=N), 1692 (C=O); MS: m/z = 307 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.71(s, 3H, $OCH_3$), 3.75 (S, 3H, $OCH_3$), 6.92–7.90 (m, 7H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 54.2, 54.3, 105.8, 110.5, 118.8, 120.2, 121.3, 122.5, 125.7, 130.8, 132.3, 135.6, 137.8, 140.5, 145.3, 162.5, 165.2. Anal. Calcd. for $C_{17}H_{13}N_3O_3$ : C, 66.44; H, 4.2; N, 13.6. Found: C, 66.38; H, 4.16; N, 13.42.

**General procedure for the synthesis of 6–9.** Dissolved (0.01/0.02 mole) of appropriate aldehyde or ketone in 40 mL of hot rectified spirit, added a solution of 3,4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione (0.01 mole) 3 in 25 mL of rectified spirit and added (0.02/0.04 mole) of anhydrous potassium carbonate. Swirled to mix and set aside for 5–6 h. The reaction mixture was finally refluxed for 3 h. Distilled off the ethanol and added 100 mL of $H_2O$. Filtered, washed the crystalline product first with water, and finally with a little cold ethanol and recrystallized from about 100 mL of hot rectified spirit to obtain the product **6–9**.

***3,11-Dihydro-2H-11-oxopyrido[2,1-b]quinazoline-4-carbaldehyde (6a).*** It was obtained from glutaraldehyde (1.00 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 80–82°C; yield 62%; IR (KBr) ν/cm$^{-1}$: 1305–1320 (C—N), 1610 (C=N), 1695 (C=O); MS: m/z = 226 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.7–1.85 (brs, 4H, 2×$CH_2$), 5.7 (s, 1H, CH-1), 6.87–7.90 (m, 4H, ArHs), 9.96 (s, 1H, CHO); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 22.3, 25.5, 110.8, 114.7, 120.3, 135.0, 135.2, 136.8, 138.9, 156.9, 160.2, 163.4, 189.3. Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.04; H, 4.42; N, 12.38. Found: C, 68.05; H, 4.37; N, 12.42.

***4-Aceto-3,11-dihydro-2H-1-methyl pyrido [2,1-b]quinazolin-11-one (6b).*** It was obtained from heptane-2,6-dione (1.28 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 88–90°C; yield 66%; IR (KBr) ν/cm$^{-1}$: 1305–1320 (C—N), 1615 (C=N), 1690 (C=O); MS: m/z = 254 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.78–2.02 (brs, 4H, 2×$CH_2$), 2.15 (s, 3H, $CH_3$), 2.43 (s, 3H, $COCH_3$), 6.92–7.23 (m, 4H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.6, 20.7, 21.8, 31.7, 112.1, 115.6, 126.3, 128.2, 134.3, 136.1, 144.5, 147.1, 160.2,

162.4, 194.5. Anal Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.56; H, 5.51; N, 11.02. Found: C, 70.42; H, 5.42; N, 11.0.

***1,5-Bis(2,4-dioxo-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-3-ylidene)pentane (7a).*** It was obtained from gluteraldehyde (2.00 g, 0.02 mole) and **3** (1.62 g, 0.01 mole); m.p. 74–76°C; yield 72%; IR (KBr) ν/cm$^{-1}$: 1310–1320 (C—N), 1615 (C=N), 1700 (C=O); MS: m/z = 388 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.52–2.20 (m, 6H, 3×$CH_2$), 5.2 (t, 2H, methine protons), 6.92–7.25 (m, 8H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.2, 15.8, 24.3, 24.5, 26.2, 110.5, 110.0, 114.0, 114.8, 122.3, 122.5, 135.5, 138.8, 155.3, 155.7, 158.2,159.3, 160.2, 162.3, 180.5, 180.8. Anal. Calcd. for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.12; N, 14.43. Found: C, 63.10; H, 4.11; N, 14.01.

***1,5-Dimethyl-1,5-bis(2,4-dioxo-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-3-ylidene) pentane (7b).*** It was obtained from heptane-2,6-dione (2.56 g, 0.02 mole) and **3** (1.62 g, 0.01 mole); m.p. 80–82°C; yield 70%; IR (KBr) ν/cm$^{-1}$: 1300–1320 (C—N), 1620 (C=N), 1705 (C=O); MS: m/z = 416 ($M^+$);$^1$H NMR(200 MHz, $CDCl_3$): δ(ppm) = 1.40–2.32 (m, 6H, 3×$CH_2$), 2.32 (s, 6H, 2×$CH_3$), 6.68–7.20 (m, 8H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 14.2, 14.4, 22.2, 30.4, 30.6, 110.8, 114.8, 115.2, 120.3, 120.8, 131.3, 131.6, 133.2, 133.8, 160.2, 160.4, 164.0,164.5, 165.2, 166.2, 180.5, 180.9. Anal. Calcd. for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.80; N, 13.46. Found: C, 65.84; H, 4.78; N, 13.10.

***6-Aceto-12H-11-methylbenzo [g] pyrido [2,1-b] quinazolin-12-one (8).*** It was obtained from *o*-acetophenylpropan-2-one (1.76 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 85–87°C; yield 64%; IR (KBr) ν/cm$^{-1}$: 1300–1315 (C—N), 1620 (C=N), 1705 (C=O); MS: m/z = 302 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.80–2.05 (m, 4H, 2 × $CH_2$), 2.22 (s, 3H, $CH_3$), 2.50 (s, 3H, $COCH_3$), 5.73 (t, 1H, methine proton), 5.78 (t, 1H, methine proton), 7.42–7.84 (m, 4H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 13.1, 22.1, 110.2, 114.4, 120.6, 122.8, 124.6, 124.9, 125.5, 125.8, 126.5, 128.8, 130.3, 136.7, 140.1, 144.7, 160.4, 161.5, 186.5. Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.49; H, 4.63; N, 9.27. Found: C, 75.31; H, 4.62; N, 9.19.

***3-(1-o-Acetobenzylethylidene)-3,4-dihydro-2H-pyrido[1,2-a] pyrimidine-2,4-dione (9).*** It was obtained from *o*-acetophenylpropan-2-one (1.76 g, 0.01 mole) and **3** (1.62 g, 0.01 mole); m.p. 84–86°C; yield 78%; IR (KBr) ν/cm$^{-1}$: 1300–1338 (C—N), 1585 (C=N), 1680–1710 (C=O); MS: m/z = 320 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.70 (s, 3H, $CH_3$), 2.35 (s, 3H, $COCH_3$), 2.8–3.0 (brs, 2H, $CH_2$), 6.94–7.28 (m, 7H, ArHs), 8.1 (d, 1H, H-5); $^{13}$C NMR (50 MHz, $CDCl_3$): (ppm) = 13.5, 111.1, 115.7, 125.6, 125.8, 126.4, 126.5, 126.8, 129.5, 129.8, 130.1, 130.5, 136.8, 142.1, 147.7, 150.1, 184.4, 190.5, 196.5. Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.25; H, 5.0; N, 8.75. Found: C, 71.18; H, 4.8; N, 8.71.

**Procedure for the synthesis of 10.** Dissolved 9 (0.01 mole) in 40 mL of hot rectified spirit, added 20 mL 10% ethanolic KOH and refluxed for about 3 h and distilled off the ethanol. The reaction mixture was cooled, acidified with very dilute HCl to the pH 5–6 and set aside for 5–6 h. Colorless crystalline compound was formed, filtered, washed the crystalline product first with water twice and finally with a little cold ethanol and recrystallized from about 100 mL of hot rectified spirit to obtain the product **10**. It was characterized as follows:

***12,14-Dihydro-7H-13-methylbenzo [5,6] [8] annuleno [1,2-d] pyrido [1,2-a] pyrimidine-7,14-dione.*** m.p. 78–80°C; yield 20%; IR (KBr) ν/cm$^{-1}$: 1300–1310 (C—N), 1625 (Cdsbond]N), 1700 (C=O); MS: m/z = 302 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 2.22 (s, 3H, $CH_3$), 2.6–2.8 (brs, 2H, $CH_2$), 6.90–7.25 (m, 8H, ArHs), 7.95 (d, 1H, CH-1); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 15.2, 30.8, 111.5, 119.5, 120.3, 126.7, 126.8, 128.2, 129.2, 132.2, 136.8, 137.4, 138.8, 140.2, 151.6, 156.5, 169.5, 175.5. Anal. Calcd. for $C_{19}H_{14}N_2O_2$ : C, 75.49; H, 4.63; N, 9.27. Found: C, 75.38; H, 4.50; N, 9.25.

**General procedure for the synthesis of 11–12.** Dissolved appropriate 2-aminobenzaldehyde in 40 mL of hot rectified spirit, added a solution of 2,3,4,5-tetrahydropyrido [1,2-*a*] [1,3] diazepine-2,5-dione (0.01 mole) **2** in 25 mL of rectified spirit, and added 0.02 mole of fused sodium acetate. Swirled to mix and set aside for 5–6 h. The reaction mixture was finally refluxed for 3 h. Distilled off the ethanol and added 100 mL of $H_2O$. Filtered, washed the crystalline product first with water thrice and finally with a little cold ethanol, and recrystallized from about 100 mL of hot rectified spirit to obtain the product **11–12**.

***2,3,14,15-Tetramethoxypyrido [1′,2′:1,2] quino [3″,2″:6,7] [1,3] diazepino [4,5-b] quinoline (11a).*** It was obtained from 4,5-dimethoxy-2-aminobenzaldehyde (6-amino veratraldehyde) (3.62 g, 0.02 mole) and **2** (1.76 g, 0.01 mole); m.p. 230–232°C; yield 52%; IR (KBr) ν/cm$^{-1}$: 1300–1325 (C—N), 1605 (C=N), 1695 (C=O); MS: m/z = 466 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.72–3.82 (overlappedpeaks, 12H, 4×$OCH_3$), 6.92–7.25 (m, 10H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 55.2, 55.8, 56.2, 56.3, 103.5, 104.8, 105.5, 106.7, 106.8, 107.5, 110.5, 121.5, 121.8, 123.5, 123.9, 124.0, 130.8, 132.4, 132.7, 136.5, 144.2, 142.3, 145.4, 150.0, 152.2, 160.2, 164.8. Anal. Calcd. for $C_{27}H_{22}N_4O_4$ : C, 69.52; H, 4.72; N, 12.01. Found: C, 69.41; H, 4.71; N, 12.0.

***2,3;14,15-Bismethylenedioxypyrido[1′,2′:1,2]quino[3″,2″:6,7][1,3]diazepino [4,5-b] quinoline (11b).*** It was obtained from 4,5-methylenedioxy-2-aminobenzaldehyde(6-aminopiperonal) (3.30 g, 0.02 mole) and **2** (1.76 g, 0.01 mole); m.p. 238–240°C; yield 50%; IR (KBr) ν/cm$^{-1}$: 1305–1315 (C—N), 1625 (Cdsbond]N), 1690 (C=O); MS: m/z = 434 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.95 (s, 2H, $CH_2O_2$), 6.05 (s, 2H, $CH_2O_2$), 6.90–7.25 (m, 10H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 90.2, 91.3, 102.1, 105.2, 106.9, 107.4, 108.2, 110.2, 122.1, 123.5, 123.8, 124.2, 130.1, 132.5, 135.4, 135.8, 136.5, 142.2, 145.2, 148.2, 152.5, 153.8, 155.2, 165.4, 166.2. Anal. Calcd. for $C_{25}H_{14}N_4O_4$ : C, 69.12; H, 3.22; N, 12.90. Found: C, 69.10; H, 3.20; N, 12.88 .

***2,3-Dimethoxypyrido [1′,2′:1,2] [1:3] diazepino [4,5-b] quinolin-12(13H)-one (12a).*** It was obtained from 4,5-dimethoxy-2-aminobenzaldehyde (6-amino veratraldehyde) (1.81 g, 0.01 mole) and **2** (1.76 g, 0.01 mole); m.p. 151–153°C; yield 56%; IR (KBr) ν/cm$^{-1}$: 1300–1325 (C—N), 1600 (C=N), 1690 (C=O); MS: m/z = 309 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.65–2.85 (brs, 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 6.9–7.28 (m, 7H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 34.3, 56.3, 56.5, 106.3, 108.0, 111.1, 116.1, 121.9, 124.3, 134.2, 137.4, 144.1, 150.8, 152.8, 164.4, 167.7, 170.8. Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.85; N, 13.59. Found: C, 65.09 ; H, 4.83; N, 13.51.

***[1,3]Dioxolo[4,5-g]pyrido [1′,2′:1,2] [1:3] diazepino [4,5-b] quinolin-12(13H)-one (12b).*** It was obtained from 4,5-methylenedioxy-2-aminobenzaldehyde (6-aminopiperonal) (1.65 g, 0.01 mole) and **2** (1.76 g, 1 mole); m.p. 140–142°C; yield 62%; IR (KBr) ν/cm$^{-1}$: 1305–1315 (C—N), 1625 (C=N), 1692 (C=O); MS: m/z = 293 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.68–2.83 (brs, 2H, $CH_2$), 5.9 (s, 2H, $CH_2O_2$), 6.80–7.25 (m, 7H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 34.5, 91.2, 106.3, 108.2, 110.3, 114.3, 120.8, 123.0, 124.2, 132.3, 134.2, 140.1, 150.2, 152.4, 160.2, 168.8, 170.2. Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.75; N, 14.33. Found: C, 65.48; H, 3.70; N, 14.01.

**General procedure for the synthesis of 1, 13, and 14.** Dissolved (0.01 mole) of **2** in 40 mL of hot rectified spirit, added to it a solution of malealdehyde or succinaldehyde or *o*-phthaldehyde (0.01 mole) in 25 mL of rectified spirit, and added 0.02 moles of $(NH_4)_2CO_3$, a few drops of dilute $NH_3$ and two drops of piperidene. Swirled to mix and set aside for 5–6 h. The reaction mixture was finally refluxed for 3 h, distilled off the ethanol, and added dilute HCl till a pH between 5 and 6 of the reaction was achieved. Filtered, washed the crystalline product first with water twice and finally with a little cold ethanol and recrystallized from about 100 mL of hot rectified spirit to obtain the product **1**, **13**, and **14**.

***6H,11H-Pyrido[1,2-b][2,4]benzodiazepine-6,11-dione (1)*** M.p. 152–154°C; yield 76% and superimposable IR with that of authentic sample obtained through (Scheme 1).

***6,8,9,11-Tetrahydropyrido[1,2-b][2,4]benzodiazepine-6,11-dione (13).*** It was obtained from succinaldehyde (0.86 g, 0.01 mole) and 2 (1.76 g, 0.01 mole); m.p. 140–142°C; yield 75%; IR (KBr) ν/cm$^{-1}$: 1310–1315 (C—N), 1610–1625 (C=C), 1625 (C=N), 1680–1715 (C=O); MS: m/z = 226 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 1.90–2.10 (m, 4H, 2×$CH_2$), 6.85–7.85 (m, 6H, ArHs and two methine protons); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 25.6, 26.8, 110.8, 114.8, 124.2, 135.2, 135.7, 137.2, 140.8, 146.2, 160.2, 162.4, 180.2. Anal.Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.86; N, 12.38. Found: C, 69.06; H, 4.85; N, 12.33.

***6H,13H-Pyrido[1,2-a]naphtho[2,3-e][1,3]diazepine-6,13-dione (14).*** It was obtained from *o*-phthaldehyde (1.34 g, 0.01 mole) and **2** (1.76 g, 0.01 mole); m.p. 234–236°C; yield 55%; IR (KBr) ν/cm$^{-1}$: 1305–1315 (C—N), 1605 (C=N), 1685 (C=O); MS: m/z = 274 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 7.20–8.40 (m, 10H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 110.2, 115.4, 124.3, 128.6, 128.8, 129.0, 129.6, 130.1, 130.2, 132.1, 132.5, 134.0, 134.4, 137.1, 164.2, 164.6, 180.2. Anal. Calcd. for $C_{17}H_{10}N_2O_2$ : C, 74.45; H, 3.64; N, 10.21. Found; C, 74.40; H, 3.63; N, 10.18.

**General procedure for the synthesis of 15a–15d.** A mixture of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione (3.24 g, 20 mmol) **3** and the aromatic aldehyde (10 mmol ) in ethylene glycol (30 mL) in presence of ammonium acetate (20 mmol) was heated at 140°C for about 4–5 h and then cooled to room temperature. The reaction mixture was poured into 300 mL water. The solid was filtered and then washed with water twice to remove excess of ammonium acetate. The crude solid was crystallized from 80–85% EtOH.

***6,13,14,15-Tetrahydro-14-(4-methoxyphenyl)dipyrido[1,2-a:1′, 2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (15a).*** It was obtained from **3** (1.62 g, 10 mmole) and *p*-anisaldehyde (0.60 mL, 5 mmol); m.p. 244–246°C; yield 76%; IR (KBr) ν/cm$^{-1}$: 1320–1330 (C—N), 1590 (C=N), 1670 (C=O), 3280 (NH); MS: m/z = 423 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.71 (s, 3H, $OCH_3$), 5.18 (s, 1H,6-CH), 6.92–7.23 (m, 12H, ArHs), 9.26 (s, 1H, NH); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.4, 50.8, 54.3, 56.2, 62.4, 108.4, 110.5, 114.2, 114.3, 115.2, 115.7, 124.2, 124.3, 128.3, 128.5, 130.1, 135.5, 136.5, 152.4, 128.8, 162.5, 165.0, 166.2, 168.5. Anal. Calcd. for $C_{24}H_{17}N_5O_3$: C, 68.08; H, 4.01; N, 16.54. Found: C, 67.10; H, 4.0; N, 16.10.

***6,13,14,15-Tetrahydro-14-(4-methylphenyl)dipyrido[1,2-a:1′, 2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (15b).*** It was obtained from **3** (1.62 g, 10 mmole) and *p*-tolualdehyde (0.58 ml, 5 mmol); m.p. 238–240°C; yield 77%; IR (KBr) ν/cm$^{-1}$: 1305–1315 (C—N), 1662 (C=N), 1670 (C=O), 3240 (NH); MS: m/z = 407 ($M^+$); $^1$H NMR (200 MHz,$CDCl_3$): δ (ppm) = 2.30 (s, 3H, $CH_3$), 5.20 (s, 1H, 6-CH), 6.90–7.20 (m, 12H, ArHs), 9.01 (s, 1H, NH); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 20.2, 24.3, 50.2, 64.3, 106.8, 110.2, 111.0, 115.2, 115.8, 124.1, 124.3, 128.2, 128.4, 129.5, 129.7, 135.0, 135.5, 137.2, 137.8, 150.8, 160.2, 160.4, 162.5, 168.8. Anal. Calcd. for $C_{24}H_{17}N_5O_2$: C, 70.76; H, 4.17; N, 17.19. Found: C, 69.58; H, 4.09 ; N, 17.12.

***6,13,14,15-Tetrahydro-14-(3,4-dimethoxyphenyl)dipyrido[1, 2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (15c).*** It was obtained from 3 (1.62 g, 10 mmole) and veratraldehyde (0.83 g, 5 mmol); m.p.244–246°C; yield 83%; IR (KBr) ν/cm$^{-1}$:1320–1330 (C—N), 1590 (C=N), 1670 (C=O), 3410 (NH); MS: m/z = 453 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.90 (s, 1H, 6-CH), 6.9–7.21 (m, 11H, ArHs), 9.56 (s, 1H, NH); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.3, 50.8, 56.2, 56.5, 64.2, 108.1, 110.1, 111.3, 114.8, 115.3, 116.8, 120.1, 122.3, 122.5, 132.1, 135.6, 142.8, 147.5, 150.2, 155.8, 160.5, 162.4, 164.0, 164.2, 170.2. Anal. Calcd. for $C_{25}H_{19}N_5O_4$: C, 66.22; H, 4.19; N, 15.45. Found: C, 65.90; H, 4.17; N, 15.12.

***6,13,14,15-Tetrahydro-14-[1,3]benzodioxol-5yldipyrido[1,2-a:1′,2′-a′] pyrido[2″,3″-d:6″,5″-d′] dipyrimidine-13,15-dione (15d).*** It was obtained from **3** (1.62 g, 10 mmole) and piperonal (0.75 mL, 5 mmol); m.p. 238–240°C; yield 75%; IR (KBr) ν/cm$^{-1}$: 1315–1325 (C—N), 1615 (C=N), 1670 (C=O), 3410 (NH); MS: m/z = 437 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.89 (s, 1H, 6-CH), 6.10 (s, 2H, $CH_2O_2$), 6.90–7.25 (m, 11H, ArHs), 9.28 (s, 1H, NH); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.2, 50.8, 56.4, 64.2, 90.2, 107.2, 110.1, 111.3, 114.7, 115.1, 116.2, 116.8, 120.2, 122.3, 122.5, 132.1, 135.5, 140.2, 147.2, 152.2, 160.2, 160.5, 163.5, 168.8. Anal. Calcd. for $C_{24}H_{15}N_5O_4$: C, 65.90; H, 3.43; N, 16.01. Found: C, 64.70; H, 3.41; N, 15.85.

**General procedure for the synthesis of 16a–16d.** A mixture of 3, 4-dihydro-2*H*-pyrido [1,2-*a*] pyrimidine-2,4-dione (3.24 g, 20 mmol) 3 and the aromatic aldehyde (10 mmol) in ethylene glycol (30 mL) in presence of $P_2O_5$ (20 mmol) was heated at 140°C for about 4–5 h and then cooled to room temperature. The reaction mixture was poured into 300 mL water cautiously and slowly. The solid formed was filtered and, then washed with water twice to remove excess of adhered materials. The crude solid was recrystallized from 80–85% EtOH.

***14,15-Dihydro-13H-14-(4-methoxyphenyl)dipyrido[1,2-a:1′, 2′-a′] pyrano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (16a).*** It was obtained from 3 (1.62 g, 10 mmole) and anisaldehyde

(0.60 mL, 5 mmol); m.p. 270–272°C; yield 69%; IR (KBr) ν/cm$^{-1}$: 1315–1330 (C—N), 1595 (C=N), 1675 (C=O); MS: m/z = 424 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.70 (s, 3H, $OCH_3$), 4.63 (s, 1H, 6-CH), 6.92–7.32 (m, 12H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 23.7, 54.1, 56.7, 77.7, 90.5, 110.5, 111.1, 114.3, 114.7, 115.2, 115.5, 124.1, 124.2, 128.3, 128.5, 134.7, 135.1, 136.1, 136.4, 160.2, 162.1, 163.4, 164.2, 168.3. Anal. Calcd. for $C_{24}H_{16}N_4O_4$: C, 67.92; H, 3.77; N, 13.20. Found: C, 67.96; H, 3.76; N, 13.17.

***14,15-Dihydro-13H-14-(4-methylphenyl)dipyrido[1,2-a:1′,2′-a′]pyrano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (16b).*** It was obtained from **3** (1.62 g, 10 mmole) and *p*-tolualdehyde (0.58 mL, 5 mmol); m.p. 264–266°C; yield 66%; IR (KBr) ν/cm$^{-1}$: 1300–1310 (C—N), 1598 (C=N), 1675 (C=O); MS: m/z = 408 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.30 (s, 3H, $CH_3$), 4.93 (s, 1H, 6-CH), 6.72–7.41 (m, 12H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 20.2, 23.3, 50.5, 77.2, 90.2, 110.2, 111.0, 114.5, 114.9, 124.2, 124.7, 128.1, 128.5, 129.5, 129.5, 134.8, 135.2, 136.2, 136.5, 160.1, 162.2, 163.5, 164.0, 168.2. Anal. Calcd. for $C_{24}H_{16}N_4O_3$: C, 70.58; H, 3.92; N, 13.72. Found: C, 70.55; H, 3.91; N, 13.78.

***14,15-Dihydro-13H-14-(3,4-dimethoxyphenyl)dipyrido[1,2-a:1′,2′-a′] pyrano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (16c).*** It was obtained from **3** (1.62 g, 10 mmol) and veratraldehyde (0.83 g, 5 mmol); m.p. 280–282°C; yield 70%; IR (KBr) ν/cm$^{-1}$: 1320–1330 (C—N), 1620 (C=N), 1675 (C=O); MS: m/z = 454($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm) = 3.72 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.70 (s, 1H, 6-CH), 6.90-7.25 (m, 11H,ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 27.1, 52.0, 52.3, 55.4, 74.6, 94.6, 95.2, 98.9, 110.1, 110.4, 115.8, 115.9, 120.8, 122.3, 122.8, 136.5, 137.1, 154.1, 157.1, 159.1, 160.5, 163.1, 164.0, 164.2, 175.6. Anal. Calcd. for $C_{25}H_{18}N_4O_5$: C, 66.12; H, 4.21; N, 11.00. Found: C, 65.22; H, 4.19; N, 10.6.

***14,15-Dihydro-13H-14-dipyrido[1,2-a:1′,2′-a′]pyrano[2″,3″-d:6″,5″-d′] dipyrimidine-13,15-dione (16d).*** It was obtained from **3** (1.62 g, 10 mmol) and piperonal (0.75 mL, 5 mmol); m.p. 245–247°C; yield 64%; IR (KBr) ν/cm$^{-1}$: 1310–1320 (C—N), 1620 (C=N), 1675 (C=0); MS: m/z = 438 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ(ppm)= 5.52 (s, 1H, 6-CH), 5.98 (s, 2H, $CH_2O_2$), 7.01–7.80 (m, 11H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 22.4, 50.5, 77.2, 90.3, 95.5, 110.1, 110.3, 114.8, 115.1, 115.5, 115.8, 120.8, 124.1, 124.3, 130.2, 135.5, 135.7, 142.5, 144.3, 160.5, 160.8, 164.2, 165.2, 170.0. Anal. Calcd.for $C_{24}H_{14}N_4O_5$: C, 65.75; H, 3.19; N, 12.78. Found: C, 65.12; H, 3.18; N, 12.52.

**General procedure for the synthesis of 17a–17d.** A mixture of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione(3.24 g, 20 mmol) **3** and the aromatic aldehyde (10 mmol ) in ethylene glycol (30 mL) in presence of $P_2S_5$ (20 mmol) was heated at 140°C for about 4–5 h and then cooled to room temperature. The reaction mixture was poured into 300 mL of water. The solid was filtered and then washed with water twice to remove excess of $P_2S_5$. The crude solid was crystallized from 80–85% EtOH.

***14,15-Dihydro-13H-14-(4-methoxyphenyl)dipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17a).*** It was obtained from **3** (1.62 g, 10 mmol) and *p*-anisaldehyde (0.60 mL, 5 mmol); m.p. 240–242°C; yield 62%; IR (KBr) ν/cm$^{-1}$: 1168 (C—S), 1320–1330 (C—N), 1590 (C=N), 1678 (C=O); MS: m/z = 408 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.72 (s, 3H, $OCH_3$), 4.64 (s, 1H, 6-CH), 7.01–7.20 (m, 12H, ArHs); $^{13}$C–NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.5, 52.1, 54.3, 56.2, 110.5, 110.8, 114.1, 114.5, 115.5, 115.8, 118.2, 124.1, 124.3, 128.2, 128.5, 130.2, 135.5, 135.7, 154.0, 158.2, 160.0, 160.2, 162.1, 168.5. Anal. Calcd. for $C_{24}H_{16}N_4O_3S$: C, 70.58; H, 3.92; N, 13.72; S, 7.84. Found: C, 70.55; H, 3.91; N, 13.6; S, 7.67.

***14,15-Dihydro-13H-14-(4-methylphenyl)dipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17b).*** It was obtained from 3 (1.62 g, 10 mmol) and *p*-tolualdehyde (0.58 mL, 5 mmol); m.p. 252–254°C; yield 66%; IR (KBr) ν/cm$^{-1}$: 1185 (C—S), 1305–1315 (C—N), 1630 (C=N), 1678 (C=O); MS: m/z = 424 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3H, $CH_3$), 5.50 (s, 1H, 6-CH), 6.90–7.30 (m, 12H, ArHs); $^{13}$C NMR (50 MHZ, $CDCl_3$): δ (ppm) = 20.2, 25.3, 52.0, 54.1, 111.0, 111.2, 114.3, 114.5, 115.1, 115.3, 118.3, 124.3, 124.5, 128.1, 128.3, 130.1, 135.3, 135.5, 154.2, 158.1, 160.1, 160.3, 162.3, 169.3. Anal. Calcd. for $C_{24}H_{16}N_4O_2S$: C, 67.92; H, 3.77; N, 13.20; S, 7.54. Found: C, 66.81; H, 3.76; N, 12.80; S, 7.16

***14,15-Dihydro-13H-14-(3,4-dimethoxyphenyl)dipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17c).*** It was obtained from **3** (1.62 g,10 mmol) and veratraldehyde (0.83 g, 5 mmol); m.p. 260–262°C; yield 76%; IR (KBr) ν/cm$^{-1}$: 1180 (C—S), 1320–1330 (C—N), 1595 (C=N), 1678 (C=O); MS: m/z = 470 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.72 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 4.74 (s, 1H, 6-CH), 6.70–7.20 (m, 11H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.4, 50.4, 56.1, 56.4, 64.4, 108.0, 110.0, 111.2, 114.5, 115.1, 115.5, 116.7, 120.0, 122.7, 132.0, 134.3, 135.5, 142.7,147.3, 150.2, 155.4, 160.5, 162.4, 164.0, 170.5. Anal. Calcd. for $C_{25}H_{18}N_4O_4S$: C, 63.82; H, 3.82; N, 11.90; S, 6.80. Found: C, 62.80; H, 3.81; N, 11.10; S, 5.90.

***14,15-Dihydro-13H-14-[1,3]benzodioxol-5yldipyrido[1,2-a:1′,2′-a′] thiopyarano[2″,3″-d:6″,5″-d′]dipyrimidine-13,15-dione (17d).*** It was obtained from 3 (1.62 g, 10 mmol) and piperonal (0.75 mL, 5 mmol); m.p. 250–252°C; yield 72%; IR (KBr) ν/cm$^{-1}$: 1178 (C—S), 1310–1330 (C—N), 1625 (C=N), 1678 (C=O); MS: m/z = 454 ($M^+$); $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.74 (s, 1H, 6-CH), 6.05 (s, 2H, $CH_2O_2$), 7.10–7.30 (m, 11H, ArHs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm) = 24.3, 50.7, 64.1, 90.1, 107.1, 110.2, 111.2, 115.0, 115.5, 116.1, 116.6, 120.1, 122.2, 122.4, 132.0, 135.4, 140.1, 147.3, 152.3, 160.3, 160.3, 163.4, 164.3, 170.2. Anal. Calcd. for $C_{24}H_{14}N_4O_4S$: C, 63.43; H, 3.08; N, 12.33; S, 7.04. Found: C, 62.13; H, 2.82; N, 12.12; S, 6.20.

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## REFERENCES AND NOTES

[1] Posha, M. A.; Jayashankara, V. P. Indian J Heterocycl Chem 2006, 15, 397.

[2] Fryer, R. I. In Bicyclic Diazepines in the Chemistry of Heterocyclic Compounds; Taylor, E., Ed.; Wiley: New York, 1991; Vol. 50, Chapter II.

[3] Haris, R. C.; Straley, J. M. U.S. Pat. 1,537,757; Chem Abstr 1970, 173, 100054 w.

[4] Guerreo, F. A.; Blanco, C.; Guevara, U.; Martinez, R. J.; Campo, A. E. Proc West Pharmacol Soc 1992, 35, 153.

[5] Remers, W. A.; Mabilia, M.; Hopfinger, A. J. J Med Chem 1986, 29, 2492.

[6] Pellon, P. F.; Carrasco, R.; Rodes, L. Synth Commun 1996, 26, 3869.

[7] Murugan, V.; Padmavathy, N. P.; Ramasarma, G. V. S.; Sharma, S. V.; Suresh, V. Indian J Chem 2003, 13, 143.

[8] Brown, D. J. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 148.

[9] Gupta, D. P.; Ahmad, S. A.; Shankar, K. Indian J Chem 1988, 27B, 106.

[10] Parmar, S. S.; Singh, S. P. J Heterocycl Chem 1979, 16, 448.

[11] Ram, V. J.; Srimal, R. C.; Kuschwaha, D. S.; Mishra, L. J Prakt Chem 1990, 332, 629.

[12] Srivastava, V. K.; Singh, S.; Gulati, A.; Shankar, H. Indian J Chem 1987, 26B, 652.

[13] Pandey, V. K.; Gupta, M.; Mishra, D. Indian Drugs 1996, 33, 409.

[14] Umio, S.; Kariyone, K.; Zenno, H.; Kamiya, T. Jpn. Pat. 12,670 (1970); Chem Abstr 1968, 68, 2195.

[15] Shetty, B. V. U.S. Pat. 2,549,634 (1970); Chem Abstr 1971, 75, 5940.

[16] Otto, H.; Houlohan, W. W. Swiss Pat. 499,544 (1971); Chem Abstr 1971, 75, 20435.

[17] Saksena, R. K.; Amin Khan, M. Indian J Chem 1989, 28B, 443.

[18] Mukerji, M. L.; Nautiyal, S. R.; Prasad, C. R.; Dhwan, B. N. Indian J Med Res 1980, 71, 480.

[19] Malhotra, S.; Koul, S. K.; Sharma, R. L.; Anand, K. K.; Gupta, O. P.; Dhar, K. L. Indian J Chem 1988, 27, 937.

[20] Gupta, O. P.; Sharma, M. L.; Ray Ghatak, B. J.; Atal, C. K. Indian J Med Res 1977, 66, 680.

[21] Gupta, O. P.; Sharma, M. L.; Ray Ghatak, B. J.; Atal, C. K. Indian J Med Res 1977, 66, 865.

[22] Gupta, O. P.; Wakhloo, R. L.; Sharma, M. L.; Atal, C. K. J Obstet Gynaecol India 1979, 29, 935.

[23] Atal, C. K. A Text Book of Chemistry and Pharmacology of Vasicine; Regional Research Laboratory: Jammu, 1980; pp 1–155.

[24] Holla, B. S.; Poojary, K. N.; Poojary, B.; Subramanaya, K.; Suchetha, N. Indian J Chem 2005, 44, 2114.

[25] Smith, R. L.; Barret, R. J.; Bush, E. S. J Pharmacol Exp Ther 1995, 275, 1050.

[26] (a) Awouters, F.; Vermeire, J.; Smeyers, F.; Vermote, P.; Vanbeek, R.; Niemegeers, C. J. E. Drug Dev Res 1986, 8, 95; (b) Hermeez, I.; Breining, T.; Debreczy, L. V.;Rodriguer. L. J Med Chem 1983, 26, 1494.

[27] Matsutani, S.; Mizushima, Y. Eur. Pat. Appl. 89-102635 (1989).

[28] Yanagihara, Y.; Kassai, H.; Kawashima, T.; Shida, T. Jpn J Pharmacol 1988, 48, 91.

[29] Hermeez, I.; Kokosi, J.; de Vos, C.; Rodriguez, L. J Med Chem 1987, 30, 1543.

[30] Knoll, K.; Meszaros, Z.; Szentmiklosi, P.; Furst, S. Arzneim Forsch 1971, 21, 717.

[31] (a) Roma, G.; Cinone, N.; Dibraceio, M.; Grossi, G.; Leoncini, G.; Signorello, M. G.; Carotti, A. Bio Org Med Chem 2000, 8, 751; (b) Leoncini, G.; Signorello, M. G.; Roma, G.; Di Braccio, M. Biochem Pharmacol 1997, 53, 1667.

[32] Abass, M.; Mayas, A;, S. Heteroatom Chem 2007, 18, 19.

[33] Lappin, G. R.; Petersen, Q. R.; Wheeler, C. E. J Org Chem 1950, 15, 377.

[34] Shur, M.; Israeltam, S. S. J Org Chem 1968, 33, 3015.

[35] Roma, G.; Di Braccio, M.; Babli, A.; Mazzei, M.; Ermili, A. J Heterocycl Chem 1987, 24, 329.

[36] Sharma, R. L.; Kumar, S.; Kour, D.; Singh, J. J Heterocycl Chem 2006, 43, 1177.

[37] Sachar, A.; Gupta, P.; Gupta, S.; Sharma, R. L. Indian J Chem 2009, 48B, 1187.

[38] Wooley, R. E.; Blue, J. L. J Med Microbiol 1975, 8, 189.

[39] Castillow, J. C.; Debeer, E. J. J Pharm Exp Ther 1947, 90, 104.

[40] Kobayshi, S.; Hasebawa, K.; Muri, M.; Takagi, H. Arzneim Forech Drug Res 1970, 20, 43.

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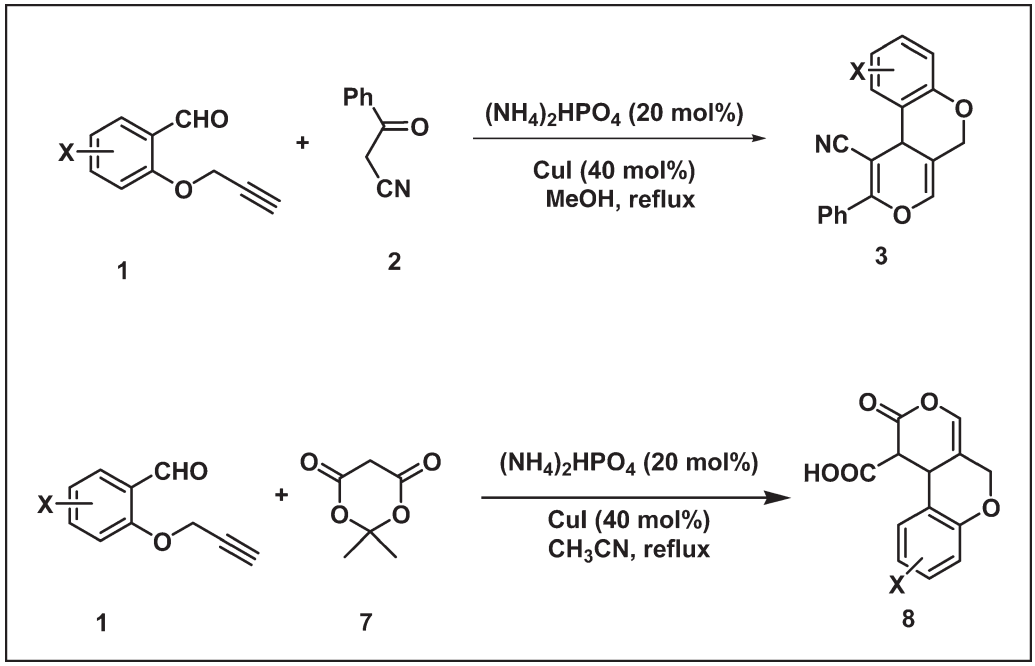


A new strategy involving domino Knoevenagel hetero-Diels-Alder reaction is described for the preparation of pyrano[3,4-*c*]chromenes scaffold. Reaction of *O*-propargylated salicylaldehyde with benzoylacetonitrile or Meldrum's acid in the presence of CuI and diammonium hydrogen phosphate affords pyrano[3,4-*c*]chromenes with good yields and high bond-forming efficiency.

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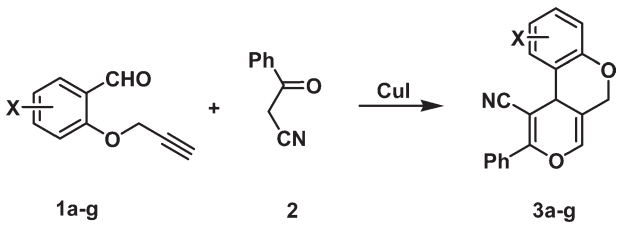
## INTRODUCTION

The hetero-Diels-Alder reaction is one of the most powerful methods for the preparation of heterocyclic compounds and it has wide applications in the synthesis of biologically active compounds and natural products [1]. Among these reactions, domino Knoevenagel hetero-Diels-Alder reactions provide efficient and rapid means for the construction of polyheterocyclic compounds [2], especially pyran moieties. 2H-pyran derivatives are present in many natural products with different biological activities [3]. A family of xanthone natural products with potent antiviral activity has been isolated from plants, and it is a potent inhibitor of human immunodeficiency virus-1 reverse transcriptase [4]. Some 2H-chromene family are effective photoaffinity reagents for the cytochrome P450 superfamily of enzymes and probably other proteins as well [5]. Because of the unique properties of pyranochromene skeletons, the developments of synthetic methods that enable facile access to these useful entities are desirable.

In most reported reactions, in domino Knoevenagel hetero-Diels-Alder reactions, alkenes were used as a dienophile. The use of alkynes was limited due to their less reactivity when compared with alkenes. The activation of alkynes toward a variety of organic transformations is an exciting field in organic synthesis. In the recent years, the most important strategy for this aim usually consists of applying transition metal catalysts [6]. The activation of alkynes using various metals has

**Scheme 1.** Synthesis of pyrano[3,4-*c*]chromene in the presence of CuI.




1a-g 2 3a-g

been extensively investigated and described in the literature [7]. Selection of the proper Lewis acid to achieve this purpose is more important. Among the metal catalysts, coinage metals including copper, silver, and gold play an essential role in this field [8]. Therefore, development of new synthetic strategy based on coinage metals is very attractive.

During the past decade, copper (Cu) (I)-catalyzed cyclization of alkynes has represented a convenient tool for the preparation of heterocycles [8]. Copper (I) iodide (CuI), which has been applied in the synthetic and medicinal chemistry, has received much attention due to several advantages over the other coinage metals; including the low cost, insensitivity to air, simple experimental procedure, and no toxicity. Therefore, discovery of novel Cu (I)-catalyzed reaction of alkynes is of great interest [9].

## RESULTS AND DISCUSSION

Following our research work to introduce domino Knoevenagel hetero-Diels-Alder reaction using unactivated alkynes with CuI [10] and to enlarge the scope of this synthetic methodology, herein, we report a domino Knoevenagel hetero-Diels-Alder reaction using *O*-propargylated salicyclaldehyde derivatives **1**(**a**–**g**) and benzoylacetonitrile **2** as unactivated terminal alkynes and an active methylene compound, respectively, in the presence of CuI (Scheme 1). The products are functionalized pyrano[3,4-*c*]chromenes **3**(**a**–**g**).

Initially, *O*-propargylated salicylaldehydes as the starting material were prepared in excellent yields using reaction of propargyl bromide and salicylaldehydes derivatives in dimethyl formamide and in the presence of $K_2CO_3$. To optimize the desired reaction conditions, the reaction of compound **1a** with benzoylacetonitrile **2** was used as the model system. The experimental results are summarized in Table 1.

Heating aldehyde **1a** and **2** in methanol under reflux condition for 72 h did not lead to the desired product. So, CuI was used as the Lewis acid. The reaction was done using different ratios of CuI in the presence of diammonium hydrogen phosphate (DAHP) or triethylamine as the base. The yields and reaction times are summarized in Table 1.

According to the obtained results, methanol was selected as the best solvent and the optimized molar ratio of CuI was 40%.

Under the optimal reaction conditions, pyrano[2,3-*c*]chromenes **3a**–**g** were prepared in 61–75% yields (Table 2). The best result was obtained using aldehyde **1d** (entry 4) that contained a nitro group. It seems that the electron-withdrawing substituent increase the yields of this transformation, as opposed to decreased yield obtained with electron-donating substituent (entry 3).

Structures of the products were confirmed by their spectroscopic data. In $^1$H NMR of compounds **3a**–**g**, the —$OCH_2$ group resonates at $\delta = 4.60$ and 4.72 ppm as a doublet with $J = 11.5$–11.8 Hz. The —CH proton appears at $\delta = 4.79$–4.93 ppm as a singlet, and the olefinic proton =CH resonates at $\delta = 7.12$–7.22 ppm as a singlet. The corresponding signal of the —$OCH_2$ and the shielded olefinic =C—CN carbons in $^{13}$C NMR appear at 65.0–66.4 and 83.8–85.7 ppm, respectively.

This reaction involves two steps: (a) the Knoevenagel condensation between benzoylacetonitrile **2** and the propargylated salicylaldehydes **1a**–**g**. DAHP acts as a mild base for Knoevenagel condensation and formation of 1-oxa-1,3-butadiene that could react as a heterodiene to form the intermediate. (b) hetero-Diels-Alder reaction of olefinic intermediate in the presence of CuI to afford compounds **3a**–**g**. Although the mechanism for this transformation is not clear, it seems that CuI could active the unactivated triple bond to act as a dienophile in hetero-Diels-Alder reaction (Scheme 2).

As a logical extension of domino Knoevenagel hetero-Diels-Alder reaction with unactivated alkynes, we became interested in the synthesis of functionalized pyranochromene derivatives, whose structures have been found in vast numbers of natural products and pharmaceuticals. Reaction of *O*-propargylated salicylaldehyde

**Table 1**

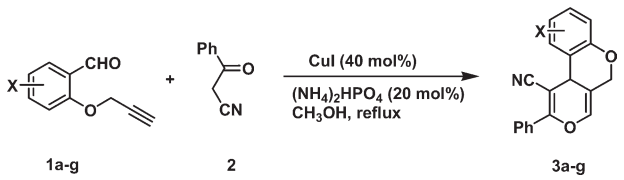
Synthesis of pyrano[3,4-*c*]chromene using domino Knoevenagel hetero-Diels-Alder reaction, the role of base type and molar ratio of CuI on the formation of product **3a**.

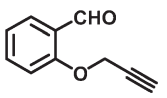
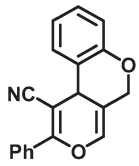
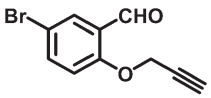
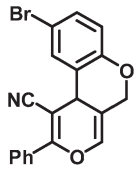
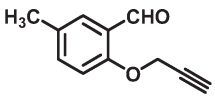
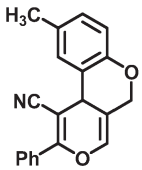
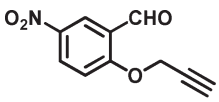
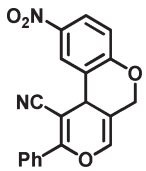
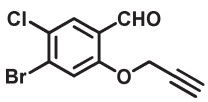
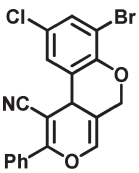
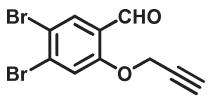
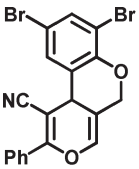
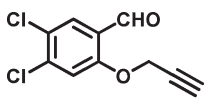
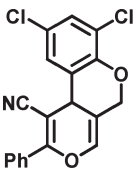
| Entry | Lewis acid | Solvent | Base | Time (h)[a] | Yield (%) |
|---|---|---|---|---|---|
| 1 | – | MeOH | $(NH_4)_2HPO_4$ | 72 | – |
| 2 | CuI (20%) | MeOH | $(NH_4)_2HPO_4$ | 72 | Trace |
| 3 | CuI (30%) | MeOH | $(NH_4)_2HPO_4$ | 48 | 40 |
| 4 | CuI (40%) | MeOH | $(NH_4)_2HPO_4$ | 48 | 61 |
| 5 | CuI (50%) | MeOH | $(NH_4)_2HPO_4$ | 48 | 57 |
| 5 | CuI (40%) | MeOH | – | 72 | – |
| 6 | CuI (40%) | MeCN | $(NH_4)_2HPO_4$ | 48 | 50 |
| 7 | CuI (40%) | MeCN | $Et_3N$ | 48 | 28 |

[a] Completion of the reaction.

**Table 2**

CuI-mediated domino hetero-Diels-Alder reaction of aldehydes **1a**–**g** with **2**[a].

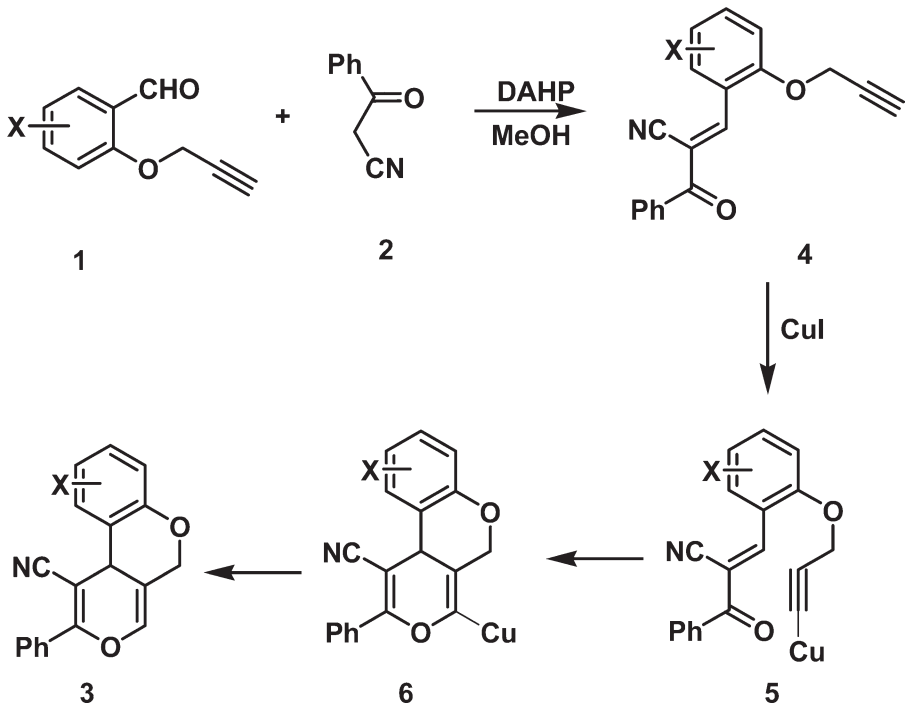



| Entry | Aldehyde | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **3a** | 48 | 61 |
| 2 |  **1b** |  **3b** | 32 | 65 |
| 3 |  **1c** |  **3c** | 24 | 61 |
| 4 |  **1d** |  **3d** | 20 | 75 |
| 5 |  **1e** |  **3e** | 12 | 70 |
| 6 |  **1f** |  **3f** | 16 | 67 |
| 7 |  **1g** |  **3g** | 12 | 67 |

[a] All of the reaction were performed with propargylated aldehydes **1a**–**g** (1 mmol), benzoylacetonitrile **2** (1.2 mmol), $(NH_4)_2HPO_4$ (20 mol %), and CuI (40 mol %) in methanol at reflux.

[b] Isolated yield.

**Scheme 2.** Plausible mechanism for the synthesis of pyrano[3,4-*c*]chromene skeleton *via* domino Knoevenagel hetero-Diels-Alder reaction using CuI.




**Scheme 3.** Synthesis of pyrano[3,4-*c*]chromenes **8** in the presence of CuI and Meldrum's acid.

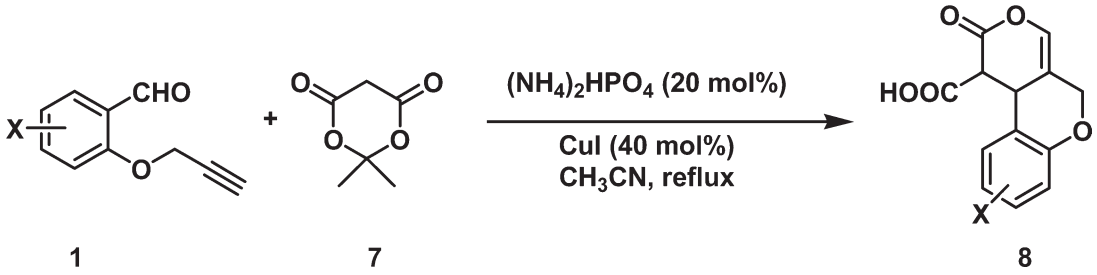
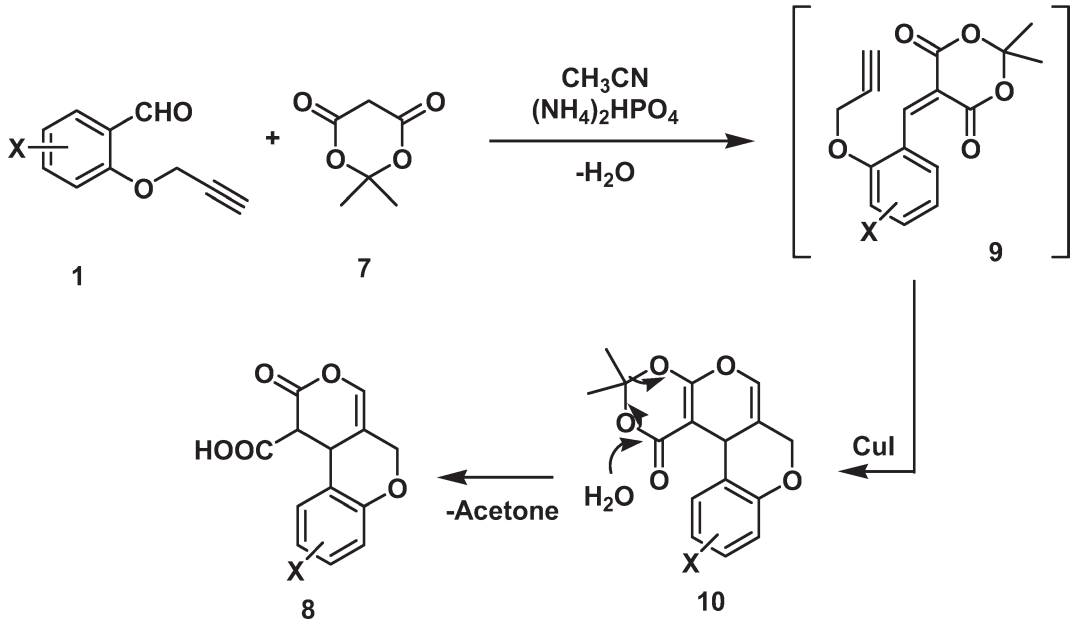



**Table 3**

Synthesis of pyrano[3,4-*c*]chromene using domino Knoevenagel hetero-Diels-Alder reaction, the role of solvent, base type, and molar ratio of CuI on the formation of product **8a**.

| Entry | Lewis acid | Solvent | Base | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | – | MeCN | $(NH_4)_2HPO_4$ | 120 | – |
| 2 | CuI (20%) | MeCN | $(NH_4)_2HPO_4$ | 120 | 40 |
| 3 | CuI (30%) | MeCN | $(NH_4)_2HPO_4$ | 72 | 45 |
| 4 | CuI (40%) | MeCN | $(NH_4)_2HPO_4$ | 72 | 68 |
| 5 | CuI (50%) | MeCN | $(NH_4)_2HPO_4$ | 72 | 60 |
| 6 | CuI (40%) | MeOH | $(NH_4)_2HPO_4$ | 80 | 50 |
| 7 | CuI (40%) | EtOH | $(NH_4)_2HPO_4$ | 96 | Trace |
| 8 | CuI (40%) | $H_2O$ | $(NH_4)_2HPO_4$ | 96 | Trace |
| 9 | CuI (40%) | MeCN | – | 72 | – |
| 13 | CuI (40%) | MeCN | $Et_3N$ | 48 | 33 |
| 14 | CuI (40%) | MeCN | $K_2CO_3$ | 72 | 38 |

**Scheme 4.** Plausible mechanism for the synthesis of pyrano[3,4-*c*]chromene skeleton *via* activation of π-triple bond using CuI.




with Meldrum's acid **7** in the presence of CuI should afford the desired pyranochromenes **8** (Scheme 3).

Reaction of *O*-propargylated salicylaldehyde **1a** with Meldrum's acid **7** was selected as a model, and the reaction was done in the presence of different ratios of CuI and also diammonium hydrogen phosphate as a base. The details were summarized in Table 3. In this reaction, the best yield was obtained using 40% CuI. The presence of CuI is necessary for the progress of reaction and without CuI, the Knoevenagel product were obtained as the sole product.

On the basis of established Meldrum's acid chemistry, it is reasonable to assume that the formation of aryliden Meldrum's acid apparently results from initial addition of Meldrum's acid with *O*-propargylated salicylaldehyde to obtain *in situ* dieneone **8** (Scheme 4). This intermediate under the reflux conditions and hetero-Diels-Alder reaction converted to pyran skeleton.

The presence of the pyran skeleton is supported by the spectroscopic data. In the $^1$H NMR of compound **8a**, the —$OCH_2$ group shows two separated doublet with $J = 12$ Hz and also a carboxylic acid peak at $\delta = 12.75$ ppm. The high $J$ value is related to the torsion angle that is 174.6°. The structure of compound **8a** was confirmed using X-ray structure data. The product **8a** could form a dimmer *via* intermolecular hydrogen bonding between two carboxylic acid groups (Figs. 1 and 2).

Under the optimal reaction conditions, the best result was obtained using aldehyde **1d** (entry 4) that contained a nitro group (Table 4). In entry 4, the desired product could be decarboxylated and the final product does not contain the carboxylic acid functional group and the product **8d** is the sole product of reaction. Existence of a catalyst such as CuI is necessary to activate the triple bond through complexation. CuI could coordinate the triple bond and the activated triple bond is ready to proceed hetero-Diels-Alder reaction to form pyrano[3,4-*c*]chromene. Reactions were done under Argon conditions to prevent the oxidation of Cu (I) to Cu (II).

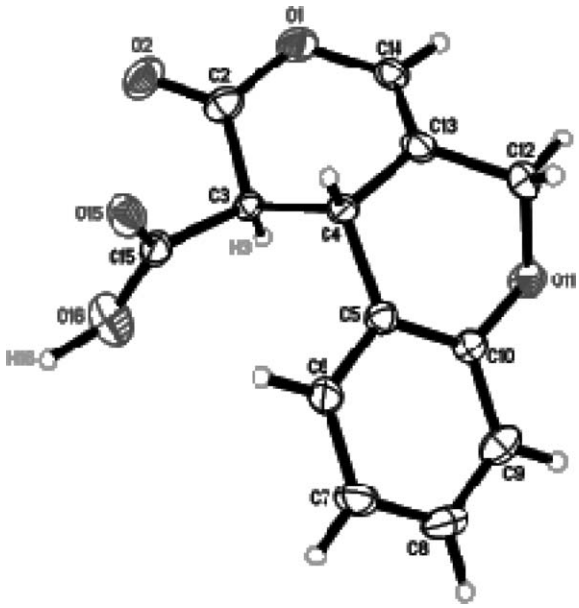



**Figure 1.** X-ray structure of compound **8a**.

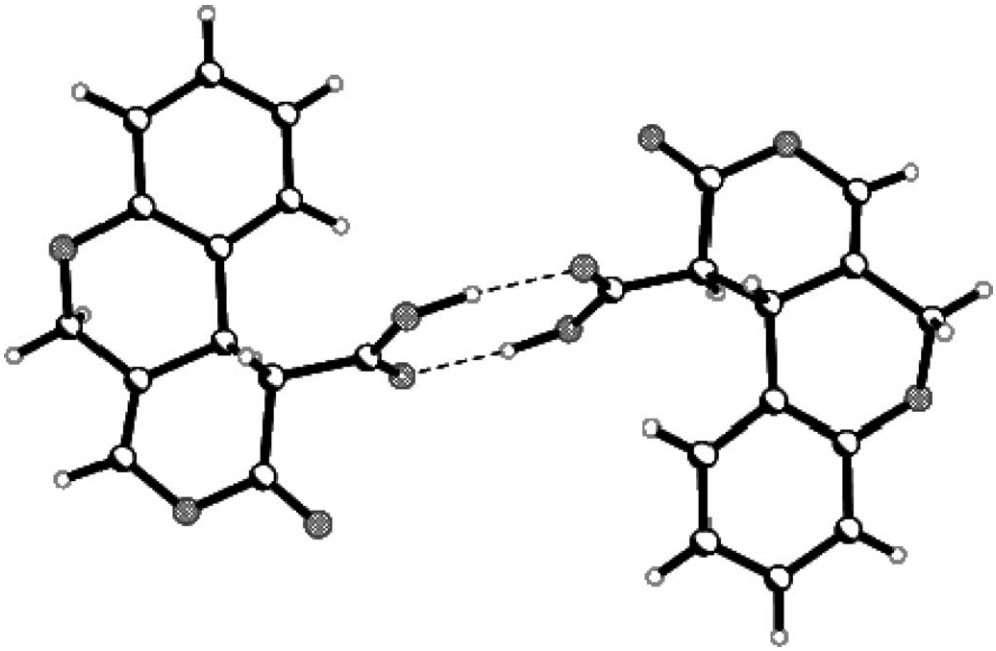


**Figure 2.** Intermolecular hydrogen bonding in compound **8a**.

## CONCLUSIONS

In conclusion, we have described an efficient approach with a high bond-forming efficiency for the synthesis of pyrano[3,4-*c*]chromene skeleton *via* domino Knoevenagel hetero-Diels-Alder reaction started from simple and inexpensive materials. Reaction of *O*-propargylated salicylaldehyde with active methylene compounds such as benzoylacetonitrile and Meldrum's acid leads to functionalized pyranochromenes. In this reaction, CuI (40%) was used as Lewis acid for the activation of unactivated alkynes and DAHP (20%) as the base. The products have nitrile and carboxylic acid functional groups that could be used for further conversion.

## EXPERIMENTAL

Commercially available materials were used without further purification. Melting points were determined with Electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FTIR (FTLA 2000) spectrometer. $^{1}$H NMR and $^{13}$C NMR were run on a Bruker DRX-300 AVANCE at 500 and 300 MHz for $^{1}$H NMR and 125 and 75 MHz for $^{13}$C NMR. $CDCl_3$ and DMSO-$d_6$ were used as solvents. High resolution mass spectra were recorded on JEOL JMS-700 (HR-EI) spectrometer and Mass spectra were obtained using a GC-MS Hewlett Packard (EI, 70 eV) instrument.

**General procedure for the synthesis of pyranochromenes 3a–g derivatives *via* hetero-Diels-Alder reactions.** A solution of *O*-propargylated salicylaldehydes **1a–g** (1 mmol), benzoylacetonitrile (174 mg, 1.2 mmol), CuI (0.4 equiv., 76 mg), and $(NH_4)_2HPO_4$ (28 mg, 0.2 equiv.) in methanol (25 mL) was refluxed. The progress of reaction was monitored by thin layer chromatography (Petroleum ether: EtOAc 3:1). After completion of the reaction, the mixture of reaction was filtered and the solvent was evaporated under reduced pressure. The obtained oil was crystalizated in diethyl ether.

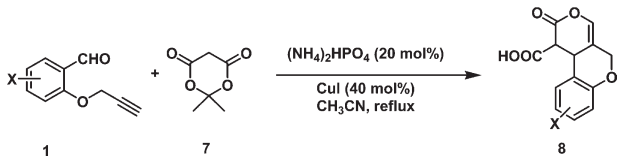
***2-Phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitri le (3a).*** This compound was obtained as a white solid; yield 61%; mp (Dec) 200.3°C; ir (potassium bromide): 2203, 1710, 1615, 1578 $cm^{-1}$; $^{1}$H NMR (500 MHz, DMSO-$d_6$): δ 4.60 (d, $J$ = 11.5 Hz, 1H, —$OCH_2$), 4.72 (d, $J$ = 11.5 Hz, 1H, —$OCH_2$), 4.79 (s, 1H, —CH), 6.85 (d, $J$ = 7.9 Hz, 1H, $H_{Ar}$), 7.01 (t, $J$ = 7.5 Hz, 1H, $H_{Ar}$), 7.15 (s, 1H, =CH), 7.22 (t, $J$ = 7.5 Hz, 1H, $H_{Ar}$), 7.53–7.61 (m, 3H, $H_{Ar}$), 7.69 (d, $J$ = 7.9 Hz, 1H, $H_{Ar}$), 7.75 ppm (d, $J$ = 7.2 Hz, 2H, $H_{Ar}$); $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 31.8, 66.0, 85.7, 110.3, 118.3, 120.7, 121.8, 125.7, 127.0, 129.0, 129.3, 129.5, 132.2, 132.3, 137.8, 155.1, 163.6 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{19}H_{13}NO_2$: 287.0946; Found: 287.0959.

***9-Bromo-2-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (3b).*** This compound was obtained as a white solid; yield 65%; mp 197–198°C; IR (potassium bromide): 2204, 1707, 1614, 1577 $cm^{-1}$; $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 4.58 (d, $J$ = 11.6 Hz, 1H, —$OCH_2$), 4.73 (d, $J$ = 11.6 Hz, 1H, —$OCH_2$), 4.80 (s, 1H, —CH), 6.81 (d, $J$ = 8.7 Hz, 1H, $H_{Ar}$), 7.16 (s, 1H, =CH), 7.36 (dd, $J$ = 8.7, 2.1 Hz, 1H, $H_{Ar}$), 7.49–7.60 (m, 3H, $H_{Ar}$), 7.74 (d, $J$ = 7.2 Hz, 2H, $H_{Ar}$), 7.80 ppm (d, $J$ = 2.1 Hz, 1H, $H_{Ar}$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 30.6, 65.3, 84.3, 108.4, 112.0, 119.7, 126.8, 128.2, 128.6, 128.8, 131.1, 131.2, 131.5, 137.4, 153.6, 163.0 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{19}H_{12}NO_2$ $^{79}$Br: 365.0052; Found: 365.0039. $[M + 2]^{+\cdot}$ Calcd. for $C_{19}H_{12}NO_2$ $^{81}$Br: 367.0031; Found: 367.0026.

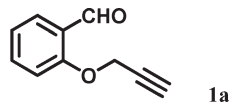
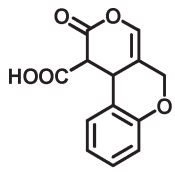
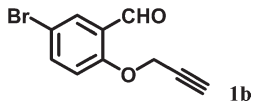
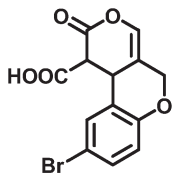
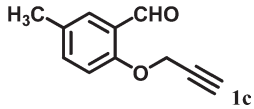
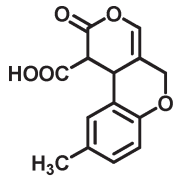
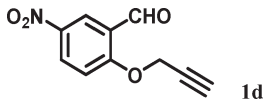
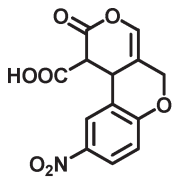
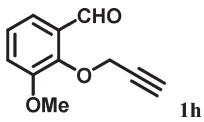
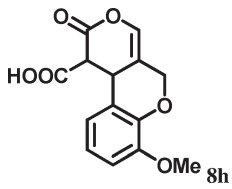
***9-Methyl-2-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (3c).*** This compound was obtained as a white solid,

**Table 4**

One-pot synthesis of pyrano[3,4-*c*]chromene *via* domino Knoevenagel hetero-Diels-Alder reaction.




1 7 8

| Entry | Aldehyde | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **8h** | 72 | 68 |
| 2 |  **1b** |  **8b** | 48 | 65 |
| 3 |  **1c** |  **8c** | 48 | 63 |
| 4 |  **1d** |  **8d** | 48 | 81 |
| 5 |  **1h** |  **8h** | 72 | 61 |

yield 61%; mp 169–171°C; IR (potassium bromide): 2205, 1708, 1620, 1600 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.25 (s, 3H, Me), 4.54 (d, $J$ = 11.6 Hz, 1H, —$OCH_2$), 4.66 (d, $J$ = 11.6 Hz, 1H, —$OCH_2$), 4.71 (s, 1H, —CH), 6.72 (d, $J$ = 8.2 Hz, 1H, $H_{Ar}$), 7.00 (d, $J$ = 8.2 Hz, 1H, $H_{Ar}$), 7.12 (s, 1H, =CH), 7.46 (s, 1H, $H_{Ar}$), 7.50–7.60 (m, 3H, $H_{Ar}$), 7.74 ppm (dd, $J$ = 7.7, 1.5 Hz, 2H, $H_{Ar}$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ 20.4, 30.9, 65.0, 84.9, 109.6, 117.2, 119.9, 124.4, 126.4, 128.1, 128.6, 128.9, 129.5, 131.3, 131.4, 136.8, 152.0, 162.7 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{20}H_{15}NO_2$: 301.1103; Found: 301.1067.

***9-Nitro-2-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (3d).*** This compound was obtained as a white solid, yield 75%; mp 185.5–187.5°C; IR (potassium bromide): 2209, 1708, 1616, 1580, 1514, 1343 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 4.76 (d, $J$ = 11.7 Hz, 1H, —$OCH_2$), 4.89 (d, $J$ = 11.7 Hz, 1H, —$OCH_2$), 4.93 (s, 1H, —CH), 7.05 (d, $J$ = 9.1 Hz, 1H, $H_{Ar}$), 7.22 (s, 1H, =CH), 7.51–7.61 (m, 3H, $H_{Ar}$),

7.75 (d, $J$ = 6.6 Hz, 2H, $H_{Ar}$), 8.10 (dd, $J$ = 9.1, 2.0 Hz, 1H, $H_{Ar}$), 8.63 ppm (d, $J$ = 2.0 Hz, 1H, $H_{Ar}$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 30.7, 66.3, 83.8, 107.2, 118.5, 119.7, 122.3, 124.5, 125.4, 128.1,128.7, 131.0, 131.7, 137.8, 140.6, 159.9, 162.9 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{19}H_{12}N_2O_4$: 332.0797; Found: 332.0769.

***7-Bromo-9-chloro-2-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (3e).*** This compound was obtained as a white solid, yield 70%; mp 195–196°C; IR (potassium bromide): 2205, 1710, 1613, 1450 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 4.71 (d, $J$ = 11.8 Hz, 1H, —$OCH_2$), 4.86 (s, 1H, —CH), 4.89 (d, $J$ = 11.8 Hz, 1H, —$OCH_2$), 7.20 (s, 1H, =CH), 7.51–7.59 (m, 3H, $H_{Ar}$), 7.67 (s, 2H, $H_{Ar}$), 7.76 ppm (d, $J$ = 6.79 Hz, 2H, $H_{Ar}$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 31.0, 66.4, 83.9, 107.7, 111.6, 119.6, 124.6, 125.3, 127.7, 128.2, 128.6, 131.0, 131.6, 137.7, 149.8, 163.1 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{79}Br^{35}Cl$: 398.9662; Found: 398.9637. $[M + 2]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{79}Br^{37}Cl$: 400.9641; Found: 400.9629. $[M + 4]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{81}Br^{37}Cl$: 402.9612; Found: 402.9644.

***7,9-Dibromo-2-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (3f).*** This compound was obtained as a white solid, yield 67%; mp 202.4–203.5°C; IR (potassium bromide): 2204, 1709, 1613, 1599 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 4.71 (d, $J$ = 11.8 Hz, 1H, —$OCH_2$), 4.87 (s, 1H, —CH), 4.89 (d, $J$ = 11.8 Hz, 1H, —$OCH_2$), 7.20 (s, 1H, =CH), 7.50–7.61 (m, 3H, $H_{Ar}$), 7.74–7.80 ppm (m, 3H, $H_{Ar}$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 30.9, 66.4, 83.9, 107.7, 111.9, 112.0, 119.6, 128.2, 128.6, 131.0, 131.6, 133.6, 137.7, 150.2, 163.1 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{79}Br_2$: 442.9157; Found: 442.9195. $[M + 2]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{79}Br^{81}Br$: 444.9136; Found: 444.9091. $[M + 4]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{81}Br_2$: 446.9115; Found: 446.9069.

***7,9-Dichloro-2-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (3g).*** This compound was obtained as a white solid, yield 67%; mp 193–195°C; ir (potassium bromide): 2205, 1710, 1611, 1600 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 4.72 (d, $J$ = 11.6 Hz, 1H, H-5), 4.85 (s, 1H, —CH), 4.90 (d, $J$ = 11.6 Hz, 1H, —$OCH_2$), 7.20 (s, 1H, =CH), 7.50–7.61 (m, 4H, $H_{Ar}$), 7.64–7.65 (m, 1H, $H_{Ar}$), 7.76 ppm (dd, $J$ = 7.3, 1.6 Hz, 2H, $H_{Ar}$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 31.0, 66.3, 83.8, 107.6, 119.6, 122.2, 124.19, 124.2, 124.7, 127.9, 128.2, 128.3, 128.6, 131.0, 131.6, 137.7, 148.9, 163.1 ppm; HR ms (70 eV, electron impact): $m/z$ $[M]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{35}Cl_2$: 355.0166; Found: 355.0198. $[M+2]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{35}Cl^{37}Cl$: 357.0138; Found: 357.0185. $[M + 4]^{+\cdot}$ Calcd. for $C_{19}H_{11}NO_2{}^{37}Cl_2$: 359.0108; Found: 359.0138.

**General procedure for the synthesis of pyranochromenes 8 derivatives *via* hetero-Diels-Alder reactions.** A solution of *O*-propargylated salicylaldehydes (1 mmol), Meldrum's acid (172 mg, 1.2 mmol), CuI (0.4 equiv., 76 mg), and $(NH_4)_2HPO_4$ (28 mg, 0.2 equiv.) in acetonitrile (25 mL) was refluxed. The progress of reaction was monitored by TLC (Petroleum ether:EtOAc 4:1). After completion of the reaction, the mixture of reaction was filtered and the solvent was evaporated under reduced pressure. Further purification was done using crystallization in acetonitrile.

***2-Oxo-1,10b-dihydro-2H,5H-pyrano[3,4-c]chromene-1-carboxylic acid (8a).*** This compound was obtained as a white solid, yield 72%; mp (Dec) 250°C; ir (potassium bromide): 3414, 1761, 1692 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.43 (d, $J$ = 12.9 Hz, 1H, —CHCOOH), 4.34–4.38 (m, 2H, —$OCH_2$, —CH), 4.65 (d, $J$ = 12.0 Hz, 1H, —$OCH_2$), 6.87 (d, $J$ = 7.7 Hz, 1H, $H_{Ar}$), 6.92 (t, $J$ = 7.4 Hz, 1H, $H_{Ar}$), 7.05 (s, 1H, =CH), 7.16 (t, $J$ = 7.4 Hz, 1H, $H_{Ar}$), 7.24 (d, $J$ = 7.7 Hz, 1H, $H_{Ar}$), 12.50 ppm (brs, 1H, —COOH); $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 32.1, 53.2, 65.0, 115.0, 118.5, 122.3, 123.8, 129.1, 129.4, 137.7, 155.6, 166.9, 170.2 ppm; ms (70 eV, electron impact): $m/z$ 246 ($M^+$), 245 ($M^+$ − H), 201 ($M^+$ − COOH), 173 ($M^+$ − $C_2HO_3$).

Colorless crystal (polyhedron), dimensions 0.37 × 0.22 × 0.13 mm$^3$, crystal system monoclinic, space group $P2_1/n$, $Z$ = 4, $a$ = 8.9193(12) Å, $b$ = 12.4115(16) Å, $c$ = 9.9814(13) Å, α = 90°, β = 97.889(3) deg, γ = 90 deg, $V$ = 1094.5(2) Å$^3$, ρ = 1.494 g/cm$^3$, $T$ = 200(2) K, $\Theta_{max}$ = 28.31°, radiation Mo Kα, λ = 0.71073 Å, 0.3° omega scans with CCD area detector, covering a whole sphere in reciprocal space, 11,243 reflections measured, 2724 unique [R(int) = 0.0243], 2510 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[1] based on the Laue symmetry of the reciprocal space, mu = 0.12 mm$^{-1}$, $T_{min}$ = 0.96, $T_{max}$ = 0.99, structure solved by direct methods and refined against $F^2$ with a Full-matrix least-squares algorithm using the SHELXTL-PLUS (6.10) software package [11], 171 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H3 and H16 at the carboxyl group, which were refined isotropically, goodness of fit 1.13 for observed reflections, final residual values $R1(F)$ = 0.061, $wR(F^2)$ = 0.158 for observed reflections, residual electron density −0.58 to 0.75 eÅ$^{-3}$. CCDC 742487 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***9-Bromo-2-oxo-1,10b-dihydro-2H,5H-pyrano[3,4-c]chromene-1-carboxylic acid (8b).*** This compound was obtained as a white solid, yield 65%; mp (°C) 230°C; IR (potassium bromide): 3447, 1768, 1680 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.47 (d, $J$ = 13.0 Hz, 1H, —CHCOOH), 4.34–4.40 (m, 2H, —$OCH_2$, —CH), 4.69 (d, $J$ = 12.1 Hz, 1H, —$OCH_2$), 6.87 (d, $J$ = 8.6 Hz, 1H, $H_{Ar}$), 7.07 (s, 1H, $H_{Ar}$), 7.32–7.38 (m, 2H, =CH, $H_{Ar}$), 12.65 ppm (brs, 1H, —COOH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 31.1, 52.0, 64.2, 112.7, 113.1, 119.7, 125.3, 130.8, 130.9, 137.1, 154.1, 165.6, 169.0 ppm; ms (70 eV, electron impact): $m/z$ 326 ($M^+$ +2), 324 ($M^+$), 281 ([$C_{13}H_9O_5{}^{81}Br$ – COOH]$^+$), 279 ([$C_{13}H_9O_5{}^{79}Br$ – COOH]$^+$), 253 ([$C_{13}H_9O_5{}^{81}Br$ – $C_2HO_3$]$^+$), 251 ([$C_{13}H_9O_5{}^{79}Br$ – $C_2HO_3$]$^+$).

***9-Methyl-2-oxo-1,10b-dihydro-2H,5H-pyrano[3,4-c]chromene-1-carboxylic acid (8c).*** This compound was obtained as a white solid; yield 63%; mp (°C) 235°C; IR (potassium bromide): 3416, 1764, 1690 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.14 (s,3H, Me), 3.39 (d, $J$ = 12.7 Hz, 1H, —CHCOOH), 4.27–4.30 (m, 2H, —$OCH_2$, —CH), 4.59 (d, $J$ = 12.0 Hz, 1H, —$OCH_2$), 6.74 (d, $J$ = 7.5 Hz, 1H, $H_{Ar}$), 6.93–7.04 (m, 3H, $H_{Ar}$, =CH), 12.55 ppm (brs, 1H, —COOH); ms (70 eV, electron impact): $m/z$ 260 ($M^+$), 215 ($M^+$ − COOH). Because of the low solubility of this compound in DMSO-$d_6$, we were not successful to have $^{13}$C NMR.

***9-Nitro-2-oxo-1,10b-dihydro-2H,5H-pyrano[3,4-c]chromene (8d).*** This compound was obtained as a white solid; yield 81%; mp 242–243°C; IR (potassium bromide): 3407, 1782, 1680 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.49–2.62 (m,

1H, ═CH), 3.32–3.43 (m, 1H, ═$CH_2$), 4.16 (dd, $J$ = 13.3, 4.4 Hz, 1H, ═$CH_2$), 4.56 (d, $J$ = 12.3 Hz, 1H, ═$OCH_2$), 4.84 (d, $J$ = 12.3 Hz, 1H, ═$OCH_2$), 7.07 (d, $J$ = 8.5 Hz, 2H, $H_{Ar}$, =CH), 8.03 (dd, $J$ = 8.5, 2.3 Hz, 1H, $H_{Ar}$), 8.33 (d, $J$ = 2.3 Hz, 1H, $H_{Ar}$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 28.4, 34.4, 64.2, 111.9, 118.0, 123.6, 124.7, 124.8, 138.1, 141.2, 159.2, 167.0 ppm; ms (70 eV, electron impact): $m/z$ 247 ($M^+$), 230 ($M^+ - OH$), 219 ($M^+ - CO$).

***7-Methoxy-2-oxo-1,10b-dihydro-2H,5H-pyrano[3,4-c]chromene-1-carboxylic acid (8h).*** This compound was obtained as a white solid; yield 61%; mp (°C) 240°C; IR (potassium bromide): 3447, 1768, 1680 $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.41 (d, $J$ = 12.6 Hz, 1H, ═CHCOOH), 3.72 (s, 3H, OMe), 4.28–4.36 (m, 2H, ═$OCH_2$, ═CH), 4.68(d, $J$ = 12.0 Hz, 1H, ═$OCH_2$), 6.79–6.90 (m, 3H, $H_{Ar}$), 7.05 (s, 1H, =CH), 12.60 ppm (brs, 1H, ═COOH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 30.4, 51.5, 54.7, 63.2, 109.8, 113.3, 118.9, 120.0, 122.6, 135.9, 143.6, 147.9, 165.2, 168.4 ppm; ms (70 eV, electron impact): $m/z$ 276 ($M^+$), 275 ($M^+ - H$), 231 ($M^+ - COOH$), 203 ($M^+ - C_2HO_3$).

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## REFERENCES AND NOTES

[1] (a) Schmidt, R. R. Acc Chem Res 1986, 19, 250; (b) Osborn, H. M. I.; Coisson, D. Mini-Rev Org Chem 2004, 1, 41; (c) Tietze, L. F.; Kettschau, G. Top Curr Chem 1997, 189, 1; (d) Waldman, H. Synthesis 1994, 353; (e) Toyota, M.; Komori, C.; Ihara, M. J Org Chem 2000, 65, 7110.

[2] Ritter, H. In Desk Reference of Functional Polymers, Syntheses and Applications; Arshady, R., Ed.; American Chemical Society: Washington, 1997; p 103, (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. Domino Reactions in Organic Synthesis; Wiley: Weinheim, 2006; (b) Tietze, L. F.; Rackelmann, N. In Multicomponent Reactions; Zhu, J.; Bienayme, H., Eds.; Wiley: Weinheim, 2005; p 121; (c) Tietze, L. F.; Rackelmann, N. Pure Appl Chem 2004, 76, 1967; (d) Shanmugasundaram, M.; Manikandan, S.; Raghunathan, R. Tetrahedron 2002, 58, 997.

[3] (a) Tietze, L. F.; Harfiel, U.; Hübsch, T.; Voß, E.; Wichmann, J. Chem Br 1991, 124, 881; (b) Tietze, L. F. Angew Chem Int Ed Engl 1983, 22, 828; (c) Tietze, L. F.; Voß, E.; Harms, K.; Sheldrick, G. M.; Tetrahedron Lett 1985, 26, 5273; (d) Tietze, L. F. J Heterocycl Chem 1990, 27, 47.

[4] Fox, M. F.; Lennon, I. C.; Meek, G. Tetrahedron Lett 2002, 43, 2899.

[5] Gartner, C. A.; Wen, B.; Wan, J.; Becker, R.; Jones, G.; Gygi, S. P.; Nelson, S. D. Biochemistry 2005, 44, 1846.

[6] (a) Li, Z.; Brouwer, C.; He, C. Chem Rev 2008, 108, 3239; (b) Tietze, L. F.; Lotz, F. Eur J Org Chem 2006, 4676; (c) Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. Tetrahedron 2008, 64, 5800; (d) Wender, P. A.; Paxton, T. J.; Williams, T. J. J Am Chem Soc 2006, 128, 14814; (e) Yanada, R.; Hashimoto, K.; Tokizane, R.; Miwa, Y.; Minami, H.; Yanada, K.; Ishikura, M.; Takemoto, Y. J Org Chem 2008, 73, 5135.

[7] Kirsch, S. F. Synthesis 2008, 3183 and references cited therein.

[8] (a) Patil, N.; Yamamoto, Y. J Org Chem 2004, 69, 5139; (b) Bock, V. D.; Hiemstra, H.; van, J.; Maarseveen, H. Eur J Org Chem 2006, 51; (c) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. J Org Chem 1995, 60, 4999; (d) Liu, F.; Ma, D. J Org Chem 2007, 72, 4844; (e) Ezquerra, J.; Pedregal, C.; Lamas, C. J Org Chem 1996, 61, 5804; (f) Cheng, G.; Hu, Y. J Org Chem 2008, 73, 4732.

[9] (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. J Am Chem Soc 2005, 127, 210; (b) Fürstner, A.; Stimson, C. C. Angew Chem Int Ed Engl 2007, 46, 8845.

[10] (a) Khoshkholgh, M. J.; Lotfi, M.; Balalaie, S.; Rominger, F. Tetrahedron 2009, 65, 4228; (b) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Rominger, F.; Gross, J. H. Tetrahedron Lett 2008, 49, 6965; (c) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Gross, J. H. Arkivoc 2009, ix, 114; (d) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Gross, J. H. Synlett 2009, 55.

[11] (a) Sheldrick, G. M. Bruker Analytical X-ray Division: Madison, Wisconsin, 2006; (b) Sheldrick, G. M. Bruker Analytical X-ray Division: Madison, Wisconsin, 2001.

# One-Step Synthesis of 2-Amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic Acid from Isoflavones and Arginine



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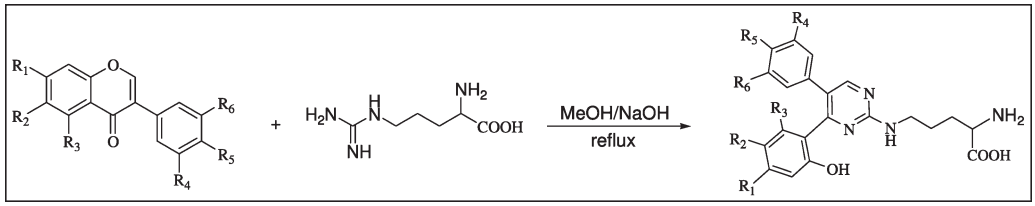


A simple and straightforward methodology toward the synthesis of novel 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid has been developed by one-step reaction of isoflavones with arginine. A series of 14 new compounds was reported. All of them were characterized by FTIR, NMR, and elemental analysis. A variety of substrates can participate in the process with good yields and high purities making this methodology suitable for library synthesis in drug discovery.

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## INTRODUCTION

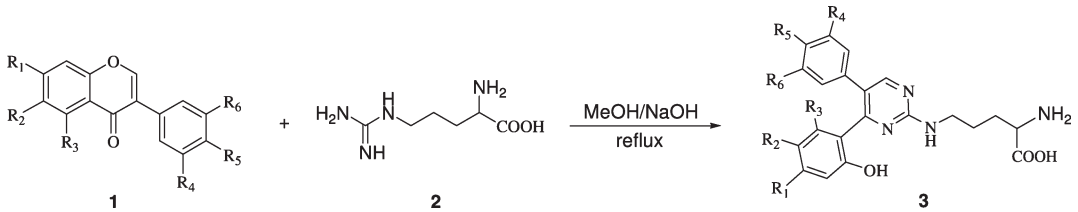
Pyrimidines are well known and widely investigated six-membered nitrogen-containing heterocyclic compounds that exhibit important biological activity [1–4]. Amino acid groups are found widely in a large variety of compounds that exhibit important biological activity, such as amino acids, are interesting drug targets because they are found on proteins, are well-known papain inhibitor [5], and present potential anti-HIV [6], anticonvulsant [7], and antiproliferative activity [8]. It is convenient to synthesize substituted pyrimidines by reaction of amidines or guanidines with α,β-unsaturated ketones [9,10], β-diketones [11,12], β-alkoxy- and β-aminovinyl ketones [13–16], and *N*-arylacetyleneic imines [17,18]. Natural isoflavones display a wide range of biological activities [19]. For instance, soybean isoflavones (daidzein and genistein) have shown pharmacological effects as antidysrhythmic [20], antioxidant [21], and anticardio-cerebral vascular disease [22]. Ipriflavone has been reported to be efficient in preventing and treating osteoporosis [23]. It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent, which readily reacts with amidines [24], guanidine [2], carbamide [25], and sulfocarbamides [26] to form the corresponding 2-substituted pyrimidines. The use of combinatorial approaches to the high-throughput synthesis of this drug-like scaffold would be a powerful advance in helping to speed up drug discovery. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles and 4,5-diphenyl-2-pyrimidinylguanidine by using a one-pot reaction of hydrazine [27] or bisguanidine [28] with isoflavones. Herein, we report a new strategy for the preparation of the unknown class of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)-pentanoic acid by the cyclocondensation of isoflavones (**1**) with arginine (**2**) (Table 1).

## RESULTS AND DISCUSSION

We turned our attention to optimize the condition of the cyclocondensations of isoflavones (**1**) with arginine (**2**) and designed a process by the cyclocondensation of 4′,7-dimethoxylisoflavone (**1a**) with arginine (**2**) as a model substrate (Table 2). As shown in Table 2, we used $K_2CO_3$ as base and **3a** yield was 37% (Table 2, entry 1). It was also found that triethylamine (TEA) was ineffective in providing the desired condensation product (Table 2, entry 2). A comparative reactivity study of bases in the reaction showed that NaOH proved to be more effective for this cyclocondensation (Table 2, entry 3). As it was shown, solvents MeOH, EtOH, THF, MeCN, *n*-BuOH, and DMF have been attempted, MeOH gave expected result (Table 2, entry 3). Further study with varying NaOH equivalents revealed that 3.0 equiv of base is necessary to obtain a high yield of the condensation product (Table 2, entry 9). Finally, the ratio of **1a** and **2** was also evaluated. The ratio of **1a**:**2** (1:3),

**Table 1**

Synthesis of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid by reaction of various isoflavones with arginine in MeOH. (For details, See Experimental.)



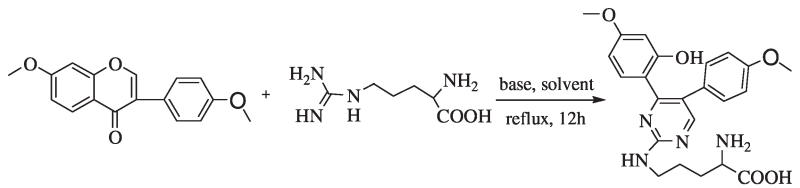

**1** **2** **3**

| Entry | Substrate | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | OMe | H | H | H | OMe | H | 8.0 | 92 |
| 2 | **1b** | OMe | H | OMe | H | OMe | H | 6.5 | 90 |
| 3 | **1c** | O$^i$Pr | H | H | H | H | H | 7.2 | 88 |
| 4 | **1d** | OMe | H | H | H | H | H | 7.0 | 85 |
| 5 | **1e** | OMe | OMe | OMe | H | OMe | H | 5.0 | 83 |
| 6 | **1f** | OMe | H | Me | H | H | H | 5.0 | 81 |
| 7 | **1g** | OBn | H | H | H | OMe | H | 7.5 | 85 |
| 8 | **1h** | OMe | H | H | H | OMe | $NO_2$ | 7.5 | 87 |
| 9 | **1i** | OMe | H | H | $^i$Pr | OH | $^i$Pr | 8.3 | 79 |
| 10 | **1j** | OMe | H | H | H | OH | H | 8.5 | 77 |
| 11 | **1k** | OH | H | H | H | OMe | H | 9.0 | 73 |
| 12 | **1l** | OH | H | H | H | H | H | 9.0 | 70 |
| 13 | **1m** | OH | H | H | H | OH | H | 12.0 | 57 |
| 14 | **1n** | OH | H | H | $^i$Pr | OH | $^i$Pr | 11.2 | 65 |

[a] Isolated yield after silica chromatography.

**Table 2**

Optimization of cyclocondensation of 4′,7-dimethoxylisoflavone **1a** with arginine **2**.[a]

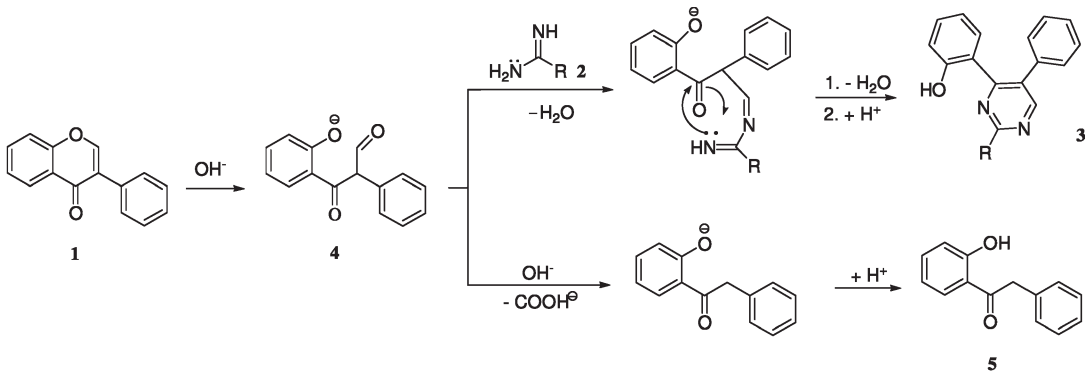



**1a** **2** **3a**

| Entry | Solvent | Base | Molar ratios **1a**/**2a**/base | Yield (%)[b] **3a** |
|---|---|---|---|---|
| 1 | MeOH | $K_2CO_3$ | 1:1:2 | 37 |
| 2 | MeOH | TEA | 1:1:2 | NR[c] |
| 3 | MeOH | NaOH | 1:1:2 | 67 |
| 4 | EtOH | NaOH | 1:1:2 | 56 |
| 5 | THF | NaOH | 1:1:2 | NR[c] |
| 6 | MeCN | NaOH | 1:1:2 | Trace |
| 7 | *n*-BuOH | NaOH | 1:1:2 | Trace |
| 8 | DMF | NaOH | 1:1:2 | NR[c] |
| 9 | MeOH | NaOH | 1:1:3 | 79 |
| 10 | MeOH | NaOH | 1:1:4 | 71 |
| 11 | MeOH | NaOH | 1:2:3 | 85 |
| 12 | MeOH | NaOH | 1:3:3 | 92 |
| 13 | MeOH | NaOH | 1:4:3 | 89 |

[a] All reaction were carried out in the appropriate solvent (15 mL) using 4′,7-dimethoxylisoflavone (**1a**, 1 mmol), arginine (**2**), and base until complete disappearance of **1a** (refluxing for 8 h, TLC check).
[b] Isolated yield after silica chromatography.
[c] No reaction.

**Scheme 1.** Proposed mechanism for the formation of **3**.




[a] R= - $NH(CH_2)_3CH(NH_2)COOH$.

the yield of **3a** was high for the cyclocondensation reaction (Table 2, entry 12).

With the optimized reaction conditions and proven results in hand, the condensation of variety of structurally divergent isoflavones (**1**) and arginine (**2**) were studied to illustrate this concise and general method for the synthesis of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid. All substrates reacted smoothly to give the corresponding 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid in 5–12 h in good to excellent yields, and the results were summarized in Table 1. All products were characterized by IR, $^1$H NMR, $^{13}$C NMR, and elemental analysis.

In general, isoflavone **1** substituted with alkoxy, benzyoxyl groups gave high yields. In contrast, the presence of the hydroxyl groups gave lower yields. As shown in Table 1, isoflavones **1a–h** (Table 1, entries 1–8) that do not contain hydroxyl groups, gave yields of **3** about 85%. Isoflavones with one hydroxyl group, **1i–l** (Table 1, entries 9–12) only gave yields of **3** about 75%, whereas those with two free hydroxyls, **1m**, **1n** (Table 1, entries 13 and 14) gave yields of roughly 60%. Condensation of trihydroxy isofalvone genistein (4′,5,7-trihydroxy-isoflavone) with **2** failed to produce product **3**. The yields of **3** are directly dependant on the number of free hydroxyl group present on the engaged isoflavone. Because the hydroxyls of isoflavone **1** under basic condition would be oxygenions, which possess stronger electron donability than alkoxy and benzyoxyl groups of the isoflavone, it is not favorable to the condensation reaction.

To explain the mechanism for the formation of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid (**3**) by the cyclocondensation of isoflavones (**1**) with arginine (**2**) in the presence of NaOH, a postulated reaction course was illustrated in Scheme 1. As it was reported that isoflavone may undergo ring-opening reaction when refluxing in the presence of alkali to form a β-diketone intermediate **4** [29]. Subsequently, attack of the primary amine group from the arginine (**2**) on the aldehyde carbon in **4**, followed by ring closure reaction between secondary amine and the carbonyl carbon to produce **3**. Meanwhile, intermediate **4** at high concentration of base may eliminate HCOOH to generate byproduct **5** [29].

## CONCLUSIONS

In summary, a convenient method for the synthesis of substituted pyrimidines bearing amino acid moiety in the 2 position was described. The protocol accepted a variety of isoflavones, arginine as starting materials and gave 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid in good to high yield. Efforts to expand the scope of the method in combination with its application to the synthesis of pharmaceutical molecules are ongoing in our laboratory.

## EXPERIMENTAL

All other commercially obtained reagents were used as received. The silica gel used for the column chromatography was purchased from Qingdao Haiyang Chemistry Plant. Thin Layer chromatography (TLC): silica gel 60 $GF_{254}$ plate; the eluant of column chromatography was the mixture of chloroform and methanol at volume ratio of 5:1. Arginine, ipriflavone, daiazein, genistein, formonone, and 5-methyl-7-methoxy-isoflavone are without further purification. Substrates **1d** and **1l** are derived from ipriflavone. Substrates **1a**, **1h**, **1i**, **1j**, and **1n** are derived from daiazein. Substrate **1b** is derived from genistein. Substrate **1g** is derived from formonone. Substrate **1e** is derived from irisolidone (4′,6-dialkoxy-5,7-dihydroxy-isoflavone), which was separated from the flower of *Pueraria lobata* by one of the authors. Melting points were measured on X-5 micromelting point apparatus and were uncorrected. IR spectra were recorded on Fourier transform infrared spectrometer using KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX-300 Advance spectrometer at 300.00 MHz in DMSO-$d_6$ with TMS as internal standard (chemical shifts in

ppm). The elemental analyses were performed with an Elementar Analysensyteme GmbH Vario EL III.

**General procedure for the preparation of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid (Table 1, entries 1–14).** The corresponding isoflavones **1** (1 mmol), arginine **2** (3 mmol), and sodium hydroxide (3, 4, and 5 mmol were used for 0, 1, and 2 free hydroxyl of **1**, respectively) were refluxed in methanol (15 mL) for 5–12 h. All reactions were monitored by TLC, which showed the disappearance of **1** that was indicative of the reaction being complete. The reaction mixture was added into water (30 mL) and adjusted to neutrality with the solution of 5% HCl. A yellow precipitate appeared and was filtered. The yellow precipitate was dissolved in a solution of 10% HCl (15 mL) and filtered. The mother liquid was neutralized with sodium hydroxide until crude product was completely precipitated. The crude product was filtered and purified by column chromatography on silica gel using chloroform–methanol (5:1) to give the corresponding pure product.

***2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3a).*** Yellow solid. mp 231.6–232.9°C. IR (KBr), ν ($cm^{-1}$): 3438, 2924, 2853, 1690, 1605, 1506, 1443, 1392, 1085, 1033, 686, 605. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.64–1.70 (m, 2H), 1.87 (d, 2H), 3.35 (s, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 3.92 (s, 1H), 6.19 (d, $J$ = 8.6 Hz, 1H), 6.37 (s, 1H), 6.90 (d, $J$ = 8.4 Hz, 3H), 7.10 (d, $J$ = 8.4 Hz, 2H), 7.62 (s, 1H), 8.21 (s, 1H), 8.35 (s, 3H), 11.98 (s, 1H); $^1$H NMR (300 MHz, DMSO-$d_6$ + $D_2O$), δ 1.66–1.73 (m, 2H), 1.79–1.88 (m, 2H), 3.35 (s, 2H), 3.71 (s, 3H), 3.75 (s, 3H), 3.91–3.95 (m, 1H), 6.22 (d, $J$ = 8.6 Hz, 1H), 6.37 (d, 1H), 6.90 (d, $J$ = 8.3 Hz, 3H), 7.10 (d, $J$ = 8.4 Hz, 2H), 8.21 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$ + $D_2O$), δ 24.5, 27.4, 51.7, 55.0, 55.1, 101.5, 104.9, 114.0, 114.4, 121.2, 129.7, 129.8, 131.6, 158.2, 158.7, 159.4, 159.7, 161.3, 161.9, 170.6. Anal. Calcd. for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78. Found C, 63.26; H, 5.76; N, 12.96.

***2-Amino-5-[4-(2-hydroxy-4,6-dimethoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3b).*** Yellow solid. mp 218.3–219.6°C. IR (KBr), ν ($cm^{-1}$): 3416, 2927, 1643, 1612, 1507, 1458, 1337, 1250, 1157, 1030, 833. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.65–1.72 (m, 2H), 1.89 (d, 2H), 3.33 (s, 2H), 3.44 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 3.88 (s, 1H), 5.96 (s, 1H), 6.11 (s, 1H), 6.78 (d, $J$ = 8.5 Hz, 2H), 7.04 (d, $J$ = 8.4 Hz, 2H), 7.33–7.43 (m, 1H), 8.24 (s, 1H), 8.56 (s, 3H), 9.62–9.86 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 24.5, 27.3, 51.7, 54.9, 55.0, 55.3, 89.8, 93.5, 113.4, 124.6, 128.8, 128.9, 156.0, 157.3, 158.1, 159.3, 161.1, 170.5. Anal. Calcd. for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found C, 61.29; H, 5.85; N, 12.16.

***2-Amino-5-[4-(2-hydroxy-4-isopropxyphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3c).*** Yellow solid. mp 243.3–244.7°C. IR (KBr), ν ($cm^{-1}$): 3436, 2926, 1609, 1441, 1386, 700, 598, 544, 466. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.22 (d, $J$ = 5.7 Hz, 6H), 1.71 (d, 2H), 1.89 (s, 2H), 3.36 (s, 2H), 3.93 (d, 1H), 4.53 (t, 1H), 6.15 (d, $J$ = 8.3 Hz, 1H), 6.33 (s, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 7.17–7.32 (m, 5H), 7.50 (s, 1H), 8.24 (s, 1H), 8.60 (s, 3H); $^1$H NMR (300 MHz, DMSO-$d_6$ + $D_2O$), δ 1.23 (d, $J$ = 5.8 Hz, 6H), 1.71 (t, 2H), 1.89 (s, 2H), 3.36 (s, 2H), 3.94 (d, 1H), 4.54 (t, 1H), 6.15 (d, $J$ = 8.3 Hz, 1H), 6.33 (s, 1H), 6.85 (d, $J$ = 7.0 Hz, 1H), 7.18–7.33 (m, 5H), 8.24 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$ + $D_2O$), δ 21.7, 24.6, 27.5, 51.7, 69.3, 102.9, 106.1, 114.1, 121.4, 126.8, 128.5, 128.6, 131.8, 137.8, 158.8, 159.7, 159.8, 162.1, 170.6. Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.84. Found C, 66.21; H, 6.55; N, 12.68.

***2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3d).*** Yellow solid. mp 223.6–224.9°C. IR (KBr), ν ($cm^{-1}$): 3435, 2925, 2828, 1624, 1529, 1430, 1375, 1072, 702. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.71 (s, 2H), 1.87 (s, 2H), 3.32 (s, 2H), 3.69 (s, 3H), 6.14 (d, $J$ = 5.3 Hz, 1H), 6.40 (s, 1H), 6.83 (s, 1H), 7.20–7.30 (m, 5H), 7.66–7.78 (m, 3H), 8.23 (s, 1H), 11.95 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 25.2, 28.4, 53.6, 55.0, 101.6, 104.7, 114.3, 121.1, 126.7, 128.5, 128.7, 131.6, 137.9, 159.3, 159.8, 161.3, 171.3. Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found C, 64.42; H, 5.77; N, 13.98.

***2-Amino-5-[4-(2-hydroxy-4,5,6-trimethoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3e).*** Yellow solid. mp 230.8–232.1°C. IR (KBr), ν ($cm^{-1}$): 3397, 2938, 1643, 1607, 1458, 1247, 1103, 549. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.69 (d, $J$ = 5.6 Hz, 2H), 1.89 (s, 2H), 3.31 (s, 2H), 3.45 (s, 3H), 3.58 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 6.30 (s, 1H), 6.77 (d, $J$ = 8.4 Hz, 2H), 7.08 (d, $J$ = 8.4 Hz, 2H), 8. 22 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 24.9, 27.9, 52.4, 54.9, 55.5, 60.4, 60.5, 95.8, 113.3, 124.0, 129.1, 129.5, 134.0, 150.8, 153.1, 157.1, 157.9, 161.0, 161.3, 171.1. Anal. Calcd. for $C_{25}H_{30}N_4O_7$: C, 60.23; H, 6.07; N, 11.24. Found C, 60.49; H, 6.26; N, 11.02.

***2-Amino-5-[4-(2-hydroxy-4-methoxy-6-methylphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3f).*** Yellow solid. mp 220.6–221.8°C. IR (KBr), ν ($cm^{-1}$): 3060, 2946, 1967, 1651, 1609, 1448, 1336, 1198, 1158, 1033, 832, 760, 703. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.68 (s, 2H), 1.83 (s, 3H), 1.89 (s, 2H), 3.36 (s, 2H), 3.65 (s, 3H), 3.89 (s, 1H), 6.16 (s, 1H), 6.30 (s, 1H), 7.16-7.19 (m, 5H), 7.40 (s, 1H), 8.30 (s, 1H), 8.56 (s, 2H), 9.55 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 20.1, 25.2, 28.1, 52.3, 55.2, 99.1, 106.2, 119.7, 124.7, 126.9, 128.3, 128.4, 137.1, 137.5, 156.1, 158.1, 159.8, 161.7, 164.2, 171.3. Anal. Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.38; H, 4.65; N, 15.38. Found C, 55.10; H, 4.50; N, 15.64.

***2-Amino-5-[4-(4-benzyl-2-hydroxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3g).*** Yellow solid. mp 254.5–255.8°C. IR (KBr), ν ($cm^{-1}$): 3425, 2927, 1620, 1599, 1521, 1423, 1402, 1055, 1021, 702, 630. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.69 (s, 2H), 1.86 (s, 2H), 3.30 (s, 2H), 3.73 (s, 3H), 5.02 (s, 2H), 6.23 (d, $J$ = 8.0 Hz, 1H), 6.47 (s, 1H), 6.87 (d, $J$ = 7.6 Hz, 3H), 7.09 (d, $J$ = 7.5 Hz, 2H), 7.34–7.39 (m, 5H), 7.63 (s, 1H), 8.18 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 25.7, 29.2, 54.5, 55.5, 69.6, 103.0, 105.9, 114.5, 121.1, 128.2, 128.3, 128.9, 130.4, 130.5, 132.1, 137.2, 158.6, 160.0, 160.1, 160.4, 160.6, 160.9, 171.4. Anal. Calcd. for $C_{29}H_{30}N_4O_4$: C, 69.86; H, 6.06; N, 11.24. Found C, 69.63; H, 6.21; N, 11.49.

***2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(3-nitro-4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3h).*** Yellow solid. mp 219.7–221.0°C. IR (KBr), ν ($cm^{-1}$): 3420, 3047, 2925, 2711, 1650, 1614, 1574, 1332, 1276, 1211, 1025, 869, 750. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.69 (s, 2H), 1.89 (s, 2H), 3.34 (s, 2H), 3.70 (s, 3H), 3.84 (s, 1H), 3.90 (s, 3H), 6.34 (s, 1H), 6.38 (s, 1H), 7.00 (s, 1H), 7.28 (d, $J$ = 8.6 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 1H), 7.66 (s, 2H), 8.28 (s, 1H), 8.52 (s, 2H), 10.91 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 24.5,

27.4, 51.9, 55.1, 56.6, 101.4, 105.2, 114.2, 115.7, 119.8, 124.4, 130.1, 131.4, 134.4, 138.8, 150.7, 157.2, 158.8, 160.3, 161.3, 162.7, 170.6. Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.14; H, 5.21; N, 14.49. Found C, 57.01; H, 5.06; N, 14.76.

***2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(3,5-diisopropyl-4-hydroxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3i).*** Yellow solid. mp 248.2–249.5°C. IR (KBr), ν ($cm^{-1}$): 3329, 2961, 2868, 1594, 1536, 1439, 1379, 1292, 1205, 1151, 1030, 835, 790. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.04 (d, $J$ = 5.0 Hz, 12H), 1.67 (s, 2H), 1.83 (s, 2H), 3.24–3.28 (t, 5H), 3.66 (s, 3H), 6.12 (s, 1H), 6.36 (s, 1H), 6.77–6.82 (d, 3H), 7.48 (s, 1H), 8.22 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 22.8, 25.3, 25.9, 28.7, 54.0, 55.1, 101.6, 104.6, 114.4, 121.7, 123.5, 128.6, 131.5, 135.3, 149.6, 159.4, 161.2, 170.4. Anal. Calcd. for $C_{28}H_{36}N_4O_5$: C, 66.12; H, 7.13; N, 11.02. Found C, 66.01; H, 7.35; N, 10.88.

***2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(4-hydroxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3j).*** Yellow solid. mp 254.5–255.8°C. IR (KBr), ν ($cm^{-1}$): 3415, 2924, 1610, 1448, 1385, 1294, 1162, 1019, 833, 630. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.68 (d, 2H), 1.86 (s, 2H), 3.33 (s, 2H), 3.81 (s, 3H), 3.88 (s, 1H), 6.20 (dd, $J_1$ = 1.6 Hz, $J_2$ = 8.7 Hz, 1H), 6.38 (s, 1H), 6.75 (d, $J$ = 8.2 Hz, 2H), 6.91 (d, $J$ = 8.7 Hz, 1H), 6.98 (d, $J$ = 8.2 Hz, 2H), 8.19 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 24.6, 27.6, 52.4, 55.1, 101.5, 104.8, 114.2, 115.5, 121.3, 128.1, 129.8, 131.6, 156.1, 159.0, 159.3, 159.8, 161.3, 171.0. Anal. Calcd. for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found C, 62.43; H, 5.81; N, 13.01.

***2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)-pyrimidin-2-ylamino]pentanoic acid (3k).*** Yellow solid. mp 240.2–241.6°C. IR (KBr), ν ($cm^{-1}$): 3435, 2923, 2854, 1642, 1535, 1446, 1266, 1003, 597, 535, 458. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.70–1.82 (m, 2H), 1.89 (s, 2H), 3.45 (s, 2H), 3.74 (s, 3H), 3.94 (d, 1H), 6.15 (d, $J$ = 8.1 Hz, 1H), 6.30 (s, 1H), 6.90 (d, $J$ = 8.4 Hz, 3H), 7.10 (d, $J$ = 8.4 Hz, 2H), 8.46 (s, 4H), 9.96–9.99 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 24.1, 27.1, 51.5, 55.1, 102.7, 107.1, 114.0, 122.2, 127.2, 129.6, 132.0, 154.1, 157.5, 158.6, 161.0, 170.4. Anal. Calcd. for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found C, 62.43, H, 5.31, N, 13.42.

***2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3l).*** Yellow solid. mp 257.1–258.6°C. IR (KBr), ν ($cm^{-1}$): 3408, 2958, 1610, 1574, 1536, 1392, 1327, 1196, 632. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.72 (s, 2H), 1.88 (s, 2H), 3.33 (s, 2H), 3.7 (s, 1H), 5.98 (d, $J$ = 7.3 Hz, 1H), 6.27 (s, 1H), 6.71 (d, $J$ = 8.5 Hz, 1H), 7.18–7.33 (m, 5H), 7.56 (s, 1H), 8.20 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 24.8, 27.9, 52.4, 103.3, 106.3, 112.1, 120.8, 126.5, 126.7, 128.5, 128.7, 131.7, 138.2, 159.6, 160.2, 161.9, 171.0. Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20. Found C, 64.20; H, 5.81; N, 14.43.

***2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-(4-hydroxyphenyl)-pyrimidin-2-ylamino]pentanoic acid (3m).*** Yellow solid. mp 275.2–276.7°C. IR (KBr), ν ($cm^{-1}$): 3409, 3111, 1666, 1612, 1507, 1447, 1403, 1249, 1216, 843. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.68 (d, 2H), 1.88 (s, 2H), 3.33 (s, 2H), 3.94 (s, 1H), 6.01 (d, $J$ = 8.5 Hz, 1H), 6.23 (s, 1H), 6.73–6.80 (m, 3H), 6.97 (d, $J$ = 8.2 Hz, 2H), 7.60 (s, 1H), 8.16 (s, 1H); $^1$H NMR (300 MHz, DMSO-$d_6$ + $D_2O$), δ 1.69 (d, 2H), 1.88 (s, 2H), 3.34 (s, 2H), 3.94 (s, 1H), 6.01 (d, $J$ = 8.2 Hz, 1H), 6.24 (s, 1H), 6.74–6.81 (m, 3H), 6.98 (d, $J$ = 6.4 Hz, 2H), 8.16 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$ + $D_2O$), δ 24.5, 27.5, 51.7, 103.0, 106.2, 112.7, 115.5, 121.0, 128.4, 129.8, 131.8, 156.2, 159.2, 159.5, 159.8, 160.0, 161.9, 170.6. Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found C, 61.20; H, 5.51; N, 13.46.

***2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-(3,5-diisopropyl-4-hydroxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3n).*** Yellow solid. mp. 268.7–269.9°C. IR (KBr), ν ($cm^{-1}$): 3419, 2961, 2871, 1597, 1536, 1447, 1401, 1213, 592. $^1$H NMR (300 MHz, DMSO-$d_6$), δ 1.06 (d, $J$ = 5.0 Hz, 12H), 1.67 (s, 2H), 1.84 (s, 2H), 3.24–3.28 (t, 5H), 5.93 (d, $J$ = 8.0 Hz, 1H), 6.23 (s, 1H), 6.74 (d, $J$ = 8.3 Hz, 1H), 6.80 (s, 2H), 7.50 (s, 2H), 8.20 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$), δ 22.8, 25.2, 26.0, 28.6, 53.9, 103.2, 106.0, 112.0, 121.2, 123.6, 128.9, 131.6, 135.5, 149.6, 159.2, 160.0, 160.2, 170.7. Anal. Calcd. for $C_{27}H_{34}N_4O_5$: C, 65.57; H, 6.93; N, 11.33. Found C, 65.35; H, 6.75; N, 11.54.

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## REFERENCES AND NOTES

[1] Gazivoda, T.; Šokčević, M.; Kralj, M.; Šuman, L.; Pavelić, K.; Clercq, E. D.; Andrei, G.; Snoeck, R.; Balzarini, J.; Mintas, M.; Raić-Malić, S. J Med Chem 2007, 50, 4105.

[2] Xie, F. C.; Zhao, H. B.; Zhao, L. Z.; Lou, L. G.; Hu, Y. H. Bioorg Med Chem Lett 2009, 19, 275.

[3] Deshmukh, M. B.; Salunkhe, S. M.; Patil, D. R.; Anbhule, P. V. Eur J Med Chem 2009, 44, 2651.

[4] Musonda, C. C.; Whitlock, G. A.; Witty, M. J.; Brun, R.; Kaiser, M. Bioorg Med Chem Lett 2009, 19, 401.

[5] Yamamoto, D.; Matsumoto, K.; Ohishi, H.; Ishida, T.; Inoue, M.; Kitamura, K.; Hanada, K. FEBS Lett 1990, 263, 134.

[6] Zhang, Y. J.; Wang, J. H.; Lee, W. H.; Wang, Q.; Liu, H.; Zheng, Y. T.; Zhang, Y. Biochem Biophys Res Commun 2003, 309, 598.

[7] Gavernet, L.; Elvira, J. E.; Samaja, G. A.; Pastore, V.; Cravero, M. S.; Enrique, A.; Estiu, G.; Bruno-Blanch, L. E. J Med Chem 2009, 52, 1592.

[8] Sassatelli, M.; Debiton, É.; Aboab, B.; Prudhomme, M.; Moreau, P. Eur J Med Chem 2006, 41, 709.

[9] Funabiki, K.; Nakamura, H.; Matsui, M.; Shibata, K. Synlett 1999, 756.

[10] Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. J. Angew Chem Int Ed Engl 2005, 44, 6951.

[11] Bellur, E.; Langer, P. Tetrahedron 2006, 62, 5426.

[12] Sevenard, D. V.; Khomutov, O. G.; Koryakova, O. V.; Sattarova, V. V.; Kodess, M. I.; Stelten, J.; Loop, I.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. Synthesis 2000, 1738.

[13] Zanatta, N.; Cortelini, M. de F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 1997, 34, 509.

[14] Madruga, C. da C.; Clerici, E.; Martins, M. A. P.; Zanatta, N. J Heterocycl Chem 1995, 32, 735.

[15] Zanatta, N.; Fagundes, M. B.; Ellensohn, R.; Marques, M.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 1998, 35, 451.

[16] Soufyane, M.; van den Broek, S.; Khamliche, L.; Mirand, C. Heterocycles 1999, 51, 2445.

[17] Yu, H. B.; Huang, W. Y. J Fluorine Chem 1997, 84, 65.

[18] Yu, H. B.; Huang, W. Y. J Fluorine Chem 1998, 87, 69.

[19] (a) Agullo, G.; Gamet-Payrastre, L.; Manenti, S.; Viala, C.; Remesy, C.; Chap, H.; Payrastre, B. Biochem Pharmacol 1997, 53, 1649; (b) Wang, I. K.; Lin-Shiau, S. Y.; Lin, J. K. Eur J Cancer 1999, 35, 1517.

[20] Fan, L. L.; Zhao, D. H.; Zhao, M. Q.; Zeng, G. Y. Acta Pharm Sin 1985, 20, 647.

[21] (a) Tlkkanen, M. J.; Wahala, K.; Ojala, S.; Vihtna, V.; Adletcteutr, H. Proc Natl Acad Sci USA 1998, 95, 3106; (b) Record, I. R.; Dreosti, I. E.; McInerney, J. K. J Nutr Biochem 1995, 6, 481.

[22] (a) Potter, S. M. J Nutr 1995, 125, 606; (b) Sirtori, C. R.; Lovati, M. R.; Manzoni, C.; Monetti, M.; Pazzucconi, F.; Gatti, E. J Nutr 1995, 125, 598; (c) Adlercreutz, H.; Goldin, B. R.; Gorbach, S. L.; Hockerstedt, K. A. V.; Watanabe, S.; Hamalainen, E. K.; Markkanen, M. H.; Makela, T. H.; Wahala, K. T.; Hase, T. A.; Fotsis, T. J Nutr 1995, 125, 757; (d) Ozaki, Y.; Yatomi, Y.; Jinnai, Y.; Kume, S. Biochem Pharmacol 1993, 46, 395.

[23] (a) Reginster, J. Y. L. Bone Miner 1993, 23, 223; (b) Ruenitz, P. C. Curr Med Chem 1995, 2, 791.

[24] Xie, F. C.; Li, S. K.; Bai, D. L.; Lou, L. G.; Hu, Y. H. J Comb Chem 2007, 9, 12.

[25] Sherman, W. R.; Taylor, J. E. C. Org Synth 1957, 37, 15.

[26] (a) Foster, H. M.; Snyder, H. R. Org Synth 1963, 4, 638; (b) Crosby, D. G.; Berthold, R. V.; Johnson, H. E. Org Synth 1963, 43, 68.

[27] Zhang, Z. T.; Tan, D. J.; Xue, D. Helv Chim Acta 2007, 90, 2096.

[28] Zhang, Z. T.; Xu, F. F.; Gao, M. X.; Qiu, L. J Comb Chem 2009, 11, 880.

[29] Varga, M.; Bátori, S.; Kövári-Rádkai, M.; Prohászka-Német, I.; Vitányi-Morvai, M.; Böcskey, Z.; Bokotey, S.; Simon, K.; Hermecz, I. Eur J Org Chem 2001, 20, 3911.

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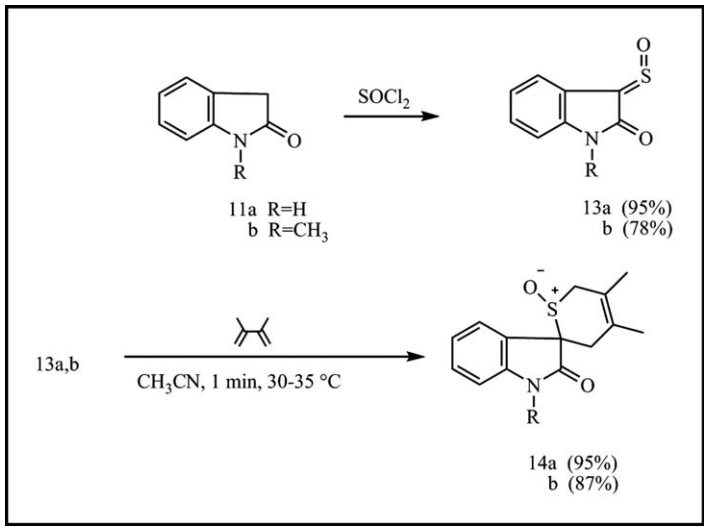


Oxindole was found to react readily with thionyl chloride to give (in an excellent yield) the isolable sulfine (**13a**), which on heating (refluxing acetonitrile) gave isoindigo (**15a**). The dark violet 3-sulfinato-oxindole (**13a**) readily reacted with 2,3-dimethylbutadiene to give a colorless cyclo-adduct (**14a**). The sulfine also reacted readily with various nucleophilic reagents, thus, thioloacetic acid gave 3-carboxymethylthiolo-oxindole (**23a**).

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## INTRODUCTION

Sulfines, which can be considered as oxides of thiones, are nonlinear and have the general structure **1**, and as indicated in Figure 1, E and Z isomers are possible [1–6].

Several synthetic methods [1–6] for the production of sulfines are available and perhaps the simplest and most general route is given by Zwanenburg, which involves treatment of silylated molecules, such as silylated ketones with thionyl chloride [5–7]. In a few cases, keto derivatives have been reported to yield α-oxo-sulfines directly (*i.e.*, without activation). For example, Hull and Faull reacted the anion of ethyl 4-chloroacetoacetate with phenyl isothiocyanate in dimethoxyethane and obtained 52% of the thiophene derivative **2**. By changing the solvent to dioxane, the yield of **2** could be improved to 87%. The thiophene **2** reacted readily with thionyl chloride to yield the isolable α-oxosulfine **3** [8]. In terms of yields, acetonitrile was found to be a more suitable solvent than dimethoxyethane. The α-oxosulfine **3** could readily be intercepted by 2,3-dimethylbutadiene to give **4**, which could be fully characterized by $^{1}$H and $^{13}$C NMR spectroscopy. In Scheme 1, the sulfine **3** is drawn as the more stable E-isomer although the Z-isomer is more likely to be formed initially due to attack of $SOCl_2$ on the enol tautomer of **2**, which would yield an intermediate sulfinyl chloride stabilized by hydrogen bonding. This sulfinyl chloride is then biased to give primarily the Z-sulfine. However the E-isomer is thermodynamically more stable and will eventually be formed. The structure (determined by X-ray technique) of **4** showed that its sulfine precursor **3** leading to **4** had indeed exclusively been the E-isomer [6].

Interestingly, the related (to **2**) molecule **5**, when treated with $SOCl_2$, failed to yield an isolable sulfine. Instead, the coupled molecule **6** was isolated [8] indicating that the intermediate sulfine is unstable in this case. Interception with 2,3-dimethylbutadiene is however possible [6], which gave a separable mixture of diastereomers; thus, indicating that the kinetic product (the Z-isomer) only had been partially converted to the E-isomer. This type of cycloaddition with 2,3-dimethylbutadiene is a standard operation to trap and to characterize sulfines, as have been done with intermediate sulfines generated

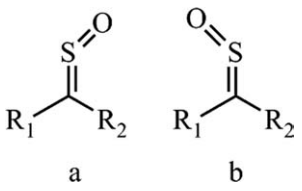


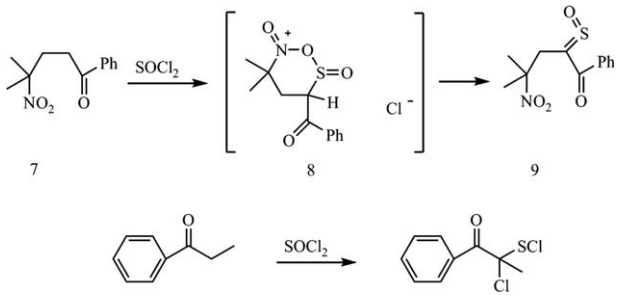
**Figure 1.** E and Z isomers of sulfines.

from doubly activated methylene compounds, such as dibenzoylmethane [2,7,9,10].

Another stable α-oxosulfine is given by Black, who reported formation of the α-oxosulfine **9** from the nitroketone **7**. The nitro group is considered to play an important role as indicated in Scheme 2. The intermediate **8** could not be isolated but its presence was supported by an ABX pattern observed during an NMR study of the reaction [11]. The product, the stable α-oxo-sulfine **9**, featured diagnostic resonances at 188.9 and 189.3 ppm in the $^{13}C$ NMR spectrum.

The structure of **9** was confirmed by X-ray crystallography [11]. Simple aromatic ketones (like propiophenone) gave α-chlorosulfenyl chlorides and not α-oxosulfines (Scheme 2) [11].

**Scheme 2**



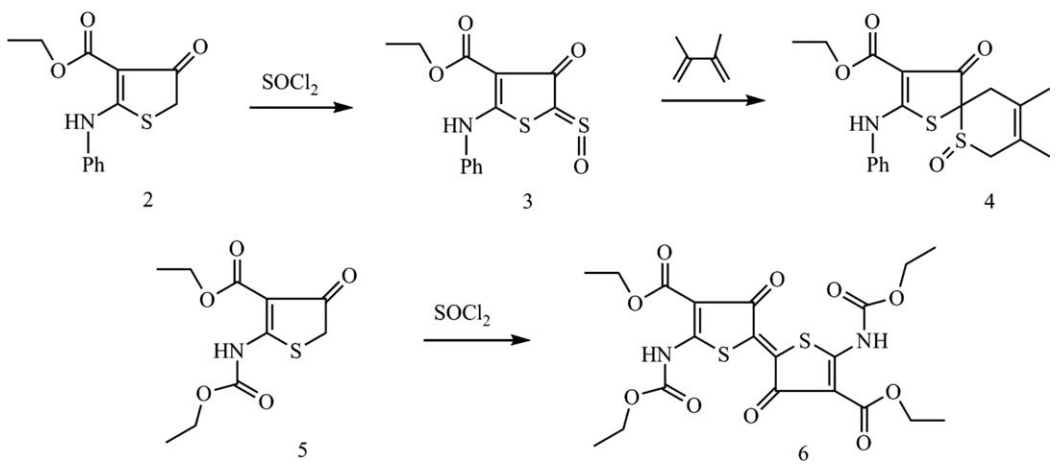
## RESULTS AND DISCUSSION

It has now, somewhat surprisingly, been found that several sulfines in the indole series can readily and quickly (2–3 min) be prepared in excellent yields by the reaction of oxindole itself (**11a**) with thionyl chloride in acetonitrile at 30–35°C that gave the α-oxosulfine **13a** as a dark violet solid. *N*-Methyloxindole similarly gave **13b**. Many years ago, oxindole had been treated with thionyl chloride as reagent and solvent at reflux temperature. Under these conditions isoindigo (**15a**) was the sole product [12] and it seems that the sulfine **13a** has never been isolated before. The sulfine **13a** was isolated in 95% yield accompanied with a small amount of 3-chloro-oxindole (2%, isolated) and can be recrystallized from acetonitrile but prolonged heating in this medium will convert **13a** to isoindigo (Scheme 3).

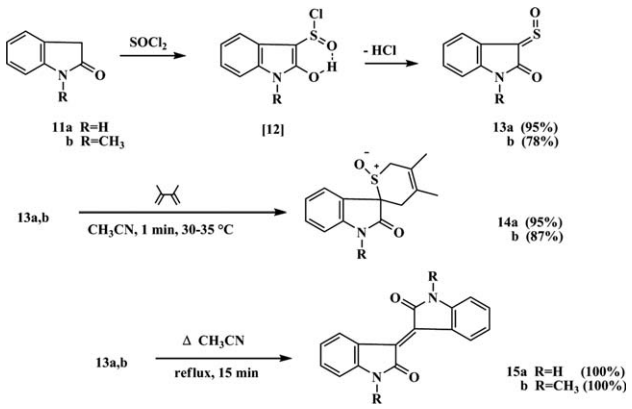
In analogy with the known sulfine **3**, the indolic sulfine **13a** and 2,3-dimethylbutadiene readily (within 2 min at 30–35°C in acetonitrile) gave the colorless adduct **14a** as a single diastereomer. The same is true for the *N*-methyl derivative **13b**, which gave **14b**. It is assumed that the sulfine **13a** is formed *via* an initial electrophilic attack in 3-position of oxindole leading to the nonisolable intermediate sulfinyl chloride **12**, which quickly will eliminate HCl leading to the α-oxosulfine **13a** (E-isomer). However, it is assumed that initially the kinetic product, the Z-isomer, is formed but that it will quickly be converted to the more stable E-isomer. This E-stereochemistry was deduced from the fact that only one isomer of the *S*-oxide **14a** was obtained. Interestingly, other sulfines generated in other ways, for example, *via* diazo compounds, usually will give diastereomeric mixtures with 2,3-dimethylbutadiene [13–16].

A solution of **13a** in DMSO-$d_6$ features a $^{13}C$ NMR spectrum similar to but distinctively different from that of isatin [17,18]. In isatin (**10**), the signals from carbon

**Scheme 1**



**Scheme 3**




atoms 2 and 3 appeared at 159.4 and 184.3 ppm [17], respectively, whereas the corresponding signals from the sulfine **13a** appeared at 160.0 and 168.9 ppm, respectively. In the proton NMR spectrum, the signal from the 4-H proton was shifted significantly more downfield in the spectrum of **13a** (8.08 ppm) as compared with 7.47 for isatin **10** and actually even more so in isoindigo **15a** (9.10 ppm). These data clearly indicate that the proton in position 4 is strongly influenced by the anisotropic deshielding of the cone of interaction from the SO group (for **13a**) and the C═O group in the neighboring ring (for **15a**).The general similarity of the spectra of **10** and **13a**, however, was taken as evidence that the species present in the solution is (**13a**) actually not an adduct, as a result of nucleophilic addition of DMSO to **13a**. A solution of **13a** in DMSO is, however, not permanently stable and after 7 days 90% of the sulfine will be converted to isoindigo **15a**. This type of conversion was faster for derivatives substituted with halogen atoms in the benzene ring.

The sulfines **13a** and **13b** can, under dry conditions, be stored for several months at room temperature without decomposition. In the presence of moisture, the sulfines will eliminate $SO_2$ and the starting materials, that is, the oxindoles **11a** and **11b**, will be formed slowly. This type of decomposition has been observed previously for other sulfine derivatives on several occasions [11,19]. When **13a** and **13b** are dissolved in chloroform and saturated with water, the cleavage process is quite quick (*e.g.*, total decomposition within 15 min at 40°C).

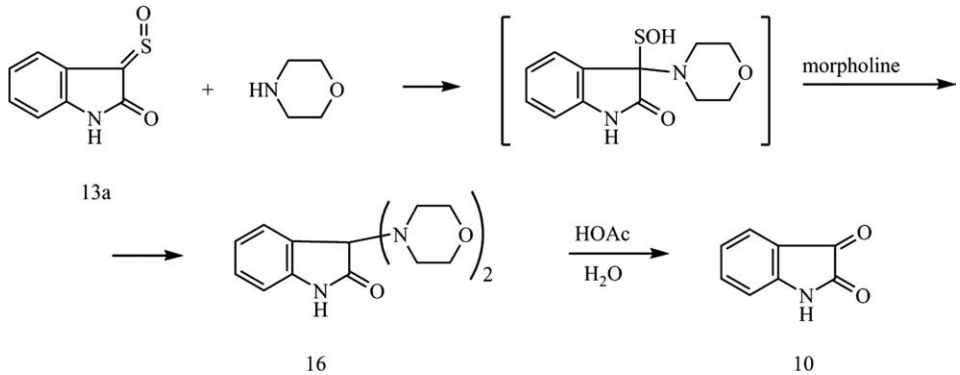
A number of substituted oxindoles, for example, [20–25] 6-chloro-oxindole, 6-bromo-oxindole, and 5-nitro-oxindole likewise could be converted to sulfines as well as adducts with 2,3-dimethyl-butadiene. All these derivatives of **13a** substituted in the benzene ring could readily be converted to ring-substituted derivatives of isoindigo.

As expected, the sulfine **13a** reacted readily with a number of nucleophilic reagents. Thus, morpholine gave the known [26] adduct **19** (previously prepared form isatin and morpholine) as shown in Scheme 4. Thus, addition of morpholine to a solution of the sulfine **13a** in acetonitrile at 35°C quickly faded the dark violet color and a solid precipitated within 2 min, which consists of **16** and morpholinium sulfite, which could be easily removed by extraction of the mixture with water. The nature of the side-product, morpholinium sulfite, was established in an independent experiment, wherein morpholine dissolved in water was reacted with sulfur dioxide. As indicated in Scheme 4, the sulfine **13a** could be converted to isatin **10**. However, simple treatment with water could not effect this transformation.

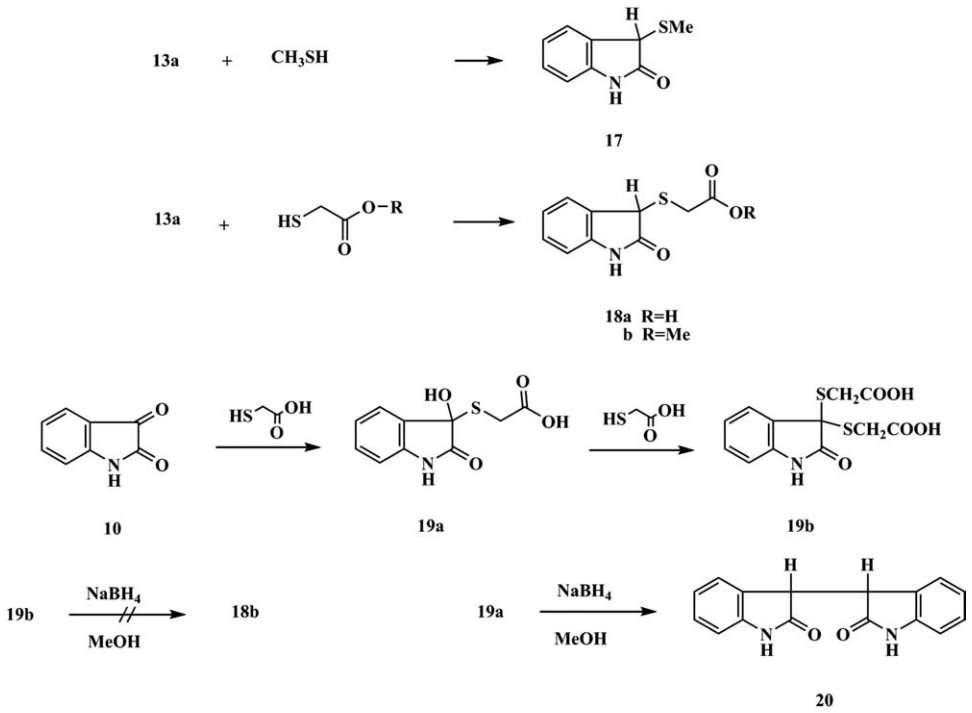
Thiols also reacted readily with the sulfine **13a**, thus, methanethiol gave the known [17] compound **17** and thiolacetic acid and methyl thiolacetate, respectively, the new molecules **18a** and **18b**, both in excellent yields. The NMR data of **18a** are in disagreement with those reported in the literature, wherein a mixture composed of isatin, pentafluoroaniline, and thiolacetic acid has been claimed to give **18a**. This unusual experiment should be repeated [27].

Although isatin and thiolacetic acid readily could be converted to the adduct **19a**, this molecule could not be converted to **18a** because the adduct **19a** is quite labile

**Scheme 4**



**Scheme 5**




under basic as well as acidic conditions. The product formed was a coupled reduction product of isatin, namely isatid **20**, a well-known molecule [28,29]. Treatment of the adduct **19a** with acetic anhydride at ambient temperature quickly cleaved the adduct yielding isatin **10**. The bis-adduct **19b**, however, is quite stable under these conditions (Scheme 5).

## EXPERIMENTAL

Melting points were uncorrected and determined using a Büchi B-545 apparatus. NMR spectra were obtained in DMSO-$d_6$ on a Bruker 300-MHz spectrometer. IR (neat) was recorded with an Avatar 330 FTIR apparatus (Thermo Nicolet).

**Ethyl 2-phenylamino-4-oxo-4,5-dihydrothiophene-3-carboxylate (2).** Ethyl 4-chloro-acetoacetate (16.5 g, 0.1 mol) in dioxane (80 mL) was treated with sodium hydride (4.5 g, 60% in oil) at 30°C. When the evolution of hydrogen had ceased (~20 min), phenyl isothiocyanate (13.5 g, 0.1 mol) in dioxane (20 mL) was added at 25–30°C to the stirred mixture. The temperature was allowed to reach 40°C, and at this point, a thick slurry was formed. After 1 h at 35–40°C, the mixture was poured into water and the solid formed was collected, washed with water, and recrystallized from ethanol, 22.9 g (87%), mp. 146–148°C (lit. [8] 146–148°C). IR 3198, 2983, 2926, 1643, 1555, 1548, 1406, 1382, 1344, 1283, 1223, 1152, 1037, 997, 800, 784, 754 $cm^{-1}$; $^1H$ NMR δ: 1.25 (t, 3H, $CH_3$), 3.67 (s, 2H, $CH_2$), 4.22 (q, 2H, $OCH_2$), 7.36–7.51 (m, 5H, arom CH), 11.2 (br s, 1H, NH); $^{13}C$ NMR δ: 14.4 (q), 38.0 (t), 59.3 (t), 97.0 (s), 125.1 (d), 127.8 (d), 129.5 (d), 137.3 (s), 156.1 (s), 182.7 (s), 190.5 (s).

**Ethyl 2-phenylamino-4-oxo-5-sulfinato-4,5-dihydrothiophene-3-carboxylate (3).** The ester **2** (2.63 g, 10 mmol) in acetonitrile (35 mL) was treated with thionyl chloride (1.25 mL, 15 mmol) at 35°C. A precipitate of yellow needles was collected after 1 h, (2.90 g, 96%), mp. >260°C dec.; IR 3161, 2968, 1641, 1538, 1408, 1377, 1172, 1018, 941, 788 $cm^{-1}$; $^1H$ NMR δ: 1.44 (t, 3H, $CH_3$), 4.24 (q, 2H, $OCH_2$), 7.38–7.57 (m, 5H, arom CH), 11.4 (br. s, 1H, NH); $^{13}C$ NMR δ: 14.3 (q), 59.6 (t), 97.5 (s), 125.9 (d), 129.1 (d), 129.4 (d), 137.0 (s), 163.5 (s), 172.1 (s), 178.8 (s), 191.0 (s).

**The adduct (4).** The yellow sulfine **3** (3.09 g, 10 mmol) was suspended in acetonitrile (85 mL) and 2,3-dimethylbutadiene in excess was introduced to the stirred mixture at 50–55°C. The solution obtained was concentrated and the colorless product was collected (3.25 g, 86%); mp. 200–202°C (lit. [6] 200–202°C); IR 3162, 3058, 2974, 1660, 1548, 1415, 1400, 1210, 1063, 1032, 800, 769, 696 $cm^{-1}$; $^1H$ NMR δ: 1.27 (t, 3H, $CH_3$), 1.59 (s, 6H, 2 $CH_3$), 2.75 (2H, $CH_2$), 3.45 (2H, $CH_2$), 4.26 (q, 2H, $OCH_2$), 7.40–7.55 (m, 5H, arom CH), 11.4 (s, 1H, NH); $^{13}C$ NMR δ: 14.3 (q), 19.0 (q), 19.2 (q), 39.7 (t), 52.3 (t), 59.7 (t), 79.0 (s), 97.2 (s), 119.1 (s), 125.4 (d), 126.7 (s), 128.3 (d), 129.7 (d), 137.2 (s), 164.2 (s), 180.4 (s), 188.1 (s).

**2-Oxindole-3-thione *S*-oxide 13a.** Thionyl chloride (15.0 mL) was added during 3 min to a stirred solution of oxindole (13.3 g, 0.1 mol) in acetonitrile (120 mL) at 25–30°C. The dark violet product started to separate within 1 min and the reaction is completed in 10 min. The sulfine **13a** was collected and dried in a desiccator (17.08 g, 95%); mp. ~120°C dec; IR: NH 3240 (br), 1702, 1666, 1607, 1456, 1326, 1201, 1126, 1089, 1070, 764 $cm^{-1}$; $^1H$ NMR δ: 6.83 (d), 7.00 (d), 7.40 (d), 8.07 (d, 4-H), 10.9 (s, NH); $^{13}C$ NMR δ: 110.5 (d), 122.1 (s), 122.6 (d), 126.1 (d), 134.3 (d), 140.7 (s), 166.0 (s), 169.0 (s); Anal. calcd. for $C_8H_5NO_2S$: C, 53.2; H, 2.88; N, 7.78 Found: C, 53.5; H, 3.15; N, 7.65.

***N*-Methyl-2-oxindole-3-thione *S*-oxide 13b.** The procedure given for the parent compound **13a** was used, except that methyl acetate was used as medium starting with *N*-methyl-oxindole. Before isolation of the product, part of the solvent was partially evaporated; (Yield 78%); mp 130–140°C (violent dec);$^1$H NMR δ: 3.12 (s, 3H, $NCH_3$), 7.05–7.11 (dd+d, 2H arom CH), 7.49 (dd, 1H, arom CH), 8.10 (d, 1H, 4-H); $^{13}$C NMR δ: 125.8 (q), 109.5 (d), 120.9 (s), 121.7 (d), 125.8 (d), 134.2 (d), 141.8 (s), 164.5 (s), 168.2 (s); Anal. calcd. for $C_9H_7NO_2S$: C, 56.1; H, 3.70; N, 7.28. Found: C, 55.7, H, 3.80; N, 7.35.

**The adduct 14a.** The sulfine **13a** (179 mg, 1 mmol) was suspended in acetonitrile (5.0 mL), and 2,3-dimethyl-butadiene (123 mg, 1.5 mmol) was introduced at 30–35°C. The dark violet starting material went into solution and was soon replaced by the colorless adduct **14a**, which has a low solubility in acetonitrile, 247 mg, (95%); mp. 195–196°C; IR 3255, 2919, 2888, 1716 (s), 1617, 1469, 1324, 1186, 1030, 738, 678 cm$^{-1}$; $^1$H NMR δ: 1,63 (s, 3H, $CH_3$), 1.79 (s, 3H, $CH_3$), 2.61 (2H, $CH_2$), 3.60 (2H, $CH_2$), 6.91 (d, 1H), 7.03 (dd, 1H), 7.20 (d, 1H), 7.33 (dd, 1H), 10.8 (s, 1H, NH) $^{13}$C NMR δ: 19.2 (q), 19.6 (q), 35.4 (t), 50.1 (t), 66.1 (s), 109.8 (d), 118.2 (s), 122.1 (s), 125.3 (s), 125.3 (d), 125.8 (s), 129.7 (d), 143.1 (s), 174.5 (s). Anal. calcd. for $C_{14}H_{15}NO_2S$: C, 64.33; H, 5.78; N, 7.25; Found, C, 64.12; H, 5.90; N, 7.15.

**The adduct 14b.** The same procedure as for **14a** was used. Yield (94%), mp. 191–192°C; IR; 3060 (w), 1704 (s), 1609, 1468, 1372, 1344, 1052 (s), 755 (s) cm$^{-1}$; $^1$H NMR δ: 1.69 (s, 3H, $CH_3$), 1.80 (s, 3H, $CH_3$), 2.62 (2H, $CH_2$), 3.17 (s, 3H, $NCH_3$), 3.62 (2H, $CH_2$), 7.10–7.46 (m, 4H, arom CH); $^{13}$C NMR δ: 19.2 (q), 19.6 (q), 26.6 (q), 35.3 (t), 50.2 (t), 65.5 (s), 108.9 (d), 118.2 (s), 122.7 (d), 124.6 (s), 125.0 (d), 125.7 (s), 129.8 (d), 144.5 (s), 172.9 (s). Anal. calcd. for $C_{15}H_{17}NO_2S$: C, 65.80; H, 6.23; N, 5.11 Found: C, 65.91; H, 6.32; N, 5.15.

**6-Bromo-2-oxindole-3-thione *S*-oxide.** The procedure given for **13a** was used, starting with 6-bromo-oxindole [24]. Yield 98%, mp. 140°C dec. $^1$H NMR δ 7.10 (dd, 1H, 5-H), 7.18 (d, 1H, 7-H), 7.94 (d, 1H, 4-H). $^{13}$C NMR δ: 113.3 (d), 123.5 (s), 125.3 (d), 127.1 (d), 127.2 (s), 141.8 (s), 165.7 (s), 167.8 (s). Anal. calcd. for $C_8H_4BrNO_2S$: C, 37.61; H, 1.57; N, 5.46 Found: C, 37.40; H, 1.66; N, 5.30.

**Adduct between 6-bromo-2-oxindole-3-thione *S*-oxide and 2,3-dimethylbutadiene.** The procedure described for **14a** was used. Yield 98%, mp. 220°C dec. IR 3110, 3080, 1720, 1609, 1447, 1038, 821 cm$^{-1}$; $^1$H NMR δ 1.68 (s, 3H, $CH_3$), 1.77 (s, 3H, $CH_3$), 2.62 (2H, $CH_2$), 3.61 (2H, $CH_2$), 7.06 (d, 1H, 7-H, $J$ = 1.83 ppm), 7.11 (d, 1H, 4-H, $J$ = 8.25), 7.22 (dd, 1H, 5-H), 11.0 (s, 1H, NH). $^{13}$C NMR δ; 19.7 (q), 20.1 (q), 35.7 (t), 50.8 (t), 66.7 (s), 113.2 (d), 118.8 (s), 123.1 (s), 125.0 (s), 125.2 (d), 126.4 (s), 127.6 (d), 145.3 (s), 175.1 (s). Anal. calcd. for $C_{11}H_{14}BrNO_2S$: C, 49.39; H, 4.13; N, 4.09 Found: C, 49.19; H, 4.29; N, 3.97.

**6-Chloro-2-oxindole-3-thione *S*-oxide.** The procedure above was used. Yield 92%, IR 3102, 1712, 1606, 1330, 1104, 1067, 808, 719 cm$^{-1}$; $^{13}$C NMR δ 109.1 (d), 120.8 (d), 124.7 (s), 125.7 (s), 131.7 (d), 145.1 (s), 165.9 (s), 167.8 (s).

**Adduct between 5-bromo-2-oxindole-3-thione *S*-oxide and 2,3-dimethylbutadiene.** Yield: 87%, mp. 220°C dec. IR 3176, 3145, 2902, 1715, 1618, 1468, 1300, 1227, 1039, 823 cm$^{-1}$; $^1$H NMR δ 1.70 (s, 3H, $CH_3$), 1.78 (s, 3H, $CH_3$), 2.57 (2H, $CH_2$), 3.62 (2H, $CH_2$), 6.88 (d, 1H, 7-H), 7.26 (d, 1H, 4-H), 7.53 (dd, 1H, 6-H), 11.0 (s, 1H, NH). $^{13}$C NMR δ 19.2 (q), 19.6 (q), 34.7 (t), 50.0 (t), 65.9 (s), 111.7 (s), 113.6 (d), 117.8 (s), 125.7 (d), 127.7 (s), 127.9 (s), 132.4 (d), 142.3 (s), 174.1 (s).

**Adduct between 6-chloro-2-oxindole-3-thione *S*-oxide and 2,3-dimethylbutadiene.** Yield: 92%, mp. 190°C dec. IR 3193, 1720, 1614, 1481, 1449, 1322, 1238, 1040, 926, 806 cm$^{-1}$; $^1$H NMR δ 1.68 (s, 3H, $CH_3$), 1.77 (s, 3H, $CH_3$), 2.56 (2H, $CH_2$), 3.62 (2H, $CH_2$), 6.93 (d, 1H, 7-H), 7.09 (dd, 1H, 5-H), 7.17 (d, 1H, 4-H), 11.0 (br s, 1H, NH). $^{13}$C NMR δ; 19.2 (q), 19.6 (q), 35.1 (t), 50.2 (t), 66.0 (s), 109.9 (d), 113.6 (s), 121.7 (d), 124.0 (s), 125.8 (s), 126.7 (d), 134.1 (s), 144.6 (s), 174.6 (s). Anal. calcd. for $C_{14}H_{14}ClNO_2S$. C, 56.90; H, 4.75; N, 4.69. Found: C, 56.71; H, 4.90; N, 4.58.

**6,6′-Dichloroisoindigo.** The 6-chloro-S-oxide (2.0 g) obtained above was heated at reflux in acetonitrile (50 mL) for 1 h and the dark blue precipitate of 6,6′-dichloroisoindigo was collected and washed with ethanol. Yield: 96% mp. > 300°C. The spectroscopic data were in agreement with those in the literature [30,31].

**5-Nitro-2-oxindole-3-thione *S*-oxide.** The procedure above was used. Yield: 75%, mp. (violent dec.) 140°C. $^1$H NMR δ; 7.03 (d, 7-H, $J_1$ = 8.75), 8.27 (dd, 6-H, $J_1$ = 8.75, $J_2$ = 2.31), 8.72 (d, 4-H, $J_2$ = 2.31), 11.6 (s, NH). $^{13}$C NMR δ; 110.7 (d), 120.4 (d), 121.4 (s), 129.6 (d), 142, 2 (s), 145.7 (s), 166.0 (s), 167.0 (s). No acceptable elemental analysis data could be obtained for this molecule, but its adduct could be analyzed.

**Adduct between 5-nitro-2-oxindole-3-thione *S*-oxide and 2,3-dimethylbutadiene.** The procedure above was used. Yield: 84%, mp. 150°C dec. $^1$H NMR δ: 1.67 (s, 3H, $CH_3$), 1.73 (s, 3H, $CH_3$), 2.50 (2H, $CH_2$), 3.65 (2H, $CH_2$), 7.09 (d, 1H, 7-H), 7.93 (d, 1H, 4-H), 8.30 (dd, 1H, 6-H, $J_1$ = 8.75, $J_2$ = 2.31), 11.5 (s, 1H, NH). $^{13}$C NMR δ; 19.2 (q), 19.5 (q), 34.4 (t), 50.3 (t), 65.9 (s), 109.9 (d), 118.1 (s), 120.5 (d), 125.9 (s), 126.1 (s), 126.8 (d), 142.4 (s), 149.3(s), 175.0 (s). Anal. calcd. for $C_{14}H_{14}N_2O_4S$: C, 31.30; H, 4.59; N, 4.56. Found: C, 31.19; H, 4.63; N, 4.45.

**Isoindigo 15a.** The sulfine **13a** (1.79 g, 10 mmol) in acetonitrile (35 mL) was refluxed until no more precipitate of the product **15a** was formed (∼15 min). Yield: (100%); mp. >300°C; $^1$H NMR δ; 6.83 (d), 6.91 (dd), 7.40 (dd), 9.06 (d), 10.9 (s, NH); $^{13}$C NMR δ; 109.5 (d), 121.1 (d), 121.7 (s), 129.4 (d), 132.4 (d), 133.4 (s), 144.2 (s), 169.1 (s). UV in agreement with data in ref. 30. The $^1$H NMR data were in agreement with those in the literature [32,33]. However, the signal just above 9.0 ppm was incorrectly reported as a singlet.

***N*,*N*′-Dimethylisoindigo 15b.** The same procedure as for **15a** was used, Yield 100%, mp. 270–271°C (lit. [33] 270°C; 267–269°C [34]); IR 3130 (w), 2980 (w), 1681 (s), 1605, 1469, 1374, 1338, 1089, 1076, 944, 866, 773, 740 cm$^{-1}$; $^1$H NMR δ: 3.20 (s, 6H, $2NCH_3$), 7.0–7.5 (m, 6H, arom CH), 9.12 (2d, 2H, 4-H); $^{13}$C NMR δ: 26.1 (q), 108.5 (d), 120.6 (s), 121.8 (d), 129.1 (d), 132.7 (d), 132.8 (s), 145.1 (s), 168.0 (s).

**3,3′-Bis(morpholino)oxindole 16.** Morpholine (261 mg, 3 mmol) was added to the sulfine **13a** (358 mg, 2 mmol) in acetonitrile (6 mL). A white solid appeared within 2 min, which was collected and washed with water after 30 min at 25°C, 395 mg (64%), mp. 177–179°C (lit. [26] 177–179°C). The spectral data were in agreement with those in the literature [26].

***S*-Methyl-3-thiolo-oxindole 17.** A stream of methanthiol was introduced into a stirred suspension of the sulfine **13a**, 1.79 g, 10 mmol) in acetonitrile (80 mL) at 35°C. When the dark violet starting material had been consumed (~1 h) the solution was evaporated and the crude product recrystallized form ethanol, 1.41 g (72%) mp. 125–127°C (lit. [18] 125.5–127°C). The NMR data were in agreement with those reported in the literature [21]. The signal from the 3-C carbon atom resonated at 45.5 ppm.

***S*-Carboxymethyl-3-thiolo-oxindole 18a.** The sulfine **13a** (358 mg, 2 mmol) was added to a solution of thioloacetic acid (202 mg, 2.3 mmol) in acetonitrile (8 mL). As there seemed to be no reaction at ambient temperature the reaction mixture was heated at reflux for 20 min. During this period, the solution became colorless. After concentration and treatment with ether, the product was obtained as colorless crystals, 360 mg, (81%) mp. 160–162°C. IR 3280, 1700, 1621, 1469, 1177, 1120, 872, 740 $cm^{-1}$; $^1H$ NMR δ: 3.48 (q, 2H, $CH_2$, $J = 15.2$ ppm), 4.81 (s, 1H, 3-CH), 6.85–7.34 (m, 4H, arom CH), 10.6 (s, 1H, NH), 12.8 (br. s, 1H, OH). $^{13}C$ NMR δ: 40.7 (t), 50.6 (d), 109.6 (d), 121.8 (d), 124.9 (d), 126.4 (s), 129.5 (d), 143.0 (s), 170.0 (s), 175.2 (s). Anal. calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.07; N, 6.27; Found: C, 53.63; H, 4.20; N, 6.05.

**Methyl *S*-carboxymethyl-3-thiolo-oxindole 18b.** Methyl thioloacetate (233 mg, 2.3 mmol) was added to the sulfine **13a** (351 mg, 2.0 mmol) in acetonitrile (6.0 mL) at 45°C. The color faded quickly. After 10 min the solution was evaporated and the oil obtained was treated with methyl acetate/diisopropyl ether (1:4), which gave crystals of the product, 371 mg (79%), mp. 109–110°C; IR: 3146, 1730, 1704, 1673, 1617, 1470, 1281, 1266, 1005, 743, 676 $cm^{-1}$; $^1H$ NMR 3.53 (q, 2H, $CH_2$), 3.63 (s, 3H, $OCH_3$), 4.84 (s, 1H, 3-CH), 6.83–7.33 (m, 4H, arom CH), 10.6 (s, 1H, NH); $^{13}C$ NMR 40.1 (t), 50.6 (q), 52.2 (d), 109.7 (d), 121.8 (d), 125.2 (d), 126.3 (s), 129.4 (d), 143.0 (s), 169.1 (s), 175.1 (s). Anal. calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90 Found: C, 55.73; H, 4.78, N, 5.90.

**The monocarboxylic acid 19a.** Isatin (14.7 g, 0.1 mmol) and thioloacetic acid (9.2 g, 0.1 mol) was heated in dioxan (30 mL) for 0.5 h. After concentration, the residue was treated with methanol/water 1:2, which gave the title compound, 20.1 g (84%), mp. 191–193°C. IR 3288, 3100–2550, 1728, 1693, 1613, 1469, 1422, 1267, 1131, 916, 822, 749 $cm^{-1}$; $^1H$ NMR δ: 3.75 (2H, q), 6.88 (d, 1H), 7.02 (dd, 1H), 7.13 (dd, 1H), 7.39 (d, 1H), 10.4 (s, 1H); $^{13}C$ NMR δ: 29.7 (t), 77.9 (s), 109.9 (d), 121.9 (d), 124.0 (d), 129.1 (s), 130.1 (d), 139.8 (s), 171.1 (s), 174.6 (s). Anal. calcd. for $C_{10}H_8NO_4S$: C, 50.20; H, 3.79; N, 5.84; Found: C, 49.81; H, 3.85; N, 5.72.

**The dicarboxylic acid 19b.** Isatin (14.7 g, 0.1 mmol) and thioloacetic acid (20.2 g, 0.22 mmol) in dioxane (50 mL) was heated to reflux for 3 h. After concentration, the residue was treated with methanol/water 1:1, which quickly yielded crystals of the product 26.8 (86%); mp. 202–204 °C. IR 3288, 3170–2300, 1731, 1697, 1615, 1469, 1175, 1057, 904, 750 $cm^{-1}$; $^1H$ NMR δ: 3.96 (s, 4H), 6.90 (d, 1H), 7.03 (dd, 1H), 7.29 (dd, 1H), 7.33 (d, 1H), 10.9 (s, 1H, NH), 12.7 (s, 2H, OH); $^{13}C$ NMR δ: 32.4 (t), 55.1 (s), 110.3 (d), 122.4 (d), 124.3 (d), 127.8 (s), 130.1 (d), 140.3 (s), 170.0 (s), 173.6 (s). Anal. calcd. for $C_{12}H_{11}NO_5S_2$: C, 45.99; H, 3.54; N, 4.47 Found: C, 45.85; H, 3.66; N,4.32.

## REFERENCES AND NOTES


[1] Zwanenburg, B. Houben-Weyl 2002, E 11/2, 911.

[2] Zwanenburg, B. Sci Synth 2004, 27, 135.

[3] Zwanenburg, B.; Damen, T. J. G.; Philipse, H. J. F.; De Laet, R. C.; Lucassen, A. C. B. Phosphorus Sulfur Silicon 1999, 153/154, 119.

[4] Zwanenburg, B. Rec Trav Chim 1982, 101, 1.

[5] Lenz, B. G.; Regeling, H.; van Rozendaal, H. L. M.; Zwanenburg, B. J Org Chem 1985, 50, 2930.

[6] Lenz, B. G.; Haltiwanger, R. C.; Zwanenburg, B. JCS Chem Commun 1984, 502.

[7] Lenz, B. G.; Regeling, H.; Zwanenburg, B. Tetrahedron Lett 1984, 25, 5947.

[8] Faull, A. W.; Hull, R. J Chem Soc Perkin Trans 1, 1981, 1078.

[9] Morita, H.; Takeda, M.; Yoshimura, T.; Fujii, T.; Ono, S.; Shimasaki, C. J Org Chem 1999, 64, 6730.

[10] Pfeifer, K.-P.; Himbert, G. Tetrahedron Lett 1990, 31, 5725.

[11] Black D. St. C.; Fallon, G. D.; Gatehouse, B. M.; Wishart, J. D. Aust J Chem 1984, 37, 777.

[12] De Martiis, F. Ann Chim (Rome) 1957, 47, 1238.

[13] O'Sullivan, O. C. M.; Collins, S. G.; Maguire, A. R. Syn Lett 2008, 659.

[14] Sander, W.; Strehl, A.; Maguire, A. R.; Collins, S.; Kelleher, P. G. Eur J Org Chem 2000, 3329.

[15] Maguire, A. R.; Kelleher, P. G.; Lawrence, S. E. Tetrahedron Lett 1998, 39, 3849.

[16] Boccardo, G.; Capozzi, G.; Giuntini, M.; Menichetti, S.; Nativi, C.; Tetrahedron 1997, 53, 17383.

[17] Gassman, P. G.; Cue, B. W., Jr., Luh, T.-Y. J Org Chem 1977, 42, 1344.

[18] Gassman, P. G.; van Bergen, T. J. J Am Chem Soc 1974, 96, 5508.

[19] Strating, J.; Thijs, L.; Zwanenburg, B. Rec Trav Chem 1967, 86, 641.

[20] Giovannini, E.; Portmann, P. Helv Chim Acta 1948, 31, 1375.

[21] Gassman, P. G.; Gilbert, D. P.; Luh, T.-Y. J Org Chem 1977, 42, 1340.

[22] Coutts, R. T.; Hindmarsch, K. W.; Mah, E. Can J Chem 1970, 48, 3747.

[23] Sumpter, W. C.; Miller, M.; Hendrick, L. N. J Am Chem Soc 1945, 67, 1656.

[24] Kosuge, T.; Ishida, H.; Inaba, A.; Nukaya, H. Chem Pharm Bull 1985, 33, 1414.

[25] Bergman, J.; Bergman, S.; Brimert, T. Tetrahedron 1999, 55, 10447.

[26] Bergman, J.; Stålhandske, C.; Vallberg, H. Acta Chem Scand 1997, 51, 753.

[27] Joshi, K. C.; Dandia, A.; Bhagat, S. J Fluorine Chem 1990, 48, 169.

[28] Bergmann, E. D. J Am Chem Soc 1955, 77, 1549.

[29] Ziegler, E.; Kappe, T.; Salvador, R. Monatshefte f Chemie 1963, 94, 453.

[30] Perpète, E. A.; Preat, J.; André, J.-M.; Jacquemin, D. J Phys Chem 2006, 110, 5629.

[31] Shermolovich, Y. G.; Emets, S. V.; Tolmachev, A. A. Chem Het Comp 2003, 39, 1076.

[32] Lathourakis, G. E.; Litinas, K. E. J Chem Soc Perkin Trans 1, 1996, 491.

[33] Banerji, A.; Maiti, S. Ind J Chem B 1994, 33, 532.

[34] Harley-Mason, J.; Ingleby, R. T. J. J Chem Soc 1958, 4782.

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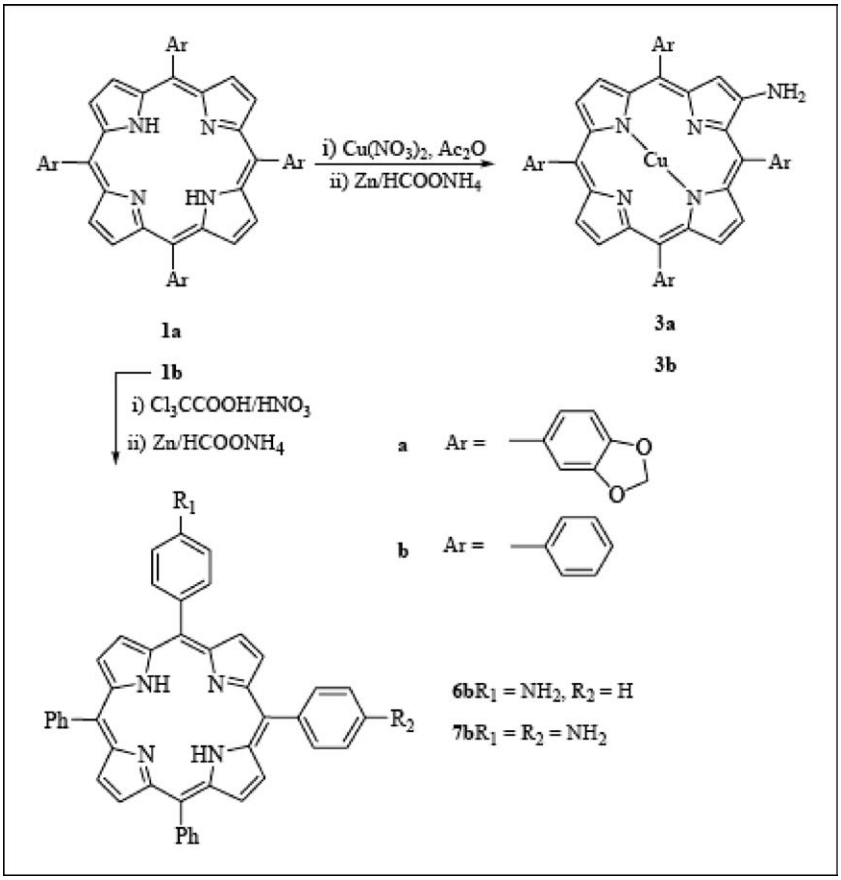


Modified nitration of tetraphenylporphyrin at para of phenyl with $HNO_3/Cl_3CCOOH$ and one-pot nitration of free tetraarylporphyrins to metalized 2-nitroporphyrin in high yield are described. A novel reducer of $Zn/HCOONH_4$ has been developed for above nitro of porphyrin into amino effectively.

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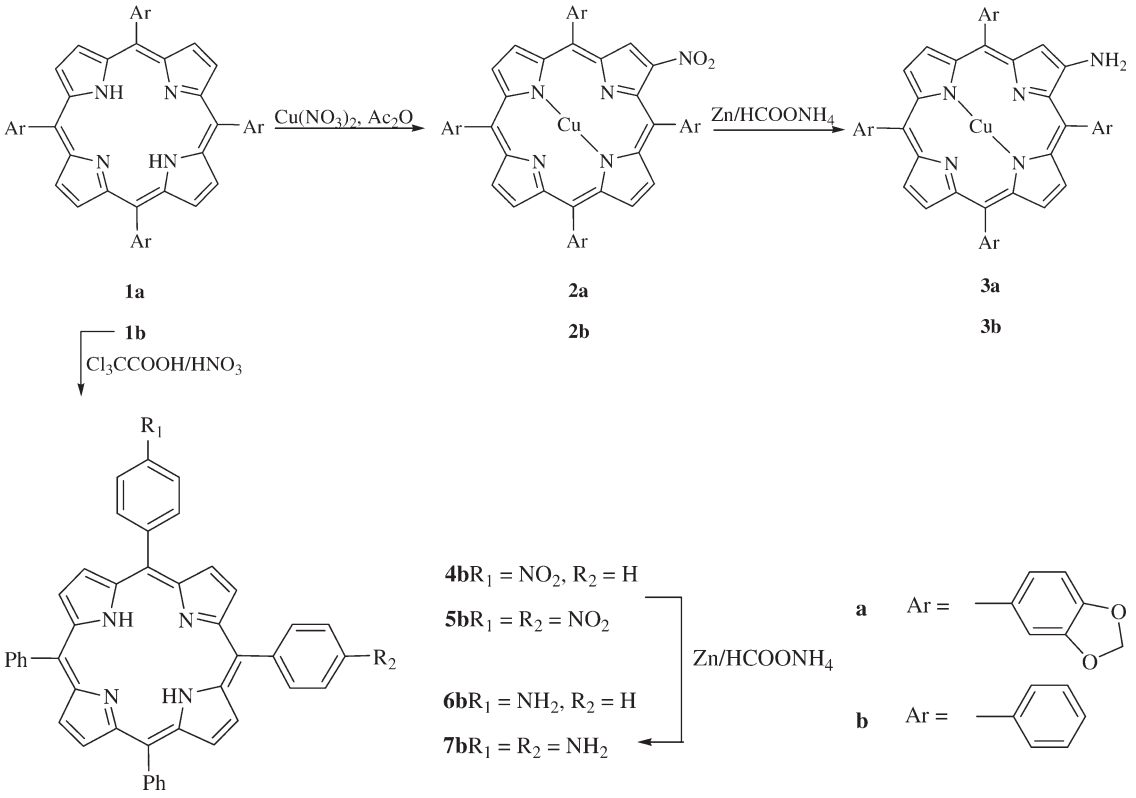
## INTRODUCTION

Over the last three decades, functionalization of porphyrins has received considerable attention for introducing functions into porphyrins could varied the properties of porphyrins and afford availability of diverse porphyrin architecture by arising a energetic bond for further functionalization [1]. Therefore, fairish efforts were underway in various laboratories to explore novel and available approach to modify porphyrins [2]. *meso*-Tetraarylporphyrin (TAP) including tetraphenylporphyrin (TPP) is one of the most readily available synthetic porphyrin [3], so modifying its porphyrin macrocycle or aryl around was an available way to get various novel porphyrins [4]. The nitration modification has been investigated in detail by many reagents [5]. The sort of porphyrin containing amino function has wide use in the architecture of porphyrins with extended π-system, chlorines, porphyrin assembly, supermolecule propertie [6].

We have afforded access to nitro TPP by nitration of para of phenyl, which was transformed into widely useful amino function for subsequent modification [7].

**Scheme 1.** Synthesis of amino porphyrin via nitration and reduction.




Herein, we report the synthesis of TAP by modified Alder–Longo method condensing pyrrole with acid sensitive 3,4-methylenndioxyphenylaldehyde, sequent modified nitration of phenyl, as well as one-pot nitration of porphyrin periphery. A rapid and efficient process for reduction of nitro group at phenyl or β of porphyrin into amino has been developed.

## RESULTS AND DISCUSSION

On account of the fact that *meso*-TPP **1b** was particularly readily prepared, it should be a handy way to achieve a variety of substituted porphyrins by introducing suitable group to TPP, especially at the phenyl rings. A few workers reported phenyl para nitration of TPP with fuming nitric acid, or $NaNO_2$/TFA (trifluoroacetic acid). As shown in Scheme 1, condensation of pyrrole with aromatic aldehyde in refluxing xylene under *meta*-nitrobenzoic acid provided porphyrin **1a** and **1b** in moderate yield of somewhat 50%. The starting porphyrin TPP was subjected to nitration to afford porphyrin containing mono and bis-nitro phenyl. Instead of TFA/$NaNO_2$, which was used in the Smith's method, the solid trichloroacetic acid and concentrated nitric acid was found to be effect, preferable control for this reaction. In chloroform, TPP was translated into porphyrins **4b** and **5b** at room temperature under air condition with total yield 81%.

In the molecule of TAP, β-site of pyrrolic is another active site as well as para-site of phenyl, and nitration at this site with various reagents and the further reduction had been investigated in detail by many researchers [8]. The earlier works showed that there were two steps, including metallization of free porphyrins with chloride or acetate and nitration using nitrate salt. Cuprous ion was found to readily insert into core of free porphyrins during treatment with cuprous ion, implying that metallization and nitration both could be likely conducted by sole cuprous nitrate. The previous nitration through two steps may be pieced together. The attempt to ''one-pot'' nitration with acetic anhydride and cuprous nitrate was successful in excellent yield. Nitration of free base porphyrins **1a** and **1b** by $Cu(NO_3)_2$ and $Ac_2O$ for 2 h resulted in **2a** and **2b** with nitro group at β-site.

Nitrobenzenes were successfully converted into corresponding azoaryl by Zn/$HCOONH_4$ [9], similarly, we would prepare azoaryl porphyrin [10] from nitro compound. As shown in Scheme 1, an unpredicted amino porphyrin was achieved starting with **4b** under similar conditions. No azoaryl products came into being no matter how we regulated the reaction conditions, such as

temperature, stoichiometry of reagent, solvent, and reaction times. Treatment of nitro porphyrins **4b** and **5b** at room temperature in $CHCl_3$ with large excess Zn/$HCOONH_4$ gave rapidly corresponding amino porphyrins over a few minutes in yield up to 90%. As alike as **4b** and **5b** with *para*-nitrophenyl porphyrin, easy reduction of **2a** and **2b** with nitro at β-site produced **3a** and **3b** in high yield.

Most reductions of nitro were actualized by $SnCl_2$/HCl or hydrogenation with Pd/C. However, many functions were sensitive to strong acid, as well as the hardness of separating inorganic objects was trying. Although Pd/C is high efficient, it is somewhat inconstant. An attempt of reduction was unsuccessful, the great mass of material spared when crude nitration product from TPP was performed with Pd/C. The value of here process is nevertheless very obvious: milder conditions, simpler experimental procedure.

In summary, we have shown an effective nitration at para of phenyl of tetraphenylporphyirn with $HNO_3$/$Cl_3CCOOH$, and ''one-pot'' nitration of free TAPs by $Cu(NO_3)_2$/$(CH_3CO)_2O$ excellently. The process for reduction of nitro at above porphyrins into amino using Zn/$HCOONH_4$ was rapid, convenient, and excellent. Further transformation for application of amino porpyrins is underway.

## EXPERIMENTAL

**General.** Pyrrole was purchased from Aldrich and distilled under reduced pressure immediately before use. All other reagents and solvents were used as received from Aldrich. Solvents were reagent grade unless otherwise specified and were dried and distilled by standard method. The UV-visible spectra were obtained on a Perkin-Elmer LS-5B spectrofluroimeter. $^1H$ NMR spectra were recorded on BRUKER AVANCE DMX 500 spectrometer. Elementary analyses were obtained on a Carlo Erba 1106 Elemental Analyzer.

Porphyrins **1b**, **1a** were synthesized by literature methods [7]. Spectra of porphyrins **1b–7b** were agreement with literature.

***5,10,15,20-Tetra (3,4-methylendioxy)phenylporphyrin (1a).*** Porphyrin **1a** was synthesized in yield 48%. $^1H$ NMR (deuterichloroform): δ 8.92–8.80 (8H, m, β -pyrrole), 7.70–7.63 (m, 8H), 7.24–7.17 (m, 8H), 6.25 (s, 4H), −2.73 (s, 2H). UV $\lambda_{max}$: 419.0, 516.0, 554.0, 597.0, 648.0 nm. *Anal*. Calcd. for $C_{48}H_{30}N_4O_8$: C, 72.90; H, 3.82; N, 7.09. Found: C, 72.73; H, 3.91; N, 7.17.

***5-(4-Nitrophenyl)-10,15,20-triphenyl-porphyrin (4b) and 5,10-di(4-nitrophenyl)-15,20-diphenyl-porphyrin (5b).*** To a solution of porphyrin **1b** (1 g, 1.6 mmol) and trichloroacetic acid (30 g) in chloroform (100 mL) was slowly added $HNO_3$ (6.0 mL, 75%, 15.5 mmol) over 2 min with fierce stir at room temperature under atmosphere. The mixture was stirred for 5 min. Reaction was quenched with water, and the mixture was neutralized with ammonium hydroxide aqueous solution to pH = 7. Chloroform (100 mL) was added, and the organic layer was washed with water (4 × 150 mL), and dried over magnesium sulfate. Solvent was removed with evaporation under reduced pressure. The crude product was purified by column chromatography to provide **4b** (370 mg, 36%) and **5b** (506 mg, 45%).

**General procedure for nitration of β at porphyrin.** To a solution of porphyrins in $Ac_2O$ and chloroform, $Cu(NO_3)_2$ was added. The mixture was heated to reflux, kept for 2 h. Solvent was evaporated in a vacuum. Purification on silica gel gave nitro porphyrins in yields of about 90%.

***(2-nitro-5,10,15,20- tetra (3,4-methylendioxy)phenylporphyrinato)copper-II (2a).*** Porphyrin **1a** (500 mg, 0.8 mmol) in $Ac_2O$ (20 mL, 0.2 mol) by $Cu(NO_3)_2 \bullet 3H_2O$ (800 mg, 3.3 mmol) gave porphyrin **2a** in yield 86%. IR: $NO_2$ 1508, 1345 $cm^{-1}$. UV: $\lambda_{max}$ 432, 552.5, 595.5 nm. *Anal*. Calcd. for $C_{48}H_{27}CuN_5O_{10}$: C, 64.25; H, 3.03; N, 7.80. Found: C, 64.33; H, 3.09; N, 7.65.

**General procedure for reduction of nitro function to amino function.** To a solution of nitro porphyrins in $CHCl_3$, Zn powder, and $HCOONH_4$ was added with fierce stirring. The mixture was kept at room temperature for a little of 5 min. The solid inorganic was removed by filtration. Solution of porphyrin was washed by water, followed by drying with magnesium sulfate. Solvent was evaporated in a vacuum. The crude product was purified on a silica gel column, providing amino porphyrins in yield of 82–90%.

***(2-Amino-5,10,15,20-tetra (3,4-methylendioxy)phenylporphyrinato)copper-II (3a).*** Porphyrin **2a** (200 mg, 0.8 mmol) in $CHCl_3$ (50 mL) with Zn powder (5.0 g, 0.1 mol) and $HCOONH_4$ (8.0 g, 0.1 mol) gave porphyrin **3a** in yield 86%. IR: $NH_2$, 3475, 1483, 1247, 1036 $cm^{-1}$. UV: $\lambda_{max}$ 419, 547, 596nm. *Anal*. Calcd. for $C_{48}H_{29}CuN_5O_8$: C, 66.47; H, 3.37; N, 8.07. Found: C, 66.32; H, 3.43; N, 8.16.

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## RERENCES AND NOTES

[1] Kadish, K. M.; Smith, K. M.; Guilard R. The porphyrin Handbook; Academic Press: San Diego, 2000–2003; Vol. 1–20.

[2] (a) Arnold, D. P.; Johnson, A. W.; Mahendram, M. J Chem Soc Perkin Trans 1978, 1, 366; (b) Jiang, X.; Nurco, D. J.; Smith, K. M. J Chem Soc Chem Commun 1996, 1759; (c) Yeung, M.; Ng, A. C. H.; Drew, M. G. B.; Vorpagel, E.; Breitung, E. M.; McMahon, R. J.; Ng, D. K. P. J Org Chem 1998, 63, 7143.

[3] (a) Adler, A. D.; Longo, F. R.; Finarelli, J. D. J Org Chem 1967, 39, 476; (b) Lindsey, J. S.; Wagner, R. W. J Org Chem 1989, 54, 828.

[4] (a) Tabushi, I.; Kugimiya, S. J Am Chem Soc 1986, 108, 6926; (b) Tommaso, A. V.; Timothy, K. Inorg Chem 1999, 38, 2246; (c) Burrell, A. K.; Campbell, W. M.; Officer, D. L.; Gordon, K. C.; McDonald, M. R. J Chem Soc Dalton Trans 1999, 19, 3349.

[5] (a) Anura, W; Lanurent, J; Daniel, J. N.; Smith, K. M. Tetrahedron 2001, 57, 4261; (b) Guangzhen, G. M.; James, B. R.; Skov, K. A. Can J Chem 1994, 72, 1894.

[6] (a) Crossly, N. J.; Burn, P. L.; Langford, S. J.; Pyke, S. M.; Stark, A. G. J Chem Soc Chem Commun 1991, 1567; (b) Seaaler, J. L.; Brown, C. T.; O'Connor, D.; Springs, S. L.; Wang, R.; Sathiosatham, M.; Hirose, T. J Org Chem 1998, 63, 7370; (c) Promarak, V.;

Burn, P. L. J Chem Soc Perkin Trans 2001, 1, 14; (d) Starnes, S. D.; Arundundram, S.; Saunders, C. H. Tetrahedron Lett 2002, 43, 7785.

[7] (a) Wu, J.; Shi, W. M.; Wu, D. Chem Lett 2004, 33, 460; (b) Wu, J.; b. Shi, W. M.; Zhang, G.; Dai, G. F.; Zhang, Y. X.; Zhao, J.; Tao, J. C. Bioorg Med Chem 2008, 16, 5665.

[8] (a) Baldwin, J. E.; Crossley, M. J.; Bernardis, J. Tetrahedron 1982, 38, 685; (b) Catalano, M. M.; Crossley, M. J.; Harding, M. M.; King, L. G. J Chem Soc Chem Commun 1984, 1535; (c) Evans, B.; Smith, K. M.; Cavaleiro, J. A. S. J Chem Soc Perkin Trans 1978, 1, 768.

[9] (a) Gowda, S.; Gowda, D. C. Synthesis 2002, 4, 460; (b) Srinivasa, G. R.; Abiraj, K.; Gowda, D. C. Syn Commu 2003, 33, 4221.

[10] (a) Hombrecher, H. K.; Lüdtke, K. Tetrahedron 1993, 49, 9489; (b) Autret, M.; Plouzennec, M. Le; Moinet, C.; Simonneaux, G. J Chem Soc Chem Commun 1994, 1169.

# Synthesis of Some Novel 3-Alkyl/aryl-6-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles



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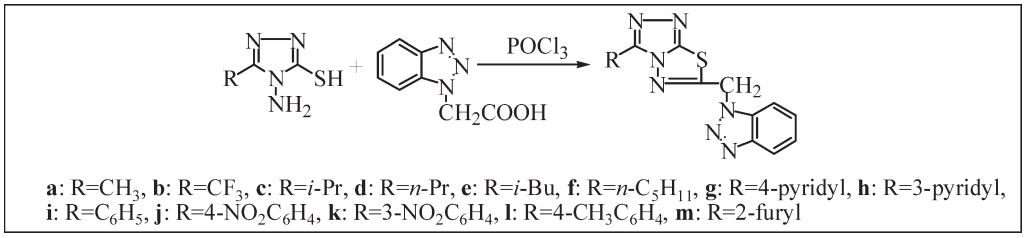


**a**: R=$CH_3$, **b**: R=$CF_3$, **c**: R=*i*-Pr, **d**: R=*n*-Pr, **e**: R=*i*-Bu, **f**: R=*n*-$C_5H_{11}$, **g**: R=4-pyridyl, **h**: R=3-pyridyl, **i**: R=$C_6H_5$, **j**: R=4-$NO_2C_6H_4$, **k**: R=3-$NO_2C_6H_4$, **l**: R=4-$CH_3C_6H_4$, **m**: R=2-furyl

A series of 3-alkyl/aryl substituted-6-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles **4a–m** are prepared by the condensation of 3-alkyl/aryl substituted-4-amino-5-mercapto-1,2,4-triazoles **2a–m** with benzotriazole-1-yl acetic acid **3** through a single step reaction. The structures of all newly synthesized compounds are established on the basis of their IR, $^1$H NMR, and elemental analyses data. Two selected compounds **4l** and **4m** are investigated for their analgesic and anti-inflammatory activities; they showed weak anti-inflammatory activity and no analgesic activity.

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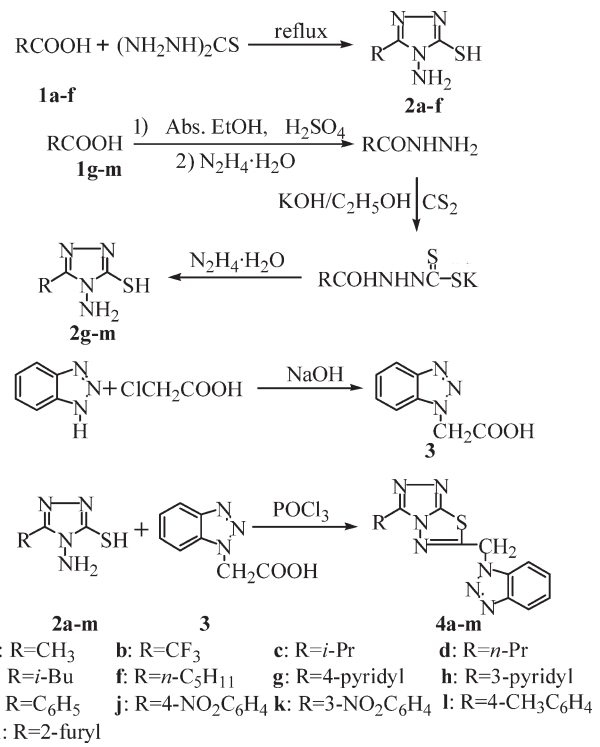
## INTRODUCTION

1,2,4-Triazoles and their heterocyclic derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities, such as antifungal [1], antibacterial [2], antihypertensive [3], antileishmanial [4], anti-inflammatory [5], antiviral [6] activities. A large number of thiadiazole-containing ring system exhibits antibacterial [7] and antituberculosis [8] properties. Moreover, a survey of literature reveal that [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole rings received much attention during recent years on account of their prominent utilization as antifungal [9], anti-inflammatory [10,11], antiviral, analgesic [12], anthelmintic [13], anti-HIV-1 [14], and antibacterial agents [15]. A triazolo thiadiazole system may be viewed as a cyclic analogue of two very important components thiosemicarbazide [16] and biguanide [17], which often display diverse biological activities. On the other hand, benzotriazole derivatives are of wide interest because of their diverse biological activity and potential clinical applications such as anti-inflammatory, antiviral, inactivator of Severe acute respiratory syndrome (SARS) protease and so on [18]. Therefore, it is envisaged that chemical entities with both [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles and benzotriazole would generate new interesting biological activities. In continuation of our ongoing research program aimed at developing new biologically active nitrogen and sulphur containing heterocycles, here we report the reaction of 3-alkyl/aryl substituted-4-amino-5-mercapto-1,2,4-triazoles **2a–m** with benzotriazole-1-yl acetic acid **3** in the presence of phosphorous oxychloride to give 3-alkyl/aryl-6-((1*H*-benzo[*d*][1,2,3]-triazol-1-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles **4a–m** (Scheme 1). In view of the reported biological activities of triazolo thiadiazoles, two selected compounds **4l** and **4m** are studied for their anti-inflammatory and analgesic activities.

## RESULTS AND DISCUSSION

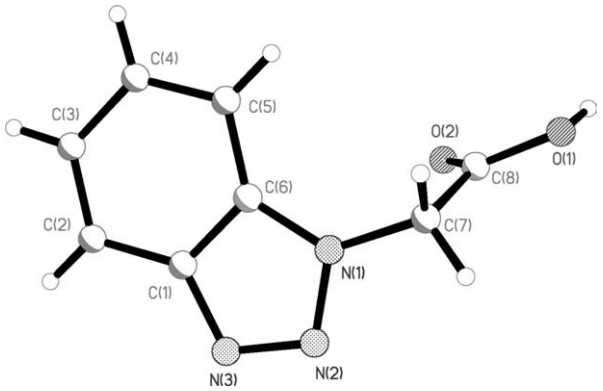
The reaction sequences employed for synthesis of title compounds are shown in Scheme 1. The 3-alkyl-4-amino-5-mercapto-1,2,4-triazoles **2a-f** are synthesized by reacting alkyl acid with thiocarbohydrazide [19]. The required aromatic hydrazides are prepared by esterification of aromatic acid **1g-m** followed by treatment with hydrazine hydrate in absolute ethanol. The aromatic hydrazides are allowed to react with carbon disulphide in the presence of potassium hydroxide in ethanol to afford the corresponding intermediate potassium dithiocarbazinate. This salt undergoes ring closure with an excess of 80% hydrazine hydrate to give 4-amino-3-aryl-5-mercapto-1,2,4-triazoles **2g-m** [20]. Benzotriazole-1-yl acetic acid **3** is prepared by treating benzotriazole with chloroacetic acid in sodium hydroxide solution

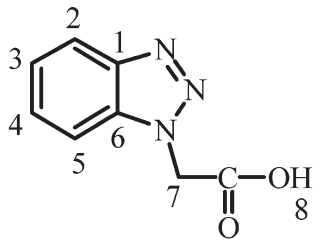
**Scheme 1**




[21]. Condensation of 3-alkyl/aryl substituted-4-amino-5-mercapto-1,2,4-triazoles **2a–m** with benzotriazole-1-yl acetic acid **3** in presence of boiling phosphorous oxychloride yield 3-alkyl/aryl substituted-6-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles **4a–m** in 53–98% yields. Phosphorous oxychloride is necessary for this condensation, which activate the carbonyl group of acids and increase its electrophilicity to enhance the addition of 1,2,4-triazoles to the target compounds.

The structural elucidation of **3** is completed by analysis of gHSQC and gHMBC data. We can see that $^{3}J_{H7\text{-}C6}$ (Fig. 1). In addition, we get the single crystal of compound **3**. So compound **3** is benzotriazol-1-yl-acetic acid but not benzotriazol-2-yl-acetic acid.




NMR data for compound **3** (DMSO-$d_6$).

| Position | δ | |
|---|---|---|
| | $\delta_H$ | $\delta_C$ |
| 1 | – | 145.7 |
| 2 | 8.07(d) | 119.7 |
| 3 | 7.42 (t) | 124.6 |
| 4 | 7.58 (t) | 128.1 |
| 5 | 7.84 (d) | 111.4 |
| 6 | – | 134.2 |
| 7 | 5.66 (s) | 169.3 |
| 8 | 13.43 (brs) | – |

**Figure 1.** Benzotriazole-1-yl acetic acid.

The structure assignments to new compounds **4a–m** are based on their elemental analyses and spectral data (IR, $^{1}$H NMR). The IR spectra of the cyclized products **4a–m** show a characteristic absorption at 1445–1592 $cm^{-1}$ attributed to benzene ring of benzotriazole stretching. The band in the range of 1610–1614 $cm^{-1}$ indicate the absorption of C=N. In the $^{1}$H NMR spectra of compounds **4a-m**, the absorption bands characteristic of the $-CO_2H$ and $-NH_2$ groups are absent, thereby indicating the involvement of the amino group of triazole and the carboxylic group of benzotriazole-1-yl acetic acid in the condensation reaction. Moreover, we discover $CH_2$ resonance appear singlets at 6.08–6.79 ppm. Thus, it is further confirmed the involvement of these functional groups in the cyclization of triazoles to triazolo thiadiazoles.

The inhibition ratio of compounds **4l** and **4m** are 8 and 22%, they show weak anti-inflammatory activity (Table 1). **4l** and **4m** are further tested for their analgesic activity; unfortunately the results are not very good, as they show no analgesic activity (Table 2).

**Table 1**

Anti-inflammatory activity tests.

| | Inhibition ratio |
|---|---|
| **4l** | 8% |
| **4m** | 22% |

**Table 2**

Analgesic activity tests.

| | 20 min | 40 min | 60 min |
|---|---|---|---|
| **4l** | 0 | 0 | 12.76% |
| **4m** | 10.07% | 0 | 0 |

## EXPERIMENTAL

The IR spectra are obtained as potassium bromide pellets with a FTS-40 spectrometer (BIO-RAD, U.S.A). The one-dimensional ($^1$H) and two-dimensional (gHSQC, gHMBC) NMR spectra are obtained on a Varian Inova-400 (400 MHz) spectrometer using $CDCl_3$ or DMSO-$d_6$ as solvent (shown in detail in data part) and tetramethylsilane as an internal standard, chemical shifts are given in ppm. Elemental analyses (C, H, N) are performed on a Perkin-Elmer Analyzer 2400. Melting points are determined using a Büchi B-540 instrument and are uncorrected (Tables 3–6).

**Table 3**

Crystal data and summary of data collection and structure refinment.

| Compound | $C_8H_7N_3O_2$ |
|---|---|
| Color/shape | Colorless/chip |
| Formula weight | 177.17 |
| Temperature (°C) | 293(2) |
| Crystal system | Monoclinic |
| Space group | P2(1)/c |
| Cell constants | |
| a (Å) | 13.234(2) |
| b (Å) | 4.4889(7) |
| c (Å) | 15.142(2) |
| α (°) | 90.00 |
| β (°) | 113.135(3) |
| γ (°) | 90.00 |
| Volume (Å$^3$) | 827.2(2) |
| Formula units/units cell | 4 |
| $D_{calc}$ (g cm$^{-3}$) | 1.423 |
| $F$ (000) | 368.0 |
| Absorption coefficient, m $\mu^{-1}$ | 0.106 |
| Diffractometer/Scan | Enraf-Noius CAD4, ω/2θ |
| Radiation, graphite | λ = 0.71073 Å |
| Monochromator Mo Kα | |
| Reflections for cell measurement and θ range (°) | 27.48, 3.35–27.48 |
| Index ranges | $-17 \le h \le 17$; $-5 \le k \le 5$; $-19 \le l \le 19$ |
| Reflection observed [$1 > 2\sigma(I)$] | 1775 [R(int) = 0.0249] |
| Maximum value of θ(°) | 27.48 |
| Computing | Data collection CAD4<br>Cell refinement CAD4<br>Data reduction PCSDP |
| Structure solution | SHELXL-97 |
| Structure refinement | SHELXL-97 |
| Data/restrains/parameters | 1775/0/123 |
| Goodness-of-fit on $F^2$ | 1.071 |
| Final $R$ indices | $R_1 = 0.0406$; $wR_2 = 0.1115$ |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.208 and −0.186 |

**Table 4**

The fractional coordinates and mean temperature factors with estimated standard deviations.

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| O1 | 0.39231 (10) | 0.5275 (3) | 0.16463 (9) | 0.0530 (4) |
| O2 | 0.26751 (15) | 0.2779 (4) | 0.19909 (10) | 0.0896 (6) |
| N1 | 0.34289 (11) | 0.5060 (3) | 0.38224 (9) | 0.0421 (4) |
| N2 | 0.38836 (12) | 0.3101 (4) | 0.45424 (9) | 0.0472 (4) |
| N3 | 0.32632 (12) | 0.2965 (4) | 0.50331 (10) | 0.0484 (4) |
| C1 | 0.23907 (14) | 0.4873 (4) | 0.46255 (11) | 0.0435 (4) |
| C2 | 0.15091 (16) | 0.5552 (5) | 0.48832 (15) | 0.0580 (5) |
| H2B | 0.1442 | 0.4699 | 0.5418 | 0.070 |
| C3 | 0.07567 (18) | 0.7523 (5) | 0.43111 (17) | 0.0670 (6) |
| H3B | 0.0155 | 0.8006 | 0.4455 | 0.080 |
| C4 | 0.08574 (16) | 0.8857 (5) | 0.35093 (16) | 0.0635 (6) |
| H4A | 0.0321 | 1.0196 | 0.3141 | 0.076 |
| C5 | 0.17192 (15) | 0.8249 (4) | 0.32535 (13) | 0.0525 (5) |
| H5A | 0.1788 | 0.9136 | 0.2725 | 0.063 |
| C6 | 0.24864 (13) | 0.6217 (4) | 0.38365 (11) | 0.0404 (4) |
| C7 | 0.39868 (14) | 0.5775 (5) | 0.31981 (11) | 0.0472 (4) |
| H7A | 0.4739 | 0.5066 | 0.3489 | 0.057 |
| H7B | 0.4009 | 0.7922 | 0.3136 | 0.057 |
| C8 | 0.34422 (15) | 0.4428 (4) | 0.22160 (12) | 0.0456 (4) |
| H1 | 0.360 (2) | 0.419 (6) | 0.1049 (19) | 0.094 (8) |

**Benzotriazole-1-yl acetic acid (3).** Add 4.8 g (40 mmol) benzotriazole, 3.8 g (40 mmol) chloroacetic acid, 3.2 g (80 mmol) sodium hydroxide, and 100 mL water into a round bottom flask, reflux slowly for 3 h, filter immediately after reflux. The filtrate is cooled at room temperature and acidified with dilute hydrochloric acid till no deposit appear. It is filtered and washed thoroughly with cold water, dried, and recrystallized from butanol, Yield 78%, mp 216–218°.

gHMBC: (DMSO-$d_6$): $^3J_{H3\text{-}C1}$, $^3J_{H5\text{-}C1}$, $^3J_{H4\text{-}C2}$, $^3J_{H5\text{-}C3}$, $^3J_{H2\text{-}C4}$, $^3J_{H3\text{-}C5}$, $^3J_{H4\text{-}C6}$, $^3J_{H2\text{-}C6}$, $^3J_{H7\text{-}C6}$. Anal. Calcd. for $C_8H_7N_3O_2$ (177.16): C, 54.24; H, 3.98; N, 23.72. found: C, 54.43; H, 3.92; N, 23.61.

**General procedure for preparation synthesis of 3-alkyl/aryl substituted-6-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (4a–m).** An equimolar mixture of respective triazole **2a–m** (1 mmol) and benzotriazole-1-acetic acid (1 mmol) in phosphorus oxychlorid (8 mL) are refluxed for 7 h. Excess of phosphorus oxychlorid is removed under reduced pressure. The resulting reaction mass is cooled and gradually poured onto crushed ice with stirring, the result mixture is allowed to stand overnight and the solid separated out is filtered. Finally, the filter cake is washed thoroughly with water till the pH of the filtrate is raised to 7, dried, and recrystallized from a mixture of DMF and ethanol.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-methyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4a).** This compound was obtained as white needle solid, 87% yield, mp 141–142°; IR (KBr): 3090, 2986, 2933, 1608, 1592, 1536, 1494, 1464, 1290 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.75 (s, 3H), 6.13 (s, 2H), 7.45–8.16 (m, 4H). Anal. Calcd. for $C_{11}H_9N_7S$ (271.30): C, 48.70; H, 3.34; N, 36.14. Found: C, 48.82; H, 3.28; N, 36.27.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4b).** This compound was obtained as white solid, 93% yield, mp 148–151°; IR (KBr): 3094, 2937, 1613, 1592, 1544, 1524, 1497, 1295 cm$^{-1}$; $^1$H

**Table 5**

Selected bond lengths.

| | | |
|---|---|---|
| O1 | C8 | 1.3136 (19) |
| O1 | H1 | 0.97 (3) |
| O2 | C8 | 1.193 (2) |
| N1 | N2 | 1.3448 (19) |
| N1 | C6 | 1.359 (2) |
| N1 | C7 | 1.4457 (19) |
| N2 | N3 | 1.3074 (19) |
| N3 | C1 | 1.374 (2) |
| C1 | C6 | 1.388 (2) |
| C1 | C2 | 1.402 (2) |
| C2 | C3 | 1.359 (3) |
| C2 | H2B | 0.9300 |
| C3 | C4 | 1.406 (3) |
| C3 | H3B | 0.9300 |
| C4 | C5 | 1.368 (3) |
| C4 | H4A | 0.9300 |
| C5 | C6 | 1.392 (2) |
| C5 | H5A | 0.9300 |
| C7 | C8 | 1.501 (2) |
| C7 | H7A | 0.9700 |
| C7 | H7B | 0.9700 |

NMR ($CDCl_3$): δ 6.21 (s, 2H), 7.47–8.17 (m, 4H). Anal. Calcd. for $C_{11}H_6N_7F_3S$ (325.27): C, 40.62; H, 1.86; N, 30.14. Found: C, 40.79; H, 1.91; N, 30.32.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-isopropyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4c).** This compound was obtained as brown solid, 66% yield, mp 238–240°; IR (KBr): 3077, 2962, 1612, 1565, 1549, 1467, 1445, 1260 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.23 (d, 6H), 2.67 (m, 1H), 6.50 (s, 2H), 7.45–8.10 (m, 4H). Anal. Calcd. for $C_{13}H_{13}N_7S$ (299.35): C, 52.16; H, 4.38; N, 32.75. Found: C, 52.27; H, 4.42; N, 32.58.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-propyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4d).** This compound was obtained as gray solid, 82% yield, mp 130–132°; IR (KBr): 3085, 2971, 1610, 1584, 1572, 1493, 1468, 1263 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.21 (t, 3H), 1.86 (m, 2H), 2.42 (t, 2H), 6.53 (s, 2H), 7.43–8.12 (m, 4H). Anal. Calcd. for $C_{13}H_{13}N_7S$ (299.35): C, 52.16; H, 4.38; N, 32.75. Found: C, 51.94; H, 4.33; N, 32.59.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-isobutyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4e).** This compound was obtained as light yellow solid, 58% yield, mp 129–131°; IR (KBr): 3088, 2988, 2937, 1613, 1590, 1570, 1483, 1448, 1293 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 0.88 (d, 6H), 2.11 (m, 1H), 2.84 (d, 2H), 6.55 (s, 2H), 7.46–8.14 (m, 4H). Anal. Calcd. for $C_{14}H_{15}N_7S$ (313.38): C, 53.66; H, 4.82; N, 31.29. Found: C, 53.83; H, 4.89; N, 31.38.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-pentyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4f).** This compound was obtained as pink solid, 94% yield, mp 105–108°; IR: 3080, 2991, 2939, 1611, 1585, 1567, 1484, 1455, 1298 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.93 (t, 3H), 1.33–1.90 (m, 6H), 3.10 (t, 2H), 6.08 (s, 2H), 7.45–8.16 (m, 4H). Anal. Calcd. for $C_{15}H_{17}N_7S$ (327.41): C, 55.03; H, 5.23; N, 29.95. Found: C, 55.19; H, 5.19; N, 30.13.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4g).** This compound was obtained as brown solid, 53% yield, mp 208–211°; IR (KBr): 3072, 2954, 1613, 1581, 1568, 1475, 1459, 1274 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.25 (s, 2H), 7.49–8.86 (m, 8H). Anal. Calcd. for $C_{15}H_{10}N_8S$ (334.36): C, 53.88; H, 3.01; N, 33.51. Found: C, 53.76; H, 3.07; N, 33.62.

**6-((*1H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-(pyridin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4h).** This compound was obtained as brown solid, 59% yield, mp 149–152°; IR (KBr): 3071, 2938, 1612, 1586, 1566, 1471, 1464, 1268 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 6.36 (s, 2H), 7.53–8.88 (m, 8H). Anal. Calcd. for $C_{15}H_{10}N_8S$ (334.36): C, 53.88; H, 3.01; N, 33.51. Found: C, 54.01; H, 3.08; N, 33.69.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4i).** This compound was obtained as brown solid, 98% yield, mp 205–207°; IR (KBr): 3084, 2953, 1614, 1585, 1550, 1471, 1463, 1265 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 6.63 (s, 2H), 7.49–8.16 (m, 9H). Anal. Calcd. for $C_{16}H_{11}N_7S$ (333.37): C, 57.65; H, 3.33; N, 29.41. Found: C, 57.81; H, 3.27; N, 29.27.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-(4-nitrophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4j).** This compound was obtained as muddy color solid, 98% yield, mp 172–175°; IR (KBr): 3089, 2973, 1611, 1582, 1574, 1462, 1453, 1283 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 6.75 (s, 2H), 7.55–8.25 (m, 8H). Anal. Calcd. for $C_{16}H_{10}N_8O_2S$ (378.37): C, 50.79; H, 2.66; N, 29.61. Found: C, 50.93; H, 2.71; N, 29.47.

**Table 6**

Selected bond angles (°).

| | | | |
|---|---|---|---|
| C8 | O1 | H1 | 108.6 (15) |
| N2 | N1 | C6 | 110.99 (13) |
| N2 | N1 | C7 | 119.63 (14) |
| C6 | N1 | C7 | 129.29 (15) |
| N3 | N2 | N1 | 108.07 (14) |
| N2 | N3 | C1 | 108.69 (14) |
| N3 | C1 | C6 | 108.22 (14) |
| N3 | C1 | C2 | 130.92 (17) |
| C6 | C1 | C2 | 120.85 (18) |
| C3 | C2 | C1 | 116.46 (19) |
| C3 | C2 | H2B | 121.8 |
| C1 | C2 | H2B | 121.8 |
| C2 | C3 | C4 | 122.24 (19) |
| C2 | C3 | H3B | 118.9 |
| C4 | C3 | H3B | 118.9 |
| C5 | C4 | C3 | 122.1 (2) |
| C5 | C4 | H4A | 118.9 |
| C3 | C4 | H4A | 118.9 |
| C4 | C5 | C6 | 115.62 (18) |
| C4 | C5 | H5A | 122.2 |
| C6 | C5 | H5A | 122.2 |
| N1 | C6 | C1 | 104.02 (15) |
| N1 | C6 | C5 | 133.28 (15) |
| C1 | C6 | C5 | 122.70 (16) |
| N1 | C7 | C8 | 112.86 (14) |
| N1 | C7 | H7A | 109.0 |
| C8 | C7 | H7A | 109.0 |
| N1 | C7 | H7B | 109.0 |
| C8 | C7 | H7B | 109.0 |
| H7A | C7 | H7B | 107.8 |
| O2 | C8 | O1 | 124.73 (17) |
| O2 | C8 | C7 | 123.80 (15) |
| O1 | C8 | C7 | 111.46 (15) |

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-(3-nitrophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4k).** This compound was obtained as light blue solid, 82% yield, mp 148–151°; IR (KBr): 3084, 2970, 1614, 1578, 1563, 1471, 1458, 1263 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 6.79 (s, 2H), 7.61–8.22 (m, 8H). Anal. Calcd. for $C_{16}H_{10}N_8O_2S$ (378.37): C, 50.79; H, 2.66; N, 29.61. Found: C, 50.62; H, 2.59; N, 29.73.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-*p*-tolyl-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole (4l).** This compound was obtained as white solid, 98% yield, mp 207–210°; IR (KBr): 3071, 2940, 1610, 1588, 1544, 1471, 1462, 1271 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.38 (s, 3H), 6.62 (s, 2H), 7.36–8.16(m, 8H). Anal. Calcd. $C_{17}H_{13}N_7S$ (347.40): C, 58.78; H, 3.77; N, 28.22. Found: C, 58.61; H, 3.83; N, 28.35.

**6-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-(furan-2-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (4m).** This compound was obtained as white solid, 64% yield, mp 189–192°; IR (KBr): 3082, 2963, 1612, 1587, 1550, 1482, 1448, 1282 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 6.62 (s, 2H), 6.76–8.15 (m, 7H). Anal. Calcd. for $C_{14}H_9N_7OS$ (323.33): C, 52.01; H, 2.81; N, 30.32. Found: C, 52.22; H, 2.75; N, 30.45.

**Anti-inflammatory activity.** This activity is performed by the following procedure of Winter *et al*. [22] on groups of six animals each. A freshly prepared suspension of carrageen in (1.0% w/v, 0.1 mL) is injected in the planter region of right hind paw of each rat. One group is kept as control and the animals of the other group are pretreated with the test drugs suspended in 1.0% CMC given orally 1 h before the carrageenin treatment. The volume is measured before and after 4 h of carrageenin treatment with the help of pleythysmometer. The percent anti-inflammatory activity is calculated according to the formula given below:

$$\%\text{Anti-inflammatory activity} = (V_c - V_t/V_c) \times 100$$

where $V_t$ represents the mean increase in paw volume in rats treated with test compounds and $V_c$ represents the mean increase in paw volume in control group of rats. Data are expressed as mean ± S.E.M., Student's *t*-test is applied to determine the significance of the difference between the control group and rats treated with the test compounds.

**Analgesic activity.** This activity is performed by Eddy's hot plate technique [23], Mice (Swiss strain) of either sex weighing between 25 and 35 g are used for the experiment. In this method heat is used as a source of pain. Animals are individually placed on a hot plate, maintained at constant temperature (55°C) and the reaction of animals, such as paw licking or jumping response (whichever appears first) is taken as the end point. A cut-off time of 15 s is taken as maximum analgesic response to avoid injury to the paws. The tested compounds and diclofenac sodium (standard) at a dose of 30 mg/kg body weight in 1% gum acacia are given as suspension orally to animals and observe the reaction time of animals on the hot plate at 20, 40, and 60 min after the compound administration.

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## REFERENCES AND NOTES

[1] Heeres, J.; Backx, L. J. J Med Chem 1984, 27, 894.

[2] Goswami, B. N.; Kataky, J. C. S.; Baruah, J. N. J Heterocycl Chem 1984, 21, 1225.

[3] Czarnocka-Janowicz, A.; Foks, H.; Nasal, A.; Petrusewicz, J.; Damasiewicz, B.; Radwanska, A.; Kaliszan, R. Pharmazie 1991, 46, 109.

[4] Singh, K.; Hasan, A.; Pratap, R.; Guru, P. Y.; Bhakuni, D. S. J Indian Chem Soc 1989, 66, 686.

[5] Labanauskas, L.; Udrenaite, E.; Gaidelis, P.; Brukštus, A. IL Farmaco 2004, 59, 255.

[6] Al-Soud, Y. A.; Al-Dweri, M. N.; Al-Masoudi, N. A. IL Farmaco 2004, 59, 775.

[7] Foroumadi, A.; Mirzaei, M.; Shafiee, A. IL Farmaco 2001, 56, 621.

[8] Foroumadi, A.; Asadipour, A.; Mirzaei, M.; Karimi, J.; Emami, S. IL Farmaco 2002, 57, 765.

[9] Karabasanagouda, T.; Adhikari, A. V.; Shetty, N. S. Eur J Med Chem 2007, 42, 521.

[10] Mathew, V.; Keshavayya, J.; Vaidyab, V. P. Eur J Med Chem 2006, 41, 1048.

[11] Amir, M.; Kumar, H.; Sadique, A. J. Bioorg Med Chem Lett 2007, 17, 4504.

[12] Mathew, V.; Keshavayya, J.; Vaidyab, V. P.; Giles, D. Eur J Med Chem 2007, 42, 823.

[13] Imtiaz, H.; Kumar, V. Indian J Chem 1992, 31B, 673.

[14] Awad, L. F.; El Ashry, E. S. H. Carbohydr Res 1998, 312, 9.

[15] Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N.; Garoufalias, S. P.; Pannecouque, C. IL Farmaco 2002, 57, 253.

[16] Joshi, K. C.; Giri, S. J Indian Chem Soc 1963, 40, 42.

[17] Haglind, J. Proceedings of 3rd International Congress of Chemotherapy, Stuttgart 1963, 1, 887; Chem Abstr 1966, 64, 16509.

[18] Zhang, S. S.; Zhang, H. Q.; Li, D.; Sun, L. H.; Ma, C. P.; Wang, W.; Wan, J.; Qu, B. Eur J Pharmacol 2008, 584, 144.

[19] Kroger, C. F.; Tenor, E.; Beyer, H. Liebigs Ann Chem 1961, 643, 121.

[20] Reid, J. R.; Heindel, N. D. J Heterocycl Chem 1976, 13, 925.

[21] Li, Y. X.; Liu, F. A.; Liu, X. M. Acta Scientiarum Naturalium Universitatis Jilinensis 1992, 3, 122.

[22] Winter, C. A.; Riseny, E. A.; Nuss, G. W. Proc Soc Exp Biol Med 1962, 111, 544.

[23] Eddy, N. B.; Leimbach, D. J. J Pharmacol Exp Ther 1953, 107, 385.

# Microwave-Assisted Brønsted Acidic Ionic Liquid-Promoted One-Pot Synthesis of Heterobicyclic Dihydropyrimidinones by a Three-Component Coupling of Cyclopentanone, Aldehydes, and Urea

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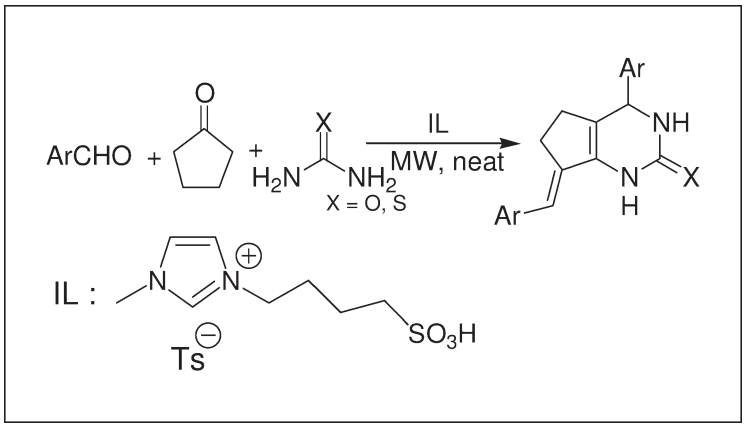


A simple and efficient method has been developed for the synthesis of heterobicyclic dihydropyrimidinone derivatives through a solvent-free one-pot three-component condensation of aromatic aldehydes, cyclopentanone, and urea or thiourea in the presence of Brønsted acidic ionic liquid under microwave irradiation. The catalyst can be reused at least six times without any noticeable decrease in catalytic activity.

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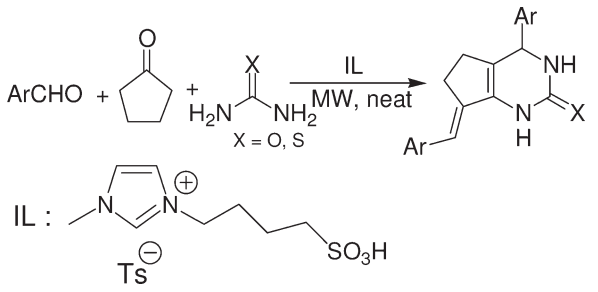
## INTRODUCTION

Dihydropyrimidinones and their derivatives are a very important class of bioactive compounds because of their pharmacological properties [1]. They are known to exhibit a wide range of biological activities, such as calcium channel blockers [2], antihypertensive agents [3], α-adrenergic antagonists [4], and neuropeptide Y antagonists [5]. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the molecules [6]. Most notable among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors [7]. Therefore, such a wide spectrum of biological activity allows consideration of the dihydropyrimidinone structural unit as one of the most important drug-like scaffolds.

The Biginelli reaction, which was discovered more than a century ago is one of the most important reactions in the synthesis of dihydropyrimidinones based on acid-catalyzed three-component condensation of 1,3-dicarbonyl compound, aldehyde, and urea [8]. The scope of the original condensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of structurally diversified multifunctionalized dihydropyrimidinones [9]. The use of the common open-chain β-dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic β-diketones, β-ketolactones, cyclic β-diesters or β-diamides, benzocyclic ketones, and α-keto acids.

Microwave- (MW-) promoted reactions have been attracting increasing research interest from chemists in recent years, not only because these reactions exhibit some particular or unexpected reactivities in some cases but also because they are significantly useful for green chemistry [10]. In our corresponding investigations, we have reported few MW-promoted multicomponent coupling reactions for various chemical transformation as well as synthesis of useful heterocyclic compounds [11]. The application of Brønsted acidic task-specific ionic liquids (TSILs) as catalytic materials is growing continuously in the catalytic field. Combining the useful characteristics of solid acids and mineral acids, TSILs have been synthesized to replace traditional mineral liquid acids, such as hydrochloric acid and sulfuric acid in chemical reactions. In view of green chemistry, the

**Scheme 1**




substitution of harmful liquid acids by reusable TSILs is the most promising catalyst in chemistry [12].

Recently, it was found that some fused pyrimidinones carrying an arylidene moiety are potential antitumor agents [13]. In addition, some of these analogues also showed a distinctive pattern of selectivity toward individual cell line, such as that of leukemia [14]. Because of the various therapeutic utility of arylidene heterobicyclic pyrimidinones, a number of synthetic procedures for this type of derivatives were developed using different protocols [15]. Pan and coworkers described an efficient alternative for the synthesis of these fused pyrimidinones by a three-component condensation with aromatic aldehyde, cyclopentanone, and urea or thiourea in presence of stoichiometric amounts of TMSCl as additional reagent and mixed DMF/$CH_3CN$ as reaction solvent appeared to be necessary to obtain satisfactory results [16a]. Very recently, Xu and Shen revealed that ytterbium chloride could efficiently promote this one-pot three-component condensation under solvent-free conditions without using any additional reagents [16b]. In connection with our earlier work on the synthesis of dihydropyrimidinones [17], herein we report an efficient Brønsted acidic ionic liquid catalyzed this Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea for the synthesis of arylidene heterobicyclic pyrimidinones using MW irradiation under solvent-free conditions (Scheme 1). To the best of our knowledge, this is the first report of a functionalized ionic liquid-catalyzed synthesis of heterobicyclic dihydropyrimidinones.

## RESULTS AND DISCUSSION

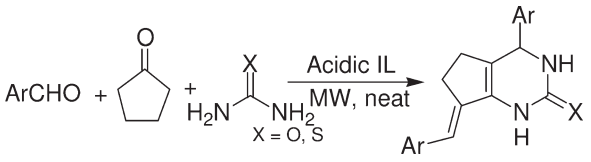
The experimental procedure is very simple. To optimize the reaction conditions, the reaction of benzaldehyde, cyclopentanone, and urea was selected as the model in presence of catalytic amount of acidic ionic liquid under MW irradiation. The best result was obtained when the reaction of cyclopentanone, benzaldehyde, and urea was carried in a 2:2:1.2 mole ratio in presence of acidic ionic liquid (5 mol %) under MW irradiation (250 W, 90°C) for 5 min. In a blank reaction, without acidic ionic liquid, no desired product was obtained in 5 min. But, very low yield (10–15%) was obtained after longer time irradiation (15–20 min).

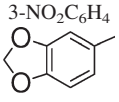
Under these optimized conditions, the reaction between various aromatic aldehydes and cyclopentatone in presence of urea was investigated (Table1). It was found that all the reactions proceeded smoothly to give the corresponding arylidene pyrimidinones in high yields. Both aromatic aldehydes bearing electron-donating and electron-withdrawing gave excellent yields. The mildness of the procedure makes it very selective, as it tolerates a variety of functionalities, including bromo, chloro, fluro, methoxy, nitro, and methylenedioxy groups. The present procedure was equally effective for thiourea also. The results are summarized in Table 1, which clearly demonstrates the generality and scope of the reaction with respect to various aromatic aldehydes. No organic solvents were required to isolate the product from the reaction mixture. Only ethanol was used for recrystallization to provide analytically pure samples. Use of just 5 mol % IL is sufficient to push the reaction forward. Higher amount of IL did not improve the reaction forward.

Our interest in the preparation of novel scaffolds prompted us to attempt the extension of this reaction to condensations of cyclohexanone and /or aliphatic aldehydes in the Biginelli-type reaction. Unfortunately, the

**Table 1**

IL promoted microwave-assisted one-pot synthesis of pyrimidinone.

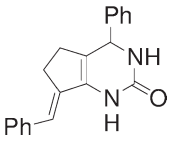
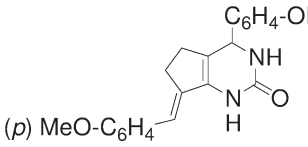
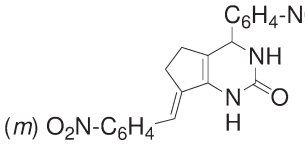



| Entry | Ar | X | Time (min) | Yield[a] (%) | Ref. |
|---|---|---|---|---|---|
| 1 | Ph | O | 5 | 82 | 16a |
| 2 | 4-$MeC_6H_4$ | O | 5 | 73 | 16a |
| 3 | 4-MeO-$C_6H_4$ | O | 5 | 64 | 16a |
| 4 | 4-$BrC_6H_4$ | O | 5 | 77 | 16b |
| 5 | 4-$ClC_6H_4$ | O | 5 | 79 | 16a |
| 6 | 4-$FC_6H_4$ | O | 5 | 91 | 16a |
| 7 | 2-$ClC_6H_4$ | O | 5 | 68 | 16a |
| 8 | 4-$NO_2C_6H_4$ | O | 5 | 83 | 16a |
| 9 | 3-$NO_2C_6H_4$ | O | 5 | 67 | 16a |
| 10 |  | O | 5 | 82 | |
| 11 | 1-Naphthyl | O | 6 | 84 | 16b |
| 12 | Ph | S | 10 | 82 | 16a |
| 13 | 4-$MeC_6H_4$ | S | 12 | 64 | 16b |
| 14 | 4-$ClC_6H_4$ | S | 10 | 78 | 16a |
| 15 | 4-$FC_6H_4$ | S | 8 | 73 | 16b |
| 16 | 4-$NO_2C_6H_4$ | S | 18 | 75 | 16a |

[a] Yields refer to isolated pure product.

**Table 2**

Comparison of the present protocol with recently reported methods.

| | | Present method | | Reported method [16b] | | Reported method [16a] | |
|---|---|---|---|---|---|---|---|
| Entry | Product | Time | Yield (%)[a] | Time | Yield (%)[b] | Time | Yield (%)[c] |
| 1 |  | 5 min | 82 | 3 h | 79 | 2–3 h | 93 |
| 2 |  | 5 min | 64 | 5 h | 69 | 2–3 h | 86 |
| 3 |  | 5 min | 67 | 5 h | 50 | 2–3 h | 78 |

[a] Present reaction conditions: acidic ionic liquid (5 mol%) at 90°C (250 W microwave).
[b] Reported reaction conditions: 3 mol% $YbCl_3$ at 90°C.
[c] Reported reaction conditions: stoichiometric amount of TMSCl in DMF/$CH_3CN$ solvent at rt.

reaction did not produce the corresponding benzylidene pyrimidinones under the present reaction conditions, instead leads to multiple products whose identities are yet to be established.

The recovery and reusability of the ionic liquid were investigated. After completion of the reaction, crushed ice (20 g) was added to the reaction mixture and the solid product was filtered. The aqueous layer consisting of the acidic IL was extracted with diethyl ether (5 mL) to remove the organic impurities. The catalyst was recovered after removal of water under reduced pressure and reused for subsequent reactions. It showed the same activity as a fresh catalyst with out any loss of activity in terms of yield and purity. After six recycles, the catalyst had a high activity and gave the desired product in good yield (78%, entry 1).

The efficiency of the present protocol can be realized by comparing some of the results presented here with recently reported two methods as shown in the Table 2, which compares reaction time, yields, and reaction conditions. Thus, it is clear form the Table 2 that the present protocol can act as an effective method with respect to times and reaction conditions.

The mechanism of this reaction is uncertain. The reaction may proceed through the formation of acyl imine intermediate, by the reaction of the aldehyde with urea and activated acid [16a]. Another hypothesis is that dibenzylidene cyclopentanone is the key intermediate produced by reaction of benzaldehyde with cyclopentanone in presence of acidic IL [16b].

## CONCLUSIONS

In conclusion, the present MW-assisted one-pot procedure provides an efficient synthesis of heterobicyclic dihydropyrimidinones by acidic IL-catalyzed condensation of aldehyde, cyclopentanone, and urea or thiourea under solvent-free conditions. We believe our procedure will find important applications in the synthesis of biologically active scaffolds to cater the needs of academia as well as pharmaceutical industries. Further exploration of this chemistry and biological evaluation of the synthesized scaffolds are in progress and will be reported in due course.

## EXPERIMENTAL

Melting points were determined on a glass disk with an electrical bath and are uncorrected. $^1H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were run in DMSO-$d_6$ solutions. IR spectra were taken as KBr plates. Elemental analyses were done by Perkin–Elmer autoanalyzer. The synthesis of the Brønsted acidic ionic liquid, 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]Ts was carried out using a method similar to that reported [18].

**Typical procedure for the synthesis of 4-benzo[1,3]-dioxol-5-yl-7-benzo[1,3]dioxol-5-ylmethylene-1,3,4,5,6,7-hexahydrocyclopentapyrimidin-2-one (entry 10, Table 1).** To a mixture of piperonal (300 mg, 2 mmol), cyclopentanone (177 μL, 168 mg, 2 mmol), and urea (72 mg, 1.2 mmol) acidic ionic liquid (39 mg, 5 mol %) was added. The mixture was irradiated in a MW reactor (CEM, Discover) at 90°C (250 W) for 5 min as required to complete the reaction. The mixture, after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5–10 min. the solid separated was filtered under suction (water aspirator), washed with ice-cold water (20 mL) and then recrystallized from hot ethanol to afford pure product (320 mg, 82%) as white powder. mp 253–255°C; IR (KBr): 1679, 1492, 1452, 1242 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.61 (s, 1H), 7.07 (s, 1H), 6.87 (s, 3H), 6.79–6.71 (m, 3H), 6.52 (s, 1H), 5.98 (s, 4H), 5.04 (s, 1H), 2.76 (s, 2H), 2.76 (br, 1H), 2.48 (br, 1H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 153.5, 147.9, 147.8, 146.9, 145.9, 137.9, 137.7, 136.3, 132.5, 122.6, 120.1, 118.1, 116.9, 108.9, 108.5, 107.8, 107.2, 101.4, 101.3, 57.4, 28.7, 28.6; Anal. Cald for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.51; H, 4.54; N, 7.01.

The catalyst recovered for the aqueous layer was dried under vacumn and reused for subsequent reactions.

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## REFERENCES AND NOTES

[1] (a) Kappe, C. O. Tetrahedron 1993, 49, 6937; (b) Kappe, C. O.; Fabian, W. M. F. Tetrahedron 1997, 53, 2803; (c) Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[2] (a) Ronyar, G. C.; Kinball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. J Med Chem 1995, 38, 119; (b) Aswal, K. S.; Rovnyak, G. C.; Kinball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Mallay, M. F. J Med Chem 1990, 33, 2629.

[3] (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. J Med Chem 1991, 34, 806; (b) Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. J Cardiovasc Pharmacol 1995, 26, 289.

[4] (a) Nagarathnam, D.; Wong, W. C.; Miao, S. W.; Patance, M. A.; Gluchowski, C. PCT Int Appl WO 9717969, 1997; (b) Nagarathnam, D.; Wong, W. C.; Miao, S. W.; Patance, M. A.; Gluchowski, C. Chem Abstr 1997, 127, 65783; (c) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberg, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. PCT Int WO 9907695, 1999; (d) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberg, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. Chem Abstr 1999, 130, 182478.

[5] (a) Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT Int. Appl. WO 9833791, 1998; (b) Bruce, M. A.; Pointdexter, G. S.; Johnson, G. Chem Abstr 1998, 129, 148989.

[6] Snider, B. B.; Shi, Z. J Org Chem 1993, 58, 3828.

[7] (a) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. Tetrahedron Lett 1996, 37, 6977; (b) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De, B. C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Ports, B. C. M. J Org Chem 1995, 60, 1182.

[8] (a) Biginelli, P. Gazz Chem Ital 1893, 23, 360; (b) Biginelli, P. Ber 1891, 24, 2962.

[9] (a) Kappe, C. O. Acc Chem Res 2000, 33, 879; (b) Singh, M.; Devi, N. S. J Org Chem 2009, 74, 3141.

[10] (a) Polshettiwar, V.; Varma, R. S. Acc Chem Res 2008, 41, 629; (b) Roberts, B. A.; Strauss, C. R. Acc Chem Res 2005, 38, 653; (c) Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250.

[11] (a) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. Tetrahedron 2003, 59, 813; (b) Ranu, B. C.; Samanta, S.; Hajra, A. Synlett 2002, 987; (c) Ranu, B. C.; Hajra, A. Tetrahedron 2001, 57, 4767; (d) Ranu, B. C.; Hajra, A.; Jana, U. Synlett 2000, 75; (e) Ranu, B. C.; Hajra, A.; Jana, U. Tetrahedron Lett 2000, 41, 531; (f) Rahman, M.; Roy, A.; Majee, A.; Hajra. A. J Chem Res 2009, 178; (g) Hajra, A.; Kundu, D.; Majee, A. J Heterocyclic Chem 2009, 46, 1019.

[12] (a) Wasserschield, P.; Welton, T. In Ionic Liquid in Synthesis; Wiley-VCH, Weinheim, Germany, 2008; (b) Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H., Jr. J Am Chem Soc 2002, 124, 5962; (c) Fang, D.; Zhou, X.-L.; Ye, Z. -W.; Liu, Z.-L. Ind Eng Chem Res 2006, 45, 7982; (c) Leng, Y.; Wang, J.; Zhu, D.; Ren, X.; Ge, H.; Shen, L. Angew Chem Int Ed 2009, 48, 168.

[13] El-Subbagh, H. I.; Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.; Al-Obaid, A. M. J Med Chem 2000, 43, 2915.

[14] (a) Lorand, T.; Deli, J.; Szabo, D.; Foeldesi, A.; Zschunke, A. Pharmazie 1985, 40, 536; (b) Elgemeie, G. E. H.; Attia, A. M. E.; Alkabai, S. S. Nucleos Nucleot Nucl 2000, 19, 723.

[15] (a) El-Subbagh, H. I.; Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.; Al-Obaid, A. M. J Med Chem 2000, 43, 2915; (b) Lorand, T.; Deli, J.; Szabo, D.; Foeldesi, A.; Zschunke, A. Pharmazie 1985, 40, 536; (c) Hammam, A. E. G.; Sharaf, M. A.; El-Hafez, N. A. A. Indian J Chem B 2001, 40, 213.

[16] (a) Zhu, Y.; Huang, S.; Pan, Y. Eur J Org Chem 2005, 2354; (b) Zhang, H.; Zhou, Z.; Yao, Z.; Xu, F.; Shen, Q. Tetrahedron Lett 2009, 50, 1622.

[17] (a) Ranu, B. C.; Hajra, A.; Jana, U. J Org Chem 2000, 65, 6270; (b) Ranu, B. C.; Hajra, A.; Dey, S. S. Org Process Res Dev 2002, 6, 817; (c) Kundu, S. K.; Majee, A.; Hajra, A. Indian J Chem B 2009, 48, 408.

[18] (a) Akbari, J.; Heydari, A. Tetrahedron Lett 2009, 50, 423; (b) Du, Z.; Li, Z.; Deng, Y. Synth Commun 2005, 35, 1343.

# Synthesis and Structural Study of *N*-Methyl-2-methylthiopyrimidine Derivatives from Trihalomethylated Enones



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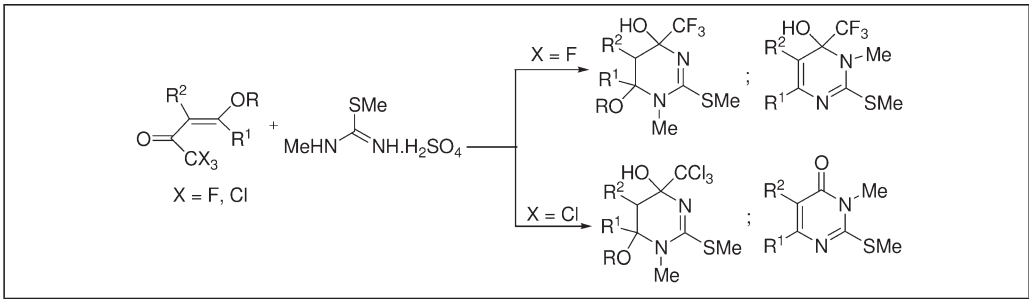


The synthesis and chemoselective study of a novel series *N*-methyl-2-methylthio-tetrahydropyrimidines and or *N*-methyl-2-methylthiodihydropyrimidines, from the cyclocondensation reaction of β-alkoxyvinyl trihalomethyl ketones (enones) with 1,2-dimethylisothiourea sulfate is described. It was found that the chemoselectivity depends on both the reaction conditions and the steric and electronic effects of the substituents on the enones.

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## INTRODUCTION

Pyrimidines have a long history of biological activity in fields ranging from pharmaceutics to agriculture. The $N^1$-alkylation of pyrimidines is one way of functionalizing the pyrimidine ring to achieve important physical and bioactive properties. For example, *N*-alkylated nucleic acid bases are widely known for being the most effective antiviral [1] and antitumoral agents, [2] as well as for exhibiting anti-inflammatory [3] and herbicidal activity [4]. In addition, *N*-alkylated pyrimidines, obtained by alkylating agents, such as diazoalkanes [5], alkyl halides [6], and alkylsulfates, among others [7], are important compounds for mutagenic and carcinogenic studies in living systems.

Very few studies have reported on the synthesis of *N*-alkylated 2-methylthiopyrimidines by cyclocondensation reactions using nonsymmetric *S*-alkylthioureas. Probably, the main reason for this is that thioureas are weak nucleophiles, and they do not react very well with 1,3-dicarbonyl compounds or derivatives thereof in a [3 + 3] atom fragment synthesis, which is the main strategy for the preparation of pyrimidine compounds. β-Alkoxyvinyl ketones, however, allow the possibility of direct cyclization with weak nucleophiles because it has been demonstrated that these enones readily react with weak nucleophiles, such as ureas [8], *N*-methylurea [9], *N*-methylthioureas [10], and 2-methyl-2-thiopseudourea [11].

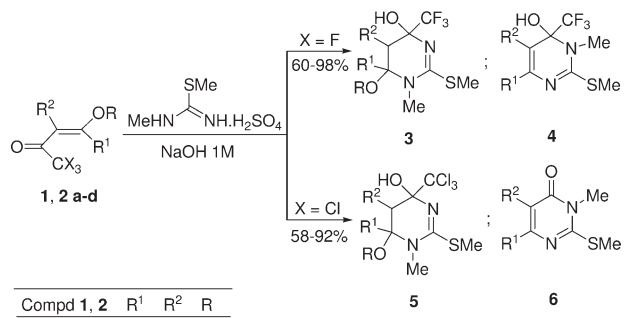
We have reported the synthesis of a series of 4-trihalomethyl-2-methylthiopyrimidines from the reaction of 1,1,1-trifluoro[chloro]-4-alkoxy-alk-3-en-2-ones (tri-halomethylated enones) with 2-methyl-2-thiopseudourea sulfate in the presence of pyridine or acid catalysis [12]. More recently, we reported the synthesis of a new series of 2-methylthiotetrahydropyrimidines from the same enones under a modified procedure [11].

Continuing in our interest in the synthesis of pyrimidine derivatives from trihalomethylated enones, this article aims to study the chemoselectivity and yields of the synthesis of a series of *N*-methyl-2-methylthio-pyrimidines carried out by the cyclocondensation of trihalomethylated enones with the nonsymmetric dinucleophile 1,2-dimethylisothiourea. A detailed NMR study of the structure of the pyrimidines derivatives was carried out to determine the correct position of the *N*-methyl group on the pyrimidine scaffold and to understand the factors that led to such chemoselectivity.

## RESULTS AND DISCUSSION

The reaction of enones **1a–d** and **2a–d** with 1,2-dimethylisothiourea sulfate, carried out in the presence of 1 *M* sodium hydroxide solution under mild conditions, furnished *N*-methyl-2-methylthiotetrahydropyrimidines or *N*-methyl-2-methylthiodihydropyrimidines depending

**Scheme 1**




| Compd **1**, **2** | $R^1$ | $R^2$ | R |
|---|---|---|---|
| **a** | H | H | Et |
| **b** | Me | H | Me |
| **c** | H | -$(CH_2)_2$- | |
| **d** | H | -$(CH_2)_3$- | |

on the reaction conditions and the type and positions of the substituents on the trihalomethylated enones (Scheme 1). Table 1 reports the optimized reaction conditions, the yields, and the correct structure of the obtained compounds.

The reaction of enones **1a** and **2a** with 1,2-dimethylisothiourea sulfate in the presence of 1 *M* sodium hydroxide solution at room temperature furnished tetrahydropyridines **3a** and **5a**, respectively. Both products **3a** and **5a** were composed of two diastereo-isomers, whose structure and composition are described in the next section. When the reaction of enone **2a** was carried out at 50°C for 5 h, 3-methyl-2-(methyl-thio)pyrimidin-4-(3*H*)-one (**6a**) was obtained in 92% yield.

Enones bearing a methyl group at the β-position ($R^1$ = Me) such as **1b** and **2b** reacted with 1,2-dimethyl-isothiourea sulfate in the presence of sodium hydroxide solution furnishing dihydropyrimidine **4b** and **6b** with the *N*–methyl group at the $N^3$–position of the pyrimidine ring. We speculate that a steric effect between the *N*–methyl group and β-methyl group of enones **1b** and **2b** was responsible for the formation of compounds **4b** and **6b** ($N^3$**–**regioisomers). In addition, the methoxy group was eliminated because hemi-aminals from ketones are less stable than those from aldehydes. Furthermore, in compound **6b** the elimination of the $CCl_3$ group was expected for reactions carried out under aqueous basic conditions [13]. In a previous study, compound **4b** exhibited significant inhibition of ATP and ADP hydrolysis in synaptosomes from rat cerebral cortex [14].

The reaction of enones **1c** and **1d** with 1,2-dimethylisothiourea sulfate in the presence of 1 *M* sodium hydroxide solution furnished hexahydrofuro[2,3-*d*]pyrimidin-4-ol (**3c**) and hexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-4-ol (**3d**), respectively. Although, products **3c** and **3d** show three stereogenic centers and additionally the possibility of two regioisomers due to the $N^1$**–** and $N^3$–methylation, only a single compound of each product was isolated, which means that the reactions were highly stereoselective and regioselective for these two enones under the conditions given in Table 1.

Enone **2d** reacted with 1,2-dimethylisothiourea sulfate in the presence of 1 *M* sodium hydroxide solution to furnish 3-methyl-2-(methylthio)-4a,5,6,7-tetrahydro-3*H*-pyrano[2,3-*d*]pyrimidin-4(8a*H*)-one (**5d**) in good yields. Under the same condition used to obtain compound **5d**, the enone **2c** failed to give the expected product **5c** and only starting material was isolated. One can observe that enones **2a**–**d** showed the elimination of the trichloro-methyl group instead of the hydroxyl group, except for the reaction of enone **2a** when carried out at room temperature. The elimination of the trichloromethyl group under basic reaction conditions has been reported previously [13].

## STRUCTURAL STUDIES

All compounds were fully analyzed by $^1$H and $^{13}$C NMR as well as 2D NMR experiments such as COSY HH [15], NOESY [16], HMQC [17], and HMBC [18]. Figure 1 shows the atom numbering used for NMR assignment of compounds **3**–**6**. Yields, selected physical and $^1$H and $^{13}$C NMR spectral data are presented in the experimental part.

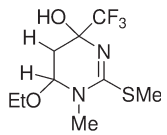
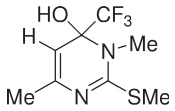
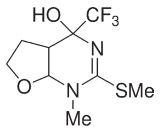
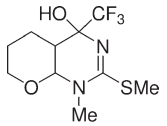
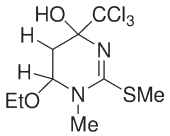
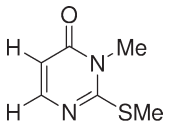
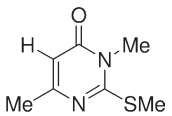
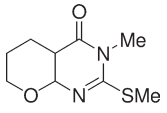
The correct position of the *N*–methyl group ($N^1$– or $N^3$–positions) of all *N*–methyl-2-methylthiopyrimidines was determined by two-dimensional HMBC NMR experiments, as shown in Figure 1 [9,10]. In this experiment, when the *N*–methyl group is at the $N^1$–position, two cross-peaks between the hydrogen atoms of the *N*–methyl group and C–2 and C–6 are observed (Fig. 1, structure **I**). When the *N*–methyl group is at the $N^3$–position, two cross-peaks between the hydrogen atoms of the *N*–methyl group and C–2 and C–4 are observed (Fig. 1, structure **II**). The cross-peak between the hydrogens of the SMe group and the C–2 assigns this carbon in both structures **I** and **II**. The same strategy was used to assign all the other compounds obtained in this study.

Compound **3a** was obtained as a mixture of two stereoisomers (**3a** and **3a′**), as shown in Figure 2.

The major isomer, isolated in 82%, shows both hydroxy- and ethoxy-groups in an axial position whereas the minor isomer shows the hydroxyl group at an axial position and the ethoxy group at an equatorial position. Compound **3a** was obtained as the major isomer probably because of the formation of a hydrogen-bond between the hydroxyl hydrogen and the oxygen atom of the ethoxy group, which could stabilize this structure. The structure of **3a** and **3a′** was proposed from the interpretation of the coupling constant of H–6 with H–5 and H–5′ as reported previously [11]. A similar trend as observed for **3a** was observed for **5a**.

**Table 1**

Optimized reaction conditions and structure of the obtained compounds.

| Entry | Enone | Reaction conditions[a] | | Structure of the obtained products | Yield (%)[d] |
|---|---|---|---|---|---|
| | | Molar ratio[b] Enone/Nu[c]/Base | *T* (°C)/ time (h) | | |
| 1 | **1a** | 1.0:1.5:1.5 | r.t./1 |  **3a**[e] | 77 |
| 2 | **1b** | 1.0:1.5:1.5 | 0/2.2 |  **4b** | 98 |
| 3 | **1c** | 1.0:1.1:1.1 | 10/0.7 |  **3c** | 64 |
| 4 | **1d** | 1.0:1.1:1.1 | 0/1 |  **3d** | 60 |
| 5 | **2a** | 1.0:2.0:2.0 | r.t./1 |  **5a**[e] | 58 |
| 6 | **2a** | 1.0:1.5:1.5 | 50/5 |  **6a** | 92 |
| 7 | **2b** | 1.0:2.0:2.0 | 30/2.4 |  **6b** | 95 |
| 8 | **2d** | 1.0:1.1:1.1 | 0/1.2 |  **5d** | 70 |

[a] Reaction conditions: NaOH 1M.
[b] Molar ratio: enone/dinucleophile/base.
[c] Nu = 1,2-dimethylisothiourea sulfate.
[d] Yields of isolated products.
[e] Obtained as a mixture of two diastereoisomers.

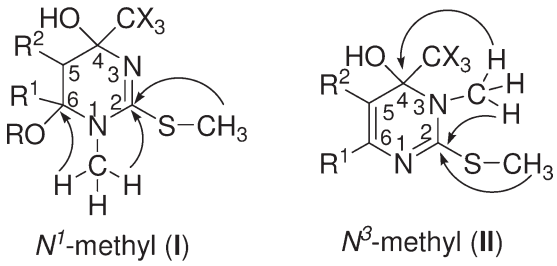



**Figure 1.** Strategy for the assignment of the position of the *N*-methyl group by HMBC.

Compound **3c** has, besides three asymmetric carbons, the possibility of two regioisomers due to the $N^1$– and/or $N^3$–alkylation. However, this compound showed only one set of signals in both $^1$H and $^{13}$C NMR spectra indicating that the reaction was both highly stereoselective and regioselective. Observation of a strong cross-peak between H–4a and H–7a in the NOESY experiment indicates that these hydrogens are close in space, which suggests that the furopyrimidine ring closure was accomplished with *cis* configuration. The most probable structure for **3d** is the furopyrimidine rings in the *cis* configuration, the $CF_3$ group in pseudo-equatorial positions *cis* to H–4a and *trans* to C–5, and the methyl group bound to $N^1$ because three bond cross-peaks between the hydrogens of the *N*–methyl group and C–2 and C–7a were observed in the HMBC spectrum (Fig. 3). Compound **3d** also has three asymmetric carbons and the possibility of $N^1$–Me and/or $N^3$–Me isomers. As observed for **3c**, **3d** also showed only one set of signals in both $^1$H and $^{13}$C NMR spectra indicating that the reaction was both highly stereoselective and regioselective. The coupling constant between H–4a and H–8a of 12.2 Hz indicates a *trans*-diaxial position of these two hydrogens, consequently, the pyranopyrimidine ring closure occurred with *trans* configuration. The methyl

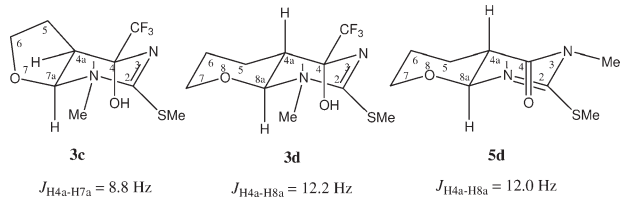



**Figure 3.** Structure of compounds **3c**, **3d**, and **5d**.

group is attached to $N^1$ because three bond cross-peaks between the hydrogens of the *N*–methyl group and C–2 and C–8a were observed on the HMBC spectrum (Fig. 3). Compound **5d** showed the same general structure as **3d**, however, **5d** exhibited the $N^3$–methyl group and the $CCl_3$ group was eliminated with the formation of a carbonyl group, which was the tendency for all trichloromethyl-bearing enones when the reaction was carried out in basic medium [13].

The tridimensional structure of tetrahydropyrimidines proposed in this study are consistent with the structure of related pyrimidines proposed by Saloutin, *et al*. [19]

Presumably, the reaction starts with the Michael addition of the amino groups of the 1,2-dimethylisothiourea at the β-carbon atom of enone **1** or **2** furnishing both structures **I** (path 1) and/or **II** (path 2), as shown in Scheme 2.

Both hemi-aminals and trifluoromethyl groups are stable under basic conditions, although, hemi-aminals derived from aldehydes are more stable than those from ketones. Thus, after the addition of the first nitrogen of 1,2-dimethylisothiourea at the carbon–carbon double

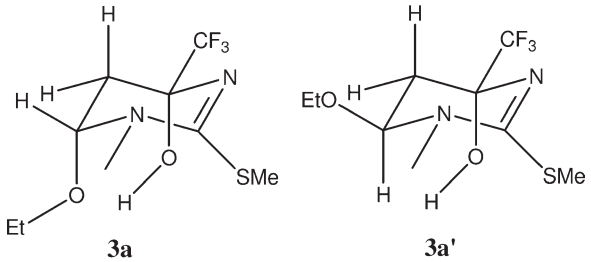
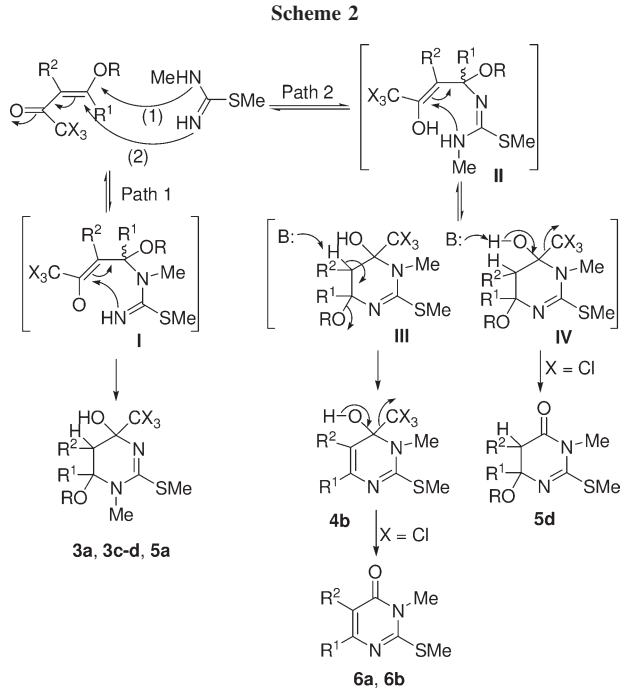



**Figure 2.** Structure of compounds **3a** and **3a′**.

**Scheme 2**



bond, the carbonyl becomes activated for the addition of the second nitrogen furnishing the tetrahydropyrimidines **3a**, **3c–d**, and **5a**. When enones **1** and **2** were β-methyl substituted ($R^1$ = Me), they reacted with 1,2-dimethylisothiourea giving $N^3$-methyldihydropyrimidines **4b** and **6b**, probably due to a steric effect between the *N*-methyl group and β-methyl group of enones **1b** and **2b**. In addition, the formation of compounds **4b** and **6b** occurred with the elimination of the methoxy group because hemi-aminals from ketones are less stable than those from aldehydes. Enones **2** bearing a trichloromethyl group also furnished $N^3$-methylpyrimidines because of the easy elimination of the trichloromethyl group under basic conditions [13].

In summary, from these results it can be concluded that steric and electronic effects determined the position of the methyl group at the $N^1$– *versus* $N^3$–positions of the pyrimidine ring according to the following observations: when $R^1$ = H, $N^1$–methyltetrahydropyrimidines were the only regioisomer isolated (**3a**, **3c–d**, **5a**, and **5d**). This is because hemi-aminals from aldehydes are more stable than those from ketones. An exception to this rule was observed when X = Cl. In this case, due to the facile elimination of the $CCl_3$ group under basic conditions only $N^3$–methylpyrimidinones **6a**, **6b**, and **5d** were obtained. We speculate that a steric effect between the *N*–methyl group and β-methyl group of the enones **1b** was responsible for the formation of compounds **4b**, where $N^3$–methyldihydropyrimidines were obtained.

## EXPERIMENTAL

The 1,1,1-trihalo-4-alkoxy-3-alken-2-ones (**1**, **2**) were prepared according to ref. [20]. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. IR spectra were measured on a Bruker IFS 28 spectrophotometer on KBr pellets. Elemental analysis was performed on a Vario EL Elementar Analysensysteme. 1H, 13C, and 2D NMR spectra were acquired on a Bruker DPX 400 spectrometer ($^1$H at 400.13 MHz and $^{13}$C at 100.62 MHz) in $CDCl_3$ or DMSO-$d_6$, using TMS as the internal reference.

**General procedure for the synthesis of *N*-methyl-2-methylthio-pyrimidines (3–6).** A solution of 1.0 *M* sodium hydroxide (7.5 mL, 7.5 mmol) and 1,2-dimethylisothiourea sulfate (1.14 g, 7.5 mmoles) was added drop wise under vigorous magnetic stirring to the enones **1a–d, 2a–d** (5.0 mmoles). The mixture was stirred for a period of time and temperature specified at Table 1 and extracted with chloroform (3 × 15 mL). The organic layer was dried under anhydrous sodium carbonate, filtered, and the solvent evaporated. Products were purified by recrystallizations and the solvent used for the purification is reported for each compound together with the melting point.

***6-Ethoxy-1-methyl-2-(methylthio)-4-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrimidin-4-ol (3a, 3a′).*** This compound was obtained as an orange powder in 77% yield, mp 68°C (hexane/ethyl acetate, 9:1). **3a**: $^1$H NMR: δ 1.24 (t, 3H, *J* = 7.0 Hz, $CH_3$), 2.02 (dd, 1H, *J* = 14.0, 3.6 Hz, H–5), 2.37 (s, 3H, S-$CH_3$), 2.47 (dd, 1H, *J* = 14.0, 3.0 Hz, H–5), 3.04 (s, 1H OH), 3.14 (s, 3H, *N*–$CH_3$), 3.62 (qua, 2H, *J* = 7.0 Hz, $CH_2$), 4.62 (dd, 1H, *J* = 3.6, 3.0 Hz, H–6); $^{13}$C NMR: δ = 13.7 (S–$CH_3$), 15.0 ($CH_3$), 30.1 (C–5), 37.6 (*N*–$CH_3$), 64.2 ($CH_2$), 80.3 (q, $J_{C\text{-}F}$ = 31.0 Hz, C–4), 86.4 (C–6), 123.7 (q, $J_{C\text{-}F}$ = 283.2 Hz, $CF_3$), 160.1 (C–2). **3a′**: $^1$H NMR: δ 1.24 (t, 3H, *J* = 7.0 Hz, H–8), 2.03 (dd, 1H, *J* = 13.8, 9.0 Hz, H–5), 2.15 (s, 1H OH), 2.33 (s, 3H, S–$CH_3$), 2.40 (dd, 1H, *J* = 13.8, 0.8 Hz, H–5), 2.98 (s, 3H, *N*–$CH_3$), 3.70 (q, 2H, *J* = 7.0 Hz, $CH_2$), 4.39 (dd, 1H, *J* = 9.6, 0.8 Hz, H–6); $^{13}$C NMR: δ 14.5 (S–$CH_3$), 15.0 ($CH_3$), 30.8 (C–5), 32.1 (*N*–$CH_3$), 64.2 ($CH_2$), 80.5 (q, $J_{C\text{-}F}$ = 31.0 Hz, C–4), 83.7 (C–6), 123.9 (q, $J_{C\text{-}F}$ = 284.0 Hz, $CF_3$), 158.4 (C–2). Anal. Calcd. for $C_9H_{15}O_2N_2F_3S$ (272.29): C, 39.70; H, 5.55; N, 10.29 Found: C, 39.28; H, 5.23; N, 10.02.

***1-Methyl-2-(methylthio)-4-(trifluoromethyl)-1,4,4a,5,6,7a-hexahydrofuro-[2,3-d]pyrimidin-4-ol (3c).*** This compound was obtained as a white powder in 64% yield, mp 82–86°C (hexane); $^1$H NMR: δ 2.06–2.11 (m, 2H, H–4a, H–5), 2.15–2.24 (m, 2H, H–5), 2.37 (s, 3H, S–$CH_3$), 2.89 (s, 1H, OH), 3.01 (s, 3H, *N*–$CH_3$), 4.13 (dd, 2H, *J* = 9.0, 5.0 Hz, H–6), 4.49 (d, 1H, *J* = 8.8 Hz, H–7a); $^{13}$C NMR: δ 14.6 (S–$CH_3$), 23.9 (C–5), 32.2 (*N*–$CH_3$), 44.4 (C–4a), 68.3 (C–6), 82.4 (q, $J_{C\text{-}F}$ = 30.8 Hz, C–4), 86.3 (C–7a), 124.4 (q, $J_{C\text{-}F}$ = 283.0 Hz, $CF_3$), 163.6 (C–2). Anal. Calcd. for $C_9H_{13}O_2N_2F_3S$ (270.27): C, 40.00; H, 4.85; N, 10.36. Found: C, 39.92; H, 4.94; N, 10.50.

***1-Methyl-2-(methylthio)-4-(trifluoromethyl)-1,4a,5,6,7,8a-hexahydro-1H-pyrano[2,3-d]pyrimidin-4-ol (3d).*** This compound was obtained as a white powder in 60%, yield, mp 158–161°C (hexane); $^1$H NMR: δ 1.51–1.65 (m, 4H, H–4a, H–5, H–6), 1.85 (br s, 1H, H–5), 2.28 (s, 3H, S–$CH_3$), 2.86 (s, 3H, *N*–$CH_3$), 3.48 (m, 1H, H–7), 3.95 (m, 1H, H–7), 4.25 (d, 1H, *J* = 13.2 Hz, H–8a), 6.38 (s, 1H, OH); $^{13}$C NMR: δ 13.8 (S–$CH_3$), 22.8 (C–5), 25.2 (C–6), 32.1 (*N*–$CH_3$), 40.9 (C–4a), 66.6 (C–7), 82.4 (q, $J_{C\text{-}F}$ = 29.0 Hz, C–4), 86.1 (C–8a),125.9 (q, $J_{C\text{-}F}$ = 286.0 Hz, $CF_3$), 155.1 (C–2). Anal. Calcd. for $C_{10}H_{15}O_2N_2F_3S$ (284.30): C, 42.25; H, 5.32; N, 9.85. Found: C, 42.34; H, 5.27; N, 9.86.

***6-Ethoxy-1-methyl-2-(methylthio)-4-(trichloromethyl)-1,4,5,6-tetrahydropyrimidin-4-ol (4a, 4a′).*** This compound was obtained as a brown powder in 58% yield, mp 105–106°C (hexane), Ir: ν($cm^{-1}$) 3440, 2998, 1678. **4a**: $^1$H NMR: δ 1.25 (t, 3H, *J* = 7.0 Hz, $CH_3$), 2.40 (s, 3H, S–$CH_3$), 2.41 (dd, 1H, *J* = 14.0, 3.6 Hz, H–5), 2.74 (dd, 1H, *J* = 14.0, 2.4 Hz, H–5), 3.16 (s, 3H, *N*–$CH_3$), 3.21 (s, 1H, OH), 3.62 (qua, 2H, *J* = 7.0 Hz, $CH_2$), 4.63 (dd, 1H, *J* = 3.6, 2.4 Hz, H–6); $^{13}$C NMR: δ 13.8 (S–$CH_3$), 14.9 ($CH_3$), 31.3 (C–5), 37.4 (*N*–$CH_3$), 64.2 ($CH_2$), 86.9 (C–6), 87.0 (C–4), 107.1 ($CCl_3$), 161.9 (C–2). **4a′**: $^1$H NMR: δ 1.26 (t, 3H, *J* = 7.0 Hz, $CH_3$), 2.35 (s, 3H, S–$CH_3$), 2.41 (dd, 1H, *J* = 13.0, 10.0 Hz, H–5), 2.43 (s, 1H, OH), 2.67 (dd, 1H, *J* = 13.0, 5.2 Hz, H–5), 2.98 (s, 3H, *N*–$CH_3$), 3.60 (qua, 2H, *J* = 7.0 Hz, $CH_2$), 4.68 (dd, 1H, *J* = 10.0, 5.2 Hz, H–6); $^{13}$C NMR: δ 14.31 (S–$CH_3$), 15.04 ($CH_3$), 31.52 (*N*–$CH_3$), 31.7 (C–5), 62.9 ($CH_2$), 85.0 (C–6), 88.8 (C–4), 108.2 ($CCl_3$), 163.7 (C–2). Anal. Calcd. for $C_9H_{15}O_2N_2Cl_3S$ (321.65): C, 33.61; H, 4.70; N, 8.71. Found: C, 33.30; H, 4.49; N, 8.39.

***3,6-Dimethyl-2-(methylthio)-4-(trifluoromethyl)-3,4-dihydropyrimidin-4-ol (4b).*** This compound was obtained as dark yellow powder in 98% yield, mp 58–60°C (hexane/ethyl acetate, 9:1); Ir: ν($cm^{-1}$) 3432, 1684. $^1$H NMR: δ 1.85 (d, 3H, *J* = 1.6 Hz, $CH_3$), 2.37 (s, 3H, S–$CH_3$), 3.15 (qua, 3H, $J_{H\text{-}F}$ = 1.6 Hz,

*N*–$CH_3$), 3.15–3.16 (s, 1H, OH, underneath to *N*–$CH_3$), 4.82 (m, 1H, H–5); $^{13}$C NMR: δ 14.5 (S–$CH_3$), 22.9 ($CH_3$), 30.45 (q, $J_{C\text{-}F}$ = 2.1 Hz, *N*–$CH_3$), 84.5 (q, $J_{C\text{-}F}$ = 31.8 Hz, C–4), 96.8 (C–5), 124.6 (q, $J_{C\text{-}F}$ = 288.0 Hz, $CF_3$), 147.2 (C–6), 160.3 (C–2). Anal. Calcd. for $C_8H_{11}ON_2F_3S$ (240.25): C, 39.99; H, 4.61; N, 11.66. Found: C, 39.59; H, 4.41; N, 11.59.

***3-Methyl-2-(methylthio)pyrimidin-4(3H)-one (6a).*** This compound was obtained as light yellow powder in 92% yield, mp 113–115°C (hexane); $^1$H NMR: δ 2.57 (s, 3H, S–$CH_3$), 3.51 (s, 3H, *N*–$CH_3$), 6.19 (d, 1H, *J* = 6.0 Hz, H–5), 7.76 (d, 1H, *J* = 6.4 Hz, H–6); $^{13}$C NMR: δ 15.0 (S–$CH_3$), 30.2 (*N*–$CH_3$), 109.8 (C–5), 151.7 (C–6), 162.0 (C–4), 163.7 (C–2). Anal. Calcd. for $C_6H_8ON_2S$ (156.20): C, 48.32; H, 5.69; N, 18.79. Found: C, 48.12; H, 5.50; N, 18.52.

***3,6-Dimethyl-2-(methylthio)pyrimidin-4(3H)-one (6b).*** This compound was obtained as yellow powder in 95% yield, mp 83–85°C (hexane); $^1$H NMR: δ 2.22 ($CH_3$), 2.57 (s, 3H, S–$CH_3$), 3.48 (s, 3H, *N*–$CH_3$), 6.05 (d, 1H, H–5); $^{13}$C NMR: δ 14.9 (S–$CH_3$), 23.6 ($CH_3$), 29.8 (*N*–$CH_3$), 107.2 (C–5), 161.8 (C–6), 162.2 (C–2), 162,3 (C–4). Anal. Calcd. for $C_7H_{10}ON_2S$ (170.23): C, 49.39; H, 5.92; N, 16.46. Found: C, 49.51; H, 5.67; N, 16.38.

***3-Methyl-2-(methylthio)-1,4a,5,6,7,8a-hexahydro-4H-pyrano-[2,3-d]pyrimidin-4-one (5d).*** This compound was obtained as white powder in 70% yield, mp 85–86°C (hexane/ethyl acetate, 9:1); $^1$H NMR: δ 1.45–1.56 (m, 1H, H–5), 1.66–1.73 (m, 2H, H–6), 2.20 (dd, 1H, *J* = 12.0, 4.0 Hz, H–4a), 2.32–2.40 (m, 1H, H–5), 2.45 (s, 3H, S–$CH_3$), 3.21 (s, 3H, *N*–$CH_3$), 3.50–3.60 (m, 1H, H–7), 4.10–4.16 (m, 1H, H–7), 4.52 (d, 1H, *J* = 12.0 Hz, H–8a); $^{13}$C NMR: δ 142 (S–$CH_3$), 22.7 (C–5), 24.8 (C–6), 29.1 (*N*–$CH_3$), 42.3 (C–4a), 67.1 (C–7), 88.7 (C–8a), 155.1 (C–2), 170.4 (C–4). Anal. Calcd. for $C_9H_{14}O_2N_2S$ (214.28): C, 50.45; H, 6.59; N, 13.07. Found: C, 50.27; H, 6.43; N, 13.25.

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## REFERENCES AND NOTES

[1] (a) Amblard, F.; Nolan, S. P.; Schinazi, R. F.; Agrofoglio, L. A. Tetrahedron 2005, 61, 537; (b) Maruenda, H.; Johnson, F. J Med Chem 1995, 38, 2145; (c) Faul, M. M.; Huff, B. E.; Dunlap, S. E.; Frank, S. A.; Fritz, J. E.; Kaldor, S. W.; Le-Torneau, M. E.; Staszak, M. A.; Ward, J. A.; Werner, J. A.; Winneroski, L. L. Tetrahedron 1997, 53, 8085; (d) Bronson, J.; Ghazzouli, J. I.; Hitchcock, M. J. M.; Webb, R. R.; Martin, J C. J Med Chem 1989, 32, 1457.

[2] Hattori, H.; Nozawa, E.; Iino, T.; Yoshimura, Y.; Shuto, S.; Shimamoto, Y.; Nomura, M.; Fukushima, M.; Tanaka, M.; Sasaki, T.; Matsuda, A. J Med Chem 1998, 41, 2892.

[3] Senda, S.; Hirota, K.; Banno, K. J Med Chem 1972, 15, 471.

[4] (a) Tice, C. M.; Bryman, L.; Roemmele, M. R. C. Eur. Pat. 733622 (1994); (b) Tice, C. M.; Bryman, L.; Roemmele, M. R. C. Chem Abstr 1996, 125, 275903s; (c) Tice, C. M. (1994) U.S. Pat. 5300477; (d) Tice, C. M. Chem Abstr 1994, 122, 31543w.

[5] Wong, J. L.; Fuchs, D. S. J Org Chem 1971, 36, 848.

[6] (a) Danel, K.; Larsen, E.; Pedersen, B. E.; Vestergaard, B. F.; Nielsen, C. J Med Chem 1996, 39, 2427; (b) Jane, D. E.; Hoo, K.; Kamboj, R.; Deverill, M.; Bleakman, D.; Mandelzys, A. J Med Chem 1997, 40, 3645; (c) Ogilvie, K. K.; Beaucage, S. L. Tetrahedron Lett 1978, 19, 1663.

[7] Yamauchi, K.; Kinoshita, M. J Chem Soc Perkin Trans 1 1973, 391.

[8] Pacholski, I. L.; Blanco, I.; Martins, M. A. P.; Zanatta, N. J Braz Chem Soc 1991, 2, 118.

[9] Zanatta, N.; Faoro, D.; Fernandes, L. da, S.; Brondani, P. B.; Flores, D. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. Eur J Org Chem. 2008, 5832.

[10] Zanatta, N.; Madruga, C. C.; Marisco, P. C.; Flores, D. C.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 2000, 37, 1213.

[11] Zanatta, N.; Madruga, C. C.; Marisco, P. C.; da Rosa, L. S.; Fernandes, L. da S. Flores, D. C.; Flores, A. F. C.; Burrow, R. A.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 2008, 45, 221.

[12] Zanatta, N.; Madruga, C. C.; Clerice, E.; Martins, M. A. P. J Heterocycl Chem 1995, 32, 735.

[13] (a) Zanatta, N.; da Silva, F. M.; da Rosa, L. S.; Jank, L.; Bonacorso, H. G.; Martins, M. A. P.Tetrahedron Lett 2007, 48, 6531. (b) Bonacorso, H. G.; Lourega, R. V.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 2007, 48, 4835; (c) Zanatta, N.; Amaral, S. S.; Esteves-Souza, A.; Echevarria, A.; Brondani, P. B.; Flores, D. C.; Bonacorso, H. G.; Flores, A. F. C.; Martins, M. A. P. Synthesis 2006, 2305; (d) Zanatta, N.; Lopes, E. C. S.; Fantinel, L.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 2002, 39, 943; (e) Bonacorso, H. G.; Lourega, R. V.; Wastowski, A. D.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 9315; (f) Flores, A. F. C.; Zanatta, N.; Rosa, A.; Brondani, S.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 5005; (g) Zanatta, N.; Cortelini, M. F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 1997, 34, 509.

[14] Cechin, S. R.; Schetinger, M. R. C.; Zanatta, N.; Madruga, C. C.; Pacholski, I. L.; Flores, D. C.; Bonacorso, H. G.; Martins, M. A. P.; Morsch, V. M. Chem Res Toxicol 2003, 16, 1433.

[15] Nagayama, K; Kumar, A.; Wüthrich, K.; Ernst, R. R. J Magn Reson 1980, 40, 321.

[16] Wagner, G.; Wüthrich, K. J Mol Biol 1982, 155, 347.

[17] Bax, A.; Subramanian, S. J Magn Reson 1986, 67, 565.

[18] Bax, A.; Summers, M. F. J Am Chem Soc 1986, 108, 2093.

[19] Saloutin, V. I.; Burgart, Ya. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin, O. N. J Fluor Chem 2000, 103, 17–23.

[20] Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. Synthesis 1991, 483.

# A Convenient One-Pot Procedure for the Synthesis of 2-Aryl Quinazolines Using Active $MnO_2$ as Oxidant



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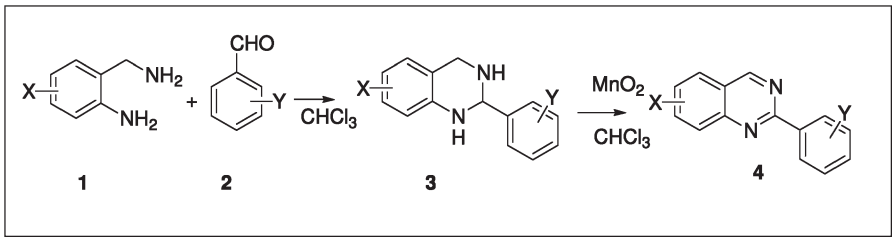


A variety of 2-aryl quinazolines were synthesized from the condensation of 2-aminobenzylamines and aryl aldehydes to form 2-aryl-1,2,3,4-tetrahydroquinazolines and subsequent oxidation of the intermediates with $MnO_2$.

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## INTRODUCTION

The quinazoline ring is a frequently encountered moiety in organic syntheses as well as in medicinal chemistry [1–10]. Many alkaloids containing a quinazoline skeleton in the molecule exhibit anticonvulsant, antibacterial, antidiabetic, and anticancer activities [6,11–14]. A number of methods for the synthesis of quinazolines are known [15–19]. We found five basic types of synthetic strategies for the synthesis of 2-substitued quinazolines: (1) three-step reaction from aryl azides to form 2-alkylquinazolines [20], (2) reaction of amidines with cyano- or nitro-activated *o*-fluorobenzaldehydes [21], (3) condensation of *o*-phenyl oxime of 2-aminoacetophenone with aldehydes or ketones by irradiation with microwaves to form 4-methylquinazolines [22], (4) reaction of 2-aminobenzaldehyde with an acyl halide and by heating the obtained amide in a sealed tube with saturated alcoholic ammonia [19,23–26], and then dehydrogenation with mercuric EDTA complex or aromatization with alkaline potassium ferricyanide [27,28], (5) condensation of 1,3-diamines **1** with aromatic aldehydes **2** to form 2-aryl-1,2,3,4-tetrahydroquinazolines **3**, and then oxidation of **3** to form the 2-aryl substituted quinazolines **4** (Scheme 1).

The fifth synthetic strategy involves two steps: condensation and oxidation. The condensation products, 2-aryl-1,2,3,4-tetrahydroquinazolines, have been prepared in solvent-free [29] and a number of solvents, including benzene or xylene, methanol or ethanol/acetic acid mixtures [30,31], alkali media [32,33], $H_2O$ [34], and ionic liquids [35]. Vandeneynde et al. reported alternative methods where aldehydes were converted, *in situ*, to *N*-(1-chloroalkyl)pyridinium, which reacted with 2-aminobenzylamine to yield tetrahydroquinazoline hydrochloride salts **3**·**HCl** [36]. Two oxidation regents were used to oxidize 2-aryl-tetrahydroquinazolines to the corresponding quinazolines **4**. One is 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and the other tetrachloro-1,4-benzoquinone (TCQ) [36]. More recently, Coskun reported a reaction where the *in situ* formed 2-substituted-1,2,3,4-tetrahydroquinazolines were oxidized to quinazolin-1-oxides [37].

No one-pot reaction to synthesize 2-arylquinazolines was reported. The methods described above to synthesize the 2-arylquinazolines either require multistep preparations of special reagents/reactants, or suffer severe limitations such as tedious experimental procedure and poor yields. Here we report the first one-pot synthesis of 2-aryl substituted quinazolines, from condensation of 1,3-diamines **1** with aryl aldehydes **2** to form 2-aryl-1,2,3,4-tetrahydroquinazolines **3**, and oxidation of **3** to form the 2-aryl substituted quinazolines **4**, using $MnO_2$ as the oxidant.

## RESULTS AND DISCUSSION

The condensation of 2-aminobenzylamine and benzaldehyde was selected as the model reaction. Among the

**Scheme 1**

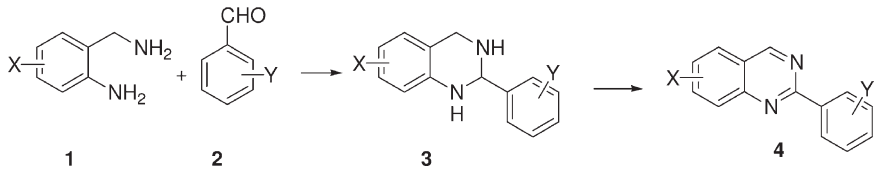



**Table 1**

The solvent effect on the condensation reaction.

| Entry | Solvent | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | $H_2O$ | 4 | 85 |
| 2 | $CHCl_3$ | 10 | 84 |
| 3 | THF | 16 | 66 |
| 4 | $CH_3OH$ | 17 | 73 |
| 5 | $CH_3CN$ | 16 | 74 |
| 6 | $CH_2Cl_2$ | 18 | 63 |

[a] Isolated yield based on 2-aminobenzylamine.

solvents we screened, we found $CHCl_3$ or $H_2O$ was the best solvent to give the product in high yield (Table 1, entries 1 and 2). Other solvents such as THF, $CH_3OH$, $CH_3CN$, and $CH_2Cl_2$ gave lower yields (entries 3–6). This is consistent with the findings of Gawinecki et al. [38].

Several oxidants were evaluated for the transformation of tetrahydroquinazoline **3** to quinazoline **4** in $CHCl_3$ (Table 2). Among the oxidants we used, only DDQ and $MnO_2$ were effective for the transformation from the tetrahydroquinazoline to the quinazoline (Table 2, entries 4–5).

We then evaluated the solvent effects on the oxidation of the tetrahydroquinazoline to the quinazoline. The reaction did not proceed in water or in $CH_3COOH$ (Table 3, Entries 1 and 2). Moderate yields were obtained in $CH_3OH$, $C_2H_5OH$, $CH_2Cl_2$, $CH_3CN$, Dioxane, DMF, and THF (Entries 3–9). The best yield was obtained in $CHCl_3$ (Entry 10). Because both condensation and oxidation reactions proceed well in $CHCl_3$, we envisioned that the synthesis of quinazolines might proceed in one pot.

We then investigated the one-pot reactions of 2-aminobenzylamines and benzaldehydes to synthesize 2-arylqunazolines without isolating the tetrahydroquinazoline intermediate. First, the reaction of 2-aminobenzylamine with benzaldehyde gave tetrahydroquinazoline in $CHCl_3$ at room temperature. After TLC indicated the reaction was completed, we added 4.0 mol equivalents of $MnO_2$. After refluxing for 12 h, the corresponding quinazoline was isolated in 70% yield. To explore the generality and scope of this one-pot reaction, we synthesized 2-arylquinazolines from a variety of 2-aminobenzylamines and aryl aldehydes (Table 4).

A variety of substituents are tolerated on both 2-aminobenzylamines and benzaldehydes. For the 2-aminobenzylamines, ortho F or $CF_3$ substituents slowed the reaction, probably due to the electronic and steric effect in the first step (entries 15–18). For benzaldehydes, the electron-withdrawing substituents speeded the reaction. Overall the reaction gave 2-arylquinazolines in yields from 26 to 75%.

## CONCLUSION

In summary, We have developed an one-pot method to synthesize a variety of 2-arylquinazoline derivatives, from the condensation of 1,3-diamines and aryl aldehydes to form 2-aryl-1,2,3,4-tetrahydroquinazolines and subsequent oxidation of tetrahydroquinazolines with

**Table 2**

The effect of oxidants on the oxidation of 2-phenyltetrahydroquinazoline to quinazoline.

| Entry | Oxidant | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | NBS | 36 | 0 |
| 2 | $Br_2$ | 36 | 0 |
| 3 | $Pb(OAC)_4$ | 36 | 0 |
| 4 | DDQ | 36 | 65 |
| 5 | $MnO_2$ | 36 | 70 |

[a] Isolated yield.

**Table 3**

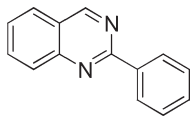
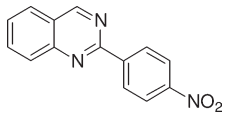
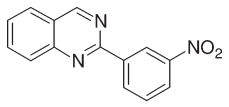
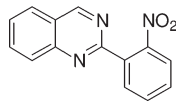
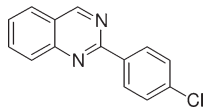
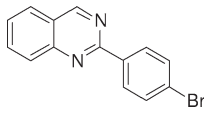
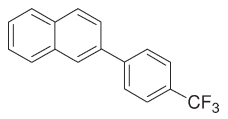
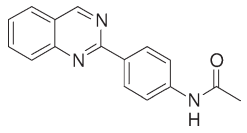
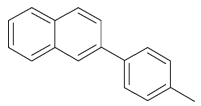
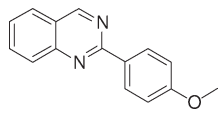
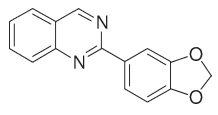
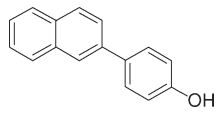
The solvent effect on the oxidation of 2-phenyltetrahydroquinazolin.

| Entry | Solvent | $Time_1$ (h) | $Time_2$ (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $H_2O$ | 5 | 24 | – |
| 2 | $CH_3COOH$ | 4 | 12 | – |
| 3 | $CH_3OH$ | 24 | 12 | 37 |
| 4 | $C_2H_5OH$ | 24 | 12 | 35 |
| 5 | $CH_2Cl_2$ | 36 | 12 | 30 |
| 6 | $CH_3CN$ | 16 | 12 | 51 |
| 7 | Dioxane | 15 | 12 | 54 |
| 8 | DMF | 16 | 8 | 54 |
| 9 | THF | 16 | 12 | 68 |
| 10 | $CHCl_3$ | 10 | 12 | 70 |

[a] Isolated yield.

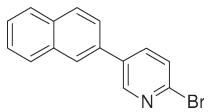
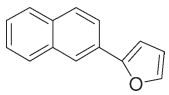
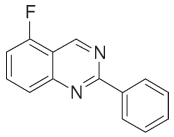
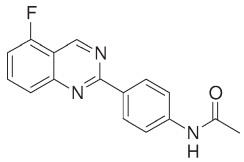
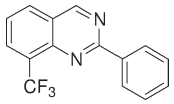
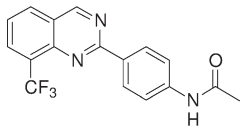
**Table 4**

One-pot synthesis of 2-arylquinazolines.

| Entry | Product | $Time_1$ (h) | $Time_2$ (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  | 10 | 12 | 70 |
| 2 |  | 6 | 12 | 72 |
| 3 |  | 5 | 12 | 62 |
| 4 |  | 5 | 12 | 52 |
| 5 |  | 5 | 12 | 66 |
| 6 |  | 5 | 12 | 75 |
| 7 |  | 7 | 12 | 50 |
| 8 |  | 8 | 12 | 66 |
| 9 |  | 10 | 12 | 56 |
| 10 |  | 10 | 12 | 48 |
| 11 |  | 9 | 12 | 40 |
| 12 |  | 10 | 12 | 30 |

(*Continued*)

**Table 4**
(*Continued*)

| Entry | Product | $Time_1$ (h) | $Time_2$ (h) | Yield[a] (%) |
|---|---|---|---|---|
| 13 |  | 10 | 12 | 50 |
| 14 |  | 4 | 13 | 48 |
| 15 |  | 20 | 14 | 42 |
| 16 |  | 20 | 14 | 40 |
| 17 |  | 20 | 12 | 48 |
| 18 |  | 20 | 20 | 26 |

[a] Isolated yield based on 2-aminobenzylamines.

$MnO_2$ in moderate to high yield. This method provided quick access to different quinazolines.

## EXPERIMENTAL

Melting points were determined on an Electrothermal 9100 capillary melting point apparatus. $^1$H NMR spectra were recorded on a Bruker AV400 (400 MHz) spectrometer, and chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. $^{13}$C NMR spectra were recorded on a Bruker AV400 spectrometer, and chemical shifts are reported in parts per million relative to solvent resonance as the internal standard ($CDCl_3$, δ 77.16). IR spectra were recorded as solid in pellets on a Perkin-Elmer FTIR 683 spectrometer. Mass spectra were obtained with a TRIO 2 (electronic ionization 70 eV) spectrometer and a Perkin-Elmer Claruss 500 mass spectrometer (electronic ionization 20 eV).

**General procedure for the synthesis of 2-aryltetrahydroquinazolines.** A mixture of 2-aminobenzylamine (1.1 mmol), aryl aldehyde (1.0 mmol), and 10 mL of solvent were stirred at room temperature. The reaction was followed by TLC. When the reaction was completed, 4 mmol of active $MnO_2$ was added and refluxed. After the reaction was completed, the organic material was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$, and the solvents were removed. The residue was purified by flash chromatography on silica gel column, using petroleum/ethyl acetate as eluate to give products.

***2-Phenylquinazoline.***[37] This compound was obtained as yellow solid, mp 91–92°C; $^1$H NMR (dimethyl sulfoxide $d_6$): δ 7.53–7.56 (m, 3H, Ar—H), 7.69–7.73 (m, 1H, Ar—H), 8.00–8.04 (m, 2H, Ar—H), 8.13 (d, $J$ = 8.0 Hz, 1H), 8.54–8.56 (m, 2H, Ar—H), 9.67 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 123.6, 127.1, 127.3, 128.6, 128.7, 130.6, 134.1, 138.0, 150.8, 160.5, 161.1.

***2-(4-Nitro-phenyl)quinazoline.***[33] This compound was obtained as yellow solid, mp 197–198°C; $^1$H NMR (deuteriochloroform): δ 7.70 (t, 1H, $J$ = 7.2 Hz), 7.89–7.96 (m, 1H), 8.38 (d, 2H, $J$ = 8.8 Hz), 8.83 (d, 2H, $J$ = 8.8 Hz), 9.50 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 123.8, 123.9, 127.2, 128.3, 128.9, 129.4, 134.6, 143.8, 149.2, 150.6, 158.8, 160.7.

***2-(3-Nitro-phenyl)quinazoline.***[33] This compound was obtained as yellow solid, mp 194–195°C; $^1$H NMR (deuteriochloroform): δ 7.68–7.73 (m, 2H), 7.98 (t, $J$ = 8.0 Hz, 2H), 8.14 (d, $J$ = 8.0 Hz, 1H), 8.34 (d, $J$ = 8.0 Hz, 1H), 8.98 (d, $J$

= 7.6 Hz, 1H), 9.51 (s, 2H); $^{13}$C NMR (deuteriochloroform): δ 123.6, 123.9, 125.1, 127.3, 128.1, 128.8, 129.6, 134.2, 134.6, 139.9, 150.6, 158.7, 160.8.

***2-(2-Nitro-phenyl)quinazoline.***[37] This compound was obtained as yellow solid, mp 91–92°C; $^1$H NMR (deuteriochloroform): δ 7.68–7.73 (m, 2H), 7.98 (t, $J$ = 8.0 Hz, 2H), 8.14 (d, $J$ = 8.0 Hz, 1H), 8.34 (d, $J$ = 8.0 Hz, 1H), 8.98 (d, $J$ = 7.6 Hz, 1H), 9.51 (s, 2H); $^{13}$C NMR (deuteriochloroform): δ 123.6, 124.0, 125.1, 127.2, 128.1, 128.8, 129.6, 134.2, 134.6, 139.8, 148.9, 150.6, 158.7, 160.8.

***2-(4-Chloro-phenyl)quinazoline.***[33] This compound was obtained as yellow solid, mp 116–117°C; $^1$H NMR (deuteriochloroform): δ 7.49 (d, $J$ = 7.6 Hz, 2H), 7.62–7.65 (m, 1H, Ar—H), 7.90–7.95 (m, 2H, Ar—H), 8.07 (d, $J$ = 8.4 Hz, 1H), 8.58 (d, $J$ = 8.8 Hz, 2H, Ar—H), 9.46 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 123.6, 127.2, 127.5, 128.6, 128.9, 129.9, 134.3, 136.5, 136.9, 150.7, 160.1, 160.6.

***2-(4-Bromo-phenyl)-quinazoline.*** This compound was obtained as yellow solid, mp 131–132°C; IR (potassium bromide): 2925, 1693, 1618, 1582, 1546, 1405, 1369, 1067 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 7.62–7.68 (m, 3H, Ar—H), 7.91–7.95 (m, 2H), 8.08 (d, 1H, $J$ = 8.4 Hz), 8.51 (d, 2H, $J$ = 8.4 Hz), 9.46 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 123.7, 125.5, 127.2, 127.6, 128.6, 130.2, 131.8, 134.4, 136.9, 150.7, 160.1, 160.6. HRMS calcd. for $C_{14}H_9BrN_2$: 283.9949, found: 283.9951.

***2-(4-Trifluoromethyl-phenyl)quinazoline.*** This compound was obtained as brown-yellow solid, mp 120–122°C; IR (potassium bromide): 2925, 2854, 1621, 1553, 1326, 1163, 1116 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 7.68 (t, $J$ = 7.6 Hz, 1H), 7.78 (d, $J$ = 8.4 Hz, 2H), 7.94–7.98 (m, 2H, Ar—H), 8.12 (d, $J$ = 8.4 Hz, 1H), 8.75 (d, $J$ = 8.4 Hz, 2H), 9.51 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 122.7 (q, $J$ = 262.0 Hz), 123.7, 123.9, 127.2, 128.3, 128.9, 129.4, 134.6, 143.8, 149.2, 150.6, 158.8, 160.7. HRMS calcd. for $C_{15}H_9F_3N_2$: 274.0718, found: 274.0720.

***2-(4-Acetamido-phenyl)quinazoline.*** This compound was obtained as brown-yellow solid, mp 136–139°C; IR (potassium bromide): 3445, 3259, 2925, 1697, 1602, 1532, 1408, 1312, 799 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 2.23 (s, 3H), 7.39 (br s, 1H), 7.60 (t, $J$ = 7.6 Hz, 1H), 7.68 (d, $J$ = 8.4 Hz, 2H), 7.88–7.93 (m, 2H), 8.06 (d, $J$ = 8.4 Hz, 1H), 8.59 (d, $J$ = 8.4 Hz, 2H), 9.44 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 24.8, 119.4, 123.5, 127.1, 128.5, 129.5, 131.1, 133.9, 134.1, 140.2, 150.8, 160.5, 168.4. HRMS calcd. for $C_{16}H_{13}N_3O$: 263.1059, found: 263.1057.

***2-(4-Methyl-phenyl)quinazoline.***[36] This compound was obtained as yellow solid, mp 99–101°C; IR (potassium bromide): 3027, 2922, 2854, 1620, 1610, 1589, 1552, 1402, 1380, 797, 726 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 2.44 (s, 3H), 7.33 (d, $J$ = 7.2 Hz, 2H), 7.57–7.60 (m, 1H), 7.87–7.91 (m, 2H), 8.05 (d, $J$ = 8.8 Hz, 1H), 8.50 (d, $J$ = 7.2 Hz), 9.44 (d, $J$ = 0.8 Hz); $^{13}$C NMR (deuteriochloroform): δ 21.5, 123.5, 127.1, 128.6, 129.4, 134.1, 135.3, 140.9, 150.8, 160.5.

***2-(4-Methoxyl-phenyl)quinazoline.***[36] This compound was obtained as yellow solid, mp 85–86°C; $^1$H NMR (deuteriochloroform): δ 3.89 (s, 3H), 7.03 (d, $J$ = 8.8 Hz, 2H), 7.56 (t, $J$ = 7.6 Hz, 1H), 7.82–7.89 (m, 2H, Ar—H), 8.02 (d, $J$ = 8.4 Hz, 1H), 8.56 (d, $J$ = 8.8 Hz, 2H), 9.41(s, 1H); $^{13}$C NMR (deuteriochloroform): δ 55.4, 113.9, 123.3, 126.8, 127.1, 128.4, 130.2, 130.7, 134.0, 150.8, 160.4, 160.8, 161.8.

***2-(Benzo[1,3]dioxol-5-yl)quinazoline.*** This compound was obtained as yellow solid, mp 123–125°C; IR (potassium bromide): 2921, 2850, 1618, 1584, 1568, 1502, 1460, 1256, 1099, 1039, 793 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 6.06 (s, 2H, $OCH_2O$), 6.97 (d, 1H, $J$ = 8.4 Hz, Ar—H), 7.59 (s, 1H, Ar—H), 7.91–7.89 (m, 2H, Ar—H), 8.04–8.03 (m, 1H, Ar—H), 8.20 (s, 1H, Ar—H), 8.23 (d, 1H, $J$ = 7.0 Hz, Ar—H), 9.41 (s, 1H, Ar—H); $^{13}$C NMR (deuteriochloroform): δ 29.7, 46.5, 69.4, 101.2, 107.1, 108.3, 115.0, 118.2, 120.1, 121.3, 126.2, 127.3, 135.8, 143.7, 147.7. HRMS calcd. for $C_{15}H_{10}N_2O_2$: 250.0742, found: 250.0740.

***2-(4-Hydroxyl-phenyl)quinazoline.*** This compound was obtained as yellow solid, mp 210–212°C; IR (potassium bromide): 3168, 1670, 1606, 1555, 1457, 1405, 1385, 1240, 1165, 799 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 6.92 (d, $J$ = 8.4 Hz, 3H), 7.64–7.69 (m, 1H), 7.97 (d, $J$ = 3.2 Hz, 2H), 8.09 (d, $J$ = 8.0 Hz, 1H), 8.41 (d, $J$ = 8.8 Hz, 2H), 9.61 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 115.9, 116.3, 123.4, 127.4, 128.1, 128.2, 128.9, 130.4, 135.1, 150.4, 160.5, 161.5. HRMS calcd. for $C_{14}H_{10}N_2O$: 222.0793, found: 222.0795.

***2-(6-Bromo-pyridin-3-yl)-quinazoline.*** This compound was obtained as black solid, mp 158–160°C; IR (potassium bromide): 3061, 2924, 1619, 1572, 1448, 1404, 1088, 734 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 7.61–7.69 (m, 2H, Ar—H), 7.92–7.96 (m, 2H), 8.07 (d, $J$ = 8.8 Hz, 1H), 8.73 (dd, 1H, $J$ = 1.6, 8.4Hz), 9.45 (s, 1H), 9.55 (d, $J$ = 1.6 Hz, 1H); $^{13}$C NMR (deuteriochloroform): δ 123.9, 127.2, 127.9, 128.0, 128.7, 133.0, 134.6, 138.2, 144.2, 150.6, 150.7, 158.3, 160.7. HRMS calcd. for $C_{13}H_8BrN_3$: 284.9902, found: 284.9905.

***2-(2-Furyl)quinazoline.***[37] This compound was obtained as black solid, mp 131–132°C; $^1$H NMR (deuteriochloroform): δ 6.63 (dd, $J$ = 2.0, 3.6 Hz, 1H), 7.46 (d, $J$ = 3.2 Hz, 1H), 7.59–7.63 (m, 1H), 7.70 (d, $J$ = 0.8 Hz, 1H), 7.89–7.93 (m, 2H), 8.09 (d, $J$ = 9.2 Hz, 1H), 9.39 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 112.4, 114.1, 123.4, 127.3, 128.4, 134.6, 145.4, 150.4, 152.5, 154.1, 160.8.

***2-Phenyl-5-flouroquinazoline.*** This compound was obtained as yellow solid, mp 111–113°C; IR (potassium bromide): 3058, 2925, 1635, 1582, 1555, 1465, 1398, 1240, 790, 699 cm$^{-1}$. $^1$H NMR (deuteriochloroform): δ 7.22 (t, 1H, $J$ = 8.4 Hz), 7.53–7.56 (m, 3H, Ar—H), 7.83–7.90 (m, 2H, Ar—H), 8.62–8.63 (m, 2H, Ar—H), 9.74 (s, 1H); $^{13}$C NMR (deuteriochloroform): δ 110.9 (d, $J$ = 19.0 Hz), 114.1, 124.6 (d, $J$ = 4.0 Hz), 128.7 (d, $J$ = 6.0 Hz), 131.0, 134.1 (d, $J$ = 10.0 Hz), 137.6, 152.0, 154.9 (d, $J$ = 3.0 Hz), 157.0 (d, $J$ = 257.0 Hz), 161.2. HRMS calcd. for $C_{14}H_9FN_2$: 224.0750, found: 224.0752.

***2-(4-Acetamido-phenyl)-5-flouroquinazoline.*** This compound was obtained as yellow solid, mp 207–208°C; IR (potassium bromide): 3536, 3283, 3126, 2926, 1633, 1656, 1580, 1556, 1463, 1397, 1376, 1347, 1237, 1089, 822. $^1$H NMR (dimethyl sulfoxide $d_6$): δ 2.10 (s, 3H), 7.49 (t, $J$ = 8.8 Hz, 1H), 7.77 (d, $J$ = 8.4 Hz, 2H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.97–8.03 (m, 1H), 8.48 (d, $J$ = 8.8 Hz, 2H), 9.78 (s, 1H), 10.23 (br s, 1H); $^{13}$C NMR (deuteriochloroform): δ 24.5, 111.7 (d, $J$ = 18.0 Hz), 113.9 (d, $J$ = 16.0 Hz), 119.1 (d, $J$ = 8.0 Hz), 124.6 (d, $J$ = 4.0 Hz), 129.6, 131.9, 135.7 (d, $J$ = 10.0Hz), 142.6, 151.2, 155.6, 156.8 (d, $J$ = 246 Hz), 160.7 169.2. HRMS calcd. for $C_{16}H_{12}FN_3O$: 281.0964, found: 281.0967.

***2-Phenyl-8-trifluoromethylquinazoline.*** This compound was obtained as yellow solid, mp 94–96°C; IR (potassium

bromide): 3070, 1621, 1590, 1568, 1468, 1475, 1410, 1343, 1281, 1159, 1078, 773 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide $d_6$): δ 7.54 (d, $J = 4.0$ Hz, 3H), 7.66 (t, $J = 7.6$ Hz, 1H), 8.10 (d, $J = 7.6$ Hz, 1H), 8.23 (d, $J = 7.2$ Hz, 1H), 8.68 (d, $J = 4.0$ Hz, 2H), 9.52 (s, 1H); $^{13}C$ NMR (dimethyl sulfoxide $d_6$): δ 123.7(q, $J = 242.2$ Hz), 125.8, 128.7, 129.0, 131.3, 131.4, 132.1, 132.2, 137.4, 147.7, 160.7, 161.4. HRMS calcd. for $C_{15}H_9F_3N_2$: 274.0718, found: 274.0721.

***2-(4-Acetamido-phenyl)-8-trifluoromethylquinazoline.*** This compound was obtained as yellow solid, mp 166–168°C; IR (potassium bromide): 3265, 3121, 2926, 2853, 1675, 1601, 1596, 1471, 1327, 1286, 1139, 833, 775 $cm^{-1}$. $^1H$ NMR (dimethyl sulfoxide $d_6$): δ 2.23 (s, 3H), 7.56–7.72 (m, 3H), 7.84 (d, $J = 7.6$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 8.22 (d, $J = 6.8$ Hz, 1H), 8.64 (d, $J = 8.0$ Hz, 1H), 9.49 (s, 1H). $^{13}C$ NMR (dimethyl sulfoxide $d_6$): δ 24.3, 113.0, 113.2, 116.3, 121.7 (q, $J = 248.3$), 124.9, 127.1, 129.1, 129.8, 131.1, 131.8, 136.7, 138.5, 144.3, 169.5. HRMS calcd. for $C_{17}H_{12}F_3N_3O$: 331.09325, found: 331.09367.

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## REFERENCES AND NOTES

[1] Witt, A.; Bergman, J. Curr Org Chem 2003, 7, 659.

[2] Lau, H.; Ferlan, J. T.; Brophy, V. H.; Rosowsky, A.; Sibley, C. H. Antimicrob Agents Chemother 2001, 45, 187.

[3] Purohit, D. M.; Shah, V. H. Indian J Heterocycl Chem 1999, 8, 213.

[4] Desai, P.; Naik, B.; Desai, C. M.; Patel, D. Asian J Chem 1998, 10, 615.

[5] Dyakonov, A. L.; Telezhenetskaya, M. V. Khim Prir Soedin 1997, 297.

[6] Dempcy, R. O.; Skibo, E. B. Biochemistry 1991, 30, 8480.

[7] Calvert, A. H.; Jones, T. R.; Dady, P. J.; Grzelakowskasztabert, B.; Paine, R. M.; Taylor, G. A.; Harrap, K. R. Eur J Cancer 1980, 16, 713.

[8] Yakhontov, L. N.; Liberman, S. S.; Zhikhareva, G. P.; Kuzmina, K. K. Khim Farm Zh 1977, 11, 14.

[9] Hynes, J. B.; Buck, J. M. J Med Chem 1975, 18, 1191.

[10] Spence, G. G.; Taylor, E. C.; Buchardt, O. Chem Rev 1970, 70, 231.

[11] Michael, J. P. Nat Prod Rep 2003, 20, 476.

[12] Michael, J. P. Nat Prod Rep 2002, 19, 742.

[13] Michael, J. P. Nat Prod Rep 1999, 16, 697.

[14] Chan, J. H.; Hong, J. S.; Kuyper, L. F.; Jones, M. L.; Baccanari, D. P.; Tansik, R. L.; Boytos, C. M.; Rudolph, S. K.; Brown, A. D. J Heterocycl Chem 1997, 34, 145.

[15] Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Tetrahedron 2005, 61, 10153.

[16] Undheim, K.; Benneche, T. In Comprehensive Heterocyclic Chemistry II. Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon Press: London, 1996; pp 93–231.

[17] Gilchrist, T. L. In Heterocyclic Chemistry, 3rd ed.; Gilchrist, T. L., Ed.; Academic Press: New York, 1997; pp 285–294.

[18] Armarego, W. L. F. In Advance Heterocyclic Chemistry; Katritzky, A. R., Ed.; Academic Press: New York, 1979; Vol. 24, pp 1–62.

[19] Armarego, W. L. F. Adv Heterocycl Chem 1963, 1, 253.

[20] Erba, E.; Pocar, D.; Valle, M. J Chem Soc Perkin Trans 1 1999, 421.

[21] Kotsuki, H.; Sakai, H.; Morimoto, H.; Suenaga, H. Synlett 1999, 1993.

[22] Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. Chem Commun 2008, 2935.

[23] Siegle, J.; Christensen, B. E. J Am Chem Soc 1951, 73, 5777.

[24] Schofield, K.; Swain, T.; Theobald, R. S. J Chem Soc 1952, 1924.

[25] Albert, A.; Hampton, A. J Chem Soc 1954, 505.

[26] Schofield, K. J Chem Soc 1954, 4034.

[27] Mohrle, H.; Seidel, C. M. Arch Pharm 1976, 309, 471.

[28] Elderfield, R. C.; Williamson, T. A.; Gensler, W. J.; Kremer, C. B. J Org Chem 1947, 12, 405.

[29] Correa, W. H.; Papadopoulos, S.; Radnidge, P.; Roberts, B. A.; Scott, J. L. Green Chem 2002, 4, 245.

[30] Kempter, G.; Ehrlichmann, W.; Plesse, M.; Lehm, H. U. J Prakt Chem 1982, 324, 832.

[31] Coskun, N.; Cetin, M. Tetrahedron Lett 2004, 45, 8973.

[32] Busch, M. J Prakt Chem 1896, 53, 414.

[33] Busch, M. J Prakt Chem 1895, 51, 113.

[34] Sinkkonen, J.; Zelenin, K. N.; Potapov, A. K. A.; Lagoda, I. V.; Alekseyev, V. V.; Pihlaja, K. Tetrahedron 2003, 59, 1939.

[35] Kitazume, T.; Zulfiqar, F.; Tanaka, G. Green Chem 2000, 2, 133.

[36] Vandeneynde, J. J.; Godin, J.; Mayence, A.; Maquestiau, A.; Anders, E. Synthesis 1993, 867.

[37] Coskun, N.; Cetin, M. Tetrahedron 2007, 63, 2966.

[38] Gawinecki, R.; Kolehmainen, E.; Kuczek, A.; Pihlaja, K.; Osmailowski, B. J Phys Org Chem 2005, 18, 737.

# Sulfamic Acid-Catalyzed Synthesis of 13-Aryl-indeno[1,2-*b*]-naphtha[1,2-e]pyran-12(13*H*)-ones under Solvent-Free Conditions

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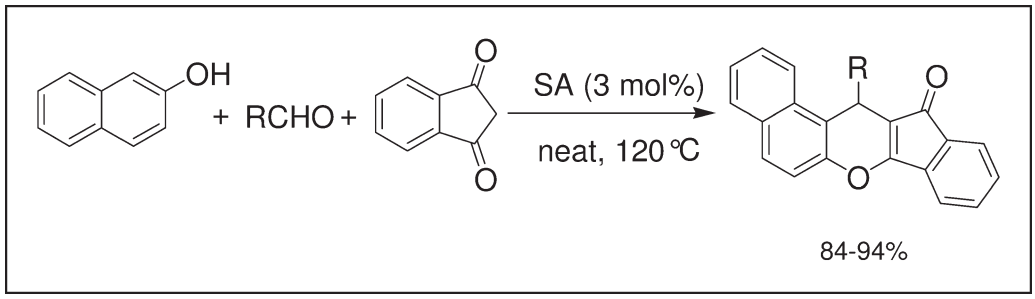


The reaction of β-naphthol with arylaldehydes and 2H-indene-1,3-dione in the presence of sulfamic acid (3 mol %) under solvent-free conditions led to 13-aryl-indeno[1,2-*b*]naphtho[1,2-*e*]pyran-12(13*H*)-ones in good yields.

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## INTRODUCTION

Multicomponent reactions have attracted considerable attention as they are performed without need to isolate any intermediate during their processes; this reduces time and saves both energy and raw materials [1]. They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules.

Natural compounds possessing naphthopyran moiety have been attracted by their antimicrobial [2], antitumor [3], antifungal [4], cytotoxic [5], antioxidative, and 5-lipoxygenase inhibitory activity [6]. A variety of naphthopyran derivatives have been isolated and identified as natural phytochemicals [7]. A plethora of biological activities have also been associated with a large number of synthetic naphthopyran analogs [8]. Indenopyrans are a ''privileged medicinal scaffolds,'' which are used for the development of pharmaceutical agents of various applications. Compounds with the motif show a wide range of pharmacological activities, such as antiulcer [9], antiallergenic [10], and antidepressant activities [11].

Molecule frame works for the development of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*] xanthen-11-ones have also been described [12]. However, there is no report about the synthesis of 13-aryl-indeno[1,2-*b*]naphtho[1,2-*e*]pyran-12(13*H*)-ones, which may show potential pharmaceutical activities.

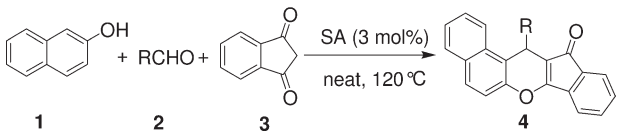
In recent years, the use of solid acidic catalysts has offered important advantages in organic synthesis, for example, operational simplicity, environmental compatibility, nontoxic, low cost, and ease of isolation. A tremendous upsurge of interest in various chemical transformations processes by catalysts under heterogeneous conditions has occurred. One of those heterogeneous catalysts is sulfamic acid (SA). It makes reaction processes convenient, more economic, and environmentally benign. Owing to the numerous advantages associated with this cheap and nonhazardous catalyst, SA has been explored as a powerful catalyst for various organic transformations [13]. We now report a highly efficient procedure for the preparation of 13-aryl-indeno[1,2-*b*]naphtho[1,2-*e*]pyran-12(13*H*)-ones using SA as an efficient and versatile catalyst under solvent-free conditions (Scheme 1).

## RESULTS AND DISCUSSION

Initially, to optimize the reaction temperatures, the reaction of β-naphthol (1 mmol) with benzaldehyde (1 mmol) and 2H-indene-1,3-dione was studied under solvent-free conditions in the presence of 3 mol % SA at different temperatures. The results are summarized in Table 1. As shown in Table 1, the reaction at 120°C proceeded in highest yield.

To optimize the catalyst loading, 0, 1, 2, 3, 4, and 5 mol % of was tested, respectively. The results are

**Scheme 1**




summarized in Table 2. A 3 mol % loading of SA was sufficient to push the reaction forward and 2 mol % of SA was not enough. Higher amounts of SA did not lead to significant change in the reaction yields.

Based on the optimized reaction conditions, a range of 13-aryl-indeno[1,2-*b*]naphtho[1,2-*e*]pyran-12(13*H*)-ones (**4**) was synthesized by the reaction of β-naphthol (**1**, 1 mmol) with arylaldehydes (**2**, 1 mmol) and 2H-indene-1,3-dione (**3**, 1 mmol). The reaction proceeded at 120°C within 4 h in excellent yields after the addition of the catalyst SA (Table 3). All of the products **4** exhibited a singlet in their $^1$H spectra at δ = 5.58–6.01 ppm for H-13 and also a distinguishing peak at δ = 28.8–35.7 ppm for C-13 in their $^{13}$C NMR spectra. The resonance of carbonyl group in their $^{13}$C NMR spectrum of **4** appeared at δ = 191.7–192.4 ppm. When this reaction was carried out with aliphatic aldehyde, such as butanal or pentanal, TLC and $^1$H NMR spectra of the reaction mixture showed a mixture of starting materials and numerous products, the yield of the expected product was very poor. In 2-naphthol, the electron density at the benzylic C-1 position (which is in conjugation with the aromatic ring) is higher than that at the C-3 position. Thus, the regioselective formation of the *ortho*-quinone methide from this compound involving the C-1 and C-2 positions is favored. In simple phenolic compounds and 1-naphthol (which are weaker nucleophiles compared with 2-naphthol), the electron density at the *ortho* position of the hydroxyl group is not sufficient for the reaction of these compounds with the aldehydes leading to the formation of the corresponding *ortho*-quinone methides. When the reaction of 1-naphthol (1 mmol) with benzaldehyde (1 mmol) and 2H-indene-1,3-dione was carried out under solvent-free conditions in the presence of 3 mol % SA at 120°C, the yield of the expected product was 0%.

In conclusion, we have demonstrated a rapid and very efficient SA-catalyzed one-pot synthesis of 13-aryl-indeno[1,2-*b*]naphtho[1,2-*e*]pyran-12(13*H*)-ones under solvent-free conditions. The current methodology has the advantages of operational simplicity, neutral and mild reaction conditions, high to excellent yields of products, lack of toxicity, and low costs.

**Table 1**

Temperature optimization for the synthesis of 13-phenyl-indeno [1,2-b]naphtha [1,2-e]pyran-12(13H)-ones.[a]

| Entry | Temp. (°C) | Yield (%)[b] |
|---|---|---|
| 1 | 80 | 56 |
| 2 | 90 | 62 |
| 3 | 100 | 76 |
| 4 | 110 | 82 |
| 5 | 120 | 89 |
| 6 | 130 | 87 |
| 7 | 140 | 88 |

[a] Reaction conditions: β-naphthol (1 mmol); benzaldehyde (1 mmol); 2H-indene-1,3-dione (1 mmol); SA (0.03 mmol); solvent-free; 3 h.
[b] Isolated yield after chromatographic purification.

**Table 2**

The amounts of catalyst optimization for the synthesis of 13-phenyl-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-ones.[a]

| Entry | SA (mol %) | Yield (%)[b] |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1 | 58 |
| 3 | 2 | 79 |
| 4 | 3 | 89 |
| 5 | 4 | 88 |
| 6 | 5 | 87 |

[a] Reaction conditions: β-naphthol (1 mmol); benzaldehyde (1 mmol); 2H-indene-1,3-dione (1 mmol); solvent-free;120°C; 3 h.
[b] Isolated yield after chromatographic purification.

## EXPERIMENTAL

NMR spectra were determined on Bruker AV-400 spectrometer in $CDCl_3$ and were expressed in δ values relative to tetramethylsilane, coupling constants (*J*) were measured in Hz; IR spectra were determined on FTS-40 infrared spectrometer; Mass spectra were recorded on a Finnigan LCQ Advantage mass spectrometer; Elemental analysis were recorded on a Vario ELIII elemental analyzer; Melting points were determined on a Mel-Temp capillary tube apparatus and were uncorrected; Commercially available reagents were used throughout without further purification unless otherwise stated.

**Table 3**

Synthesis of 13-aryl-indeno[1,2-b]naphtho [1,2-e]pyran-12(13H)-ones using SA as catalyst.[a]

| Entry | R | Time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $C_6H_5$ | 3 | **4a** | 89 |
| 2 | 4-Cl-$C_6H_4$ | 2 | **4b** | 92 |
| 3 | 3-$NO_2$-$C_6H_4$ | 3 | **4c** | 89 |
| 4 | 2-F-5-$CF_3$-$C_6H_3$ | 4 | **4d** | 86 |
| 5 | 4-Me-$C_6H_4$ | 4 | **4e** | 86 |
| 6 | 2,4-$Cl_2$-$C_6H_3$ | 3 | **4f** | 93 |
| 7 | 2-Cl-$C_6H_4$ | 2 | **4g** | 94 |
| 8 | 4-MeO-$C_6H_4$ | 4 | **4h** | 84 |
| 9 | 4-F-$C_6H_4$ | 2 | **4i** | 92 |
| 10 | 3,4-$Cl_2$-$C_6H_3$ | 3 | **4j** | 91 |

[a] Reaction conditions: β-naphthol (1 mmol); arylaldehyde (1 mmol); 2H-indene-1,3-dione (1 mmol); SA (0.03 mmol); solvent-free;120°C.
[b] Isolated yield after chromatographic purification.

**General procedure for the preparation of 4.** To a mixture of β-naphthol (1 mmol), aldehyde (1 mmol) and 2H-indene-1,3-dione (1 mmol), SA (0.03 mmol) was added. The mixture was stirred (use a high power electric mixer) at 120°C for an appropriate time (Table 3). After completion of the reaction (TLC), the reaction mixture was treated with water (10 mL) and extracted with $CH_2Cl_2$ (2 × 10 mL), filtered and the solvent evaporated *in vacuo*. Products were puried by silica gel column chromatography using petroleum ether:chloroform (2:3) as eluent.

***13-Phenyl-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4a).*** Yellow solid, mp 202–203°C. IR (KBr) ν: 3080, 1660, 1236, 1006 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.89–7.82 (m, 3H), 7.51 (d, $J$ = 8.8 Hz, 1H), 7.43–7.29 (m, 8H), 7.23 (t, $J$ = 8.0 Hz, 2H), 7.12 (t, $J$ = 7.6 Hz, 1H), 5.64 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.3, 167.3, 149.0, 143.7, 136.9, 132.4, 132.2, 131.9, 131.8, 130.1, 129.6, 128.5, 128.4, 128.1, 127.1, 126.6, 125.2, 124.4, 121.6, 118.3, 117.1, 116.6, 111.0, 35.7 ppm. MS (ESI): $m/z$ 361 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{16}O_2$: C, 86.65; H, 4.47. found: C, 86.73; H, 4.38.

***13-(4-Chlorophenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4b).*** Yellow solid, mp 225–226°C. IR (KBr) ν: 3042, 1667, 1235, 1015 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.88–7.84 (m, 2H), 7.75 (t, $J$ = 9.2 Hz, 1H), 7.51 (d, $J$ = 8.8 Hz, 1H), 7.45–7.25 (m, 8H), 7.18 (d, $J$ = 8.4 Hz, 2H), 5.63 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.3, 167.3, 149.0, 142.1, 136.7, 132.3, 132.2, 131.9, 131.6, 130.2, 129.9, 129.5, 128.7, 128.6, 127.3, 125.4, 124.2, 121.7, 118.4, 117.7, 116.0, 110.4, 35.1 ppm. MS (ESI): $m/z$ 395 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{15}ClO_2$: C, 79.09; H, 3.83. found: C, 79.29; H, 3.75.

***13-(3-Nitrophenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4c).*** Yellow solid, mp 240–241°C. IR (KBr) ν: 3075, 1665, 1232, 1005 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.99 (d, $J$ = 8.4 Hz, 1H), 7.93 (d, $J$ = 8.8 Hz, 1H), 7.89–7.87 (m, 1H), 7.79 (d, $J$ = 7.6 Hz, 1H), 7.68 (d, $J$ = 8.8 Hz, 1H), 7.55 (d, $J$ = 9.2 Hz, 1H), 7.47–7.41 (m, 6H), 7.35–7.31 (m, 1H), 5.77 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.1, 167.7, 149.2, 148.5, 145.7, 136.5, 134.4, 132.5, 132.1, 132.0, 131.3, 130.5, 130.4, 129.4, 128.8, 127.5, 125.5, 125.5, 123.9, 123.0, 121.9, 118.7, 117.9, 115.0, 109.5, 35.6 ppm. MS (ESI): $m/z$ 406 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{15}NO_4$: C, 77.03; H, 3.73; N, 3.46. found: C, 76.85; H, 3.70; N, 3.58.

***13-(2-Fluoro-5-(trifluoromethyl)phenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4d).*** Yellow solid, mp 216–217°C. IR (KBr) ν: 3042, 1659, 1230, 1007 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.91–7.81 (m, 3H), 7.54–7.32 (m, 9H), 7.17 (t, $J$ = 8.8 Hz, 1H), 5.92 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 191.7, 168.1, 149.0, 136.6, 132.4, 132.1, 131.9, 131.8, 131.4, 130.5, 130.2, 128.7, 127.6, 127.3, 126.1, 125.5, 124.8, 123.1, 122.1, 121.8, 118.7, 117.8, 116.5, 116.2, 115.2, 109.1, 28.8 ppm. MS (ESI): $m/z$ 447 $[M + H]^+$. *Anal*. calcd for $C_{27}H_{14}F_4O_2$: C, 72.65; H, 3.16. found: C, 72.48; H, 3.12.

***13-(4-Methylphenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4e).*** Yellow solid, mp 192–193°C. IR (KBr) ν: 2980, 1675, 1237, 1010 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.88–7.82 (m, 3H), 7.50 (d, $J$ = 9.2 Hz, 1H), 7.43–7.28 (m, 6H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.02 (d, $J$ = 8.0 Hz, 2H), 5.61 (s, 1H), 2.24 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.4, 167.2, 149.0, 140.8, 136.9, 136.1, 132.4, 132.2, 131.9, 130.0, 129.5, 129.2, 128.4, 128.0, 127.1, 125.2, 124.4, 121.6, 118.2, 117.7, 116.8, 111.2, 35.3, 21.0 ppm. MS (ESI): $m/z$ 375 $[M + H]^+$. *Anal*. calcd for $C_{27}H_{18}O_2$: C, 86.61; H, 4.85. found: C, 86.49; H, 4.92.

***13-(2,4-Dichlorophenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4f).*** Yellow solid, mp 252–253°C. IR (KBr) ν: 3052, 1677, 1232, 1025 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.89–7.81 (m, 3H), 7.51–7.41 (m, 7H), 7.35–7.31 (m, 1H), 7.02–6.97 (m, 2H), 6.01 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 191.6, 167.5, 148.8, 140.1, 136.7, 133.5, 132.9, 132.3, 132.2, 131.9, 131.7, 131.6, 130.4, 130.0,129.4, 128.6, 127.8, 127.5, 125.5, 123.8, 121.7, 118.5, 117.7, 116.5, 110.0, 32.4 ppm. MS (ESI): $m/z$ 429 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{14}Cl_2O_2$: C, 72.74; H, 3.29. found: C, 72.85; H,3.18.

***13-(2-Chlorophenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4g).*** Yellow solid, mp 240–241°C. IR (KBr) ν: 3048, 1671, 1230, 1018 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.91–7.81 (m, 3H), 7.51–7.30 (m, 8H), 7.06–7.02 (m, 3H), 6.05 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 191.7, 167.4, 148.8, 136.8, 132.8, 132.3, 132.2, 131.9, 131.8, 130.8, 130.2, 129.8, 129.7, 128.5, 127.9, 127.4, 127.3, 125.3, 124.1, 121.6, 118.3, 117.7, 117.1, 32.7 ppm. MS (ESI): $m/z$ 395 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{15}ClO_2$: C, 79.09; H, 3.83. found: C, 79.25; H, 3.92.

***13-(4-Methoxylphenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4h).*** Yellow solid, mp 225–226°C. IR (KBr) ν: 2945, 1676, 1232, 1004 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.87–7.82 (m, 3H), 7.49 (d, $J$ = 9.2 Hz, 1H), 7.43–7.27 (m, 6H), 7.23 (d, $J$ = 8.8 Hz, 2H), 6.75 (d, $J$ = 8.8 Hz, 2H), 5.58 (s, 1H), 3.71(s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.5, 167.0, 158.1, 148.9, 136.9, 136.1, 132.4, 132.2, 131.9, 131.8, 130.0, 129.5, 129.1, 128.4, 127.1, 125.2, 124.4, 121.6, 118.2, 117.7, 116.8, 113.9, 111.2, 55.1, 34.8 ppm. MS (ESI): $m/z$ 391 $[M + H]^+$. *Anal*. calcd for $C_{27}H_{18}O_3$: C, 83.06; H, 4.65. found: C, 82.96; H, 4.75.

***13-(4-Fluorophenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-one (4i).*** Yellow solid, mp 208–209°C. IR (KBr) ν: 3052, 1668, 1230, 1016 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.90–7.76 (m, 3H), 7.50 (d, $J$ = 8.8 Hz, 1H), 7.43–7.28 (m, 8H), 6.91 (t, $J$ = 8.4 Hz, 2H), 5.63 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.3, 167.2, 149.0, 139.4, 136.8, 132.3, 131.9, 131.7, 130.2, 129.8, 129.7, 129.6, 128.5, 127.2, 125.3, 124.3, 121.7, 118.3, 117.7, 116.3, 115.5, 115.3, 35.0 ppm. MS (ESI): $m/z$ 379 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{15}FO_2$: C, 82.53; H, 4.00. found: C, 82.44; H, 4.17.

***13-(3,4-Dichlorophenyl)-indeno[1,2-b]naphtho[1,2-e]pyran-12(13H)-ones (4j).*** Yellow solid, mp 245–246°C. IR (KBr) ν: 3050, 16728, 1238, 1023 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.93–7.86 (m, 2H), 7.73–7.71 (m, 1H), 7.52 (d, $J$ = 9.2 Hz, 1H), 7.48–7.22 (m, 9H), 5.61 (s, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 192.1, 167.5, 149.1, 143.8, 136.6, 132.6, 132.4, 132.2, 131.9, 131.5, 130.7, 130.4, 130.2, 130.0, 128.7, 127.6, 127.5, 125.5, 124.0, 121.8, 118.5, 117.8, 115.3, 35.0 ppm. MS (ESI): $m/z$ 429 $[M + H]^+$. *Anal*. calcd for $C_{26}H_{14}Cl_2O_2$: C, 72.74; H, 3.29. found: C, 72.60; H,3.40.

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## REFERENCES AND NOTES

[1] Devi, I.; Bhuyan, P. Tetrahedron Lett 2004, 45, 8625.

[2] Baker, R. A.; Tatum, J. H.; Nemec, S. Mycopathologia 1990, 111, 9.

[3] Nicolaou, K. C.; Skokotas, G.; Furaya, S.; Suemune, H.; Nicolaou, D. C. Angew Chem Int Ed Eng 1990, 29, 1064.

[4] Kodama, O.; Ichikawa, H.; Akatsuka, T.; Santisopasri, V.; Kato, A.; Hayashi, Y. J Nat Prod 1993, 56, 292.

[5] Hussein, A. A.; Barberena, I.; Capson, T. L.; Kursar, T. A.; Coley, P. D.; Solis, P. N.; Gupta, M. P. J Nat Prod 2004, 67, 451.

[6] Bucar, F.; Resch, M.; Bauer, R.; Burits, M.; Knauder, E.; Schubert-Zsilavecz, M. Pharmazie 1998, 53, 875.

[7] (a) El-Hady, S.; Bukuru, J.; Kesteleyn, B.; Van Puyvelde, L.; Van, T. N.; De Kimpe, N. J Nat Prod 2002, 65, 1377; (b) Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. Nat Prod Rep 1999, 16, 267; (c) Li, Y. Q.; Li, M. G.; Li, W.; Zhao, J. Y.; Ding, Z. G.; Cui, X. L.; Wen, M. L. J Antibiot 2007, 60, 757.

[8] (a) Karnik, A. V.; Kulkarni, A. M.; Malviya, N. J.; Mourya, B. R.; Jadhav, B. L. Eur J Med Chem 2008, 43, 2615; (b) Jin, T.-S.; Zhang, J.-S. Liu, L.-B.; Wang, A.-Q.; Li, T.-S. Synth Commun 2006, 36, 2009; (c) Suryavanshi, J. P.; Pai, N. R. Indian J Chem Sec B 2006, 45, 1227; (d) Kulkarni, A. M.; Malviya, N. J.; Karnik, A. V. Indian J Chem Sec B 2004, 43, 839; (e) Costi, M. P.; Tondi, D.; Pecorari, P.; Rinaldi, M.; Celentano, G.; Ghelli, S.; Antolini, L.; Barlocco, D. J Heterocyclic Chem 1999, 36, 1043.

[9] Pelz, K.; Dobson, T. A. US patent 3,904,617, 1975; Chem Abstr 2008, 84, 164794.

[10] Goerlitzer, K.; Dehne, A.; Engler, E. Arch Pharm 1983, 316, 264.

[11] Jirkovsky, I.; Humber, L. G.; Noureldin, R. Eur J Med Chem 1976, 11, 571.

[12] (a) Gao, S.; Tsai, C. H. C.; Yao, F. Synlett 2009, 949; (b) Khurana, J. M.; Magoo, D. Tetrahedron Lett 2009, 50, 4777; (c) Li, J.; Tang, W.; Lu, L.; Su, W. Tetrahedron Lett 2008, 49, 7117; (d) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Srinivas, Y. Synlett 2007, 3107.

[13] (a) Jin, T. S.; Sun, G.; Li, Y. W.; Li, T. S. Green Chem 2002, 4, 255; (b) Nagarajan, R.; Magesh, C. J.; Perumal, P. T. Synthesis 2004, 69; (c) Rajitha, B.; SunilKumar, B.; Thirupathi Reddy, Y.; Narsimha Redd, P.; Sreenivasulu, N. Tetrahedron Lett 2005, 46, 8691; (d) Venu Madhav, J.; Naveen Kumar, V.; Rajitha, B. Synth Commun 2008, 38, 1799.

# Design, Synthesis, and Characterization of Some Novel Pyrazolo [1,5-a] Pyrimidines as Potent Antimicrobial Agents



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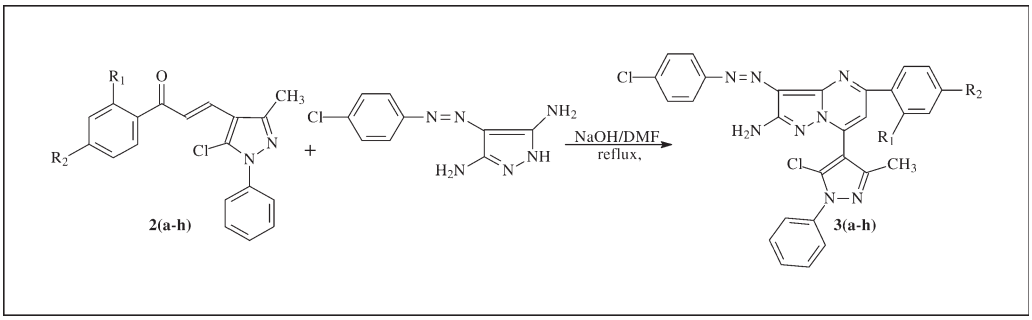


A novel series of pyrazolo [1,5-a] pyrimidines were synthesized by the condensation of substituted chalcones with 5-amino pyrazole in presence of dimethyl formamide. All the synthesized products were characterized by the spectral analysis. Further, all newly synthesized compounds were screened for their antimicrobial activity. Most of the compounds showed potent activity.

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## INTRODUCTION

Pyrazole nucleus has wide applications in medicinal chemistry. The ring system plays an important role in many biological processes, and many therapeutic agents contain pyrazole moiety. Several pyrazoles with antimicrobial, antiviral, and anticancer properties have been reported [1]. Certain alkyl pyrazoles have shown significant antiallergic, anti-inflammatory, and antiarthritic properties [2,3]. Many pyrazole-fused heterocyclic compounds have been to exhibit biological activity and widely used studied in pesticide and medicine [4–6]. Pyrazolopyrimidines are of considerable chemical and pharmacological importance as purine analogues [7,8], and have antitumor, antileukemic activities. Pyrazolo [1,5-a] pyrimidines useful properties, as antimetabolites in purine biochemical reactions [9–11]. These interesting biological activities reported for pyrazolopyrimidines have stimulated chemists to develop new class of these compounds.

## RESULTS AND DISCUSSION

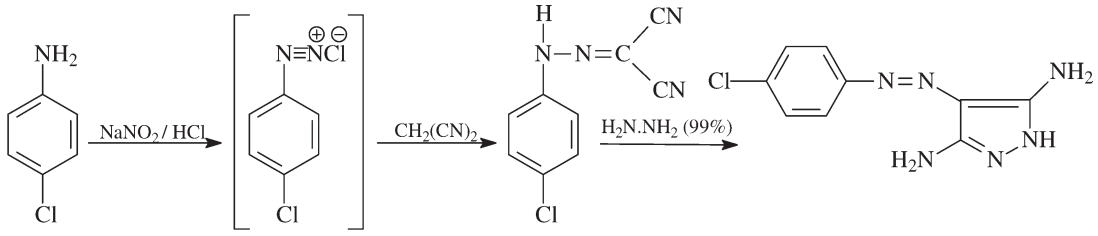
In continuation of our work on the synthesis of some new bioactive heterocyclic compounds [12–15], herein we report a new series of pyrazolo [1,5-a] pyrimidines by the condensation of chalcones with the 5-amino pyrazole in dimethyl formamide (DMF).

The starting 5-amino pyrazole was prepared in two steps from the corresponding amine by the diazotization and then treatment with malononitrile followed by reaction with hydrazine hydrate [16] (Scheme 1), while the novel α,β-unsaturated carbonyl compounds **2(a–h**) were prepared in the presence of base by conventional Claisen–Schmidt condensation of substituted acetophenones and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Scheme 2). Finally, the synthesis of pyrazolo [1,5-a] pyrimidines **3(a–h**) were attempted by the reacting 5-amino pyrazole with α,β-unsaturated carbonyl compounds (chalcones) using NaOH in presence of DMF as reaction solvent (Scheme 3).

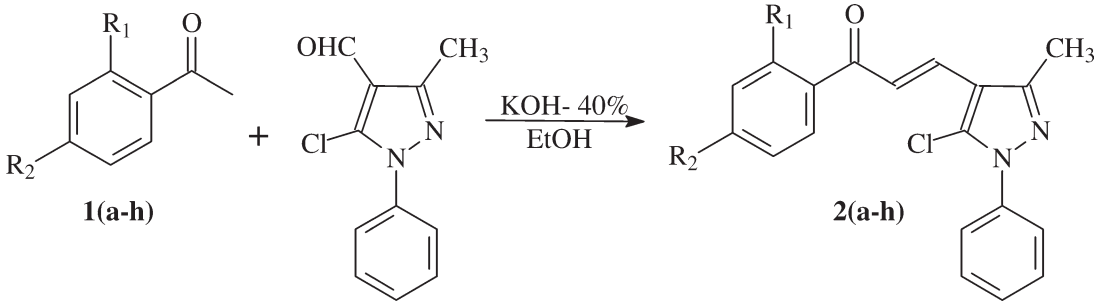
The formation of products were assumed to proceed through the Micheal-type addition of the ring nitrogen in 5-amino pyrazole (which is more active) to the activated double bond followed by intramolecular cyclization [17,18] with the elimination of water and dehydrogenation. The structures of compounds were appropriately established by the spectroscopic and analytical methods.

The results of the antimicrobial screening data are given in Table 1. In comparison with reference drugs, compounds **3a**, **3b**, and **3c** showed effective activity against all the tested microbes. Compounds **3a** and **3b** showed near to par activity against *Bacillus subtilis*. Only the compound **3a** was showed potent activity against *Escherichia coli* than standard penicillin drug.

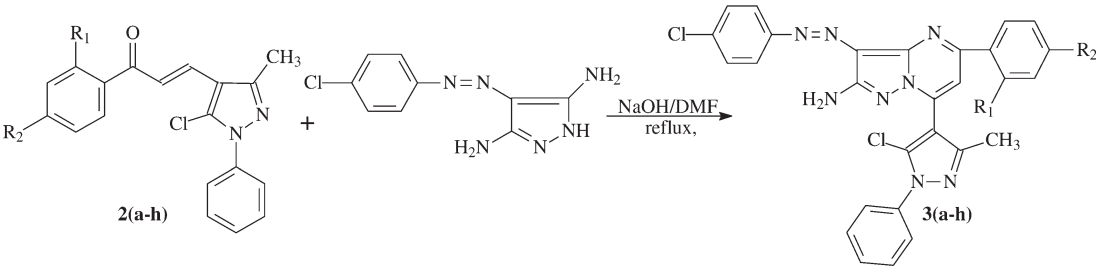
**Scheme 1.** Synthesis of 5-amino pyrazole.




**Scheme 2.** Synthesis of chalcones.




**Scheme 3.** Synthesis of pyrazolo [1,5-a] pyrimidines.




Compound **3b** showed stronger activity against *Aspergillus flavus* than reference Nystatin drug. On the other hand, compounds **3(d–h)** displayed moderate antimicrobial activity.

**Table 1**

Antimicrobial activity of synthesized compounds **3(a–h)**.

| Product | A | B | C | D |
|---|---|---|---|---|
| **3a** | 25 | 27 | 17 | 15 |
| **3b** | 22 | 26 | 16 | 18 |
| **3c** | 22 | 27 | 16 | 15 |
| **3d** | 18 | 15 | 14 | 12 |
| **3e** | 20 | 18 | 11 | 10 |
| **3f** | 18 | 21 | 12 | 11 |
| **3g** | 14 | 16 | 10 | 8 |
| **3h** | 16 | 20 | 12 | 15 |
| Reference1 | 24 | 28 | NA | NA |
| Reference2 | NA | NA | 18 | 16 |

Zone of inhibitions are expressed in mm.
A = *Escherichia coli*, B = *Bacillus subtilis*, C = *Fusarium moniliformae*, D = *Aspergillus flavus*, Reference 1 = Penicillin, Reference 2 = Nystatin, NA = Not Applicable.

As far as the antimicrobial results are concerned only the three compounds displayed very good activity. Pyrazolo [1,5-a] pyrimidines carrying *p*-chloro phenyl, *p*-hydroxy phenyl, and *p*-methoxy phenyl at $C_5$-position emerged as active in both antibacterial and antifungal screening. The substitution of *o*-hydroxy phenyl may increase the antimicrobial activity against various pathogens. When we compared the activity of substituted compounds with a nonsubstituted compound (**3g**), the substituted compounds showed higher activity.

## CONCLUSIONS

In summary, we have designed and synthesized some novel pyrazolo [1,5-a] pyrimidines by the condensation of substituted chalcones with 5-amino pyrazole in presence of a base (solid sodium hydroxide) in dimethylformamide. The preliminary *in vitro* antimicrobial screening of this series revealed that compounds **3a**, **3b**, and **3c** showed potent activity when compared with standard drug. Therefore, the present study is useful drugs in

medicinal investigation against bacterial and fungal diseases.

## EXPERIMENTAL

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. $^1$H NMR spectra were recorded in DMSO-$d_6$ on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

**General procedure for the synthesis of chalcone derivatives 2(a–h).** A mixture of substituted acetophenone **1** (1 mmol), 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (1 mmol) and NaOH (2 mmol) were dissolved in ethanol (20 mL) solution. The reaction mixture was heated for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were poured in ice cold water and then acidified by dil. HCl. The solid obtained was filtered and washed with cold water. Then crude product was crystallized from acetic acid to give the corresponding product **2**.

***1-(4-chloro-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2a).*** Color, Dark yellow; Yield, 81%; IR (KBr): 1648 (>C=O), 1598 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), δ 7.05–8.22 (m, 11H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 357 ($M^+$), 359 (M+2), 361 (M+4); Anal. Calcd for $C_{19}H_{14}N_2OCl_2$: C, 63.88; H, 3.95; N, 7.84%. Found: C, 63.96; H, 3.83; N, 7.98%.

***1-(4-hydroxy-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2b).*** Color, Yellow; Yield, 78%; IR (KBr): 1652 (>C=O), 1608 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.31 (s, 3H, $CH_3$), δ 5.58 (s, 1H, OH), δ 7.11–8.29 (m, 11H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 338 ($M^+$), 340 (M+2); Anal. Calcd for $C_{19}H_{15}N_2O_2Cl$: C, 67.36; H, 4.46; N, 8.27%. Found: C, 67.48; H, 4.35; N, 8.36%.

***1-(4-methoxy-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2c).*** Color, Yellow; Yield, 80%; IR (KBr): 1651 (>C=O), 1602 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.34 (s, 3H, $CH_3$), δ 3.32 (s, 3H, $OCH_3$), δ 7.08–8.21 (m, 11H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 352 ($M^+$), 354 (M+2); Anal. Calcd for $C_{20}H_{17}N_2O_2Cl$: C, 68.09; H, 4.86; N, 7.94%. Found: C, 68.02; H, 4.97; N, 7.82%.

***1-(4-fluoro-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2d).*** Color, Yellow; Yield, 76%; IR (KBr): 1648 (>C=O), 1615 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), δ 7.12–8.26 (m, 11H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 340 ($M^+$), 342 (M+2); Anal. Calcd for $C_{19}H_{14}N_2OFCl$: C, 69.97; H, 4.14; N, 8.22%. Found: C, 66.91; H, 4.27; N, 8.35%.

***1-(4-nitro-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2e).*** Color, Reddish yellow; Yield, 75%; IR (KBr): 1646 (>C=O), 1599 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.31 (s, 3H, $CH_3$), δ 7.06–8.21 (m, 11H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 368 ($M^+$), 370 (M+2); Anal. Calcd for $C_{19}H_{14}N_3O_3Cl$: C, 61.71; H, 4.38; N, 11.63%. Found: C, 61.84; H, 4.31; N, 11.72%.

***1-(4-bromo-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2f).*** Color, Yellow; Yield, 78%; IR (KBr): 1652 (>C=O), 1605 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), δ 7.10–8.29 (m, 11H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 400 ($M^+$), 402 (M+2), 404 (M+4); Anal. Calcd for $C_{19}H_{14}N_2OClBr$: C, 56.81; H, 3.51; N, 6.97%. Found: C, 56.72; H, 3.62; N, 6.91%.

**Table 2**

Yields and physical data of synthesized products **3(a–h)**.

| Entry | Product | $R_1$ | $R_2$ | Time (h) | Yield (%) | M.P. (°C) |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | Cl | 4 | 72 | 173–175 |
| 2 | **3b** | H | OH | 4 | 68 | 210–212 |
| 3 | **3c** | H | $OCH_3$ | 4 | 70 | 188–190 |
| 4 | **3d** | H | F | 5 | 68 | 166–168 |
| 5 | **3e** | H | $NO_2$ | 5 | 65 | 225–227 |
| 6 | **3f** | H | Br | 4 | 60 | 194–196 |
| 7 | **3g** | H | H | 5 | 65 | 152–154 |
| 8 | **3h** | OH | H | 5 | 66 | 178–180 |

***1-(phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2g).*** Color, Pale yellow; Yield, 76%; IR (KBr): 1650 (>C=O), 1595 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.32 (s, 3H, $CH_3$), δ 7.06–8.28 (m, 12H, Ar-H + CH=CH) ppm; M.S. (*m*/*z*): 322 ($M^+$), 324 (M+2); Anal. Calcd for $C_{19}H_{15}N_2OCl$: C, 70.72; H, 4.68; N, 8.68%. Found: C, 70.84; H, 4.56; N, 8.75%.

***1-(2-hydroxy-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-propenone (2h).*** Color, Yellow; Yield, 78%; IR (KBr): 1652 (>C=O), 1606 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), δ 7.05–8.22 (m, 11H, Ar-H + CH=CH), δ 10.82 (s, 1H, OH) ppm; M.S. (*m*/*z*): 338 ($M^+$), 340 (M+2); Anal. Calcd for $C_{19}H_{15}N_2O_2Cl$: C, 67.36; H, 4.46; N, 8.27%. Found: C, 67.48; H, 4.52; N, 8.18%.

**Typical procedure for the synthesis of pyrazolo [1,5-a] pyrimidines 3(a–h).** A mixture of **2a** (1 mmol), 5-amino pyrazole (1 mmol), and 1–2 pallets of NaOH were dissolved in DMF (15 mL). The reaction mixture was refluxed for the period as shown in Table 2. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and the solvent was evaporated under reduced pressure. The crude product was recrystallized from aqueous acetic acid to give the product **3a**. Similarly, other analogues of this were synthesized by using the same procedure.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-chloro-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3a).*** Color, Brown; IR (KBr): 3256 (—$NH_2$), 1616 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), δ 5.21 (bs, 2H, $NH_2$), δ 7.12–8.28 (m, 13H, Ar-H), δ 8.34 (s, 1H, 6H-of pyrimidine) ppm; $^{13}$C NMR (DMSO-$d_6$): δ 10, 101, 112, 118 (2 × C), 120, 121 (2 × C), 124, 126, 127 (2 × C), 128 (2 × C), 129 (2 × C), 130 (2 × C), 131, 132, 133, 135, 136, 138, 151, 158, 163, 166 ppm; M.S. (*m*/*z*): 573 ($M^+$), 575 (M+2), 577 (M+4), 579 (M+6); Anal. Calcd for $C_{28}H_{19}N_8Cl_3$: C, 58.60; H, 3.34; N, 19.53%. Found: C, 58.56; H, 3.42; N, 19.64%.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-hydroxy-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3b).*** Color, Brown; IR (KBr): 3251 (—$NH_2$), 1618 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.29 (s, 3H, $CH_3$), δ 5.25

(bs, 2H, $NH_2$), δ 5.68 (s, 1H, OH), δ 7.08–8.21 (m, 13H, Ar-H), δ 8.32 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m*/*z*): 555 ($M^+$), 557 (M+2), 559 (M+4); Anal. Calcd for $C_{28}H_{20}N_8OCl_2$: C, 60.55; H, 3.63; N, 20.17%. Found: C, 60.42; H, 3.71; N, 20.11%.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-methoxy-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3c).*** Color, Dark brown; IR (KBr): 3322 (—$NH_2$), 1616 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), δ 5.28 (bs, 2H, $NH_2$), δ 3.38 (s, 1H, OH), δ 7.05–8.25 (m, 13H, Ar-H), δ 8.38 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m*/*z*): 569 ($M^+$), 571 (M+2), 573 (M+4); Anal. Calcd for $C_{29}H_{22}N_8OCl_2$: C, 61.17; H, 3.89; N, 19.68%. Found: C, 61.31; H, 3.76; N, 19.76%.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-fluoro-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3d).*** Color, Brown; IR (KBr): 3286 (—$NH_2$), 1618 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.21 (s, 3H, $CH_3$), δ 5.32 (bs, 2H, $NH_2$), δ 7.11–8.28 (m, 13H, Ar-H), δ 8.32 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m*/*z*): 557 ($M^+$), 559 (M+2), 561 (M+4); Anal. Calcd for $C_{28}H_{19}N_8FCl_2$: C, 60.33; H, 3.44; N, 20.10%. Found: C, 60.42; H, 3.38; N, 20.24%.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-nitro-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3e).*** Color, Brown; IR (KBr): 3318 (—$NH_2$), 1617 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), δ 5.25 (bs, 2H, $NH_2$), δ 7.15–8.31 (m, 13H, Ar-H), δ 8.41 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m*/*z*): 584 ($M^+$), 586 (M+2), 588 (M+4); Anal. Calcd for $C_{28}H_{19}N_9O_2Cl_2$: C, 56.16; H, 3.25; N, 21.57%. Found: C, 56.28; H, 3.18; N, 21.66%.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-bromo-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3f).*** Color, Reddish brown; IR (KBr): 3338 (—$NH_2$), 1615 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.24 (s, 3H, $CH_3$), δ 5.18 (bs, 2H, $NH_2$), δ 7.11–8.26 (m, 13H, Ar-H), δ 8.35 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m*/*z*): 618 ($M^+$), 620 (M+2), 622 (M+4), 624 (M+6); Anal. Calcd for $C_{28}H_{19}N_8Cl_2Br$: C, 54.39; H, 3.10; N, 18.12%. Found: C, 54.32; H, 3.21; N, 18.23%.

***2-Amino-3-(4-chloro-phenylazo)-5-(phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3g).*** Color, Brown; IR (KBr): 3352 (—$NH_2$), 1618 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.28 (s, 3H, $CH_3$), δ 5.28 (bs, 2H, $NH_2$), δ 7.05–8.21 (m, 14H, Ar-H), δ 8.31 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m*/*z*): 539 ($M^+$), 541 (M+2), 543 (M+4); Anal. Calcd for $C_{28}H_{20}N_8Cl_2$: C, 62.35; H, 3.74; N, 20.77%. Found: C, 62.46; H, 3.68; N, 20.66%.

***2-Amino-3-(4-chloro-phenylazo)-5-(4-hydroxy-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3h).*** Color, Brown; IR (KBr): 3238 (—$NH_2$), 1616 (—C=N); $^1$H NMR (DMSO-$d_6$): δ 2.21 (s, 3H, $CH_3$), δ 5.22 (bs, 2H, $NH_2$), δ 7.11–8.28 (m, 13H, Ar-H), δ 8.38 (s, 1H, 6H-of pyrimidine), δ 11.56 (s, 1H, OH) ppm; M.S. (*m*/*z*): 555 ($M^+$), 557 (M+2), 559 (M+4); Anal. Calcd for $C_{28}H_{20}N_8OCl_2$: C, 60.55; H, 3.63; N, 20.17%. Found: C, 60.62; H, 3.68; N, 20.24%.

**Antimicrobial activity.** The antimicrobial activities of the synthesized compounds **3(a–h)** were determined by agar well diffusion method [19]. The compounds were evaluated for antibacterial activity against *Escherichia coli* (MTCC 2939) and *Bacillus subtilis* (MTCC 1789). The antifungal activity was evaluated against *Fusarium moniliformae* (MTCC 156) and *Aspergillus flavus* (MTCC 2501) were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic penicillin (25 μg/mL) and nystatin (25 μg/mL) was used as reference drug for antibacterial and antifungal activity, respectively. Dimethyl sulphoxide (1%, DMSO) was used a control with out compound.

The culture strains of bacteria were maintained on nutrient agar slant at 37 ± 0.5°C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of $10^5$ CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 25 μg/mL separately for each bacterial strain. All the plates were incubated at 37 ± 0.5°C for 24 h. Zone of inhibition of compounds in mm were noted.

For antifungal activity, all the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27 ± 0.2°C for 24–48 h, until sporulation. Spore of strains were transferred into 5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spore properly). The spores were counted by haemocytometer ($10^6$ CFU/mL). Sterile PDA plate was prepared containing 2% agar; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27 ± 0.2°C for 12 h. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL of compound solution at fixed concentration 25 μg/mL. The plates were kept in refrigerator for 20 min for diffusion and then incubated at 27 ± 0.2°C for 24–28 h. After incubation, zone of inhibition of compounds were measured in mm along with standard.

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## REFERENCES AND NOTES

[1] Greenhill, J. V. Comprehensive Heterocycl Chem 1984, 5, 305.

[2] Di Parsia, M. T.; Suarez, C.; Vitolo, M. J.; Marquez, V. E. J Med Chem 1981, 24, 117.

[3] Nugent, R. A.; Murphy, M.; Schlachter, S. T.; Dunn, C. J.; Smith, R. J.; Staite, N. D.; Galinet, L. A.; Shields, S. K.; Aspar, D. G.; Richard, K. A.; Rohloff, N. A. J Med Chem 1993, 36, 134.

[4] Antonini, I.; Polucci, P. J Med Chem 2001, 44, 3329.

[5] Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. Synlett 2002, 7, 1155.

[6] Kapplinger, C.; Beckert, R. A. Synlett 2000, 11, 1679.

[7] Bendich, A. Jr.; Russell, P. J.; Fox, J. J. J Am Chem Soc 1654, 76, 6073.

[8] Kabayasahi, S. J Pharm Bull 1973, 21, 941.

[9] Alexander, J. O.; Wheeler, G. R.; Hill, P. D.; Morris, M. P. Biochem Pharmacol 1966, 15, 881.

[10] Elion, G. B.; Callahan, S.; Nathan, H.; Bieher, S.; Rundles, R. W.; Hitachings, G. H. Biochem Pharmacol 1963, 12, 85.

[11] Earl, R. A.; Pugmire, R. J.; Revankar, G. R.; Townsend, L. B. J Org Chem 1975, 40, 1822.

[12] Dawane, B. S.; Konda, S. G.; Bodade, R. G.; Bhosale, R. B. J Heterocycl Chem 2010, 47, 237.

[13] Dawane, B. S.; Konda, S. G.; Shaikh, B. M.; Bhosale, R. B. Acta Pharm 2009, 59, 473.

[14] Dawane, B. S.; Konda, S. G.; Chavan, S. A.; Kamble, V. T.; Bhosale, R. B.; Baseer, S. M. E-J. Chemistry 2009, 651, 8358.

[15] Dawane, B. S.; Konda, S. G.; Mandawad, G. G.; Shaikh, B. M. Eur J Med Chem 2010, 45, 387.

[16] Saleh, N. M.; Ammar, Y. A.; Micky, J. A.; Abbas, H. A. S.; EL-Gaby, M. S. A. Ind J Chem B 2004, 43, 2195.

[17] Ammar, Y. A.; El-Sharief, A. M.; Zahran, M. A. Sh.; El-Said, M. Z.; El-Said, V. H. J Chem Res 1995, 7, 324.

[18] El-Gaby, M. S. A.; Sayed, A. Z.; Abu-Shanab, F. A.; Hessein, A. M. Phosphorus Sulfur Silicon 2000, 164, 1.

[19] Shrinivasan, D.; Sangeetha, N.; Suresh, T.; Lakshmanaperumalsamy, P. J Ethnophrmacol 2001, 74, 217.

# Synthesis of Hexa(methyl/phenyl) Substituted Pyrazolines and Thermolysis to Hexasubstituted Cyclopropanes



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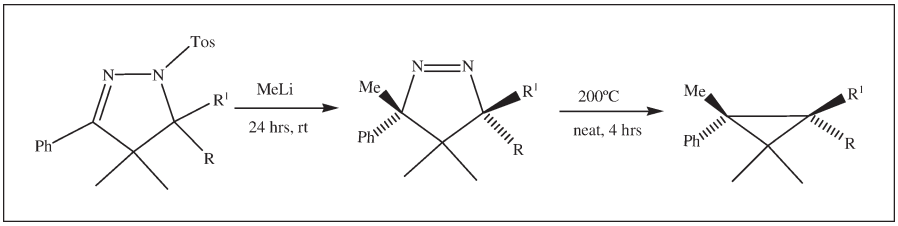


Addition of methyllithium to the 3-position of 4,5-dihydro-3,4,4,5,5-pentasubstituted-*N*-tosyl-1H-pyrazoles [**1a** 4,4,5,5-tetramethyl-3-phenyl; **1b** 4,4,5-trimethyl-3,5-diphenyl; **1c** 4,4-dimethyl-3,5,5-triphenyl] produced the corresponding hexasubstituted pyrazolines, **2a-c**, as the only isolable products. For **2b**, the 3,5-phenyl groups were found to be exclusively *cis*, indicative of facial specificity for the addition reaction. The reaction of phenyllithium with **1b** yielded **2c** as the minor product. For phenyllithium addition, direct attack on sulfur of the tosyl group with subsequent loss of phenyl *p*-tolylsulfone was the major pathway *vs*. the $S_N2i$ attack at carbon-3. Thermolysis of pyrazolines **2a-c**, at 200°C, smoothly produced the hexasubstituted cyclopropanes [**3a** 1,1,2,2,3-pentamethyl-3-phenylcyclopropane; **3b** cis-1,1,2,3-tetramethyl-2,3-diphenylcyclopropane; **3c** 1,1,2-trimethyl-2,3,3-triphenylcyclopropane] in excellent yield.

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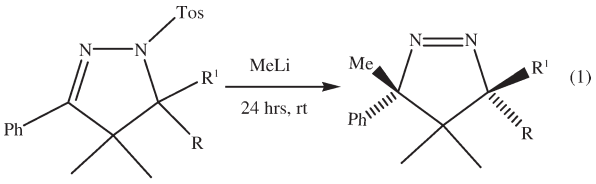
## INTRODUCTION

We have an ongoing interest in the development of general methods for the synthesis of highly substituted cyclopropanes, particularly hexasubstituted systems. Historically, preferred methods for cyclopropane synthesis include pyrazoline thermolysis [For a review and recent articles see ref 1] and carbene/carbenoid addition [2] to alkenes. However, the latter method generally does not work well for the preparation of hexasubstituted compounds. Our approach has focused on synthesis and subsequent thermolysis of highly substituted pyrazolines. We have developed a methodology for the efficient synthesis of a series of 1-alkoxy and 1-acetoxy-1,2,2,3,3-pentasubstituted cyclopropanes [3]. However, routes to hexa(alkyl/aryl) substituted cyclopropanes are scarce and often highly specialized. [For cyclopropanation with dimethylcarbene, From photolysis of hexaalkylcyclohexane-1,3,5-trione, From reduction of α,γ-dibromides see ref. 4]. We report here a route to hexa(methyl/phenyl) substituted cyclopropanes *via* the synthesis and subsequent thermolysis of hexasubstituted pyrazolines.

## RESULTS AND DISCUSSION

Addition of methylithium to 4,5-dihydro-3,4,4,5,5-pentasubstituted-N-tosyl-1H-pyrazoles, **1a-c**, under argon (rxn 1) yielded the hexasubstituted pyrazolines, **2a-c**, respectively, as the only isolated products, in variable yields. Recovered (unreacted) starting materials accounted for the remaining product balance. The 3,5-phenyl groups in




**1a** R = R¹ = Me
**b** R = Ph; R¹ = Me
**c** R = R¹ = Ph

**2a** R = R¹ = Me (87%)
**b** R = Ph; R¹ = Me (59%)
**c** R = R¹ = Ph (55%)

**2b** were found to be exclusively cis based on NMR data, indicating preferential reaction of the methyllithium with only one face of **1b**. Compounds **2a-c** were characterized by spectra and physical data.

The synthesis of **2c** was also accomplished in 25% yield by the reaction of phenyllithium with **1b**. The remaining products were indicative of the formation of 4,5-dihydro-4,4,5,5-tetramethyl-3-phenyl-1H-pyrazole [with subsequent air oxidation and decomposition] and phenyl tolylsulfone. Unlike the reaction with methyllithium, that with phenyllithium yielded products

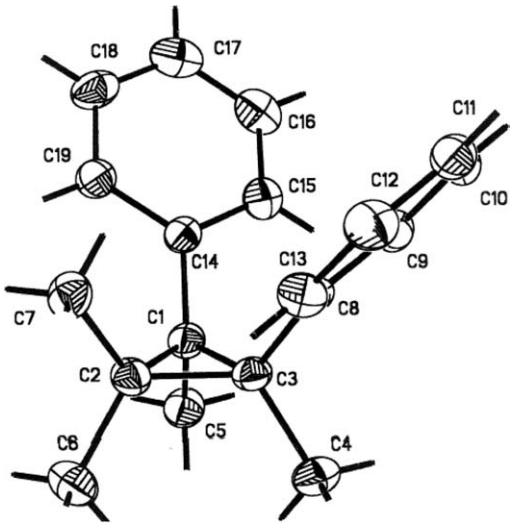
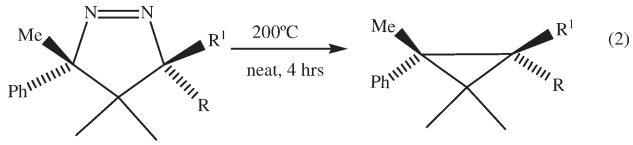



**Figure 1.** X-ray structure of **3b**.

indicative of preferential attack of phenyllithium on the tosyl group.

Thermolysis of pyrazolines **2a-c**, neat, at 200°C, produced the hexasubstituted cyclopropanes in excellent yield (rxn 2). The thermolysis of *cis* **2b** yielded *cis* **3b** in




(2)

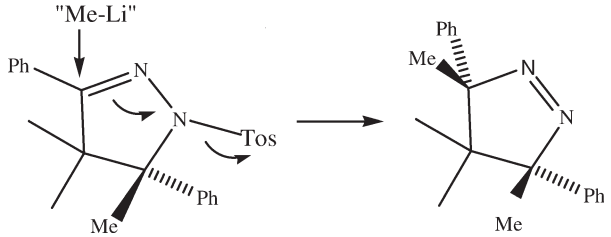
**2a-c**

**3a** R = R$^1$ = Me
**b** R = Ph; R$^1$ = Me (major)
**c** R = R$^1$ = Ph

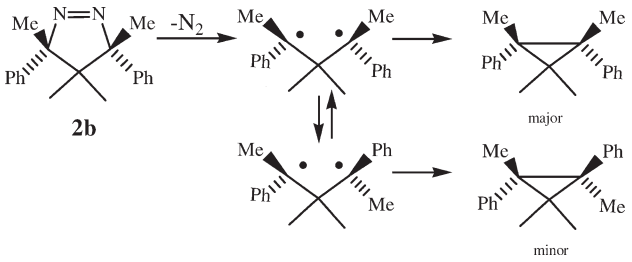
84% isolated yield. Analysis of the reaction mixture indicated that the product was a 95%/5% mixture of the *cis*/*trans* cyclopropane. Retention of configuration occurred with 95% efficiency. The cyclopropanes were characterized by spectra and physical data. The structure of **3b**, the major product, was confirmed by X-ray crystallography (Fig. 1) to have the *cis*-2,3-diphenyl configuration.

The addition of methyllithium to the 3-position of N-tosylated 4,5-dihydro-1H-pyrazoles to yield a tetrasubsti-

**Scheme 1.** Proposed pathway for methyl addition to position-3 for **1b**.




**Scheme 2.** Proposed mechanism for the thermolysis of **2b**.




tuted pyrazoline (4H-pyrazole) had been documented, but there appear to be no additional reports since that early work [5]. This is likely due to the inherent properties (air sensitivity, etc.) of selected 4,5-dihydro-1H-pyrazoles [6]. In addition, attempted N-tosylation of 4,5-dihydro-1H-pyrazoles with tosyl chloride, surprisingly, can yield unexpected products, 3-chloro pyrazolines [7] rather than the expected N-tosylated compounds. Recent development of synthetic methodology for the synthesis of 4,5-dihydro, *N*-tosyl-1H-pyrazoles was the key for the preparation of the required starting materials [8]. The addition of methyllithium to the *N*-tosyl 4,5-dihydro-1H-pyrazoles proceeded smoothly to generate the highly substituted pyrazolines. Interestingly, the results for conversion of **1b** to **2b** indicate a facial specificity of the attack of the methyllithium by an $S_N2i$ mechanism as shown in Scheme 1 below.

For methyllithium, this route appears to be the favored mode of attack. Results with phenyllithium showed this route to be the minor pathway with direct reaction of phenyllithium with the sulfur of the tosyl group being the major pathway that appears to limit the scope of reaction 1.

Thermolysis of pyrazolines to cyclopropanes, in high yield, is a well established route [1]. Thermal decomposition of pyrazolines to cyclopropanes generally is thought to occur *via* a diradical mechanism that favors retention of configuration [1,9]. The present results are consistent with the diradical mechanism shown below in Scheme 2 for thermolysis of **2b**.

In conclusion, the addition of methyllithium to *N*-tosyl-4,5-dihydro-1H-pyrazoles and subsequent thermolysis of the pyrazolines is a useful method for the synthesis of highly substituted cyclopropanes. The method has obvious limitations in that the substituents must be stable to organolithium reagents but appears to provide a more general route to this type of highly substituted strained ring compound. Work is in progress to explore the scope of this route.

## EXPERIMENTAL

The *N*-tosylated-4,5-dihydro-1H-pyrazoles, **1a-c**, were prepared according to published results [8]. Methyllithium (1.6*M*)

in diethyl ether and phenyl lithium (1.8*M*) in cyclohexane-ether were purchased from Sigma–Aldrich Company and used without further purification. All solvents were commercially available. Anhydrous toluene, anhydrous ether, and methanol were purchased from Aldrich Company and used without further purification. Tetrahydrofuran (Aldrich) was distilled from sodium and benzophenone before use. Acetone, ethanol, and hexane were purchased from Fisher Scientific Company. All $^1$H and $^{13}$C NMR spectra were obtained from a Varian Unity Plus 300 MHz instrument. Mass spectra were obtained from a Shimadzu GP-5000 Mass Spectrometer. Elemental analyses were performed at the Department of Chemistry at Georgia State University and at Atlantic Microlab, Atlanta, Georgia. Melting points were recorded in a calibrated Thomas Hoover Unimelt apparatus. Exact mass analyses were performed at the Georgia Institute of Technology. X-ray crystallography was performed at Emory University.

**Synthesis of 3,3,4,4,5-pentamethyl-5-phenyl-4,5-dihydro-3H-pyrazole (2a).** 4,4,5,5-Tetramethyl-3-phenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**1a**) (0.30 g, 0.8415 mmol) was dissolved in anhydrous toluene (25 mL) under argon atmosphere. The solution was cooled to 0°C with an ice bath. Then, methyllithium (2 mL, 3.2 mmol, 3.8 mole equiv) was added to the solution using a dried glass syringe. The solution was stirred for 30 min at 0°C and 24 h at room temperature. Then, the reaction was quenched with 10 mL of saturated, degassed ammonium chloride solution. Diethyl ether (20 mL) was added to the mixture before washing with saturated sodium bicarbonate (2 × 20 mL) solution and deionized water (30 mL). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate [95:5]) to give **2a** in an isolated yield of 87% (0.158 g, 0.732 mmol) as a clear and viscous liquid; $^1$H NMR ($CDCl_3$) 300 MHz: δ 0.34 (s, 3H), δ 1.07 (s, 3H), δ 1.30 (s, 3H), δ 1.35 (s, 3H), δ 1.60 (s, 3H), δ 7.25–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$) 300 MHz: 20.5, 23.9, 23.9, 24.1, 25.1, 41.8, 91.7, 96.0, 125.5, 126.8, 128.0, 143.8; Exact Mass Anal. Calcd. for $C_{14}H_{21}N_2$ = 217.17047. Found: 217.17060.

**Synthesis of *cis*-3,4,4,5-tetramethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (2b).** 4,4,5-Trimethyl-3,5-diphenyl-1(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**1b**) (1.0 g, 2.389 mmol) was dissolved in 50 mL of anhydrous THF under argon atmosphere. The solution was cooled to 0°C with an ice bath. Then, methyllithium (4.48 mL, 7.17 mmol, 3 equiv) was added to the solution using a dried glass syringe. The solution was stirred for 30 min at 0°C and 24 additional hours at room temperature. The mixture was quenched with 10 mL of saturated, degassed ammonium chloride solution. Diethyl ether (20 mL) was added to the mixture before washing with saturated sodium bicarbonate (2 × 20 mL) solution and deionized water (40 mL). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate [97:3]) to give **2b** in an isolated yield of 59% (0.391 g, 1.409 mmol) mp = 144–145°C; $^1$H NMR ($CDCl_3$) 300 MHz: δ 0.26 (s, 3H), δ 1.34 (s, 3H), δ 1.68 (s, 6H), δ 7.25–7.36 (m, 10H); $^{13}$C NMR ($CDCl_3$) 300 MHz: 20.2, 23.9, 28.5, 42.9, 96.7, 125.3, 126.9, 128.1, 143.6; IR peaks: 3064 cm$^{-1}$, 2990 cm$^{-1}$, 1599 cm$^{-1}$, 703 cm$^{-1}$; Anal. Calcd. for $C_{19}H_{22}N_2$ = C, 81.97, H, 7.97, N, 10.06% Found: C, 81.79, H, 8.19, N, 9.66%.

**Synthesis of 3,4,4-trimethyl-3,5,5-triphenyl-4,5-dihydro-3H-pyrazole (2c).** 4,4-Dimethyl-3,5,5-triphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**1c**) (0.5 g, 1.040 mmol) was dissolved in anhydrous THF (50 mL) under argon atmosphere. The solution was cooled to 0°C with an ice bath. Then, methyllithium (2.6 mL, 4.16 mmol, 4 Eq.) was added to the solution using a dried glass syringe. The solution was stirred for 30 min at 0°C and 36 additional hours at room temperature. The mixture was quenched with 10 mL of saturated, degassed ammonium chloride solution. Diethyl ether (20 mL) was added to the reaction before washing with saturated sodium bicarbonate (2 × 40 mL) solution and deionized water (40 mL). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by chromatatron (hexane/ethyl acetate) to give **2c** in an isolated yield of 55% (0.19 g, 0.558 mmol) mp = 117–118°C; $^1$H NMR $CDCl_3$) 300 MHz: δ 0.15 (s, 3H), δ 1.16 (s, 3H), δ 1.56 (s, 3H), δ 7.16–7.97 (m, 15H); $^{13}$C NMR ($CDCl_3$) 300 MHz: 20.7, 21.8, 27.3, 46.6, 96.6, 97.6, 125.7, 126.5, 126.7, 127.0, 127.2, 128.0, 128.1, 142.6, 143.5, 143.9; Anal. Calcd. for $C_{24}H_{24}N_2$: C, 84.67, H, 7.11, N, 8.23% Found: C, 84.73, H, 7.19, N, 8.26%.

**Synthesis of 1,1,2,2,3-pentamethyl-3-phenylcyclopropane (3a).** 3,3,4,4,5-Pentamethyl-5-phenyl-4,5-dihydro-3H-pyrazole (**2a**) (0.100 g, 0.462 mmol) was placed in an NMR tube and purged with argon gas. The tube was then heated in a silicon oil bath at 200°C ± 2 for 4 h. When the viscous liquid was heated, evolution of gas (nitrogen) was observed. The NMR tube was removed from the oil bath after 4 h of heating and hexane was added to dissolve the products. The crude product was purified by chromatatron (hexanes) to yield 93% of **3a** (0.081 g, 0.429 mmol) as a clear viscous liquid. $^1$H NMR ($CDCl_3$) 300 MHz: δ 0.92 (s, 6H), δ 1.16 (s, 6H), δ 1.23 (s, 3H), δ 7.1–7.3 (m, 5H); lit. $^1$H NMR δ 0.91 (s, 6H), δ 1.15 (s, 6H), δ 1.23 (s, 3H), δ 7.12 (m, 5H) (Gloss *et al*., 1966; $^{13}$C NMR ($CDCl_3$) 300 MHz: 18.5, 21.70, 21.74, 23.9, 29.7, 33.6, 125.0, 127.9, 130.7, 146.0.

**Synthesis of *cis*-1,1,2,3-tetramethyl-2,3-diphenylcyclopropane (3b).** 3,4,4,5-Tetramethyl-3,5-diphenyl-3H-pyrazole (**2b**) (0.1 g, 0.359 mmol) was placed in an NMR tube and purged with argon gas. The tube was then heated in a silicon oil bath at 200°C ± 2 for 4 h. When heated, the crystals melted and evolution of nitrogen gas was observed. The NMR tube was removed from the oil bath after 4 h of heating and hexane was added to dissolve the product. The crude product was purified by chromatatron (hexanes) and recrystallized from methanol to give **2b** in 84% yield (0.075 g, 0.301 mmol) as colorless crystals, mp = 79–81°C. $^1$H NMR ($CDCl_3$) 300 MHz: δ 1.12 (s, 3H), δ 1.37 (s, 3H), δ 1.47 (s, 6H), δ 7–7.4 (m, 10H); $^{13}$C NMR ($CDCl_3$) 300 MHz: 18.7, 23.2, 25.4, 27.0, 35.5, 125.3, 127.4, 131.1, 145.6; X-ray structure was obtained at Emory University; IR peaks: 3083–2927 cm$^{-1}$, 1599 cm$^{-1}$, 1577 cm$^{-1}$, 699 cm$^{-1}$. Anal. Calcd. for $C_{19}H_{22}$: C, 91.14, H, 8.86; found: C, 90.93, H, 9.04%.

**Synthesis of 1,1,2-trimethyl-2,2,3-triphenylcyclopropane (3c).** 3,4,4-Trimethyl-3,5,5-triphenyl-4,5-dihydro-3H-pyrazole (**2c**) (0.1 g, 0.2937 mmol) was placed in an NMR tube and purged with argon gas. The tube was then heated in a silicon oil bath at 200°C ± 2 for 4 h. When heated, the crystals

melted and evolution of nitrogen gas was observed. The NMR tube was removed from the oil bath after 4 h of heating, and hexane was added to dissolve the products. The crude product was purified by chromatatron (hexanes) to give **2c** in 91% yield (0.83 g, 0.267 mmol) as a colorless viscous liquid. $^{1}$H NMR ($CDCl_3$) 300 MHz: δ 1.32 (s, 3H), δ 1.33 (s, 3H), δ 1.38 (s, 3H), δ 6.9–7.6 (m, 15H); $^{13}$C NMR ($CDCl_3$) 300 MHz: 22.2, 26.8, 27.2, 28.1, 37.9, 46.2, 125.0, 125.3, 125.5, 127.5, 127.9, 128.1, 131.0, 131.3, 143.9, 144.3, 144.4. MS Molecular Ion – 312. Anal. Calcd. for $C_{24}H_{24}$: C, 92.24, H, 7.74%; Found: C, 92.39, H, 7.60%.

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## REFERENCES AND NOTES

[1] (a) Engel, P. S. Chem Rev 1980, 80, 99; (b) Towns, K. K.; Vasquez, P. C.; Kennedy, G. D.; Baumstark, A. L. Heterocycl Commun 2006, 12, 337; (c) Garcia Ruano, J. L.; Alonso de Diego, S. A.; Martin, M. R.; Torrenta, E.; Martin Castro, A. M. Org Lett 2004, 6, 4945; (d) Anisimova, N. A.; Berkova, G. A.; Ya, P. T.; Deiko, L. I. Russ J Gen Chem 2002, 72, 460.

[2] Maas, G. Top Curr Chem 1987, 137, 75.

[3] [a] Kennedy, G. D.; Baumstark, A. L.; Dotrong, M.; Thomas, T.; Narayanan, N. J Heterocycl Chem 1991, 238, 1773; [b] Vasquez, P. C.; Bennett, D. C.; Towns, K. K.; Kennedy, G. D.; Baumstark, A. L. Heteroatom Chem 2000, 11, 299.

[4] (a) Fischer, P.; Schaefer, G. Angew Chem 1981, 93, 895; (b) Hostettler, H. U. Tetrahedron Lett 1965, 1941; (c) Kelso, R. G.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. J Am Chem Soc 1955, 77, 1751.

[5] Pirkle, W. H.; Hoover, D. J. J Org Chem 1980, 45, 3407.

[6] Vasquez, P. C.; Baumstark, A. L. In Advances in Oxygenated Processes, Vol. 4; Baumstark, A. L., Ed.; JAI Press, Greenwich, CN, 1995; p 107.

[7] Szwec, J.; Vasquez, P. C.; Franklin, P. J.; Kennedy, G. D.; Baumstark, A. L. Heterocycl Commun 2004, 10, 133.

[8] Truong, P.; Kennedy, G. D.; Vasquez, P. C.; Baumstark, A. L. Heterocycl Commun 2008, **14**, 449.

[9] Dreibelbis, R. L.; Khatri, H. N.; Walborsky, H. M. J Org Chem 1975, 40, 2074.

# Structural Studies of 2-Methyl-7-substituted Pyrazolo[1,5-*a*]pyrimidines



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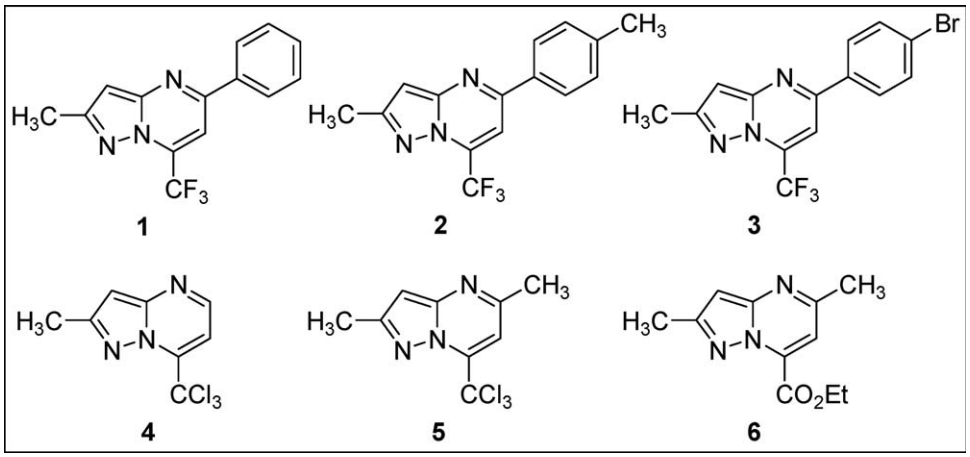
*Dedicated to our friend Professor Luis Castedo on the occasion of his 70th birthday.*




Six pyrazolo[1,5-*a*]pyrimidines bearing a 7-trifluoromethyl (three compounds), a 7-trichloromethyl (two compounds), and a 7-ethoxycarbonyl (one compound) have been structurally characterized. The new X-ray structures of 2-methyl-5-(*p*-bromophenyl)-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**3**) and 2-methyl-7-trichloromethylpyrazolo[1,5-*a*]pyrimidine (**4**) are reported. The combined use of GIAO/B3LYP/6-311++G(d,p) calculations with NMR spectroscopy in solution and in the solid state allows to establish some general rules that can be useful for characterizing related compounds. Compounds **3** and **4** present in the solid-state interesting intra- and intermolecular halogen bonds.

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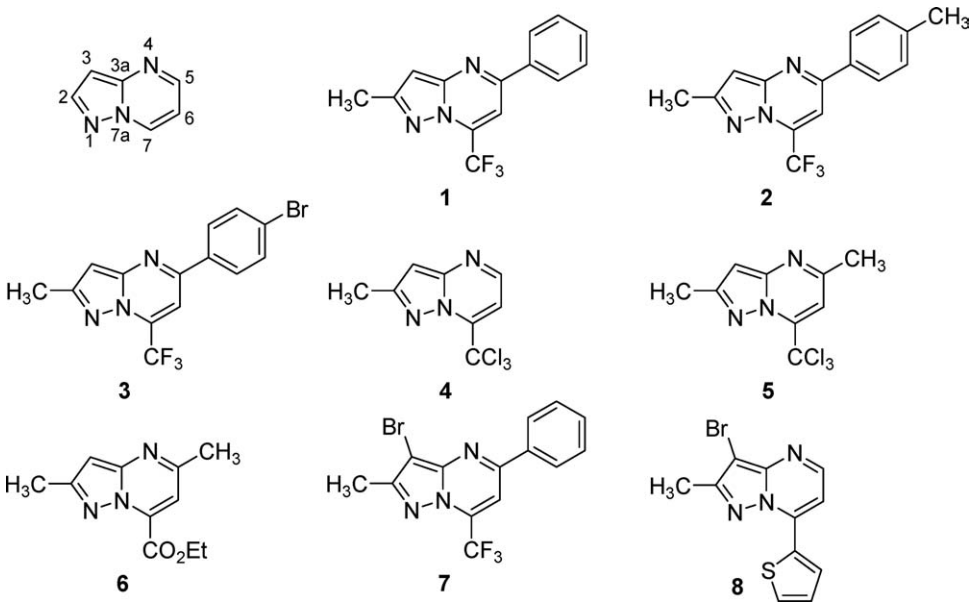
## INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidines are purine analogues and as such have useful properties as antimetabolites in purine biochemical reactions. Compounds of this class have attracted wide pharmaceutical interest because their activity as inhibitors of HMG-CoA reductase [1], COX-2 [2], AMP phosphodiesterase [3], KDR kinase [4], and as selective peripheral benzodiazepine receptor ligands [5] as well as antianxiety agents [6]. Recently, other pharmaceutical activities have been reported, for example, as compounds for the treatment of sleep disorders [7], as oncological agents [8], and estrogen receptor ligands [9]. Other activities include hypnotic [10] inhibitors of human cyclin-dependent kinase 2 [11] and high affinity for $GABA_A$ receptors [12].

These examples explain the high interest in variously substituted pyrazolo[1,5-*a*]pyrimidines. As a consequence, the synthesis of these compounds has been approached by different methods [13]. In the literature, there is a large number and variety of such type of fused heterocycles bearing a $CF_3$ substituent at position 7 [14] but 7-trichloromethyl substituted pyrazolo[1,5-*a*]pyrimidines are much less frequent [15].

Because most studies on these compounds are related to their synthesis or to their biological properties, we decided to devote one paper to a structural study to establish the general patterns for their characterization. The six compounds **1–6** that we have analyzed are reported in Scheme 1 together with their atom numbering.

**Scheme 1**




## RESULTS AND DISCUSSION

The synthesis of the following compounds was already described: 2-methyl-5-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**1**) [14], 2-methyl-5-(*p*-tolyl)-7-trifluoromethylpyrazolo [1,5-*a*]pyrimidine (**2**) [16], 2-methyl-7-trichloromethylpyrazolo[1,5-*a*]pyrimidine (**4**) [17], and 2,5-dimethyl-7-trichloromethylpyrazolo[1,5-*a*]pyrimidine (**5**) [17,18].

Even if 2-methyl-5-(*p*-bromophenyl)-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**3**) is commercially available (from Asinex), it was never described before and our preparation has been included here. Ethyl 2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**6**) is a new compound.

Some of us already reported the X-ray molecular structures of derivatives **2** and **5** [16,18] and those of compounds **7** (a 3-bromo derivative of **1**) and **8** had also been published [14a,17].

**Crystallography.** In the molecule of the title compounds (Scheme 1 and Fig. 1), the bond lengths are within the related range (Table 1) [19–22]. In particular, the formally single C(3a)-N(4) and C(7)-N(7a) bonds are only slightly longer than the formally double C(2)-N(1) bond, although each of these single bonds is significantly shorter than the formally single C(3a)-N(7a) bond. Similarly, the lengths of the C(2)-C(3) and C(3)-C(3a) bonds, formally single and double bonds, respectively, differ by less than 0.02 Å. These observations, together with the planarity at atom N1, suggest that this heterocyclic system exhibits a degree of naphthalene-type delocalization, involving a peripheral system of 10 π electrons with only modest participation by the cross-

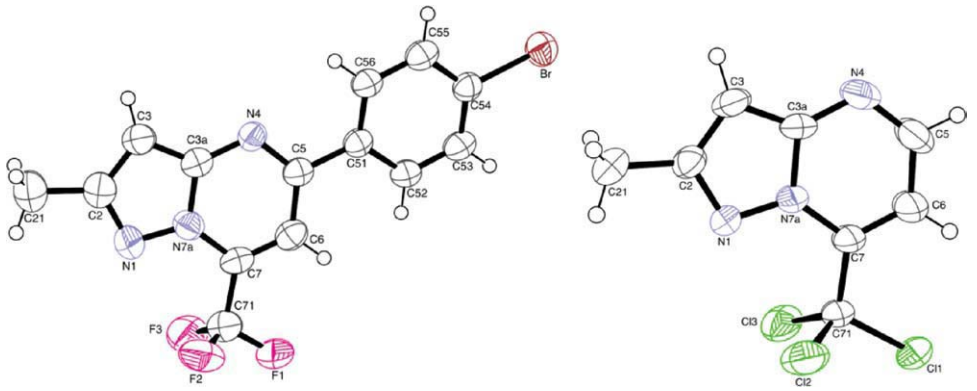



**Figure 1.** The X-ray molecular structures of compounds **3** and **4** (ORTEP plot, 50% probability for the ellipsoids. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Table 1**
Selected bond lengths (Å) and bond angles (°).

| | 3 | 4 |
|---|---|---|
| N(7a)-N(1) | 1.355(6) | 1.351(3) |
| N(1)-C(2) | 1.333(8) | 1.343(4) |
| C(2)-C(3) | 1.395(8) | 1.386(5) |
| C(3)-C(3a) | 1.376(8) | 1.372(5) |
| C(3a)-N(4) | 1.346(7) | 1.341(5) |
| N(4)-C(5) | 1.314(7) | 1.320(7) |
| C(5)-C(6) | 1.423(8) | 1.393(6) |
| C(6)-C(7) | 1.340(8) | 1.349(6) |
| C(7)-N(7a) | 1.361(7) | 1.367(4) |
| N(7a)-C(3a) | 1.400(8) | 1.409(4) |
| N(7a)-N(1)-C(2) | 103.7(5) | 104.0(2) |
| N(1)-C(2)-C(3) | 113.1(5) | 113.1(3) |
| C(2)-C(3)-C(3a) | 105.7(6) | 105.6(3) |
| C(3)-C(3a)-N(4) | 132.8(6) | 132.9(3) |
| C(3a)-N(4)-C(5) | 117.5(5) | 115.7(3) |
| N(4)-C(5)-C(6) | 122.2(5) | 125.0(5) |
| C(5)-C(6)-C(7) | 119.7(6) | 119.9(4) |
| C(6)-C(7)-N(7a) | 118.7(5) | 116.4(3) |
| C(7)-N(7a)-N(1) | 127.9(5) | 126.8(2) |
| N(7a)-C(3a)-C(3) | 104.9(5) | 105.5(3) |
| N(7a)-C(3a)-N(4) | 122.3(5) | 121.5(3) |
| N(1)-N(7a)-C(3a) | 112.6(5) | 111.7(2) |
| C(7)-N(7a)-C(3a) | 119.5(5) | 121.4(3) |

ring bond (C3a-N7a) [23]. Five-membered pyrazole ring is planar with r.m.s. deviations from the plane of 0.0015 and 0.0025 Å in compounds **3** and **4**, respectively. The six-membered pyrimidine ring is also planar with r.m.s. deviations from the plane of 0.0062 and 0.0131 Å in compounds **3** and **4**, respectively. The angle torsion N(1)-N(7a)-C(3a)-N(4) for compounds **3** and **4** is –179.4(5) and 178.1(17)°, showing that the pyrazole and pyrimidine rings are in the same plane. The geometry of the pyrazolopyrimidine system is similar to that reported in the literature [16].

The molecular structure of compounds **3** and **4** reveals that the intermolecular interactions are related to the nature of substituent. Compound **4** that is not substituted in position 5 of the pyrazolopyrimidine ring shows intra- and intermolecular interactions similar to those found in a related compound with a 5-methyl group [18]: it shows two intramolecular interactions between Cl(2)···N(1) and Cl(3)···N(1) with interatomic distances of 3.097(6) and 3.093(6) Å, respectively. In this molecule, the crystal packing forms an infinite chain along plane *ab* through the intermolecular interaction Cl(1)···N(4) with interatomic distances of 3.115(3) Å ($x+1/2, -y+1, z$) (Fig. 2).

The crystal structure of compound **3** shows that the pyrazolopyrimidine and phenyl rings are almost in the same plane with a C(6)-C(5)-C(51)-C(52) torsion angle of 11.2(8)°. This finding indicates that there is a small π-resonance between the pyrazolopyrimidine system and the aryl ring [18,24,25]. In addition, interesting intermolecular interactions between the halogens atoms as F(1) atom of the trifluoromethyl group of one molecule and the F(3) atom of the trifluoro methyl group of another molecule, with an interatomic distance of 2.899(6) Å ($x+1,y,z$) are observed.

The fluorine atom as halogen bonding has been related to noncovalent interactions, however, while, the Ar-ArF stacking motif formed between nonfluorinated and perfluorinated aromatic rings is rated an important supramolecular synthon [26], the contacts of C-F···H [27,28], C-F···F [29] and C-F···πF [30] type are not yet sufficiently clear [31,32]. On the other hand, the ability of the fluorine–fluorine intermolecular interactions in directing the supramolecular structure of synthons concerning atoms of aliphatic systems is unknown. Thus,

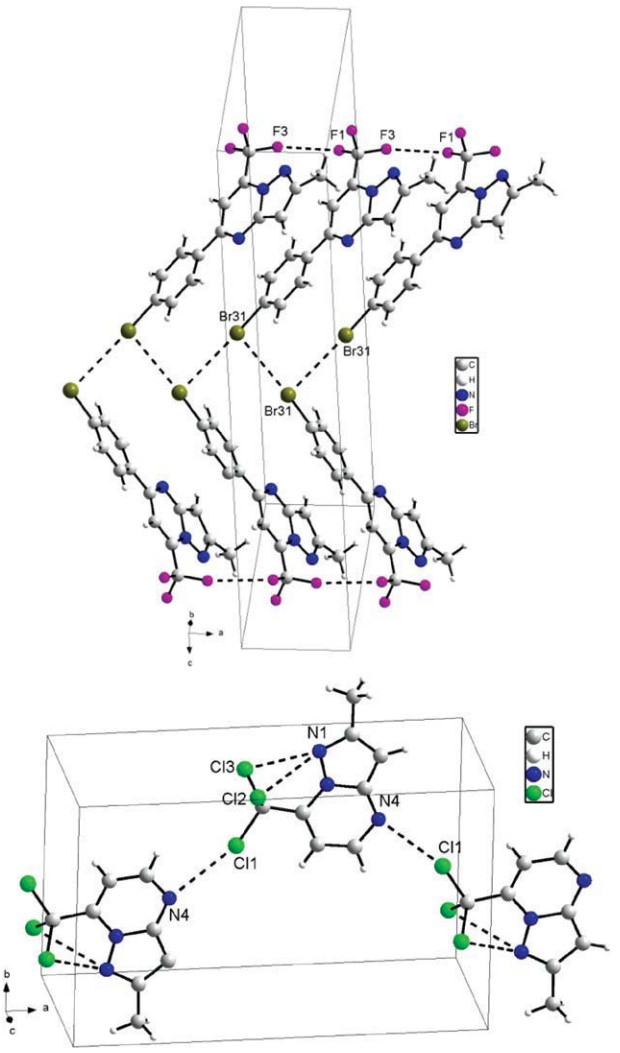



**Figure 2.** A stereoview of part of the crystal structure of **3** and **4** showing the packing along the *ab* plane. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

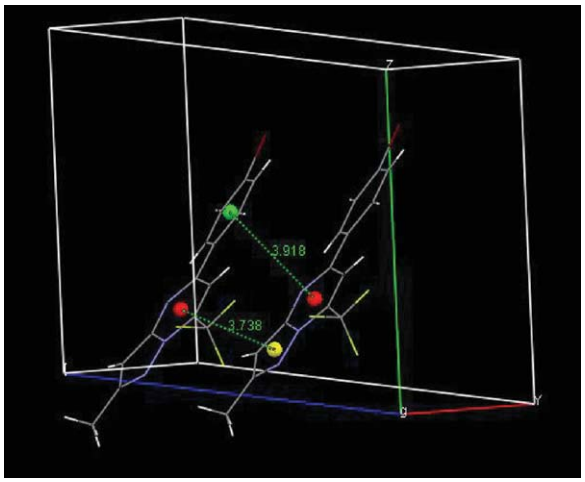



**Figure 3.** A 3D-view of part of the crystal structure of compound **3** showing π-π interactions between pyrazole···pyrimidine and pyrimidine···phenyl ring-centroid. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

we present here, for the first time, an intermolecular noncovalent interaction between fluorine atoms of aliphatic systems that fix the supramolecular structure of a pyrazolopyrimidine bearing a trifluoromethyl group. The interatomic distance appeared to be less than the sum of van der Waals radii of the atoms involved in the interaction [33].

The bromine atoms are also involved in the molecular packing of compound **3**, which forms an infinite chain along plane *ab* through the intermolecular interaction Br(31)···Br(31) with an interatomic distance of 3.6584(9) Å ($x+1/2,-y+3/2,-z+2$) (Fig. 2). In case of bromine–bromine intermolecular interaction, the interatomic distance also appeared to be less than the sum of van der Waals radii of the atoms involved in the interaction [33]. Recently, we have reported intermolecular Br···Br contacts of about 3.9 Å in crystals of bromopyrazoles [34]. Moreover, pyrazolopyrimidines are interlinked by noncovalent π-π stacking interactions between aromatic rings. As a result, the molecules of **3** and **4** form chains by means of F···F, Br···Br, and Cl···N interactions, respectively, and these chains are themselves linked into sheets by π-π stacking interaction.

In **3**, the weak π-π stacking interactions involve the pyrimidine rings of two adjacent molecules at ($x$, $y$, $z$) and ($1+x$, $y$, $z$), where the ring-centroid separation with the pyrazole ring is 3.738 Å; the ring-centroid separation between the pyrimidine and the phenyl is 3.918 Å (Fig. 3). In **4**, the π-π stacking interaction involves the fused heterocyclic rings of the molecules at ($x$, $y$, $z$) and ($1.5 - x$, $-y$, $-0.5 + z$), with a ring-centroid separation of 3.813 Å between the pyrimidines and of 3.631 Å between the pyrazoles (Fig. 4). These values are similar to those reported in the literature for similar compounds [35].

**NMR.** We have reported in Tables 2–4 the NMR results concerning compounds **1–6**.

The CPMAS chemical shifts, although less precise (some signals overlap) than those in solution, are linearly related to the DMSO-$d_6$ values: CPMAS (ppm) = (0.993 ± 0.002) DMSO (ppm), $n = 79$, $R^2 = 0.9997$.This means that the structures in solution (mainly the torsion angles) are similar to those in the solid-state determined by X-ray crystallography.

**Computational studies.** Initially, we optimized the geometries of pyrazolo[1,5-*a*]pyrimidines **1-6** at the B3LYP/6-31G(d) level verifying that they correspond to the minima (frequency calculations). A further optimization was carried out at the B3LYP/6-311++G(d,p) level and represented the result in Figure 5.

The calculated geometries are very similar (bond distances and bond angles) to those determined experimentally for compounds **2**, **3**, **4**, and **5**; even the sensitive torsion angles are much alike. On these geometries, we calculated [GIAO/B3LYP/6-311++G(d,p)//B3LYP/6-311++ G(d,p)] the absolute shieldings (σ, ppm) and transformed them into chemical shifts (δ, ppm) by means of the following three equations: $\delta^1H = 31.0 - 0.970\ \sigma^1H$; $\delta^{13}C = 175.7 - 0.963\ \sigma^{13}C$; $\delta^{15}N = -152.0 - 0.946\ \sigma^{15}N$ that we have previously devised based on a statistic analysis of many data [36].

In these works, we established that the absolute shieldings corresponding to carbon atoms bearing halogen atoms systematically deviate. In this article and based on the previous reports[36], we have corrected the C-Br atom in *para* position of compound **3** by –20.1

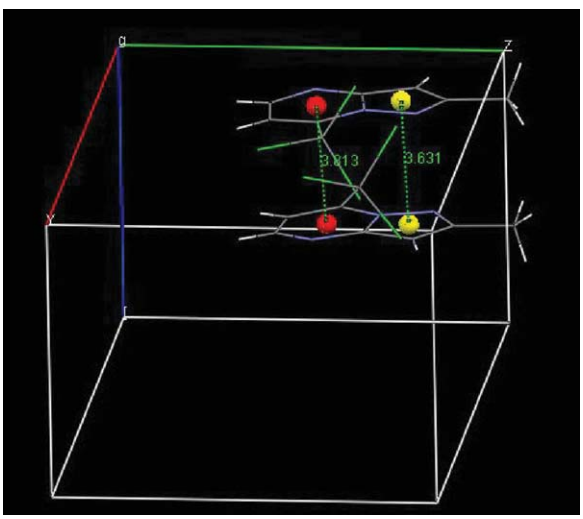



**Figure 4.** A 3D-view of part of the crystal structure of compound **4** showing π-π interactions between pyrazole···pyrazole and pyrimidine··· pyrimidine ring-centroid. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Table 2**

$^1$H NMR data in DMSO-$d_6$ of compounds **1–6** (chemical shifts δ in ppm and coupling constants *J* in Hz).

| Nuclei | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| Me-2 | 2.47 (s) | 2.47 (s) | 2.48 (s) | 2.52 (s) | 2.47(s) | 2.40 |
| H-3 | 6.78 (s) | 6.74 (s) | 6.80 (s) | 6.84 (s) | 6.64 (s) | 6.49 |
| H-6 | 8.00 (s) | 7.96 (s) | 8.04 (s) | 7.67 (d) | 7.55 (s) | 7.20 |
| R-5 | 7.56 (m, 3H, H3′, H4′, H5′) 8.26 (m, 2H, H2′, H6′) | 2.37 ($CH_3$); 7.34 (m, 2H, H3′,H5′) 8.16 (m, 2H, H2′, H6′) | 7.74 (m, 2H,H3′,H5′) 8.22 (m, 2H, H2′, H6′) | 8.70 (d), $^3J_{5,6} = 4.5$ | 2.63 (s,$CH_3$) | 2.53 (s, $CH_3$) |
| R-7 | – | – | – | – | – | 1.35 (t, $CH_3$); 4.44 (q,$CH_2O$) |

**Table 3**

$^{13}$C and $^{15}$N NMR data in DMSO-$d_6$ of compounds **1–6** (chemical shifts δ in ppm and coupling constants *J* in Hz).

| Nuclei | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| N1[a] | −105.1 | −105.4 | −105.0 | −99.8 | −101.6 | −104.0 |
| C2 | 156.0 | 155.9 | 156.1 | 154.4 | 154.1 | 154.6 |
| C3 | 97.3 | 97.1 | 97.5 | 97.1 | 95.9 | 95.2 |
| C3a | 149.5 | 149.5 | 149.4 | 150.4 | 150.2 | 149.3 |
| N4[a] | −101.7 | −103.4 | −101.4 | −90.7 | −96.2 | −96.3 |
| C5 | 154.6 | 154.6 | 153.5 | 149.0 | 158.7 | 158.3 |
| C6 | 103.6 $^3J_{CF} = 3.8$ | 103.4 $^3J_{CF} = 4.2$ | 103.5 $^3J_{CF} = 3.8$ | 104.7 | 105.5 | 108.5 |
| C7 | 132.4 $^2J_{CF} = 37.7$ | 132.4 $^2J_{CF} = 36.4$ | 132.4 $^2J_{CF} = 36.4$ | 141.1 | 140.7 | 134.9 |
| N7a[a] | −172.4 | −172.7 | −171.9 | −171.2 | −172.9 | −169.5 |
| Me-2 | 14.3 $^1J$= 125.4[b] | 14.3 $^1J$= 129.9[b] | 14.3 $^1J$= 128.3[b] | 14.5 $^1J$= 125.9[b] | 14.5 $^1J$ = 126.8[b] | 14.3 $^1J$ = 129.0[b] |
| R-5 | 135.7 (C1′) 127.4 (C2′) 129.0 (C3′) 131.0 (C4′) | 133.0 (C1′) 127.3 (C2′) 129.6 (C3′) 141.1 (C4′) 20.9 ($CH_3$) | 134.9 (C1′) 129.3 (C2′) 131.9 (C3′) 124.9 (C4′) | – | 24.5 $^1J$ = 129.7[b] | 24.1 $^1J$ = 125.8[b] |
| R-7 | 119. 6 $^1J_{CF} = 273.9$ | 119. 6 $^1J_{CF} = 275.0$ | 119.5 $^1J_{CF} = 273.8$ | 88.7[b] | 88.7[b] | 160.1 (CO) 62.6 ($CH_2$) 13.8 ($CH_3$) |

[a] Observed in the ($^1$H-$^{15}$N) gs-HMBC spectra.
[b] Observed in the ($^1$H-$^{13}$C) gs-HMBC spectra.

**Table 4**

$^{13}$C and $^{15}$N CPMAS NMR data of compounds **1–6** (chemical shifts δ in ppm).

| Nuclei | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| N1 | −99.7 | −100.3 | −103.3 | −92.5 | −99.5 | −94.5 |
| C2 | 157.2 | 155.4 | 156.3 | 153.0 | 153.4 | 153.9 |
| C3 | 92.2 | 99.2 | 97.8 | 95.7 | 93.6 | 93.7 |
| C3a | 148.2 | 150.1 | 149.2 | 149.1 | 148.2 | 151.1 |
| N4 | −99.7 | −100.3 | −103.3 | −92.5 | −99.5 | −94.5 |
| C5 | 152.0 | 152.5 | 153.6 (br) | 145.4 | 156.2 | 157.6 |
| C6 | 102.3 | 99.2 | 101.0 (br) | 104.4 | 104.9 | 112.3 |
| C7 | 131.7 | 131.8 | 133.6 | 141.2 | 139.0 | 131.7 |
| N7a | −171.0 | −171.7 | −170.3 | −168.3 | −173.3 | −166.2 |
| Me-2 | 13.2 | 12.9 | 14.0/13.0 | 17.4 | 14.8 | 14.7 |
| R-5 | 136.2 (C1′) 128.6 (C2′, C3′, C4′) | 131.8 (C1′) 127.5/124.9 (C2′) 131.8/128.7 (C3′) 141.7 (C4′) 20.8 ($CH_3$) | 133.6 (C1′, C3′) 128.5 (C2′, C4′) | – | 26.4 | 24.6 |
| R-7 | 119.9 (br) | 120 (vbr) | 120.4 (br) | [a] | [a] | 161.8 (CO) 63.8 ($CH_2$) 14.0 ($CH_3$) |

[a] Not observed.

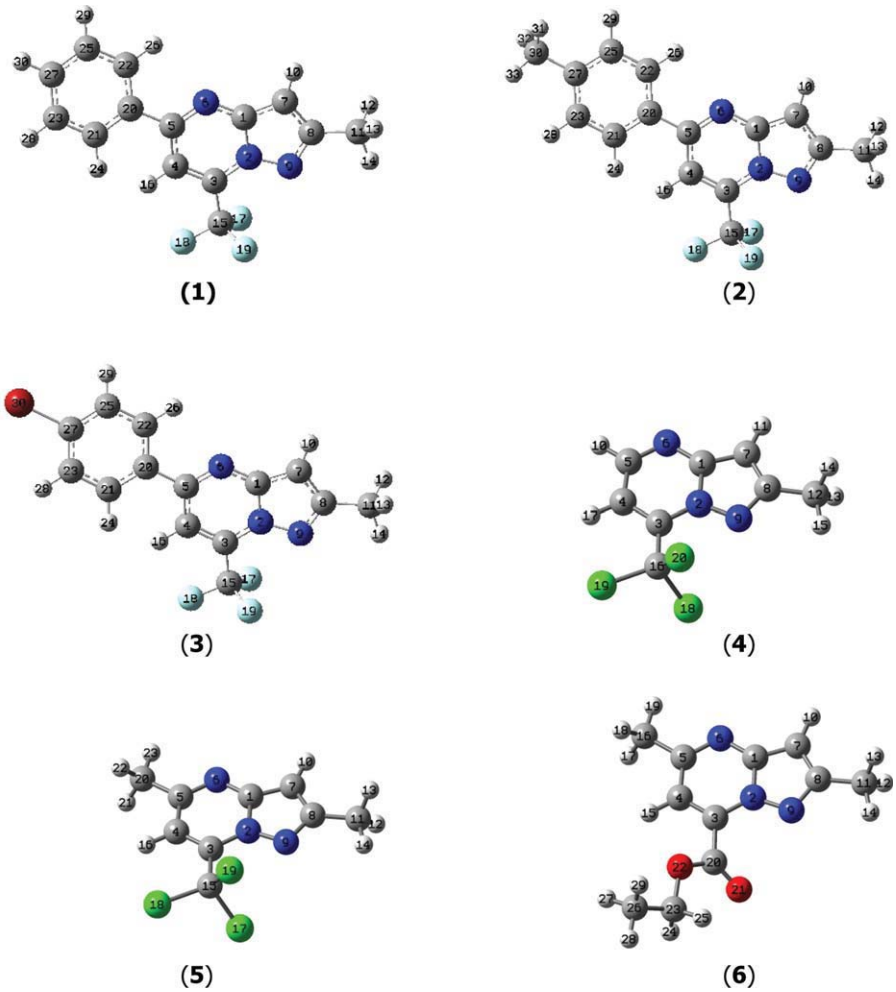



**Figure 5.** The six optimized structures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ppm, the $CF_3$ atoms of compounds **1**, **2**, and **3** by +2.8 ppm and the $CCl_3$ atoms of compounds **4** and **5** by –33.3 ppm. With these corrections, we obtained the plot of Figure 6. The trendline corresponds to Exp. DMSO-$d_6$ (ppm) = (0.999 ± 0.001) Calc. (ppm), $n$ = 114, $R^2$ = 0.9998. The very good quality of this regression verifies the signals assignment.

In solution, the *ortho* and *meta* signals correspond to averaged values (the same for the H atoms of the methyl groups) but in the solid state the splittings present in compound **2** probably correspond to the absence of free rotation of the *p*-tolyl group at position 5 (Scheme 2).

## CONCLUSIONS

The main conclusions of our investigations are:

1. In the gas-phase, theoretical calculations [B3LYP/6-311++G(d,p) optimized geometries and GIAO/B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) abso-

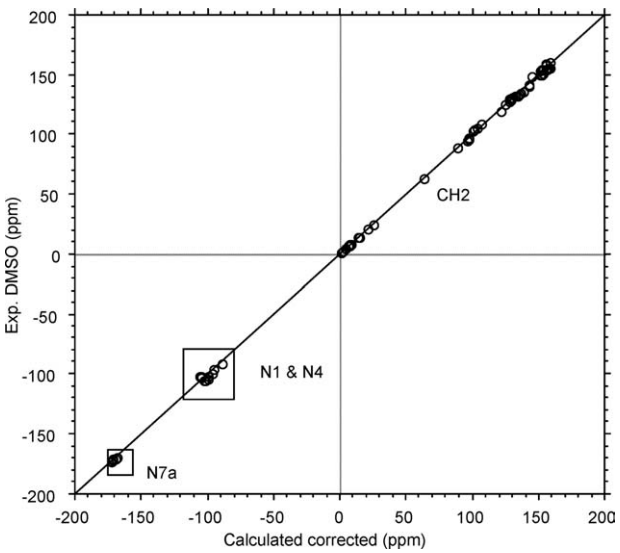
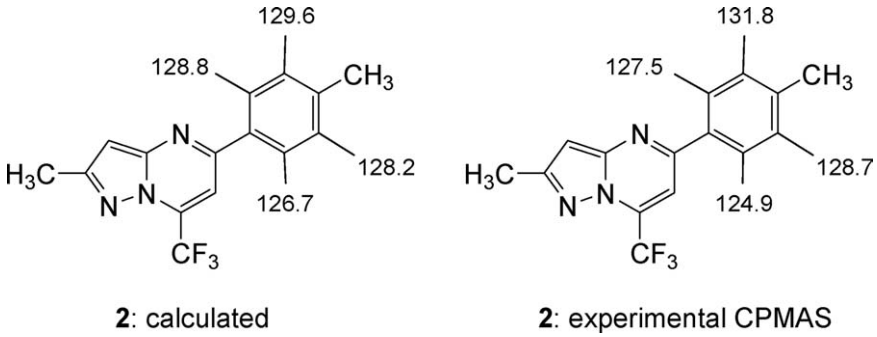



**Figure 6.** Plot of experimental *vs.* calculated chemical shifts.

**Scheme 2**




**2**: calculated **2**: experimental CPMAS

lute shieldings] of each monomer account well for the properties in condensed phases: solution (NMR) and solid state (NMR and crystallography).

2. In DMSO-d6 solution, NMR results are consistent with the proposed structures providing chemical shifts (in brackets mean values in ppm) useful for characterizing new series of pyrazolo[1,5-a]pyrimidines: δN7a(−172) < δN1(−103.5) < δN4(−98); δC2-Me(155) ≈ δC5-Ar(154) > δC7(135) > δC6(105); δC2-Me(155) > δC5-H(149) > δC7(135) > δC6(105); δC5-Me(158) > δC2-Me(155) > δC7(135) > δC6(105). The CPMAS data show similar trends, meaning that the structures in solution are close to those in the solid state.
3. X-Ray crystallographic studies show interesting halogen interactions (X...X, X...N), both the F···F at 2.90 Å and the Br...Br at 3.66 Å for 3 and the Cl...N at 3.115 Å for 4, of great importance in crystal engineering [37,38].

## EXPERIMENTAL

**General.** 3-Amino-5-methyl-1*H*-pyrazole was obtained commercially from Aldrich (ACS grade) and used without further purification. The heterocyclic precursors were synthesized in accordance with methodologies developed in our laboratory [37]. The crystals used for the data collection were obtained by crystallization of compounds from hexane followed by slow evaporation at room temperature. All solvents (Merck) were dried in accordance with procedures carried out in our laboratory [38]. Melting points were determined on a Microquimica MQAPF–302 melting point apparatus.

**2-Methyl-7-trifluoromethyl-5-(p-bromophenyl)pyrazolo[1,5-a]pyrimidine (3).** A solution of 3-amino-5-methyl-1*H*-pyrazole (1.0 mmol) in acetic acid (5 mL) was added to a stirred solution of 4-(*p*-bromophenyl)-1,1,1-trifluoro-4-methoxy-3-buten-2-one (1.0 mmol) in acetic acid (5 mL). The mixture was stirred for 16 h and after the reaction time the product was extracted with chloroform (3 × 10 mL), washed with distilled water (3 × 10 mL), and dried on magnesium sulfate. The solvent was removed in a rotary evaporator and compound **3** was purified by recrystallization from hexane, and was obtained in 86% yield. M.p. 171–173°C.

**Ethyl 2,5-dimethylpyrazolo[1,5-a]pyrimidine-7-carboxylate (6).** A solution of 3-amino-5-methyl-1*H*-pyrazole (1.0 mmol) in acetic acid (5 mL) was added to a stirred solution of ethyl 4-methoxy-2-oxo-3-pentenoate (1.0 mmol) in acetic acid (5 mL). The mixture was stirred for 16 h and after the reaction time, the product was extracted with chloroform (3 × 10 mL), washed with distilled water (3 × 10 mL), and dried on magnesium sulfate. The solvent was removed in a rotary evaporator and the product was purified by crystallization from hexane, and was obtained in 91% yield. M.p. 74–76°C.

**Crystallography.** The diffraction measurements were carried out by graphite-monochromated Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer [39]. The structures were solved with direct methods using the SHELXS-97 program and refined on *F2* by full-matrix least-squares with the SHELXL97 package [40]. Absorption correction was performed by the Gaussian method [41]. Anisotropic displacement parameters for nonhydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH3), 0.97 Å (methylene CH2), 0.98 Å (methyne CH), 0.93 Å (aromatic CH) and 0.82 Å (OH) using a riding model. Hydrogen isotropic thermal parameters were kept equal to *U*iso(H) = *xU*eq (carrier C atom), with $x = 1.5$ for methyl groups and $x = 1.2$ otherwise. The valence angles C—C—H and H—C—H of methyl groups were set to 109.5° and H atoms were allowed to rotate around the C—C bond. Molecular graphics were prepared using ORTEP for Windows [42]. The crystal data and details concerning data collection and structure refinement are given in Table 5.

Crystallographic data for structures have been deposited with the Cambridge Crystallographic Data Center (2-methyl-7-trichloromethylpyrazolo[1,5-*a*]pyrimidine CCDC 734995; 2-methyl-5-(*p*-bromophenyl)-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine CCDC 734998). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

**NMR measurements.** $^{1}$H (400.13 MHz), $^{13}$C (100.61 MHz), and $^{15}$N (40.56 MHz) spectra in solution were obtained with a Bruker DRX-400 instrument, with a 5-mm inverse-detection H-X probe equipped with a gradient coil, at 300 K. Chemical shifts (δ in ppm) are given from solvent DMSO-$d_6$ 2.49 for $^{1}$H and 39.5 for $^{13}$C, external nitromethane (0.00) for $^{15}$N NMR. Coupling constants (*J* in Hz) are accurate to ± 0.2

**Table 5**

Crystal data and structure refinement for compounds **4** and **3**.

| | **3** | **4** |
|---|---|---|
| Formula | $C_{14}$ $H_9$ Br $F_3$ $N_3$ | $C_8$ $H_6$ $Cl_3$ $N_3$ |
| *Mr* | 356.15 | 250.51 |
| CCDC | 734,998 | 734,995 |
| Temperature (K) | 293 (2) | 296 (2) |
| Wavelength (Å) | 0.71073 | 0.71073 |
| Crystal system | Orthorhombic | Orthorhombic |
| Space Group | $P2_12_12_1$ | $Pca2_1$ |
| Unit cell parameters | | |
| a (Å) | 4.7574 (7) | 15.307 (2) |
| b (Å) | 11.0476 (17) | 9.4510 (14) |
| c (Å) | 26.177 (5) | 6.9446 (10) |
| α (°) | 90 | 90 |
| β (°) | 90 | 90 |
| γ (°) | 90 | 90 |
| V (Å$^3$) | 1375.8 (4) | 1004.7 (3) |
| Z | 4 | 4 |
| Density (calculated) (g/cm$^3$) | 1.719 | 1.656 |
| Absorption coefficient (mm$^{-1}$) | 3.018 | 0.871 |
| F (000) | 704 | 504 |
| Crystal size (mm) | 0.758 × 0.088 × 0.05 | 0.35 × 0.25 × 0.13 |
| θ range for data collection (°) | 2.00 to 27.36 | 2.15 to 28.33 |
| *h,k,l* range | $-6 \leq h \leq 6$ | $-20 \leq h \leq 20$ |
| | $-14 \leq k \leq 14$ | $-12 \leq k \leq 11$ |
| | $-33 \leq l \leq 33$ | $-5 \leq l \leq 9$ |
| $T_{max}/T_{min}$ | 0.9330/0.5595 | 0.8951/0.7502 |
| Reflections collected | 13211 | 9557 |
| Independent reflections | 3093 [R(int) = 0.0623] | 2091 [R(int) = 0.0396] |
| Data/restraints/parameters | 3093/0/190 | 2091/1/127 |
| Absorption correction | Gaussian | Gaussian |
| Refinement method | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| Final R indices [I>2σ(I)] | $R1 = 0.0441$, w$R2 = 0.0991$ | $R1 = 0.0459$, w$R2 = 0.1196$ |
| R indices (all data) | $R1 = 0.0905$, w$R2 = 0.1262$ | $R1 = 0.0682$, w$R2 = 0.1342$ |
| Goodness of fit on $F^2$ | 1.008 | 1.052 |
| Largest diff. peak and hole (eÅ$^{-3}$) | 0.280 and –0.391 | 0.466 and –0.291 |

Hz for $^1$H and ± 0.6 Hz for $^{13}$C and $^{15}$N. 2D-inverse-proton-detected heteronuclear-shift-correlation spectra ($^1$H-$^{13}$C) gs-HMQC, ($^1$H-$^{13}$C) gs-HMBC and ($^1$H-$^{15}$N) gs-HMBC were acquired and processed using standard pulse sequences [43]. Solid-state $^{13}$C (100.73 MHz) and $^{15}$N (40.60 MHz) CPMAS-NMR spectra have been obtained with a Bruker WB-400 spectrometer at 300 K with a wide-bore 4-mm DVT probehead. Samples were carefully packed in $ZrO_2$ rotors. $^{13}$C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the $Me_4Si$ [for the carbonyl atom δ (glycine) = 176.1 ppm] and $^{15}$N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ $^{15}$N ($MeNO_2$) = δ $^{15}$N($NH_4Cl$)-338.1 ppm. Typical acquisition parameters for $^{13}$C CPMAS were: spectral width, 40 kHz; recycle delay, 5–60 s; acquisition time, 30 ms; contact time, 2–4 ms; and spin rate, 12 kHz. In order to distinguish protonated and unprotonated carbon atoms, the NQS (Non-Quaternary Suppression) experiment by conventional cross-polarization was recorded; before the acquisition the decoupler is switched off for a very short time of 25 (s. Typical acquisition parameters for $^{15}$N CPMAS were: spectral width, 40 kHz; recycle delay, 5–60 s; acquisition time, 35 ms; contact time, 7 ms; and spin rate, 6 kHz [44].

**Computational details.** The optimization of the geometries of the structures were first carried out at the B3LYP/6-31G(d) and afterwards reoptimized at the B3LYP/6-311++G(d,p) computational level [45–50] within the Gaussian-03 package [51]. Frequency calculations at the first level were carried out to confirm that the obtained structures correspond to energy minima. GIAO absolute shieldings [52,53] were calculated on the B3LYP/6-311++G(d,p) optimized geometries.

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## REFERENCES AND NOTES


[1] Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Sakashita, M.; Kitahara, M.; Sakoda, R. Bioorg Med Chem Lett 2001, 11, 1285.

[2] Almansa, C.; Merlos, M.; Rafanell, J. G.; Arriba, A. F.; Cavalcanti, F. L.; Gómez, L. A.; Miralles, A.; Forn, J. J Med Chem 2001, 44, 350.

[3] Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebben, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. Bioorg Med Chem Lett 2002, 12, 2767.

[4] Fraley, M. E.; Rubino, R. S.; Hoffman, W. F.; Hambaugh, S. R.; Arrington, K. L.; Hungate, R. W.; Bilodeau, M. T.; Tebben, A. J.; Rutledge, R. Z.; Kendall, R. L.; McFall, R. C.; Huckle, W. R.; Coll, K. E.; Thomas, K. A. Bioorg Med Chem Lett 2002, 12, 3537.

[5] Selleri, S.; Bruni, F.; Costagli, C.; Costanzo, A.; Guerrini, G.; Ciciani, G.; Costa, B.; Martini, C. Bioorg Med Chem 2001, 9, 2661.

[6] Kirkpatrick, W. E.; Okabe, T.; Hillyard, I. W.; Robins, R. K.; Novinson, T.; Dren, A. T. J Med Chem 1977, 20, 386.

[7] O'Donnell, P. B.; Thiele, W. J. U.S. Pat. 6,384,221 (2002).

[8] Kendall, R. L.; Rubino, R.; Rutledge, R.; Bilodeau, M. T.; Fraley, M. E.; Thomas, K. A., Jr.; Hungate, R. W. U.S. Pat. 6,235,741 (2001).

[9] Compton, D. R.; Carlson, K. E.; Katzenellenbogen, J. A. Bioorg Med Chem Lett 2004, 14, 5681.

[10] Wang, S. Q.; Fang, L.; Liu, X. J.; Zhao, K. Chin Chem Lett 2004, 15, 885.

[11] (a) Williamson, D. S.; Parratt, M. J.; Bower, J. F.; Moore, J. D.; Richardson, C. M.; Dokurno, P.; Cansfield, A. D.; Francis, G. L.; Hebdon, R. J.; Howes, R.; Jackson, P. S.; Lockie, A. M.; Murray, J. B.; Nunns, C. L.; Powles, J.; Robertson, A.; Surgenor, A. E.; Torrance, C. J. Bioorg Med Chem Lett 2005, 15, 863; (b) Paruch, K.; Dwyer, M. P.; Alvarez, C.; Brown, C.; Chan, T.-Y.; Doll, R. J.; Keertikar, K.; Knutson, C.; McKittrick, B.; Rivera, J.; Rossman, R.; Tucker, G.; Fishmann, T. O.; Hruza, A.; Madison, V.; Nomeir, A. A.; Wang, Y.; Lees, E.; Parry, D.; Sgambellone, N.; Seghezzi, W.; Schultz, L.; Shanahan, F.; Wiswell, D.; Xu, X.; Zhou, Q.; James, R. A.; Paradkar, V. M.; Park, H.; Rokosz, L. R.; Stauffer, T. M.; Guzi, T. J. Bioorg Med Chem Lett 2007, 17, 6220.

[12] Popik, P.; Kostakis, E.; Krawczyk, M.; Nowak, G.; Szewczyk, B.; Krieter, P.; Chen, Z.; Russek, S. J.; Gibbs, T. T.; Farb, D. H.; Skolnick, P.; Lippa, A. S.; Basile, A. S. J Pharmacol Exp Ther 2006, 319, 1244.

[13] (a) Alcalde, E.; Mendoza, J.; García-Marquina, J. M.; Almera, C.; Elguero, J. J Heterocycl Chem 1974, 11, 423; (b) Sanz, D.; Claramunt, R. M.; Saini, A.; Kumar, V.; Aggarwal, R.; Singh, S. P.; Alkorta, I.; Elguero, J. Magn Reson Chem 2007, 45, 513; (c) Wu, Y.-C.; Li, H. J.; Liu, L.; Wang, D.; Yang, H.-Z.; Chen, Y. J. J Fluoresc 2008, 18, 357–363; (d) Borges, J. C.; Oliveira, C. D.; Pinheiro, L. C. S.; Marra, R. K. F.; Khan, M. A.; Wardell, J. L.; Wardell, S. M. S. V.; Bernardino, A. M. R. J Braz Chem Soc 2007, 18, 1571; (e) Ghagare, M. G.; Birari, D. R.; Shelar, D. P.; Toche, R. B.; Jachak, M. N. J Heterocycl Chem 2009, 46, 327; (f) Ghotekar, B. K.; Jachak, M. N.; Toche, R. B. J Heterocycl Chem 2009, 46, 708.

[14] (a) Filyakova, V. I.; Kuznetsova, O. A.; Ulomskii, E. N.; Rybalova, T. V.; Gatilov, Yu. V.; Kodess, M. I.; Rusinov, V. L.; Pashkevich, K. I. Russ Chem Bull Int Ed 2002, 51, 332; (b) Martins, M. A. P.; Cunico, W.; Scapin, E.; Emmerich, D. J.; Fiss, G. F.; Rosa, F. A.; Bonacorso, H. G.; Zanatta, N.; Flores, A. F. C. Lett Org Chem 2006, 3, 358; (c) Dalinger, I. L.; Vatsade, I. A.; Shevelev, S. A.; Ivanchtchenko, A. J Comb Chem 2005, 7, 236; (d) Gregg, B. T.; Tymoshenko, D. O.; Razzano, D. A.; Johnson, M. R. J Comb Chem 2007, 9, 507.

[15] Grohe, K. Synthesis 1975, 645.

[16] Frizzo, C. P.; Campos, P. T.; Marzari, M. R. B.; Machado, P.; Martins, M. A. P. Acta Crystallogr Sect E 2008, E64, o212.

[17] Martins, M. A. P.; Scapin, E.; Frizzo, C. P.; Rosa, F. A.; Bonacorso, H. G.; Zanatta, N. J Braz Chem Soc 2009, 20, 205.

[18] Frizzo, C. P.; Scapin, E.; Campos, P. T.; Moreira, D. N.; Martins, M. A. P. J Mol Struct 2009, 933, 142.

[19] Elgemeie, G. H.; Alia, H. A.; Jones P. G. Acta Crystallogr Sect E 2002, E58, o1247.

[20] Portilla, J.; Quiroga, J.; Cobo, J.; Nogueras, M.; Low, J. N.; Glidewell, C. Acta Crystallogr Sect C 2005, C61, o398.

[21] Portilla, J.; Quiroga, J.; Cobo, J.; Low, J. N.; Glidewell, C. Acta Crystallogr Sect C 2006, C62, o186.

[22] Portilla, J.; Quiroga, J.; de la Torre, J. M.; Cobo, J.; Low; J. N.; Glidewell, C. Acta Crystallogr Sect C 2006, C62, o521.

[23] Glidewell, C.; Lloyd, D. M. G. Tetrahedron 1984, 40, 4455.

[24] Li, M.; Wang, S.; Wen, L.; Zhang, X.; Ke, Z. J Chem Crystallogr 2005, 35, 667.

[25] Low, J. N.; Cobo, J.; Mera, J.; Quiroga, J.; Glidewell, C. Acta Crystallogr Sect C 2004, C60, o265.

[26] James, S. L. In Encyclopedia of Supramolecular Chemistry; Atwood, J. L., Steed, J. W., Eds.; CRC Press: Boca Raton, 2004; p 1093.

[27] Kishikawa, K.; Oda, K.; Aikyo, S.; Kohmoto, S. Angew Chem Int Ed 2007, 46, 764.

[28] Ponzini, F.; Zagha, R.; Hardcastle, K.; Siegel, J. S. Angew Chem Int Ed 2000, 39, 2323.

[29] Madhavi, N. N. L.; Desiraju, G. R.; Bilton, C.; Howard, J. A. K.; Allen, F. H. Acta Crystallogr Sect B 2000, B56, 1063.

[30] Prasanna, M. D.; Guru Row, T. N. Cryst Eng Commun 2000, 2, 134.

[31] Schwarzer, A.; Seichter, W.; Weber, E.; Stoeckli-Evans, H.; Losada, M.; Hulliger, J. Cryst Eng Comm 2004, 6, 567–572.

[32] Dunitz, J. D.; Schweizer, W. B. Chem Eur J 2006, 12, 6804.

[33] Pyykko, P. Chem Rev 1997, 97, 597.

[34] García, M. A.; Cabildo, P.; Claramunt, R. M.; Pinilla, E.; Torres, M. R.; Alkorta, I.; Elguero, J. Inorg Chim Acta, to appear.

[35] Low, J. N.; Cobo, J.; Quiroga, J.; Portilla, J.; Glidewell, C Acta Crystallogr Sect C 2004, C60, o604.

[36] (a) Alkorta, I.; Elguero, J. Struct Chem 1998, 9, 187; (b) Cavero, E.; Giménez, R.; Uriel, S.; Beltrán, E.; Serrano, J. L.; Alkorta, I.; Elguero, J. Cryst Growth Des 2008, 8, 838; (c) Alkorta, I.; Blanco, F.; Elguero, J. J Mol Struct Theochem 2009, 896, 92; (d) Silva, A. M. S.; Sousa, R. M. S.; Jimeno, M. L.; Blanco, F.; Alkorta, I.; Elguero, J. Magn Reson Chem 2008, 46, 859; (e) Santa María, M. D.; Claramunt, R. M.; Herranz, F.; Alkorta, I.; Elguero, J. J Mol Struct 2009, 920, 323; (f) Santa María, M. D.; Claramunt, R. M.; Alkorta, I.; Elguero, J. Magn Reson Chem 2009, 47, 472; (g) Alkorta, I.; Elguero, J.; Limbach, H.-H.; Shenderovich, I. G.; Winkler, T. Magn Reson Chem 2009, 47, 585; (h) Claramunt, R. M.; Sanz, D.; López, C.; Pinilla, E.; Torres, M. R.; Elguero, J.; Nioche, P.; Raman, C. S. Helv Chim Acta, to appear; (i) Blanco, F.; Alkorta, I.; Elguero, J. Magn Reson Chem 2007, 45, 797.

[37] (a) Colla, A.; Clar, G.; Martins, M. A. P.; Krimmer, S.; Fischer, P.; Synthesis 1991, 483; (b) Flores, A. F. C.; Brondani, S.; Zanatta, N.; Rosa, A.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 8701; (c) Martins, M. A. P.; Guarda, E. A.; Frizzo, C. P.; Scapin, E.; Beck, P.; Costa, A. C.; Zanatta, N.; Bonacorso, H. G. J Mol Catal A 2007, 266, 100; (d) Martins, M. A. P.; Guarda, E. A.; Frizzo, C. P.; Moreira, D. N.; Marzari, M. R. B.; Zanatta, N.; Bonacorso, H. G. Catal Lett 2009, 130, 93.

[38] Perrin, D. D.; Armarego, L. F. Purification of Laboratory Chemicals, 3rd ed.; Pergamon Press: New York, 1996.

[39] Bruker (2006). APEX2 (Version 2.1), COSMO (Version 1.56), BIS (Version 2.0.1.9), SAINT (Version 7.3A) and SADABS (Version 2004/1) and XPREP (Version 2005/4). Bruker AXS Inc.: Madison, Wisconsin, USA, 2006.

[40] Sheldrick, G. M. SHELXL-97, Program for Crystal Structure Solution and Refinement. University of Göttingen: Germany, 1997.

[41] Coppens, P.; Leiserowitz, L.; Rabinovich, D. Acta Crystallogr 1965, 18, 1035.

[42] Farrugia, L. J. ORTEP-III for Windows, J Appl Cryst 1997, 30, 565.

[43] Braun, S.; Kalinowki, H.-O.; Berger, S. 200 and More Basic NMR Experiments. Wiley-VCH: Weinheim, 2004.

[44] Perona, A.; Sanz, D.; Claramunt, R. M.; Elguero, J. Magn Reson Chem 2008, 46, 930.

[45] Becke, A. D. Phys Rev A 1988, 38, 3098.

[46] Becke, A. D. J Chem Phys 1993, 98, 5648.

[47] Lee, C.; Yang, W.; Parr, R. G. Phys Rev B 1988, 37, 785.

[48] Hariharan, P.A.; Pople, J. A. Theor Chim Acta 1973, 28, 213.

[49] Ditchfield, R.; Hehre, W. J.; Pople, J. A. J Chem Phys 1971, 54, 724.

[50] Frisch, M. J.; Pople, J. A.; Krishnam, R.; Binkley, J. S. J Chem Phys 1984, 80, 3265.

[51] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C. and Pople, J. A. Gaussian 03, Gaussian, Inc.: Pittsburgh PA, 2003.

[52] Ditchfield, R. Mol Phys 1974, 27, 789.

[53] London, F. J Phys Radium 1937, 8, 397.

# Synthesis and Anti-*Helicobacter pylori* Activity of 4-(Coumarin-3-yl)thiazol-2-ylhydrazone Derivatives



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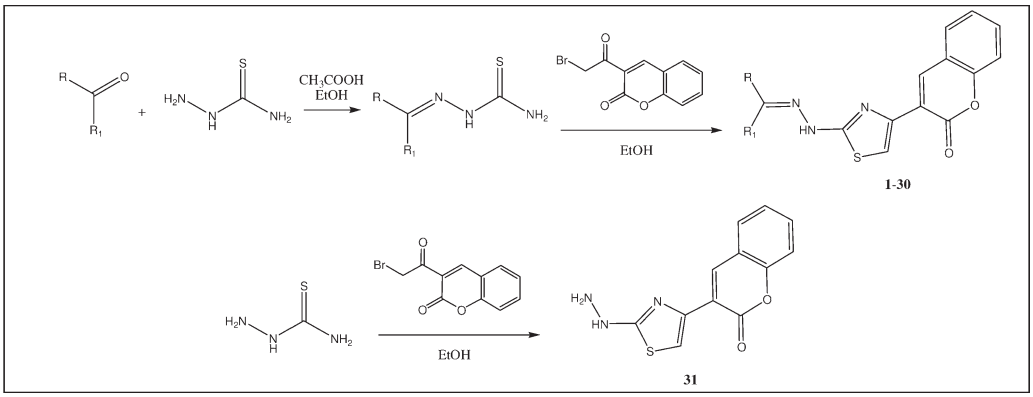


A novel class of coumarin-thiazole conjugated systems (**1–31**) were synthesized by Hantzsch condensation between α-bromo-3-acetyl coumarin and several thiosemicarbazone intermediates. This scaffold was also evaluated for selective antibacterial activity against 20 isolates of *H. pylori* clinical strains, including four metronidazole resistant ones.

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## INTRODUCTION

*Helicobacter pylori* are spiral-shaped Gram-negative bacteria with polar flagella that live near the surface of the human gastric mucosa. They have evolved specific mechanisms to avoid the bactericidal acid environment in the gastric lumen to survive near, to attach to, and to communicate with the human gastric epithelium and host immune system. This interaction sometimes results in severe gastric pathology. In fact, *H. pylori* infection is indeed the most known risk factor for the development of gastroduodenal ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.

*H. pylori* infections are difficult to cure and successful treatment generally requires the simultaneous somministration of several antibacterial agents. Antibiotic resistance has resulted in unsatisfactory eradication with dual and now triple therapy in many countries. Newer antibiotics and changes in dosing and duration of therapy may overcome resistant strains but may only provide limited improvement in eradication rates [1–3].

In our previous works [4,5] and from the analysis of the structure of natural coumarins reported as potent anti-*H. pylori* agents [6], we have pointed out that the coumarin ring might play an important role in determining activity and seemed to be crucial for the selective antimicrobial activity of such compounds. Recently, we have synthesized and chemically and biologically characterized some new conjugated coumarin-thiazole systems, which were endowed with interesting industrial properties and especially antimicrobial activity on *H. pylori* clinical strains [7].

Furthermore, interest in these structures has renewed due to the recent discovery of their promising antibacterial, antifungal, and antimycobacterial activity [8–11].

Moving from these indications, in this report we described the synthesis and selective antimicrobial evaluation of a new series of 4-(coumarin-3-yl)thiazol-2-ylhydrazone derivatives which differ for the electronic and steric characteristics on the hydrazone nitrogen (aliphatic chains, cycloaliphatic moiety, and heterocyclic rings).

## RESULTS AND DISCUSSION

The coumarin-thiazole derivatives (**1–30**) were prepared in high yields (69–99%) according to a protocol

**Table 1**

Structure of derivatives **1–31**.

| Comp | R | $R_1$ |
|---|---|---|
| **1** [ref. 12] | $CH_3$ | $CH_3$ |
| **2** | $CH_2CH_3$ | $CH_3$ |
| **3** | $CH(CH_3)_2$ | $CH_3$ |
| **4** | $(CH_2)_2CH_3$ | $CH_3$ |
| **5** | $CH_2CH_3$ | $CH_2CH_3$ |
| **6** | $(CH_2)_2CH{=}CH_2$ | $CH_3$ |
| **7** | $(CH_2)_4CH_3$ | $CH_3$ |
| **8** | $(CH_2)_3CH_3$ | $CH_2CH_3$ |
| **9** | $(CH_2)_5CH_3$ | $CH_3$ |
| **10** | 2-$CH_3$-Cyclopentyliden | |
| **11** | 3-$CH_3$-Cyclopentyliden | |
| **12** | Cyclooctyliden | |
| **13** | Cyclohexyl | $CH_3$ |
| **14**[ref. 11] | Fur-2-yl | H |
| **15** | Fur-2-yl | $CH_3$ |
| **16** | Tiophen-2-yl | H |
| **17** | Tiophen-2-yl | $CH_3$ |
| **18**[ref. 13] | Phenyl | $CH_3$ |
| **19** | Pyridin-2-yl | $CH_3$ |
| **20** | Pyridin-3-yl | H |
| **21** | Pyridin-3-yl | $CH_3$ |
| **22** | Pyridin-4-yl | H |
| **23** | Pyridin-4-yl | $CH_3$ |
| **24** | 1*H*-indol-3-yl | H |
| **25**[ref. 14] | 3,4-Methylendioxophenyl | H |
| **26** | Naphtalen-1-yl | H |
| **27** | Naphtalen-2-yl | $CH_3$ |
| **28**[ref. 15] | Coumarin-3-yl | $CH_3$ |
| **29** | 2-COOH-9*H*-fluoren-5-yliden | |
| **30** | Thiazol-2-yl | $CH_3$ |
| **31**[ref. 16] | H | H |

used in our laboratory (Table 1). Different carbonyl compounds reacted directly with thiosemicarbazide in ethanol with catalytic amounts of acetic acid, and the obtained thiosemicarbazones were subsequently converted into 4-(coumarin-3-yl)-2-thiazolylhydrazones by reaction with α-bromo-3-acetyl coumarin in the same solvent at room temperature (Hantzsch condensation). α-Bromo-3-acetyl coumarin has been synthesized by direct halogenation of 3-acetyl coumarin with bromine in chloroform. Moreover, knowing that all reported structures possess an imine bond, which could be hydrolyzed in the acidic environment of the stomach (reproduced in the biological assay), we also synthesized and assayed their common intermediate (**31**) by direct reaction between thiosemicabazide and α-bromo-3-acetyl coumarin in ethanol at room temperature.

All synthesized products were purified with petroleum ether and diethyl ether and, if requested, by chromatography before characterization by spectroscopic methods (IR and $^1$H NMR) and elemental analysis. The compounds, correctly analyzed for their molecular formula, showed in the IR spectrum strong bands at 1710 and 1600 $cm^{-1}$ due to the presence of a δ-lactone C=O and C=N group, respectively.

Moreover, the presence of a C=N double bond can give rise to isomeric geometry E/Z. The $^1$H NMR (in $CDCl_3$) spectra analysis revealed that the E isomer was more favored and stable than the Z-configuration. The amounts of both conformers were measured by area integration of the signal relative to the $CH_3$ ($R^1$) protons (area ratio of proton signals E:Z was generally 6:1). The low-field signal was assigned to the E isomer, as it is widely accepted in thiosemicarbazone derivatives [17]. Our choice, as reaction medium, of a polar alcoholic solvent appeared to be preferred to obtain the E-configuration and limit the interconversion according to the results of our previous theoretical and chromatographic study for similar compounds [18].

Then, all compounds were evaluated, as mixture of E/Z conformers, against 20 clinical strains of *H. pylori*, which are more resistant to conventional therapy. Metronidazole was used as standard antibacterial drug (Table 2).

Most of the assayed compounds showed no anti-*H. pylori* activity or comparable activity with respect to Metronidazole (MIC $\geq$ 16 μg/mL). Only some compounds (**14**, **21**, and **26**), bearing a specific heterocyclic ring (furan, pyridine, and naphthalene) on the hydrazone nitrogen, possessed MIC values slightly inferior to the reference drug (MIC = 8 μg/mL) against some clinical *H. pylori* strains. Unfortunately, it was not possible to correlate this biological activity with lipophilicity (Clog*P*).

## EXPERIMENTAL

The chemicals, solvents for synthesis and spectral grade solvents were purchased from Aldrich (Italy) and used without further purification. Melting points are uncorrected and were determined automatically on an FP62 apparatus (Mettler-Toledo). $^1$H NMR spectra were recorded at 400 MHz on a Bruker spectrometer. Chemical shifts are expressed as δ units (parts per millions) relative to the solvent peak. Coupling constants *J* are valued in Hertz (Hz). IR spectra were registered on a Perkin Elmer FTIR Spectrometer Spectrum 1000 in KBr. Elemental analysis for C, H, and N were recorded on a Perkin-Elmer 240 B microanalyzer and the analytical results were within ±0.4% of the theoretical values for all compounds. All reactions were monitored by TLC performed on 0.2-mm-thick silica gel plates (60 $F_{254}$ Merck). Lipophilicity parameter, Clog*P*, has been calculated for each molecule by using ChemDraw ultra 8.0. The synthesis of some compounds has been described in previous references (Table 1) and was performed with slight changes. Their analytical and spectral data were in full agreement with those reported in the literature.

**Typical procedure for the thiosemicarbazones synthesis.** The appropriate carbonylic compound (50 mmol) was dissolved in 100 mL of ethanol and stirred vigorously at

**Table 2**

MIC values (μg/mL) of derivatives **1–31** and **M** (metronidazole) against 20 *H. pylori* strains.

| Compound | Metronidazole sensitive strains (16 strains) | Metronidazole resistant strains (4 strains) |
|---|---|---|
| **1** | ≥16 | >16 |
| **2** | ≥16 | >16 |
| **3** | ≥16 | >16 |
| **4** | ≥16 | >16 |
| **5** | ≥16 | >16 |
| **6** | ≥16 | ≥16 |
| **7** | ≥16 | ≥16 |
| **8** | ≥16 | ≥16 |
| **9** | ≥16 | ≥16 |
| **10** | ≥16 | ≥16 |
| **11** | ≥16 | ≥16 |
| **12** | ≥16 | ≥16 |
| **13** | ≥16 | >16 |
| **14** | 8–≥16 | 8–≥16 |
| **15** | ≥16 | ≥16 |
| **16** | >16 | ≥16 |
| **17** | ≥16 | ≥16 |
| **18** | ≥16 | >16 |
| **19** | ≥16 | ≥16 |
| **20** | ≥16 | ≥16 |
| **21** | 8–≥16 | ≥16 |
| **22** | ≥16 | ≥16 |
| **23** | ≥16 | ≥16 |
| **24** | >16 | ≥16 |
| **25** | ≥16 | ≥16 |
| **26** | 8–≥16 | ≥16 |
| **27** | ≥16 | ≥16 |
| **28** | >16 | >16 |
| **29** | ≥16 | >16 |
| **30** | >16 | >16 |
| **31** | ≥16 | >16 |
| M | 0.5–16 | >16 |

room temperature with an equimolar amount of thiosemicarbazide for 24 h with catalytic amount of acetic acid. The desired thiosemicarbazone precipitated from reaction mixture was filtered and crystallized from suitable solvent and dried.

**Typical procedure for the Hantzsch protocol for the preparation of derivatives 1–30.** Equimolar amounts of the prepared thiosemicarbazones (50 mmol) and freshly synthesized 3-α-bromo-acetyl coumarin (50 mmol), both dissolved in ethanol, were reacted at room temperature under magnetic stirring for 4 h. The precipitate was filtered and dried to give compounds **1–30** in 69–99% yield.

***3-(2-(2-Butylidenehydrazynyl)thiazol-4-yl)-2H-chromen-2-one (2).*** Light brown crystals, 96% yield, mp 205–210°C; $^1$H NMR ($CDCl_3$): δ 1.15–1.18 (t, 3H, $J$ = 7.2, $CH_3$), 2.20 (s, 3H, $CH_3$), 2.42–2.47 (q, 2H, $J$ = 7.2, $CH_2$), 7.35–7.39 (m, 1H, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.8 Hz, $J_{7\text{-}5}$ = 2.3 Hz, $C_7$H-chrom), 7.41–7.43 (dd, 1H, $J_{5\text{-}6}$ =7.9, $J_{5\text{-}7}$ = 2.4 Hz, $C_5$H-chrom), 7.62–7.65 (m, 1H, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.8 Hz, $J_{6\text{-}8}$ = 2.3 Hz, $C_6$H-chrom), 7.68 (s, 1H, $C_5$H-thiaz.), 7.77–7.83 (dd, 1H, $J_{8\text{-}7}$ = 7.8 Hz, $J_{8\text{-}6}$ = 2.2 Hz, $C_8$H-chrom.), 10.75 (bs, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.13; H, 4.37; N, 14.06.

***3-(2-(2-(3-Methyl-2-butylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (3).*** Yellow crystals, 99% yield, mp 170–173°C; $^1$H NMR ($CDCl_3$): δ 0.95–0.97 (d, $J$ = 6.6 Hz, 6H, 2 × $CH_3$), 1.98–2.11 (m, $J$ = 6.6 Hz, 1H, CH), 2.17 (s, 3H, $CH_3$), 7.35–7.38 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.3 Hz, $J_{7\text{-}5}$ = 1.8 Hz, 1H, $C_7$H-chrom.), 7.39–7.41 (dd, $J_{5\text{-}6}$ = 7.3 Hz, $J_{5\text{-}7}$ = 1.8 Hz, 1H, $C_5$H-chrom.), 7.61–7.65 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.3 Hz, $J_{6\text{-}8}$ = 1.8 Hz, 1H, $C_6$H-chrom.), 7.79–7.82 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.9 Hz, 1H, $C_8$H-chrom.), 7.84 (s, 1H, $C_5$H-thiaz.), 8.54 (s, 1H, $C_4$H-chrom.), 12.00 (br s, 1H, NH, $D_2O$ exch.); *Anal*. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.41; H, 5.24; N, 12.82.

***3-(2-(2-(2-Pentanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (4).*** Orange crystals, 82% yield, mp 186–187°C; $^1$H NMR ($CDCl_3$): δ 0.97–1.03 (t, $J$ = 7.4 Hz, 3H, $CH_3$), 1.59–1.65 (m, $J$ = 7.4 Hz, $J$ = 5.6 Hz, 2H, $CH_2$), 2.18 (s, 3H, $CH_3$), 2.33–2.38 (t, $J$ = 5.6 Hz, 2H, $CH_2$), 7.34–7.37 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.6 Hz, $J_{7\text{-}5}$ = 2.1 Hz, 1H, $C_7$H-chrom.), 7.62–7.65 (dd, $J_{5\text{-}6}$ = 7.6 Hz, $J_{5\text{-}7}$ = 2.2 Hz, 1H, $C_5$H-chrom.), 7.68–7.75 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.7 Hz, $J_{6\text{-}8}$ = 2.1 Hz, 1H, $C_6$H-chrom.), 7.77–7.81 (dd, $J_{8\text{-}7}$ = 7.8 Hz, $J_{8\text{-}6}$ = 2.1 Hz, 1H, $C_8$H-chrom.), 7.85 (s, 1H, $C_5$H-thiaz.), 8.62 (s, 1H, $C_4$H-chrom.), 11.90 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.39; H, 5.22; N, 12.83.

***3-(2-(2-(3-Pentanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (5).*** Yellow crystals, 82% yield, mp 180–183°C; $^1$H NMR ($CDCl_3$): δ 1.16–1.19 (t, $J$ = 7.3 Hz, 6H, 2 × $CH_3$), 2.40–2.46 (m, 4H, 2 × $CH_2$), 7.35–7.37 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 6.8 Hz, $J_{7\text{-}5}$ = 1.4 Hz, 1H, $C_7$H-chrom.), 7.38–7.41 (dd, $J_{5\text{-}6}$ = 6.8 Hz, $J_{5\text{-}7}$ = 1.4 Hz, 1H, $C_5$H-chrom.), 7.59–7.63 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$= 6.8 Hz, $J_{6\text{-}8}$ = 1.4 Hz, 1H, $C_6$H-chrom.), 7.78–7.80 (dd, $J_{8\text{-}7}$ = 6.8 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, $C_8$H-chrom.), 7.84 (s, 1H, $C_5$H-thiaz.), 8.61 (s, 1H, $C_4$H-chrom.), 12.01 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.38; H, 5.24; N, 12.82.

***3-(2-(2-(5-Hexen-2-ylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (6).*** Light yellow crystals, 73% yield, mp 195–197°C; $^1$H NMR ($CDCl_3$): δ 2.19 (s, 3H, $CH_3$), 2.38–2.45 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 2.48–2.53 (m, $J$ = 6.5 Hz, $J$ = 7.2 Hz, 2H, $CH_2$), 5.05–5.08 (dd, $J_{cis}$ = 8.8 Hz, $J_{gem}$ = 1.7 Hz, 1H, CH=), 5.09–5.13 (dd, $J_{trans}$ = 17.7 Hz, $J_{gem}$ = 1.7 Hz, 1H, CH=), 5.78–5.85 (m, $J_{cis}$ = 8.8 Hz, $J_{trans}$ = 17.8 Hz, $J$ = 7.2 Hz 1H, CH=), 7.36–7.40 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.5, $J_{7\text{-}5}$ = 1.5, 1H, $C_7$H-chrom.), 7.41–7.43 (dd, $J_{5\text{-}6}$ = 7.5, $J_{5\text{-}7}$ = 1.5, 1H, $C_5$H-chrom.), 7.62–7.64 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.5, $J_{6\text{-}8}$ = 1.4, 1H, $C_6$H-chrom.), 7.79–7.81 (dd, $J_{8\text{-}7}$ = 7.6, $J_{8\text{-}6}$ = 1.4, 1H, $C_8$H-chrom.), 7.86 (s, 1H, $C_5$H-thiaz.), 8.61 (s, 1H, $C_4$H-chrom.), 12.00 (br s, 1H, NH, $D_2O$ exch.); *Anal*. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.75; H, 5.04; N, 12.38.

***3-(2-(2-(2-Heptanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (7).*** Yellow crystals, 99% yield, mp 198–201°C; $^1$H NMR (DMSO-$d_6$): δ 0.93–0.95 (m, 3H, $CH_3$), 1.22–1.30 (m, 2H, $CH_2$), 1.32–1.38 (m, 2H, $CH_2$), 1.55–1.61 (m, 2H, $CH_2$), 2.18 (s, 3H, $CH_3$), 2.36–2.40 (m, 2H, $CH_2$), 7.37–7.39 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.1 Hz, $J_{7\text{-}5}$ = 3.7 Hz, 1H, $C_7$H-chrom.), 7.40–7.42 (dd, $J_{5\text{-}6}$ = 7.16, $J_{5\text{-}7}$ = 3.8, 1H, $C_5$H-chrom.), 7.61–7.66 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.2 Hz, $J_{6\text{-}8}$ = 3.8 Hz, 1H, $C_6$H-chrom.), 7.79–7.81 (dd, $J_{8\text{-}7}$ = 7.1, $J_{8\text{-}6}$ = 3.7, 1H, $C_8$H-chrom.), 7.84 (s, 1H, $C_5$H-thiaz.), 8.61 (s, 1H, $C_4$H-chrom.), 12.06 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.15; H, 5.93; N, 11.84.

***3-(2-(2-(3-Heptanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (8).*** Yellow crystals, 77% yield, mp 175–180°C; $^1$H NMR ($CDCl_3$): δ 0.95–0.98 (m, 3H, $CH_3$), 1.13–1.19 (m, 2H, $CH_2$), 1.34–1.40 (m, 2H, $CH_2$), 1.55–1.62 (m, 3H, $CH_3$), 2.39–2.42 (m, 2H, $CH_2$), 2.45–2.51 (m, 2H, $CH_2$), 7.36–7.38 (m, 1H, $C_7$H-chrom.), 7.39–7.41 (m, 1H, $C_5$H-chrom.), 7.60–7.64 (m, 1H, $C_6$H-chrom.), 7.79–7.82 (m, 1H, $C_8$H-chrom.), 7.83 (s, 1H, $C_5$H-thiaz.), 8.61 (s, 1H, $C_4$H-chrom.), 12.14 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.25; H, 5.95; N, 11.81.

***3-(2-(2-(2-Octanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (9).*** Yellow crystals, 74% yield, mp 149–150°C; $^1$H NMR (DMSO-$d_6$): δ 0.84–0.88 (m, 3H, $CH_3$), 1.25–1.32 (m, 6H, 3 × $CH_2$), 1.47–1.51 (m, 2H, $CH_2$), 1.88–1.91 (m, 3H, $CH_3$), 2.19–2.23 (m, 2H, $CH_2$), 7.37–7.39 (m, 1H, $C_7$H-chrom.), 7.42–7.44 (m 1H, $C_5$H-chrom.), 7.60–7.64 (m, $C_6$H-chrom.), 7.68 (s, 1H, $C_5$H-thiaz.), 7.77–7.80 (m, 1H, $C_8$H-chrom.), 8.53 (s, 1H, $C_4$H-chrom.), 10.71 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{20}H_{23}N_3O_2S$: C, 65.01; H, 6.27; N, 11.37. Found: C, 65.06; H, 6.28; N, 11.35.

***3-(2-(2-(2-Methylcyclopentylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (10).*** Yellow crystals, 79% yield, mp 143–145°C; $^1$H NMR ($CDCl_3$): δ 1.21–1.23 (m, 3H, $CH_3$), 1.31–1.39 (m, 1H, cyclopentyl), 1.71–1.77 (m, 1H, cyclopentyl), 1.95–2.02 (m, 1H, cyclopentyl), 2.05–2.12 (m, 1H, cyclopentyl), 2.25–2.33 (m, 1H, cyclopentyl), 2.37–2.46 (m, 1H, cyclopentyl), 2.58–2.64 (m, 1H, cyclopentyl), 7.27–7.33 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.7 Hz, $J_{7\text{-}5}$ = 3.63 Hz, 1H, $C_7$H-chrom.), 7.34–7.37 (dd, $J_{5\text{-}6}$ = 7.8, $J_{5\text{-}7}$ = 3.6, 1H, $C_5$H-chrom.), 7.50–7.54 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.7 Hz, $J_{6\text{-}8}$ = 3.7 Hz, 1H, $C_6$H-chrom.), 7.57–7.60 (dd, $J_{8\text{-}7}$ = 7.7, $J_{8\text{-}6}$ = 3.6, 1H, $C_8$H-chrom.), 7.88 (s, 1H, $C_5$H-thiaz.), 8.49 (s, 1H, $C_4$H-chrom.), 12.00 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.75; H, 5.04; N, 12.39.

***3-(2-(2-(3-Methylcyclopentylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (11).*** Light yellow crystals, 99% yield, mp 214–216°C; $^1$H NMR ($CDCl_3$): δ 1.10–1.12 (m, 3H, $CH_3$), 1.49–1.56 (m, 1H, cyclopentyl), 2.10–2.12 (m, 1H, cyclopentyl), 2.14–2.17 (m, 1H, cyclopentyl), 2.19–2.22 (m, 1H, cyclopentyl), 2.54–2.62 (m, 1H, cyclopentyl), 2.64–2.73 (m, 1H, cyclopentyl), 2.75–2.81 (m, 1H, cyclopentyl), 7.35–7.38 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.9 Hz, $J_{7\text{-}5}$ = 3.3 Hz, 1H, $C_7$H-chrom.), 7.38–7.40 (dd, $J_{5\text{-}6}$ = 8.0, $J_{5\text{-}7}$ = 3.2, 1H, $C_5$H-chrom.), 7.63–7.67 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.9 Hz, $J_{6\text{-}8}$ = 3.3 Hz, 1H, $C_6$H-chrom.), 7.77–7.79 (dd, $J_{8\text{-}7}$ = 7.9, $J_{8\text{-}6}$ = 3.4, 1H, $C_8$H-chrom.), 7.84 (s, 1H, $C_5$H-thiaz.), 8.59 (s, 1H, $C_4$H-chrom.), 11.80 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.65; H, 5.06; N, 12.38.

***3-(2-(2-(Cyclooctylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (12).*** Yellow crystals, 69% yield, mp 143–145°C; $^1$H NMR ($CDCl_3$): δ 1.47–1.50 (m, 2H, cyclooctyl), 1.52–1.58 (m, 4H, cyclooctyl), 1.79–1.84 (m, 4H, cyclooctyl), 2.43–2.46 (m, 4H, cyclooctyl), 7.27–7.30 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.5 Hz, $J_{7\text{-}5}$ = 1.6 Hz, 1H, $C_7$H-chrom.), 7.38–7.40 (dd, $J_{5\text{-}6}$ = 7.4, $J_{5\text{-}7}$ = 1.7, 1H, $C_5$H-chrom.), 7.50–7.54 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.4 Hz, $J_{6\text{-}8}$ = 1.7 Hz, 1H, $C_6$H-chrom.), 7.69–7.71 (dd, $J_{8\text{-}7}$ = 7.4, $J_{8\text{-}6}$= 1.7, 1H, $C_8$H-chrom.), 7.87 (s, 1H, $C_5$H-thiaz.), 8.51 (s, 1H, $C_4$H-chrom.), 11.97 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.33; H, 5.76; N, 11.45.

***3-(2-(2-(1-(Cyclohexyl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (13).*** Yellow crystals, 69% yield, mp 195–200°C; $^1$H NMR (DMSO-$d_6$): δ 1.48–1.52 (m, 2H, cyclohexyl), 1.75–1.79 (m, 4H, cyclohexyl), 2.41–2.45 (m, 4H, cyclohexyl), 7.37–7.41 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.5 Hz, $J_{7\text{-}5}$ = 1.8 Hz, 1H, $C_7$H-chrom.), 7.41–7.43 (dd, $J_{5\text{-}6}$ = 7.6, $J_{5\text{-}7}$ = 1.9, 1H, $C_5$H-chrom.), 7.53–7.57 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.5 Hz, $J_{6\text{-}8}$ = 1.8 Hz, 1H, $C_6$H-chrom.), 7.68–7.70 (dd, $J_{8\text{-}7}$ = 7.9, $J_{8\text{-}6}$ = 1.7, 1H, $C_8$H-chrom.), 7.85 (s, 1H, $C_5$H-thiaz.), 8.54 (s, 1H, $C_4$H-chrom.), 11.75 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.33; H, 5.77; N, 11.45.

***3-(2-(2-(1-(Furan-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (15).*** Light green crystals, 77% yield, mp 218–220°C; $^1$H NMR (DMSO-$d_6$): δ 2.25 (s, 3H, $CH_3$), 6.57–6.58 (d, $J_{3\text{-}4}$ = 1.7 Hz, 1H, $C_3$H-furan), 6.84–6.86 (dd, $J_{4\text{-}5}$ = 3.3 Hz, $J_{4\text{-}3}$ = 1.7 Hz, 1H, $C_4$H-furan), 7.37–7.41 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.6 Hz, $J_{7\text{-}5}$ = 2.9 Hz, 1H, $C_7$H-chrom.), 7.44–7.47 (dd, $J_{5\text{-}6}$ = 7.6 Hz, $J_{5\text{-}7}$ = 2.6 Hz, 1H, $C_5$H-chrom.), 7.61–7.63 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.2 Hz, $J_{6\text{-}8}$ = 2.9 Hz, 1H, $C_6$H-chrom.), 7.73–7.75 (d, $J_{5\text{-}4}$ = 3.3 Hz, 1H, $C_5$H-furan), 7.76 (s, 1H, $C_5$H-thiaz.), 7.80–7.83 (dd, $J_{8\text{-}7}$ = 7.6 Hz, $J_{8\text{-}6}$ = 2.9 Hz, 1H, $C_8$H-chrom.), 8.56 (s, 1H, $C_4$H-chrom.), 11.25 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96. Found: C, 61.56; H, 3.72; N, 11.98.

***3-(2-(2-(Thiophen-2-ylmethylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (16).*** Yellow crystals, 99% yield, mp 230–235°C; $^1$H NMR (DMSO-$d_6$): δ 7.08–7.12 (m, 1H, thiophene), 7.37–7.40 (m, 1H, thiophene), 7.41 (s, 1H, $C_5$H-thiaz.), 7.43–7.48 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 6.8 Hz, $J_{7\text{-}5}$ = 3.4 Hz, 1H, $C_7$H-chrom.), 7.58–7.62 (dd, $J_{5\text{-}6}$ = 6.3 Hz, $J_{5\text{-}7}$ = 3.3 Hz, 1H, $C_5$H-chrom.), 7.63–7.68 (m, 1H, thiophene), 7.75–7.78 (m, 1H, $C_8$H-chrom.), 7.82–7.87 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 6.3 Hz, $J_{6\text{-}8}$ = 3.4 Hz, 1H, $C_6$H-chrom.), 8.24 (s, 1H, CH=N), 8.53 (s, 1H, $C_4$H-chrom.), 12.10 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{17}H_{11}N_3O_2S_2$: C, 57.77; H, 3.14; N, 11.89. Found: C, 57.72; H, 3.15; N, 11.90.

***3-(2-(2-(1-(Thiophen-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (17).*** Yellow crystals, 92% yield, mp 221–223°C; $^1$H NMR (DMSO-$d_6$): δ 2.31 (s, 3H, $CH_3$), 7.03–7.06 (m, 1H, thiophene), 7.37–7.40 (m, 1H, $C_7$H-chrom.), 7.45–7.47 (dd, $J_{5\text{-}6}$ = 7.4 Hz, $J_{5\text{-}7}$ = 2.1 Hz, 1H, $C_5$H-chrom.), 7.52–7.55 (m, 1H, thiophene), 7.57–7.60 (m, 1H, thiophene), 7.61–7.64 (m, 1H, $C_6$H-chrom.), 7.77 (s, 1H, $C_5$H-thiaz.), 7.81–7.84 (dd, $J_{8\text{-}7}$ = 7.4, $J_{8\text{-}6}$ = 2.5, 1H, $C_8$H-chrom.), 8.57 (s, 1H, $C_4$H-chrom.), 11.20 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{17}H_{11}N_3O_2S_2$: C, 57.61; H, 3.41; N, 11.86. Found: C, 57.60; H, 3.42; N, 11.86.

***3-(2-(2-(1-(Pyridin-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (19).*** Orange crystals, 99% yield, mp 258–262°C; $^1$H NMR (DMSO-$d_6$): δ 2.41 (s, 3H, $CH_3$), 7.37–7.40 (m, 1H, $C_7$H-chrom.), 7.42–7.47 (dd, $J_{5\text{-}6}$ = 7.5 Hz, $J_{5\text{-}7}$ = 1.9 Hz, 1H, $C_5$H-chrom.), 7.50–7.54 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.3 Hz, $J_{6\text{-}8}$ = 1.2 Hz, 1H, $C_6$H-chrom.), 7.55–7.61 (m, 1H, $C_5$H-pyridine), 7.81 (s, 1H, $C_5$H-thiaz.), 7.82–7.84 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.3 Hz, 1H, $C_8$H-chrom.), 8.05–8.10 (m, 1H, $C_4$H-pyridine), 8.11–8.13 (m, 1H, $C_3$H-pyridine), 8.58 (s, 1H, $C_4$H-chrom.), 8.63–8.65 (m, 1H, $C_6$H-pyridine), 11.77 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.95; H, 3.88; N, 15.45.

***3-(2-(2-(1-(Pyridin-3-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (20).*** Yellow crystals, 99% yield, mp 257–258°C; $^1$H NMR (DMSO-$d_6$): 7.32–7.35 (m, 1H, $C_7$H-chrom.), 7.38–7.41 (dd, $J_{5\text{-}6}$ = 7.5 Hz, $J_{5\text{-}7}$ = 1.3 Hz, 1H, $C_5$H-chrom.), 7.60–7.64 (m, 1H, $C_6$H-chrom.), 7.80–7.83 (dd, $J_{8\text{-}7}$ = 7.6 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, $C_8$H-chrom.), 7.84 (s, 1H, $C_5$H-thiaz.), 7.85–7.88 (m, 1H, $C_5$H-pyridine), 8.17 (s, 1H, CH=N), 8.48–8.52 (m, 1H, $C_4$H-pyridine), 8.56 (s, 1H, $C_4$H-chrom.), 8.73–8.75 (m, 1H, $C_6$H-pyridine), 9.01 (s, 1H, $C_2$H-pyridine), 12.75 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08. Found: C, 62.07; H, 3.48; N, 16.10.

***3-(2-(2-(1-(Pyridin-3-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (21).*** Yellow crystals, 99% yield, mp 269–270°C; $^1$H NMR (DMSO-$d_6$): δ 2.41 (s, 3H, $CH_3$), 7.40–7.44 (m, 1H, $C_7$H-chrom.), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.8 Hz, $J_{5\text{-}7}$ = 1.7 Hz, 1H, $C_5$H-chrom.), 7.58–7.62 (m, 1H, $C_6$H-chrom.), 7.80–7.83 (dd, $J_{8\text{-}7}$ = 7.7 Hz, $J_{8\text{-}6}$ = 1.7 Hz, 1H, $C_8$H-chrom.), 7.84 (s, 1H, $C_5$H-thiaz.), 7.87–7.90 (m, 1H, $C_5$H-pyridine), 8.52 (s, 1H, $C_4$H-chrom.), 8.55–8.58 (m, 1H, $C_4$H-pyridine), 8.72–8.74 (m, 1H, $C_6$H-pyridine), 9.07 (s, 1H, $C_2$H-pyridine), 11.75 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.98; H, 3.90; N, 15.46.

***3-(2-(2-(1-(Pyridin-4-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (22).*** Orange crystals, 99% yield, mp > 300°C; $^1$H NMR (DMSO-$d_6$): 7.40–7.43 (m, 1H, $C_7$H-chrom.), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.9 Hz, $J_{5\text{-}7}$ = 1.4 Hz, 1H, $C_5$H-chrom.), 7.59–7.63 (m, 1H, $C_6$H-chrom.), 7.85–7.88 (dd, $J_{8\text{-}7}$ = 7.6 Hz, $J_{8\text{-}6}$ = 1.5 Hz, 1H, $C_8$H-chrom.), 7.91 (s, 1H, $C_5$H-thiaz.), 8.07–8.10 (d, $J$ = 4.1 Hz, 2H, pyridine), 8.16 (s, 1H, CH=N), 8.55 (s, 1H, $C_4$H-chrom.), 8.81–8.83 (d, $J$ = 4.5 Hz, 2H, pyridine), 13.00 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08. Found: C, 62.05; H, 3.46; N, 16.08.

***3-(2-(2-(1-(Pyridin-4-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (23).*** Yellow crystals, 98% yield, mp 215–220°C; $^1$H NMR (DMSO-$d_6$): δ 2.41 (s, 3H, $CH_3$), 7.42–7.46 (m, 1H, $C_7$H-chrom.), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.4 Hz, $J_{5\text{-}7}$ = 1.6 Hz, 1H, $C_5$H-chrom.), 7.64–7.68 (m, 1H, $C_6$H-chrom.), 7.76–7.78 (dd, $J_{8\text{-}7}$ = 7.5 Hz, $J_{8\text{-}6}$ = 1.9 Hz, 1H, $C_8$H-chrom.), 7.85 (s, 1H, $C_5$H-thiaz.), 8.45–8.48 (d, $J$ = 5.8 Hz, 2H, pyridine), 8.67 (s, 1H, $C_4$H-chrom.), 8.78–8.81 (d, $J$ = 5.8 Hz, 2H, pyridine), 10.75 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.95; H, 3.98; N, 15.45.

***3-(2-(2-(1-(1H-indol-4-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (24).*** Yellow crystals, 90% yield, mp 248–250°C; $^1$H NMR (DMSO-$d_6$): 6.95–6.98 (t, $J$ = 3.5, 1H, $C_5$H-indole), 7.12–7.15 (t, $J$ = 3.7, 1H, $C_6$H-indole), 7.32 (s, 1H, $C_2$H-indole), 7.39–7.43 (m, $J_{7\text{-}6} = J_{7\text{-}8}$ = 7.3 Hz, $J_{7\text{-}5}$ = 1.7 Hz, 1H, $C_7$H-chrom.), 7.44–7.46 (d, $J$ = 3.7, 1H, $C_7$H-indole), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.3 Hz, $J_{5\text{-}7}$ = 1.7 Hz, 1H, $C_5$H-chrom.), 7.49–7.53 (m, 1H, $C_6$H-chrom.), 7.55 (s, 1H, $C_5$H-thiaz.), 7.58–7.60 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.3 Hz, 1H, $C_8$H-chrom.), 7.62–7.64 (d, $J$ = 3.5, 1H, $C_4$H-indole), 8.16 (s, 1H, CH=N), 8.57 (s, 1H, $C_4$H-chrom.), 10.79 (br s, 1H, NH, $D_2O$ exch.), 11.51 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{21}H_{14}N_4O_2S$: C, 65.27; H, 3.65; N, 14.50. Found: C, 65.25; H, 3.64; N, 14.51.

***3-(2-(2-(1-(Naphthalen-1-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (26).*** Yellow crystals, 70% yield, mp 240–242°C; $^1$H NMR (DMSO-$d_6$): 7.40–7.44 (m, 1H, $C_7$H-chrom.), 7.49–7.51 (dd, $J_{5\text{-}6}$ = 7.8 Hz, $J_{5\text{-}7}$ = 1.5 Hz, 1H, $C_5$H-chrom.), 7.53–7.55 (m, 1H, $C_6$H-chrom.), 7.56 (s, 1H, $C_5$H-thiaz.), 7.57–7.60 (dd, $J_{8\text{-}7}$ = 7.8 Hz, $J_{8\text{-}6}$ = 1.3 Hz, 1H, $C_8$H-chrom.), 7.77–7.81 (m, 2H, naphtalene), 7.82–7.85 (m, 1H, naphtalene), 7.97–8.02 (m, 2H, naphtalene), 8.08–8.10 (m, 1H, naphtalene), 8.12 (s, 1H, CH=N), 8.22–8.24 (m, 1H, naphtalene), 8.60 (s, 1H, $C_4$H-chrom.), 11.54 (br s, 1H, NH, $D_2O$ exch.); *Anal*. Calcd. for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21. Found: C, 70.00; H, 4.15; N, 10.22.

***3-(2-(2-(1-(Naphthalen-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (27).*** Yellow crystals, 91% yield, mp 244–245°C; $^1$H NMR (DMSO-$d_6$): 7.38–7.42 (m, 1H, $C_7$H-chrom.), 7.46–7.48 (dd, $J_{5\text{-}6}$ = 7.4 Hz, $J_{5\text{-}7}$ = 1.8 Hz, 1H, $C_5$H-chrom.), 7.49–7.53 (m, 1H, $C_6$H-chrom.), 7.54 (s, 1H, $C_5$H-thiaz.), 7.58–7.60 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, $C_8$H-chrom.), 7.77–7.82 (m, 2H, naphtalene), 7.90–7.94 (m, 2H, naphtalene), 7.98–8.01 (m, 1H, naphtalene), 8.08–8.10 (m, 1H, naphtalene), 8.21–8.23 (m, 1H, naphtalene), 8.59 (s, 1H, $C_4$H-chrom.), 11.50 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21. Found: C, 70.00; H, 4.15; N, 10.22.

***9-(2-(4-(2H-2-oxo-chromen-3-yl)thiazol-2-yl)hydrazono)-9H-fluorene-2-carboxylic acid (29).*** Yellow crystals, 99% yield, mp 190–192°C; $^1$H NMR (DMSO-$d_6$): 7.28–7.30 (m, 1H, fluorene), 7.38–7.42 (m, 1H, $C_7$H-chrom.), 7.45–7.47 (dd, $J_{5\text{-}6}$ = 7.7 Hz, $J_{5\text{-}7}$ = 1.3 Hz, 1H, $C_5$H-chrom.), 7.49–7.53 (m, 1H, $C_6$H-chrom.), 7.56 (s, 1H, $C_5$H-thiaz.), 7.57–7.61 (m, 2H, fluorene), 7.62–7.64 (dd, $J_{8\text{-}7}$ = 7.4 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, $C_8$H-chrom.), 7.78–7.82 (m, 2H, fluorene), 8.33–8.38 (m, 2H, fluorene), 8.57 (s, 1H, $C_4$H-chrom.), 11.77 (br s, 1H, COOH, $D_2O$ exch.), 12.50 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{26}H_{15}N_3O_4S$: C, 67.09; H, 3.25; N, 9.03. Found: C, 67.13; H, 3.25; N, 9.04.

***3-(2-(2-(1-(Thiazol-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (30).*** Light brown crystals, 99% yield, mp 256–260°C; $^1$H NMR (DMSO-$d_6$): δ 2.43 (s, 3H, $CH_3$), 7.39–7.43 (m, 1H, $C_7$H-chrom.), 7.46–7.48 (dd, $J_{5\text{-}6}$ = 8.0 Hz, $J_{5\text{-}7}$ = 1.6 Hz, 1H, $C_5$H-chrom.), 7.63–7.67 (m, 1H, $C_6$H-chrom.), 7.79 (s, 1H, $C_5$H-thiaz.), 7.83–7.85 (dd, $J_{8\text{-}7}$ = 7.9 Hz, $J_{8\text{-}6}$ = 1.8 Hz, 1H, $C_8$H-chrom.), 7.86–7.89 (m, 2H, thiazole), 8.72 (s, 1H, $C_4$H-chrom.), 11.75 (br s, 1H, NH, $D_2O$ exch.); Anal. Calcd. for $C_{17}H_{12}N_4O_2S_2$: C, 55.42; H, 3.28; N, 15.21. Found: C, 55.47; H, 3.28; N, 15.24.

**Procedure for the synthesis of derivative 31.** 3-α-Bromoacetyl coumarin (50 mmol) was dissolved in 2-propanol and reacted with an equimolar amount of thiosemicarbazide at room temperature under magnetic stirring for 4 h. The precipitate was filtered and dried to give intermediate **31**.

***H. pylori* culture.** The *H. pylori* strains used in this study were maintained at −80°C in Wilkins Chalgren broth with 10% (v/v) horse serum (Seromed) and 20% (v/v) glycerol (Merck) until required for the experiments. Before being used the bacteria were subcultured twice on Columbia agar base (Difco Laboratories) supplemented with 10% horse serum and 0.25% Bacto yeast extract (Difco). Plates were incubated for 72 h at 37°C in an atmosphere of 10% $CO_2$ in a gas incubator.

**Anti-*Helicobacter pylori* activity.** Antimicrobial activity against *H. pylori* was determined by the agar dilution standard method [19]. The strains were inoculated onto Columbia agar base (Difco) supplemented with 10% horse serum and 0.25%

bacto yeast extract (Difco) and were incubated for 72 h at 37°C in an atmosphere of 10% $CO_2$ in a gas incubator. Colonies were suspended in Wilkins Chalgren broth to achieve a turbidity equivalent to 0.5 Mc Farland. Columbia agar plates with 10% horse serum were prepared by using twofold dilutions of the antimicrobial agents (128–0.0039 μg/mL). The inoculum was delivered to the surface of the agar plates with a Steer's replicator to obtain $\sim 5 \times 10^5$ CFU per spot. Growth control plates without antibiotics were inoculated in each series of tests. All plates were incubated at 37°C for 72 h under conditions (10% $CO_2$ in a gas incubator). The minimal inhibitory concentration was defined as the lowest concentration of drug inhibiting visible bacterial growth.

## REFERENCES AND NOTES

[1] Hunt, R. H. Scand J Gastroenterol 1996, 220, 3.

[2] Bardhan, P. K. Clin Infect Dis 1997, 25, 973.

[3] IARC. IARC monographs on the evaluation of carcinogenic risks to humans, Vol. 61; IARC: Lyon, 1994; pp 177–240.

[4] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Scaltrito, M. M.; Brenciaglia, M. I. Eur J Med Chem 2006, 41, 208.

[5] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Zicari, A.; Scaltrito, M. M.; Sisto, F. Bioorg Med Chem Lett 2007, 17, 3065.

[6] Kawase, M.; Motohashi, N. Curr Med Chem Anti-Infect Agents 2004, 3, 89.

[7] Chimenti, F.; Carradori, S.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Bizzarri, B. J Heterocycl Chem 2009, 46, 575.

[8] Raghu, M.; Nagaraj, A.; Reddy, Ch. S. J Heterocycl Chem 2009, 46, 261.

[9] Rao, V. R.; Reddy, M. M. M. Indian J Heterocycl Chem 2003, 13, 69.

[10] Kalluraya, B.; Isloor, A. M.; Shenoy, S. Indian J Heterocycl Chem 2001, 11, 159.

[11] Kalluraya, B.; Vishwanatha, P.; Isloor, A. M.; Rai, G.; Kotian, M. Bollettino Chimico Farmaceutico 2000, 139, 263.

[12] Rao, V. R.; Kumar, V. R.; Vardhan, V. A. Phosphorus Sulfur 1999, 152, 257.

[13] Srimanth, K.; Rao, V. R. Indian J Chem B 1999, 38B, 473.

[14] Gursoy, A. J Fac Pharm Istanbul U 1974, 10, 57.

[15] Gursoy, A.; Eczacilik F. J Fac Pharm Istanbul U 1973, 9, 51.

[16] Rao, V. R.; Srimanth, K. J Chem Res S 2002, 9, 420.

[17] Benassi, R.; Benedetti, A.; Taddei, F.; Cappelletti, R.; Nardi, D.; Tajana, A. Org Magn Reson 1982, 20, 26.

[18] Cirilli, R.; Ferretti, R.; La Torre, F.; Secci, D.; Bolasco, A.; Carradori, S.; Pierini, M. J Chromatogr A 2007, 1172, 160.

[19] National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic bacteria. Approved standard M11-A6, 6th ed.; National Committee for Clinical Laboratory Standards: Villanova, PA, 2004.

# Synthesis of Novel Functionalized 4-Aza-2,3-didehydropodophyllotoxin Derivatives with Potential Antitumor Activity



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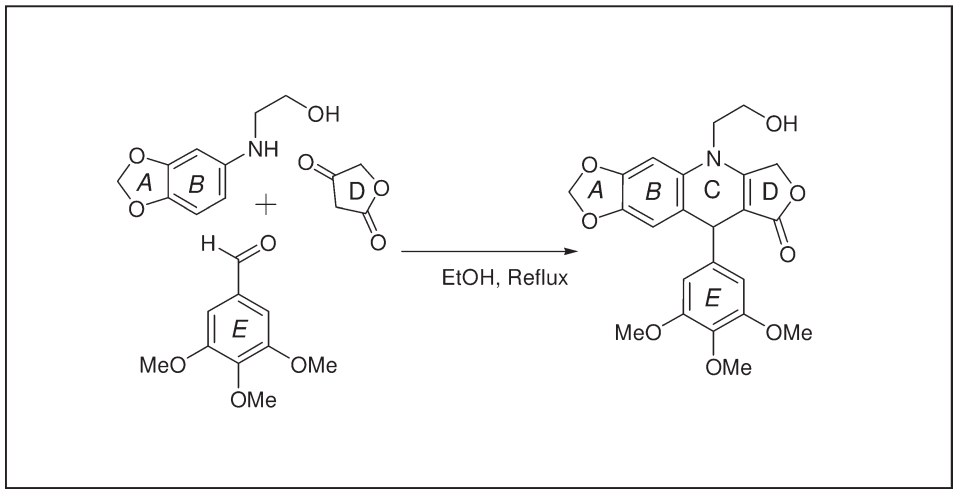


Novel arylamino alcohols were synthesized and these alcohols were used to prepare 12 novel *N*-(2-hydroxy-ethyl)-2,3-didehydroazapodophyllotoxins, in one step, by simple reflux in ethanol. Isolated yields in the range of 50–70% were obtained.

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## INTRODUCTION

Podophyllotoxin (Fig. 1) is the starting material for the semi-synthesis of the anticancer drugs etoposide, etopophos and tenoposide. These antineoplastic pharmaceuticals block DNA topoisomerase II and have been used for the treatment of small and large cell lung, refractory testicular, stomach and pancreatic cancers, as well as myeloid leukemias [1a]. The podophyllotoxin core structure possesses a dual mode of action, i.e., inhibition of DNA topoisomerase II and of microtubule assembly through binding to tubulin, both of which are considered to be responsible for its antitumor activity. Podophyllotoxin is the precursor to a new derivative, CPH-82 or Reumacon®, which is being used to treat active rheumatoid or psoriatic arthritis in Europe. It is used to reduce inflammation. Podophyllotoxin is also the precursor of other derivatives used for the drug development of psoriasis and malaria [1b]. Several podophyllotoxin preparations are in the market for dermatological use to treat genital warts, e.g., imiquimod. Several new members of the podophyllotoxin derivatives have emerged as potentially superior chemotherapeutics, displaying improved water solubility and bioavailability, such as Nippon-Kayaku's NK-611 [2], GL-331 and Taiho's TOP-53 [3,4]. Podophyllotoxin derivatives also display anti-HIV-1 [5,6] and antibacterial [7] activities.

Currently, the commercial sources of podophyllotoxin are the rhizomes and roots of plants, such as *Podophyllum peltatum, Podophyllum emodi,* and American mayapple. *Podophyllum emodi* is an endangered species from the Himalayas [8]. Synthesis of podophyllotoxin is a multistep process, involving multicomponents and expensive reagents. The latest reported method for the synthesis of podophyllotoxin involves 5 steps and 20 reagents with 7.6% overall yield [9]. This tedious synthesis limits the new derivatives research of podophyllotoxin core. Podophyllotoxin contains 5 rings denoted as A, B, C, D, and E (Fig. 1). The basic structure of podophyllotoxin with rings A, B, C, D, and E was modified in different but limited ways since decades, in search of new chemical entities for drug discovery [10,11]. Derivatives of 4-aza-2,3-didehydropodophyllotoxin derivatives have also been synthesized as a strategy to develop podophyllotoxin analogs aimed at improving biological activity (Fig. 2) [12–14]. Some of those derivatives showed twice the cytotoxicity against P-388 leukemia cells as compared with podophyllotoxin [13].

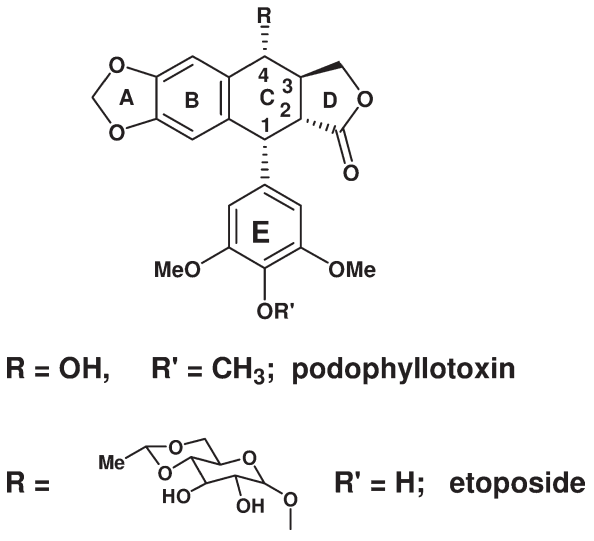



**Figure 1.** Structures of podophyllotoxin and etoposide.

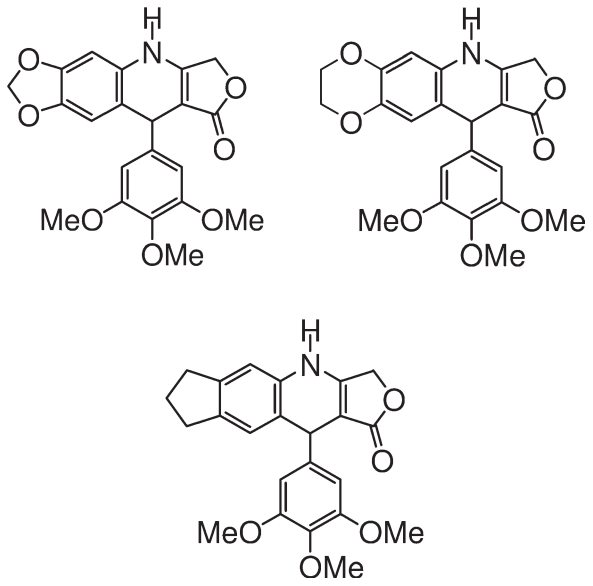



**Figure 2.** Structures of 4-aza-2,3-didehydropodo-phyllotoxin derivatives [13].

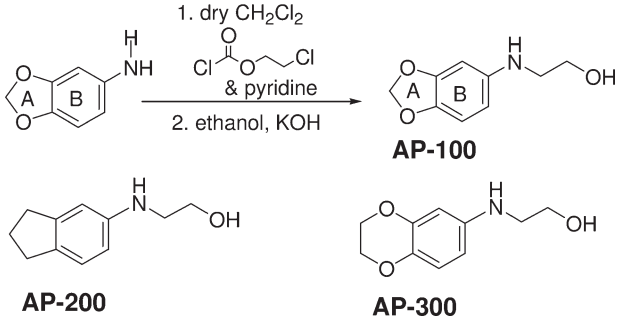
Many cytotoxic drugs have been conjugated to carriers for the selective targeting of organs and tissues [15]. To our best knowledge, no podophyllotoxin derivative has been conjugated to carriers for selective tissue targeting. In this work we report a facile and high-yielding synthetic procedure for the preparation of *N*-(2-hydroxy-ethyl)-2,3-didehydroazapodophyllotoxin derivatives with the potential to be conjugated to tissue-targeting carriers.

## RESULTS AND DISCUSSION

Although there is an N—H bond at position 4 in the ''C'' ring of 4-aza-2,3-didehydropodophyllotoxin derivatives, nucleophilic substitution to electrophiles, such as acetic anhydride or an acyl chloride to form amides was not successful in our laboratory. Furthermore, attempts to use a strong base such as NaH or LDA to abstract the proton of the amine was not effective. Therefore, for the synthesis and biological activity studies of OH-functionalized derivatives of 4-aza-2,3-didehydropodophyllotoxin at the N atom in ring ''C,'' we synthesized some new arylamino alcohols (**AP-100** to **AP-300**, Scheme 1) to prepare N-(2-hydroxy-ethyl)-2,3-didehydroazapodophyllotoxins in one step, by simple refluxing in ethanol as reported previously [14]. The novelty in our work is the preparation of hydroxy-functionalized 2,3-didehydroazapodophyllotoxin derivatives, in two simple steps, which have a functional group which is available for further modifications. The novel arylamino alcohols were prepared by reacting commercially-available substituted anilines with 2-chloroethylchloroformate in dry dichloromethane in the presence of pyridine followed by reacting with KOH in ethanol (Scheme 1). These arylamino alcohols are not stable for long periods of time at room temperature and, thus, were synthesized freshly before used. Compounds **AP-101** to **AP-304** were prepared following the procedure reported by Tratrat et. al. [14] by reacting novel arylamino alcohol with tetronic acid and substituted aldehyde in ethanol (Fig. 3). Isolated yields were in the order of 60%. This is a straightforward one-step multicomponent synthesis, which involves simple isolation of the products by filtration and recrystallization. Isolated yields were in the 50–70% range.

Structures were corroborated with the help of $^{1}$H, COSY, $^{13}$C, DEPT45, DEPT90, DEPT135, HETCOR NMR, as well as $^{1}$H-NMR coupled with deuterium exchange experiments, FTIR spectroscopy, HRMS and elemental analyses.

**Scheme 1.** Synthesis of arylamino alcohols. Structures of three examples of *N*-(2-hydroxy-ethyl)-2,3-didehydroazapodophyllotoxins are shown to indicate the structural variation of the arylamino alcohol precursor used.



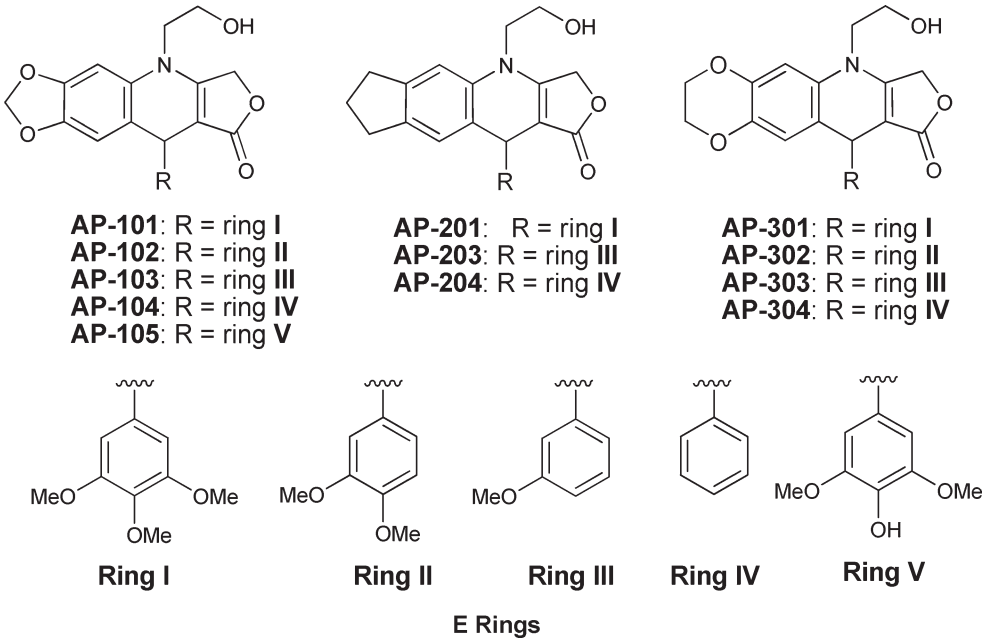



**Figure 3.** Structures of 4-aza-2,3-didehydropodo-phyllotoxin derivatives prepared in this work.

Compounds **AP-101** to **AP-304** were prepared following the procedure reported by Tratrat et al. [14] by reacting novel arylamino alcohol with tetronic acid and substituted aldehyde in ethanol (Fig. 3). The mechanism for the formation of **AP-101** is shown in Scheme 2. When the final ring closure is completed, the carbon atom, here assigned as **9**, has a unique $^{13}$C-NMR chemical shift of ca. 39 ppm (Fig. 5). The proton attached to this carbon also has a unique chemical shift (s, 1H, 4.8 ppm, Fig. 4). Both types of chemical shifts for this carbon and proton were found uniform in the entire azapodophyllotoxin derivatives synthesized in this work. Some other specific carbons also corroborate the structure of the cyclisized scaffold, i.e. **8a** at 95 ppm and **5a** at 160 ppm. These chemical shifts were also uniformly found in the entire series of the azapodophyllotoxins synthesized in this work.

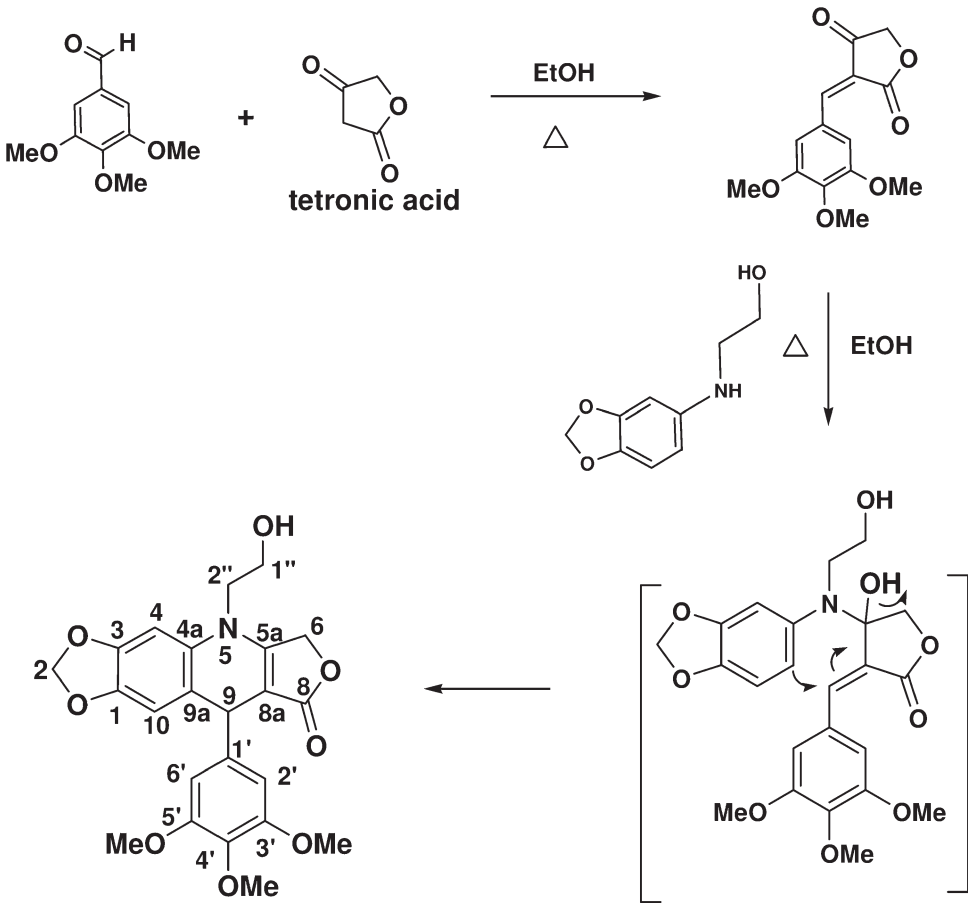
HETCOR NMR studies reveal other interesting findings (Fig. 5). Protons at carbon **2″** of all the azapodophyllotoxin derivatives are expected to be equivalent but these are not. One of them appears at ~3.6 ppm and the other at ~3.8 ppm and the latter may be interacting with protons at carbons **6** (Fig. 5). In fact, protons at position 6 are showing a broad peak probably due to that interaction. Also, protons at carbon **1″** are expected to be splitted into a triplet by two equal protons. However, these are unusually shaped as a doublet of doublets with J values of ~22 Hz and ~15 Hz, as protons at **2″** are not equivalent.

Itokawa and Takeya [12] have previously shown that (-)-4-aza-4-deoxypodophyllotoxin, which possess exactly the same enantiomeric form like podophyllotoxin, showed the same $IC_{50}$ value of 0.0050 μg/mL against P388 leukemia cells. But interestingly, when strain between ring ''C'' and ''D'' was eliminated in 4-aza-2,3-didehydropodophyllotoxin analogue by dehydration at the 2,3 positions, the enhanced $IC_{50}$ against P388 leukemia cells was observed, i.e., 0.0018 μg/mL as compare to 0.0043 μg/mL for podophyllotoxin [13]. Therefore, the synthesis of 4-aza-2,3-didehydro podophyllotoxin analogues with hydroxyl functionality, as in podophyllotoxin, has an excellent potential for the development of new drug entities not only as anti-tumor drugs but also for the treatment of psoriatic arthritis, HIV-1, genital warts, malaria, and bacterial infections as well.

In this work we have further modified the 4-aza-2,3-didehydropodophyllotoxin core by functionalizing position 4 at the ''C'' ring in a similar fashion as that occurring in podophyllotoxin derivatives. Libraries of these new heterocyclic compounds should be accessible by this straightforward one-step multicomponent synthesis, which involves simple isolation of the products by filtration and recrystallization and requires no further purification steps. Although the new compounds are racemic, we hope that the separation and testing of individual enantiomers may lead to more potent compounds.

This work will open a new area of 4-aza-2,3-didehydropodophyllotoxin analogues having almost similar structural functionalities to podophyllotoxin and will help to develop a library of new bioactive chemical entities which could be conjugated to carriers for tissue targeting. Whether these compounds may exert their

**Scheme 2.** Synthesis of **AP-101**.




cytotoxic effect through podophyllotoxin-like antitubulin mechanism, target topoisomerase II, or have a totally independent mode of action, constitutes the subject of further investigation, which will be reported in due course.

## EXPERIMENTAL

Melting points were determined on a MEL-TEMP instrument and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR Spectrometer on ATS mode. $^{1}$H, COSY, $^{13}$C, DEPT45, DEPT90, DEPT135 and HETCOR NMR spectra were measured on a Bruker 400 Ultra shield Spectrometer using DMSO-$d_6$ as solvent. All chemical shifts are reported in parts per million relative to tetramethylsilane. Coupling constants ($J$) are reported in Hz. HRMS analyses were performed at the University of Florida (Gainesville) Mass Spectrometry facility. Absorption spectra were obtained in DMSO, using DMSO as blank, with an Agilent 8453 absorption spectrometer. Elemental analysis were performed at Atlanta Microlab GA.

**Synthetic procedure for compounds AP-100 to AP-300.**

***2-[(3,4-Methylenedioxy)anilino]ethanol (AP-100).*** To a solution of 3,4-(-methylenedioxy)-aniline (5 g, 35.37 mmol) in dry dichloromethane (100 mL) and pyridine (3.6 mL, 44.57 mmol) at room temperature 2-chloroethylchloroformate (3.8 mL, 35.37 mmol) was slowly added. The mixture was stirred at room temperature (25°C) for 2.5 h and washed with water (5.0 mL × 4), dried over anhydrous magnesium sulphate and concentrated under vacuum. The residue was dissolved in ethanol (100 mL), treated with potassium hydroxide (8.6 g, 141.48 mmol) and heated at 90°C for 4 h. The mixture was dried under vacuum and the residue was dissolved in dichloromethane (150 mL), the precipitate was washed with dichloromethane twice (25 mL each). The combined organic phases were washed with water (5× mL) and brine. The organic phase was dried over anhydrous magnesium sulphate and concentrated under vacuum. The solid was purified by silica gel (120 g) flash chromatography with hexane-ethylacetate gradient to give compound **AP-100** (3.89 g, 61%) as brown needles. MP: 53–54°C, IR ($cm^{-1}$); 3283, 3162, 2869, 16360, 1496, 1232, 1190, 1122, 1073, 1031, 931, 883, 847, 782, 720, 692; $^{1}$H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) 3.01 (q, $J$ = 11.84 Hz and 5.9 Hz, 2H), 3.54 (q, $J$ = 11.64 Hz and 5.78 Hz, 2H), 4.64 (t, $J$ = 5.71 Hz, 1H), 5.17 (t, $J$ = 5.76 Hz, 1H), 5.82 (s, 2H), 6.00 (dd, $J$ = 8.58 Hz and 2.16 Hz, 1H), 6.30 (d, $J$ = 2Hz, 1H), 6.65 (d, $J$ = 8.58 Hz, 1H); $^{13}$C-NMR (DMSO-*d*6, 100 MHz): δ 59.42, 94.85, 99.65, 102.88, 108.18, 137.63, 144.66, 147.51; HRMS *m*/*z*: 182.0818 found (Calculated for $C_9H_{11}NO_3$, $[M+H]^+$ requires 182.0812).

***2-(Indan-5-ylamino)-ethanol (AP-200).*** 2-(Indan-5-ylamino)-ethanol (AP-200) was synthesized from a similar reaction

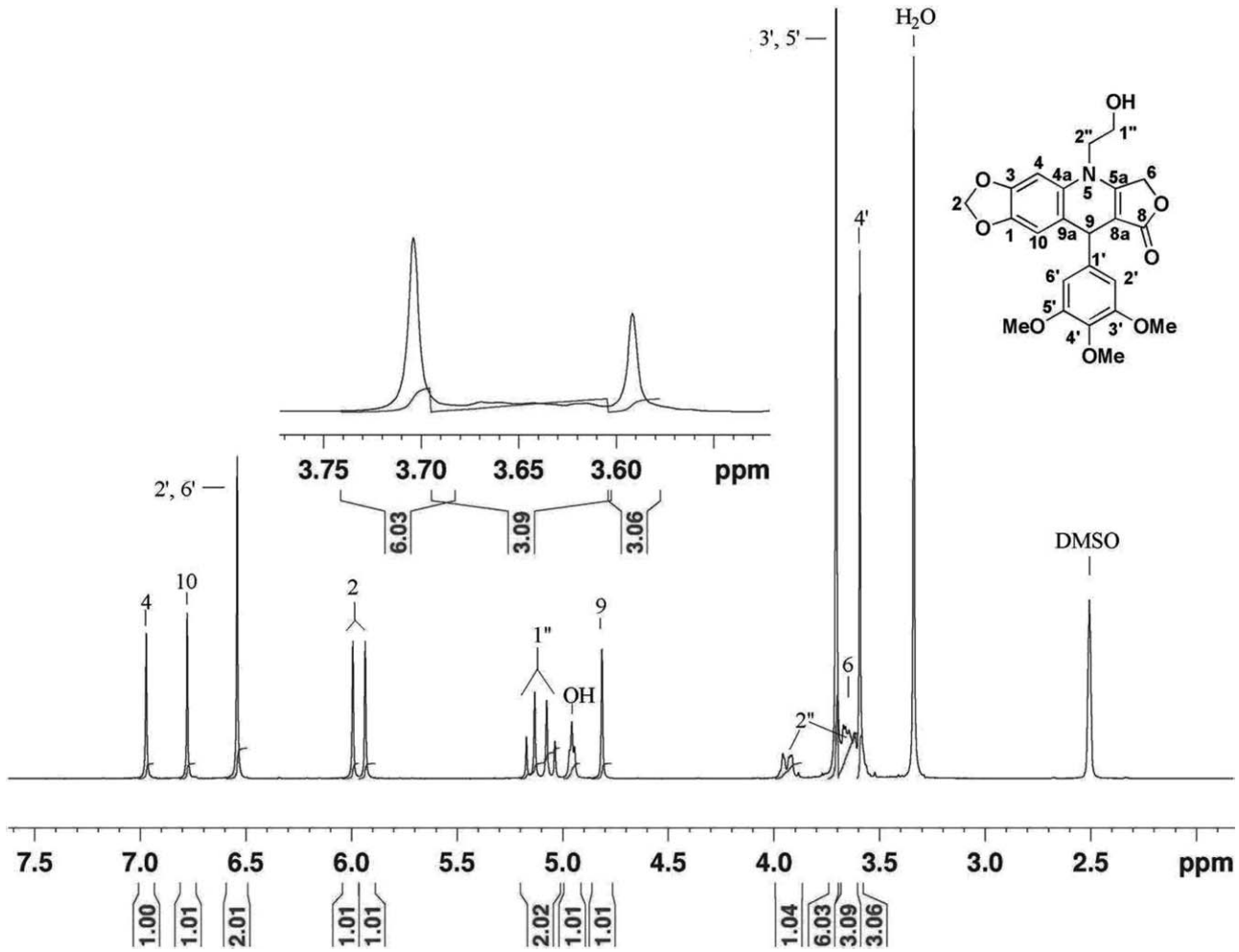



**Figure 4.** $^{1}$H-NMR spectrum of AP-101 in DMSO-$d_6$.

between 5-aminoindan (9.04 gm, 64.50 mmol) and 2-chloroethylchloroformate (6.86 mL, 64.50 mmol). After flash chromatography, **AP-200** was obtained (6.79 g, 59% yield) as a dark brown oil showing: IR ($cm^{-1}$); 3345, 2940, 2837, 1615, 1494, 1456, 1329, 1290, 1260, 1212, 1157, 1119, 1058, 949, 840, 802, 703; $^{1}$H-NMR ($CDCl_3$, 400 MHz),: δ (ppm) 2.01 (m, 2H), 2.78 (q, $J$ = 15.43 Hz, and 7.72 Hz, 4H), 3.20 (t, $J$ = 5.20 Hz, 2H), 3.27 (s, 2H), 3.74 (t, $J$ = 5.22 Hz, 2H), 6.42 (dd, $J$ = 8.03 Hz and 2.27 Hz, 1H), 6.53 (s, 1H), and 6.99 (d, $J$ = 8.11 Hz, 1H); $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 25.44, 31.69, 32.87, 46.56, 60.91, 109.43, 111.65, 124.53, 133.56, 145.22, 146.58; HRMS *m/z*: 178.1229 found (Calculated for $C_{11}H_{15}NO$, $[M+H]^+$ requires 178.1226).

***2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-ethanol (AP-300).*** 2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-ethanol (AP-300) was synthesized from a similar reaction between 1,4-benzodioxan-6-amine (9.33 gm, 61.11 mmol) and 2-chloroethylchloroformate (6.5 mL, 61.11 mmol). The solid crude product was purified by silica gel (200 g) flash chromatography with hexane-ethyl acetate gradient to give the title compound (7.68 g, 64%) as a dark brown oil showing IR ($cm^{-1}$); 3373, 2928, 2876, 1625, 1595, 1502, 1460, 1325, 1276, 1205, 1171, 1062, 961, 919, 883, 828, 794, 745; $^{1}$H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.10 (t, $J$ = 5.19 Hz, 2H), 2.80 (m, 4H), 3.20 (t, 2H), 3.27 (br, 2H), 3.74 (t, $J$ = 5.18 Hz, 2H), 6.43 (d, $J$ = 2.0 Hz), 6.65 (d, $J$ = 8.58 Hz, 1H); $^{13}$C-NMR ($CDCl_3$, 100 MHz): δ 47.00, 61.09, 64.21, 64.76, 102.21, 107.37, 117.69, 136.03, 143.15, 144.06; HRMS *m/z*: 196.0968 found (calculated for $C_{10}H_{13}NO_3$, $[M+H]^+$ requires 196.0980).

**General synthesis of 4-aza-2,3-didehydropodophyllotoxin derivatives.** An equimolar mixture of tetronic acid, a substituted aniline and an aromatic aldehyde dissolved in the minimum volume of ethanol was refluxed for 30 to 90 min. After cooling, the precipitate was filtered off, washed with minimal cold ethanol and then recrystallized from ethanol.

***5-(2-Hydroxyethyl)-9-(3,4,5-trimethoxyphenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5H)-one (AP-101).*** Reaction time: 30 min. The product was washed with cold ethanol and dried under high vacuum, recrystallization from ethanol yielded 70% as a white crystalline powder, MP: 241–243°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3498, 2936, 1727, 1652, 1589, 1504, 1476, 1320, 1232, 1192, 1117, 1033, 1011, 931, 787, 760, 686; 1 H-NMR (DMSO-$d_6$, 400 MHz): δ 3.59 (s, 3H, 4′C—$OCH_3$), 3.64 (m, 3H, 6C—H and 2″C—H), 3.70 (s, 6H, 3′-$OCH_3$ and 5′-$OCH_3$) 3.92 (m,1H, 2″C—H), 4.81 (s, 1H, 9C—H), 4.95 (t, 1H, OH),

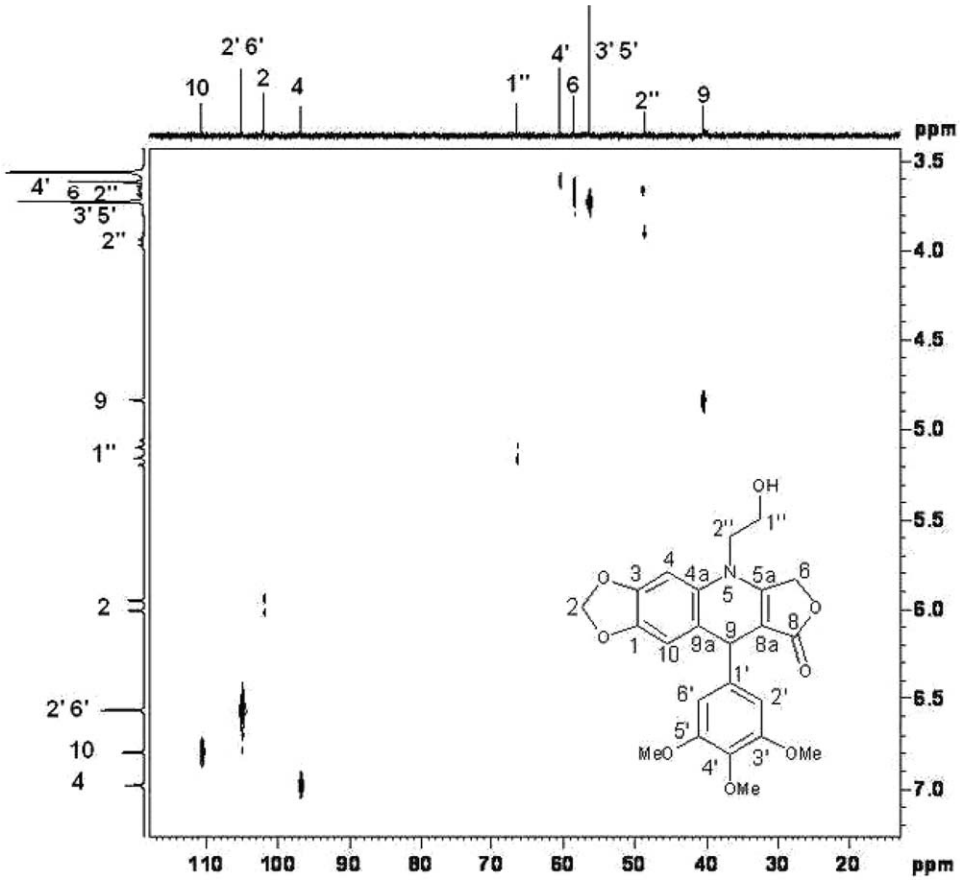



**Figure 5.** HETCOR spectrum of AP-101.

5.07 (d, $J$ = 15.89 Hz, 1H, 1″C—H), 5.13 (d, $J$ = 15.89 Hz, 1H, 1″C—H), 5.99 (d, $J$ = 22.75 Hz, 2H, 2C—H), 6.519 (s, 2H, 2′C—H and 6′-H), 6.77 (s, 1H, 10C—H), 6.97(s, 1H, 4C—H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 40.34, 48.44, 56.17, 56.29, 58.47, 60.22, 66.15, 95.23, 96.59, 101.73, 104.95, 104.95, 110.37, 119.80, 131.13, 136.38, 143.40, 143.62, 147.29, 153.19, 160.99, 172.67;HRMS m/z: 442.1491 found (calculated for $C_{23}H_{23}NO_8$, [M+H]+ requires 442.1496); *Anal*. Calcd. For [$C_{23}H_{23}NO_8$]; C, 62.58; H, 5.25; N, 3.17; O, 29.00. Found C, 62.55; H, 5.26; N, 3.20; O, 29.03

***9-(3,4-Dimethoxyphenyl)-5-(2-hydroxyethyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5H)-one (AP-102).*** Reaction time: 30 min. The crude product was washed with cold ethanol and dried under high vacuum. Recrystallization from ethanol yielded 63% as a white crystalline powder; MP: 204–205°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, cm$^{-1}$); 3418, 2929, 1742, 1654, 1593, 1508, 1473, 1425, 1363, 1327, 1230, 1209, 1122, 1040, 1014, 989, 876, 847, 808, 759, 680; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 3.68 (m, 9H, 2′,3′C—$OCH_3$, 1″C—H and 2″C—H), 3.85 (m,1H, 2″C—H), 4.81 (s, 1H, 9C—H), 4.99 (t, 1H, OH), 5.07 (d, $J$ = 15.68 Hz, 1H, 1″C—H), 5.14 (d, $J$ = 15.68 Hz, 1H, 1″C—H), 5.92 (s, 1H, 2C—H), 5.98 (s, 1H, 2C—H), 6.68 (s, 1H, 10C—H), 6.69 (dd, 1H $J$ = 8.37 Hz and 2.4 Hz, 6′C—H), 6.79 (d, $J$ = 8.15 Hz, 1H, 5′C—H ) 6.86 (d, $J$ = 7.5Hz, 1H, 2′C—H), 6.95 (s, 1H,4C—H); $^{13}$C-NMR (DMSO- $d_6$, 100 MHz): δ 39.10, 47.86, 55.17, 55.27, 57.80, 65.48, 94.85, 95.89, 101.09, 109.85, 111.14, 111.60, 119.04, 119.39, 130.62, 139.88, 146.58, 147.10, 148.40, 160.04, 172.07; HRMS *m/z*: 412.1383 found (calculated for $C_{22}H_{21}NO_7$, [M+H]$^+$ requires 412.1391). *Anal*. Calcd. For [$C_{22}H_{21}$NO7]; C, 63.23; H, 5.14; N, 3.40. Found C, 64.19; H, 5.04; N, 3.38.

***5-(2-Hydroxyethyl)-9-(3-methoxyphenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5H)-one (AP-103).*** Reaction time: 30 min. The crude product was washed with cold ethanol and dried under high vacuum. A white crystalline powder was obtained, which was purified by recrystallization from ethanol; yield 54%, MP: 140–141°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, cm$^{-1}$); 3422, 2924, 1743, 1654, 1593, 1507, 1473, 1425, 1327, 1230, 1209, 1121, 1041, 1014, 988, 876, 848, 808, 759, 680; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 3.68 (m, 6H, 3′C—$OCH_3$, 1″C—H and 2″C—H), 3.85 (m,1H, 2″C—H), 4.87 (s, 1H, 9C—H), 5.01 (t, $J$ = 4.85 Hz, 1H, OH), 5.03 (d, $J$ = 15.48 Hz, 1H, 1″C—H), 5.10 (d, $J$ = 15.48 Hz, 1H, 1″C—H), 5.92 (s, 1H, 2C—H), 5.98 (s, 1H, 2C—H), 6.65 (s, 1H, 2′C—H), 6.71 (br, 1H, 10C—H), 6.78 (d, $J$ = 8.26Hz, 1H, 4′C—H), 6.78 (d, $J$ = 8.15 Hz, 1H, 5′C—H ) 6.80 (s, 1H, 6′C—H), 6.95 (s, 1H,4C—H), 7.15(t, $J$ = 8.08Hz, 1H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 39.95, 48.12, 54.85, 57.96, 65.72, 94.77, 96.18, 101.33, 110.04, 111.30, 113.49, 119.04, 119.76, 129.30, 130.99, 143.16, 146.88, 148.66, 159.23, 160.39, 172.18; HRMS *m/z*: 382.1288 found (calculated for $C_{21}H_{19}NO_6$, [M+H]$^+$ requires 382.1285). *Anal*. Calcd. For

$[C_{21}H_{19}NO6]$; C, 66.13; H, 5.02; N, 3.67. Found C, 66.09; H, 5.00; N, 3.81.

***5-(2-Hydroxyethyl)-9-phenyl-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5H)-one (AP-104).*** Reaction time: 30 min. The crude product was washed with cold ethanol and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol; yield 62 %, MP: 180–181°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3278, 2880, 1709, 1641, 1480, 1438, 1369, 1339, 1242, 1198, 1020, 936, 876, 742, 700; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 3.64 (m, 3H, 1″C—H and 2″C—H), 3.79 (m,1H, 2″C—H), 4.88 (s, 1H, 9C—H), 5.01 (t, $J$ = 4.84 Hz, 1H, OH), 5.05 (br 2H, 1″C—H), 5.90 (s, 1H, 2C—H), 5.96 (s, 1H, 2C—H), 6.59 (s, 1H, 10C—H), 6.94 (s, 1H, 4C—H) 7.14 (br, 1H, 4′C—H), 7.21(br, 4H, 2′C—H, 3′C—H, 5′C—H and 6′C—H); $^{13}$C-NMR (DMSO- $d_6$, 100 MHz): δ 40.43, 48.62, 58.43, 66.24, 95.35, 96.71, 101.83, 110.60, 119.65, 126.75, 127.99, 128.77, 131.54, 143.67, 147.36, 147.60, 160.88, 172.69; HRMS *m/z*: 352.1178 found (calculated for $C_{20}H_{17}NO_5$, $[M+H]^+$ requires 352.1179).

***9-(4-Hydroxy-3,5-dimethoxyphenyl)-5-(2-hydroxyethyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5H)-one (AP-105).*** Reaction time: 30 min. The crude product was washed with cold ethanol and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol; yield 69%, MP: 237–238°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3551, 3345, 2940, 1708, 1638, 1605, 1509, 1481, 1456, 1367, 1322, 1242, 1198, 1108, 1068, 1016, 919, 860, 818, 763, 687; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 3.66 (m, 9H, 5′and 3′C—$OCH_3$, 1″C—H and 2″C—H), 3.92 (m, 1H, 2″C—H), 4.75 (s, 1H, 9C—H), 4.95 (t, $J$ = 4.85 Hz, 1H, OH), 5.02 (d, $J$ = 15.43 Hz, 1H, 1″C—H), 5.12 (d, $J$ = 15.43 Hz, 1H, 1″C—H), 5.92 (s, 1H, 2C—H), 5.98 (s, 1H, 2C—H), 6.48 (s, 2H, 2′and 6′ C—H), 6.74 (s, 1H, 10C—H), 6.95 (s, 1H,4C—H), 8.10(s, 1H, 4′C—OH); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 40.16, 48.50, 56.40, 58.53, 66.15, 95.50, 96.56, 101.75, 105.27, 110.47, 120.35, 131.13, 134.58, 138.19, 143.60, 147.21, 148.32, 160.86, 172.79; HRMS *m/z*: 428.1345 found (calculated for $C_{22}H_{21}NO_8$, $[M+H]^+$ requires 428.1340).; *Anal*. Calcd. For $[C_{22}H_{21}NO_8]$; C, 61.82; H, 4.95; N, 3.28. Found C, 61.74; H, 4.84; N, 3.24.

***4-(2-Hydroxyethyl)-10-(3,4,5-trimethoxyphenyl)-3,4,6,7,8,10-hexahydro-1H-cyclopenta[g]furo[3,4-b]quinolin-1-one (AP-201).*** Reaction time: 30 min. The crude product was washed with 1:1 ethylacetate-hexane (V/V) and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol: ethylacetate mixture 1:1; yield 49%, MP: 153–154°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3422, 2929, 1743, 1655, 1620, 1593, 1508, 1473, 1426, 1363, 1328, 1293, 1231, 1210, 1123, 1066, 1043, 1015, 989, 876, 848, 823, 808, 791, 759, 744, 681; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 1.96 (m, 2H, 7C—H), 2.71 (m, 2H, 6C—H), 2.81 (m, 2H, 8C—H), 3.58 (s, 3H, 4′-$OCH_3$), 3.66 (m, 9H, 3′and 5′, C—$OCH_3$, 1″C—H and 2″C—H), 3.98 (m, 1H, 2″CH), 4.86 (s, 1H, 10C—H), 4.98 (t, $J$ = 4.85 Hz, 1H, OH), 5.05 (d, $J$ = 15.98 Hz, 1H, 1″C—H), 5.15 (d, $J$ = 15.98 Hz, 1H, 1″C—H), 6.53 (s, 2H, 2′ and 6′ C—H), 7.06 (s, 1H, 9C—H), 7.10 (s, 1H, 5C—H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 25.17, 31.52, 32.32, 39.94, 47.68, 55.74, 55.74, 57.83, 59.77, 65.73, 95.29, 104.53, 109.92, 124.76, 126.33, 134.48, 135.85, 138.83, 143.32, 143.33, 152.73, 160.81, 172.27; HRMS *m/z*: 438.1903 found (calculated for $C_{25}H_{27}NO_6$, $[M+H]^+$ requires 438.1911). *Anal*. Calcd. For $[C_{25}H_{27}NO_6]$; C, 68.63; H, 6.22; N, 3.20. Found C, 68.51; H, 6.31; N, 3.16.

***4-(2-Hydroxyethyl)-10-(3-methoxyphenyl)-3,4,6,7,8,10-hexahydro-1H-cyclopenta[g]furo[3,4-b]quinolin-1-one (AP-203).*** Reaction time: 30 min. The crude product was washed with 1:1 ethylacetate-hexane (V/V) and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol: ethylacetate mixture 1:1; yield 51%, MP: 158–159°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3378, 2933, 1718, 1643, 1597, 1476, 1431, 1366, 1347, 1321, 1262, 1243, 1202, 1172, 1161, 1095, 1020, 1001, 877, 845, 813, 780, 765, 746, 699, 671; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 1.95 (m, 2H, 7C—H), 2.68 (m, 2H, 6C—H), 2.81 (m, 2H, 8C—H), 3.66 (m, 6H, 3′C—$OCH_3$, 1″C—H and 2″C—H one), 3.84 (m, 1H, 2″C—H one), 4.90 (s, 1H, 10C—H), 5.01 (t, $J$ = 4.85 Hz, 1H, OH), 5.04 (d, $J$ = 13.32 Hz, 1H, 1″C—H), 5.12 (d, $J$ = 13.32 Hz, 1H, 1″C—H), 6.69 (m, 1H, 4′C—H), 6.78 (m, 2H, 2′and 6′C—H), 6.95 (s, 1H, 9C—H), 7.08 (s, 1H, 5C—H), 7.12(t, 1H, 5′C—H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 25.66, 31.98, 32.82, 40.23, 48.32, 55.33, 58.25, 66.22, 95.77, 110.42, 111.57, 114.15, 120.35, 124.96, 126.99, 129.79, 135.26, 139.28, 143.89, 149.46, 159.68, 161.08, 172.69; HRMS *m/z*: 378.1700 found (calculated for $C_{23}H_{23}NO_4$, $[M+H]^+$ requires 378.1700). *Anal*. Calcd. For $[C_{23}H_{23}NO_4]$; C, 73.19; H, 6.14; N, 3.71. Found C, 72.88; H, 6.14; N, 3.76.

***4-(2-Hydroxyethyl)-10-phenyl-3,4,6,7,8,10-hexahydro-1H-cyclopenta[g]furo[3,4-b]quinolin-1-one (AP-204).*** Reaction time: 30 min. The crude product was washed with 1:1 ethylacetate-hexane (V/V) and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol: ethylacetate mixture 1:1; yield 52%, MP: 191–192°C;); UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3386, 2952, 2857, 1730, 1637, 1477, 1444, 1413, 1355, 1323, 1203, 1059, 1034, 1015, 994, 880, 852, 812, 754, 737, 701; $^1$H-NMR (DMSO-$d_6$, 400 MHz),: δ 1.95 (m, 2H, 7C—H), 2.68 (m, 2H, 6C—H), 2.81 (m, 2H, 8C—H), 3.69 (m, 3H, 1″C—H and 2″-H), 3.86 (m, 1H, 2″C—H), 4.94 (s, 1H, 10C—H), 5.04 (t, $J$ = 4.85 Hz, 1H, OH), 5.09 (d, $J$ = 15.55 Hz, 1H, 1″C—H), 5.15 (d, $J$ = 15.55 Hz, 1H, 1″C—H), 6.92 (s, 1H, 9C—H), 7.09 (s, 1H, 5C—H), 7.15(m, 4H, 2′,3′,4′and 6′C—H); $^{13}$C-NMR (DMSO- $d_6$, 100 MHz): δ 25.65, 31.96, 32.82, 40.31, 48.33, 58.25, 66.23, 95.77, 110.44, 125.09, 126.63, 127.07, 128.06, 128.74, 135.35, 139.31, 143.88, 147.92, 161.08, 172.69; HRMS *m/z*: 348.1597 found (calculated for $C_{22}H_{21}NO_3$, $[M+H]^+$ requires 348.1594). *Anal*. Calcd. For $[C_{22}H_{21}NO_3]$; C, 76.06; H, 6.09; N, 4.03. Found C, 75.73; H, 6.06; N, 4.06.

***6-(2-Hydroxyethyl)-10-(3,4,5-trimethoxyphenyl)-2,3,7,10-tetrahydro-[1,4]dioxino[2,3-g]furo[3,4-b]quinolin-9(6H)-one (AP-301).*** Reaction time: 60 min. The crude product was washed with cold ethanol and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol; yield 61%, MP: 256–257°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3506, 2936, 1733, 1650, 1591, 1506, 1474, 1367, 1295, 1203, 1120, 1065, 993, 894, 755, 686; $^1$H-NMR (DMSO- $d_6$, 400 MHz): δ 3.59 (s, 3H, 4′C—$OCH_3$), 3.70 (m, 9H, 3′and 5′, C—$OCH_3$, 1″C—H and 2″C—H), 3.89 (m, 1H, 2″C—H), 4.16 (m, 4H, 2and3C—H)

4.80 (t, $J$ = 4.85 Hz, 1H, OH), 4.96 (s, 1H, 10C—H), 5.07 (d, $J$ = 15.29 Hz, 1H, 1″C—H), 5.13 (d, $J$ = 15.29 Hz, 1H, 1″C—H), 6.53 (s, 2′and6′C—H), 6.71 (s, 1H, 11C—H), 6.75 (s, 1H, 5C—H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 39.67, 48.32, 56.24, 58.32, 60.29, 64.42, 64.72, 66.23, 95.14, 103.38, 104.95, 119.07, 120.33, 130.49, 136.36, 139.87, 142.89, 143.52, 153.24, 161.12, 172.79; HRMS $m/z$: 456.1647 found (calculated for $C_{24}H_{25}NO_8$, $[M+H]^+$ requires 356.1653). *Anal.* Calcd. For $[C_{24}H_{25}NO_8]$; C, 63.29; H, 5.53; N, 3.08. Found C, 63.04; H, 5.44; N, 3.04.

***10-(3,4-Dimethoxyphenyl)-6-(2-hydroxyethyl)-2,3,7,10-tetrahydro-[1,4]dioxino[2,3-g]furo[3,4-b]quinolin-9(6H)-one (AP-302).*** Reaction time: 90 min. The crude product was washed with cold ethanol and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol; yield 65%, MP: 210–211°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3497, 2932, 1726, 1647, 1504, 1474, 1440, 1347, 1268, 1206, 1133, 1067, 1025, 1004, 892, 812, 758, 706; $^1$H-NMR (DMSO- $d_6$, 400 MHz): δ 3.68 (m, 9H, 3′and 4′, C—$OCH_3$, 1″C—H and 2″C—H), 3.82 (m, 1H, 2″C—H), 4.16 (m, 4H, 2and3C—H), 4.99 (t, $J$ = 4.85 Hz, 1H, OH), 4.80 (s, 1H, 10C—H), 5.06 (d, $J$ = 15.07 Hz, 1H, 1″C—H), 5.10 (d, $J$ = 15.07 Hz, 1H, 1″C—H), 6.61 (s, 1H, 11C—H), 6.66 (dd, $J$ = 7.99 Hz and 1.91 Hz, 1H, 6′C—H), 6.73 (s, 1H, 5C—H), 6.79 (t, $J$ = 8.38 Hz, 1H, 5′C—H), 6.84 (d, $J$ = 1.91 Hz, 1H, 2′C—H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 39.05, 48.38, 55.90, 55.99, 58.28, 64.43, 64.73, 66.15, 95.39, 103.27, 111.86, 112.34, 119.20, 119.72, 120.55, 130.65, 139.82, 140.57, 142.80, 147.74, 149.05, 160.75, 172.78; HRMS $m/z$: 426.1553 found (calculated for $C_{23}H_{23}NO_7$, $[M+H]^+$ requires 426.1547). *Anal.* Calcd. For $[C_{23}H_{23}NO_7]$; C, 64.93; H, 5.45; N, 3.29. Found C, 64.92; H, 5.34; N, 3.32.

***6-(2-Hydroxyethyl)-10-(3-methoxyphenyl)-2,3,7,10-tetrahydro-[1,4]dioxino[2,3-g]furo[3,4-b]quinolin-9(6H)-one (AP-303).*** Reaction time: 90 min. The crude product was washed with cold ethanol and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol; yield 60%, MP: 175–176°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 3424, 2936, 1720, 1641, 1581, 1483, 1442, 1367, 1296, 1274, 1250, 1206, 1155, 1060, 1036, 1004, 907, 868, 806, 772, 753, 713, 695; $^1$H-NMR (DMSO- $d_6$, 400 MHz): δ 3.68 (m, 6H, 3′C—$OCH_3$, 1″C—H and 2″C—H), 3.78 (m, 1H, 2″C—H), 4.16 (m, 4H, 2 and 3 C—H), 4.85 (s, 1H, 10C—H), 5.01 (t, $J$ = 4.82 Hz, 1H, OH), 5.07 (d, $J$ = 15.63 Hz, 1H, 1″C—H), 5.14 (d, $J$ = 15.63 Hz, 1H, 1″C—H), 6.59 (s, 1H, 11C—H), 6.71 (br, 1H, 6′C—H), 6.74 (s, 1H, 5C—H), 6.76 (s, 1H, 2′C—H), 6.78 (br, 1H, 4′C—H), 7.15 (t, $J$ = 8.09 Hz, 1H, 5′C—H ); $^{13}$C-NMR (DMSO- $d_6$, 100 MHz): δ 39.48, 48.45, 55.35, 58.25, 64.43, 64.73, 66.21, 95.13, 103.37, 111.65, 114.05, 119.22, 120.03, 120.26, 129.79, 130.77, 139.83, 142.91, 149.17, 159.71, 160.89, 172.72; HRMS $m/z$: 396.1452 found (calculated for $C_{22}H_{21}NO_6$, $[M+H]^+$ requires 396.1442). *Anal.* Calcd. For $[C_{22}H_{21}NO_6]$; C, 66.83; H, 5.35; N, 3.54. Found C, 66.68; H, 5.27; N, 3.52.

***6-(2-Hydroxyethyl)-10-phenyl-2,3,7,10-tetrahydro-[1,4]dioxino[2,3-g]furo[3,4-b]quinolin-9(6H)-one (AP-304).*** Reaction time: 90 min. The crude product was washed with cold ethanol and dried under high vacuum yielding a white crystalline powder which was purified by recrystallization from ethanol; yield 68%, MP: 229–230°C; UV–Vis $\lambda_{max}$ (nm): 261, 322; IR ($\nu_{max}$, $cm^{-1}$); 2956, 2876, 1719, 1637, 1581, 1475, 1437, 1363, 1292, 1250, 1203, 1149, 1065, 1007, 923, 893, 832, 806, 753, 734, 695; $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ 3.66 (m, 3H, 1″C—H and 2″C—H), 3.79 (m, 1H, 2″C—H), 4.14 (m, 4H, 2and3C—H), 4.88 (s, 1H, 10C—H), 5.04 (br, 1H, OH), 5.08 (d, $J$ = 15.48 Hz, 1H, 1"C—H), 5.13 (d, $J$ = 15.48 Hz, 1H, 1"C—H), 6.59 (s, 1H, 11C—H), 6.74 (s, 1H, 5C—H), 7.21 (br, 2H, 2′and6′C—H), 7.24 (br, 2H, 3′ and 5′C—H), 7.14 (t, $J$ = 6.87 Hz, 1H, 4′C—H); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): δ 39.57, 48.46, 58.25, 64.43, 64.72, 66.21, 95.25, 103.39, 119.30, 120.16, 126.67, 127.99, 128.75, 130.85, 139.86, 142.72, 147.60, 160.86, 172.71; HRMS $m/z$: 366.1338 found (calculated for $C_{21}H_{19}NO_5$, $[M+H]^+$ requires 366.1336). *Anal.* Calcd. For $[C_{21}H_{29}NO_5]$; C, 69.03; H, 5.24; N, 3.83. Found C, 68.64; H, 5.29; N, 3.84.

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## REFERENCES AND NOTES

[1] (a) Loike, J. D.; Horwitz, S. B. Biochemistry 1976, 15, 5435; (b) Leander, K.; Rosen, B., U.S. Pat. 4,788,216 (1988).

[2] Rassmann, I.; Thodtmann, R.; Mross, M.; Huttmann, A.; Berdel, W. E.; Manegold, C.; Fiebig, H. H.; Kaeserfrolich, A.; Burk, K.; Hanauske, A. R. Invest New Drugs 1998, 16, 319.

[3] Mross, K.; Huettmann, A.; Herbst K.; Hanauske, A. R.; Schilling, T.; Manegold, C.; Burk, K.; Hossfeld, D. K. Cancer Chemother Pharmacol 1996, 38, 217.

[4] Utsugi, T.; Shibata, J.; Sugimoto, Y.; Aoyagi, K.; Wierzba, K.; Kobunai, T.; Terada, T.; Oh-hara, T.; Tsuruo, T.; Yamada, Y. Cancer Res 1996, 56, 2809.

[5] Chen, S. W.; Wang, Y. H.; Jin, Y.; Tian, X.; Zheng, Y. T.; Luo, D. Q.; Tu, Y. Q. Bioorg Med Chem Lett 2007, 17, 2091.

[6] Zhu, X. K.; Jian G.; Zhiyan, X.; Mark, C. L.; Lee, K. H. Bioorg Med Chem 2004, 12, 4267.

[7] Nanjundaswamy, N.; Satish, S.; Lokanatha, R. K. M.; Shashikanth, S.; Raveesha, K. A. Int J Biomed Sci 2007, 2, 113.

[8] Moraes, R. M.; Lata, H.; Bedir, E.; Maqbool, M.; Cushman, K. In Janick, J.; Whipkey A., Eds. Trends in New Crops and New Uses; ASHS Press, Alexandria, VA, 2002; p527.

[9] Aaron, J. R.; Andrew, J. S.; Craig, I. T.; Michael, S. S. J Am Chem Soc 2003, 125, 12108.

[10] Wang, Z. Q.; Kuo, Y. H.; Schnur, D.; Bowen, J. P.; Liu, S. Y.; Han, F. S.; Chang, J. Y.; Cheng, Y. C.; Lee, K. H. J Med Chem 1990, 33, 2660.

[11] Xiao, Z.; Xiao, Y. D.; Feng, J.; Golbraikh, A.; Tropsha, A.; Lee, K. H. J Med Chem 2002, 45, 2294.

[12] Hitotsuyanagi, Y.; Kobayashi, M.; Morita, H.; Itokawa, H.; Takeya, K. Tetrahedron Lett 1999, 40, 9107.

[13] Hitotsuyanagi, Y.; Fukuyo, M.; Tsuda, K.; Kobayashi, M.; Ozeki, A.; Itokawa, H.; Takeya, K. Bioorg Med Chem Lett 2000, 10, 315.

[14] Tratrat, C.; Sylviane, G. R.; Husson H. P. Org Lett 2002, 19, 3187.

[15] Henne, W. A.; Doorneweerd, D. D.; Hilgenbrink, A. R.; Kularatne, S. A.; Low, P. S. Bioorg Med Chem Let 2006, 16, 5350.

# An Efficient and Clean Synthesis of Indeno[1,2-*b*]pyrazolo[4,3-*e*]-pyridin-5(1*H*)-one Derivatives under Microwave Irradiation in Water



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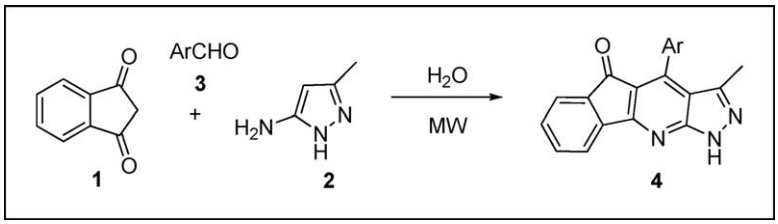


A series of new indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one derivatives were synthesized by three-component reactions of 1,3-indandione, 3-methyl-1*H*-pyrazol-5-amine, and aldehyde in water under microwave irradiation without any catalyst.

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## INTRODUCTION

Many recent efforts were made to make organic synthesis eco-friendlier. In this way, usual but hazardous volatile organic solvents were replaced with water and/or conventional heating was substituted by microwave irradiation (MW). Green chemistry is brewing which protects the environment, not by cleaning it up, but by inventing new chemistry and new chemical processes that prevent pollution [1]. In essence, it prompts the chemical and pharmaceutical manufacturer to consider how human life is impacted after these chemicals are generated and introduced into their society [2]. Thus, it has become clear that the combined approach of microwave heating and aqueous medium offers a nearly synergistic strategy in the sense that the combination in itself offers greater potential than the two parts in isolation [3].

Now, with growing concern over the environmental impact of chemicals, cleaner green reaction conditions in organic reaction have been advocated. Multicomponent reactions, an important class of organic tandem reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of atoms of the starting materials [4]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings both of solvents and of reagents.

Six-membered nitrogen-containing heterocycles, especially onychine derivatives (Fig. 1) are abundant in nature and exhibit diverse and important biological properties [5]. Indenopyridines [6], as a member of this family exhibit cytotoxic [7], phosphodiesterase inhibitory [8], adenosine A2a receptor antagonistic [9], antiinflammatory/antiallergic [10], coronary dilating [11], and calcium modulating activities [12]. The synthesis of these molecules has attracted considerable attention [13]. Shi *et al.* [14] reported the reaction of 5-amino-3-methyl-1-phenylpyrazole with arylaldehyde and 1,3-indandione to give indeno[2,1-*e*]pyrazolo derivatives in ionic liquid with the disadvantage of long time and pollution to the environment. Considering the significance of this kind of organic molecules, a more efficient and environmental friendly approach would be established to synthesis the set of onychine derivatives so as to provide candidate compounds for bioassay and enrich compound libraries. As the continuation of our research devoted to the development of green organic chemistry by performing reactions under using water conditions [15], we describe the synthesis of indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-ones in water under microwave irradiation without catalyst (Scheme 1).

## RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for successful microwave-promoted synthesis in

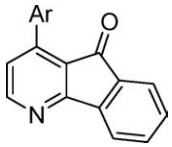



**Figure 1.** Structure of oychine.

view of a rapid rise of temperature in the reaction mixture. To search for the optimal solvent, the reaction of 1,3-indandione **1**, 3-methyl-1*H*-pyrazol-5-amine **2** and *p*-chlorobenzaldehyde **3a** were examined by using solvents of ethanol, DMF, ethylene glycol, acetic acid, and water, respectively. All the reactions were carried out at 120°C with the maximum power of 250 W and the results are summarized in Table 1. As shown in Table 1, the reaction in water resulted in higher yields and shorter reaction time than others. So water was chosen as the appropriate solvent.

Moreover, to further optimize the reaction temperature, the synthesis of **4a** was performed in water at the temperatures ranging from 100 to 140°C in the increment of 10°C each time at the maximum power of 250 W. As illustrated in Table 2, when the temperature was increased from 100 to 130°C, the yield of **4a** was obviously improved from 50 to 83%. However, no significant increase in the yield of **4a** was observed as the reaction temperature was further raised to 140°C. Therefore, the temperature of 130°C was chosen for all further microwave-assisted reactions.

Based on these optimized conditions [water, 130°C], the reactions proceeded smoothly. A series of compounds **4** were synthesized with this simple procedure. The results were summarized in Table 3 and the results indicated that aromatic aldehydes bearing either electron withdrawing or electron donating functional groups, such as chloro, nitro, bromo, or methyl are suitable for the reaction.

A tentative mechanism for the formation of products **4** is outlined in Scheme 2, which proceeded *via* a reaction sequence of condensation, addition, cyclization, dehydration, and aromatization. First, the condensation of 1,3-indandione **1** and aldehyde **3** gave the intermediate product **5**. The addition of **2** to **5** then furnished the intermediate product **7**, which cylices to dihydropyrine **9** and subsequently dehydrogenated to afford the fully aromatized compound **4**.

**Scheme 1**

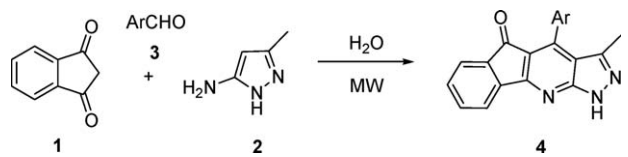



**Table 1**

Solvent optimization for the synthesis of **4a**.

| Entry | Solvent | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | EtOH | 13 | 40 |
| 2 | DMF | 18 | trace |
| 3 | Glycol | 12 | 50 |
| 4 | HOAc | 10 | 70 |
| 5 | Water | 10 | 77 |

All the products were characterized by IR, $^1$H NMR, and HRMS (ESI).

In summary, we demonstrated an efficient and clean route for the one-pot, three-component synthesis of highly functionalized indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one derivatives in good yields. This method has the obvious advantages on short reaction time, high yield, operational simplicity, and environmental friendliness. Besides, this method may provide a shortcut for further investigations on the pharmacological activities of this type of compounds as important and novel onychine analogues.

## EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FTIR-Tensor 27 spectrometer. $^1$H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-$d_6$ as solvent and TMS as internal standard. HRMS (ESI) was determined by using micrOTOF-QII HRMS/MS instrument (BRUKER).

**General procedure for the synthesis of compounds 4 with microwave irradiation.** Typically, a mixture of aromatic 1,3-indandione **1** (1.0 mmol), 3-methyl-1*H*-pyrazol-5-amine **2** (1.0 mmol), aldehyde **3** (1.0 mmol), and water (2.0 mL) was added to the reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under MW at 250 W power (initial power 100 W) and 130°C for several minutes. Upon completion, monitored by TLC, the reaction vessel was cooled to room temperature. The solid compound was collected by filtration and recrystallized from EtOH (95%) to give pure azapodophyllotoxin derivatives **4**.

**Table 2**

Temperature optimization for the synthesis of **4a**.

| Entry | T (°C) | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | 100 | 12 | 50 |
| 2 | 110 | 12 | 55 |
| 3 | 120 | 10 | 77 |
| 4 | 130 | 8 | 83 |
| 5 | 140 | 8 | 81 |

**Table 3**

Synthesis of products **4**.

| Entry | 4 | Ar | Time (min) | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|
| 1 | **4a** | 4-$ClC_6H_4$ | 8 | 83 | >300 |
| 2 | **4b** | 4-$BrC_6H_4$ | 10 | 80 | >300 |
| 3 | **4c** | 4-$CH_3C_6H_4$ | 8 | 77 | >300 |
| 4 | **4d** | 2-$ClC_6H_4$ | 10 | 79 | 209–210 |
| 5 | **4e** | 3-$NO_2C_6H_4$ | 7 | 80 | 243–244 |
| 6 | **4f** | 3,4-$(CH_3O)_2C_6H_3$ | 8 | 77 | 245–246 |
| 7 | **4g** | $C_6H_5$ | 10 | 78 | 258–259 |
| 8 | **4h** | 3,4,5-$(CH_3O)_3C_6H_2$ | 10 | 76 | 240–242 |
| 9 | **4i** | Thien-2-yl | 13 | 77 | 263–264 |

***4-(4-chlorophenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4a).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.78 (s, 1H, NH), 7.65 (d, 2H, $J$ = 6.8 Hz, ArH), 7.40 (t, 1H, $J$ = 7.6 Hz, ArH), 7.34–7.28 (m, 3H, ArH), 7.23 (t, 2H, $J$ = 8.4 Hz, ArH), 7.19 (d, 1H, $J$ = 6.8 Hz, ArH), 1.87 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3197, 3056, 2882, 1717, 1698, 1559, 1542, 1491, 1436, 1363, 1340, 1290, 1245, 1185, 1130, 1082, 989, 811, 777, 709. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}ClN_3O$: 346.0742 $[M+H]^+$, found: 346.0793 $[M+H]^+$.

***4-(4-bromophenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4b).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.80 (s, 1H, NH), 7.91 (d, 1H, $J$ = 7.2 Hz, ArH), 7.73, (d, 4H, $J$ = 8.4 Hz, ArH), 7.61–7.54 (m, 3H, ArH), 7.49 (d, 3H, $J$ = 8.0 Hz, ArH), 1.94 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3198, 3056, 2994, 1712, 1684, 1594, 1536, 1491, 1432, 1338, 1302, 1256, 1208, 1183, 1115, 1071, 995, 811, 762, 730. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}BrN_3O$: 390.0237 $[M+H]^+$, found: 390.0212 $[M+H]^+$.

***3-methyl-4-p-tolylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4c).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.74 (s, 1H, NH), 7.88 (d, 1H, $J$ = 7.2 Hz, ArH), 7.71, (t, 1H, $J$ = 7.2 Hz, ArH), 7.58–7.51 (m, 2H, ArH), 7.39 (d, 2H, $J$ = 8.0 Hz, ArH), 7.33 (d, 2H, $J$ = 8.0 Hz, ArH), 2.44 (s, 3H, $CH_3$), 1.92 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3190, 3048, 2962, 1710, 1612,1562, 1511, 1475, 1449, 1338, 1300,1255, 1207, 1179, 1116, 1072, 987, 809, 786, 733. HRMS (ESI) *m/z*: calc. for $C_{21}H_{16}N_3O$: 326.1288 $[M+H]^+$, found: 326.1317 $[M+H]^+$.

***4-(2-chlorophenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4d).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.87 (s, 1H, NH), 7.94 (d, 1H, $J$ = 7.6 Hz, ArH), 7.76, (t, 1H, $J$ = 7.6 Hz, ArH), 7.67 (d, 1H, $J$ = 7.6 Hz, ArH), 7.62–7.57 (m, 3H, ArH), 1.86 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3153, 3109, 2997, 1714, 1602, 1572, 1550, 1473, 1439, 1340, 1303, 1280, 1251, 1183, 1155, 1060, 991, 807, 752, 711. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}ClN_3O$: 346.0742 $[M+H]^+$, found: 346.0744 $[M+H]^+$.

***3-methyl-4-(3-nitrophenyl)indeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4e).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.87 (s, 1H, NH), 8.43 (d, 2H, $J$ = 9.2 Hz, ArH), 8.04 (d, 1H, $J$ = 7.6 Hz, ArH), 7.93 (d, 1H, $J$ = 7.2 Hz, ArH), 7.85 (t, 1H, $J$ = 7.6 Hz, ArH), 7.77–7.73 (m, 1H, ArH), 7.62–7.55 (m, 2H, ArH), 1.94 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3190, 3117, 2990, 1754, 1634, 1599, 1504, 1488, 1457, 1385, 1300, 1294, 1236, 1177, 1120, 1070, 985, 800, 765, 713. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}N_4O_3$: 357.0979 $[M+H]^+$, found: 357.1005 $[M+H]^+$.

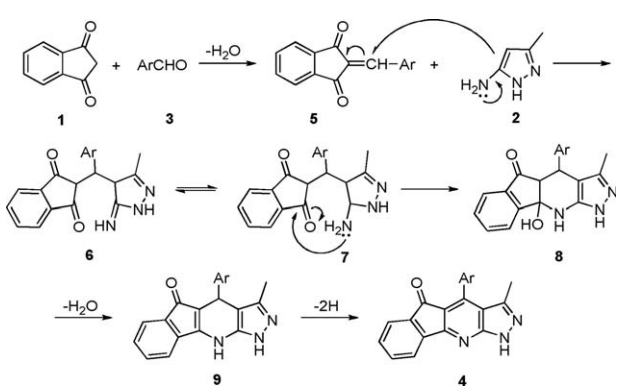
***4-(3,4-dimethoxyphenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4f).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.73 (s, 1H, NH), 7.90 (d, 1H, $J$ = 7.2 Hz, ArH), 7.72, (t, 1H, $J$ = 7.2 Hz, ArH), 7.61 (d, 1H, $J$ = 7.2 Hz, ArH), 7.55 (t, 1H, $J$ = 7.6 Hz, ArH), 7.15 (d, 1H, $J$ = 1.2 Hz, ArH), 7.10–7.04 (m, 2H, ArH), 3.86 (s, 3H, $CH_3$), 3.77 (s, 3H, $CH_3$), 2.01 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3054, 3001, 2934, 1699, 1608, 1559, 1542, 1490, 1437, 1338, 1309, 1285, 1263, 1169, 1139, 1086, 1025, 801, 766, 726. HRMS (ESI) *m/z*: calc. for $C_{22}H_{18}N_3O_3$: 372.1343 $[M+H]^+$, found: 372.1333 $[M+H]^+$.

***3-methyl-4-phenylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4g).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.77 (s, 1H, NH), 7.91 (d, 1H, $J$ = 7.2 Hz, ArH), 7.73 (t, 1H, $J$ = 7.2, ArH), 7.61–7.48 (m, 8H, ArH), 1.90 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3102, 2994, 1708, 1671, 1592, 1562, 1541, 1498, 1446, 1339, 1305, 1256, 1240, 1189, 1140, 1094, 978, 805, 760, 705. HRMS (ESI) *m/z*: calc. for $C_{20}H_{14}N_3O$: 312.1132 $[M+H]^+$, found: 313.1148 $[M+H]^+$.

***3-methyl-4-(3,4,5-trimethoxyphenyl)indeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4h).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm): 13.76 (s, 1H, NH), 7.91 (d, 1H, $J$ = 7.2 Hz, ArH), 7.73, (t, 1H, $J$ = 7.6 Hz, ArH), 7.62 (d, 1H, $J$ = 6.8 Hz, ArH), 7.56 (t, 1H, $J$ = 7.2 Hz, ArH), 6.83 (s, 2H, ArH), 3.78 (d, 9H, $J$ = 3.2 Hz, $CH_3$), 1.86 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3193, 3107, 2967, 1709, 1583, 1562, 1504, 1464, 1433, 1344, 1318, 1296, 1250, 1163, 1126, 1005, 967, 809, 777, 729. HRMS (ESI) *m/z*: calc. for $C_{23}H_{20}N_3O_4$: 402.1444 $[M+H]^+$, found: 402.1434 $[M+H]^+$.

***3-methyl-4-(thiophen-2-yl)indeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4i).*** $^1$H NMR (400 MHz, DMSO-$d_6$) (δ, ppm):

**Scheme 2**



13.81 (s, 1H, NH), 7.91–7.86 (m, 2H, ArH), 7.73 (t, 1H, $J$ = 7.6 Hz, ArH), 7.62 (d, 1H, $J$ = 7.2 Hz, ArH), 7.56 (t, 1H, $J$ = 7.2 Hz, ArH), 7.36 (d, 1H, $J$ = 3.6 Hz, ArH), 7.28–7.25 (m, 1H, ArH), 2.04 (s, 3H, $CH_3$). IR (KBr, ν, $cm^{-1}$): 3096, 3053, 2983, 1707, 1684, 1590, 1559, 1473, 1435, 1334, 1302, 1252, 1225, 1178, 1130, 1078, 972, 808, 771, 730. HRMS (ESI) *m*/*z*: calc. for $C_{18}H_{12}N_3OS$: 318.0696 $[M+H]^+$, found: 318.0696 $[M+H]^+$.

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## REFERENCES AND NOTES

[1] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: Oxford, 2000.

[2] Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. T.; Wei, X. Y.; Zong, Z. M. Tetrahedron Lett 2005, 46, 7169.

[3] Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. Tetrahedron 2000, 56, 7747.

[4] (a) Hulme, C.; Gore, V. Curr Med Chem 2003, 10, 51; (b) Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471; (c) Domling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3168; (d) Nair, V.; Rajesh, C.; Vinod, A. V.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. Acc Chem Res 2003, 36, 899; (e) Zhu, J. Eur J Org Chem 2003, 7, 1133; (f) Domling, A. Curr Opin Chem Biol 2002, 6, 306.

[5] Strunz, G. M.; Buckingham, J. A. The Alkaloids; Academic Press: New York, 1985, 26, 89.

[6] Manpadi, M.; Uglinskii, P. Y.; Rastogi, S. K. Org Biomol Chem 2007, 5, 3865.

[7] Miri, R.; Javidnia, K.; Hemmateenejad, B.; Azarpira, A.; Amirghofran, Z. Bioorg Med Chem 2004, 12, 2529.

[8] Heintzelman, G. R.; Averill, K. M.; Dodd, J. H. PCT Int Appl WO 2002085894 A1 20021031, 2002; (b) Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. Tetrahedron 2000, 56, 7747.

[9] Heintzelman, G. R.; Averill, K. M.; Dodd, J. H.; Demarest, K. T.; Tang, Y.; Jackson, P. F. US Pat Appl Publ 2004082578 A1 20040429, 2004.

[10] Cooper, K.; Fray, M. J.; Cross, P. E.; Richardson, K. Eur Pat Appl EP 299727 A1 19890118, 1989.

[11] Vigante, B.; Ozols, J.; Sileniece, G.; Kimenis, A.; Duburs, G. U. S. S. R. SU, 794006 19810107, 1989.

[12] Safak, C.; Simsek, R.; Altas, Y.; Boydag, S.; Erol, K. Boll Chim Farm 1997, 136, 665.

[13] (a) Tadic, D.; Cassels, B. K.; Cave', A.; Goulart, M. P. F.; de Oliveira, A. B. Phytochemistry 1987, 26, 1551; (b) Alves, T.; de Oliveira, A. B.; Snieckus, V. Tetrahedron Lett 1988, 29, 2135; (c) Emelen, K. V.; Wit, T. D.; Hoornaert, G. J.; Compernolle, F. Tetrahedron 2002, 58, 4225.

[14] Shi, D. Q.; Yang, F.; Ni, S. N. J Heterocycl Chem 2009, 46, 469.

[15] (a) Tu, S. J.; Cao, X. D.; Hao, W. J.; Zhang, X. H.; Yan, S.; Wu, S. S.; Han, Z. G.; Shi, F. Org Biomol Chem 2009, 7, 557; (b) Tu, S. J.; Zhang, X. H.; Han, Z. G.; Cao, X. D.; Wu, S. S.; Yan, S.; Hao, W. J.; Ma, N. J Comb Chem 2009, 11, 428; (c) Jiang, B.; Cao, L. J.; Tu, S. J.; Zheng, W. R.; Yu, H. Z. J Comb Chem 2009, 11, 612.

# Synthesis of 2,3-Dihydroimidazo[2,1-*b*]thiazole Derivatives *via* Cyclization of *N*-Allylimidazoline-2-thiones



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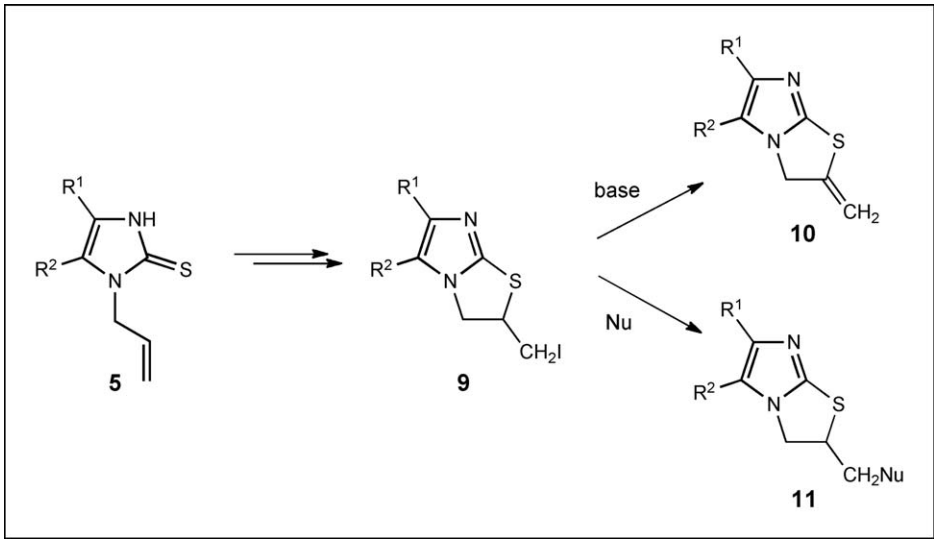


A novel method for the preparation of 2,3-dihydroimidazo[2,1-*b*]thiazole **9** by iodination and subsequent cyclization of the easily available *N*-allylimidazoline-2-thiones **5**, is described. Selected transformations of the iodomethyl derivatives **9**, leading to methylidene compounds **10** or the sulfide **11** (Nu = RS), via elimination with a base or via substitution with an enolizable imidazoline-2-thione (the term ''1,3-dihydroimidazole-2-thione'' will be used alternatively), respectively, are presented.

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## INTRODUCTION

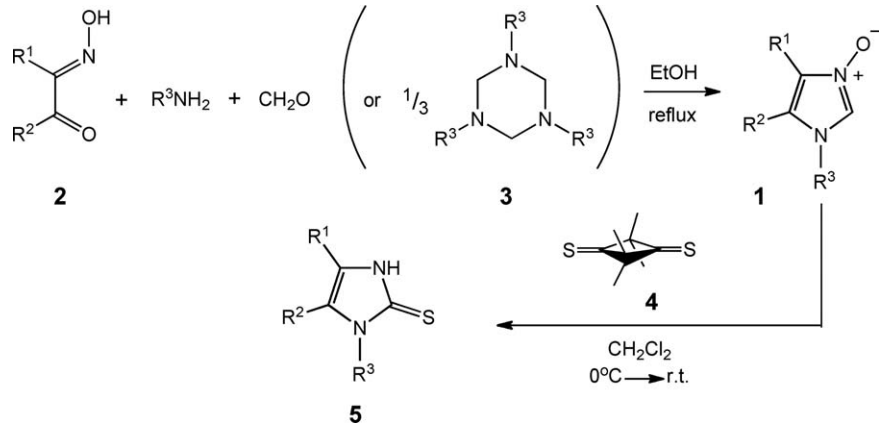
In a series of recent articles, a convenient approach to 2-unsubstituted imidazole *N*-oxides **1**, including optically active derivatives, has been reported [2]. In general, the applied method is based on the condensation of α-(hydroxyimino)ketones **2** with a primary aliphatic amine and formaldehyde. Alternatively, the corresponding hexahydro-1,3,5-triazines **3**, being trimers of formaldehyde imines, can be used (Scheme 1).

Irrespective of the substitution pattern, the reaction of **1** with 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**4**) resulted in the ''sulfur transfer reaction'' leading to 1,3-dihydroimidazole-2-thiones **5** in high-yield [2b,2d,3]. In addition to *N*-alkyl and *N*-cycloalkyl substituted imidazole *N*-oxides **1**, some of the corresponding *N*-allyl derivatives were also obtained in good yields [2a]. However, the latter have not been explored for further conversions yet.

In spite of the fact that *N*-allyl-1,3-dihydroimidazole-2-thiones seem to be attractive starting materials for diverse cyclization reactions involving the allyl group, there are only few reports on their synthesis available to date. The first approach, reported already in 1895, was the condensation of *N*-allylthiourea with 2-hydroxy-1,2-diphenylethanone (benzoine) [4]. The second synthesis described the condensation of isothiocyanic acid and acetals of *N*-allyl α-aminoacetaldehyde [5]. In addition, the reaction of allylisothiocyanate with glucosamine is reported to yield the desired product [6], and the analogous condensation with 1-amino-3-methylbutan-2-one gave *N*-allyl-5-isopropylimidazoline-2-thione [7].

The goal of this study was the preparation of a series of less known *N*-allyl-1,3-dihydroimidazole-2-thiones and their subsequent cyclization to corresponding fused *N*,*S*-heterocycles. Heterocyclic thiones with an allyl-substituted *N*-atom attached to the C=S group are known

**Scheme 1**




to undergo an intramolecular 1,5-cyclization to yield fused thiazoles. Thus, treatment of the *N*-allyltriazolethione **6** with iodine in ethanol at room temperature gave the thiazolo[2,3-*c*][1,2,4]triazole hydroiodide **7** [8] (Scheme 2). The analogous bromide was obtained from the reaction with bromine in chloroform.

To the best of our knowledge, there are no analogous reactions with imidazoline thiones, described so far. However, in the case of benzimidazoline-2-thiones, a similar cyclization has been observed [9].

## RESULTS AND DISCUSSION

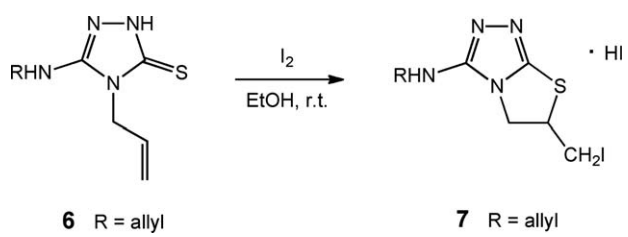
In accordance with the known procedure [2], heating of 1,3,5-triallylhexahydro-1,3,5-triazine (**3a**, $R^3$ = allyl) and 3-(hydroxyimino)butan-2-one (**2a**, $R^1 = R^2$ = Me) in ethanol gave the expected 1-allyl-4,5-dimethylimidazole *N*-oxide (**1a**) in 78% yield (Scheme 1, Table 1). The imidazoline-2-thione **5a** was prepared from **1a** by treatment with 0.5 mol equivalents of **4** in dichloromethane at room temperature. The same procedures were applied for the synthesis of **5b**–**5f**.

Solutions of the purified imidazoline-2-thiones **5** in ethanol were treated with iodine at room temperature, and the corresponding hydroiodides **8** precipitated directly from the reaction mixture. The subsequent neutralization with aqueous sodium acetate solution gave 2,3-dihydroimidazo[2,1-*b*]thiazoles **9** as crystalline products, with the exception of **9e** (Scheme 3, Table 1).

The structure of products **9** was proved by means of spectroscopic methods. For example, the $^{13}$C-NMR spectrum of **9b** showed the signals for three imidazole C-atoms at 145.3, 141.7, and 133.6 ppm as well as two triplets for $CH_2$ groups at 49.3 and 7.3 ppm (assigned to $CH_2N$ and $CH_2I$, resp.), and a doublet for a CH group at 52.2 ppm.

The presence of the iodomethyl group in compounds **9** enables further transformation with basic and nucleophilic agents. In fact, treatment of **9a** with triethylamine in ethanol afforded, after elimination of HI, the exomethylidene derivative **10a**. Furthermore, the attempted substitution of iodide with potassium cyanide, carried out either in acetone or in ethanol, led to the same elimination product **10a**. On the other hand, the reaction of **9f** with the enolizable 1,4,5-trimethylimidazoline-2-thione (**5g**) in ethanol, led successfully to the sulfide **11** in good yield (Scheme 4).

**Scheme 2**




**6** R = allyl **7** R = allyl

**Table 1**

Synthesis of 1-allylimidazole *N*-oxides **1**,1-allyl-1,3-dihydroimidazole-2-thiones **5**, and 2,3-dihydro-2-(iodomethyl)imidazo[2,1-*b*]thiazoles **9**.

| | | | | Yield [%] | | |
|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | **1** | **5** | **9** |
| **a** | Me | Me | All[a] | 78 | 84 | 36 |
| **b** | MeCO | Me | All | 54 | 71 | 65 |
| **c** | $EtO_2C$ | Me | All | 36 | 52 | 61 |
| **d** | PhNHCO | Me | All | 77 | 89 | 74 |
| **e** | Me | Ph | All | [b] | 39[c] | 39 |
| **f** | Ph | Ph | All | 73 [2a] | 76 | 52 |

[a] All = allyl.
[b] Not isolated in pure form.
[c] Overall yield starting from **3a** via **1e.**

**Scheme 3**


## CONCLUSIONS

The presented study shows that treatment of the easily available *N*-allyl-1,3-dihydroimidazole-2-thiones **5** with iodine results in the cyclization leading to imidazo[2,1-*b*]thiazole derivatives **9**, bearing an iodomethyl group as an additional reaction center. As selected transformations of these products, the elimination of HI and the substitution with 1,4,5-trimethylimidazoline-2-thione, as an example of an *S*-nucleophile, are presented.

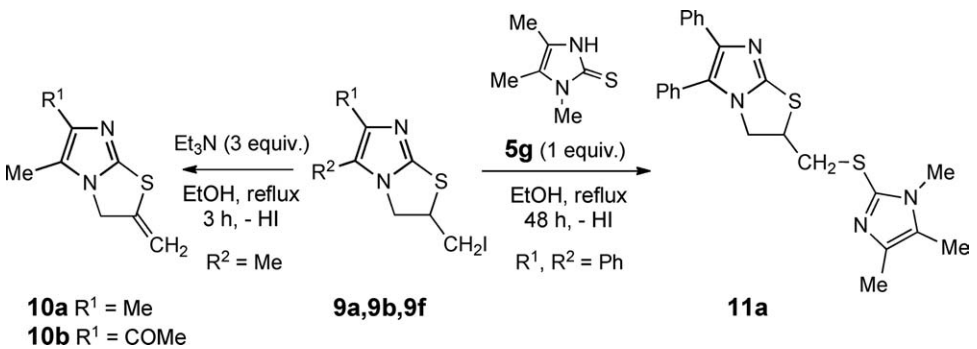
The importance of imidazo[2,1-*b*]thiazoles is well documented, as many derivatives of them display diverse biological activities [10] (see also [11]). The presented synthetic approach supplements the already reported methods for the preparation of 2,3-dihydroimidazo[2,1-*b*]thiazoles, which are based on reactions either of appropriate imidazole or thiazole derivatives. In the case of imidazole derivatives, the bis-alkylation of imidazoline-2-thiones with 1,2-dibromoethane was most frequently applied [12]. Another approach is the thermal cyclization of *N*-vinylimidazoline-2-thiones, which leads to the aromatized fused system [13]. The non-aromatized parent system was obtained via a formal vinyl transfer reaction of the parent imidazoline-2-thione with *S*-vinyl-*S*-(4-methylphenyl)-*N*-tosylimine [14]. The reactions starting with 1,3-thiazole derivatives are described to a comparable extent. As a typical example, the cyclocondensation of an α-bromoacetophenone with 2-amino-1,3-thiazoles can be mentioned [11a]. A very recent report deals with a multistep procedure, in which the alkylation of 2-amino-1,3-thiazole with propargyl bromide and subsequent cyclization are the key steps [11c]. In the light of the already reported approaches, our method, presented in this article, enlarges the number of synthetic tools for the preparation of new, diversely substituted imidazo[2,1-*b*]thiazoles. Of special importance is the availability of differently substituted α-(hydroxyimino)ketones **2**, which are key starting materials for the presented multi-step procedure.

## EXPERIMENTAL

Melting points were determined in capillaries using a Melt-Temp II apparatus (Aldrich) and are uncorrected. IR Spectra were recorded on a NEXUS FT-IR spectrophotometer as KBr pellets; absorptions in $cm^{-1}$. $^1H$- and $^{13}C$-NMR spectra were measured on a Tesla BS567A (80 MHz) or Varian Gemini 200 (200 and 50 MHz, resp.) instrument or a Bruker AC 400 instrument (400 and 100 MHz, resp.) in a suitable solvent ($CDCl_3$, $CD_3OD$ or DMSO-$d_6$); chemical shifts (δ) were given in ppm (TMS = 0 ppm), coupling constants *J* in Hz. The multiplicity of the $^{13}C$ signals was deduced from DEPT spectra. The HRMS spectra were registered on a Finnigan MAT-95 instrument.

**Synthesis of 4,5-disubstituted 1-allyl-1*H*-imidazole 3-oxides (1a–f).** In the cases of **1a**, **1d**, **1e**, and **1f**, the solution of 1,3,5-triallylhexahydro-1,3,5-triazine (**3a**, 0.69g, 3.3 mmol) and the corresponding α-(hydroxyimino)ketone of type **2** (10 mmol) in ethanol (15 mL) was refluxed for the required time (ca. 3 h, TLC monitoring, silica gel, MeOH). The solvent was removed under reduced pressure and the crude product was

**Scheme 4**



washed several times with $Et_2O$ and purified thereby. In the cases of **1b** and **1c**, a solution of **3a** (0.94g, 4.5 mmol) in $Et_2O$ (2 mL) was added to the magnetically stirred and cooled solution (water/ice external bath) of the corresponding α-(hydroxyimino)ketone **2** (10 mmol) in 5 mL $Et_2O$. When the addition was complete, the cooling bath was removed and the stirring was continued for 24 h at room temperature. Then, the colorless precipitate was filtered off and purified by flash chromatography ($SiO_2$). Acetone was used first as an eluent to remove the remaining **2**, followed by a mixture of ethyl acetate and MeOH (1:1). Next, the same reaction was repeated using recovered **2**. The combined fractions of the crude product **1** were purified by recrystallization from an appropriate solvent. The 1-allyl-4-methyl-5-phenyl-1*H*-imidazole 3-oxide (**1e**) could not be obtained in pure form and, therefore, the crude product was converted immediately into the corresponding imidazole-2-thione **5e**. The protocol for the synthesis of thiones of type **5**, as well as spectroscopic and analytical data for 1-allyl-4,5-diphenyl-1*H*-imidazole 3-oxide (**1f**), were already reported [2a].

***1-Allyl-4,5-dimethyl-1H-imidazole 3-oxide (1a).*** The crude product was purified by flash chromatography on silica using AcOEt with increasing amounts of MeOH (up to 1:1 ratio) to give **1a** in 78% yield (1.19 g). Light yellow semi-solid, hygroscopic. IR (KBr): ν 3100–2900vs (br.), 1627m, 1443m, 1393s, 1378s, 1335s, 1187m, 1148m, 1004m, 926m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 8.18 (s, 1H, H—C(2)); 5.91–5.72 (m, 1H, —CH=); 5.26–4.95 (m, 2H, $=CH_2$); 4.37–4.34 (m, 2H, $—CH_2—$); 2.13, 2.06 (2s, 6H, 2Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 131.3 (d, —CH=); 126.3, 125.2 (2s, C(4), C(5)); 121.3 (d, C(2)); 118,5 (t, $=CH_2$); 47.8 (t, $—CH_2—$); 8.3, 7.0 (2q, 2 Me). EI-HRMS: 152.0975 ($M^+$, $C_8H_{12}N_2O^+$; calcd. 152.0950).

***4-Acetyl-1-allyl-5-methyl-1H-imidazole 3-oxide (1b).*** Yield 0.97 g (54%). Colorless crystals, mp 39–40°C ($CH_2Cl_2$/$Et_2O$). IR (KBr): ν 3117s, 1660vs, 1557s, 1420m, 1407m, 1333m, 1274m, 1145m, 950m, 731m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.93 (s, 1H, H—C(2)); 6.15–5.68 (m, 1H, —CH=); 5.46–5.04 (m, 2H, $=CH_2$); 4.54–4.44 (m, 2H, $—CH_2—$); 2.82 (s, 3H, MeCO); 2.48 (s, 3H, Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 191.3 (s, C=O); 132.0, 129.6 (2s, C(4), C(5)); 130.2 (d, —CH=); 125.6 (d, C(2)); 119.6 (t, $=CH_2$); 47.6 (t, $—CH_2—$); 30.6 (q, *Me*CO); 9.9 (q, Me). EI-HRMS: 180.0905 ($M^+$, $C_9H_{12}N_2O_2^+$; calcd. 180.0899).

***Ethyl 1-allyl-5-methyl-3-oxido-1H-imidazole-4-carboxylate (1c).*** The crude product was purified by flash chromatography on silica using AcOEt with increasing amounts of MeOH (up to 1:1 ratio) to give **1c** in 36% yield (0.76 g). Colorless semi-solid. IR (KBr): ν 3150–2950s, 1706vs, 1458m, 1326m, 1285m, 1180m, 1091m, 742m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 8.27 (s, 1H, H—C(2)); 6.03–5.84 (m, 1H, —CH=); 5.36–5.06 (m, 2H, $=CH_2$); 4.61–4.58 (m, 2H, $—CH_2—$); 4.40 (q, $J$ = 7.1, 2H, Me$CH_2$O); 2.46 (s, 3H, Me); 1.39 (t, $J$ = 7.1, 3H, *Me*$CH_2$O). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 158.8 (s, C=O); 131.8, 121.6 (2s, C(4), C(5)); 130.4 (d, —CH=); 126.8 (d, C(2)); 118.7 (t, $=CH_2$); 60.5 (t, Me$CH_2$O); 47.6 (t, $CH_2$N); 13.8 (q, *Me*$CH_2$O); 9.5 (q, Me). EI-HRMS: 210.1017 ($M^+$, $C_{10}H_{14}N_2O_3^+$; calcd. 210.1004).

***1-Allyl-5-methyl-3-oxido-N-phenyl-1H-imidazole-4-carboxamide (1d).*** Yield 1.98 g (77%). Yellow solid, mp 115–117°C ($CH_2Cl_2$/$Et_2O$). IR (KBr): ν 3119m, 1664m, 1621s, 1598s, 1565s, 1498m, 1447m, 1418m, 1309m, 1277m, 759m. $^1$H-NMR (80 MHz, $CDCl_3$): δ 12.90 (s, 1H, NH); 7.88 (s, 1H, H—C(2)); 7.77–7.61 (m, 2 arom. H); 7.44–6.99 (m, 3 arom. H); 6.07–5.67 (m, 1H, —CH=); 5.46–5.03 (m, 2H, $=CH_2$); 4.52–4.42 (m, 2H, $—CH_2—$); 2.63 (s, 3H, Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 157.2 (s, C=O); 138.0, 131.7, 121.9 (3s, 1 C(Ph), C(4), C(5)); 130.2 (d, —CH=); 128.9, 125.2, 124.1, 120.5 (4d, 5 CH(Ph), C(2)); 119.9 (t, $=CH_2$); 47.8 (t, $—CH_2—$); 9.55 (q, Me). EI-HRMS: 257.1173 ($M^+$, $C_{14}H_{15}N_3O_2^+$; calcd. 257.1164).

***Synthesis of 1,3,5-triallylhexahydro-1,3,5-triazine (3a).*** The allylamine (50 mL, 38 g, 0.67 mol) was carefully dissolved in methanol (80 mL) and cooled to 0°C. Then, solid paraformaldehyde (21 g, 0.7 mol) was added in small portions, the obtained suspension was allowed to reach r.t. and was stirred overnight. Next day, the solvent was removed *in vacuo* and the oil was short-path distilled at 95–100°C/2 mm Hg to give **3a** in 84% yield. All spectra of **3a** corresponded with literature data [15].

**Synthesis of 4,5-disubstituted 1-allyl-2,3-dihydroimidazole-2-thiones (5a–f).** To the magnetically stirred solution of *N*-oxide **1** (10 mmol) in $CH_2Cl_2$ (30 mL), the solution of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**4**, 0.95 g, 5.5 mmol) in dichloromethane (8 mL) was added at 0°C. After the ice-bath was removed, stirring was continued overnight. The solvent was removed to dryness, the residue was washed with two portions of ether (10 mL each), and the crude product was recrystallized from an appropriate solvent.

***1-Allyl-2,3-dihydro-4,5-dimethylimidazole-2-thione (5a).*** Yield 1.40 g (84%). Light yellow crystals, mp 147–149°C ($CHCl_3$/$Et_2O$). IR (KBr): ν 3166m, 3088s, 2949m, 2923m, 1661w, 1497m, 1431m, 1412m, 1397m, 1236m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 12.17 (br. s, 1H, NH); 6.16–5.69 (m, 1H, —CH=); 5.30–4.92 (m, 2H, $=CH_2$); 4.71–4.61 (m, 2H, $—CH_2—$); 2.08, 2.04 (2s, 6H, 2 Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 157.5 (s, C=S); 131.7 (d, —CH=); 121.3, 119.9 (2s, C(4), C(5)); 116.7 (t, $=CH_2$); 46.3 (t, $—CH_2—$); 8.7, 8.6 (2q, 2Me). EI-HRMS: 168.0726 ($M^+$, $C_8H_{12}N_2S^+$; calcd. 168.0721).

***4-Acetyl-1-allyl-2,3-dihydro-5-methylimidazole-2-thione (5b).*** Yield 1.39 g (71%). Pale yellow crystals, mp 145–148°C (MeOH). IR (KBr): ν 3150–2900vs, 1641vs, 1596m, 1492m, 1414s, 1385m, 1375m, 1353m, 1262m, 1177m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 11.74 (br. s, 1H, NH); 5.90–5.71 (m, 1H, —CH=); 5.18–4.94 (m, 2H, $=CH_2$); 4.79–4.29 (m, 2H, $—CH_2—$); 2.42, 2.40 (2s, 6H, 2 Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 186.1 (s, C=O); 162.2 (s, C=S); 134.2, 124.2 (2s, C(4), C(5)); 130.4 (d, —CH=); 117.6 (t, $=CH_2$); 46.3 (t, $—CH_2—$); 28.5 (q, *Me*CO); 10.9 (q, Me). EI-HRMS: 196.0681 ($M^+$, $C_9H_{12}N_2OS^+$; calcd. 196.0670).

***Ethyl 1-allyl-2,3-dihydro-5-methyl-2-thioxoimidazole-4-carboxylate (5c).*** The crude product was purified by flash chromatography on silica using AcOEt to give **5c** in 52% yield (1.17 g). Colorless crystals, mp 146–148°C ($CHCl_3$/petroleum ether). IR (KBr): ν 3150–2900s (br.), 1698 vs, 1497m, 1462m, 1417s, 1372m, 1359m, 1267m, 1173m, 1158m, 1088m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 11.10 (br. s, 1H, NH); 6.01–5.82 (m, 1H, —CH=); 5.28–5.04 (m, 2H, $=CH_2$); 4.81–4.74 (m, 2H, $—CH_2—$); 4.34 (q, $J$ = 7.1, 2H, Me$CH_2$O); 2.47 (s, 3H, Me); 1.38 (t, $J$ = 7.1, 3H, *Me*$CH_2$O). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 162.4 (s, C=S); 158.6 (s, C=O); 134.8, 115.5 (2s, C(4), C(5)); 130.7 (d, —CH=); 117.4 (t, $=CH_2$); 60.8 (t,

Me*C*$H_2$O); 46.3 (t, $CH_2$N); 13.9 (q, *Me*$CH_2$O); 9.9 (q, Me). EI-HRMS: 226.0777 ($M^+$, $C_{10}H_{14}N_2O_2S^+$; calcd. 226.0776).

***1-Allyl-2,3-dihydro-5-methyl-N-phenyl-2-thioxoimidazole-4-carboxamide (5d).*** Yield 2.43 g (89%). Colorless solid, mp 259–262°C (decomp.) (EtOH). IR (KBr): ν 3252m, 3200–2900s (br.), 1640vs, 1599m, 1533m, 1497m, 1447s, 1403m, 1362m, 761m. $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 12.53, 9.56 (2br.s, 2H, 2 NH); 7.60–7.56 (m, 2 arom. H); 7.32–7.24 (m, 2 arom. H); 7.07–6.99 (m, 1 arom. H); 5.92–5.76 (m, 1H, ═CH═); 5.12 (dd, $J$ = 10.4, 1.2, 1H); 4.92 (dd, $J$ = 17.2, 1.4, 1H); 4.66–4.64 (m, 2H, ═$CH_2$═); 2.38 (s, 3H, Me). $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 161.6, 156.5 (2s, C═O, C═S); 138.4, 133.4, 117.7 (3s, 1 C(Ph), C(4), C(5)); 131.9 (d, ═CH═); 128.8, 123.8, 119.7 (3d, 5 CH(Ph)); 116.8 (t, ═$CH_2$); 45.6 (t, ═$CH_2$═); 9.9 (q, Me). EI-HRMS: 273.0940 ($M^+$, $C_{14}H_{15}N_3OS^+$; calcd. 273.0936).

***1-Allyl-2,3-dihydro-4-methyl-5-phenylimidazole-2-thione (5e).*** The crude *N*-oxide **1e** prepared according to the general protocol was subsequently transformed into **5e** by treatment with **4** in $CH_2Cl_2$ solution [3]. Pure product was obtained by flash chromatography on silica using acetone, then MeOH, in 39% overall yield (0.83 g). Colorless needles, mp 164–165°C (EtOH). IR (KBr): ν 3150–2900vs (br.), 1599m, 1506s, 1485m, 1424m, 1388m, 1243m, 1198m, 763m, 700m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 12.39 (br. s, 1H, NH); 7.46–7.40 (m, 3 arom. H); 7.32–7.27 (m, 2 arom. H); 5.95–5.76 (m, 1H, ═CH═); 5.20–4.88 (m, 2H, ═$CH_2$); 4.62–4.58 (m, 2H, ═$CH_2$═); 2.16 (s, 3H, Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 158.8 (s, C═S); 132.1 (d, ═CH═); 130.2, 128.8, 128.7 (3d, 5 CH(Ph)); 128.3, 127.4, 122.2 (3s, 1 C(Ph), C(4), C(5)); 117.3 (t, ═$CH_2$); 46.9 (t, ═$CH_2$═); 9.3 (q, Me). EI-HRMS: 230.0882 ($M^+$, $C_{13}H_{14}N_2S^+$; calcd. 230.0878).

***1-Allyl-2,3-dihydro-4,5-diphenylimidazole-2-thione (5f).*** Yield 2.22 g (76%). Colorless crystals, mp 293–296°C (EtOH). IR (KBr): ν 3100–2900vs (br.), 1508m, 1493s, 1482s, 1425m, 1397m, 1388m, 1238m, 1199m, 918m, 773s, 702s. $^1$H-NMR (200 MHz, $CDCl_3$): δ 11.36 (br. s, 1H, NH); 7.48–7.43 (m, 3 arom. H); 7.35–7.31 (m, 2 arom. H); 7.24 (s, 5 arom. H); 5.93–5.77 (m, 1H, ═CH═); 5.18–4.89 (m, 2H, ═$CH_2$); 4.62–4.57 (m, 2H, ═$CH_2$═). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 160.7 (s, C═S); 131.9 (d, ═CH═); 134.2, 128.5, 127.4, 125.4 (4s, 2 C(Ph), C(4), C(5)); 131.1, 129.6, 129.1, 128.8, 128.0, 126.4 (6d, 10 CH(Ph)); 117.8 (t, ═$CH_2$); 47.1 (t, ═$CH_2$═). EI-HRMS: 292.1047 ($M^+$, $C_{18}H_{16}N_2S^+$; calcd. 292.1034).

**Synthesis of 5,6-disubstituted 2,3-dihydro-2-(iodomethyl)-imidazo[2,1-*b*]thiazoles (9a–f).** To a solution (or suspension) of the corresponding imidazoline-2-thione **5** (10 mmol) in dry ethanol (*ca*. 20 mL), an equimolar amount of nicely powdered iodine (2.54 g) was added in small portions, and vigorous stirring was continued for 24 h at room temperature. The resulting mixture was cooled and the yellow precipitate of crude **8** was filtered off. After evaporation of the solvent, the residue was washed with few portions of ether, filtered off and combined. If necessary, the crude hydroiodide **8** was recrystallized from hot EtOH. The obtained salt was suspended in ethanol (*ca*. 10 mL), an aqueous solution (5%) of AcONa (1.64 g, 20 mmol) was added, and stirring was continued for 1 h at room temperature. The resulting product **9** was filtered off and crystallized from an appropriate solvent.

***2,3-Dihydro-2-iodomethyl-5,6-dimethylimidazo[2,1-b]thiazole (9a).*** The isolated hydroiodide **8a** was dissolved in ethanol (*ca*. 5 mL), an aqueous solution (5%) of AcONa (20 mmol) was added, and the solution was stirred for 30 min at room temperature. The mixture was extracted with chloroform, the combined organic phases were washed with an aqueous solution (10%) of $Na_2S_2O_3$, dried ($CaCl_2$), and after filtration the solvent was evaporated. The crude product was purified by flash chromatography on silica ($CHCl_3$) to give 1.06 g (36%) of **9a** as a colorless solid; mp 83–86°C (decomp., $CHCl_3$). IR (KBr): ν 3010–2870vs (br.), 1585m, 1483s, 1452m, 1421m, 1382m, 1367m, 1314m, 1227m, 1187m, 807m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 4.42–4.29 (m, 1H); 4.00–3.85 (m, 2H); 3.45 (dd, $J$ = 10.2, 4.7, 1H); 3.31 (t, $J$ = 10.5, 1H); 2.02, 1.99 (2s, 6H, 2 Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 143.2, 137.8, 121.3 (3s, 3 C(imidazole)); 51.9 (d, CH); 49.4 (t, $CH_2$N); 12.8, 8.8 (2q, 2 Me); 8.1 (t, $CH_2$I). EI-HRMS: 293.9689 ($M^+$, $C_8H_{11}IN_2S^+$; calcd. 293.9688).

*Selected Data for* ***8a***. Yellow crystals. mp 146–149°C (decomp., EtOH). IR (KBr): 3054vs (br.), 2960–2870vs, 1646m, 1498m, 1442m, 1176m. $^1$H-NMR (80 MHz, $CD_3OD$): δ 5.18–4.93 (m, 1H); 4.54 (dd, $J$ = 12.0, 7.7, 1H); 4.35 (dd, $J$ = 12.0, 4.0, 1H); 3.78 (s, 1H); 3.74 (d, $J$ = 5.8, 1H); 2.25 (s, 6H, 2 Me).

***6-Acetyl-2,3-dihydro-2-iodomethyl-5-methylimidazo[2,1-b]thiazole (9b).*** Yield 2.09 g (65%). Yellow crystals, mp 152–153°C (EtOH). IR (KBr): ν 1655vs, 1547s, 1492m, 1464m, 1411w, 1370s (br.), 1282m, 1212m, 1178m, 1158s, 951m, 548m. $^1$H-NMR (400 MHz, $CDCl_3$): δ 4.52–4.45 (m, 1H); 4.13–4.04 (m, 2H); 3.54 (dd, $J$ = 10.4, $J$ = 4.0, 1H); 3.36 (t, $J$ = 10.8, 1H); 2.48, 2.42 (2s, 6H, 2 Me). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 195.0 (s, C═O); 145.3, 141.7, 133.6 (3s, 3 C(imidazole)); 52.2 (d, CH); 49.3 (t, $CH_2$N); 27.3 (q, *Me*CO); 11.2 (q, Me); 7.3 (t, $CH_2$I). EI-HRMS: 321.9648 ($M^+$, $C_9H_{11}IN_2OS^+$; calcd. 321.9637).

*Selected data for* ***8b***. Yellow needles, mp 178–180°C (EtOH). IR (KBr): ν 3040–2750vs (br.), 1664vs, 1590m, 1525m, 1483m, 1412s, 1340m, 1303m, 1239m, 1179m. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 5.01–4.94 (m, 1H); 4.50 (dd, $J$ = 12.0, 7.6, 1H); 4.25 (dd, $J$ = 12.0, 4.0, 1H); 3.79–3.71 (m, 2H); 2.53, 2.44 (2s, 6H, 2 Me).

***Ethyl 2,3-dihydro-2-iodomethyl-5-methylimidazo[2,1-b]thiazole-6-carboxylate (9c).*** The crude **8c** was suspended in ethanol (5 mL), an aqueous solution (5%) of AcONa (20 mmol) was added, and the solution was stirred for 30 min at room temperature. The mixture was extracted with few portions of chloroform, the combined organic phases were washed with an aqueous solution (10%) of $Na_2S_2O_3$ and dried ($CaCl_2$), and the solvent was evaporated to give **9c** in 61% overall yield (2.14 g). Colorless solid, mp 130–134°C (decomp., $CHCl_3$). IR (KBr): ν 1694vs, 1497s, 1459m, 1396m, 1376m, 1345m, 1195m, 1173s, 1157s, 1089m, 782m. $^1$H-NMR (400 MHz, $CDCl_3$): δ 4.53–4.48 (m, 1H); 4.27 (q, $J$ = 7.2; Me*C*$H_2$O); 4.15 (dd, $J$ = 11.6, 7.2, 1H); 4.05 (dd, $J$ = 11.6, 4.0, 1H); 3.53 (dd, $J$ = 10.4, 4.8, 1H); 3.38 (t, $J$ = 10.4, 1H); 2.46 (s, 3H, Me); 1.31 (*t*, J = 7.0, *Me*$CH_2$O). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 163.1 (s, C═O); 146.6, 135.0, 132.8 (3s, 3 C(imidazole)); 60.4 (t, Me*C*$H_2$O); 52.2 (d, CH); 49.7 (t, $CH_2$N); 14.4, 10.9 (2q, 2 Me); 7.8 (t, $CH_2$I). EI-HRMS: 351.9779 ($M^+$, $C_{10}H_{13}IN_2O_2S^+$; calcd. 351.9742).

***2,3-Dihydro-2-iodomethyl-5-methyl-N-phenylimidazo[2,1-b]thiazole-6-carboxamide (9d).*** Yield 2.97 g (74%). Colorless crystals, mp 195–203°C (decomp., EtOH). IR (KBr): ν 3281m,

1656s, 1593s, 1569m, 1523s, 1490s, 1440s, 1385m, 1301m, 1235m, 1189m, 1173m, 756m. $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 9.68 (br s, 1H, NH); 7.84–7.80 (m, 2 arom. H); 7.34–7.26 (m, 2 arom. H); 7.07–7.00 (m, 1 arom. H); 4.86–4.80 (m, 1H); 4.36 (dd, $J$ = 11.6, 7.6, 1H); 4.05 (dd, $J$ = 11.6, 4.8, 1H); 3.75–3.65 (m, 2H); 2.53 (s, 3H, Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 161.1 (s, C=O); 144.5, 139.0, 134.3, 132.6 (4s, 1 C(Ph), 3 C(imidazole)); 128.5, 122.9, 119.7 (3d, 5 CH(Ph)); 53.2 (d, CH); 49.1 (t, $CH_2N$); 10.4 (t, $CH_2I$); 10.2 (q, Me). EI-HRMS: 398.9917 ($M^+$, $C_{14}H_{14}IN_3OS^+$; calcd. 398.9902).

***2,3-Dihydro-2-iodomethyl-6-methyl-5-phenylimidazo[2,1-b]thiazole (9e).*** Workup analogous to that described for **9a** gave 1.39 g (39%) of **9e** as a colorless semi-solid after column chromatography (silica, $CHCl_3$/AcOEt 9:1). IR (KBr): ν 1603m, 1492m, 1474m, 1457s, 1423m, 1376m, 764m, 700m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 7.49–7.42 (m, 2 arom. H); 7.36–7.29 (m, 3 arom. H); 4.54–4.41 (m, 1H); 4.18 (d, $J$ = 5.2, 2H); 3.61–3.41 (m, 2H); 2.28 (s, 3H, Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 146.2, 140.1, 130.7, 129.7 (4s, C(Ph), 3 C(imidazole)); 128.8, 127.7, 127.3 (3d, 5 CH(Ph)); 52.2 (d, CH); 51.2 (t, $CH_2N$); 14.0 (q, Me); 7.7 (t, $CH_2I$). EI-HRMS: 355.9851 ($M^+$, $C_{13}H_{13}IN_2S^+$; calcd. 355.9844).

*Selected data for **8e**.* Pale yellow solid, mp 108–109°C (decomp., $CHCl_3$). IR (KBr): ν 3000–2450vs (br.), 1624m, 1598m, 1504m, 1515m, 1200m, 766m, 749m, 701m. $^1$H-NMR (80 MHz, $CDCl_3$): δ 7.51 (s, 5 arom. H); 5.37–5.04 (m, 1H); 4.69 (dd, $J$ = 12.0, 7.2, 1H); 4.28 (dd, $J$ = 12.0, 4.0, 1H); 4.01–3.75 (m, 2H); 2.43 (s, 3H, Me).

***2,3-Dihydro-2-iodomethyl-5,6-diphenylimidazo[2,1-b]thiazole (9f).*** Yield 2.17 g (52%). Colorless solid, mp 173–176°C (decomp., EtOH). IR (KBr): ν 1600m, 1504m, 1475s, 1456m, 1441m, 1336m, 1123w, 965w, 772s, 700s. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.52–7.33 (m, 7 arom. H); 7.28–7.17 (m, 3 arom. H); 4.57–4.50 (m, 1H); 4.20 (dd, $J$ = 11.6, 6.8, 1H); 4.13 (dd, $J$ = 11.6, 4.0, 1H); 3.61 (dd, $J$ = 10.4, 4.8, 1H); 3.53 (t, $J$ = 10.6, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 147.2, 142.2, 134.0, 130.2, 127.0 (5s, 2 C(Ph), 3 C(imidazole)); 130.8, 129.2, 129.1, 128.5, 128.3, 126.9 (6d, 10 CH(Ph)); 52.4 (d, CH); 51.2 (t, $CH_2N$); 7.7 (t, $CH_2I$). EI-HRMS: 418.0009 ($M^+$, $C_{18}H_{11}IN_2OS^+$; calcd. 418.0002).

*Selected data for **8f**.* Pale yellow solid, mp 212–218°C (decomp., EtOH). IR (KBr): ν 3050–2700vs (br.), 1514s, 1443m, 1173m, 1100m, 769s, 733m, 698s. $^1$H-NMR (80 MHz, $CDCl_3$): δ 7.52, 7.38 (2s, 10 arom. H); 5.19–4.94 (m, 1H); 4.65 (dd, $J$ = 12.0, 7.4, 1H); 4.32 (dd, $J$ = 12.0, 4.5, 1H); 3.83 (d, $J$ = 6.4, 2H).

**Synthesis of 5,6-disubstituted 2,3-dihydro-2-methylidenimidazo[2,1-*b*]thiazoles (10).** To a solution of **9** (1.0 mmol) in ethanol (5 mL), freshly distilled $Et_3N$ (3.0 mmol, 0.30 g) was added and the resulting solution was refluxed for 3 h. The mixture was cooled to room temperature, filtered through a Celite plug, and the solvents were evaporated. Purification by flash chromatography (silica, $CHCl_3$) gave pure substance.

***2,3-Dihydro-5,6-dimethyl-2-methylidenimidazo[2,1-b]thiazole (10a).*** Yield 53 mg (32%). Mp 107–110°C ($CHCl_3$). Decomposes during the storage at room temperature. IR (KBr): ν 2922s (br.), 1624m, 1482s, 1443s, 1374m, 1304m, 1266m, 1170m, 862m. $^1$H-NMR (200 MHz, $CDCl_3$): δ 5.39 (q-like, $J$ ≈ 2.3, 1H); 5.29 (q-like, $J$ ≈ 2.5, 1H); 4.67 (t, $J$ = 2.5, 2H); 2.11 (s, 6H, 2 Me). $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 142.9, 142.5, 137.3, 121.4 (4s, 4 C); 107.9 (t, $=CH_2$); 49.8 (t, $CH_2$); 12.9, 8.9 (2q, 2 Me).

***6-Acetyl-2,3-dihydro-5-methyl-2-methylidenimidazo[2,1-b]thiazole (10b).*** Yield 0.12 g (62%). Mp 82–85°C ($CH_2Cl_2$/hexane). IR (KBr): ν 1656vs, 1631m, 1550s, 1499m, 1460m, 1379s, 1356m, 1187m, 1166m, 951m, 891m. $^1$H-NMR (400 MHz, $CDCl_3$): δ 5.40 (q-like, $J$ ≈ 2.3, 1H); 5.31 (q-like, $J$ ≈ 2.7, 1H); 4.70 (t, $J$ = 2.4, 2H); 2.44, 2.41 (2s, 6H, 2 Me). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 195.0 (s, C=O); 144.9, 141.0, 140.5, 137.2 (4s, 4 C); 109.5 (t, $=CH_2$); 49.2 (t, $CH_2$); 27.3 (q, *Me*CO); 11.0 (q, Me). EI-HRMS: 194.0529 ($M^+$, $C_9H_{10}IN_2OS^+$; calcd. 194.0515).

**Synthesis of 2,3-dihydro-5,6-diphenyl-2-{[(1,4,5-trimethyl-1*H*-imidazol-2-yl)sulfanyl]methyl}imidazo[2,1-*b*]thiazole (11).** A mixture of equimolar amounts of **9f** (0.8 g, 1.9 mmol) and 1,4,5-trimethyl-2,3-dihydroimidazole-2-thione (**5g**, 0.27 g, 1.9 mmol) in ethanol (10 mL) was heated to reflux for 48 h. Then, half of the solvent was evaporated, the resulting solution treated with AcONa (0.35g, 5% aqueous solution), vigorously stirred, and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were dried ($CaCl_2$), filtered, and the solvent was evaporated to dryness. The resulting solid was purified by column chromatography (silica, $CHCl_3$/AcOEt 1:1) to give 0.26 g (32%) of **11** as a colorless solid. Mp 155–157°C (acetone). IR (KBr): ν 2920m, 1602m, 1504m, 1477m, 1458s, 1441s, 1394m, 1335m, 1123m, 769m, 697s. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.41–7.07 (m, 10 arom. H); 4.55–4.50 (m, 1H); 4.22 (dd, $J$ = 11.6, 6.8, 1H); 4.07 (dd, $J$ = 11.6, 4.8, 1H); 3.70–3.62 (m, 1H); 3.45 (s, 3H, MeN); 3.36 (dd, $J$ = 14.0, 7.2, 1H); 2.13, 2.07 (2s, 6H, 2 Me). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 147.4, 142.4, 136.1, 134.4, 132.3, 130.4, 127.6, 126.4 (8s, 8 C); 129.1, 129.0, 128.3, 128.2, 126.9, 126.7 (6d, 10 CH(Ph)); 52.0 (d, CH); 49.9, 39.4 (2t, 2 $CH_2$); 31.6, 11.5, 9.1 (3q, 3 Me). EI-HRMS: 432.1453 ($M^+$, $C_{24}H_{24}N_4S_2^+$; calcd. 432.1442).

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## REFERENCES AND NOTES

[1] Presented these results at the 22nd International Congress on Heterocyclic Chemistry, St. John's, Canada, August 2-7, 2009.

[2] (a) Mlostoń, G.; Jasiński, M.; Linden, A.; Heimgartner, H. Helv Chim Acta 2006, 89, 1304; (b) Mlostoń, G.; Mucha, P.; Urbaniak, K.; Broda, K.; Heimgartner, H. Helv Chim Acta 2008, 91, 232; (c) Mucha, P.; Mlostoń, G.; Jasiński, M.; Linden, A.; Heimgartner, H. Tetrahedron: Asymmetry 2008, 19, 1600; (d) Jasiński, M.; Mlostoń, G.; Linden, A.; Heimgartner, H. Helv Chim Acta 2008, 91, 1916; (e) Mlostoń, G.; Mucha, P.; Tarka, R.; Urbaniak, K.; Linden, A.; Heimgartner, H. Pol J Chem 2009, 83, 1105; (f) Mlostoń, G.; Romański, J.; Jasiński, M.; Heimgartner, H. Tetrahedron: Asymmetry 2009, 20, 1073.

[3] Mlostoń, G.; Gendek, T.; Heimgartner, H. Helv Chim Acta 1998, 81, 1585.

[4] Müller, H. Liebigs Ann Chem 1895, 284, 25.

[5] Jones, R. G.; Kornfeld, E. C.; McLaughlin, K. C.; Anderson, R. C. J Am Chem Soc 1949, 71, 4000.

[6] (a) Neuberg, C.; Wolff, H. Ber Dtsch Chem Ges 1901, 34, 3840; (b) Krüger, F.; Rudy, H. Liebigs Ann Chem 1963, 669, 146.

[7] Doney, J. J.; Altland, H. W. J Heterocycl Chem 1979, 16, 1057.

[8] Khripak, S. M.; Slivka, M. V.; Vilkov, R. V.; Usenko, R. N.; Lendel, V. G. Chem Heterocycl Compd 2007, 43, 781.

[9] Korotkikh, N. I.; Raenko, G. F.; Aslanov, A. F.; Shvaika, O. P. Chem Heterocycl Compd 1994, 30, 621.

[10] Karimian, K. Expert Opin Ther Pat 2009, 19, 369.

[11] (a) Gürsoy, E.; Güzeldemirci, N. U. Eur J Med Chem 2007, 42, 320; (b) Meriç, A.; Incesu, Z.; Hatipoglu, I. Med Chem Res 2008, 17, 30; (c) Kamali, T. A.; Bakherad, M.; Nasrollahzadeh, M.; Farhangi, S.; Habibi, D. Tetrahedron Lett 2009, 50, 5459.

[12] (a) Shilcrat, S. C.; Hill, D. T.; Bender, P. E.; Griswold, D. E.; Bauers, P. W.; Eggleston, D. S.; Lantos, I.; Pridgen, L. N. J Heterocycl Chem 1991, 28, 1181; (b) Bender, P. E.; Hill, D. T.; Offen, P. H.; Razgaitis, K.; Lavanchy, P.; Stringer, O. D.; Sutton, B. M.; Griswold, D. E.; DiMartino, M.; Walz, D. T.; Lantos, I.; Ladd, C. B. J Med Chem 1985, 28, 1169; (c) Nagarajan, K.; Bhat, G. A. Indian J Chem Sect B 1977, 15, 629; (d) Mazur, I. A.; Kochergin, P. M.; Fomenko, V. I. Pharm Chem J 1969, 8, 436.

[13] Barluenga, J.; Pérez Carlón, R.; Joglar, J.; López Ortiz, F. Tetrahedron 1993, 49, 6619.

[14] Ikeda, K.; Hata, S.; Tanaka, Y.; Yamamoto, T. Org Prep Proced Int 2000, 32, 401.

[15] Barluenga, J.; Bayón, A. M.; Campos, P.; Asensio, G.; Gonzalez-Nuñez, E.; Molina, Y. J Chem Soc Perkin Trans 1 1988, 1631.

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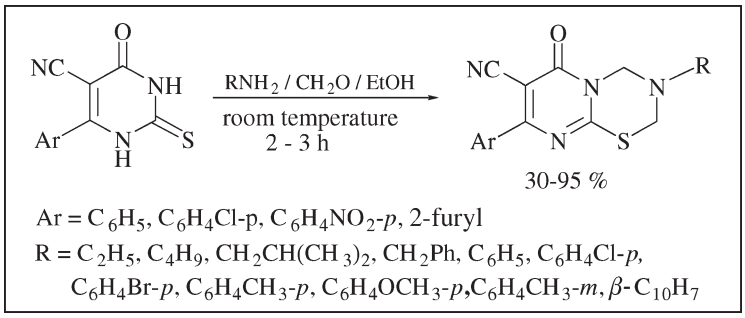


Reaction of 6-aryl-5-cyano-2-mercapto-3,4-dihydropyrimidin-4-ones with formaldehyde and primary amines in suitable solvent via a double Mannich reaction gave the corresponding 8-aryl-7-cyano-3-*N*-substituted-pyrimido[2,1-b]-1,3,5-thiadiazin-6-ones rather than the isomeric products 6-aryl-7-cyano-3-N-substituted-pyrimido[2,1-b]-1,3,5-thiadiazin-8-ones. The cyclization method was found to be the most favored for the formation of the linear products rather than the angular isomers. This was confirmed not only by using spectral analysis and molecular mechanical calculations but also by X-ray single crystal structure determination.

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## INTRODUCTION

Although a few publications have been appeared since last 12 years describing the synthesis of 1,3,5-thiadiazines but literature survey on this class of heterocyclic system showed that 1,3,5-thiadiazines and its fused heterocycles possess a broad spectrum of biological interest [1]. It was found that functionalized thiadiazines have insecticidal [2], antibacterial [3], herbicidal [4], and fungicidal [5] effects. The broad biological activities of pyrimidine [6–12] and fused pyrimidine derivatives, prompted us to synthesize new derivative of pyrimidines fused heterocycles. During last decade, we were investigating the behavior of Mannich reaction toward the multifunctional heterocyclic compounds such as 5-mercapto-3-aryl-1,2,4-triazole (Fig. 1). We investigated this reaction in acidic, basic, and neutral mediums, and we concluded that in all cases only one isomeric product **1** was isolated, rather than the other isomeric products **2** [13–15].

Those findings encouraged us to investigate continually the use of functionality factor and the reaction medium. One of the advantages of this reaction is a wide variety to synthesize a number of varieties of poly heterocyclic compounds in one pot reaction which is difficult to obtain by another procedure. Pyrazolothiadiazines [13], Triazolothiadiazines [13,15], and thiadiazinobenzimidazoles [14] were also obtained in high-yields using double or triple Mannich reaction in one pot reaction. We have recently described that similar compounds could be synthesized *via* modification of Mannich reaction using di-functional compounds [13–15]. We found that the cyclization reactions to form the corresponding thiadiazines 1 are different from that reported by Wang and co-workers [16]. They suggested that the thiadiazine derivatives **2** were formed rather than the isomeric derivatives **1**.

In our laboratory, we investigated the Mannich reaction of polyfunctional heterocyclic compounds like 5-mercaptotriazoles, 5-aminopyrazoles, and 2-mercaptobenzimidazoles, which gave the corresponding 1,2,4-triazolo[3,2-b]-1,3,5-thiadiazines **1**, pyrazolo[3,4-d]pyrimidines **3**, and 1,3,5-thiadiazino[3,2-a]benzimidazoles **4**, respectively in high-yield [13–15] (Fig. 2).

## RESULTS AND DISCUSSION

In this study, we focused on the susceptibility and selectivity of the cyclization of 6-aryl-5-cyano-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**5a–d**) towards the double Mannich reaction. On treatment of the poly

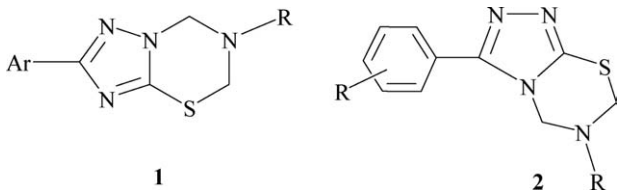


**Figure 1.** 1,2,4-Triazolo[3,2-b]-1,3,5-thiadiazines **1** and **2**.

functional compounds **5a–d** with one equivalent of variant primary aliphatic and aromatic amines with excess of formaldehyde (37%) in ethanol, ethanol/dioxane and ethanol/acetic acid at room temperature the reaction might proceed to afforded the corresponding 8-aryl-7-cyano-3-N-substituted-pyrimido[2,1-b]-1,3,5-thiadiazin-6-ones (**6–9**) or the other isomeric products 6-aryl-7-cyano-3-N-substituted-pyrimido[2,1-b]-1,3,5-thiadiazin-8-ones (**10–13**) or possible a mixture of both isomeric products. However, based on TLC the reaction gave only single isolable products **6–9** in high-yields, (Scheme 1).

The IR spectra of the products lacked the NH absorption peaks and showed the C≡N and C=O peaks at 2220–2240 and 1650–1700 $cm^{-1}$, respectively, whereas the $^1$H-NMR spectra of the reaction products were characterized by the appearance of two signals at δ 5.9–4.8 and 6.1–5.0 attributed to the two methylene groups $SCH_2N$ and $NCH_2N$ respectively in addition to the other protons at the expected chemical shifts. The Mass spectra of the synthesized compounds showed the expected molecular ion peaks and its CHNS analysis were found to be in agreement with the calculated ones. All these data presented here can't confirm which one of these isomers, **6–9** and **10–13** is formed.

We need a solid argument to prove whether the isomeric products formed **6–9** or **10–13**. This directed us to think about the tautomerism of compound **5a–d**, whether their structure existed in the form A or B. For example compound **5a** ($R$ = Ph) is in equilibrium with the two forms A and B as shown in Figure 3.

Based on resonance effect, the tautomer A is more favorable than B as both the CN and CO groups are conjugated with the diene system. Further, this assumption was supported by the molecular mechanics calculations–MMXE, which showed that tautomer A is more stable than B. If double Mannich reaction occurred with tautomer A the product will be the isomeric compounds **6–9**, whereas, the isomeric products **10–13** could be obtained in case of the existence of the tautomer B in the reaction medium (Figure 3).

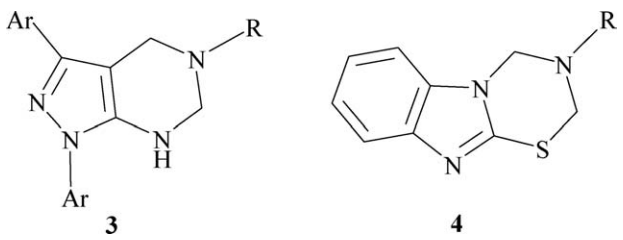
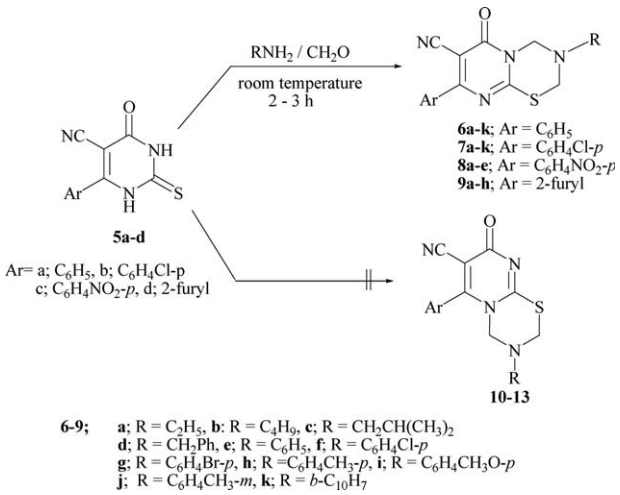


**Figure 2.** Pyrazolo[3,4-d]pyrimidines **3** and 1,3,5-thiadiazino[3,2-a]benzimidazoles **4**.

**Scheme 1.** Synthesis of pyrimido[2,1-b]-1,3,5-thiadiazines **6–9**.




Mechanistically, the formation of the cyclized compounds could be explained either by the addition of SH (route a) or NH (route b) group to the formed imines, which resulted from the condensation of formaldehyde with primary amine, (Scheme 2; Table 1). Based on both molecular modeling study and X-ray analysis of **6h** (Figures 4 and 5), the structure of the reaction product was assigned as the isomeric products **6–9** of lower energy rather than the isomeric products **10–13**. The formation of single product only indicates that the reaction is proceeded regioselectively. Recently, similar results were obtained by Dotsenko et al [17].

X-ray analysis of compound **6h** (Ar = $C_6H_5$, R = $C_6H_4CH_3$-$p$) $C_{20}H_{16}N_4OS$ VA/01/890 $P2_1/c$ 150K IPDS, Bond Distances (Ångstroms) (see Table 2–4).

## BIOLOGICAL ACTIVITY

The antimicrobial activity of some synthesized compounds were determined by the usual disk assay [18] at

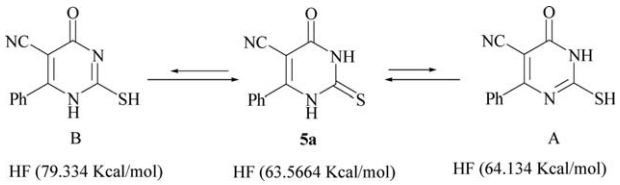
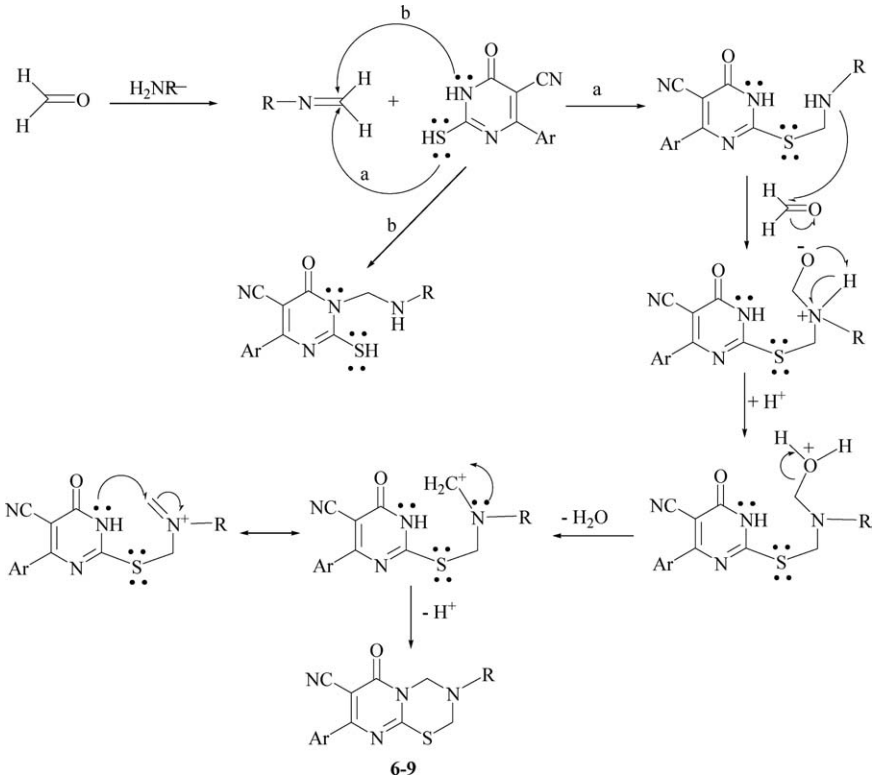



**Figure 3.** Tautomerism of the thiouracil derivative.

**Scheme 2.** The suggested mechanism of formation of the isomers **6–9**.




a concentration of ($10^{-3}$ mol) per disk Inhibition zones in (cm) around filter paper disks (3 mm in diameter) were measured and the average of these reading was considered. From the antimicrobial used such as: a, *Bacillus cereus*; b, *E. coli*.

| Compound no. | +Ve bacterial *Bacillus* | Diameter of inhibitor (cm) | −Ve bacterial *E. Coli* | Diameter of inhibitor (cm) |
|---|---|---|---|---|
| **6a** | + | 0.6 | + | 1.5 |
| **6f** | + | 1 | + | 2 |
| **6h** | + | 0.2 | + | 0.9 |
| **7c** | + | 0.7 | + | 1 |
| **7i** | + | 0.3 | + | 1 |
| **7k** | − | − | + | 0.8 |
| **8b** | + | 0.7 | + | 2 |
| **8d** | + | 0.5 | + | 2.2 |
| **9e** | − | − | + | 1 |
| **9g** | − | − | + | 0.9 |
| **DMSO** | − | − | − | − |
| **CHL** | + | 4 | + | 3.2 |

CHL, chloramphenicol as standard.

The antimicrobial activity study revealed that all compounds screened showed moderate to weak antimicrobial activity, except compounds **6f**, **8b**, and **8d** have good effect.

## EXPERIMENTAL

Melting points were determined using Gallen Camp melting point apparatus and are uncorrected. The IR-spectra were measured on a Shimatzu-470 spectrometer using KBr technique (ν $cm^{-1}$). The $^1$H-NMR spectra were measured on a Varian EM-390,90MHz spectrometer (Spectral Unit, Assuit University, Egypt) and dx 500.13 MHz spectrometer (Department of Physical Chemistry, Geneva) using $CDCl_3$, DMSO- $d_6$ as a solvent and TMS was used as internal standard, δ ppm. The $^{13}$C-NMR spectra were measured on dx 125.77 MHz spectrometer. The mass spectra were recorded on Jeol-Jms-600H spectrometer using the direct inlet system. The elemental analyses were performed using Perkin-Elmer elemental analyzer 240-C and the X-ray diffraction analysis from faculty of science, Geneva University.

**General procedures for synthesis of 8-Arylpyrimido[2,1-b]-1,3,5-thiadiazine derivatives.** A mixture of 5-Cyano-4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine (1.0 mmole), primary amines (1.1 mmole) and formaldehyde (2 mL) was stirred in appropriate solvent (20 mL) at room temperature for 2–3 h. The resulting precipitate was collected by filtration, washed with water several times and dried well. The crude product was crystallized from the proper solvent to give the corresponding 8-phenyl-pyrimido[2,1-b]-1,3,5-thiadiazine derivatives.

***8-phenylpyrimido [2,1-b]-1,3,5-thiadiazine derivatives (6a-k).*** These compounds were obtained according to general method using ethanol as solvent.

***7-Cyano-3-ethyl-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6a).*** This compound was obtained as

**Table 1**

Heat of formations based on the molecular mechanics calculation (MMXE) of compounds **6–13**.

| No. | HF | No. | HF | No. | HF | No. | HF |
|---|---|---|---|---|---|---|---|
| **6a** | 87.700 | **10a** | 94.335 | **7i** | 80.360 | **11i** | 90.103 |
| **6b** | 71.456 | **10b** | 80.758 | **7j** | 110.106 | **11j** | 120.492 |
| **6c** | 124.489 | **10c** | 134.379 | **7k** | 136.573 | **11k** | 147.192 |
| **6d** | 117.719 | **10d** | 127.728 | **8a** | 89.755 | **12a** | 100.910 |
| **6e** | 129.488 | **10e** | 139.751 | **8b** | 76.137 | **12b** | 87.456 |
| **6f** | 116.817 | **10f** | 126.548 | **8c** | 79.074 | **12c** | 89.953 |
| **6g** | 87.322 | **10g** | 96.342 | **8d** | 121.659 | **12d** | 138.179 |
| **6h** | 116.841 | **10h** | 126.789 | **8e** | 129.529 | **12e** | 140.051 |
| **6i** | 143.271 | **10i** | 152.725 | **9a** | 69.418 | **13a** | 77.689 |
| **7a** | 78.220 | **11a** | 88.028 | **9b** | 55.812 | **13b** | 64.038 |
| **7b** | 64.609 | **11b** | 74.510 | **9c** | 56.745 | **13c** | 67.415 |
| **7c** | 67.551 | **11c** | 77.080 | **9d** | 102.831 | **13d** | 113.416 |
| **7d** | 111.687 | **11d** | 124.945 | **9e** | 108.786 | **13e** | 119.086 |
| **7e** | 117.747 | **11e** | 127.917 | **9f** | 102.033 | **13f** | 110.748 |
| **7f** | 110.986 | **11f** | 121.719 | **9g** | 113.843 | **13g** | 122.864 |
| **7g** | 122.764 | **11g** | 133.586 | **9h** | 101.168 | **13h** | 110.01 |
| **7h** | 110.371 | **11h** | 120.005 | | | | |

HF, heat of formation (kcal/mol).

colorless crystals from ethanol, yield (0.25 g, 84 %). Mp 148–150°C. IR (KBr): 3050, 2995, 2200, 1660, 1520, 1470 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 1.1 (t, *J* = 2.7 Hz, 3H, $NCH_2CH_3$), 2.7 (q, *J* = 2.7 Hz, 2H, $NCH_2CH_3$), 4.6 (s, 2H, $SCH_2N$), 4.9 (s, 2H, $NCH_2N$), 7.0–8.1 ppm (m, 5H, arom-H).

Anal. Calcd for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78; S, 10.75. Found: C, 60.12; H, 4.60; N, 18.77; S, 10.76.

***3-Butyl-7-cyano-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6b).*** This compound was obtained as colorless crystals from ethanol, yield (0.23 g, 71%). Mp 155–156°C. IR (KBr): 3080, 2995–2850, 2200, 1670, 1530, 1460 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 1.8 Hz, 3H, $CH_2CH_3$), 1.4 (m, 2H, $CH_2CH_3$), 2.3 (m, 2H, $NCH_2CH_2$), 2.7 (t, *J* = 2.25 Hz, 2H, $NCH_2CH_2$), 4.7 (s, 2H, $SCH_2N$), 5.0 (s, $NCH_2N$), 7.7–8.1 ppm (m, 5H, arom-H).

Anal. Calcd for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56; N, 17.16; S, 9.82. Found: C, 62.45; H, 5.50; N, 17.12; S, 9.72.

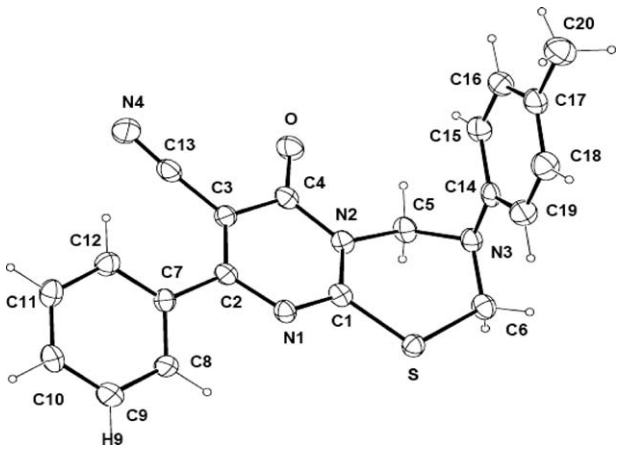



**Figure 4.** Single crystal X-ray of compound **6h** (Ar = $C_6H_5$, R = $C_6H_4CH_3$-*p*).

***7-Cyano-3-isobutyl-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6c).*** This compound was obtained as colorless crystals from ethanol, yield (0.15 g, 64%). Mp 156–158°C. IR (KBr): 3080, 2995–2800, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 0.9 (d, *J* = 2.4 Hz, 6H, CH $(CH_3)_2$), 1.8 (m, 1H, $NCH_2CH(CH_3)_2$), 2.5 (d, *J* = 2.45 Hz, 2H, $NCH_2CH$), 4.9 (s, 2H, $SCH_2N$), 5.15 (s, $NCH_2N$) 7.5–8.1 ppm (m, 4H, arom-H). Anal. Calcd for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56; N, 17.16; S, 9.82. Found: C, 62.42; H, 5.49; N, 17.10; S, 9.78.

***3-Benzyl-7-cyano-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6d).*** This compound was obtained as

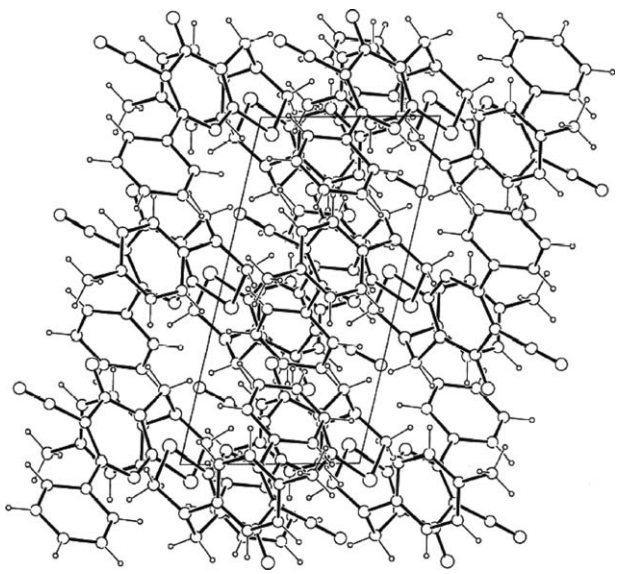


**Figure 5.** Crystal structure of compound **6h** (Ar = $C_6H_5$, R = $C_6H_4CH_3$-*p*).

**Table 2**

Bond distances (Å) of compound **6h**.

| Bond | Distance (Å) | Bond | Distance (Å) |
|---|---|---|---|
| S—C6 | 1.871(2) | S—C1 | 1.745(2) |
| N1—C1 | 1.313(2) | O—C4 | 1.228(2) |
| N2—C1 | 1.369(2) | N1—C2 | 1.357(2) |
| N2—C5 | 1.505(2) | N2—C4 | 1.405(2) |
| N3—C6 | 1.429(2) | N3—C5 | 1.438(2) |
| N4—C13 | 1.159(3) | N3—C14 | 1.433(3) |
| C2—C7 | 1.495(2) | C2—C3 | 1.398(2) |
| C3—C13 | 1.425(3) | C3—C4 | 1.460(2) |
| C7—C12 | 1.393(3) | C7—C8 | 1.403(2) |
| C9—C10 | 1.381(3) | C8—C9 | 1.392(3) |
| C11—C12 | 1.401(3) | C10—C11 | 1.383(3) |
| C14—C19 | 1.402(2) | C14—C15 | 1.396(3) |
| C16—C17 | 1.403(2) | C15—C16 | 1.384(3) |
| C17—C20 | 1.511(3) | C17—C18 | 1.378(3) |
| | | C18—C19 | 1.396(3) |

**Table 3**

Bond angles (degrees) of compound **6h**.

| Bond | Angle (degree) | Bond | Angle (degree) |
|---|---|---|---|
| C1—S—C6 | 102.49(8) | C1—N1—C2 | 119.8(1) |
| C1—N2—C4 | 120.7(1) | C1—N2—C5 | 121.2(2) |
| C4—N2—C5 | 118.1(1) | C5—N3—C6 | 110.9(1) |
| C5—N3—C14 | 117.0(2) | C6—N3—C14 | 119.9(1) |
| S—C1—N1 | 113.1(1) | S—C1—N2 | 122.9(1) |
| N1—C1—N2 | 123.9(2) | N1—C2—C3 | 120.4(2) |
| N1—C2—C7 | 114.5(1) | C3—C2—C7 | 125.1(2) |
| C2—C3—C4 | 120.3(2) | C2—C3—C13 | 126.0(2) |
| C4—C3—C13 | 113.7(1) | O—C4—N2 | 121.2(2) |
| O—C4—C3 | 124.2(2) | N2—C4—C3 | 114.6(1) |
| N2—C5—N3 | 111.1(1) | S—C6—N3 | 113.3(1) |
| C2—C7—C8 | 117.0(2) | C2—C7—C12 | 124.1(2) |
| C8—C7—C12 | 118.9(2) | C7—C8—C9 | 120.5(2) |
| C8—C9—C10 | 120.0(2) | C9—C10—C11 | 120.2(2) |
| C10—C11—C12 | 120.3(2) | C7—C12—C11 | 120.0(2) |
| N4—C13—C3 | 176.4(2) | N3—C14—C15 | 119.8(1) |
| N3—C14—C19 | 122.2(2) | C15—C14—C19 | 117.9(2) |
| C14—C15—C16 | 121.1(2) | C15—C16—C17 | 121.5(2) |
| C16—C17—C18 | 116.9(2) | C16—C17—C20 | 121.0(2) |
| C18—C17—C20 | 122.1(2) | C17—C18—C19 | 122.7(2) |
| C14—C19—C18 | 119.8(2) | | |

colorless crystals from ethanol, yield (0.28 g, 77%). Mp 162–164°C. IR (KBr): 3080, 2985, 2200, 1685, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 3.9 (s, 2H, NC$\underline{H}_2$Ph), 4.9 (s, 2H, SC$\underline{H}_2$N), 5.15 (s, 2H, NC$\underline{H}_2$N) 7.1–8.1 ppm (m, 10H, arom-H).

Anal. Calcd for $C_{20}H_{16}N_4OS$: C, 66.65; H, 4.47; N, 15.54; S, 8.90. Found: C, 66.53; H, 4.41; N, 15.50; S, 8.80.

***7-Cyano-3,8-diphenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6e).*** This compound was obtained as colorless crystals from ethanol, yield (0.27 g, 80%). Mp 214–216°C. IR (KBr): 3050, 2910, 2200, 1660, 1525, 1475 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.0 (s, 2H, SC$\underline{H}_2$N), 5.2

**Table 4**

Dihedral angles (degrees).

| Angle | Degree | Angle | Degree |
|---|---|---|---|
| C6—S—C1—N1 | −176.1(1) | C6—S—C1—N2 | 0.7(2) |
| C1—S—C6—N3 | 23.5(2) | C2—N1—C1—S | 175.7(1) |
| C2—N1—C1—N2 | −1.0(3) | C1—N1—C2—C3 | −4.4(3) |
| C1—N1—C2—C7 | 175.5(2) | C4—N2—C1—S | −170.7(1) |
| C4—N2—C1—N1 | 5.7(3) | C5—N2—C1—S | 10.1(2) |
| C5—N2—C1—N1 | −173.5(2) | C1—N2—C4—O | 175.1(2) |
| C1—N2—C4—C3 | −4.7(2) | C5—N2—C4—O | −5.6(3) |
| C5—N2—C4—C3 | 174.6(2) | C1—N2—C5—N3 | −45.6(2) |
| C4—N2—C5—N3 | 135.1(2) | C6—N3—C5—N2 | 72.5(2) |
| C14—N3—C5—N2 | −70.1(2) | C5—N3—C6—S | −60.4(2) |
| C14—N3—C6—S | 80.9(2) | C5—N3—C14—C15 | −41.7(2) |
| C5—N3—C14—C19 | 141.0(2) | C6—N3—C14—C15 | 179.2(2) |
| C6—N3—C14—C19 | 1.9(3) | N1—C2—C3—C4 | 5.0(3) |
| N1—C2—C3—C13 | −175.1(2) | C7—C2—C3—C4 | −174.9(2) |
| C7—C2—C3—C13 | 4.9(3) | N1—C2—C7—C8 | −18.9(2) |
| N1—C2—C7—C12 | 161.2(2) | C3—C2—C7—C8 | 161.0(2) |
| C3—C2—C7—C12 | −18.9(3) | C2—C3—C4—O | 179.8(2) |
| C2—C3—C4—N2 | −0.4(3) | C13—C3—C4—O | −0.1(3) |
| C13—C3—C4—N2 | 179.7(2) | C2—C7—C8—C9 | −177.8(2) |
| C12—C7—C8—C9 | 2.1(3) | C2—C7—C12—C11 | 177.8(2) |
| C8—C7—C12—C11 | −2.1(3) | C7—C8—C9—C10 | −0.6(3) |
| C8—C9—C10—C11 | −0.9(3) | C9—C10—C11—C12 | 1.0(3) |
| C10—C11—C12—C7 | 0.5(3) | N3—C14—C15—C16 | −176.5(2) |
| C19—C14—C15—C16 | 0.9(3) | N3—C14—C19—C18 | 175.5(2) |
| C15—C14—C19—C18 | −1.8(3) | C14—C15—C16—C17 | 0.8(3) |
| C15—C16—C17—C18 | −1.7(3) | C15—C16—C17—C20 | 178.9(2) |
| C16—C17—C18—C19 | 0.8(3) | C20—C17—C18—C19 | −179.8(2) |
| C17—C18—C19—C14 | 0.9(3) | | |

(s, 2H, $NCH_2N$), 6.6–7.3 ppm (m, 10H, arom-H). MS (EI, 70Ev): m/z = (%) 345.98 [$M^+$] (19.5), 285.9 (0.9), 212.91 (3.8), 211.05 (8.6), 180.02 (2.8), 178.0 (2.5), 176.0 (1.2), 169.0 (0.9), 165.0 (2.3), 158.0 (0.7), 154.93 (1.6), 153.93 (1.2), 152.98 (1.1), 149.94 (5.1), 145.94 (1.6), 145.02 (1.0), 142.03 (0.5), 140.99 (10.07), 134.06 (2.6), 133.01 (1.8), 129.06 (8.7), 128.0 (0.4), 127.0 (8.7), 122.0 (5.3), 199.0 (2.5), 118.05 (2.1), 117.04 (4.4), 107.03(2.7), 106 (42.9), 105 (100), 104.02 (93.6), 103 (2.7), 102.08 (0.5), 95.01 (2.1), 93.93 (0.7), 93.01 (4.2), 92.0 (5.3), 90.76 (16.8), 90.02 (3.9), 89.05 (6.0), 88.08 (2.6), 87 (2.2), 85.93 (15.8), 85.04 (1.2), 83.09 (1.8), 82.06 (2.1), 81.06 (1.0), 79.92 (1.1), 79.04 (6.9), 78.02 (13.1), 77.02 (46.2), 76.01 (3.8), 75.00 (4.9).

Anal. Calcd for $C_{19}H_{14}N_4OS$: C, 65.88; H, 4.07; N, 16.17; S, 9.26. Found: C, 65.80; H, 4.00; N, 16.13; S, 9.15.

***3-(4-Chlorophenyl)-7-cyano-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6f).*** This compound was obtained as yellow crystals from ethanol, yield (0.34 g, 90%). Mp 230–232°C. IR (KBr): 3060, 2940, 2200, 1680, 1540, 1470 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.5 (s, 2H, $SCH_2N$), 5.75 (s, 2H, $NCH_2N$), 7.3–7.95 ppm (m, 9H, arom-H).

Anal. Calcd for $C_{19}H_{13}ClN_4OS$: C, 59.92; H, 3.44; N, 14.71; S, 8.42. Found: C, 59.80; H, 3.41; N, 14.65; S, 8.40.

***3-(4-Bromophenyl)-7-cyano-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6g).*** This compound was obtained as green crystals from ethanol, yield (0.4 g, 95%). Mp 242-244°C. IR (KBr): 3010, 3000, 2200, 1640, 1520, 1490 $cm^{-1}$. $^1$H-NMR (500 MHz, DMSO-$d_6$): δ = 5.5 (s, 2H, $SCH_2N$), 5.7 (s, $NCH_2N$), 7.1 (d, $J$ = 10 Hz, 2H, arom-H), 7.5 (m, 5H, arom-H), 7.7 ppm (d, $J$ = 5 Hz, 2H, arom-H). $^{13}$C-NMR (125 MHz, DMSO-$d_6$) δ = 166.0, 164.5, 159.5, 143.0, 134.5, 132.0, 131.5, 128.5, 118.5, 115.0, 114.0, 92.0, 60.0, 53.0.

Anal. Calcd for $C_{19}H_{13}BrN_4OS$: C, 53.66; H, 3.08; N, 13.17; S, 7.54. Found: C, 53.55; H, 2.98; N, 13.12; S, 7.45.

***7-Cyano-3-(4-tolyl)-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6h).*** This compound was obtained as colorless crystals from benzene, yield (0.31 g, 87 %). Mp 210–212°C. IR (KBr): 3050, 2995, 2200, 1650, 1500, 1480 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 2.3 (s, 3H, $CH_3$), 5.3 (s, 2H, $SCH_2N$), 5.7 (s, 2H, $NCH_2N$), 7.1–7.9 ppm (m, 9H, arom-H).

Anal. Calcd for $C_{20}H_{16}N_4OS$: C, 66.65; H, 4.47; N, 15.54; S, 8.90. Found: C, 66.45; H, 4.35; N, 15.50; S, 8.84.

***7-Cyano-3-(4-methoxyphenyl)-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5–thiadiazin-6-one (6i).*** This compound was obtained as yellow crystals from (benzene/ cyclohexane), yield (0.35 g, 94 %). Mp 174–176°C. IR (KBr): 3080, 2995, 2200, 1600, 1530, 1480 $cm^{-1}$. $^1$H-NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 3H, $OCH_3$), 5.19 (s, 2H, $SCH_2N$), 5.60 (s, 2H, $NCH_2N$), 6.85 (d, $J$ = 5.1 Hz, 2H, arom-H), 7.00 (d, $J$ = 7 Hz, 2H, arom-H), 7.44–7.52 (m, 3H, arom-H), 7.95 ppm (d, $J$ = 9 MHz 2H, arom-H). $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 166.36, 163.26, 159.66, 155.99, 136.51, 134.32, 132.06, 128.93, 119.10, 115.16, 115.06, 93.01, 61.80, 55.59, 52.26.

Anal. Calcd for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88; S, 8.52. Found: C, 63.71; H, 4.14; N, 14.69; S, 8.49.

***7-Cyano-3-(3-tolyl)-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6j).*** This compound was obtained as yellow crystals from ethanol, yield (0.32 g, 89 %). Mp 220–222°C. IR (KBr): 3000, 2990, 2200, 1650, 1520, 1470 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 2.1 (s, 3H, $CH_3$), 5.3 (s, 2H, $SCH_2N$), 5.5 (s, 2H, $NCH_2N$), 7.0–7.8 ppm (m, 9H, arom-H).

Anal. Calcd for $C_{20}H_{16}N_4OS$: C, 66.65; H, 4.47; N, 15.54; S, 8.90. Found: C, 66.50; H, 4.41; N, 15.50; S, 8.88.

***7-Cyano-3-(2-naphthyl)-8-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (6k).*** This compound was obtained as colorless crystals from ethanol, yield (0.38 g, 95 %). Mp 238–240°C. IR (KBr): 3050, 2920, 2200, 1620, 1520, 1480 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.7 (s, 2H, $SCH_2N$), 5.9 (s, 2H, $NCH_2N$), 7.1–8.15 ppm (m, 12H, arom-H).

Anal. Calcd for $C_{23}H_{16}N_4OS$: C, 69.68; H, 4.07; N, 14.13; S, 8.09. Found: C, 69.58; H, 4.39; N, 14.08; S, 8.00.

***8-(4-Chlorophenyl)-Pyrimido[2,1-b]-1,3,5-thiadiazine derivatives (7a-k).*** These compounds were obtained according to the general method using ethanol/dioxane in a ratio of 1:1 mixture as solvent.

***8-(4-Chlorophenyl)-7-cyano-3-ethyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7a).*** This compound was obtained as colorless crystals from ethanol, yield (0.32 g, 96 %). Mp 160–162°C. IR (KBr): 3100, 2990, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 1.3 (t, $J$ = 2.7 Hz, 3H, $NCH_2CH_3$), 2.9 (q, $J$ = 2.7 Hz, 2H, $NCH_2CH_3$), 4.9 (s, 2H, $SCH_2N$), 5.2 (s, 2H, $NCH_2N$), 7.55–8.1 ppm (m, 4H, arom-H). MS (EI, 70 eV): m/z (%) = 344.97 [$M^+$ +2] (41.4), 332.97 [$M^+$] (98.4), 33.98 (30.1), 332.01 (9.8), 330.96 (17.1), 318.05 (5.5), 316.04 (1.8), 299.01 (15.8), 277.93 (27.1), 276.95 (18.7), 275.93 (46.1), 265.92(16.8), 263.93 (27.0), 262.95 (10.4), 260.98 (10.6), 248.97 (17.8), 247.97 (12.8), 246.95 (25.9), 232.02 (11.6), 230.01 (10.5), 219.04 (14.1), 218.04 (10.8), 217.02 (24.5), 215.05 (10.1), 207.03 (10.0), 205.0 (14.4), 194.06 (11.9), 190.03 (12.4), 189.01(11.8), 187.03 (11.1), 185.06 (33.6), 183.04 (10.7), 176.05 (10.9), 130.05 (13.05), 129.05 (19.6), 128.06 (13.0), 127.03 (13.7), 125.2 (14.9), 117.98 (9.48), 116.99 (23.7), 112.99 (15.6), 110.98 (12.2), 110.01 (8.2), 108.98 (5.7), 107.98 (6.6), 106.98 (6.6).

Anal. Calcd for $C_{15}H_{13}ClN_4OS$: C, 54.13; H, 3.94; N, 16.83; S, 9.63. Found: C, 54.02; H, 3.90; N, 16.82; S, 9.58.

***3-Butyl-8-(4-chlorophenyl)-7-cyano-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7b).*** This compound was obtained as colorless crystals from ethanol, yield (0.33 g, 94%). Mp 186–188°C. IR (KBr): 3050, 2990–2850, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 1.0 (t, $J$ = 1.8 Hz, 3H, $CH_2CH_3$), 1.5 (m, 2H, $CH_2CH_3$), 1.7 (m, 2H, $NCH_2CH_2$), 2.9 (t, $J$ = 1.5 Hz, 2H, $NCH_2CH_2$), 4.8 (s, 2H, $SCH_2N$), 5.2 (s, 2H, $NCH_2N$), 7.5–8.1 ppm (m, 4H, arom-H).

Anal. Calcd for $C_{17}H_{17}ClN_4OS$: C, 56.58; H, 4.75; N, 15.53; S, 8.89. Found: C, 56.57; H, 4.70; N, 15.51; S, 8.86.

***8-(4-Chlorophenyl)-7-cyano-3-isobutyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5–thiadiazin-6-one (7c).*** This compound was obtained as colorless crystals from ethanol, yield (0.23 g, 64%). Mp 198–200°C. IR (KBr): 3060, 2985–2800, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 1.0 (d, $J$ = 1.7 Hz, 6H, $CH(CH_3)_2$), 1.9 (m, 1H, $NCH_2CH(CH_3)_2$), 2.55 (d, $J$ = 2.4 Hz, 2H, $NCH_2CH$), 5.0 (s, 2H, $SCH_2N$), 5.2 (s, $NCH_2N$), 7.7–8.05 ppm (m, 4H, arom-H).

Anal. Calcd for $C_{17}H_{17}ClN_4OS$: C, 56.58; H, 4.75; N, 15.53; S, 8.89. Found: C, 56.49; H, 4.70; N, 15.50; S, 8.80.

***3-Benzyl-8-(4-chlorophenyl)-7-cyano-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7d).*** This compound was obtained as colorless crystals from ethanol, yield (0.3 g, 77%). Mp 162–164°C. IR (KBr): 3150, 2985, 2200, 1685, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 4.0 (s, 2H, $NCH_2Ph$), 4.8 (s, 2H, $SCH_2N$), 5.2 (s, $NCH_2N$) 7.6–8.15 ppm (m, 9H, arom-H).

Anal. Calcd for $C_{20}H_{15}ClN_4OS$: C, 60.83; H, 3.83; N, 14.19; S, 8.12. Found: C, 60.70; H, 3.74; N, 14.17; S, 8.10.

***8-(4-Chlorophenyl)-7-cyano-3-phenyl-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5- thiadiazin-6-one (7e).*** This compound was obtained as yellow crystals from ethanol, yield (0.22 g, 60%). Mp 168–170°C. IR (KBr): 3020, 2950, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.5 (s, 2H, $SCH_2N$), 5.8 (s, 2H, $NCH_2N$), 7.3–7.9 ppm (m, 9H, arom-H).

Anal. Calcd for $C_{19}H_{13}ClN_4OS$: C, 59.92; H, 3.44; N, 14.71; S, 8.42. Found: C, 59.82; H, 3.41; N, 14.69; S, 8.36.

***3,8-Di(4-chlorophenyl)-7-cyano-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (7f).*** This compound was obtained as yellow crystals from ethanol, yield (0.3 g, 73%). Mp 222–224°C. IR (KBr): 3020, 2970,2200, 1660, 1590, 1520 $cm^{-1}$. $^1$H-NMR (500 MHz, DMSO-$d_6$): δ = 5.7 (s, 2H, $SCH_2N$), 5.9 (s, 2H, $NCH_2N$), 7.1–8.0 ppm (m, 8H, arom-H). $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 165, 164.0, 159.0, 142.0, 137.0, 133.0, 131.0, 130.0, 128.5, 126.0, 118, 115.0, 92.0, 60.0, 53.5. MS (EI, 70Ev): m/z (%) = 418 [$M^+$ +4] (17.5), 416 [$M^+$ +2] (36.3), 414 [$M^+$] (54.8), 383.21 (16.8), 381.21 (21.3), 379.33(2.2), 379.17 (9.8), 280.17 (9.1), 278.14 (13.4), 277.28 (2.9), 277.14 (16.6), 276.15 (8.6), 263.15 (4.0), 262.12 (5.6), 249.11 (5.8), 248.17 (2.5), 247.15 (10.4), 245.115 (10.3), 240.17 (5.4), 217.19 (6.1), 197.16 (2.1), 195.17 (8.5), 193.09 (6.0), 187.12 (3.7), 175.08 (9.1), 169.10 (4.7), 167.06 (5.4), 163.05 (7.0), 162.10 (5.8), 161.08 (29.3), 155.14 (4.3), 153.12 (3.9), 151.09 (6.4), 142.08 (11.6), 141.08 (35.4), 140.08 (44.3), 139.08 (100), 138.22 (2.2), 138.06 (30.4), 137.03 (3.4), 129.07 (5.6), 127.08 (8.1), 126.12 (3.1), 125.08 (12.5), 114.11 (6.2), 113.08 (8.6), 112.09 (2.8), 111.10 (20.3), 105.14 (2.8), 99.07 (4.6), 88.10 (5.1), 86.02 (12.8), 85.06 (2.1), 84.99 (1.2), 80.98 (2.9), 77.07 (6.9), 76.6 (5.9), 75.05 (10.1), 74.05 (1.0).

Anal. Calcd for $C_{19}H_{12}Cl_2N_4OS$: C, 54.95; H, 2.91; N, 13.49; S, 7.72. Found: C, 54.89; H, 2.86; N, 13.40; S, 7.68.

***3-(4-Bromophenyl)-8-(4-chlorophenyl)-7-cyano-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7g).*** This compound was obtained as green crystals from benzene, yield (0.21 g, 47%). Mp 224–226°C. IR (KBr): 3020, 2975, 2200, 1660, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.56 (s, 2H, $SCH_2N$), 5.8 (s, 2H, $NCH_2N$), 7.2–8.0 ppm (m, 8H, arom-H).

Anal. Calcd for $C_{19}H_{12}BrClN_4OS$: C, 49.64; H, 2.63; N, 12.19; S, 6.97. Found: C, 49.56; H, 2.59; N, 12.17; S, 6.92.

***8-(4-Chlorophenyl)-7-cyano-3-(4-tolyl)-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7h).*** This compound was obtained as colorless crystals from benzene, yield (0.12 g, 30%). Mp 210–212°C. IR (KBr): 3020, 2990, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 2.2 (s, 3H, $CH_3$), 5.7 (s, 2H, $SCH_2N$), 5.8 (s, 2H, $NCH_2N$), 7.2–8.0 ppm (m, 8H, arom-H).

Anal. Calcd for $C_{20}H_{15}ClN_4OS$: C, 60.83; H, 3.83; N, 14.19; S, 8.12. Found: C, 60.56; H, 3.76; N, 14.16; S, 8.09.

***8-(4-Chlorophenyl)-7-cyano-3-(4-methoxyphenyl)-3,4-dihydro-2H-pyrimido-[2,1-b]-1,3,5-thiadiazin-6-one (7i).*** This compound was obtained as colorless crystals from benzene, yield (0.123 g, 30%). Mp 214–216°C. IR (KBr): 3020, 2990, 2200, 1640, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$) δ = 3.9 (s, 3H, $OCH_3$), 5.6 (s, 2H, $SCH_2N$), 5.8 (s, 2H, $NCH_2N$), 7.2–8.0 ppm (m, 8H, arom-H).

Anal. Calcd for $C_{20}H_{15}ClN_4O_2S$: C, 58.46; H, 3.68; N, 13.64; S, 7.80. Found: C, 58.36; H, 3.60; N, 13.61; S, 7.78.

***8-(4-Chlorophenyl)-7-cyano-3-(3-tolyl)-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7j).*** This compound was obtained as colorless crystals from ethanol, yield (0.386 g, 98%). Mp 180–182°C. IR (KBr): 3020, 2990, 2200, 1680, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 2.2 (s, 3H, $CH_3$), 5.4 (s, 2H, $SCH_2N$), 5.8 (s, $NCH_2N$), 7.1–8.1 ppm (m, 8H, arom-H).

Anal. Calcd for $C_{20}H_{15}ClN_4OS$: C, 60.83; H, 3.83; N, 14.19; S, 8.12. Found: C, 60.75; H, 3.81; N, 14.09; S, 8.09.

***8-(4-Chlorophenyl)-7-cyano-3-(2-naphthyl)-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (7k).*** This compound was obtained as green crystals from ethanol, yield (0.344 g, 80%). Mp 216–218°C. IR (KBr): 3050, 2950, 2200, 1620, 1590, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.7 (s, 2H, $SCH_2N$), 6.0 (s, 2H, $NCH_2N$), 7.5–8.0 ppm (m, 11H, arom-H).

Anal. Calcd for $C_{23}H_{15}ClN_4OS$: C, 64.11; H, 3.51; N, 13.00; S, 7.44. Found: C, 64.05; H, 3.48; N, 12.97; S, 7.38.

***8-(4-Nitrophenyl)-pyrimido[2, 1-b]-1,3,5-thiadiazine derivatives (8a-e).*** These compounds were obtained according to the general method using ethanol/acetic acid in a ratio of 2:1 as solvent.

***7-Cyano-3-ethyl-8-(4-nitrophenyl)-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one(8a).*** This compound was obtained as colorless crystals from (benzene/cyclohexane), yield (0.137 g, 40 %). Mp 162–164°C. IR (KBr): 3100, 2995, 2200, 1685, 1600, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 1.3 (t, $J$ = 2.8 Hz, 3H, $NCH_2CH_3$), 2.9 (q, $J$ = 2.8 Hz, 2H, $NCH_2CH_3$), 4.9 (s, 2H, $SCH_2N$), 5.25 (s, 2H, $NCH_2N$), 8.1–8.3 ppm (m, 4H, arom-H).

Anal. Calcd for $C_{15}H_{13}N_5O_3S$: C, 52.47; H, 3.82; N, 20.40; S, 9.34. Found: C, 52.30; H, 3.79; N, 20.36; S, 9.28.

***3-Butyl-7-cyano-8-(4-nitrophenyl)-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (8b).*** This compound was obtained as colorless crystals from (benzene/cyclohexane), yield (0.163 g, 44%). Mp 180–182°C. IR (KBr): 3080, 2995-2800, 2200, 1685, 1600, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 1.0 (t, $J$ = 3.4 Hz, 3H, $CH_2CH_3$), 1.4 (m, 2H, $CH_2CH_3$), 2.1 (m, 2H, $NCH_2CH_2$), 2.8 (t, $J$ = 3.3 Hz, 2H, $NCH_2CH_2$), 4.85 (s, 2H, $SCH_2N$), 5.2 (s, 2H, $NCH_2N$) 8.0–8.2 ppm (m, 4H, arom-H).

Anal. Calcd for $C_{17}H_{17}N_5O_3S$: C, 54.97; H, 4.61; N, 18.86; S, 8.63. Found: C, 54.90; H, 4.51; N, 18.77; S, 8.56.

***7-Cyano-3-isobutyl-8-(4-nitrophenyl)-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (8c).*** This compound was obtained as colorless crystals from ethanol, yield (0.237 g, 64%). Mp 314–316°C. IR (KBr): 3060, 2985-2800, 2200, 1670, 1550, 1510 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 1.0 (d, $J$ = 2.4 Hz, 6H, $CH(CH_3)_2$), 1.6 (m, 1H, $NCH_2CH(CH_3)_2$), 2.4 (d, $J$ = 2.3 Hz, 2H, $NCH_2CH$), 4.9 (s, 2H, $SCH_2N$), 5.2 (s, 2H, $NCH_2N$) 7.9–8.1 ppm (m, 4H, arom-H).

Anal. Calcd for $C_{17}H_{17}N_5O_3S$: C, 54.97; H, 4.61; N, 18.86; S, 8.63. Found: C, 54.90; H, 4.58; N, 18.82; S, 8.60.

***3-Benzyl-7-cyano-8-(4-nitrophenyl)-3,4-dihydro-2H-pyrimido***

***[2,1-b]-1,3,5-thiadiazin-6-one (8d).*** This compound was obtained as colorless crystals from (benzene/cyclohexane), yield (0.31 g, 77%). Mp 172–174°C. IR (KBr): 3110, 2975, 2200, 1680, 1590, 1550 $cm^{-1}$. $^1$H-NMR (500 MHz, DMSO-$d_6$): δ = 4.0 (s, 2H, $NCH_2Ph$), 5.0 (s, 2H, $SCH_2N$), 5.2 (s, 2H, $NCH_2N$), 7.4 (m, 6H, arom-H), 8.1 (d, 2H, arom-H), 8.4 ppm (d, 2H, arom-H). $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 166, 164.0, 159.0, 149.0, 140.5, 136.0, 130.0, 128.0, 127.8, 124.0, 115.0, 92, 63.5, 56.5, 53.5. MS (EI, 70Ev): m/z (%) = 405.85 [$M^+$] (2.2), 375.99 (1.2), 369.11 (1.1), 364.09 (1.1), 348.22 (1.0), 377.15 (1.2), 334.3 (1.3), 298.13 (1.4), 293.12 (1.7), 289.99 (1.2), 280.06 (1.4), 277.02 (1.2), 275.11 (1.7), 271.09 (1.6), 256.11 (6.1), 251.97 (1.5), 244.07 (1.1), 242.13 (1.4), 237.05 (1.1), 228.99 (1.0), 227.10 (1.4), 224.11 (7.8), 221.12 (1.5), 215.18 (1.8), 207.05 (1.8), 207.05 (1.8), 200.11 (19.4), 192.03 (2.0), 191.07 (1.3), 185.09 (45.2), 178.12 (3.0), 173.08 (1.0), 168.08 (1.5), 167.08 (1.5), 166.06 (3.4), 159.10 (1.5), 149.07 (20.9), 145.042 (2.0), 136.10 (2.2), 133.07 (2.9), 127.04 (1.2), 123.06 (2.9), 117.01 (11.0), 113.99 (1.4), 109.02 (11.4), 108.01 (96.3), 106.99 (5.7), 102.99 (3.6), 100.97 (1.2), 98.99 (2.6), 93.01 (100.0), 91.01 (58.0).

Anal. Calcd for $C_{20}H_{15}N_5O_3S$: C, 59.25; H, 3.73; N, 17.27; S, 7.91. Found: C, 59.15; H, 3.68; N, 17.19; S, 7.88.

***7-Cyano-8-(4-nitrophenyl)-3-phenyl-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (8e).*** This compound was obtained as yellow crystals from (benzene/cyclohexane), yield (0.226 g, 58%). Mp 154–156°C. IR (KBr): 3070, 2920, 2200, 1660, 1530, 1500 $cm^{-1}$. $^1$H-NMR (90MHz, DMSO-$d_6$): δ = 5.6 (s, 2H, $SCH_2N$), 5.8 (s, 2H, $NCH_2N$), 7.3–8.3 ppm (m, 9H, arom-H).

Anal. Calcd for $C_{19}H_{13}N_5O_3S$: C, 58.30; H, 3.35; N, 17.89; S, 8.19.Found: C, 58.42; H, 3.23; N, 17.72; S, 8.06.

***8-(2-Furyl)-pyrimido[2,1-b]-1,3,5-thiadiazine derivatives (9a-h).*** These compounds were obtained according to general method using ethanol as solvent.

***7-Cyano-3-ethyl-8-(2-furyl)-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (9a).*** This compound was obtained as pale yellow crystals from (benzene/cyclohexane), yield (0.17 g, 60 %). Mp 176–178°C. IR (KBr): 3200, 2995, 2200, 1660, 1600, 1520 $cm^{-1}$. $^1$H-NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, $J$ = 1.62 Hz, 3H, $NCH_2CH_3$), 2.77 (q, $J$ = 1.62 Hz, 2H, $NCH_2CH_3$), 4.74 (s, 2H, $SCH_2N$), 5.10 (s, 2H, $NCH_2N$), 6.60 (q, $J$ = 3.01 Hz, 1H, furan-H), 7.56 (d, $J$ = 3.0 Hz, 1H, furan-H), 7.71 ppm (d, $J$ = 1.0 Hz, 1H, furan-H). $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 159.8, 153.8, 147.2, 118.9, 114.5, 112.9, 77.3, 77.05, 76.7, 63.4, 56.3, 44.46, 12.7. MS (EI, 70Ev): m/z (%) = 288.93 [$M^+$] (100.0), 287.96 (10.5), 272.97 (2.2), 270.04 (2.1), 264.92 (2.1), 260.89 (1.9), 256.95 (1.7), 246.98 (2.2), 240.97 (5.5), 236.99 (2.7), 231.93 (52.4), 223.04 (2.1), 215.96 (3.1), 214.04 (1.5), 205.99 (1.7), 204.95 (4.3), 202.92 (21.6), 190.98 (2.2), 185.01 (51.4), 183.01 (2.3), 176.01 (5.2), 172.98 (23.1), 171.02 (5.8), 161.98 (8.1), 159.02 (4.6), 153.02 (2.4), 149.01 (13.2), 147.01 (6.7), 144.03 (6.0), 138.05 (9.0), 134.02 (4.1), 129.02 (15.5), 123.01 (4.1), 116.98 (14.4), 114.96 (7.0), 110.98 (4.1), 103.94 (10.2), 101.95 (12.8), 92.97 (76.6), 85.94 (12.2), 78.97 (13.9), 74.99 (30.4), 72.00 (35.2), 70.02 (7.9), 67.01 (1.9).

Anal. Calcd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43; S, 11.12. Found: C, 54.10; H, 4.14; N, 19.39; S, 11.10.

***3-Butyl-7-cyano-8-(2-furyl)-3,4-dihydro-2H-pyrimido [2,1-b]- 1,3,5-thiadiazin-6-one (9b).*** This compound was obtained as colorless crystals from (benzene/cyclohexane), yield (0.129 g, 41 %). Mp 160–162°C. IR (KBr): 3200, 2995, 2200, 1660, 1580, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ 1.0 (t, $J$ = 1.8 Hz, 3H, $CH_2CH_3$), 1.4 (m, 2H, $CH_2CH_3$), 2.1 (m, 2H, $NCH_2CH2$), 2.8 (t, $J$ = 1.8 Hz, 2H, NCH2CH2), 4.8 (s, 2H, $SCH_2N$), 5.05 (s, 2H, $NCH_2N$), 6.5 (s, 1H, furan-H), 7.4 (s, 1H, furan-H), 7.6 ppm (s, 1H, furan-H).

Anal. Calcd for $C_{15}H_{16}N_4O_2S$: C, 56.94; H, 5.10; N, 17.71; S, 10.14. Found: C, 56.89; H, 5.08; N, 17.69; S, 10.12.

***7-Cyano-8-(2-furyl)-3-isobutyl-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (9c).*** This compound was obtained as colorless crystals from (benzene/cyclohexane), yield (0.158 g, 50 %). Mp 176–178°C. IR(KBr): 3200, 2995, 2200, 1660, 1600, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, $CDCl_3$): δ = 1.0 (d, $J$ = 3.16 Hz, 6H, $CH(CH_3)_2$), 1.8 (m, 1H, $NCH_2CH(CH_3)_2$), 2.5 (d, $J$ = 3.2 Hz, 2H, NCH2CH), 4.7 (s, 2H, $SCH_2N$), 5.1 (s, 2H, $NCH_2N$), 6.5 (s, 1H, furan-H), 7.5 (s, 1H, furan-H), 7.7 ppm (s, 1H, furan-H).

Anal. Calcd for $C_{15}H_{16}N_4O_2S$: C, 56.94; H, 5.10; N, 17.71; S, 10.14. Found: C, 56.88; H, 5.05; N, 17.66; S, 10.10.

***3-Benzyl-7-cyano-8-(2-furyl)-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (9d).*** This compound was obtained as colorless crystals from ethanol, yield (0.28 g, 80 %). Mp 194–196°C. IR (KBr) 3200, 3030, 2900, 2200, 1650, 1560, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 3.9 (s, 2H, NCH2Ph), 4.95 (s, 2H, $SCH_2N$), 5.1 (s, 2H, $NCH_2N$), 6.9 (s, 1H, furan-H), 7.3 (m, 1H, furan-H), 7.4 (m, 5H, arom-H), 8.15 ppm (s, 1H, furan-H).

Anal. Calcd for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99; S, 9.15. Found: C, 61.69; H, 4.01; N, 15.90; S, 9.12.

***7-Cyano-8-(2-furyl)-3-phenyl-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (9e).*** This compound was obtained as yellow crystals from ethanol, yield (0.289 g, 86 %). Mp 210–212°C. IR (KBr): 3200, 3030, 2940, 2200, 1640, 1580, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.3 (s, 2H, $SCH_2N$), 5.4 (s, 2H, $NCH_2N$), 6.6 (s, 1H, furan-H), 7.1 (s, 1H, furan-H), 7.2 (m, 5H, arom-H), 7.9 ppm (s, 1H, furan-H).

Anal. Calcd for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.60; N, 16.66; S, 9.53. Found: C, 60.60; H, 3.55; N, 16.65; S, 9.51.

***3-(4-Chlorophenyl)-7-cyano-8-(2-furyl)-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thiadiazin-6-one (9f).*** This compound was obtained as yellow crystals from ethanol, yield (0.318 g, 86 %). Mp 298–300°C. IR (KBr): 3200, 3030, 2970, 2200, 1640, 1580, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): δ = 5.5 (s, 2H, $SCH_2N$), 5.7 (s, 2H, $NCH_2N$), 6.9 (s, 1H, furan-H), 7.3 (s, 1H, furan-H), 7.35 (m, 4H, arom-H), 8.15 ppm (s, 1H, furan-H).

Anal. Calcd for $C_{17}H_{11}ClN_4O_2S$: C, 55.06; H, 2.99; N, 15.11; S, 8.65. Found: C, 54.99; H, 2.90; N, 15.07; S, 8.55.

***3-(4-Bromophenyl)-7-cyano-8-(2-furyl)-3,4-dihydro-2H-pyrimido[2,1-b]-1,3,5-thia-diazin-6-one (9g).*** This compound was obtained as yellow crystals from benzene, yield (0.249 g, 60 %). Mp 270–272°C. IR (KBr): 3200, 3030, 2950, 2200, 1650, 1580, 1520 $cm^{-1}$. $^1$H-NMR (500 MHz, DMSO-$d_6$): δ = 5.45 (s, 2H, $SCH_2N$), 5.66 (s, 2H, $NCH_2N$), 6.76 (q, $J$ = 1.0 Hz, 1H, furan-H), 7.09 (d, $J$ = 9.0 Hz, 2H, arom-H.), 7.42 (d, $J$ = 4.0 Hz, 1H, furan-H ), 7.46 (d, $J$ = 9.0 Hz, 2H, arom-H), 8.08 ppm (d, $J$ = 1.0 Hz, 1H, furan-H). $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ = 159.6, 153.4, 448.7, 143.2, 142.5, 134.5, 132.7, 119.3, 119.0, 115.2, 114.6, 113.9, 62.1, 60.2, 53.8. MS (EI, 70Ev): m/z (%) = 416 [$M^+$+2] (100.0), 414 [$M^+$]

(97.72), 383.2 (27.34), 381.3 (23.49), 371.3 (1.2), 369.2 (1.46), 330.3 (1.72), 328.3 (1.74), 2.33.4 (5.87), 227.3 (2.67), 219.3 (3.45), 203.2 (13.47), 201.3 (8.38), 197.2 (2.85), 185.2 (18.92), 171.2 (3.94), 119.2 (2.38).

Anal. Calcd for $C_{17}H_{11}BrN_4O_2S$: C, 49.17; H, 2.67; N, 13.49; S, 7.72. Found: C, 49.10; H, 2.61; N, 13.48; S, 7.69.

***7-Cyano-8-(2-furyl)-3-(4-tolyl)-3,4-dihydro-2H-pyrimido [2,1-b]-1,3,5-thiadiazin-6-one (9h).*** This compound was obtained as colorless crystals from ethanol, yield (0.269 g, 77 %). Mp 280–282°C. IR (KBr): 3200, 3030, 2900, 2200, 1650, 1560, 1520 $cm^{-1}$. $^1$H-NMR (90 MHz, DMSO-$d_6$): $\delta = 2.1$ (s, 3H, $C\underline{H}_3$), 5.4 (s, 2H, $SC\underline{H}_2N$), 5.5 (s, 2H, $NC\underline{H}_2N$), 7.1 (s, 1H, furan-H), 7.3 (s, 1H, furan-H), 7.36 (m, 4H, arom-H), 8.1 ppm (s, 1H, furan-H).

Anal. Calcd for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99; S, 9.15. Found: C, 61.60; H, 3.89; N, 15.91; S, 9.11.

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## REFERENCES AND NOTES

[1] Smalley, R. K. In Comprehensive Heterocyclic Chemistry II; Boulton, A. J., Ed.; Elsevier: Oxford, 1996: Vol. 6, p 783.

[2] Nesterov, V. N.; Keivokolysko, S. G.; Dyachenko, E. D.; Dotsenko, V. V.; Litvinov, V. P. Russ Chem Bull, 1997, 46, 5.

[3] Wang, Z.; Haoxin, S.; Haijian, S. Synth Commun, 2001, 31, 2841.

[4] Liu, S.; Qian, X.; Chen, J.; Song, G. Monatsh Chem 2000, 131, 953.

[5] (a) Chande, M. S.; Dravid, R. N.; Shetgiri, N. P. Proc Indian Acad Sci Chem Sci 1988, 100, 53; (b) Ertan, M.; Bilgin, A. A.; Palaska, E.; Yulug, N. Arzneim Forsch 1992, 42, 160; (c) Ertan, M.; Ayyildiz, H. G.; Yulug, N. Arzneim Forsch 1991, 41, 1182; (d) Lal Dhar, S. Y.; Anjum, V.; Sangeeta, S. J Agric Food Chem 1994, 42, 811.

[6] Shishoo, C. J.; Devain, M. B.; Bhadit, V. S.; Jain, K. S.; Rahod, I. S.; Goyal, R. K.; Gandhi, T. P.; Patel, R. B.; Naik, S. R. Arzneim Forsch 1990, 40, 567.

[7] Sugiyama, M. T.; Sakamoto, K.; Tabata, K.; Endo, K.; Ito, M. Kobayashi; Fukumi, H. Chem Pharm Bull 1989, 37, 2122.

[8] Kienzle, F.; Kaiser, A.; Minder, R. E. Helv Chim Acta 1983, 48, 66.

[9] Jordis, U.; Sauter, F.; Siddiqi, S. M. Vest Slov Kem Drus 1986, 217, 33.

[10] Ram, V. J. Arch Pharm 1979, 312, 19.

[11] Craciunescu, D.; López, A. D.; Iriarte, E. G.; Tena, A.; Góme, A.; Ghirvu, C. Anal Real Acad National Farmac 1985, 241, 51.

[12] Newberry, R. A.; Bushell, B. J. US Pat, 3,979,402; Chem Abstr 1977, 86, 29795z.

[13] Hozien, Z. A.; Sarhan, A. A. O.; El-Sherief, H. A. H.; Mahmoud, A. M. *Z.* Naturforsch 1997, 52B, 1401.

[14] Sarhan, A. A. O.; Hafez, S. A.; El-Sherief, H. A. H.; Tarek, A. Synth Commun 2006, 35, 987.

[15] Mahmoud, A. M. Z.; El-Sherief, H. A. H.; Habib, O. M. A.; Sarhan, A. A. O. Phosphorus Sulfur Silicon and Relat Elem 2007, 182, 1757.

[16] (a) Hai-Jian, S.; Zhong-Yi, W.; Hao-Xin, S. Synth Commun 1999, 29, 2027; Chem Abstr 1999, 131, 5242; (b) Hao-Xin, S.; Hai--Jian, S.; Zong-Yi, W. Youji Huazue, 2000, 20, 344; Chem Abstr 2000, 133, 120280c; (c) Wang, Z.; You, T.; Shi, H.; Shi, H. Molecules, 1996, 1, 89.

[17] Dotsenko, V. V.; Krivokolysko, S. G.; Rusanov, E. B.; Litvinov, V. P. Russ Chem Bull Int Ed 2007, 56, 7.

[18] British Pharmacopoeia, Pharmaceutical Press London, p. 796 (1953).

# Design and Synthesis of Novel Methylene-bis-fused Pyrazoles as Biologically Active Molecules



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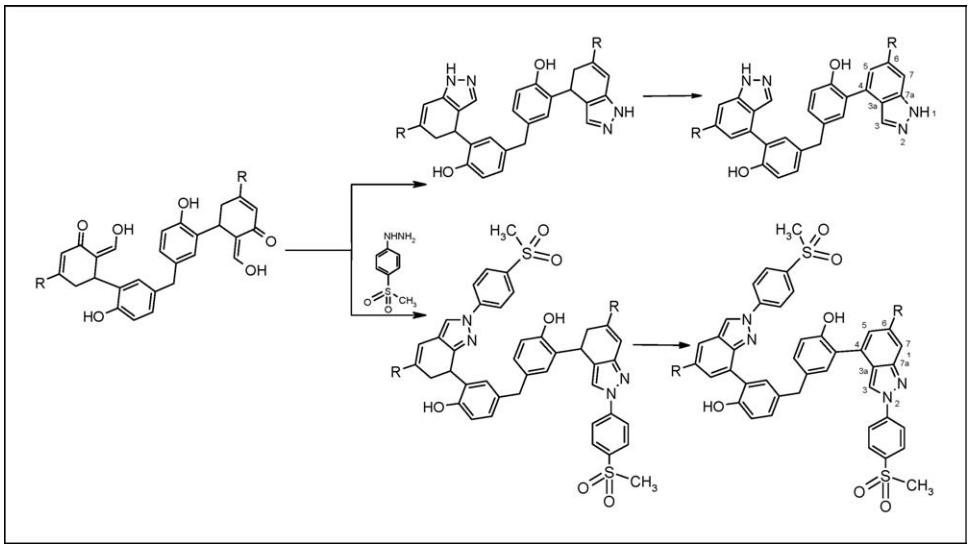

A series of novel methylene-bis-fused pyrazoles **12a–e** and methylene-bis-2-(4-methylsulfonyl)-phenyl substituted fused pyrazoles **15a–d** have been synthesized by the reaction of methylene-bis-aryl-6-hydroxymethylene-2-cyclohexenones **10** with hydrazine hydrate or (4-methylsulfonyl)-phenyl hydrazine **13**. Chemical structures of all the newly synthesized compounds were elucidated by their IR, $^1$H NMR, $^{13}$C NMR, and MS spectral data. The compounds **15a–d** were evaluated for their cyclooxygenase-2 (COX-2) inhibitory activity, and the compound **15b** showed appreciable COX-2 inhibition and selectivity. Further, all the new compounds were screened for their antimicrobial activity against Gram-positive, Gram-negative bacteria, and fungi. Amongst the screened compounds, **12c**, **15a**, and **15b** were found to be the most active against almost all the test bacteria. The compound **15b** displayed notable antibacterial activity against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), *Micrococcus luteus* (IFC 12708), *Proteus vulgaris* (ATCC 3851), and *Salmonella typhimurium* (ATCC 14028), equal to that of ampicillin. Similarly, these compounds also showed potent antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996).

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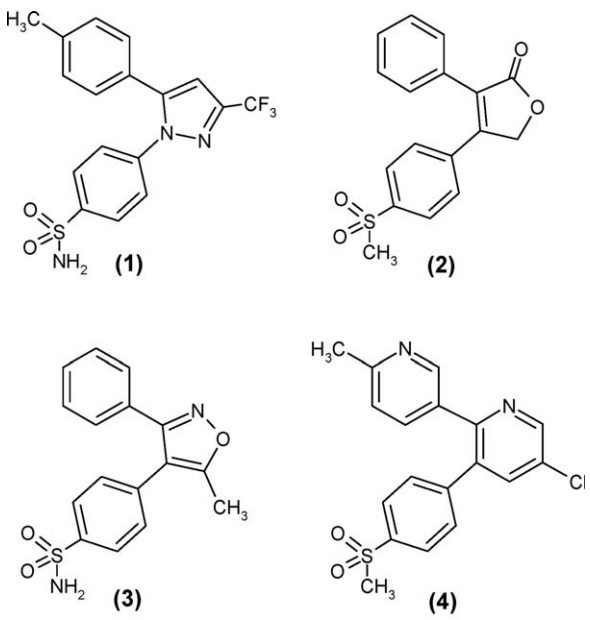
## INTRODUCTION

Pyrazole and its derivatives could be considered as possible antimicrobial agents [1,2]. The other activities include antidepressant [3], inhibitors of protein kinases [4], antiagreegating [5], antiarthritic [6], and cerebroprotectors [7]. Recently some aryl pyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitors [8], cyclooxygenase-2 (COX-2) inhibitors [9], potent activator of the nitric oxide receptor, and soluble guanylate cyclase [10] activity. Besides, great interest in the pyrazole molecule has been stimulated by some promising pharmacological, agrochemical, and analytical applications of its derivatives [11].

The role of COX-2 isoform in inflammation and the attractiveness of COX-2 as a therapeutic target for the development of anti-inflammatory drugs are very well recognized [12]. The traditional nonsteroidal anti-inflammatory drugs (NSAIDs) are nonselectively inhibit both COX-1 and COX-2, and hence, downregulate prostaglandin formation in almost all cells and tissues, which may induce gastrointestinal side effect, adversely affect the mucus-bicarbonate secretion, acid secretion, and mucosal blood flow. COX-1 inhibition may also elicit an

**Scheme 1.** COX-2 selective inhibitors.



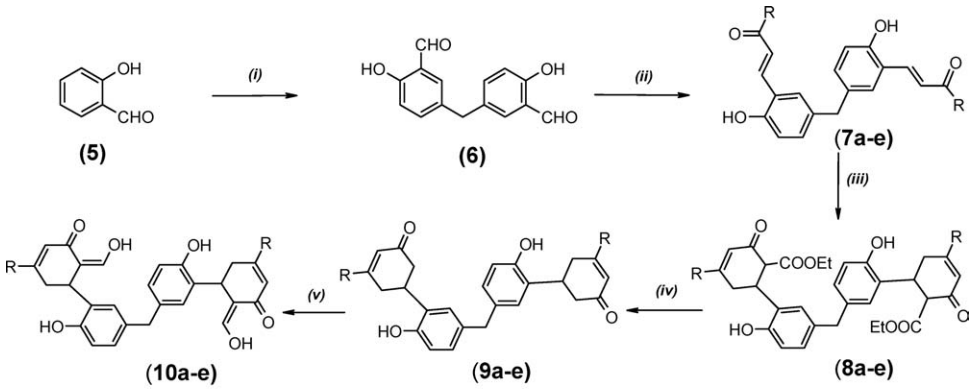

increase in 5-lipoxygenase (5-LO) activity that would potentiate production of leukotriene-$B_4$ ($LTB_4$) and vasoconstrictor peptide-leukotrienes (p-LTs) by the lipoxygenase pathway, and this may also contribute to the vascular and other mucosal damage by NSAIDs [13]. Hence, it was proposed that a selective inhibitor of COX-2 would be an attractive approach to the treatment of inflammatory conditions, without concomitant gastric and renal side effects. There are four COX-2 selective inhibitors, such as celecoxib (1), rofecoxib (2), valdecoxib (3), and etoricoxib (4) (Scheme 1), which are currently prescribed for the treatment of arthritis and inflammatory diseases. They show anti-inflammatory activity with reduced gastro intestinal side effects to traditional NSAIDs. However, the long term use of both traditional NSAIDs and coxibs has been reported to cause significant cardiovascular side effects [14].

Following the successful introduction of antimicrobial agents and COX-2 inhibitors, in continuation of our research on biologically active heterocycles [15–18] it was considered worthwhile to design and synthesize more selective COX-2 analogs, incorporating two active pharmacophores would enhance further the activity and selectivity towards the COX-2 enzyme. In this article, we explored fused pyrazoles **12a–e** and 2-substituted fused pyrazoles **15a–d** in which central five-membered scaffold is similar to that of celecosib 1, and 4-(methylsulfonyl) benzene, used as a COX-2 pharmacophore, and evaluated their *in vitro* antimicrobial and COX-2 inhibitory activity.

## RESULTS AND DISCUSSION

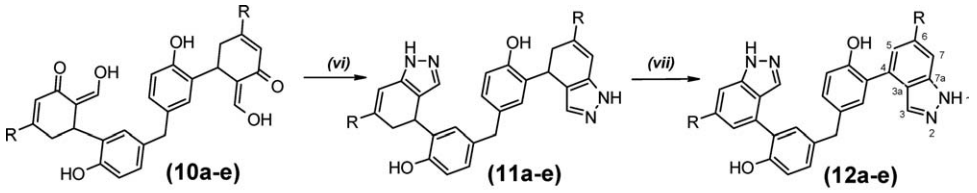
**Synthesis.** The key intermediate, **10** required for the synthesis of title compounds was prepared according to the procedure outlined in the Scheme 2. Condensation of commercially available salicylaldehyde **5** and trioxane in the presence of a mixture of conc. sulfuric acid and acetic acid gave methylene-bis-salicylaldehyde **6** in good yield [19]. Compound **6** was then reacted with the corresponding acetophenone in presence of alc. KOH at room temperature to give methylene-bis-chalcones **7a–e** (yield over 90%) [20]. Knoevenagel condensation of compounds **7a–e** with ethyl acetoacetate gave methylene-bis-aryl-6-carbethoxycyclohexenones **8a–e** (yield over 80%). Decarboxylation of **8a–e** in the presence of HCl/AcOH at reflux temperature resulted methylene-bis-aryl-cyclohexenones **9a–e** (yield over 80%), which on Claisen-like condensation with ethylformate in the

**Scheme 2.** Reagents and conditions: (i) trioxane, $H_2SO_4$/AcOH, reflux, 81%; (ii) $RCOCH_3$, KOH/EtOH, rt, 82–95%; (iii) EAA, NaOEt/EtOH, reflux, 78–86%; (iv) HCl/AcOH, reflux, 74–82%; (v) HCOOEt, NaOMe/$C_6H_6$, rt, 79–88%.




R = **a)** $C_6H_5$; **b)** 4-Br-$C_6H_4$; **c)** 4-$NH_2$-$C_6H_4$; **d)** 4-Cl-$C_6H_4$; **e)** 4-MeO-$C_6H_4$

**Scheme 3.** Reagents and conditions: (vi) hydrazinehydrate/AcOH, reflux, 80%; (vii) DDQ, $N_2$-atm, reflux, 76–83%.



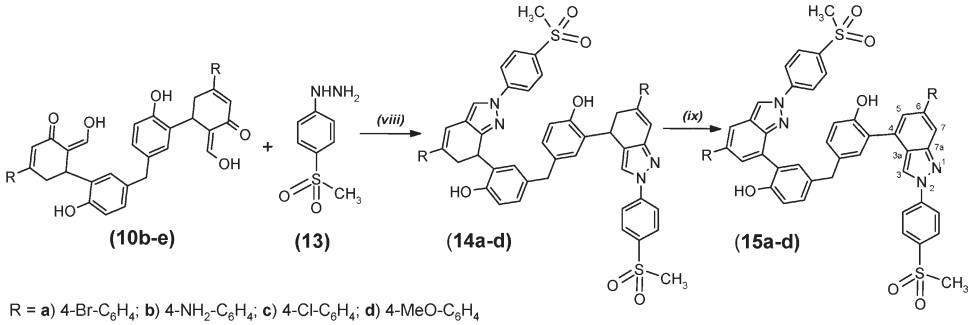

R = **a**) $C_6H_5$; **b**) 4-Br-$C_6H_4$; **c**) 4-$NH_2$-$C_6H_4$; **d**) 4-Cl-$C_6H_4$; **e**) 4-MeO-$C_6H_4$

presence of sodium methoxide at room temperature afforded methylene-bis-aryl-6-hydroxy-methylene-2-cyclohexenones **10a–e** in good yields.

The compounds **10a–e** on cyclocondensation with the hydrazine hydrate in refluxing acetic acid resulted dihydropyrazole derivatives **11a–e** in good to excellent yields (yield over 80%). Subsequent aromatization of **11a–e**, with dichlorodicyanoparabenzoquinone (DDQ) under $N_2$-atmosphere at reflux temperature gave fused pyrazoles **12a–e** in good yields (Scheme 3). The chemical structure of the compounds was elucidated by their IR, $^1$H NMR, $^{13}$C NMR, and MS spectral data. In the IR spectra of compounds **12a–e**, C═N and N─H bands were observed in the regions 1560–1585, 3390–3410 $cm^{-1}$ respectively. According to the IR spectral data, the compounds **12a–e** have pyrazole structure. In the $^1$H NMR spectra of **12a–e**, the absence of signals corresponding to methine and methylene protons of cyclohexadiene ring indicates that aromatization has indeed taken place. The ─NH proton of the pyrazole ring was observed as a broad singlet at about 8.87–8.80 ppm. The signal because of the methylene bridge proton, present in all compounds, appeared at 4.06–4.00 ppm as singlet. The N═CH proton of compounds **12a–e** appeared at 7.95–7.90 ppm as singlet. All the other aromatic and aliphatic protons of compounds **12a–e** were observed at the expected regions. In the $^{13}$C NMR spectra of compounds **12a–e**, the prominent signals corresponding to C-3, C-3a, C-4, and C-7a, for all the compounds, observed nearly at 137.2, 137.4, 155.6, 145.3 ppm, respectively.

Further, the intermediate **10** when treated with the commercially available 4-(methylsulfonyl)-phenylhydrazine **13** in refluxing ethanol gave methylsulfonyl derivative of pyrazole **14a–d** in good yield. This reaction is a regioselective transformation and the 2-substituted pyrazole could be generated almost exclusively by carrying out the condensation in the presence of hydrochloric acid and one equivalent of 4-(methyl- sulfonyl)phenyl hydrazine **13**. The compounds **14a–d** when aromatized with DDQ under $N_2$-atmosphere at reflux temperature gave 4-(methylsulfonyl)-phenyl substituted fused pyrazoles **15a–d** in good yields (Scheme 4). The chemical structures of all the synthesized compounds were confirmed by their IR, $^1$H NMR, $^{13}$C NMR, and MS spectral data. In the IR spectra of compounds **15a–d**, C═N band was observed in the region 1560–1585 $cm^{-1}$ and $SO_2$ group symmetric, asymmetric stretching bands at about 1300–1328, 1155–1165 $cm^{-1}$. In the $^1$H NMR spectrum of compounds **15a–d**, absence of the signal corresponding to NH group proved that these compounds have pyrazole nucleus with (4-methyl- sulfonyl)-phenyl group at nitrogen. Further, the ─$CH_3$ proton signal was seen as singlet at about 2.96–2.90 ppm, and the signal of N═CH proton of compounds **15a–d** appeared at 6.68–6.65 ppm proved that these compounds have pyrazole nucleus with (4-methylsulfonyl)phenyl group at nitrogen. All the other aromatic and aliphatic protons of

**Scheme 4.** Reagents and conditions: (viii) HCl/EtOH, reflux, 78–86%; (ix) DDQ/dry $C_6H_6$, $N_2$-atm, reflux, 79–86%.




R = **a**) 4-Br-$C_6H_4$; **b**) 4-$NH_2$-$C_6H_4$; **c**) 4-Cl-$C_6H_4$; **d**) 4-MeO-$C_6H_4$

**Table 1**

Antibacterial activity of compounds **12a–e** and **15a–d**.

| Compound | Minimum inhibitory concentration (MIC, μg/mL) | | | | | |
|---|---|---|---|---|---|---|
| | *B. subtilis* | *S. aureus* | *M. luteus* | *P. vulgaris* | *S. typhimurium* | *E. coli* |
| **12a** | — | — | — | — | — | — |
| **12b** | 3.12 | 6.25 | 3.12 | 6.25 | 3.12 | — |
| **12c** | 3.12 | 3.12 | 1.56 | 1.56 | 3.12 | 25.0 |
| **12d** | 25.0 | — | 25.0 | — | — | — |
| **12e** | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | — |
| **15a** | 3.12 | 3.12 | 3.12 | 3.12 | 6.25 | — |
| **15b** | 1.56 | 1.56 | 1.56 | 1.56 | 1.56 | 25.0 |
| **15c** | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | — |
| **15d** | 12.5 | 6.25 | 6.25 | 6.25 | 6.25 | — |
| Ampicillin | 1.56 | 1.56 | 1.56 | 3.12 | 3.12 | 12.5 |

—, Indicates bacteria are resistant to the compound >50 μg/mL concentration.

compounds **15a–d** were observed at the expected regions. In the $^{13}C$ NMR spectra of compounds **15a–d**, the prominent signals corresponding to C-3, C-3a, C-4, and C-7a, for all the compounds, observed nearly at 125.4, 124.0, 136.0, 153.1 ppm, respectively, provide further evidence for their structures. Mass spectra of all the synthesized compounds showed $M^+/M^+ + 1$ peaks, in agreement with their molecular formulae.

**Antibacterial activity.** The *in vitro* antibacterial activity of the newly prepared compounds, **12a–e** and **15a–d**, was assayed against gram-positive bacteria *viz. Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), and *Micrococcus luteus* (IFC 12708), Gram-negative bacteria *viz. Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922) by the broth dilution method, recommended by National Committee for Clinical Laboratory standards (NCCLS) [21]. Amphicillin was used as a standard drug, the lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, μg/mL), was determined and compared with the controls, the MIC values of the compounds assayed are presented in Table 1.

Investigation of the antibacterial screening data revealed that all the tested compounds exhibit interesting biological activity, however, with a degree of variation. Compound **15b** is highly active against all the microorganisms used (accept *E. coli*) at 1.56 μg/mL concentration, and is almost equal to the standard. Compound **12c** is also highly active against *M. luteus* and *P. vulgaris* only at the same concentration as **15b**. The compound **15a** also showed good antibacterial activity against *B. subtilis*, *S. aureus*, *M. luteus,* and *P. vulgaris*. Compound **12a** is almost inactive towards all the microorganisms used. Other compounds were also inactive towards *E. coli* bacteria. The remaining compounds showed moderate to good activity.

**Antifungal activity.** The newly prepared compounds were screened for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996). The antifungal activity of each compound was compared with standard drug Amphotericin B. MIC (μg/mL) was determined and compared with controls; the MIC values of the compounds screened are given in Table 2. The antifungal screening data showed only moderate activity of the test compounds. Among the screened compounds, only **15b** showed the highest activity against all the microorganisms used. Similarly compound **12c** is also highly active but only against *T. rubrum* and *T. mentagrophytes*. The activities of these two compounds are almost equal to

**Table 2**

Antifungal activity of compounds **12a–e** and **15a–d**.

| Compound | Minimum inhibitory concentration (MIC, μg/mL) | | | |
|---|---|---|---|---|
| | *C. albicans* | *A. fumigatus* | *T. rubrum* | *T. mentagrophytes* |
| **12a** | — | — | — | 25.0 |
| **12b** | 12.5 | 25.0 | 12.5 | 25.0 |
| **12c** | 12.5 | 12.5 | 6.25 | 6.25 |
| **12d** | — | — | 50.0 | 25.0 |
| **12e** | 50.0 | 25.0 | 50.0 | 25.0 |
| **15a** | 12.5 | 12.5 | 12.5 | 12.5 |
| **15b** | 6.25 | 6.25 | 6.25 | 6.25 |
| **15c** | 50.0 | 50.0 | 25.0 | 25.0 |
| **15d** | 25.0 | 25.0 | 12.5 | 25.0 |
| Amphotericin B | 6.25 | 3.12 | 3.12 | 3.12 |

—, Indicates fungi are resistant to the compound >50 μg/mL concentration.

the standard, the remaining compounds showed moderate to good activity.

**COX-2 inhibitory activity.** The compounds synthesized **15a–d** was evaluated as COX inhibitors in human whole blood (HWB). Among the four compounds, **15b** showed good inhibition and selectivity. Some interesting features can be deduced from the comparison of the structure of compound **15b** with that of celecoxib **1**. (i) The sulfonamide group present in celecoxib is replaced by methyl sulfonyl group, believed to be crucial for increasing the COX-2 selectivity. (ii) The 4-methylphenyl and the trifluoromethyl groups on pyrazole ring are replaced and is fused with 1,3-diarylbenzene. (iii) Two similar pharmacophores were introduced in a single molecular frame work, linked by a methylene bridge. We evaluated the compound **15b** for COX inhibition in the HWB assay, performed essentially as described [22]. The 2-(4-methylsulfonyl)phenyl-substituted compound **15b** showed 69.51% of COX-2 inhibition at 3 μM in HWB assay, compared with 90.90% inhibition observed for celecoxib **1** at the same concentration. The compound **15b** showed only moderate COX-1 inhibition at a very high concentration (50 μM) for about 21.02%.

In conclusion, a series of novel methylene-bis-fused pyrazoles **12a–e** and methylene-bis-2(4-methylsulfonyl)-phenyl substituted fused pyrazoles **15a–d** have been designed and synthesized. The antimicrobial activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria, and fungi. Among the synthesized compounds, **12c**, **15a**, and **15b** showed good activity against bacteria and fungi and emerged as potential molecules for further development. The compounds were also evaluated for their COX-2 selective inhibition, **15b** showed an appreciable COX-2 inhibition and selectivity. With this set of analogs, we are now in a position to investigate the multiple biological activities for these compounds.

## EXPERIMENTAL

Research chemicals were either purchased from Aldrich Company or Fluka or used without further purification in the reactions, or were prepared according to procedures described in the literature. Reactions were monitored by thin layer chromatography on silica gel plated (60 $F_{254}$; Merck) visualizing with ultraviolet light or iodine. Column chromatography was performed on silica gel 60 (0.043–0.060 mm), Merck. The reported yields of the products are unoptimized. Melting points were determined with a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 5000 spectrometer, using KBr pellet. $^1$H NMR, $^{13}$C NMR spectra were recorded on a Varian Gemini spectrometer, operating at 300, 75 MHz, respectively. Chemical shifts (δ) are reported as parts per million downfield from tetramethyl silane. Mass spectra were obtained on a VG micromass 7070H spectrometer.

**Ethyl-6-(5-{3-[6-(ethoxycarbonyl)-5-oxo-3-phenyl-3-cyclohexenyl]-4-hydroxybenzyl}-2-hydroxyphenyl)-2-oxo-4-phenyl- 3-cyclohexene-1-carboxylate (8a).** In a solution sodium metal (2 g) in ethanol (30 mL), a mixture of freshly distilled ethylacetoacetate (3.9 mL, 0.03 mol) and compound **7a** (4.6 g, 0.01 mol) dissolved in ethanol (20 mL) was added. The resulting solution was refluxed on a water bath for 4 h. Allowing the reaction mixture to cool and crystallization of the ppt. from ethanol to give **8a** as brown solid; Yield 82%; m.p. 150–52°C; IR (KBr): ν 3452, 3065, 1702, 1695, 1597, 1245 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 7.10–7.14 (m, 10 H, ArH), 6.80 (s, 2H, ArH), 6.79 (d, $J$ = 9.2 Hz, 2H, ArH), 6.62 (d, $J$ = 9.2 Hz, 2H, ArH), 6.10 (s, 2H, CH), 5.20 (s, 2H, OH), 4.06 (q, 4H, $CH_2$), 3.87 (q, 2H, CH), 3.81 (d, 2H, CH), 3.72 (s, 2H, $CH_2$), 2.87 (d, 4H, $CH_2$), 1.10 (t, 6H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): δ 190.1, 176.7, 154.6, 149.5, 142.3, 133.4, 130.0, 128.7, 128.2, 127.9, 125.5, 123.8, 121.9, 117.4, 61.2, 60.6, 42.1, 37.0, 30.7, 17.0. MS: $m/z$ 685 ($M^+$ + 1). The other compounds **8b–e** were prepared by the similar procedure.

**5-{2-Hydroxy-5-[4-hydroxy-3-(5-oxo-3-phenyl-3-cyclohexenyl)benzyl]phenyl-3-phenyl}-2-cyclohexen-1-one (9a).** To a mixture of glacial acetic acid (100 mL) and conc. HCl (50 mL) was added compound **8a** (6.5 g, 0.01 mol) in portions. The mixture was heated to reflux for 10 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up with ethyl acetate and washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in *vacuo* to give oil, which soon solidified; it was purified by recrystallization from ethanol to give the compound **9a** as brown solid; Yield 79%; m.p. 132–34°C; IR (KBr): ν 3357, 3025, 2932, 1687, 1596 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 7.10–7.14 (m, 10H, ArH), 7.00 (d, $J$ = 9.2 Hz, 2H, ArH), 6.82 (s, 2H, ArH), 6.62 (d, $J$ = 9.2 Hz, 2H, ArH), 6.10 (s, 2H, CH), 5.20 (s, 2H, OH), 3.83–3.87 (m, 2H, CH), 3.72 (s, 2H, $CH_2$), 2.70 (d, 4H, $CH_2$), 2.67 (d, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$): δ 190.0, 155.2, 150.1, 140.5, 132.3, 131.2, 128.5, 127.8, 127.4, 126.2, 124.5, 122.6, 116.1, 47.5, 42.0, 38.9, 31.0; MS: $m/z$ 541 ($M^+$ + 1). The other compounds **9b–e** were prepared by the similar procedure.

**5-[2-Hydroxy-5-(4-hydroxy-3-{6-[(*Z*)-1-hydroxymethylidene]-5-oxo-3-phenyl-3-cyclohexenyl}benzyl)phenyl]-6-[(*Z*)-1-hydroxymethylidene]-3-phenyl-2-cyclohexen-1-one (10a).** In a solution of 10% sodium methoxide (10 mL) in benzene (25 mL), ethylformate (2.24 mL, 0.03 mol) was added and afterward over 30 min, compound **9a** (5.4 g, 0.01 mol) dissolved in benzene (10 mL) was added. The resulting solution was stirred for 10 h at room temperature and allowed to stand over night, then evaporated to dryness. The suspension obtained was mixed with cold water and acidified with dil HCl (20 mL) and extracted three times with ether (40 mL). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give solid, was purified by crystallization in ethanol to afford pure **10a** as yellow solid; Yield 81%; m.p. 143–45°C; IR (KBr): ν 3320, 3028, 2952, 1662, 1620, 1597 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 8.97 (s, 2H, OH), 7.92 (s, 2H, CH), 7.14–7.10 (m, 10H, ArH), 6.80 (s, 2H, ArH), 6.49–6.40 (m, 4H, ArH), 5.67 (s, 2H, CH), 4.12 (t, 2H, CH), 3.72 (s, 2H, $CH_2$), 3.22 (d, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$): δ 191.3, 167.6, 156.1, 149.7, 142.0, 131.1, 130.6, 130.2, 128.9, 128.0, 127.9, 127.6, 126.2, 116.7, 115.5, 44.1, 42.0, 37.8; MS: $m/z$ 596 ($M^+$). The other compounds **10b–e** were prepared by the similar procedure.

**4-[4-Hydroxy-3-(6-phenyl-4,5-dihydro-1*H*-4-indazolyl)benzyl]-2-(6-phenyl-4,5-dihydro-1*H*-4-indazolyl)phenol (11a).** To a solution of **10a** (5.9 g, 0.01 mol) in glacial acetic acid (50 mL), hydrazine hydrate (1.5 g, 0.03 mol) was added. After stirring at 80°C for 10 h, the mixture was concentrated *in vacuo*. To the residue was added water and twice extracted with ether, washed the organic layer with saturated $NaHCO_3$ solution, subsequently with water and brine, dried over $MgSO_4$, and evaporated to dryness. The residue could be recrystallized from ethanol to afford **11a** as brown solid; Yield 79%; m.p. 123–25°C; IR (KBr): ν 3390, 3037, 2972, 1595, 1585 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.12 (bs, 2H, NH), 7.65 (s, 2H, ArH), 7.63 (s, 2H, ArH), 7.32 (d, $J$ = 9.2 Hz, 4H, ArH), 7.21 (s, 2H, ArH), 6.99–7.05 (m, 6H, ArH), 6.84 (d, $J$ = 9.1 Hz, 2H, ArH), 6.73 (d, $J$ = 9.0 Hz, ArH), 6.62 (s, 2H, OH), 4.92 (t, 2H, CH), 3.72 (s, 2H, $CH_2$), 2.92 (d, 4H, $CH_2$); $^{13}C$ NMR (DMSO-$d_6$): δ 156.2, 148.7, 143.4, 140.3, 132.8, 132.0, 130.9, 130.0, 128.9, 127.8, 126.9, 126.5, 125.4, 118.7, 117.2, 42.1, 39.3, 38.1; MS: $m/z$ 589 ($M^+$ + 1). The other compounds **11b–e** were prepared by the similar procedure.

**4-[4-Hydroxy-3-(6-aryl-1*H*-4-indazolyl)benzyl]-2(6-aryl-1*H*-4-indazolyl)phenol (12a–e).** To a solution of corresponding compound **11** (0.01 mol) in dry benzene (20 mL), DDQ (0.03 mol) dissolved in dry benzene (20 mL) was added in portions. The mixture was heated to reflux and stirred for 5 h under a nitrogen atmosphere. The precipitated DDQ-$H_2$ was filtered off and the filtrate was subjected to column chromatography on silica gel (60–120 mesh) to afford pure compounds.

**4-[4-Hydroxy-3-(6-phenyl-1*H*-4-indazolyl)benzyl]-2(6-phenyl-1*H*-4-indazolyl)phenol (12a).** This was obtained as yellow solid; Yield 83%; m.p. 137–39°C; IR (KBr): ν 3392, 3062, 2985, 1584 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 8.87 (bs, 2H, NH), 7.47 (s, 2H, ArH), 7.32–7.26 (m, 8H, ArH) 6.94 (d, $J$ = 9.0 Hz, 2H, ArH) 4.05 (s, 2H, $CH_2$); $^{13}C$ NMR (DMSO-$d_6$): δ 159.0, 155.6, 147.9, 146.1, 145.3, 141.7, 139.0, 137.2, 136.5, 134.2, 128.8, 126.9, 126.5, 125.4, 123.8, 118.2, 112.7, 42.1; MS: $m/z$ 585 ($M^+$ + 1).

**2-[6-(4-Bromophenyl)-1*H*-4-indazolyl]-4-3-[6-(4-bromophenyl)-1*H*-4-indazolyl]-4-hydroxybenzylphenol (12b).** This was obtained as brown solid; Yield 82%; m.p. 142–44°C; IR (KBr): ν 3400, 3037, 2962, 1585, 712 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.86 (bs, 2H, NH), 8.15 (s, 2H, ArH), 8.10 (s, 2H, ArH), 7.94 (s, 2H, ArH), 7.47 (s, 2H, ArH), 7.41 (d, $J$ = 8.3 Hz, 4H, ArH), 7.32–7.26 (m, 6H, ArH), 6.94 (d, $J$ = 9.0 Hz, 2H, ArH), 4.02 (s, 2H, $CH_2$); $^{13}C$ NMR (DMSO-$d_6$): δ 159.0, 155.6, 149.3, 146.1, 141.7, 139.1, 137.4, 137.1, 136.5, 134.3, 131.2, 129.4, 125.4, 123.9, 118.3, 112.7, 42.1; MS: $m/z$ 743 ($M^+$ + 1).

**2-[6-(4-Aminophenyl)-1*H*-4-indazolyl]-4-3-[6-(4-aminophenyl)-1*H*-4-indazolyl]-4-hydroxybenylphenol (12c).** This was obtained as orange solid; Yield 76%; m.p. 151–53°C; IR (KBr): ν 3395, 3061, 2937, 1585 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.84 (bs, 2H, NH), 8.15 (s, 2H, ArH), 8.10 (s, 2H, ArH), 7.94 (s, 2H, ArH), 7.62 (d, $J$ = 8.4 Hz, 4H, ArH), 7.47 (s, 2H, ArH), 7.28 (d, $J$ = 9.0 Hz, 2H, ArH), 6.94 (d, $J$ = 9.0 Hz, 2H, ArH), 6.62 (d, $J$ = 8.4 Hz, 4H, ArH), 6.32 (bs, 4H, $NH_2$), 4.02 (s, 2H, $CH_2$); $^{13}C$ NMR (DMSO-$d_6$): δ 159.1, 155.6, 149.7, 146.1, 142.4, 141.6, 139.0, 137.2, 136.5, 134.9, 134.2, 130.2, 124.2, 123.8, 118.2, 113.1, 112.7, 42.2; MS: $m/z$ 615 ($M^+$ + 1).

**2-[6-(4-Clorophenyl)-1*H*-4-indazolyl]-4-{3-[6-(4-chlorophenyl)-1*H*-4-indazolyl]-4-hydroxy}benzylphenol (12d).** This was obtained as yellow solid; Yield 81%; m.p. 115–17°C; IR (KBr): ν 3387, 3042, 2932, 1585, 686 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.86 (bs, 2H, NH), 8.15 (s, 2H, ArH), 8.10 (s, 2H, ArH), 7.94 (s, 2H, ArH), 7.82 (d, $J$ = 8.2 Hz, 4H, ArH), 7.41 (s, 2H, ArH), 7.32–7.26 (m, 6H, ArH), 7.00 (s, 2H, ArH) 6.94 (d, $J$ = 9.0 Hz, 2H, ArH) 4.02 (s, 2H, $CH_2$); $^{13}C$ NMR (DMSO-$d_6$): δ 158.7, 155.6, 147.4, 146.1, 141.7, 139.0, 137.2, 136.5, 134.9, 134.2, 134.0, 128.7, 126.4, 125.4, 123.8, 118.3, 112.7, 42.2; MS: $m/z$ 654 ($M^+$).

**4-{4-Hydroxy-3-[6-(4-methoxyphenyl)-1*H*-4-indazolyl]benzyl}-2-[6-(4-methoxyphenyl)-1*H*-4-indazolyl]phenol (12e).** This was obtained as brown solid; Yield 80%; m.p. 122–24°C; IR (KBr): ν 3400, 3042, 2962, 1584, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.87 (bs, 2H, NH), 8.14 (s, 2H, ArH), 8.10 (s, 2H, ArH), 7.94 (s, 2H, ArH), 7.47 (s, 2H, ArH), 7.39 (d, $J$ = 8.4 Hz, 4H, ArH), 7.32 (d, $J$ = 9.0 Hz, 2H, ArH), 6.94 (d, $J$ = 9.0 Hz, 2H, ArH), 6.84 (d, $J$ = 8.4 Hz, 4H, ArH), 4.02 (s, 2H, $CH_2$), 3.84 (s, 6H, $OCH_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 161.2, 159.0, 155.6, 149.5, 146.1, 141.7, 139.2, 137.4, 136.5, 134.2, 133.2, 129.4, 129.0, 125.7, 124.3, 123.8, 118.2, 112.7, 112.0, 54.7, 42.2; MS: $m/z$ 645 ($M^+$ + 1).

**4-{6-(4-Bromophenyl)-4-[5-(3-{6-(4-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-4,5-dihydro-2*H*-4-indazolyl}-4-hydroxy benzyl)-2-hydroxyphenyl]-4,5-dihydro-2*H*-2-indazolyl}-1-benzene sulfonic acid (14a).** To a stirred solution of **10b** (7.5 g, 0.01 mol) in ethanol (100 mL) and 6 *N* HCl (14.8 mL, 0.892 mol) was added 4-(methylsulfonyl)phenyl hydrazine **13** (4.1 g, 0.022 mol). The mixture was heated to reflux and stirred for 10 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up with ethyl acetate and washed with water and brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give a solid that was crystallized from diisopropyl ether (100 mL) to give pyrazole **14a** as brown solid; Yield 82%; m.p. 222–24°C; IR (KBr): ν 3400, 3062, 2937, 1585, 1328, 1165, 732 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 7.91 (s, 2H, ArH), 7.67–7.62 (m, 6H, ArH), 7.50–7.42 (m, 12H, ArH), 7.23 (s, 2H, ArH), 6.94 (s, 2H, OH), 6.84 (d, $J$ = 8.9 Hz, 2H, ArH), 6.77 (d, $J$ = 8.9 Hz, 2H, ArH), 4.87 (t, 2H, CH), 3.72 (s, 2H, $CH_2$), 3.12 (d, 4H, $CH_2$), 2.94 (s, 6H, $CH_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 156.1, 154.2, 153.5, 142.7, 138.8, 133.5, 132.3, 130.4, 129.9, 129.1, 128.0, 126.8, 126.4, 124.6, 124.2, 122.4, 120.7, 119.4, 118.2, 43.5, 42.3, 41.6, 38.7; MS: $m/z$ 1056 ($M^+$). The other compounds **14c–d** were also prepared by the similar procedure.

**4-{6-(aryl)-4-[5-(3-{6-(aryl)-2-[4-(methylsulfonyl)phenyl]-2*H*-4-indazolyl}-4-hydroxybenzyl)-2-hydroxyphenyl]-2*H*-2-indazolyl}-1-benzenesulfonic acid (15a–d).** To a solution of **14** (0.005 mol) in dry benzene (20 mL), DDQ (0.015 mol) in dry benzene (20 mL) was added in portions. The mixture was heated to reflux and stirred for 5 h under a nitrogen atmosphere. The precipitated DDQ-$H_2$ was filtered off and the filtrate was subjected to column chromatography on silica gel (60–120 mesh), to afford pure compounds.

**4-{6-(4-Bromophenyl)-4-[5-(3-{6-(4-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2*H*-4-indazolyl}-4-hydroxybenzyl)-2-hydroxyphenyl]-2*H*-2-indazolyl}-1-benzenesulfonic acid (15a).** This was obtained as brown solid; Yield 80%; m.p. 210–12°C; IR (KBr): ν 3400, 3062, 2937, 1585, 1328, 1165, 736 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 8.14 (s, 2H, ArH), 7.80 (s, 2H, ArH), 7.72 (d, $J$ = 8.3 Hz, 4H, ArH), 7.53–7.48 (m, 8H, ArH), 7.32–7.28 (m, 6H, ArH), 6.84–6.78 (m, 4H, ArH, OH), 6.72 (s, 2H, ArH), 4.02 (s, 2H, $CH_2$), 2.94 (s, 6H, $CH_3$); $^{13}C$ NMR

(DMSO-$d_6$): δ 153.1, 152.0, 143.3, 142.9, 136.7, 136.2, 133.3, 130.7, 129.8, 129.0, 128.7, 127.9, 125.4, 124.0, 123.9, 122.3, 119.7, 117.6, 111.3, 110.4, 44.3, 42.4; MS: *m*/*z* 1050 ($M^+$).

**4-{6-(4-aminophenyl)-4-[5-(3-{6-(4-aminophenyl)-2-[4-(methylsulfonyl)phenyl]-2*H*-4-indazolyl}-4-hydroxybenzyl)-2-hydroxyphenyl]-2*H*-2-indazolyl}-1-benzenesulfonic acid (15b).** This was obtained as orange solid; Yield 84%; m.p. 240–42°C; IR (KBr): ν 3400, 3065, 2932, 1589, 1328, 1162 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.14 (s, 2H, ArH), 7.80 (s, 2H, ArH), 7.72 (d, $J$ = 8.2 Hz, 4H, ArH), 7.67 (d, $J$ = 8.6 Hz, 4H, ArH), 7.53 (d, $J$ = 8.2 Hz, 4H, ArH), 7.32 (d, $J$ = 8.6 Hz, 2H, ArH), 6.94 (d, $J$ = 9.1 Hz, 2H, ArH), 6.72 (d, $J$ = 8.6 Hz, 4H, ArH), 5.96 (s, 2H, OH), 4.96 (bs, 4H, $NH_2$), 4.02 (s, 2H, $CH_2$), 2.94 (s, 6H, $CH_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 153.1, 152.0, 147.3, 145.2, 143.3, 138.2, 136.7, 130.7, 129.7, 129.0, 126.2, 125.6, 124.0, 123.9, 122.3, 121.0, 119.7, 117.6, 111.9, 110.4, 44.3, 42.4; MS: *m*/*z* 924 ($M^+ + 1$).

**4-{6-(4-Chlorophenyl)-4-[5-(3-{6-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-2*H*-4-indazolyl}-4-hydroxybenzyl)-2-hydroxyphenyl]-2*H*-2-indazolyl}-1-benzenesulfonic acid (15c).** This was obtained as yellow solid; Yield 79%; m.p. 196–98°C; IR (KBr): ν 3410, 3065, 2932, 1586, 1328, 1162, 686 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.14 (s, 2H, ArH), 7.95 (d, $J$ = 8.6 Hz, 4H, ArH), 7.80 (s, 2H, ArH), 7.68 (d, $J$ = 8.9 Hz, 4H, ArH), 7.59 (d, $J$ = 8.9 Hz, 4H, ArH), 7.47 (d, $J$ = 8.6 Hz, 4H, ArH), 7.32 (d, $J$ = 9.0 Hz, 2H, ArH), 6.90 (d, $J$ = 9.0 Hz, 2H, ArH), 6.68 (s, 2H, ArH), 5.92 (s, 2H, OH), 4.02 (s, 2H, $CH_2$), 2.96 (s, 6H, $CH_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 153.1, 152.0, 146.6, 143.3, 136.9, 136.0, 134.9, 133.3, 131.2, 130.0, 129.8, 129.0, 128.6, 125.6, 124.0, 123.9, 122.7, 122.0, 119.7, 117.6, 110.4, 109.7, 44.3, 42.2; MS: *m*/*z* 963 ($M^+ + 1$).

**4-[4-[2-Hydroxy-5-(4-hydroxy-3-{6-(4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]-2H-4-indazolyl}benzyl)phenyl]-6-(4-methoxyphenyl)-2H-2-indazolyl]-1-benzene sulfonic acid (15d).** This was obtained as brown solid; Yield 86%; m.p. 209–11°C; IR (KBr): ν 3400, 3065, 2937, 1589, 1328, 1162 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.14 (s, 2H, ArH), 7.68 (d, $J$ = 8.1 Hz, 4H, ArH), 7.68 (d, $J$ = 8.9 Hz, 4H, ArH), 7.59 (d, $J$ = 8.9 Hz, 4H, ArH), 7.47 (d, $J$ = 8.1 Hz, 4H, ArH), 7.32 (d, $J$ = 9.0 Hz, 2H, ArH), 6.90 (d, $J$ = 9.0 Hz, 2H, ArH), 6.89 (d, $J$ = 8.1 Hz, 4H, ArH), 6.68 (s, 2H, ArH), 5.96 (s, 2H, OH), 4.02 (s, 2H, $CH_2$), 3.89 (s, 6H, $OCH_3$), 2.96 (s, 6H, $CH_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 159.6, 153.9, 153.4, 152.0, 143.3, 136.7, 133.8, 133.1, 130.7, 129.8, 129.0, 125.6, 124.7, 124.0, 123.8, 122.3, 119.7, 117.6, 113.0, 110.9, 110.4, 55.6, 44.3, 42.4; MS: *m*/*z* 955 ($M^+ + 1$).

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## REFERENCES AND NOTES

[1] Baraldi, P. G.; Pavani, M. G.; Nunez, M.; Brigidi, P.; Vitali, B.; Gambari, R.; Romagnoli, R. Bioorg Med Chem 2002, 10, 449.

[2] Lee, K. Y.; Kim, J. M.; Kim, J. N. Tetrahedron Lett 2003, 44, 6737.

[3] Erhan, P.; Mutlu, A.; Tayfun, U.; Dilek, E. Eur J Med Chem 2001, 36, 539.

[4] Giesc, N. A.; Lokker, N.; Laibelman, A. M.; Searbrough, R. M. Chem Absrt 1996, 135, 105089.

[5] Bruno, O.; Ranise, A.; Bonduvalli, F.; Schenone, S.; Amico, M.; Falciani, M.; Vacca, C.; Filippli, A. Il Farmaco 1994, 49, 533.

[6] Richard, A. N.; Megan, M.; Stephen, T. S.; Colin, J. D.; Robert, J. S.; Nigel, D. S.; Louise, A. G.; Sharon, K. S.; Danielle, G. A.; Karen, A. R.; Norman, A. R. J Med Chem 1993, 36, 134.

[7] Hiroshi, K.; Yasuhiro, T.; Yoshio, S.; Fumiki, S.; Norio, O.; Akira, T. Jpn J Pharmacol 1997, 73, 317.

[8] Genin, M. J.; Bilers, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. J Med Chem 2000, 43, 1034.

[9] Habeb, A. G.; Rao, P. N. P.; Knaus, E. E. J Med Chem 2001, 44, 3039.

[10] David, L. S.; David, G. B.; Joanna, B.; Guillaume, E. B.; Richard, O. C.; Surinder, S. C.; Ian, G. C.; Patricia, A. F.; Robert, C. G.; Maria, C. G.; Adrian, J. H.; Marcel, R. K.; Qian, L.; David, J. M.; Sylvie, M.; Kenneth, L. P.; Karen, R.; Graham, D. S.; Jeremy, N. S.; Mark, A. T.; Kerry, A. W.; Grant, W.; Chi-kit, W. J Med Chem 2001, 44, 78.

[11] Al-Allaf, T. A. K.; Rashan, L. J Boll Chim Farm 2001, 140, 205.

[12] Turini, M. E.; DuBois, R. N. Annu Rev Med 2002, 53, 35.

[13] Dubois, A. Prostag Other Lipid Mediat 1999, 56, 341.

[14] Garcia, R. L. A.; Hernandez, D. S. Epidemiology 2003, 14, 240.

[15] Sanjeeva Reddy, Ch.; Nagaraj, A. Heterocycl Commun 2007, 13, 67.

[16] Sanjeeva Reddy, Ch.; Nagaraj, A. Chin Chem Lett 2007, 18, 1213.

[17] Sanjeeva Reddy, Ch.; Nagaraj, A. J Heterocyclic Chem 2007, 44, 1357.

[18] Sanjeeva Reddy, Ch.; Nagaraj, A. J Iran Chem Soc 2008, 5, 262.

[19] Marvel, C. S.; Tarkoy, N. J Am Chem Soc 1957, 79, 6000.

[20] Sanjeeva Reddy, Ch.; Nagaraj, A. J Heterocycl Chem 2007, 44, 1181.

[21] National Committee for Clinical Laboratory Standards (NCCLS). Standard methods for dilution antimicrobial susceptibility tests for bacteria, which grows aerobically; Nat Comm Lab Stands: Villanova, 1982; p 242.

[22] Young, J. M.; Panah, S.; Satchawat, C, C.; Cheung, P. S. Inflammation Res 1996, 45, 246.

# Synthesis, Structures, and Herbicidal Activity of Isoxazole Derivatives



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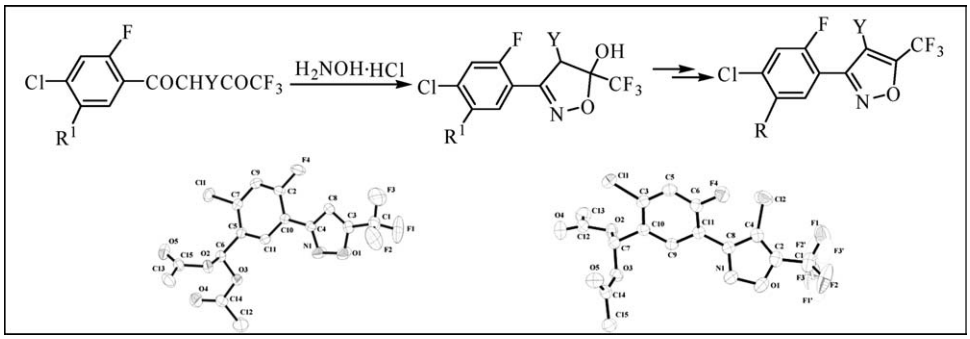


The several novel 3-substituted phenyl isoxazole derivatives were prepared from substituted phenyl-butan-1,3-dione. Their structures were confirmed by element analysis, IR, MS, and $^1$H NMR. X-ray structure analysis indicated that the dihedral angles of the phenyl ring with the isoxazole ring in compounds **4a** and **4b** were 19.46° and 49.18°, respectively. Preliminary bioassay showed that the title compounds had good activity to various weeds, and **4a** exhibited almost the same activity with **4b**. This was different from the former works, which showed that the big dihedral angle of the phenyl ring with the heterocyclic moiety was necessary for high-herbicidal activity.

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## INTRODUCTION

Herbicides inhibiting protoporphyrinogen oxidase (Protox) are the ones of the most important class of herbicides. Targeting the porphyrin pathway, these herbicides have shown high-activity and low-toxicity, and thus have become a hot-point of novel pesticides research [1]. Besides di-phenylether-type herbicides, which have been commercialized for more than 30 years, many other chemical classes belong to this family, such as azafenidin, oxadiazon, carfentrazone, etc. Substituted phenyl heterocyclic compounds are thought to be potent Protox-inhibitors, because they are similar to one half of the protoporphyrinogen IX, which is the target of Protox. Research on heterocyclic Protox inhibitors has been actively pursued, and a large number of compounds with high-bioactivity were reported [2–6]. Some samples of commercial Protox inhibitors are shown in Figure 1. Substituted phenyl isoxazoline derivatives have been reported, and some of them have high-activities [7]. We have also reported several novel 3-(substituted phenyl) isoxazole in a previous letter [8], considering that some isoxazole derivatives have displayed good biological activity [9–12], and that isoxazole moiety is more similar to the substructure of protoporphyrinogen IX than isoxazoline moiety. More importantly, a further study shows these isoxazole derivatives exhibit different structure-activity relationship from other phenyl heterocyclic compounds. Herein, details of the study, including the synthesis, their X-ray structures and the herbicidal activity of these isoxazole derivatives, are reported.

## RESULTS AND DISCUSSION

The title compounds were prepared from substituted phenyl-butan-1,3-dione. At first, the isoxazole cycle was built via a ring closure reaction of phenylbutan-1,3-dione with hydroxylamine chloride [13]. In this reaction, what we obtained were isoxazolines (**2**), which could be changed into isoxazoles via a dehydration reaction in hot concentrated sulfuric acid (98%). When **2c** was employed as the substrate, the C—O band of the methoxy group was cleaved and **3c** was obtained (Scheme 1). From compounds **3a** or **3b**, different aimed compounds can be obtained by derivation of the methyl group on Position 5 of the phenyl cycle. It can be transformed into an aldehyde through a diester, via an oxidation reaction and a hydrolytic reaction. Otherwise, the methyl group on Position 5 of the phenyl cycle can be oxidized into a carboxyl group with chromium trioxide/

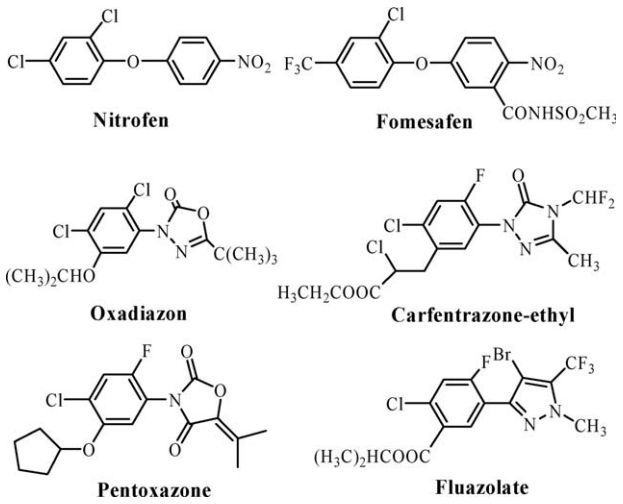



**Figure 1.** Samples of commercial Protox inhibitors.

sulfuric acid, and further transformed to an ester or amide via an acyl chloride intermediate. From compounds **3c**, different aimed compounds can be obtained via an alkylation reaction (Scheme 2).

To investigate further the structure-activity relationship of the aimed compounds, the single crystals of compounds **4a** and **4b** were prepared, and their structures were determined. The details of crystals, data collections and final refinement for compounds **4a** and **4b** are listed in Table 1. The selected bond distances (Å), angles (°) and torsion angles (°) of compounds **4a** and **4b** were given in Table 2. Both of the compounds have two planar rings, that is, the phenyl ring and the isoxazole moiety. However, the dihedral angle in **4a** [shown as C(2)—C(10)—C(4)—C(8)] is much different from that in **4b** [shown as C(5)—C(11)—C(8)—C(4)]. In compound **4a** (Fig. 2), it is 19.46°, whereas 49.18° in compound **4b** (Fig. 3). It indicated that the chlorine substitution could increase the dihedral angle of the two rings for the steric effect, which agreed with our former work [14].

Preliminary bioassay showed that compounds **4**, **5**, **7**, **8** have good activity to various weeds. Compared with fomesafen, which was a high-activity herbicide widely used, the herbicidal activity of these compounds to different weeds by stem and leaf treatment at a dosage of 1.5 kg/hm$^2$ and 150 g/hm$^2$, were shown in Table 3. Some of them have higher activity than fomesafen, especially at a lower dosage.

Here, we noticed that both compounds with chlorine substitution on isoxazole (**4b**, **5b**, **7a**∼**e**) and those without chlorine substitution on isoxazole (**4a**, **5a**, **8a**∼**f**) have high-activity.

It was reported that the ortho-position (to the phenyl ring) substituted groups on the heterocyclic moiety was necessary for high-activity to force the heterocyclic moiety out of planarity with the attached phenyl ring and to match closely the angle of the methylene bridge between two pyrrole rings of the protoporphyrinogen structure [15]. And it was reported recently that the dihalopyrrole nucleus was important for biological activity in 3-arylpyrroles [16]. However, in this research, the result was different from these former works. The tested isoxazole derivatives had high-activity no matter that Y was hydrogen or chlorine. Although the compounds with chlorine substituted had higher activity than those unsubstituted, the difference was quite little. Meanwhile, our former work indicated that the dihedral angle of the phenyl ring and the isoxazole moiety in the compound with chlorine on isoxazole ring was much bigger than those without chlorine substitution in solution [14]. These results suggest that the big dihedral angle of the phenyl ring and the isoxazole moiety may be not a key point for high-activity. We think a molecule may adjust the angle to fit closely the Protox in cells in bio-assaying. However, it needs further research.

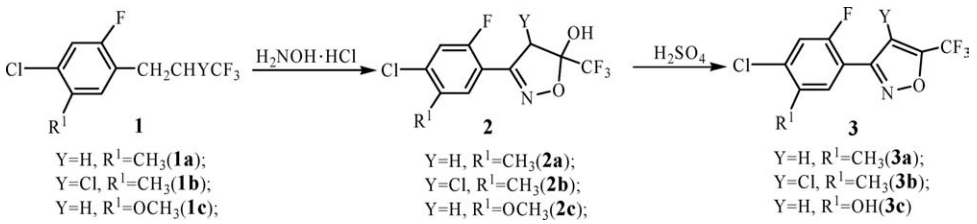
## EXPERIMENTAL

$^1$H NMR spectra were measured on a Varian VA400MHz spectrometer with TMS as an internal standard. $^{13}$C NMR spectra were obtained with broadband proton decoupling. MS was performed on a HP1100 high-performance liquid chromatography/mass selective detector. Melting points were determined using a YanacoMP-500 apparatus and were uncorrected. IR spectra were run on Nicolet 20DBX FT-IR. Elemental analysis was measured on MOD.1106 elemental analysis instrumentation.

Compounds **1a** and **1c** were synthesized by methods described in [17]. Compounds **1b** were prepared from **1a** following the procedure given in [7].

**General procedure for the preparation of compound 2.** To a solution of **1** (34 mmol) in acetic acid (100 mL), hydroxylamine chloride (5 g, 72 mmol) was added. Then the

**Scheme 1.** Building of isoxazole cycle.



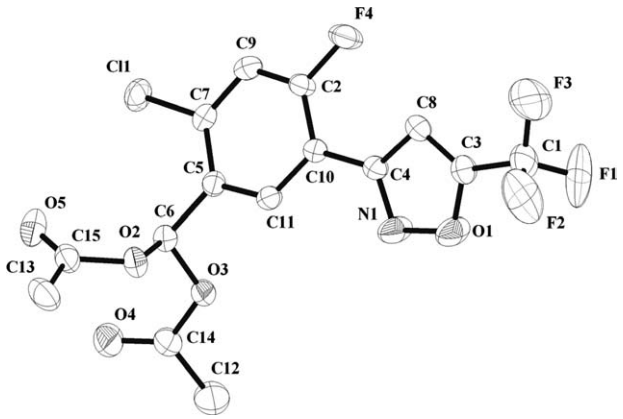



**Figure 2.** ORTEP (ellipsoids at 30% probability) diagram of compound **4a**. All hydrogen atoms are omitted for clarity.

mixture was heated to 100°C for 30 min. After the solution was cooled, it was poured into water, resulting in a white solid precipitate.

***3-(4-Chloro-2-fluoro-5-methyl)phenyl-5-hydroxy-5-trifluoromethylisoxazoline (2a).*** This compound was obtained as a white solid, yield 92%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 128.0∼130.0°C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, 1H, $J$ = 8.0 Hz, Ph), 7.18 (d, 1H, $J$ = 10.4 Hz, Ph), 3.91 (br, 1H, OH), 3.77 (dd, 1H, $J$ = 18.6 Hz, 2.0 Hz, CH), 3.57 (d, 1H, $J$ = 18.6 Hz, CH), 2.36 (s, 3H, $CH_3$); MS (API-ES, negative), $m/z$: 296.0 ($[M-H]^-$).

*Anal*. Calcd. for $C_{11}H_8O_2NClF_4$ (297.6): C, 44.39; H, 2.71; N, 4.71. Found: C, 44.51; H, 2.58; N, 4.52.

***4-Chloro-3-(4-chloro-2-fluoro-5-methyl)phenyl-5-hydroxy-5-trifluoromethylisoxazoline (2b).*** This compound was obtained as a white solid, yield 86%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 84.0∼86.0°C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, 1H, $J$ = 7.6 Hz, Ph), 7.24 (d, 1H, $J$ = 10.8 Hz, Ph), 5.70 (s, CH), 4.2∼4.4(br, 1H, OH), 2.38 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 157.9 (d, $J$ = 253.4 Hz), 153.9 (s, 138.0 (d, $J$ = 10.1 Hz), 132.9 (s), 130.9 (s), 121.8 (q, $J$ = 286.1 Hz), 117.2 (d, $J$ = 24.9 Hz), 113.4 (d, $J$ = 11.9 Hz), 104.1 (q, $J$ = 33.1 Hz), 61.1 (d, $J$ = 4.8 Hz), 19.2(s); MS (API-ES, negative), $m/z$: 330.0 ($[M-H]^-$).

*Anal*. Calcd. for $C_{11}H_7O_2NCl_2F_4$ (332.1): C, 39.79; H, 2.12; N, 4.22. Found: C, 40.01; H, 2.15; N, 4.01.

***3-(4-Chloro-2-fluoro-5-methoxy)phenyl-5-hydroxy-5-trifluoromethylisoxazoline (2c).*** This compound was obtained as a white solid, yield 99%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 149.0∼151.0°C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.05 (br, 1H, OH), 7.41 (d, 1H, $J$ = 6.0 Hz, Ph), 7.20 (d, 1H, $J$ = 10.4 Hz, Ph), 3.91 (s, 3H, $CH_3$), 3.71 (d, 1H, $J$ = 18.4 Hz, 1/2$CH_2$), 3.54 (d, 1H, $J$ = 18.4 Hz, 1/2$CH_2$); $^{13}$C NMR (100 MHz, broadband proton decoupling, $CDCl_3$) δ: 153.2 (d, $J$ = 248.0 Hz), 152.5(s), 151.5 (s), 125.9 (d, $J$ = 10.7 Hz), 122.1 (q, $J$ = 283.8 Hz), 118.3 (d, $J$ = 27.1 Hz), 115.0 (d, $J$ = 12.7 Hz), 109.8 (d, $J$ = 3.1 Hz), 104.4 (q, $J$ = 33.6 Hz), 56.6 (s), 44.1 (d, $J$ = 8.3 Hz); MS (API-ES, negative), $m/z$: 312.0 ($[M-H]^-$), 348.0 ($[M+Cl]^-$).

*Anal*. Calcd. for $C_{11}H_8O_3NClF_4$ (313.6): C, 42.12; H, 2.57; N, 4.47. Found: C, 41.95; H, 2.51; N, 4.39.

**General procedure for the preparation of compound 3.** A solution of **2** (16 mmol) in concentrated sulfuric acid (98%, 35 mL) was heated to 110, and maintained at that temperature for 3 h. After the solution was cooled, it was poured into ice-water, resulting in a white solid precipitate. The yields of all compounds were about 100%.

***3-(4-Chloro-2-fluoro-5-methyl)phenyl-5-trifluoromethylisoxazole (3a).*** This compound was obtained as a white solid. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 34.0∼34.5; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, 1H, $J$ = 7.6 Hz, Ph), 7.25 (d, $J$ = 10.4 Hz, Ph), 7.13 (d, $J$ = 3.2 Hz, 1H, isoxazole), 2.40 (s, 3H, $CH_3$); MS (API-ES, negative), $m/z$: 278.0 ($[M-H]^-$).

*Anal*. Calcd. for $C_{11}H_6ONClF_4$ (279.6): C, 47.25; H, 2.16; N, 5.01. Found: C, 46.96; H, 2.07; N, 4.83.

***4-Chloro-3-(4-chloro-2-fluoro-5-methyl)phenyl-5-trifluoromethylisoxazole (3b).*** This compound was obtained as an oily residue; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, 1H, $J$ = 7.2 Hz, Ph), 7.27 (d, 1H, $J$ = 9.6 Hz, Ph), 2.35 (s, 3H, $CH_3$); MS (API-ES, negative), $m/z$: 312.0 ($[M-H]^-$).

**Scheme 2.** Synthesis of aimed compounds.

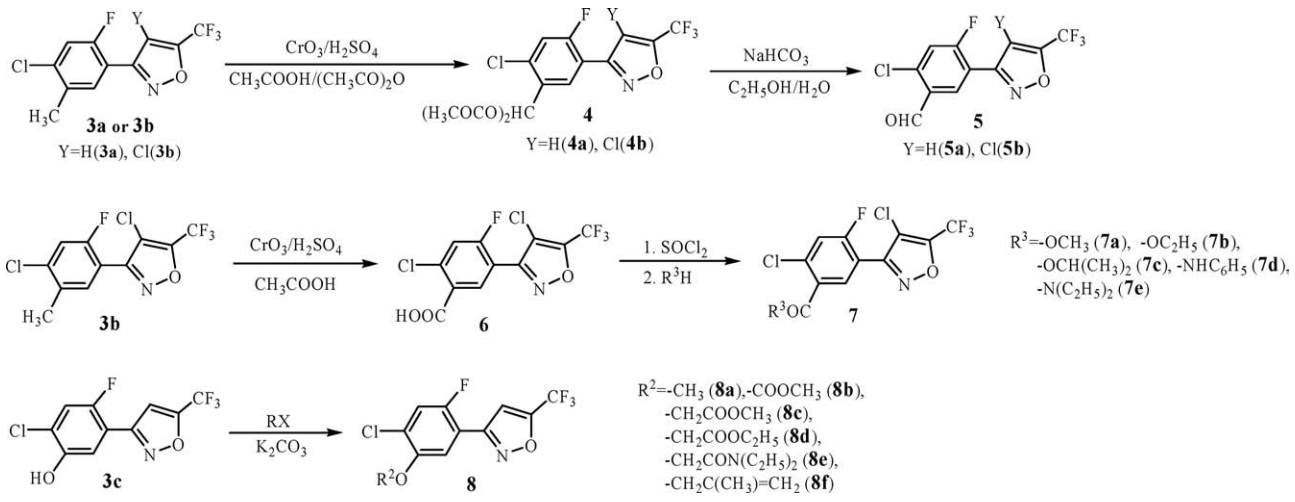


**Table 1**

Crystallographic parameters of compounds **4a** and **4b**.

| Complex | **4a** | **4b** |
|---|---|---|
| Empirical formula | $C_{15}H_{10}ClF_4NO_5$ | $C_{15}H_9Cl_2F_4NO_5$ |
| Formula weight | 395.69 | 430.13 |
| Crystal system | Orthorhombic | monoclinic |
| Space group | Pbca | C2/c |
| *a*, (Å) | 13.8903(6) | 26.3306(9) |
| *b*, (Å) | 7.6624(3) | 8.1761(3) |
| *c*, (Å) | 31.3155(12) | 19.8365(6) |
| β, (deg) | 90 | 124.992(2) |
| *V*, (Å$^3$) | 3333.0(2) | 3498.5 |
| *Z* | 8 | 8 |
| $D_{calcd}$, (g/cm$^3$) | 1.577 | 1.633 |
| *T*, (K) | 273(2) | 273(2) |
| μ (mm$^{-1}$), | 0.299 | 0.440 |
| *F*(000) | 1600 | 1728 |
| θ, (deg) | 1.96–27.58 | 2.10–29.12 |
| limiting indices | $^{-}17 \leq h \leq 14$ | $-35 \leq h \leq 35$ |
| | $^{-}9 \leq k \leq 9$ | $-10 \leq k \leq 10$ |
| | $^{-}38 \leq l \leq 40$ | $-24 \leq l \leq 26$ |
| Reflns collected/unique | 20813/3645 | 10565/4417 |
| GOF($F^2$) | 1.039 | 1.013 |
| $R_1/wR_2$ [I > 2sigma(I)] | 0.0548/0.1477 | 0.0485/0.1280 |
| $R_1/wR_2$ (all data) | 0.0996/0.1735 | 0.0829/0.1509 |
| Largest diff. peak and hole, e. Å$^{-3}$ | 0.389, −0.268 | 0.350, −0.383 |

*Anal*. Calcd. for $C_{11}H_5ONCl_2F_4$ (313.0): C, 42.07; H, 1.60; N, 4.46. Found: C, 41.96; H, 1.67; N, 4.53.

***3-(4-Chloro-2-fluoro-5-hydroxy)phenyl-5-trifluoromethylisoxazole (3c).*** This compound was obtained as a white solid. A sample suiting for analysis was obtained by recrystallization with a mixture of petroleum ether and ethyl acetate (3:1); mp 49.0∼50.5; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, 1H, $J$ = 6.4 Hz, Ph), 7.26 (d, $J$ = 9.6 Hz, Ph), 7.13 (s, 1H, isoxazole), 5.4∼6.0(br, 1H, OH); MS (API-ES, negative), *m*/*z*: 280.0 ([M-H]$^-$).

*Anal*. Calcd. for $C_{10}H_4O_2NClF_4$ (281.6): C, 42.65; H, 1.43; N, 4.97. Found: C, 42.96; H, 1.37; N, 4.85.

**General procedure for the preparation of compound 4.** To a mixture of **2** (18 mmol), acetic acid (15 mL), acetic anhydride (40 mL) and concentrated sulfuric acid (98%, 4.5 mL), was added chromium oxide (about 3 g, 30 mmol) in small portion, maintaining the temperature under 25. The reaction was monitored by TLC. After the reaction was completed, it was poured into water, recrystallized from alcohol to give **4**.

***2-Chloro-4-fluoro-5-(5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde diacetate (4a).*** This compound was obtained as a white solid, yield 57%, mp 87.0∼88.5; IR (KBr): 1768 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, 1H, $J$ = 8.0 Hz, Ph), 7.97 (s, 1H, CH), 7.34 (d, 1H, $J$ = 10.0 Hz, Ph), 7.15 (d, 1H, $J$ = 2.4 Hz, isoxazole), 2.16 (s, 6H, $2CH_3$); MS (API-ES, positive), *m*/*z*: 417.7 ([M+Na]$^+$).

*Anal*. Calcd. for $C_{15}H_{10}O_5NClF_4$ (395.7): C, 45.53; H, 2.55; N, 3.54. Found: C, 45.86; H, 2.67; N, 3.39.

***2-Chloro-4-fluoro-5-(4′-chloro-5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde diacetate (4b).*** This compound was obtained as a white solid, yield 68%, mp 97.0∼98.5°C; IR (KBr): 1773, 1759 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.97 (s, 1H, CH),7.81 (d, 1H, $J$ = 6.8 Hz, Ph), 7.37 (d, 1H, $J$ = 9.2 Hz, Ph), 2.14 (s, 6H, $CH_3$); MS (API-ES, positive), *m*/*z*: 451.7 ([M+Na]$^+$).

*Anal*. Calcd. for $C_{15}H_9O_5NCl_2F_4$ (430.1): C, 41.89; H, 2.11; N, 3.26. Found: C, 42.03; H, 2.17; N, 3.31.

**General procedure for the preparation of compound 5.** A slurry of **4** (5 mmol), sodium bicarbonate (2 g, 24 mmol), alcohol (10 mL) and water (2 mL) was refluxed for 2 h. After the solution was cooled, it was poured into water, resulting in **5** as a white solid precipitate.

***2-Chloro-4-fluoro-5-(5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde (5a).*** This compound was obtained as a white solid, yield 82%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 78.5∼80.0°C; IR (KBr): 1621 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 10.42 (s, 1H, CHO), 8.56 (d, 1H, $J$ = 7.2 Hz, Ph), 7.40 (d, 1H, $J$ = 10.0 Hz, Ph), 7.14 (s, 1H, isoxazole); MS (API-ES, negative), *m*/*z*: 359.6 ([M+$CH_3OH$+Cl]$^-$).

*Anal*. Calcd. for $C_{11}H_4O_2NClF_4$ (293.6): C, 45.00; H, 1.37; N, 4.77. Found: C, 44.86; H, 1.31; N, 4.95.

***2-Chloro-4-fluoro-5-(4′-chloro-5′-trifluoromethyl)isoxazol-3-yl-benzaldehyde (5b).*** This compound was obtained as a white solid, yield 78%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 77.5∼78.5°C; IR (KBr): 1694 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 10.44 (s, 1H, CHO), 8.21 (d, 1H, $J$ = 7.2 Hz, Ph), 7.43 (d, 1H, $J$ = 8.8 Hz, Ph); MS (API-ES, negative), *m*/*z*: 393.6 ([M+$CH_3OH$ +Cl]$^-$).

*Anal*. Calcd. for $C_{11}H_3O_2NCl_2F_4$ (228.0): C, 40.28; H, 0.92; N, 4.27. Found: C, 40.55; H, 0.97; N, 4.49.

***Procedure for the Preparation of 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoic acid (6).*** To a

**Table 2**

Selected bond distances (Å), angles (deg) and torsion angles (deg) of compounds **4a** and **4b**.

| **4a** | | **4b** | |
|---|---|---|---|
| Cl(1)—C(7) | 1.725(3) | Cl(1)—C(3) | 1.727(2) |
| F(4)—C(2) | 1.349(3) | C(5)—F(4) | 1.350(3) |
| O(1)—N(1) | 1.401(3) | N(1)—O(1) | 1.398(3) |
| O(1)—C(3) | 1.325(4) | O(1)—C(2) | 1.339(3) |
| C(10)—C(4) | 1.475(4) | C(8)—C(11) | 1.472(3) |
| C(4)—C(8) | 1.401(4) | C(4)—C(8) | 1.415(3) |
| C(4)—N(1) | 1.299(4) | N(1)—C(8) | 1.300(3) |
| C(8)—C(3) | 1.320(4) | C(2)—C(4) | 1.327(3) |
| C(6)—C(5) | 1.495(4) | C(7)—C(10) | 1.504(3) |
| C(3)—C(1) | 1.483(4) | C(1)—C(2) | 1.488(4) |
| | | Cl(2)—C(4) | 1.691(3) |
| O(2)—C(6)—O(3) | 106.2(2) | O(2)—C(7)—O(3) | 105.40(16) |
| C(7)—C(5)—C(6) | 122.7(2) | C(3)—C(10)—C(7) | 120.9(2) |
| F(4)—C(2)—C(10) | 118.3(2) | F(4)—C(5)—C(11) | 118.5(2) |
| N(1)—C(4)—C(10) | 118.1(3) | N(1)—C(8)—C(11) | 119.8(2) |
| C(4)—N(1)—O(1) | 105.6(2) | C(8)—N(1)—O(1) | 106.2(2) |
| C(3)—O(1)—N(1) | 107.6(2) | C(2)—O(1)—N(1) | 107.94(19) |
| C(8)—C(3)—O(1) | 111.1(3) | C(4)—C(2)—O(1) | 110.4(2) |
| C(3)—C(8)—C(4) | 104.5(3) | C(2)—C(4)—C(8) | 104.8(2) |
| C(8)—C(3)—C(1) | 133.5(3) | C(4)—C(2)—C(1) | 133.6(3) |
| C(9)—C(7)—Cl(1) | 117.8(2) | C(6)—C(3)—Cl(1) | 118.32(17) |
| C(2)—C(10)—C(4)—C(8) | 19.46 | C(5)—C(11)—C(8)—C(4) | 49.18 |
| C(11)—C(5)—C(6)—O(2) | 63.33 | C(9)—C(10)—C(7)—O(3) | 27.12 |

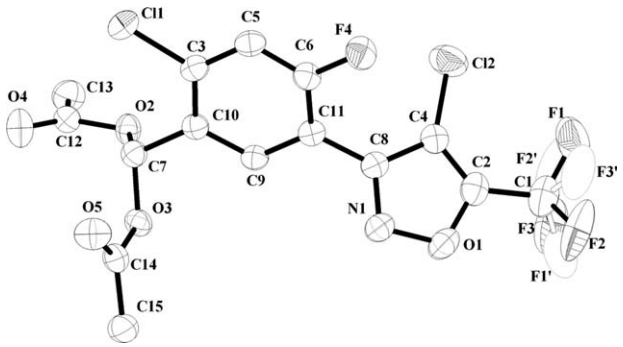



**Figure 3.** ORTEP (ellipsoids at 30% probability) diagram of compound **4b**. All hydrogen atoms are omitted for clarity.

mixture of 4-chloro-3-(4-chloro-2-fluoro-5-methyl)phenyl-5-trifluoromethylisoxazole (**3b**) (12 g, 38 mmol), acetic acid (150 mL) and concentrated sulfuric acid (98%, 15 mL), was added chromium oxide (about 10 g, 0.1 mol) in small portion, maintaining the temperature under 25. The reaction was monitored by TLC. After the reaction was completed, it was poured into water, recrystallized from alcohol, resulting in a white solid precipitate 10 g (79%).

**General procedure for the preparation of compound 7.** To a solution of 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoic acid (**6**) (1.8 g, 5.2 mmol) in toluene (10 mL), thionyl chloride (1 mL, 14 mmol) and *N*,*N*-dimethyllformamide (3 drops) were added. Then, after the mixture was refluxed for 2 h, the solvent was removed in vacuum. After the oil obtained was cooled, methanol (10 mL) was added and refluxed for 2 h. After the solution was cooled, it was poured into water, resulting in a white solid precipitate.

***Methyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoate (7a).*** This compound was obtained as a white solid, yield 89%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 60.5∼61.5°C; IR (KBr): 1711 (C=O) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, 1H, $J$ = 7.2 Hz, Ph), 7.42 (d, 1H, $J$ = 9.2 Hz, Ph), 3.95 (s, 3H, $CH_3$); MS (API-ES, positive), $m/z$: 379.8 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{12}H_5O_3NCl_2F_4$ (358.1): C, 40.25; H, 1.41; N, 3.91. Found: C, 40.01; H, 1.50; N, 4.13.

***Ethyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoate (7b).*** This compound was obtained as a white solid, yield 83%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 25.5∼26.0°C; IR (KBr): 1793 (C=O) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, 1H, $J$ = 7.2 Hz, Ph), 7.41 (d, 1H, $J$ = 9.6 Hz, Ph), 4.42 (q, 2H, $J$ = 7.2 Hz, $CH_2$), 1.41 (t, 3H, $J$ = 7.2 Hz, $CH_3$); MS (API-ES, positive), $m/z$: 393.7 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{13}H_7O_3NCl_2F_4$ (372.1): C, 41.96; H, 1.90; N, 3.76. Found: C, 42.09; H, 1.98; N, 3.84.

***Isopropyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzoate (7c).*** This compound was obtained as a white solid, yield 84%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 40.0∼40.5°C; IR (KBr): 1735 (C=O) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, 1H, $J$ = 7.6 Hz, Ph), 7.41 (d, 1H, $J$ = 9.6 Hz, Ph), 5.29 (sept, 1H, $J$ = 6.4 Hz, CH), 1.40 (d, 6H, $J$ = 6.4 Hz, $2CH_3$); MS (API-ES, positive), $m/z$: 407.7 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{14}H_9O_3NCl_2F_4$ (386.1): C, 43.55; H, 2.35; N, 3.63. Found: C, 43.28; H, 2.27; N, 3.42.

***N-phenyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzamide (7d).*** This compound was obtained as a yellow solid, yield 86%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 173.0∼175.0°C; IR (KBr): 1651 (C=O) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.0∼8.1(m, 8H, Ph+NH); MS (API-ES, positive), $m/z$: 440.8 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{17}H_8O_2N_2Cl_2F_4$ (419.2): C, 48.71; H, 1.92; N, 6.68. Found: C, 48.53; H, 2.01; N, 6.86.

***N,N-diethyl 2-chloro-4-fluoro-5-[(4-chloro-5-trifluoromethyl)isoxazole-3-yl]benzamide (7e).*** This compound was obtained as a yellow solid, yield 80%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 87.5∼88.5°C; IR (KBr): 3272 (N—H), 1640 (C=O) $cm^{-1}$; $^1H$

**Table 3**

Herbicidal activity of aimed compounds (% inhibition).

| | *Echinochloa crusgalli*/% | | *Setaria viridis*/% | | *Abutilon theophrasti*/% | | *Acalypha australis*/% | |
|---|---|---|---|---|---|---|---|---|
| Compound | 1.5 kg/hm$^2$ | 150 g/hm$^2$ | 1.5 kg/hm$^2$ | 150 g/hm$^2$ | 1.5 kg/hm$^2$ | 150 g/hm$^2$ | 1.5 kg/hm$^2$ | 150 g/hm$^2$ |
| **4a** | 95.17 | 76.22 | 94.56 | 86.21 | 87.09 | 87.09 | 61.90 | 35.90 |
| **4b** | 99.40 | 80.95 | 97.73 | 93.52 | 92.28 | 91.34 | 61.54 | 36.63 |
| **5a** | 79.41 | 74.82 | 96.89 | 49.62 | 92.04 | 87.39 | 33.70 | 19.80 |
| **5b** | 99.67 | 79.85 | 98.15 | 97.31 | 94.11 | 93.22 | 50.55 | 46.15 |
| **7a** | 98.50 | 68.21 | 98.64 | 91.91 | 89.51 | 54.15 | 98.06 | 96.98 |
| **7b** | 99.20 | 87.84 | 98.90 | 98.25 | 100.00 | 82.89 | 100.00 | 100.00 |
| **7c** | 99.04 | 68.25 | 98.03 | 95.43 | 92.42 | 45.69 | 100.00 | 90.21 |
| **7d** | 74.48 | 63.68 | 54.76 | 9.68 | 77.70 | 38.22 | 78.29 | 65.50 |
| **7e** | 99.27 | 76.70 | 98.44 | 73.25 | 77.13 | 64.69 | 100.00 | 97.54 |
| **8a** | 81.95 | 80.95 | 66.69 | 64.51 | 92.28 | 79.79 | 49.08 | 42.49 |
| **8b** | 80.85 | 80.08 | 77.38 | 68.04 | 97.58 | 91.22 | 40.66 | 26.37 |
| **8c** | 85.61 | 78.01 | 96.80 | 70.56 | 90.69 | 89.51 | 89.01 | 36.99 |
| **8d** | 91.77 | 81.51 | 92.77 | 77.04 | 95.05 | 83.97 | 64.21 | 52.01 |
| **8e** | 75.72 | 74.15 | 92.68 | 60.81 | 91.99 | 90.81 | 40.66 | 15.75 |
| **8f** | 82.31 | 80.78 | 81.16 | 49.62 | 93.75 | 82.38 | 51.28 | 17.95 |
| fomesafen | 96.39 | 56.96 | 95.85 | 48.29 | 79.06 | 71.98 | 100.00 | 64.55 |

NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, 1H, $J$ = 7.2 Hz, Ph), 7.36 (d, 1H, $J$ = 9.6 Hz, Ph), 3.3∼3.9 (bd, 2H, $CH_2$), 3.2 (br, 2H, $CH_2$), 1.28 (m, 3H, $CH_3$), 1.12 (m, 3H, $CH_3$); MS (API-ES, positive), $m/z$: 398.9 ($[M+H]^+$).

*Anal*. Calcd. for $C_{15}H_{12}O_2N_2Cl_2F_4$ (399.17): C, 45.14; H, 3.03; N, 7.02. Found: C, 45.13; H, 2.96; N, 6.91.

**General procedure for the preparation of compound 8.** To a slurry of 3-(4-chloro-2-fluoro-5-hydroxy)phenyl-5-trifluoromethylisoxazole (**3c**) (1.5 g, 5 mmol), anhydrous potassium carbonate (1.7 g, 25 mmol) in acetone (15 mL), was added dimethyl sulfate (0.75 mL, 7.5 mmol) or corresponding chlorides. The mixture reacted at room temperature or refluxed, allowed to cool and poured into water, resulting in a white solid precipitate.

***3-(4-Chloro-2-fluoro-5-methoxy)phenyl-5-trifluoromethylisoxazole (8a).*** This compound was obtained as a white solid (reacted at room temperature for 3 h), yield 89%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 80.0∼80.5°C; $^1$H NMR (400 MHz, CDCl3) δ: 7.54 (d, 1H, $J$ = 6.4 Hz, Ph), 7.28 (d, 1H, $J$ = 10.0 Hz, Ph), 7.15 (d, 1H, $J$ = 3.2 Hz, isoxazole), 3.96 (s, 3H, $OCH_3$); MS (API-ES, negative), $m/z$: 329.6 ($[M + Cl]^-$).

*Anal*. Calcd. for $C_{11}H_6O_2NClF_4$ (295.6): C, 44.69; H, 2.05; N, 4.74. Found: C, 44.61; H, 2.00; N, 4.54.

***Ethyl 2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenyl carbonate (8b).*** This compound was obtained as a white solid (refluxed for 2 h), yield 96%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 97.0∼98.0°C; IR (KBr): 1772 (C=O) $cm^{-1}$; $^1$H NMR (400 MHz, CDCl3) δ: 7.94 (d, 1H, $J$ = 7.2 Hz, Ph), 7.37 (d, 1H, $J$ = 10.0 Hz, Ph), 7.15 (d, 1H, $J$ = 2.4 Hz, isoxazole), 4.37 (q, 2H, $J$ = 7.2 Hz, $CH_2$), 1.42 (t, 1H, $J$ = 7.2 Hz, $CH_3$); MS (API-ES, positive), $m/z$: 375.8 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{13}H_8O_4NClF_4$ (353.7): C, 44.15; H, 2.28; N, 3.96. Found: C, 44.43; H, 2.31; N, 3.87.

***Methyl 2′-[2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenoxy]acetate (8c).*** This compound was obtained as a white solid (refluxed for 2 h), yield 88%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 92.0∼94.0°C; IR (KBr): 1735 (C=O) $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, 1H, $J$ = 6.0 Hz, Ph), 7.32 (d, 1H, $J$ = 10.0 Hz, Ph), 7.15 (d, 1H, $J$ = 2.4 Hz, isoxazole), 4.78 (s, 2H, $OCH_2COO$), 3.83 (s, 3H, $CH_3$); MS (API-ES, positive), m/z: 375.8 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{13}H_8O_4NClF_4$ (353.7): C, 44.15; H, 2.28; N, 3.96. Found: C, 44.39; H, 2.38; N, 4.07.

***Ethyl 2′-[2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenoxy]acetate (8d).*** This compound was obtained as a white solid (refluxed for 2 h), yield 91%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 72.5∼73.0°C; IR (KBr): 1729 (C=O) $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.51(d, 1H, $J$ = 6.0 Hz, Ph), 7.32 (d, 1H, $J$ = 10.0 Hz, Ph), 7.15 (d, 1H, $J$ = 2.4 Hz, isoxazole), 4.76 (s, 2H, $OCH_2COO$), 4.29 (q, 2H, $J$ = 7.2 Hz, Et-$CH_2$), 1.32 (t, 3H, $J$ = 7.2 Hz, Et-$CH_3$); MS (API-ES, positive), $m/z$: 368.0 ($[M+H]^+$).

*Anal*. Calcd. for $C_{14}H_{10}O_4NClF_4$ (367.7): C, 45.73; H, 2.74; N, 3.81. Found: C, 45.50; H, 2.66; N, 3.86.

***N,N-diethyl 2′-[2-chloro-4-fluoro-5-[(5-trifluoromethyl)isoxazole-3-yl]phenoxy]acetamide (8e).*** This compound was obtained as a white solid (refluxed for 2 h), yield 84%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 78.5∼80.0°C; IR (KBr): 1647 (C=O) $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, 1H, $J$ = 6.0 Hz, Ph), 7.28 (d, 1H, $J$ = 9.6 Hz, Ph), 7.12 (d, 1H, $J$ = 2.8 Hz, isoxazole), 4.82 (s, 2H $OCH_2CO$), 3.3∼3.5 (m, 4H, 2Et—$CH_2$), 1.26 (t, 3H, $J$ = 7.2 Hz, Et—$CH_3$), 1.13 (t, 3H, $J$ = 7.2 Hz, Et—$CH_3$); MS (API-ES, positive), $m/z$: 416.9 ($[M+Na]^+$).

*Anal*. Calcd. for $C_{16}H_{15}O_3N_2ClF_4$ (394.7): C, 48.68; H, 3.83; N, 7.10. Found: C, 49.04; H, 3.59; N, 7.01.

***3-[4-Chloro-2-fluoro-5-(2′-methyl)allyl]phenyl-5-trifluoromethylisoxazole (8f).*** This compound was obtained as a white solid (refluxed for 6 h), yield 88%. A sample suiting for analysis was obtained by recrystallization with alcohol; mp 82.0∼82.5°C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, 1H, $J$ = 6.4 Hz, Ph), 7.28 (d, 1H, $J$ = 10.0 Hz, Ph), 7.15 (d, 1H, $J$ = 3.6 Hz, isoxazole), 5.18 (s, 1H, =CH), 5.05 (s, 1H, =CH), 4.55(s, 2H, $OCH_2$), 1.87 (s, 3H, $CH_3$); MS (API-ES, negative), $m/z$: 333.9 ($[M-H]^-$).

*Anal*. Calcd. for $C_{14}H_{10}O_2NClF_4$ (335.7): C, 50.09; H, 3.00; N, 4.17. Found: C, 49.89; H, 2.90; N, 3.98.

**Crystal structure determination.** Saturated solution of **4a** and **4b** in EtOAc were covered with n-hexane, and stand in air at room temperature to give single crystals. The data were obtained on a Bruker SMART APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Empirical absorption corrections were performed using the SADABS program. Structures were solved by direct methods and refined by full-matrix least-squares based on all data using $F^2$ using shelx97. All of the non-hydrogen atoms were refined anisotropic ally. All of the hydrogen atoms were generated and refined in ideal positions.

**Post-emergence herbicidal activity test.** Compounds were formulated as 22 g/L emulsible concentrates, which were diluted with water to the required concentration and applied to pot-grown plants in a greenhouse.

Seeds of assayed weeds (*Echinochloa crusgalli*, *Setaria viridis, Abutilon theophrasti*, and *Acalypha australis*) were germinated in water at 30°C under dark conditions for 48 h. The germinated seeds were placed in a pot (0.1 $m^2$) as 10 seeds per-pot. While *Echinochloa crusgalli* was in the third-leaf stage, *Setaria viridis* was in the second-leaf stage, *Abutilon theophrasti* and *Acalypha australis* had two or three leaves, the diluted formulation was applied. Fifteen days after treatment, the upper-soil parts of the plants were cut off, and their weights were measured freshly (*FW*). The degree of weeds control by the test compounds was calculated with the following formulation:

$$\text{Inhibition} = \frac{CK - FW}{CK} \times 100\%$$

where *CK* is the fresh weight of untreated weed.

Each test was repeated three times.

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## REFERENCES AND NOTES

[1] Zhou, Y.; Miao, W.; Cheng, L.; Wang, D.; Bai, Z. Chin J Pestic Sci 2002, 4, 1.

[2] Hamper, B. C.; Mao, M. K.; Gary, P. W. US Patent 5,869,688 (1999); Chem Abstr 1999, 130, 168364.

[3] Menges, M.; Hamprecht, G.; Menke, O.; Reinhard, R.; Schafer, P.; Zagar, C.; Westphalen, K.-O.; Otten, M.; Walter, H. WO PCT 99/06,394 (1999); Chem Abstr 1999, 130, 168361.

[4] Huang, M.; Huang, K.; Ren, Y.; Lei, M.; Huang, L.; Hou, Z.; Liu, A.; Ou, X. J Agri Food Chem 2005, 53, 7908.

[5] Twang, I. T.; Hong, K. S.; Choi, J. S.; Kim, H. R.; Jeon, D. J.; Cho, K. Y. Pestic Biochem Phys 2004, 80, 123.

[6] Theodoridis, G.; Bahr, J. T.; Hotzman, F. W.; Sehgel, S.; Suarez, D. P. Crop Prot 2000, 19, 533.

[7] Menke, O.; Menges, M.; Hamprecht, G.; Reinhard, R.; Schafer, P.; Zagar, C.; Westphalen, K.-O.; Misslitz, U.; Walter, H. WO PCT 99/05,130 (1999); Chem Abstr 1999, 130, 139336.

[8] Zhou, Y.; Miao, W.; Cheng, L. Chin Chem Lett 2003, 14, 897.

[9] Melo, T. P. Pinho e Melo, T. M. V. D. Curr Org Chem 2005, 9, 925.

[10] Lerch, R. N.; Lin, C. H.; Leigh, N. D. J Agri Food Chem 2007, 55, 1893.

[11] Zhong, B.; Li, Z.; Song, H. Acta Crystallogr E 2005, *E61*, o2621.

[12] Dayan, F. E.; Duke, S. O.; Reddy, K. N.; Hamper, B. C.; Leschinsky, K. L. J Agri Food Chem 1997, 45, 967.

[13] Pavlik, J. W.; Lowell, J. A.; Ervithayasuporn, V. J Heterocycl Chem 2005, 42, 1253.

[14] Jin, K.; Zhou, Y.; Peng, Q.; Miao, W.; Cheng, L. Chin J Anal Chem 2003, 31, 14.

[15] Nandihalli, U. B.; Duke, S. O. In Porphyric pesticides; Duke, S. O., Rebeiz, C. A., Eds., American Chemical Society: Washington, DC, 1994, pp 133.

[16] Meazza, G.; Bettarini, F.; Porta, P. L.; Piccardi, P.; Signorini, E.; Portoso, D.; Fornara, L. Pestic Manage Sci 2004, 60, 1178.

[17] Reid, C. J Am Chem Soc 1950, 72, 2948.

# A Facile Solvent-Free Synthesis of 1-Alkyl/Aralkyl-2-(1-arylsulfonyl alkyl) Benzimidazoles Using ''TBAB'' as Surface Catalyst



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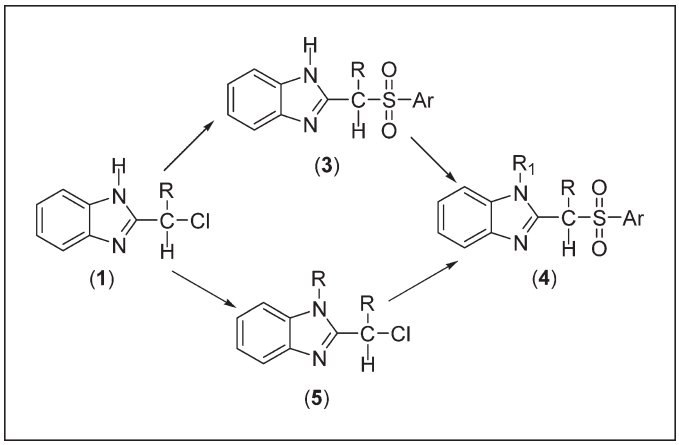


Reaction 2-(α-chloroalkyl)benzimidazoles **1** with aryl sulphinate sodium salt **2** under solvent-free conditions in the presence of tetrabutylammonium bromide as surface catalyst, by simple physical grinding using mortar and pestle, gives 1*H*-2-(α-arylsulfonylalkyl)benzimidazoles **3**. The latter on treatment with alkylating agents under solvent-free conditions results in 1-alkyl/aralkyl-2-(α-arylsulfonylalkyl)benzimidazoles **4**. Alternatively, **4** can also be prepared directly from 1-alkyl/aralkyl-2-(α-chloroalkyl)benzimidazoles **5** by reaction with **2**, which in turn could be prepared by reaction of **1** with alkylating agents under solvent-free conditions and all these reactions are free from organic solvents including experimental procedures.

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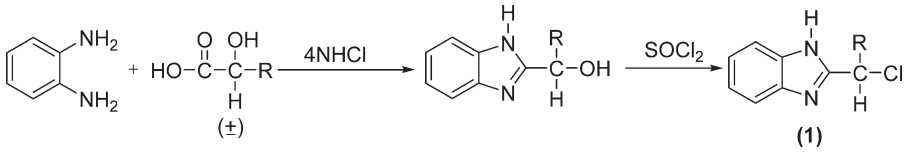
## BACKGROUND

Benzimidazoles are an important class of heterocyclic compounds, several derivatives of which have been found to be useful as intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have applications in diverse therapeutic areas including antiulcers, antihypertensive, antiviral, antifungal, anticancer, and antihistaminics to name just a few [1–3]. Sulphones exhibit noteworthy antibacterial, antimalarial, antifungal, and antitubercular properties [4–10]. In recent years, considerable attention has been paid to the reactions done under solvent-free conditions [11,12]. One of the areas of central attention in this field includes reaction between solids [13,14]. These reactions are not only of interest from an economical point of view, in many cases, but also they offer considerable synthetic advantages in terms of yield, selectivity, and simplicity of the reaction procedure. Another important goal in green chemistry is represented by the elimination of volatile organic solvents, in fact, solvent-free conditions that makes synthesis simpler, saves energy, and prevents solvent waste, hazards, and toxicity [15]. Tetrabutylammonium bromide (TBAB) is widely used as phase transfer catalyst (PTC) in many organic reactions [16–22], such as coupling reactions, Heck reaction, Suzuki-coupling of O, O-acetals to S, S-acetals and so forth. Quite a few organic reactions proceed well in solid state [23–27]. All these merits are in accord with the ''green'' requirements of energy saving and high efficiency.

## RESULTS

In continuation of our earlier work [28–31] on synthesis of new benzimidazole derivatives with potential biological activity, we now wish to report the preparation of the title compounds under solvent-free conditions, that is, without using any organic solvent, in the presence of TBAB as surface catalyst (SC) at room temperature, followed by alkylations on various types of these

**Scheme 1**




derivatives and the work up was carried out with water, without using of any organic solvent, such as ethyl acetate, $CHCl_3$, DCM, and so forth. This is totally free from organic solvent. Among alternatives, water is very benign. The use of water for organic reactions offers ''green'' chemistry benefits [32]. The results of these studies are presented in this communication.

## RESULTS AND DISCUSSION

2-(α-Chloromethyl)benzimidazole **1a** (*i.e.*, **1**, R = H) [33] (Scheme 1) on reaction with *p*-tolylsulphinate sodium salt **2a** [*i.e.*, **2**, Ar = $C_6H_4$—$CH_3$(*p*)] in solid phase by simple physical mixing/grinding in a mortar and pestle in the presence of TBAB as SC yielded a neat product on simple aqueous work up. The product has been characterized as 1*H*-2-(*p*-tolylsulfonylmethyl)benzimidazole **3a** [*i.e.*, **3**, R = H, Ar = $C_6H_4$—$CH_3$(*p*)], based on spectral and analytical data and also it was found to be identical with product reported in solution phase [34].

Previously [34], alkylations were carried out under solution phase, that is, using acetonitrile/acetone as solvent, $K_2CO_3$ as base, and TEBAC as PTC. In this work, reaction of **3a** [R = H, Ar = $C_6H_4$—$CH_3$(*p*)] with dimethylsulphate (DMS) as alkylating agent, $K_2CO_3$ as base in the presence of TBAB as SC in solid phase, that is, by simple grinding of reaction mixture in a mortar and pestle, gave the corresponding N-methylated product **4a** (Scheme 2, Table 1).

The above reaction has been found to be a general one and has been extended to other **1a** and **2a** and followed by reaction of **3a** with DMS was extended to DES and benzyl chloride to obtain N-alkyl/aralkyl-substituted derivatives of **4**, the products thus obtained were assigned structure **3**/**4** based on spectral data and analytical data (Scheme 2, Table 1), and also that were found to be identical with those reported earlier in literature [34] from solution-phase reactions. Similarly, reaction of **1a** (*i.e.*, **1**, R = H) with DMS as alkylating agent using $K_2CO_3$ as base in the presence of TBAB as catalyst in solid-phase resulted in the formation of **5a** (*i.e.*, **5**, R = H, $R^1 = CH_3$).

This reaction of **1a** with DMS was extended to DES and benzyl chloride to obtain N-alkyl/aralkyl-substituted derivatives of **5**. Alternatively, **4a** could also be obtained directly from reaction of **5a** with **2a** [*i.e.*, **2**, Ar = $C_6H_4$—$CH_3$(*p*)], under solvent-free conditions in the presence of TBAB, as a catalyst in solid phase by simple physical mixing/grinding in a mortar and pestle, yielded a neat product on simple aqueous work up. The product has been characterized as 1*H*-2-(*p*-tolylsulfonylmethyl)benzimidazole **3a**, which is identical with the product obtained from **3a** with DMS under solvent-free conditions (Scheme 3) with all respects (*i.e.*, TLC, M.P., mmp). Further, it has been extended to its other derivatives in the similar manner; the structure of the compound structure was assigned based on spectral and analytical data. (Scheme 3, Table 2).

It was found that above reactions between **1** and sodium benzenesulphinate did not occur in the absence of TBAB even after grinding the mixture of solids for 2–3 h (Scheme 4). Thus, it appears that TBAB acts like SC and that is why the addition of sodium benzenesulphinate makes the reaction much faster, because TBAB enhances the neucleophilicity of the sulphinate ion and facilitating reaction between **1** and sodium benzenesulphinate (Scheme 5). Similarly in the alkylation reactions, reaction between **1** and alkylating agent did not occur in the absence of TBAB even after grinding the mixture of solids for 2 h. But in the presence of TBAB reaction completes smoothly in short times.

As per literature search, there are number of reports for various organic transformations/methodologies under solvent-free conditions, but they were using organic solvents, such as ethyl acetate, dichloromethane, chloroform, ether, and so forth, in the work up procedure. But, in our present method, we have not used any organic solvents in the work up procedure; we have isolated the

**Scheme 2**

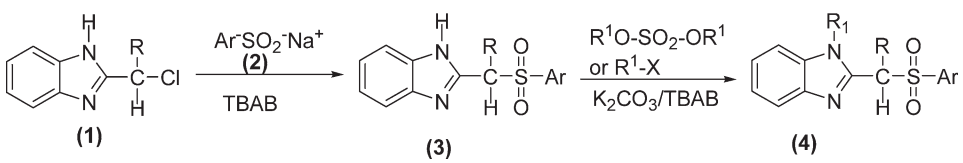


**Table 1**

Physical characterization data for **3** and **4**[a] compounds.

| SM | R | $R^1$ | Reagent (Ar)/ Alkylating agent | Product | Solution phase | | Solvent-free | | M.P. (°C) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time (h) | Yield (%) | Time (min) | Yield (%) | |
| **1a** | H | – | —$C_6H_4$—$CH_3$—*p* | **3a** | 3.5 | 79 | 4 | 90 | 202 (202) [34] |
| **1b** | H | – | —$C_6H_5$ | **3b** | 3.5 | 78 | 5 | 88 | 198–200 (198–200) [34] |
| **1c** | Me | – | —$C_6H_4$—$CH_3$—*p* | **3c** | 4 | 85 | 5 | 94 | 154–56 (154–56) [34] |
| **1d** | Me | – | —$C_6H_5$ | **3d** | 4 | 82 | 5 | 93 | 180–82 (180) [34] |
| **3a** | H | Me | DMS | **4a** | 3 | 74 | 4 | 90 | 206 (206) [34] |
| **3a** | H | Et | DES | **4b** | 3.5 | 69 | 5 | 89 | 168–70 (168) [34] |
| **3a** | H | Bn | Bn—Cl | **4c** | 3.5 | 70 | 4 | 90 | 182–84 (182) [34] |
| **3c** | Me | Me | DMS | **4d** | 3 | 73 | 5 | 89 | 172 |
| **3c** | Me | Et | DES | **4e** | 3 | 69 | 5 | 90 | 160–62 |
| **3c** | Me | Bn | Bn—Cl | **4f** | 3.5 | 71 | 5 | 92 | 170 |
| **3d** | Me | Me | DMS | **4g** | 3 | 72 | 5 | 88 | 182–84 |
| **3d** | Me | Bn | Bn—Cl | **4h** | 4 | 69 | 5 | 90 | 130–32 |

[a] Yields refers to products isolated from water without any purification.

**Scheme 3**

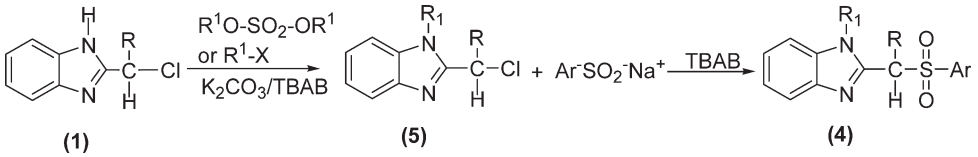


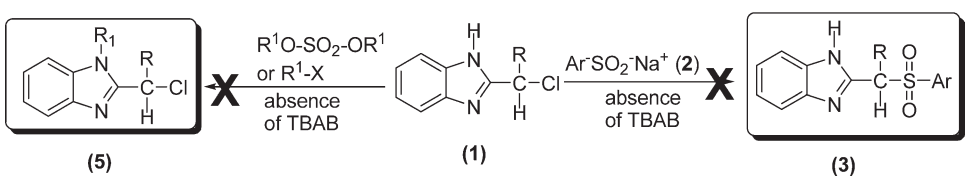

**Table 2**

Physical characterization data for **5** and **4**[a] compounds.

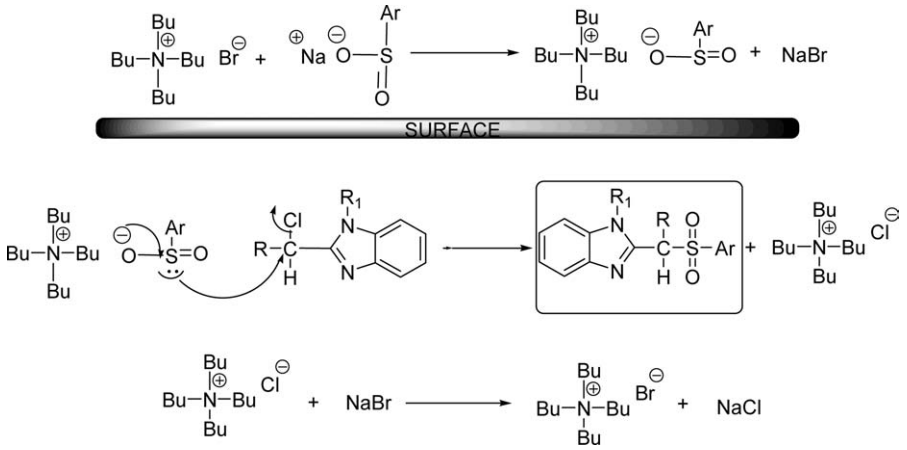
| SM | R | $R^1$ | Reagent (Ar)/Alkylating agent | Product | Solution phase | | Solvent-free | | M.P. (°C) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time (h) | Yield (%) | Time (min) | Yield (%) | |
| **1a** | H | – | DMS | **5a** | 4.0 | 62 | 8 | 92 | 94–96 (94) [34] |
| **1a** | H | – | Bn—Cl | **5b** | 4.0 | 64 | 8 | 90 | 100–02 (100) [34] |
| **1c** | Me | – | DMS | **5c** | 3.5 | 68 | 7 | 94 | 60 (60) [34] |
| **1d** | Me | – | Bn—Cl | **5d** | 3.5 | 69 | 7 | 92 | 74–76 (72–76) [34] |
| **5a** | H | Me | —$C_6H_4$—$CH_3$—*p* | **4a** | 3 | 76 | 5 | 94 | 206 |
| **5b** | H | Bn | —$C_6H_4$—$CH_3$—*p* | **4c** | 3.5 | 74 | 4 | 93 | 182–84 |
| **5c** | Me | Me | —$C_6H_4$—$CH_3$—*p* | **4d** | 3 | 76 | 5 | 96 | 172 |
| **5d** | Me | Bn | —$C_6H_4$—$CH_3$—*p* | **4f** | 3.5 | 74 | 5 | 96 | 170 |
| **5c** | Me | Me | —$C_6H_5$ | **4g** | 3 | 75 | 5 | 94 | 182–84 |
| **5d** | Me | Bn | —$C_6H_5$ | **4h** | 4 | 72 | 5 | 94 | 130–32 |

[a] Yields refers to products isolated from water without any purification.

**Scheme 4**



**Scheme 5.** The plausible mechanism: (for formation of **3**).




solid products by simple aqueous procedure using only water, which is totally free from organic solvents.

## CONCLUSIONS

In summary, we have developed a simple and efficient method for the preparation of 1-alkyl/aralkyl-2-(α-chloroalkyl)benzimidazole and 1-alkyl/aralkyl-2-(1-arylsulfonylalkyl)benzimidazoles using TBAB as SC under solvent-free conditions by simple physical grinding in mortar and pestle at room temperature. The present protocol has several advantages, completely free from organic solvents, in work up procedure water was used, which is free from organic solvent usage, fast reaction times, high yields, eco-friendly operational and experimental simplicity, readily available catalyst, and with high generality.

## EXPERIMENTAL

Melting points were determined in open glass capillaries using Buchi melting point apparatus and are uncorrected. IR spectra were recorded using potassium bromide pellets with a Perkin IR spectrometer. All $^1$H NMR spectra were recorded on a VARIAN 200-MHz instrument with an internal standard of tetramethylsilane. Mass spectra were recorded on Agilent-LC-MS instrument giving only $M^+$ values using ($M^+ + 1$) mode. Analytical TLC was performed with Silica gel GF-254 from Merck (Germany) containing fluorescent indicator. Spots were detected with UV-light or iodine. The following experimental procedures are representative of the general procedures used to synthesize all compounds.

**Typical procedure for 3.** A mixture of **1** (10 mmol), **2** (10.1 mmol), and TBAB catalytic amount (10 mol %) were ground together in a mortar with pestle at RT till the reaction was complete, as shown by TLC. The solid mixture was then suspended in water to remove inorganic impurities and the insoluble product was filtered, washed with water, and dried, gave pure product **3** (Table 1).

***3a.*** IR (KBr) cm$^{-1}$: 3000, 1308; $^1$H NMR (DMSO-$d_6$): δ 2.40 (s, 3H, —$CH_3$), 4.95 (s, 2H, —$CH_2$), 7.20–7.70 (m, 8H, Ar-H), 12.60 (bs, 1H, —NH, $D_2O$ exchangeable); $M^+ + 1$: 287; Anal. Calcd. for ($C_{15}H_{14}N_2O_2S$) requires: C, 62.92; H, 4.93; N, 9.78%; Found: C, 62.86; H, 4.87; N, 9.74%.

***3b.*** IR (KBr) cm$^{-1}$: 3000, 1300; $^1$H NMR (DMSO-$d_6$): δ 4.85 (s, 2H, —$CH_2$), 7.15–7.80 (m, 9H, Ar-H), 12.65 (bs, 1H, —NH, $D_2O$ exchangeable); $M^+ + 1$: 273; Anal. Calcd. for ($C_{14}H_{12}N_2O_2S$) requires: C, 61.75; H, 4.44; N, 10.29%; Found: C, 61.70; H, 4.40; N, 10.26%.

***3c.*** IR (KBr) cm$^{-1}$: 3000, 1298; $^1$H NMR (DMSO-$d_6$): δ 1.84 (d, $J$ = 7.16 Hz, 3H, —CH—C**H**$_3$), 2.36 (s, 3H, —$C_6H_4$—C**H**$_3$—(*p*)), 4.68 (q, $J$ = 7.14 Hz, 1H, —C**H**—$CH_3$), 7.20–7.70 (m, 8H, Ar-H), 10.30 (bs, 1H, —N**H**—, $D_2O$ exchangeable); $M^+ + 1$: 301; Anal. Calcd. for ($C_{16}H_{16}N_2O_2S$) requires: C, 63.98; H, 5.37; N, 9.33%; Found: C, 63.94; H, 5.35; N, 9.30%.

***3d.*** IR (KBr) cm$^{-1}$: 3000, 1308; $^1$H NMR (DMSO-$d_6$): δ 1.90 (d, $J$ = 7.16 Hz, 3H, —CH—C**H**$_3$), 4.70 (q, $J$ = 7.12Hz, 1H, —C**H**—$CH_3$), 7.20–7.70 (m, 9H, Ar-H), 10.30 (bs, 1H, —NH, $D_2O$ exchangeable); $M^+$+1: 287; Anal. Calcd. for ($C_{15}H_{14}N_2O_2S$) requires: C, 62.92; H, 4.93; N, 9.78%; Found: C, 62.86; H, 4.91; N, 9.74%

**Typical procedure for 4 from 3.** A mixture of **3** (10 mmol), alkylating agent (10.1 mmol), $K_2CO_3$ (11 mmol), and TBAB catalytic amount (10 mol %) were ground together in a mortar and pestle at RT till the reaction was complete, as shown by TLC. The solid mixture was then suspended in water to remove inorganic materials and water solubles. The insoluble product was filtered, washed with water, and dried, to obtain **4** (Table 1).

***4a.*** IR (KBr) cm$^{-1}$: showed the absence of a strong broad band at ~3000 cm$^{-1}$ assigned to benzimidazole, 1300; $^1$H NMR ($CDCl_3$): δ 2.45 (s, 3H, —$CH_3$), 3.95 (s, 3H, —$NCH_3$), 4.75 (s, 2H, —$CH_2$), 7.20–7.70 (m, 8H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 301; Anal. Calcd. for ($C_{16}H_{16}N_2O_2S$) requires: C, 63.98; H, 5.37; N, 9.33%; Found: C, 63.94; H, 5.32; N, 9.28%.

***4b.*** IR (KBr): showed the absence of a strong broad band at ~3000 cm$^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 1.45 (t, $J$ = 18 Hz, 3H, —$CH_2$—C**H**$_3$), 2.45 (s, 3H,

—$CH_3$), 4.45 (q, $J$ = 16 Hz, 2H, —C**H**$_2$—$CH_3$), 4.85 (s, 2H,—$CH_2$), 7.15–7.70 (m, 8H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 315; Anal. Calcd. for ($C_{17}H_{18}N_2O_2S$) requires: C, 64.94; H, 5.77; N, 8.91%; Found: C, 64.90; H, 5.72; N, 8.86%.

***4c.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 2.45 (s, 3H, —$CH_3$), 4.72 (s, 2H, —$CH_2$), 5.65 (s, 2H, —N—C**H**$_2$—Ph), 7.10–7.80 (m, 13H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 377; Anal. Calcd. for ($C_{22}H_{20}N_2O_2S$) requires: C, 70.19; H, 5.35; N, 7.44%; Found: C, 70.15; H, 5.30; N, 7.42%.

***4d.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 1.85 (d, $J$ = 7.18 Hz, 3H, —$CH_2$—C**H**$_3$), 2.40 (s, 3H, —$C_6H_4$—C**H**$_3$—(*p*)), 3.95 (s, 3H, —$NCH_3$), 4.70 (q, $J$ = 7.0 Hz, 1H, —C**H**—$CH_3$), 7.20–7.70 (m, 8H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 315; Anal. Calcd. for ($C_{17}H_{18}N_2O_2S$) requires: C, 64.94; H, 5.77; N, 8.91%; Found: C, 64.90; H, 5.75; N, 8.86%.

***4e.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 1.50 (t, $J$ = 18.0 Hz, 3H, —$CH_2$—C**H**$_3$), 1.75 (d, $J$ = 12 Hz, 3H, —CH—C**H**$_3$), 2.45 (s, 3H, —$CH_3$) 4.35 (q, $J$ = 14.6 Hz, 1H, —C**H**—$CH_3$), 4.65 (q, $J$ = 16.0 Hz, 2H, —C**H**$_2$—$CH_3$), 7.15–7.65 (m, 8H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 329; Anal. Calcd. for ($C_{18}H_{20}N_2O_2S$) requires: C, 65.83; H, 6.14; N, 8.53%; Found: C, 65.78; H, 6.10; N,8.50%.

***4f.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 1.68 (d, $J$ = 14.2 Hz, 3H, —CH—C**H**$_3$), 2.45 (s, 3H, —$CH_3$), 4.45 (q, $J$ = 14.4 Hz, 1H, —C**H**—$CH_3$), 5.55–5.90 (dd, 2H, —N—C**H**$_2$—Ph), 7.0–7.65 (m, 13H, Ar-H); $M^+$ + 1: 391; Anal. Calcd. for ($C_{23}H_{22}N_2O_2S$) requires: C, 70.74; H, 5.68; N, 7.17%; Found: C, 70.72; H, 5.64; N, 7.13%.

***4g.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 1.70 (d, $J$ = 7.18 Hz, 3H, —CH—C**H**$_3$), 3.85 (s, 3H, —$NCH_3$), 5.10 (q, $J$ = 7.0 Hz, 1H, —C**H**—$CH_3$), 7.2–7.87 (m, 9H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 301; Anal. Calcd. for ($C_{16}H_{16}N_2O_2S$) requires: C, 63.98; H, 5.37; N, 9.33%; Found: C, 63.95; H, 5.33; N, 9.29%.

***4h.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole (—NH); $^1$H NMR ($CDCl_3$): δ 1.65 (d, $J$ = 7.12 Hz, 3H, —CH—C**H**$_3$), 4.60 (q, $J$ = 7.16 Hz, 1H, —C**H**—$CH_3$), 5.50–5.70 (dd, 2H, —C**H**$_2$—Ph), 6.95–7.65 (m, 14H, Ar-H); $M^+$ + 1: 377; Anal. Calcd. for ($C_{22}H_{20}N_2O_2S$) requires: C, 70.19; H, 5.35; N, 7.44%; Found: C, 70.15; H, 5.31; N, 7.42%.

**Typical procedure for 4 from 5.** A mixture of **5** (10 mmol), **2** (10.1 mmol), and TBAB catalytic amount 10 mol % were ground together in a mortar at RT till the reaction was complete, as shown by TLC. The solid mixture was then suspended in water to remove inorganic impurities and the insoluble product was filtered, washed with water, and dried. The crude product was recrystallized from hot benzene to get the pure product **4** (Table 2).

**Typical procedure for 5.** A mixture of **1** (10 mmol), alkylating agent (10.2 mmol), $K_2CO_3$ (11 mmol), and TBAB catalytic amount 10 mol % were ground together in a mortar and pestle at RT till the completion of reaction, as shown by TLC. The solid mixture was then suspended in water to remove inorganic impurities and the insoluble product was filtered, washed with water, and dried, gave a pure **5** (Table 2).

***5a.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole; $^1$H NMR ($CDCl_3$): δ 3.95 (s, 3H, —NC**H**$_3$), 4.95 (s, 2H, —C**H**$_2$), 7.15–7.80 (m, 4H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 181; Anal. Calcd. for ($C_9H_{9Cl}N_2$) requires: C, 59.84; H, 5.02; N, 15.51%; Found: C, 59.82; H, 5.0; N, 15.47%.

***5b.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole; $^1$H NMR ($CDCl_3$): δ 4.96 (s, 2H, —$CH_2$), 5.60 (s, 2H, —C**H**$_2$—ph), 7.15–7.80 (m, 9H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 257; Anal. Calcd. for ($C_{15}H_{13}ClN_2$) requires: C, 70.18; H, 5.10; N, 10.91%; Found: C, 70.15; H, 5.07; N, 10.89%.

***5c.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole; $^1$H NMR ($CDCl_3$): δ 2.15 (d, $J$ = 7.16Hz, 3H, —CH—C**H**$_3$), 3.90 (s, 3H, —$NCH_3$), 5.30 (q, $J$ = 7.12 Hz, 1H, —C**H**—$CH_3$), 7.10–7.80 (m, 4H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 195; Anal. Calcd. for ($C_{10}H_{11}ClN_2$) requires: C, 61.70; H, 5.70; N, 14.39%; Found: C, 61.68; H, 5.66; N, 14.36%.

***5d.*** IR (KBr): showed the absence of a strong broad band at ~3000 $cm^{-1}$ assigned to benzimidazole; $^1$H NMR ($CDCl_3$): δ 2.10 (d, $J$ = 7.12Hz, 3H, —CH—C**H**$_3$), 5.10 (q, $J$ = 7.0 Hz, 1H, —C**H**—$CH_3$), 5.55 (s, 2H, —C**H**$_2$—Ph), 7.05–7.80 (m, 9H, Ar-H); $\mathbf{M}^+ + \mathbf{1}$: 271; Anal. Calcd. for ($C_{16}H_{15}ClN_2$) requires: C, 70.98; H, 5.58; N, 10.35%; Found: C, 70.94; H, 5.56; N, 10.33%.

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## REFERENCES AND NOTES

[1] (a) Erhardt, P. W. J Med Chem 1987, 30, 231; (b) Tomczuk, B. E.; Taylor, C. R., Jr.; Moses, L. M.; Sutherland, D. B.; Lo, Y. S.; Johnson, D. N.; Kinnier, W. B.; Kilpatrick, B. F. J Med Chem 1991, 34, 2993; (c) Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. Pharm Chem J 1999, 33, 232; (d) Preston, P. N. Chem Heterocycl Compd 1980, 40, 531; (e) Zimmer, C.; Wahnert, U. Prog Biophys Mol Biol 1986, 47, 31; (f) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. J Med Chem 1994, 37, 4338; (g) Soderlind, K.-J.; Gorodetsky, B.; Singh, A. K.; Bachur, N.; Miller, G. G.; Lown, J. W. Anti-cancer Drug Design 1999, 14, 19.

[2] As inhibitors of DNA topoisomerases: (a) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. J Med Chem 1996, 39, 992; (b) Chen, A. Y.; Yu, C.; Gatto, B.; Liu, L. F. Proc Natl Acad Sci USA 1993, 90, 8131; (c) Woynarowski, J. M.; McHugh, M. M.; Sigmud, R. D.; Beerman, T. A. Mol Pharmacol 1989, 35, 177.

[3] As HIV-reverse transcriptase inhibitors: Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W., Jr.; Michejda, C. J. J Med Chem 1997, 40, 4199.

[4] Bergmann, E. D.; Lavie, D. J Am Chem Soc, 1952, 74, 4948.

[5] Popoff, I. C.; Engle, A. R.; Whitaker, R. L.; Singhal, G. H. J Med Chem 1971, 14, 1166.

[6] Boundy, R. E. Burger's Medicinal Chemistry, Part II; Wolf, M. E., Ed.; John Wiley: New York, 1979.

[7] Bhingolikar, V. E.; Mahalle, S. R.; Bondge, S. P.; Mane, R. A. Indian J Chem B 2005, 44, 2589.

[8] Pandeya, S. N.; Ojha, T. J.; Srivastava, V. J Scient Ind Res 1985, 44, 150.

[9] Christopher, M. R. Contemporary Org Syn 1995, 2, 409.

[10] Simpkins, N. S. Sulfones in Organic Synthesis in Tetrahedron Organic Chemistry Series; Baldwin, J. E., Mangus, P. D., Eds.; Pergamon Press; Oxford, 1993; Vol. 10.

[11] Merzger, J. D. Angew Chem Int Ed 1998, 37, 2975.

[12] Tanaka, K.; Toda, F. Chem Rev 2000, 100, 1025.

[13] Toda, F. Acc Chem Res 1995, 28, 480.

[14] Khodaei, M. M.; Meybodi, F. A.; Rezai, F.; Salehi, P. Synth Commun 2001, 31, 2047.

[15] (a) Tanka, K. Solvent Free Organic Synthesis; Wiley-VCH: Weinhein, 2003; (b) Loupy, A. Micro Waves in Organic Synthesis; Wiley-VCH: Weinheim, 2006; (c) Varma, R. S. Advancesin Green Chemistry: Chemical Synthesis Using Microwave Irradiation; Astra Zeneca Research Foundation, Kavitha Printers: Bangalore, India, 2002; (d) Chen, Wei-Yi; Qin, Su-Dong.; Jin, J-R. Synth. Commun. 2007, 37, 47; (e) Bhattacharjya, G.; Agasti, S. S.; Ramanathan, G. Arkivoc 2006, x, 152; (f) Kurteva, V. B.; Zlatanova, V. N.; Dimitrov, V. D. Arkivoc 2006, i, 46; (g) Salehi, P.; Dabiri, M.; Khosropour, A. R.; Roozbehniya, P. J Iran Chem Soc 2006, 3, 98; (h) Chen, Wei-Yi.; Li, X. Shen.; Lu, J. Synth Commun 2008, 38, 546; (i) Massah, A. R.; Momeni, A. R.; Dabagh, M.; Aliyan, H.; Naghash, H. J. Synth Commun 2008, 38, 265; (j) Mojtahedi, M. M.; Ghasemi, M. H.; Abaee, M. S.; Bolourtchian M. Arkivoc 2005, xv, 68; (k) Bhattacharya, A. K.; Mujahid, M.; Arvind A. Natu, A. A. Synth Commun 2008, 38, 128; (l) Sharma, S. D.; Gogoi, P.; Konwar, D. Green Chem 2007, 9, 153; (m) Xia, M.; Yue-dong, L. Heteroatom Chem 2007, 18, 354; (n) Sharifi, A.; Abaee, M. S.; Mirzaei, M.; Abedi, V. Arkivoc 2006, xv, 17; (o) Reddy, P. B.; Singh, P. P.; Sawant, S. D.; Koul, S.; Taneja, S. C.; Kumar, H. M. S. Arkivoc 2006, xiii, 142.

[16] Li, J.-H.; Li, J.-L.; Xie. Y.-X. Synthesis 2007, 984.

[17] Liu, W.-J.; Xie, Y.-X.; Liang, Y.; Li, J.-H. Synthesis 2006, 860.

[18] You, E.; Li, P.; Wang. L. Synthesis 2006, 1465.

[19] Dawood, K. M.; Solodenko, W.; Kirschning, A. Arkivoc 2007, v, 104.

[20] Vincenzo, C.; Angelo, N.; Antonio, M. J. Mol Catal A Chem 2004, 214, 45.

[21] (a) Morten, L.;Klaus. K. Synthesis 2006, 4, 692; (b) Reetz, M.; de Vries, J. G. Chem Commun 2004, 1559.

[22] Carlos, B.; Avelino, C.; Hermenegildo, G.; Antonio, L. Chem Commun 2003, 606.

[23] Ranu, B. C.; Das, A.; Samanta, S. J Chem Soc Perkins Trans 2002, 1, 1520.

[24] (a) Toda, F. Syn Lett (Account) 1993, 303; (b) Toda, F. Acc Chem Res 1995, 28, 480; (c) Tanaka, K.; Toda, F. Chem Rev 2000, 100, 1025.

[25] Paul, I. C.; Curtin, D. Y. Science 1975, 197, 19.

[26] Kaupp, G.; Matthies, D. Mol Cryst Liq Cryst 1988, 61, 119.

[27] Perrin, R.; Lamartine, R.; Perrin, M.; Thozet, A. Organic Solid State Chemistry; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; p 217.

[28] Dubey, P. K.; Prasada Reddy, P. V. V.; Srinivas, K. Syn Comm 2007, 37, 1675.

[29] Dubey, P. K.; Prasada Reddy, P.V.V. Syn Comm 2007, 37, 2259.

[30] Dubey, P. K.; Naidu, A.; Ravi Kumar, C.; Prasada Reddy, P. V. V. Indian J Chem B 2003, 42, 1701.

[31] Dubey, P. K.; Prasada Reddy, P. V. V.; Srinivas, K. Lett Org Chem 2007, 4, 445.

[32] (a) Aplander, K.; Hidestal, O.; Katebzadeh K.; Lindstorm, U. M. Green Chem 2006, 8, 22; (b) Liu, R.; Dong, C.; Liang X.; Hu, X. J Org Chem 2005, 70, 729; (c) Staver, G.; Zupam, M.; Jerez M.; Staber, S. Org Lett 2004, 6, 4973; (d) Kavala, V.; Samal A. K.; Patel, B. K. Arkivoc 2005, i, 20; (e) Leadbeater, N. E. Chem Commun 2005, 2881.

[33] Bachman, G. B.; Heisey, L. V. J Am Chem Soc 1949, 71, 1985.

[34] Dubey, P. K.; Prasada Reddy, P. V. V.; Srinivas, K. Indian J Chem B 2007, 46, 488.

# An Efficient Protocol for Multicomponent Synthesis of Spirooxindoles Employing L-Proline as Catalyst at Room Temperature



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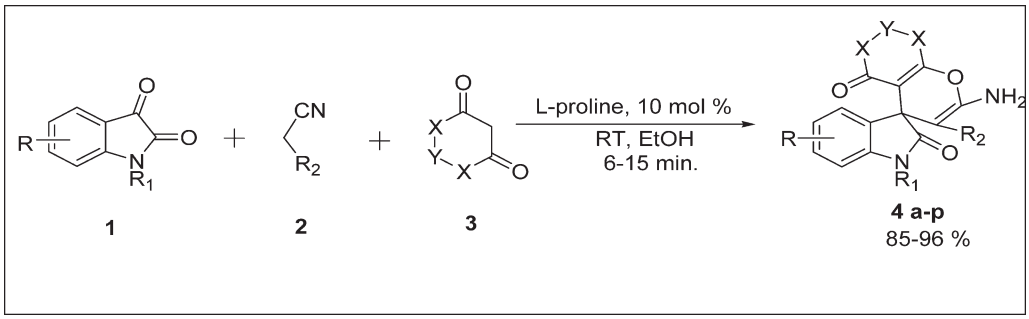


An efficient three-component one-pot synthesis of medicinally important spirooxindoles is described by the reaction of isatin, malononitrile/ethyl cyanoacetate, and dimedone/barbituric acid using L-proline as catalyst in ethanol at room temperature. This approach is convenient, mild, and affords the products in high yields without the use of chromatography.

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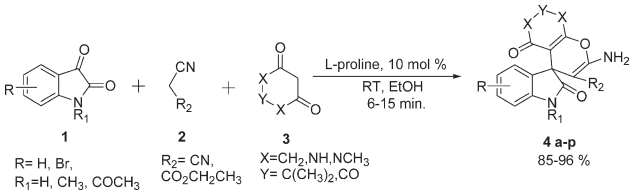
## INTRODUCTION

Indole nucleus is the most common and important feature of a variety of natural products and pharmaceuticals [1,2]. Sharing of the indole 3-carbon atom in the formation of spirooxindole system has stimulated much interest in medicinal and biological chemistry [3–9]. The unique structural array and the pharmacological activity displayed by the class of functionalized spirooxindole compounds have made them attractive synthetic targets [10]. Azaspiro derivatives are well-known [10,11], but the preparation of the corresponding oxa analogues has evolved at a relatively slow pace [12]. Among the oxygen-containing heterocycles fused with indole ring system, chromene-based structures are found to manifest diverse activities such as antidepresssant, antihypertensive, anti-tubulin, antiviral, antioxidative, *etc*., [13–23]. The current interest in 5,6,7,8-tetrahydro-4H-chromene derivatives bearing nitrile functionality, especially 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles, arises from their potential application in the treatment of human neurodegenerative disorders [24]. Owing to their medicinal utility, some reports on the multicomponent entry to chromene based spirooxindoles have appeared employing TEBA-$H_2O$ (2–6 h, 60°C) [25], electrocatalytic strategy (NaBr/ROH, 32–64 min) [26], and $InCl_3/SiO_2$ (1.5 h; MW, 3–3.5 min) [27]. Despite the availability of these methods, there remains enough scope for an efficient, high yielding, and mild approach to achieve such systems.

Multicomponent reactions (MCRs) have recently emerged as valuable tool in the preparation of structurally diverse drug-like heterocyclic compounds [28,29]. The MCR strategy offers significant advantages over conventional linear-type synthesis due to its flexible, convergent, and atom efficient nature [30]. Reactions using organocatalysts have attracted a great deal of attention in recent years to avoid the use of expensive transition metals [31]. Several amino acids have undoubtedly been the most successful catalysts in enamine- and iminium-type transformations. L-Proline has been regarded as the simplest 'enzyme' and has been elegantly used as a versatile organocatalyst in various synthetic routes for carbon—carbon and carbon—heteroatom bonds [32–34]. The rigid ring structure, easy availability, nontoxic nature, economical viability, and simple to use make this tiny molecule a remarkable organocatalyst in synthesizing molecules of biological interest.

Considering the biomedical applications of spirooxindole derivatives and in view of the limitations of the existing methods, we were prompted to exploit the catalytic potential of L-proline (10 mol %) for a facile and efficient multicomponent synthesis of functionalized spirooxindoles by the reaction of isatins, malononitrile or

**Scheme 1**




ethyl cyanoacetate, and barbituric acids or dimedone at room temperature (Scheme 1).

## RESULTS AND DISCUSSION

To optimize the reaction conditions, a typical reaction of isatin **1a**, malononitrile **2**, and dimedone **3a** was carried out in the presence of various catalysts in ethanol and water at different temperatures. The outcome is given in Table 1. The optimum concentration of the catalyst L-proline was also determined for the model reaction at 5, 10, and 15 mol % in ethanol at room temperature, affording the product **4a** in 75, 92, and 92% yields respectively. After systematic screening, the best result is obtained when the reaction is carried out with 10 mol % of L-proline in ethanol at room temperature (*cf.* entry 9). Organocatalytic activity of L-proline is mainly due to its Lewis base character, capability for inducing enamine formation, and hydrogen bonding with electronegative atoms of other functionalized groups. It is worthwhile to mention that the reaction is also catalyzed significantly by an ionic liquid [bmim]$BF_4$ in water. The use of ionic liquid alone as solvent could improve the yield of the product further (entries 14 and 15), but not comparable to the yield obtained under L-proline catalyzed conditions in ethanol (entry 9). The other catalysts viz., $ZnCl_2$, $K_2CO_3$, and KF/$Al_2O_3$ did not work well under the investigated conditions.

Under the optimized set of reaction conditions (entry 9), isatin, 5-bromoisatin, N-methylisatin, and N-acetylisatin **1** were allowed to undergo L-proline (10 mol %) catalyzed multicomponent reaction with malononitrile or ethyl cyanoacetate **2** and barbituric acid or dimedone **3** in an equimolar ratio in ethanol at room temperature. The results are given in Table 2. After the reaction was over (TLC), the resulting solid was filtered and washed from ethanol/methanol to yield pure substituted spirooxindoles **4a–4p**. All the products were crystalline and fully characterized based on their melting points, elemental analyses, and spectral data (IR, $^1$H NMR, $^{13}$C NMR).

## CONCLUSIONS

The present report describes L-proline catalyzed multicomponent synthesis of spirooxindoles in excellent yields. This protocol is efficient, simple, mild, ecofriendly, and also advantageous in terms of short reaction time and easy workup.

## EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer; whereas, NMR was run on a JEOL AL300 FT NMR spectrometer. The chemical shifts are given in δ ppm with respect to TMS as internal standard. Elemental analysis (C, H, N) for final compounds were performed on a Model

**Table 1**

Optimization of reaction conditions for the preparation of **4a**.

| Entry | Catalyst | Temperature (°C) | Time (min) | Yield[a] (%) EtOH | Yield[a] (%) $H_2O$ |
|---|---|---|---|---|---|
| 1 | Nil | RT | 120 | Trace | Nil |
| 2 | Nil | 60 | 120 | 25 | 10 |
| 3 | $ZnCl_2$ | RT | 120 | 17 | 12 |
| 4 | $ZnCl_2$ | 60 | 90 | 34 | 20 |
| 5 | $K_2CO_3$ | RT | 120 | 28 | 25 |
| 6 | $K_2CO_3$ | 60 | 90 | 56 | 52 |
| 7 | KF-$Al_2O_3$ | RT | 120 | 35 | 27 |
| 8 | KF-$Al_2O_3$ | 60 | 90 | 62 | 65 |
| 9 | L-Proline | RT | 7 | 92 | 85 |
| 10 | L-Proline | 60 | 15 | 90 | 85 |
| 11 | L-Proline | Reflux | 15 | 90 | 84 |
| 12 | [bmim]$BF_4$ | RT | 30 | 65 | 74 |
| 13 | [bmim]$BF_4$ | 60 | 20 | 68 | 79 |
| 14 | [bmim]$BF_4$ | RT | 120 | (77)[b] | |
| 15 | [bmim]$BF_4$ | 60 | 90 | (81)[b] | |

[a] Yield based on isatin.
[b] Yield obtained by the use of ionic liquid as solvent without water or ethanol.

**Table 2**

L-Proline catalyzed multicomponent synthesis of spirooxiindole derivatives **4**.

| Product | R | $R_1$ | $R_2$ | X | Y | Time (min) | Yield[a] (%) | Mp (°C) |
|---|---|---|---|---|---|---|---|---|
| **4a** | H | H | CN | $CH_2$ | $C(CH_3)_2$ | 7 | 92 | 305–306 |
| **4b** | Br | H | CN | $CH_2$ | $C(CH_3)_2$ | 6 | 87 | 304–305 |
| **4c** | H | $CH_3$ | CN | $CH_2$ | $C(CH_3)_2$ | 6 | 94 | 247–248 |
| **4d** | H | $COCH_3$ | CN | $CH_2$ | $C(CH_3)_2$ | 7 | 92 | 232–233 |
| **4e** | H | H | CN | $CH_2$ | $CH_2$ | 6 | 90 | 310–311 |
| **4f** | Br | H | CN | $CH_2$ | $CH_2$ | 6 | 86 | 273–274 |
| **4g** | H | $CH_3$ | CN | $CH_2$ | $CH_2$ | 7 | 96 | 245–246 |
| **4h** | H | $COCH_3$ | CN | $CH_2$ | $CH_2$ | 6 | 93 | 251–252 |
| **4i** | H | H | CN | NH | CO | 7 | 85 | 277–278 |
| **4j** | H | H | CN | $NCH_3$ | CO | 6 | 94 | 228–229 |
| **4k** | H | $CH_3$ | CN | $NCH_3$ | CO | 6 | 90 | 225–226 |
| **4l** | H | $COCH_3$ | CN | $NCH_3$ | CO | 7 | 91 | 228–229 |
| **4m** | H | H | $CO_2Et$ | $CH_2$ | $C(CH_3)_2$ | 12 | 87 | 228–230 |
| **4n** | Br | H | $CO_2Et$ | $CH_2$ | $C(CH_3)_2$ | 12 | 85 | 260–262 |
| **4o** | H | H | $CO_2Et$ | NH | CO | 15 | 90 | 189–190 |
| **4p** | Br | H | $CO_2Et$ | NH | CO | 15 | 86 | 264–265 |

[a] Yields based on isatins.

CE-440 CHN Analyzer. The TLC spots were detected using iodine chamber. All commercially available chemicals were purchased from Aldrich (USA) and E. Merck (Germany).

**General experimental procedure for the synthesis of spirooxindoles 4.** L-Proline (10 mol %) was added to a mixture of isatin (**1**, 1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), and dimedone or barbituric acid (1 mmol) in ethanol (2 mL), and the resulting mixture was stirred at room temperature for 6–15 min. Upon completion of the reaction (TLC), the mixture was allowed to cool to room temperature. The resulting solid was filtered and washed successively with water (2 × 20 mL) and cold ethanol (2 × 0.5 mL) to afford pure product **4** (white shiny powder).

***2-Amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4a).*** IR (KBr): 3376, 3313, 3143, 2961, 2192, 1722, 1655, 1349, 1219, 1054 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.02 (s, 3H, $CH_3$), 1.05 (s, 3H, $CH_3$), 2.10–2.19 (m, 2H, $CH_2$), 2.58 (s, 2H, $CH_2$), 6.79 (d, *J* = 7.5 Hz, 1H, Ar), 6.89 (t, *J* = 7.5 Hz, 1H, Ar), 6.97 (d, *J* = 7.5 Hz, 1H, Ar), 7.14 (t, *J* = 7.5 Hz, 1H, Ar), 7.23 (s, 2H, $NH_2$), 10.41 (s, 1H, NH) ppm; $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 27.1, 27.7, 32.0, 40.0, 46.9, 50.1, 57.5, 109.3, 110.9, 117.4, 121.8, 123.1, 128.2, 134.5, 142.1, 158.9, 164.2, 178.1, 194.9 ppm; Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.94; H, 5.17; N, 12.42.

***2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4b).*** IR (KBr): 3361, 3287, 3163, 2956, 2200, 1729, 1657, 1352, 1224, 1056 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.03 (s, 6H, $2CH_3$), 2.15 (s, 2H, $CH_2$), 2.45–2.65 (m, 2H, $CH_2$), 6.78 (d, *J* = 8.0 Hz, 1H, Ar), 7.19 (s, 1H, Ar), 7.24–7.36 (m, 3H, Ar, $NH_2$), 10.52 (s, 1H, NH) ppm; $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 27.3, 27.8, 32.2, 39.9, 47.1, 50.0, 56.8, 110.3, 111.6, 113.4, 117.3, 126.5, 131.0, 136.9, 141.5, 158.9, 165.2, 177.7, 194.9 ppm; Anal. Calcd. for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14. Found: C, 54.90; H, 3.96; N, 10.03.

***2-Amino-1′,7,7-trimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4c).*** IR (KBr): 3370, 3325, 3178, 2960, 2205, 1711, 1672, 1356, 1224, 1053 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.04 (s, 6H, 2 $CH_3$), 2.11 (s, 2H, $CH_2$), 2.56 (s, 2H, $CH_2$), 3.14 (s, 3H, $NCH_3$), 6.94–7.06 (m, 3H, Ar), 7.14–7.32 (m, 3H, Ar, $NH_2$) ppm; $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 26.5, 27.3, 27.9, 32.0, 39.9, 46.5, 50.2, 57.1, 108.2, 110.8, 116.8, 122.2, 122.9, 128.5, 134.6, 144.0, 158.9, 164.3, 176.6, 194.7 ppm; Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.67; H, 5.54; N, 11.95.

***1′-Acetyl-2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4d).*** IR (KBr): 3335, 3194, 2962, 2208, 1754, 1720, 1675, 1350, 1271, 1054 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.01 (s, 3H, $CH_3$), 1.06 (s, 3H, $CH_3$), 2.13–2.21 (m, 2H, $CH_2$), 2.57 (s, 2H, $CH_2$), 2.64 (s, 3H, $CH_3CO$), 7.17–7.26 (m, 2H, Ar), 7.29–7.38 (m, 1H, Ar), 7.55 (s, 2H, $NH_2$), 8.06 (d, *J* = 7.8 Hz, 1H, Ar) ppm; $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 6.3, 27.1, 27.8, 32.4, 39.8, 47.6, 49.5, 57.1, 110.8, 115.5, 117.3, 123.4, 126.2, 128.8, 133.0, 139.5, 158.8, 164.9, 171.0, 177.9, 195.4 ppm; Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.78; H, 5.14; N, 11.04.

***2-Amino-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro-[chromene-4,3′-indole]-3-carbonitrile (4e).*** IR (KBr): 3356, 3295, 3178, 2956, 2214, 1708, 1656, 1353, 1212, 1071 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.92–2.05 (m, 2H, $CH_2$), 2.13–2.32 (m, 2H, $CH_2$), 2.65–2.71 (m, 2H, $CH_2$), 6.76 (d, *J* = 7.5 Hz, 1H, Ar), 6.89 (t, *J* = 7.5 Hz, 1H, Ar), 7.02 (d, *J* = 7.5 Hz, 1H, Ar), 7.14 (t, *J* = 7.5 Hz, 1H, Ar), 7.24 (s, 2H, $NH_2$), 10.42 (s, 1H, NH) ppm; $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 19.10, 26.9, 36.14, 46.5, 57.3, 108.9, 112.2, 117.6, 121.5, 123.8, 128.5, 135.0, 142.3, 158.7, 166.7, 178.4, 195.2 ppm; Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67; found: C, 66.29; H, 4.33; N, 13.56.

***2-Amino-5′-bromo-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4f).*** IR (KBr): 3428, 3314, 3185, 2953, 2210, 1702, 1678, 1360, 1180, 1085 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 1.77–2.06 (m, 2H, $CH_2$), 2.12–2.37 (m, 2H, $CH_2$), 2.55–2.77 (m, 2H, $CH_2$), 6.77 (d, *J*

= 7.3 Hz, 1H, Ar), 7.16–7.63 (m, 4H, Ar, $NH_2$), 10.56 (s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 19.5, 27.0, 36.8, 47.4, 56.5, 111.5, 113.6, 117.0, 125.9, 130.8, 137.3, 141.2, 159.0, 166.9, 177.5, 195.4 ppm; Anal. Calcd. for $C_{17}H_{12}BrN_3O_3$: C, 52.87; H, 3.13; N, 10.88; found: C, 52.78; H, 3.05; N, 10.76.

***2-Amino-1′-methyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4g).*** IR (KBr): 3460, 3371, 3142, 2956, 2202, 1709, 1671, 1359, 1221 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.77–2.05 (m, 2H, $CH_2$), 2.10–2.35 (m, 2H, $CH_2$), 2.57–2.90 (m, 2H, $CH_2$), 3.15 (s, 3H, $NCH_3$), 6.86–7.11 (m, 3H, Ar), 7.18–7.37 (m, 3H, Ar, $NH_2$) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 19.6, 26.5, 26.9, 36.7, 46.4, 57.5, 108.3, 112.0, 117.6, 122.8, 124.0, 128.7, 133.4, 143.8, 158.6, 166.2, 176.7, 195.2 ppm; Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08; found: C, 67.13; H, 4.82; N, 12.95.

***1′-Acetyl-2-amino-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4h).*** IR (KBr): 3441, 3329, 3187, 2200, 1750, 1712, 1669, 1358, 1275, 1202 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.81–2.09 (m, 2H, $CH_2$), 2.14–2.42 (m, 2H, $CH_2$), 2.56 (s, 3H, $CH_3CO$), 2.60–2.86 (m, 2H, $CH_2$), 7.13–7.25 (m, 2H, Ar), 7.27–7.43 (m, 1H, Ar), 7.56 (m, 2H, $NH_2$), 8.06 (d, *J* = 7.4 Hz, 1H, Ar) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 19.8, 25.8, 26.5, 36.0, 47.9, 57.2, 111.9, 115.5, 117.1, 123.4, 125.6, 128.8, 133.1, 139.0, 158.8, 166.9, 170.6, 178.2, 195.5 ppm; Anal. Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03; found: C, 65.25; H, 4.43; N, 11.91.

***7-Amino-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4i).*** IR (KBr): 3446, 3285, 3142, 3035, 2208, 1700, 1645, 1512, 1441, 1398, 1245 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 6.76 (d, *J* = 7.9 Hz, 1H, Ar), 6.90 (t, *J* = 7.9 Hz, 1H, Ar), 7.10–7.15 (m, 2H, Ar), 7.34 (s, 2H, $NH_2$), 10.45 (s, 1H, NH), 11.04 (s, 1H, NH), 12.29 (br s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 46.8, 57.7, 86.9, 109.4, 116.8, 121.6, 124.0, 128.5, 134.1, 142.3, 149.2, 153.3, 158.5, 161.7, 177.8 ppm; Anal. Calcd. for $C_{15}H_9N_5O_4$: C, 55.73; H, 2.81; N, 21.66. Found: C, 55.60; H, 2.72; N, 21.49.

***7-Amino-1,3-dimethyl-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4j).*** IR (KBr): 3348, 3182, 3015, 2205, 1715, 1668, 1540, 1478, 1385, 1225 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 3.00 (s, 3H, $CH_3$), 3.35 (s, 3H, $CH_3$), 6.79 (d, *J* = 7.3 Hz, 1H, Ar), 6.87 (t, *J* = 7.3 Hz, 1H, Ar), 7.09–7.16 (m, 2H, Ar), 7.56 (s, 2H, $NH_2$), 10.42 (s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 27.3, 29.5, 47.8, 57.6, 87.2, 109.5, 116.7, 121.7, 123.8, 128.3, 133.4, 142.2, 149.5, 152.0, 158.0, 159.0, 177.4 ppm; Anal. Calcd. for $C_{17}H_{13}N_5O_4$: C, 58.12; H, 3.73; N, 19.93. Found: C, 57.95; H, 3.62; N, 19.81.

***7-Amino-1,1′,3-trimethyl-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4k).*** IR (KBr): 3354, 3248, 3150, 2212, 1725, 1682, 1493, 1376, 1210 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 3.02 (s, 3H, $CH_3$), 3.14 (s, 3H, $CH_3$), 3.38 (s, 3H, $CH_3$), 6.92–7.10 (m, 2H, Ar), 7.20 (d, *J* = 7.3 Hz, 1H, Ar), 7.27 (t, *J* = 7.3 Hz, 1H, Ar), 7.64 (s, 2H, $NH_2$) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 26.7, 27.5, 29.3, 47.4, 57.8, 87.6, 108.5,116.6, 122.5, 123.5, 128.9, 132.9, 143.8, 149.7, 152.2, 158.0, 159.9, 176.4 ppm; Anal. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.18; H, 4.14; N, 19.17. Found: C, 58.97; H, 4.36; N, 19.03.

***1′-Acetyl-7-amino-1,3-dimethyl-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4l).*** IR (KBr): 3385, 3310, 3208, 3186, 2218, 1725, 1695, 1660, 1500, 1387 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.61 (s, 3H, $CH_3$), 3.04 (s, 3H, $CH_3$), 3.42 (s, 3H, $CH_3$), 7.20 (t, *J* = 7.2 Hz, 1H, Ar), 7.25–7.40 (m, 2H, Ar), 7.86 (s, 2H, $NH_2$), 8.10 (d, *J* = 7.9 Hz, 1H, Ar) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 26.4, 27.6, 29.7, 48.6, 57.5, 87.2, 115.3, 116.6, 124.0, 126.0, 129.2, 132.4, 139.8, 149.5, 152.6, 158.2, 159.9, 170.8, 177.5 ppm; Anal. Calcd. for $C_{19}H_{15}N_5O_5$: C, 58.02; H, 3.84; N, 17.80. Found: C, 57.85; H, 3.92; N, 17.65.

***Ethyl 2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carboxylate (4m).*** IR (KBr): 3368, 3237, 3113, 2959, 1684, 1614, 1525, 1474, 1349 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.79 (t, *J* = 6.9 Hz, 3H, $CH_3$), 0.95 (s, 3H, $CH_3$), 1.01 (s, 3H, $CH_3$), 1.98–2.18 (m, 2H, $CH_2$), 2.45–2.61 (m, 2H, $CH_2$), 3.67–3.71 (m, 2H, $CH_2$), 6.65 (d, *J* = 7.2 Hz, 1H, Ar), 6.73 (t, *J* = 7.2 Hz, 1H, Ar), 6.81 (d, *J* = 7.2 Hz, 1H, Ar), 7.01 (t, *J* = 7.2 Hz, 1H, Ar), 7.85 (s, 2H, $NH_2$), 10.13 (s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 13.0, 26.6, 27.7, 31.5, 46.6, 50.6, 58.8, 76.3, 108.1, 113.0, 120.5, 122.1, 127.2, 135.9, 144.0, 159.0, 162.3, 167.6, 179.76, 194.5 ppm; Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.81; H, 5.72; N, 7.20.

***Ethyl 2-amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carboxylate (4n).*** IR (KBr): 3365, 3240, 3187, 2955, 1690, 1612, 1520, 1472, 1345 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.82 (t, *J* = 7.2 Hz, 3H, $CH_3$), 0.96 (s, 3H, $CH_3$), 1.0 (s, 3H, $CH_3$), 2.0–2.1 (m, 2H, $CH_2$), 2.53 (s, 2H, $CH_2$), 3.72–3.74 (m, 2H, $CH_2$), 6.62 (d, *J* = 7.8 Hz, 1H, Ar), 6.99 (s, 1H, Ar), 7.20 (d, *J* = 7.8 Hz, 1H, Ar), 7.91 (s, 2H, $NH_2$), 10.29 (s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 13.2, 26.5, 27.9, 31.5, 46.8, 50.5, 58.9, 76.5, 108.3, 113.8, 120.7, 122.1, 127.3, 136.0, 144.3, 159.2, 162.1, 167.7, 179.75, 194.7 ppm; Anal. Calcd. for $C_{21}H_{21}BrN_2O_5$: C, 54.68; H, 4.59; N, 6.07. Found: C, 54.55; H, 4.61; N, 5.92.

***Ethyl 7-amino-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carboxylate (4o).*** IR (KBr): 3425, 3318, 3162, 2201, 1692, 1650, 1578, 1468, 1390, 1342 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.77 (t, *J* = 7.2 Hz, 3H, $CH_3$), 3.69–3.72 (m, 2H, $CH_2$), 6.65 (d, *J* = 7.5 Hz, 1H, Ar), 6.77 (t, *J* = 7.5 Hz, 1H, Ar), 6.92–7.08 (m, 2H, Ar), 7.92 (s, 2H, $NH_2$), 10.21 (s, 1H, NH), 10.94 (s, 1H, NH), 12.14 (br s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 13.1, 46.2, 59.2, 76.3, 89.2, 108.3, 120.8, 122.7, 127.4, 135.3, 144.0, 149.1, 152.2, 158.6, 161.2, 167.4, 179.4 ppm; Anal. Calcd. for $C_{17}H_{14}N_4O_6$: C, 55.14; H, 3.81; N, 15.13. Found: C, 54.95; H, 3.74; N, 15.02.

***Ethyl 7-amino-5′-bromo-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carboxylate (4p).*** IR (KBr): 3420, 3315, 3160, 2201, 1692, 1655, 1579, 1463, 1395, 1348 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.79 (t, *J* = 7.5 Hz, 3H, $CH_3$), 3.70–3.73 (m, 2H, $CH_2$), 6.68 (d, *J* = 7.5 Hz, 1H, Ar), 6.94–7.11 (m, 2H, Ar), 7.93 (s, 2H, $NH_2$), 10.22 (s, 1H, NH), 10.94 (s, 1H, NH), 12.16 (br s, 1H, NH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 13.3, 46.1, 59.5, 76.4, 89.5, 108.1, 121.0, 122.9, 128.1, 135.5, 144.2,

149.3, 152.5, 158.4, 161.0, 167.2, 179.5 ppm; Anal. Calcd. for $C_{17}H_{13}BrN_4O_6$: C, 45.45; H, 2.92; N, 12.47. Found: C, 45.29; H, 2.83; N, 12.35.

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## REFERENCES AND NOTES

[1] Houlihan, W. J.; Remers, W. A.; Brown, R. K. Indoles, Part I; Wiley: New York, 1992.

[2] Sundberg, R. J. The Chemistry of Indoles; Academic Press: New York, 1970; p 56.

[3] Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273.

[4] (a) Joshi, K. C.; Chand, P. Pharmazie 1982, 37, 1; (b) Joshi, K. C.; Jain, R.; Sharma, K. J. Indian Chem Soc 1988, 115, 202.

[5] Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. Bioorg Med Chem 2004, 12, 2483.

[6] Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. Bioorg Med Chem 2006, 14, 2409.

[7] (a) Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. Farmaco 2002, 57, 715; (b) Sebahar, P. R.; Williams, R. M. J Am Chem Soc 2000, 122, 5666.

[8] (a) Ma, J.; Hecht, S. M. Chem Commun 2004, 1190; (b) Edmondson, S.; Danishefsky, S. J.; Sepp-lorenzinol, L.; Rosen, N. J Am Chem Soc 1999, 121, 2147.

[9] (a) Williams, R. M.; Cox, R. J. Acc Chem Res 2003, 36, 127; (b) Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J Braz Chem Soc 2001, 12, 273; (c) Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur J Pharmacol 2002, 444, 39; (d) Cui, C.-B.; Kakeya, H.; Osada, H. Tetrahedron 1996, 52, 12651; (e) Cui, C.-B.; Kakeya, H.; Osada, H. J Antibiot 1996, 49, 832; (f) Leclercq, J.; De Pauw-Gillet, M.-C.; Bassleer, R.; Angenot, L. J Ethnopharmacol 1986, 15, 305.

[10] (a) Fischer, C.; Meyers, C.; Carreira, E. M. Helv Chim Acta 2000, 83, 1175; (b) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. Angew Chem Int Ed 1999, 38, 3186; (c) Ashimori, A.; Bachand, B.; Overmann, L. E.; Poon, D. J. J Am Chem Soc 1998, 120, 6477; (d) Matsuura, T.; Overmann, L. E.; Poon, D. J. J Am Chem Soc 1998, 120, 6500.

[11] (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. J Am Chem Soc 2005, 127, 10130; (b) Chen, C.; Li, X.; Neumann, C. S.; Lo, M. M.-C.; Schreiber, S. L. Angew Chem Int Ed 2005, 44, 2249; (c) Bella, M.; Kobbelgaard, S.; Jorgensen, K. A. J Am Chem Soc 2005, 127, 3670.

[12] Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. J Org Chem 2006, 71, 2346.

[13] Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. Curr Med Chem 2006, 13, 199.

[14] O'Kennedy, P.; Thornes, R. D. In Coumarins: Biology, Applications and Mode of Action; O'Kennedy, R., Thornes, R. D., Eds.; Wiley: Chichester, 1997.

[15] Ellis, G. P. In The Chemistry of Heterocyclic Compounds. Chromenes, Chromanes, and Chromones; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1977; Chapter II, p 11.

[16] (a) Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K. J Med Chem 1998, 41, 787; (b) Martinez, A. G.; Marco, L. J. Bioorg Med Chem Lett 1997, 7, 3165.

[17] Kraus, G. A.; Kim, I. J Org Chem 2003, 68, 4517.

[18] Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. Mutat Res 1997, 395, 47.

[19] Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. Tetrahedron Lett 2006, 47, 3067.

[20] (a) Kitamura, R. O. S.; Romoff, P.; Young, M. C. M.; Kato, M. J.; Lago, J. H. G. Phytochemistry 2006, 67, 2398; (b) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[21] (a) Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Scaltrito, M. M.; Brenciaglia, M. I. Eur J Med Chem 2006, 41, 208; (b) Khan, K. M.; Saify, Z. S.; Khan, M. Z.; Choudhary, M. I.; Perveen, S.; Chohan, Z. H.; Supuran, C. T.; Zia-Ullah.; Atta-Ur-Rahman. J Enzyme Inhib Med Chem 2004, 19, 373; (c) Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W. Cancer Res 1975, 35, 3750.

[22] (a) Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W. F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. Bioorg Med Chem Lett 2005, 15, 1587; (b) Skommer, J.; Wlodkowic, D.; Matto, M.; Eray, M.; Pelkonen, J. Leuk Res 2006, 30, 322.

[23] Kulkarni, M. V.; Kulkarni, G. M.; Lin, C. H.; Sun, C. M. Curr Med Chem 2006, 13, 2795.

[24] Konkoy, C. S.; Fick, D. B.; Cai, S. X.; Lan, N. C.; Keana, J. F. W. PCT Int Appl, WO 0075123, 2000; Chem Abstr 2001, 134, 29313a.

[25] Zhu, S.-L.; Ji, S.-J.; Zhang, Y. Tetrahedron 2007, 63, 9365.

[26] (a) Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Demchuk, D. V.; Belyakov, P. A.; Ogibin, Y. N.; Nikishin, G. I. Electrochim Acta 2008, 53, 8346; (b) Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. Tetrahedron 2007, 63, 10543.

[27] Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. Tetrahedron 2007, 63, 2057.

[28] (a) Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005; (b) Domling, A. Chem Rev 2006, 106, 17; (c) Jimenez-Alonso, S.; Chavez, H.; Estevez-Braan, A.; Ravelo, A.; Feresin, G.; Tapia, A. Tetrahedron 2008, 64, 8938; (d) Tejedor, D.; Garcia-Tellado, F. Chem Soc Rev 2007, 36, 484; (e) Orru, R. V. A.; de Greef, M. Synthesis 2003, 10, 1471; (f) Weber, L. Drug Discov Today 2002, 7, 143; (g) Domling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3168.

[29] (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. Chem Rev 1997, 97, 449; (b) Thompson, L. A. Curr Opin Chem Biol 2000, 4, 324.

[30] (a) Weber, L. Drug Discov Today 2002, 7, 143; (b) Domling, A. Curr Opin Chem Biol 2002, 6, 306.

[31] (a) List, B. Tetrahedron 2002, 58, 5573; (b) Duthaler, R. O. Angew Chem Int Ed 2003, 42, 975; (c) Maruoka, K.; Ooi, T. Chem Rev 2003, 103, 3013; (d) France, S.; Grerin, D. J.; Miller, S. J.; Lecka, T. Chem Rev 2003, 103, 2985.

[32] (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. Acc Chem Res 2004, 37, 580; (b) Dalko, P. I.; Moisan, L. Angew Chem Int Ed 2004, 43, 5138; (c) Lacoste, E. Synlett 2006, 12, 1973.

[33] (a) Wang, Y.; Shang, Z. C.; Wu, T. X.; Fan, J. C.; Chen, X. J Mol Catal A: Chem 2006, 253, 212; (b) Srinivasan, M.; Perumal, S.; Selvaraj, S. Arkivoc 2005, xi, 201; (c) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. Adv Synth Catal 2005, 347, 1353; (d) Dodda, R.; Zhao, C. G. Synthesis 2006, 19, 3238.

[34] (a) Varala, R.; Ramu, E.; Sreelatha, N.; Adapa, S. R. Tetrahedron Lett 2006, 476, 877; (b) Varala, R.; Adapa, S. R. Org Proc Res Dev 2005, 9, 853; (c) Karade, N. N.; Budhewar, V. H.; Shinde, S. V.; Jadhav, W. N. Lett Org Chem 2007, 4, 16.

# Synthesis, Characterization, and Biological Activities of Novel (*Z*)-3-((*E*)-1-(Alkyloxyimino)ethyl)-5-arylidene-4-hydroxypyrroline-2-one Derivatives



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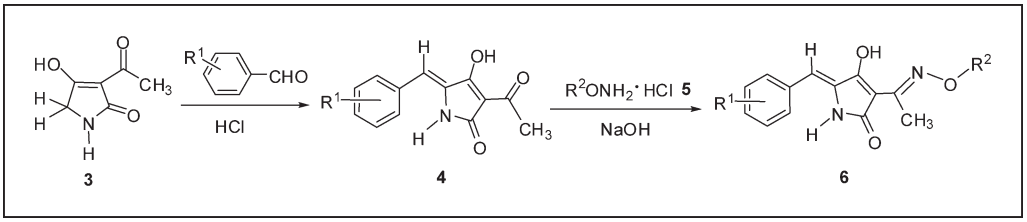


Twenty-four novel tetramic acid derivatives (*Z*)-3-((*E*)-1-(alkyloxyimino)ethyl)-5-arylidene-4-hydroxypyrroline-2-ones **6a–x** were synthesized by the reaction of (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-ones **4** with *O*-alkyl hydroxylamines **5** under reflux conditions in good yields (77.2–92.4%). Their structures were confirmed by IR, $^1$H-NMR, MS, and elemental analysis. The preliminary bioassays showed that most of the title compounds exhibited noticeable fungicidal activities against *Colletotrichum orbiculare* and a certain degree of fungicidal activities against *Fusarium gramineaum* and *Rhizoctonia cerealis* at a concentration of 100 μg/mL.

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## INTRODUCTION

Some hundreds of natural products containing the ring system pyrrolidine-2,4-dione (also known as tetramic acid) (Fig. 1) have been isolated from plants, fungi, and more recently from marine sponges [1–3]. The spectrum of biological activities displayed by these natural products is remarkable in its diversity [4–6]. An important representative of the tetramic acids is tenuazonic acid, which is a metabolite produced by some phytopathogenic fungi [7]. Since its isolation in 1957 from the culture filtrates of *Alternaria tenuis* [8], it has been found possessing antitumor, antiviral, antibacterial, and herbicidal activities [9–12]. Reutericyclin [13] is a typical 1,3-bisacyltetramic acid that is extracted from cells and culture filtrates of *Lactobacillus reuteri* and found to inhibit the growth of *Salmonella* and *Helicobacter*, the latter being the causative agent of stomach ulcers. The melophlins [14] are a class of *N*-methyl-3-acyltetramic acids recently isolated from the marine sponge *Melophlus sarassinorum*. Melophlin A and B displayed cytotoxic activity against HL60 cells at 0.2 and 0.4 μg/mL, respectively [15]. In 1971, Yuki *et al* synthesized a series of 5-subsitituted-3-(1-anilinoethylidene)pyrrolidine-2,4-dione derivatives and studied antitumor activities [16]. Zhu *et al* reported a series of 3-[(α-hydroxy-substituted)benzylidene]pyrrolidine-2,4-dione derivatives showing higher herbicidal activities [17].

Oxime ether derivatives have occupied an important position in medicinal and pesticide chemistry with a wide range of bioactivities [18]. As pesticides, they were used as insecticides, fungicides, and herbicides. Alloxydim [19], the first cyclohexanedione herbicide with an oxime ether group has been commercialized. The advantages of oxime ether derivatives, such as, high-activity against the target, low-toxicity toward the mammalians, and low-residue, have prompted chemists to design and synthesize more novel oxime ether derivatives [20].

In 1981, Tatsuaki *et al* synthesized thirteen 3-acetyl-5-subsititutedbenzylidenetetramic acids [21], the novel structures and infusive biological activities of which have aroused great interest to us. Herein, we introduced oxime ether groups into 3-acetyl-5-subsititutedbenzylidenetetramic acids to synthesize a series of novel (*Z*)-3-((*E*)-1-(alkyloxyimino)ethyl)-5-arylidene-4-hydroxy-pyrroline-2-one derivatives for the purpose of searching

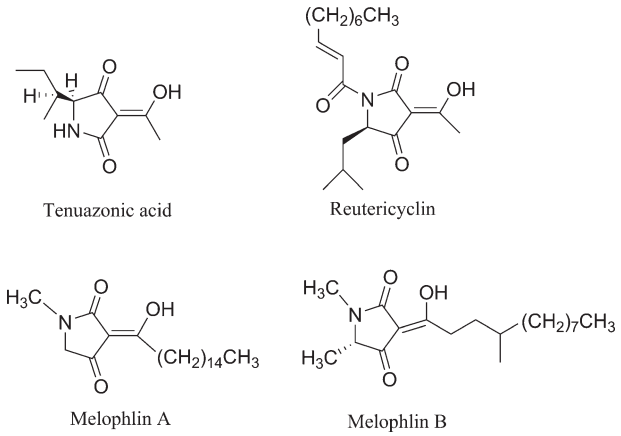



**Figure 1.** Some bioactive naturally occurring tetramic acids.

new potential pesticides with an excellent biological activities. The synthetic route is shown in Scheme 1.

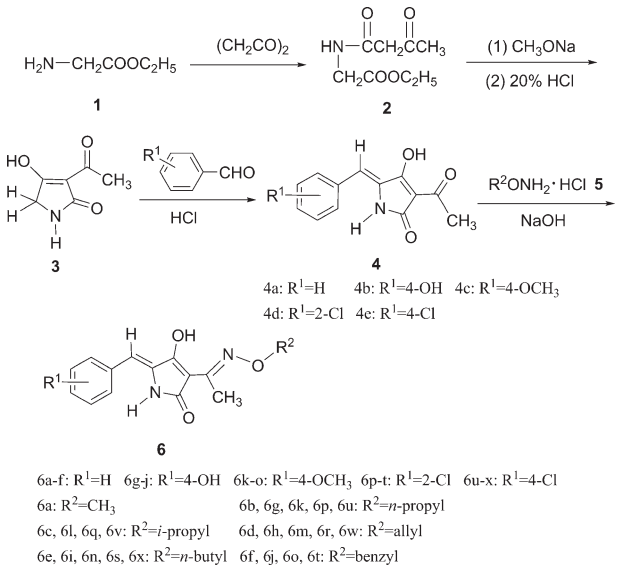
## RESULTS AND DISCUSSION

**Chemistry.** The synthesis of compounds (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-ones **4** involved the condensation of **3** (1 equivalent) with substituted benzaldehydes (2 equivalent) in the presence of dry hydrochloride [21]. The dry hydrochloride as a key catalyst was obtained by the reaction of acetyl chloride with anhydrous ethanol. In the $^1$H-NMR spectra of the compounds **4a**, **4c**, and **4e**, the protons of CH═ and NH showed the characteristic pair of signals, indicating these compounds in deuteriochloroform solution existed to a great extent as tautomers [22]. According to the literature based on a comparison of the $^1$H-NMR chemical shift data for the vinyl proton signals at the region of 6.42–6.65 ppm with those of similar tetramates, the *Z* configuration of the compounds could be assigned, and this inference was consistent with crystal structure of **6e**.

In the IR spectra of the title compounds **6**, there were medium or weak absorption bands for the enolic hydroxyl group (ν O—H) at around 3300 cm$^{-1}$ and relatively strong absorption bands for the carbonyl at around 1680 cm$^{-1}$. The characteristic absorption peak of oxime ether group existed at around 1620 cm$^{-1}$. The main characteristic of the $^1$H-NMR spectra of **6a–x** was the presence of high-frequency downfield broad singlet $\delta_H$ 7.53–9.72 presumably arising from the deshielded N—H proton linked to the carbonyl group. The singlet at $\delta_H$ 6.21–6.49 assigned to the C—H proton of CH═C and singlet at $\delta_H$ 2.32–2.57 assigned to the C—H protons of $CH_3C$═N. The signal of protons of OH group at the 4-position in NMR spectra was not been found, and this phenomena might be caused by the lability of these protons of compounds **4** and **6**, which involved in internal tautomerization in the enol form. Furthermore, the MS spectra of all the compounds **6** showed the molecular ion peak ($M^+$, 3–100%), and other fragmentation ions were consistent with their structures and could be clearly assigned.

In the crystal structure of compound **6e** (Fig. 2), the bond length C(5)—N(2) [1.295(3) Å] was close to the C═N double bond distance (1.34 Å). The bond lengths C(7)—C(9) and C(10)—C(11) were 1.354(3) Å and 1.338(3) Å, respectively, and they were close to the C═C double bond distance (1.34 Å). As a result, the benzene ring, C(10)—C(11), C(7)—C(9), C(5)—N(2), and C(8)═O(1) [1.237(2) Å] formed a large conjugated system. The bond length C(8)—N(1) [1.376(2) Å] was shorter than the normal C—N single bond (1.49 Å), suggesting the occurring of an electron density delocalization. The dihedral angle between benzene ring and pyrroline-2-one ring [N(1), O(1), O(2), C(7), C(8), C(9), C(10)] was 15.928(54)°. In addition, there was a weak π···π interaction between the parallel benzene rings (the

**Scheme 1.** General synthetic route for the target compounds **6a-x**.




4a: $R^1$=H 4b: $R^1$=4-OH 4c: $R^1$=4-$OCH_3$
4d: $R^1$=2-Cl 4e: $R^1$=4-Cl

6a-f: $R^1$=H 6g-j: $R^1$=4-OH 6k-o: $R^1$=4-$OCH_3$ 6p-t: $R^1$=2-Cl 6u-x: $R^1$=4-Cl
6a: $R^2$=$CH_3$ 6b, 6g, 6k, 6p, 6u: $R^2$=*n*-propyl
6c, 6l, 6q, 6v: $R^2$=*i*-propyl 6d, 6h, 6m, 6r, 6w: $R^2$=allyl
6e, 6i, 6n, 6s, 6x: $R^2$=*n*-butyl 6f, 6j, 6o, 6t: $R^2$=benzyl

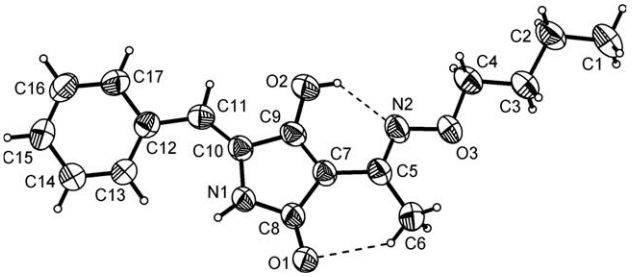



**Figure 2.** Molecular structure of compound **6e**.

**Table 1**

Antifungal activities of compounds **6a–x** (100 μg/mL, inhibitory rate percent).

| Compound | $R^1$ | $R^2$ | Inhibitory rate[a] (%) | | |
|---|---|---|---|---|---|
| | | | *F. gramineaum* | *R. cerealis* | *C. orbiculare* |
| **6a** | H | methyl | 25.0 ± 1.5 | 50.9 ± 1.6 | 74.3 ± 0.9 |
| **6b** | H | *n*-propyl | 17.9 ± 2.3 | 30.3 ± 0.9 | 30.7 ± 2.7 |
| **6c** | H | *i*-propyl | 11.7 ± 3.5 | 45.4 ± 3.1 | 28.1 ± 2.4 |
| **6d** | H | allyl | 5.1 ± 2.7 | 7.8 ± 0.9 | 33.9 ± 3.1 |
| **6e** | H | *n*-butyl | 17.9 ± 3.5 | 37.8 ± 2.6 | 44.9 ± 3.1 |
| **6f** | H | benzyl | 5.6 ± 1.0 | 29.3 ± 3.0 | 33.3 ± 1.8 |
| **6g** | 4-OH | *n*-propyl | 12.2 ± 2.3 | 14.8 ± 3.1 | 20.2 ± 4.0 |
| **6h** | 4-OH | allyl | 4.6 ± 3.2 | 15.3 ± 0.9 | 39.6 ± 3.3 |
| **6i** | 4-OH | *n*-butyl | 17.9 ± 3.2 | 29.8 ± 3.1 | 42.3 ± 3.3 |
| **6j** | 4-OH | benzyl | 13.3 ± 0.9 | 28.8 ± 2.3 | 22.3 ± 4.0 |
| **6k** | 4-$OCH_3$ | *n*-propyl | 17.8 ± 1.7 | 38.4 ± 2.1 | 53.6 ± 3.6 |
| **6l** | 4-$OCH_3$ | *i*-propyl | 19.3 ± 2.3 | 30.8 ± 1.5 | 56.3 ± 4.1 |
| **6m** | 4-$OCH_3$ | allyl | 5.8 ± 1.7 | N.A[b] | 53.6 ± 0.9 |
| **6n** | 4-$OCH_3$ | *n*-butyl | 7.8 ± 2.3 | 45.5 ± 1.8 | 57.8 ± 4.1 |
| **6o** | 4-$OCH_3$ | benzyl | 9.3 ± 0.9 | 35.9 ± 3.1 | 20.3 ± 3.6 |
| **6p** | 2-Cl | *n*-propyl | 9.8 ± 2.6 | 6.9 ± 3.1 | 73.4 ± 1.6 |
| **6q** | 2-Cl | *i*-propyl | N.A | 7.4 ± 3.2 | 54.2 ± 0.9 |
| **6r** | 2-Cl | allyl | 5.8 ± 2.3 | N.A | 23.4 ± 2.7 |
| **6s** | 2-Cl | *n*-butyl | 9.3 ± 3.1 | 13.0 ± 1.5 | 19.3 ± 3.9 |
| **6t** | 2-Cl | benzyl | 11.8 ± 2.3 | 17.0 ± 1.8 | 8.9 ± 1.8 |
| **6u** | 4-Cl | *n*-propyl | 12.3 ± 3.1 | 16.5 ± 2.3 | 24.0 ± 3.9 |
| **6v** | 4-Cl | *i*-propyl | 14.3 ± 2.4 | 16.9 ± 3.7 | 39.5 ± 2.7 |
| **6w** | 4-Cl | allyl | 9.7 ± 2.1 | 32.4 ± 1.4 | 25.0 ± 1.7 |
| **6x** | 4-Cl | *n*-butyl | 11.5 ± 1.4 | 42.3 ± 2.8 | 49.4 ± 3.0 |
| Tenuazonic acid | – | – | 10.0 ± 1.7 | 16.1 ± 3.1 | 14.5 ± 3.0 |
| Propiconazole | – | – | 98.4 ± 0.2 | 99.2 ± 0.1 | 95.1 ± 0.3 |

[a] Average of three replicates.
[b] N.A. = Not active.
Values are the mean ± S.D. of three replicates.

centroid-centroid distance was 4.36 Å) to pivotally maintain a 3D supramolecular network structure.

Furthermore, the crystal structure of compound **6e** simultaneously confirmed *E* configuration of 1-(alkyloxyimino)ethyl group and *Z* configuration of arylidene group, especially the enolic form at 4-position of the title compounds.

**Biological activity.** The results of fungicidal activities *in vitro* at a concentration of 100 μg/mL were listed in Table 1. Most of the compounds **6** exhibited notable fungicidal activities against *C. orbiculare*, thereby the inhibitory rates of the compounds **6a**, **6k**, **6l**, **6m**, **6n**, **6p**, and **6q** all exceeded 50%. Comparatively, the fungicidal activities against *R. oerealis* were moderate, but more than half of the compounds **6** were more active than tenuazonic acid. The preliminary estimation of structure-activity relationships indicated that the title compounds showed more remarkable fungicidal activities against *C. orbicular* when $R^2$ was saturated aliphatic alkyl, for example, the compound **6a** ($R^1$ was H and $R^2$ was $CH_3$) gave a best activity with $EC_{50}$ value of 1.15 μg/mL (Table 2), indicating it was significant to further modify the structure of the title compounds.

**Table 2**

$EC_{50}$ values of compounds **6a**, **6n**, and **6p** against *C. orbiculare*.

| Compound | Regression eq. | $EC_{50}$[a](μg/mL) | r[b] |
|---|---|---|---|
| **6a** | $y = 0.36423x + 4.97749$ | 1.15 | 0.99 |
| **6n** | $y = 0.92570x + 3.62689$ | 30.43 | 0.96 |
| **6p** | $y = 0.50225x + 4.19465$ | 40.13 | 0.90 |

[a] $Ec_{50}$ refer to median effect concentration.
[b] Refer to correlative coefficient.

It was worthy to clarify that the herbicidal activities of the title compounds were evaluated too. *Brassica campestris* and *Echinochloa crusgalli* (L.) *Beauv* were chosen as samples of annual dicotyledonous and monocotyledonous plants. But the herbicidal activities of all the title compounds were found to be quite weak.

## CONCLUSIONS

A series of new tetramic acid derivatives containing oxime ether group at 3-position and arylidene group at 5-position were designed and synthesized by the

reaction of (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-ones with *O*-substituted hydroxylamine hydrochlorides. The data of IR, MS, $^1$H-NMR spectra, and X-ray single-crystal structure diffraction confirmed the structures of the title compounds that contained enol structure and (3*E*, 5*Z*)-configuration. The bioassay results demonstrated that most of the title compounds, especially **6a**, possessed good activity against *C. orbiculare*. Further studies on structural modification are currently underway.

## EXPERIMENTAL

The melting points of the products were determined on a WRS-1B digital melting-point apparatus and were uncorrected. IR was recorded on a Bruker Tensor 27 FT-IR spectrometer with KBr disk. Elemental analyses were performed on Elementar Vario-III CHN analyzer. Mass spectra were recorded on a GC/MS-QP2010 spectrometer using direct-injection technique. $^1$H-NMR spectra was taken on a Mercury plus varian-300 spectrometer with TMS as the internal reference and DMSO-$d_6$ or $CDCl_3$ as the solvent. X-ray diffraction was performed with a Brucker Smart APEX II CCD diffractometer. All reagents were analytical-reagent grade or were chemically pure. The solvents were dried before use as needed.

Intermediate **3** was prepared according to the reported method [23]. The intermediates **5** *O*-allyl, *O*-methyl, and *O*-benzyl hydroxylamine hydrochlorides were synthesized starting from ethyl acetate and hydroxylamine hydrochloride via a facile three-step procedure including acetylamination, etherification, and hydrolyzation [24–26]. *O*-Propyl, *O*-isopropyl, and *O*-butyl hydroxylamine hydrochlorides were synthesized starting from hydroxylamine hydrochloride and phthalic anhydride in satisfactory yield according to the method reported by Han [27].

**General procedure for the synthesis of intermediate (*Z*)-3-acetyl-5-arylidene-4-hydroxy-pyrroline-2-ones (4).** To the solution of compound **3** (16 mmol) in ethanol (15 mL) added 8% HCl (18 mmol) in anhydrous ethanol and stirred until it dissolved, after that a substituted benzaldehyde (32 mmol) was added. The reaction mixture was refluxed for 3 h, and then cooled to give a red precipitate, which was filtered off and recrystallized from ethanol to afford the products **4a–e** in 35.2–60.8% yields.

***(Z)-3-acetyl-5-benzylidene-4-hydroxypyrroline-2-one (4a).*** Red powder, mp 224.9–225.6°C; yield, 36.9%; IR (KBr, $cm^{-1}$) ν 3210, 1697, 1678, 1627, 1455, 1280, 1228, 1084, 936; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, $COCH_3$), 6.67, 6.70 (s, s, 1H, CH=), 7.35–7.47 (m, 5H, PhH), 8.17, 8.54 (s, s, 1H, NH); Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.45; H, 4.92; N, 6.23.

***(Z)-3-acetyl-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (4b).*** Red powder, mp 262.3–263.1°C; yield, 45.2%; IR (KBr, $cm^{-1}$) ν 3373, 3174, 1682, 1606, 1575, 1449, 1357, 1228, 1087, 930; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ: 2.50 (s, 3H, $COCH_3$), 6.42 (s, 1H, CH=), 6.77 (d, 2H, PhH, $J$ = 8.4 Hz), 7.49 (d, 2H, PhH, $J$ = 8.4 Hz), 9.89 (s, 1H, NH), 10.33 (s, 1H, OH); Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 64.01; H, 4.61; N, 5.80.

***(Z)-3-acetyl-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (4c).*** Yellow powder, mp 239.3–240.1°C; yield, 60.8%; IR (KBr, $cm^{-1}$) ν 3239, 1673, 1668, 1588, 1522, 1519, 1383, 1240, 1032, 959; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, $COCH_3$), 3.87 (s, 3H, $PhOCH_3$), 6.64, 6.66 (s, s, 1H, CH=), 6.97 (d, 2H, PhH, $J$ = 6.9 Hz), 7.43 (d, 2H, PhH, $J$ = 9.3 Hz), 7.76, 8.14 (s, s, 1H, NH); Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.56; H, 5.15 N, 5.48.

***(Z)-3-acetyl-5-(2-chlorobenzylidene)-4-hydroxypyrroline-2-one (4d).*** White powder, mp 227.5–228.9°C; yield, 25.2%; IR (KBr, $cm^{-1}$) ν 3204, 1703, 1635, 1580, 1443, 1293, 1207, 1089, 938; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.57 (s, 3H, $COCH_3$), 6.89 (s, 1H, CH=), 7.32–7.48 (m, 4H, PhH), 7.97, 8.38 (s, s, 1H, NH); Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.57; H, 3.89; N, 5.42.

***(Z)-3-acetyl-5-(4-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (4e).*** White powder, mp 238.3–240.9°C; yield, 40.2%; IR (KBr, $cm^{-1}$) ν 3185, 1705, 1624, 1586, 1493, 1420, 1247, 1089, 929; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, $COCH_3$), 6.60, 6.62 (s, s, 1H, CH=), 7.35–7.41 (m, 4H, PhH), 7.84, 8.11 (s, s, 1H, NH); Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.68; H, 3.75; N, 5.23.

**General procedure for the preparation of the title compounds 6a–x.** To a solution of (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-one **4** (1.5 mmol) and *O*-substituted hydroxylamine hydrochloride **5** (1.6 mmol) in ethanol (25 mL) was added 0.2 mol/L NaOH (8 mL). Then, the reaction mixture was refluxed for 3 h. After cooling to room temperature, the mixture was poured into water (30 mL), and the precipitate was filtered. The filtrate was extracted with chloroform and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a yellow solid. Finally, the solid was collected together and recrystallized from ethanol or ethyl acetate to give title compounds **6a–x**.

***(Z)-5-benzylidene-4-hydroxy-3-((E)-1-(methoxyimino)ethyl)-pyrroline-2-one (6a).*** Yellow powder, mp 188.5–189.1°C; yield, 90.1%; IR (KBr, $cm^{-1}$) ν 3344, 3215, 3028, 2940, 1698, 1655, 1620, 1455, 1058, 903; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, $CH_3C$=N), 3.93 (s, 3H, $OCH_3$), 6.5 (s, 1H, CH=), 7.32–7.43 (m, 5H, PhH), 7.59 (s, 1H, NH); MS *m*/*z* (%): 258($M^+$, 14), 167(26), 149(84), 81(46), 69(100), 57(94); Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.62; H, 5.49; N, 10.76.

***(Z)-5-benzylidene-4-hydroxy-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6b).*** Yellow powder, mp 165.9–166.4°C; yield, 92.3%; IR (KBr, $cm^{-1}$) ν 3332, 3211, 3029, 2967, 1687, 1615, 1566, 1450, 1384, 1245, 1050, 925; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 1.71–1.83 (m, 2H, $CH_2CH_3$), 2.55 (s, 3H, $CH_3C$=N), 4.00 (t, 2H, $OCH_2$, $J$ = 6.3 Hz), 6.49 (s, 1H, CH=), 7.30–7.43 (m, 5H, PhH), 7.74 (s, 1H, NH); MS *m*/*z* (%): 286($M^+$, 92), 228(100), 212(18), 149(16), 117(70), 82(56), 45(40); Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.71; H, 6.43; N, 9.68.

***(Z)-5-benzylidene-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-pyrroline-2-one (6c).*** Yellow powder, mp 163.1–64.1°C; yield, 87.2%; IR (KBr, $cm^{-1}$) ν 3297, 3160, 3019, 2975, 1682, 1611, 1572, 1497, 1375, 1241, 1102, 909; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 1.34 (d, 6H, $CH(CH_3)_2$, $J$ = 6.3 Hz), 2.57 (s, 3H, $CH_3C$=N), 4.22–4.30 (m, 1H, OCH), 6.49 (s, 1H, CH=),

7.30–7.45 (m, 5H, PhH), 7.78 (s, 1H, NH); MS *m*/*z* (%): 286($M^+$, 100), 244(28), 225(78), 172(34), 149(32), 117(60), 82(82), 58(22); Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.48; H, 6.47; N, 9.70.

***(Z)-3-((E)-1-(allyloxyimino)ethyl)-5-benzylidene-4-hydroxypyrroline-2-one (6d).*** Red powder, mp 170.2–171.3°C; yield, 85.3%; IR (KBr, $cm^{-1}$) ν 3328, 3218, 3030, 2936, 1681, 1621, 1564, 1452, 1269, 1088, 1005, 936; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.52 (s, 3H, $CH_3C{=}N$), 4.54 (d, 2H, $OCH_2$, $J$ = 6.3 Hz), 5.40–5.48 (m, 2H, $CH{=}CH_2$), 5.95–6.08 (m, 1H, $CH{=}CH_2$), 6.49 (s, 1H, CH=C), 7.31–7.42 (m, 5H, PhH), 7.56 (s, 1H, NH); MS *m*/*z* (%): 284($M^+$, 24), 267(10), 213(18), 167(28), 149(100), 81(66), 69(68), 57(36); Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.14; H, 5.72; N, 9.80.

***(Z)-5-benzylidene-3-((E)-1-(butoxyimino)ethyl)-4-hydroxypyrroline-2-one (6e).*** Yellow crystal, mp 158.9–159.5°C; yield, 82.3%; IR (KBr, $cm^{-1}$) ν 3328, 3215, 3028, 2957, 2874, 1679, 1655, 1624, 1451, 1367, 1092, 1048, 973; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 0.97 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 1.41–1.54 (m, 2H, $CH_2CH_3$), 1.69–1.78 (m, 2H, $OCH_2CH_2$), 2.56 (s, 3H, $CH_3C{=}N$), 4.05 (t, 2H, $OCH_2$, $J$ = 6.3 Hz), 6.50 (s, 1H, CH=), 7.33–7.48 (m, 5H, PhH), 7.98 (s, 1H, NH); MS *m*/*z* (%): 300($M^+$, 82), 228(100), 210(22), 172(20), 117(64), 90(48), 82(42), 45(46); Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.25; H, 6.60; N, 9.43.

***(Z)-5-benzylidene-3-((E)-1-(benzyloxyimino)ethyl)-4-hydroxypyrroline-2-one (6f).*** Yellow powder, mp 201.7–202.5°C; yield, 90.5%; IR (KBr, $cm^{-1}$) ν 3349, 3207, 3008, 2932, 1698, 1657, 1622, 1455, 1367, 1096, 995; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.45 (s, 3H, $CH_3C{=}N$), 5.07 (s, 2H, $OCH_2$), 6.50 (s, 1H, CH=), 7.30–7.42 (m, 10H, 2PhH), 7.50 (s, 1H, NH); MS *m*/*z* (%): 334($M^+$, 18), 228(74), 210(14), 117(20), 115(26), 91(100), 77(22), 45(34); Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.19; H, 5.49; N, 8.30.

***(Z)-3-((E)-1-(propoxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-one (6g).*** Yellow powder, mp 225.2–226.5°C; yield, 80.0%; IR (KBr, $cm^{-1}$) ν 3378, 3346, 3156, 2967, 1661, 1601, 1580, 1513, 1233, 1148, 1067, 935; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ: 0.90 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 1.57–1.69 (m, 2H, $CH_2CH_3$), 2.35 (s, 3H, $CH_3C{=}N$), 4.00 (t, 2H, $OCH_2$, $J$ = 6.3 Hz), 6.21 (s, 1H, CH=), 6.73 (d, 2H, PhH, $J$ = 8.4 Hz), 7.43 (d, 2H, PhH, $J$ = 8.1 Hz), 9.71 (s, 1H, NH), 9.78 (s, 1H, OH); MS *m*/*z* (%): 302($M^+$, 4), 244(100), 227(22), 133(22), 84(38), 55(20); Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.37; H, 6.08; N, 9.20.

***(Z)-3-((E)-1-(allyloxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (6h).*** Red powder, mp 231.2–232.4°C; yield, 83.3%; IR (KBr, $cm^{-1}$) ν 3363, 3348, 3159, 2982, 1662, 1598, 1513, 1274, 1234, 1152, 1065, 958; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ: 2.33 (s, 3H, $CH_3C{=}N$), 4.60 (d, 2H, $OCH_2$, $J$ = 5.7 Hz), 5.28–5.40 (m, 2H, $CH{=}CH_2$), 5.93–6.07 (m, 1H, $CH{=}CH_2$), 6.24 (s, 1H, CH=C), 6.74 (d, 2H, PhH, $J$ = 8.4 Hz), 7.44 (d, 2H, PhH, $J$ = 8.1 Hz), 9.72 (s, 1H, NH), 9.81 (s, 1H, OH); MS *m*/*z* (%): 300($M^+$, 4), 271(14), 244(100), 226(22), 137(24), 84(52), 57(88); Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.55; H, 5.29; N, 9.40.

***(Z)-3-((E)-1-(butoxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (6i).*** Yellow powder, mp 210.2–211.2°C; yield, 85.5%; IR (KBr, $cm^{-1}$) ν 3386, 3351, 3189, 3026, 2959, 1695, 1665, 1587, 1457, 1255, 1098, 913; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ: 0.88 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 1.31–1.44 (m, 2H, $CH_2CH_3$), 1.55–1.65 (m, 2H, $OCH_2CH_2$), 2.35 (s, 3H, $CH_3C{=}N$), 4.04 (t, 2H, $OCH_2$, $J$ = 6.3 Hz), 6.21 (s, 1H, CH=), 6.73 (d, 2H, PhH, $J$ = 8.4 Hz), 7.43 (d, 2H, PhH, $J$ = 7.8 Hz), 9.71 (s, 1H, NH), 9.78 (s, 1H, OH); MS *m*/*z* (%): 316($M^+$, 3), 244(100), 227(22), 155(19), 137(25), 84(34), 55(15); Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.16; H, 6.45; N, 8.80.

***(Z)-3-((E)-1-(benzyloxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (6j).*** Yellow crystal, mp 240.3–241.9°C; yield, 78.8%; IR (KBr, $cm^{-1}$) ν 3359, 3349, 3169, 3018, 2796, 1658, 1601, 1579, 1561, 1272, 1056, 956; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ: 2.32 (s, 3H, $CH_3C{=}N$), 5.13 (s, 2H, $OCH_2$), 6.21 (s, 1H, CH=), 6.73 (d, 2H, PhH, $J$ = 8.7 Hz), 7.33–7.45 (m, 7H, PhH), 9.71 (s, 1H, NH), 9.80 (s, 1H, OH); MS *m*/*z* (%): 350($M^+$, 5), 244(100), 227(24), 133(17), 105(13), 84(33), 55(15); Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.92; H, 5.25; N, 8.08.

***(Z)-4-hydroxy-5-(4-methoxybenzylidene)-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6k).*** Yellow powder, mp 174.0–175.7°C; yield, 86.8%; IR (KBr, $cm^{-1}$) ν 3321, 3216, 2964, 2874, 1680, 1602, 1514, 1249, 1117, 1054, 1037, 928; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, 3H, $CH_2CH_3$, $J$ = 7.5 Hz), 1.71–1.80 (m, 2H, $CH_2CH_3$), 2.53 (s, 3H, $CH_3C{=}N$), 3.84 (s, 3H, $PhOCH_3$), 4.00 (t, 2H, $OCH_2$, $J$ = 7.2 Hz), 6.46 (s, 1H, CH=), 6.93 (d, 2H, PhH, $J$ = 8.7 Hz), 7.36 (d, 2H, PhH, $J$ = 8.7 Hz), 7.53 (s, 1H, NH). MS *m*/*z* (%): 316($M^+$, 6), 258(100), 202(22), 179(19), 137(25), 83(34), 45(15); Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.89; H, 6.45; N, 8.94.

***(Z)-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-5-(4-methoxybenzylidene)-pyrroline-2-one (6l).*** Yellow powder, mp 206.8–208.0°C; yield, 91.0%; IR (KBr, $cm^{-1}$) ν 3320, 3207, 2979, 2835, 1687, 1602, 1517, 1253, 1187, 1115, 1036, 980; $^1$H-NMR ($CDCl_3$, 300 MHz) δ:1.34 (d, 6H, $CH(CH_3)_2$, $J$ = 6.0 Hz), 2.55 (s, 3H, $CH_3C{=}N$), 3.84 (s, 3H, $PhOCH_3$), 4.24–4.28 (m, 1H, OCH), 6.47 (s, 1H, CH=), 6.93 (d, 2H, PhH, $J$ = 8.7 Hz), 7.36 (d, 2H, PhH, $J$ = 8.1 Hz), 7.56 (s, 1H, NH). MS *m*/*z* (%): 316($M^+$, 5), 279(16), 202(36), 167(35), 149(100), 69(53), 57(56), 45(66); Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.82; H, 6.31; N, 8.77.

***(Z)-3-((E)-1-(allyloxyimino)ethyl)-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (6m).*** Yellow powder, mp 168.7–169.7°C; yield, 90.0%; IR (KBr, $cm^{-1}$) ν 3323, 3202, 2981, 2835, 1677, 1602, 1568, 1514, 1255, 1183, 1037, 931; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, $CH_3C{=}N$), 3.85 (s, 3H, $PhOCH_3$), 4.55 (d, 2H, $OCH_2$, $J$ = 6.0 Hz), 5.40–5.47 (m, 2H, $CH{=}CH_2$), 5.95–6.06 (m, 1H, $CH{=}CH_2$), 6.51 (s, 1H, CH=C), 6.94 (d, 2H, PhH, $J$ = 9.0 Hz), 7.36 (d, 2H, PhH, $J$ = 8.7 Hz), 7.69 (s, 1H, NH). MS *m*/*z* (%): 314($M^+$, 7), 258(100), 241(19), 148(20), 132(24), 83(18), 45(21); Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.51; H, 5.72; N, 8.98.

***(Z)-3-((E)-1-(butoxyimino)ethyl)-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (6n).*** Yellow powder, mp 166.3–167.0°C; yield, 87.6%; IR (KBr, $cm^{-1}$) ν 3319, 3186, 2956, 1685, 1604, 1514, 1253, 1176, 1067, 956; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 0.95 (t, 3H, $CH_2CH_3$, $J$ = 7.5 Hz), 1.39–1.52 (m, 2H, $CH_2CH_3$), 1.67–1.76 (m, 2H, $OCH_2CH_2$), 2.52 (s, 3H, $CH_3C{=}N$), 3.84 (s, 3H, $PhOCH_3$), 4.04 (t, 2H, $OCH_2$, $J$ =

6.6 Hz), 6.45 (s, 1H, CH=), 6.92 (d, 2H, PhH, $J$ = 8.4 Hz), 7.37 (d, 2H, PhH, $J$ = 8.7 Hz), 7.66 (s, 1H, NH). MS $m/z$ (%): 330($M^+$, 5), 258(100), 202(25), 147(24), 132(37), 83(24), 45(19); Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.94; H, 6.76; N, 8.40.

***(Z)-3-((E)-1-(benzyloxyimino)ethyl)-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (6o).*** Yellow powder, mp 205.8–206.7°C; yield, 77.2%; IR (KBr, $cm^{-1}$) ν 3322, 3212, 2924, 2837, 1692, 1618, 1601, 1513, 1252, 1180, 1036, 990; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.43 (s, 3H, $CH_3C$=N), 3.84 (s, 3H, $PhOCH_3$), 5.08 (s, 2H, $OCH_2$), 6.40 (s, 1H, CH=), 6.92 (d, 2H, PhH, $J$ = 9.0 Hz), 7.34–7.40 (m, 7H, PhH), 7.56 (s, 1H, NH); MS $m/z$ (%): 364($M^+$, 4), 258(100), 243(22), 147(13), 132(14), 83(23), 45(18); Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.58; H, 5.42; N, 7.60.

***(Z)-5-(2-chlorobenzylidene)-4-hydroxy-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6p).*** Yellow powder, mp 164.7–165.9°C; yield, 82.3%; IR (KBr, $cm^{-1}$) ν 3336, 3222, 2965, 2874, 1695, 1654, 1620, 1442, 1369, 1244, 1091, 989; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 1.74–1.81 (m, 2H, $CH_2CH_3$), 2.55 (s, 3H, $CH_3C$=N), 4.00 (t, 2H $OCH_2$, $J$ = 6.6 Hz,), 6.72 (s, 1H, CH=), 7.23–7.47 (m, 4H, PhH), 7.60 (s, 1H, NH); MS $m/z$ (%): 320($M^+$, 3), 285(31), 227(100), 210(73), 115(17), 83(16), 55(19); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 61.23; H, 5.39; N, 8.83.

***(Z)-5-(2-chlorobenzylidene)-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-pyrroline-2-one (6q).*** Yellow powder, mp 187.7–189.2°C; yield, 85.7%; IR (KBr, $cm^{-1}$) ν 3340, 3224, 2977, 2944, 1683, 1618, 1442, 1396, 1246, 1087, 1041, 985; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 1.35 (d, 6H, $CH(CH_3)_2$, $J$ = 6.0 Hz), 2.56 (s, 3H, $CH_3C$=N), 4.22–4.31 (m, 1H, OCH), 6.72 (s, 1H, CH=), 7.22–7.46 (m, 4H, PhH), 7.56 (s, 1H, NH); MS $m/z$ (%): 320($M^+$, 5), 285(100), 243(32), 227(43), 198(34), 89(46), 45(20); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 61.35; H, 5.45; N, 8.78.

***(Z)-3-((E)-1-(allyloxyimino)ethyl)-5-(2-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6r).*** Yellow powder, mp 194.1–196.5°C; yield, 86.0%; IR (KBr, $cm^{-1}$) ν 3331, 3195, 3027, 2911, 1705, 1660, 1623, 1440, 1347, 1249, 1097, 1044, 993; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, $CH_3C$=N), 4.54 (d, 2H, $OCH_2$, $J$ = 6.9 Hz), 5.41–5.48 (m, 2H, $CH=CH_2$), 5.95–6.08 (m, 1H, $CH=CH_2$), 6.71 (s, 1H, CH=C), 7.22–7.48 (m, 4H, PhH), 7.76 (s, 1H, NH); MS $m/z$ (%): 318($M^+$, 7), 283(27), 227(100), 210(68), 115(10), 89(15), 45(19); Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.01; H, 4.82; N, 8.64.

***(Z)-3-((E)-1-(butoxyimino)ethyl)-5-(2-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6s).*** Yellow powder, mp 165.7–166.9°C; yield, 88.7%; IR (KBr, $cm^{-1}$) ν 3285, 3200, 2958, 2872, 1685, 1652, 1624, 1441, 1369, 1246, 1049, 976; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 0.96 (t, 3H, $CH_2CH_3$, $J$ = 7.2 Hz), 1.40–1.52 (m, 2H, $CH_2CH_3$), 1.67–1.77 (m, 2H, $OCH_2CH_2$), 2.50 (s, 3H, $CH_3C$=N), 4.05 (t, 2H, $OCH_2$, $J$ = 7.5 Hz), 6.69 (s, 1H, CH=), 7.21–7.50 (m, 4H, PhH), 7.57 (s, 1H, NH); MS $m/z$ (%): 334($M^+$, 5), 299(25), 227(100), 210(88), 114(13), 89(17), 45(22); Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 61.30; H, 5.81; N, 8.42.

***(Z)-3-((E)-1-(benzyloxyimino)ethyl)-5-(2-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6t).*** Yellow crystal, mp 205.0–205.5°C; yield, 91.3%; IR (KBr, $cm^{-1}$) ν 3331, 3236, 3029, 2930, 1698, 1620, 1565, 1442, 1369, 1095, 1041, 995; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.42 (s, 3H, $CH_3C$=N), 5.08 (s, 2H, $OCH_2$), 6.67 (s, 1H, CH=), 7.21–7.50 (m, 9H, PhH), 7.56 (s, 1H, NH); MS $m/z$ (%): 368($M^+$, 2), 308(14), 153(100), 127(65), 98(74), 63(25), 50(11); Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.54; H, 4.72; N, 7.52.

***(Z)-5-(4-chlorobenzylidene)-4-hydroxy-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6u).*** Yellow powder, mp 222.2–223.8°C; yield, 89.5%; IR (KBr, $cm^{-1}$) ν 3336, 3208, 3024, 2968, 1685, 1656, 1617, 1433, 1385, 1275, 1093, 1010, 968; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (t, 3H, $CH_2CH_3$, $J$ = 7.8 Hz), 1.74–1.81 (m, 2H, $CH_2CH_3$), 2.56 (s, 3H, $CH_3C$=N), 4.00 (t, 2H, $OCH_2$, $J$ = 6.6 Hz), 6.44 (s, 1H, CH=), 7.32–7.40 (m, 4H, PhH), 7.47 (s, 1H, NH); MS $m/z$ (%): 320($M^+$, 4), 262(100), 206(19), 152(30), 116(15), 89(32), 58(23), 45(26); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 60.14; H, 5.42; N, 8.66.

***(Z)-5-(4-chlorobenzylidene)-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-pyrroline-2-one (6v).*** Yellow powder, mp 231.3–233.6°C; yield, 81.2%; IR (KBr, $cm^{-1}$) ν 3331, 3194, 3030, 2978, 1674, 1655, 1618, 1430, 1368, 1154, 1090, 985; $^1$H-NMR ($CDCl_3$, 300 MHz) δ:1.34 (d, 6H, $CH(CH_3)_2$, $J$ = 6.3 Hz), 2.57 (s, 3H, $CH_3C$=N), 4.21–4.30 (m, 1H, OCH), 6.42 (s, 1H, CH=), 7.34–7.41 (m, 4H, PhH), 8.16 (s, 1H, NH); MS $m/z$ (%): 320($M^+$, 10), 262(100), 206(48), 151(42), 129(32), 89(48), 58(63), 45(60); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 59.47; H, 5.27; N, 8.61.

***(Z)-3-((E)-1-(allyloxyimino)ethyl)-5-(4-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6w).*** Yellow powder, mp 209.2–209.9°C; yield, 80.2%; IR (KBr, $cm^{-1}$) ν 3327, 3205, 3028, 2919, 1694, 1655, 1619, 1430, 1365, 1266, 1092, 1010, 993; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, $CH_3C$=N), 4.54 (d, 2H, $OCH_2$, $J$ = 6.9 Hz), 5.41–5.47 (m, 2H, $CH=CH_2$), 5.95–6.08 (m, 1H, $CH=CH_2$), 6.41 (s, 1H, CH=C), 7.34–7.41 (m, 4H, PhH), 8.05 (s, 1H, NH); MS $m/z$ (%): 318($M^+$, 3), 262(100), 210(10), 152(25), 116(15), 83(32), 55(19), 45(31); Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.02; H, 4.70; N, 8.87.

***(Z)-3-((E)-1-(butoxyimino)ethyl)-5-(4-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6x).*** Yellow crystal, mp 203.3–207.2°C; yield, 92.4%; IR (KBr, $cm^{-1}$) ν 3294, 3201, 3019, 2957, 1708, 1679, 1617, 1431, 1367, 1276, 1092, 1010, 974; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 0.96 (t, 3H, $CH_2CH_3$, $J$ = 7.5 Hz), 1.40–1.52 (m, 2H, $CH_2CH_3$), 1.68–1.77 (m, 2H, $OCH_2CH_2$), 2.55 (s, 3H, $CH_3C$=N), 4.04 (t, 2H, $OCH_2$, $J$ = 6.9 Hz), 6.44 (s, 1H, CH=), 7.33–7.40 (m, 4H, PhH), 7.70 (s, 1H, NH); MS $m/z$ (%): 334($M^+$, 6), 262(100), 206(42), 152(45), 113(28), 84(59), 57(46), 45(88); Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 60.55; H, 5.79; N, 8.52.

**Crystal structure determination.** The single crystal of **6e** was selected and glued on the tip of a glass fiber. Both cell dimensions and intensities were measured on a Bruker Smart APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. $\theta_{max}$ = 25.99; 6205 measured reflections; 3113 independent reflections ($R_{int}$ = 0.0385) of which 2421 had $I > 2\delta$ ($I$). Data was corrected for Lorentz and polarization effects and absorption ($T_{min}$ = 0.9781, $T_{max}$ = 0.9831). Crystal structure was solved by direct methods using the SHELXS-97 program [28]. All nonhydrogen

atoms were refined anisotropically. The C—H hydrogen atoms were positioned geometrically and refined using a riding model. The hydrogen atoms linked to nitrogen and oxygen were located from the difference Fourier map and were set as isotropic. Full-matrix least squares refinement based on $F^2$ using the weight of $1/[\sigma^2(F_o^2) + (0.1206P)^2 + 0.0717P]$ gave final values of $R = 0.0575$, $\omega R = 0.1770$, and GOF($F$) = 1.044. The maximum and minimum difference peaks and holes were 0.352 and –0.381 e $Å^{-3}$, respectively.

The crystallographic data have been deposited with Cambridge crystallographic data center, CCDC No. 734371. Copies of this information can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; or E-mail: deposit@ccdc.cam.ac.uk).

**Fungicidal assay.** Inhibition effects of the title compounds **6a–x** on phytopathogenic fungi (*Fusarium gramineaum*, *Colletotrichum orbiculare*, and *Rhizoctonia cerealis*) were tested using a radial growth inhibition technique according to literature [29]. Each compound was diluted with 0.5 mL DMF and added to potato sucrose agar medium (PSA), respectively to obtain a concentration of 100 μg/mL immediately before pouring into the petri dishes. Each concentration was tested in triplicate. Parallel controls were maintained with 0.5 mL DMF mixed with PSA medium. The discs of mycelial felt (0.5 cm diameter) of fungi were transferred aseptically to the center of Petri dishes. The treatments were incubated at 25°C in the dark. The diameter of the mycelium was measured after the fungal growth in the control treatments had covered two-thirds of the Petri dishes. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, $I$ was the growth inhibition rate (%), $C$ was the control settlement radius (mm), and $T$ was the treatment group fungi settlement radius (mm).

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## REFERENCES AND NOTES

[1] Royles, B. J. L. Chem Rev 1995, 95, 1981.

[2] Meronuck, R. A.; Steele, J. A.; Mirocha, C. J.; Christensen, C. M. Appl Microbiol 1972, 23, 613.

[3] Satan, U.; Wada, S. I.; Matsunagas, S.; Watabe, S.; Vansoest, R. W. M.; Fusetanin, N. J Org Chem 1999, 64, 2331.

[4] Hopmann, C.; Kurz, M.; Bronstrup, M.; Wink, J.; LeBeller, D. Tetrahedron Lett 2002, 43, 435.

[5] Aoki, S.; Higuchi, K.; Ye, Y.; Satari, R.; Kobayashi, M. Tetrahedron 2000, 56, 1833.

[6] Ohta, E.; Ohta, S.; Ikegami, S. Tetrahedron 2001, 57, 4699.

[7] Motta, S. D.; Soares, L. M. V. Food Chem 2000, 71, 111.

[8] Rosett, B. T.; Sankhala, R. H.; Stickings, C. E.; Taylor, M. E. U.; Thomas, R. Biochem J 1957, 67, 390.

[9] Yuki, H.; Kariya, K.; Hashimoto, Y. Chem Pharm Bull 1967, 15, 727.

[10] Gallardo, G. L.; Pen, N. I.; Chacana, P.; Terzolo, H. R.; Cabrera, G. M. World J Microbiol Biotechnol 2004, 20, 609.

[11] Lebrun, M. H.; Duvert, P.; Gaudemer, F.; Gaudemer, A.; Deballon, C. J Inorg Biochem 1985, 24, 167.

[12] Wan, Z. X.; Qiang, S.; Xu, S. C.; Shen, Z. G.; Dong, Y. F. Chi J Biol Cont 2001, 17, 10.

[13] Gänzle, M. G.; Hoeltzel, A.; Walter, J.; Jung, G.; Hammes, W. P. Appl Environ Microbiol 2000, 66, 4325.

[14] Biersack, B.; Diestel, R.; Jagusch, C.; Sasse, F.; Schobert, R. J Inorg Biochem 2009, 103, 72.

[15] Rainer, S.; Carsten, J. Tetrahedron 2005, 61, 2301.

[16] Yuki, H.; Kaizu, Y.; Yoshida, S.; Higuchi, S.; Honda, S.; Takiure, K. Chem Pharm Bull 1971, 19, 1664.

[17] Zhu, Y. Q.; Zou, X. M.; Hu, F. Z.; Yao, C. S.; Liu, B.; Yang, H. Z. J Agric Food Chem 2005, 53, 9566.

[18] Dai, H.; Li, Y. Q.; Du, D.; Qin, X.; Zhang, X.; Yu, H. B.; Fang, J. X. J Agric Food Chem 2008, 56, 10805.

[19] Liu, A. P.; Yao, J. R. Chi J Pesitic 2004, 43, 196.

[20] Fan, L.; Cui, J. G.; Wei, Y. L.; Huang, Y. M. Mod Agrochem 2008, 7, 6.

[21] Tatsuaki, Y.; Seisuke, Y.; Sadao, H.; Yohko, S.; Kimitoshi, S.; Hidetaka, Y. Pharm Soc Jpn 1981, 101, 125.

[22] Giorgos, A.; Efstathios, G.; Olga, I. M. J Heterocycl Chem 2001, 38, 1203.

[23] Harris, S. A.; Fisher, L. V.; Folkers, K. J Med Chem 1965, 8, 478.

[24] Du, Z. T.; Yue, G. R.; Ma, J. Y.; Wu, T. X.; Pan, X. F. Chem Reagents 2004, 26, 117.

[25] Wu, Y. X.; Dai, L.Y. Chi J Pestic 2004, 43, 113.

[26] Lu, J. The synthesis of a series of O-substituted hydroxylamines. M. Sc. Dissertation, Zhejiang University, China, 2006.

[27] Han, S. D.; Wang, G. C.; Li, F. Zhejiang Chemical Industry 2005, 36, 14.

[28] Sheldrick, G. M. SHELXS-97, Program for crystal structure solution; University of Göttingen: Göttingen, Germany, 1997.

[29] Chen, X.; Yang, C. L. J Agric Food Chem 2009, 57, 2441.

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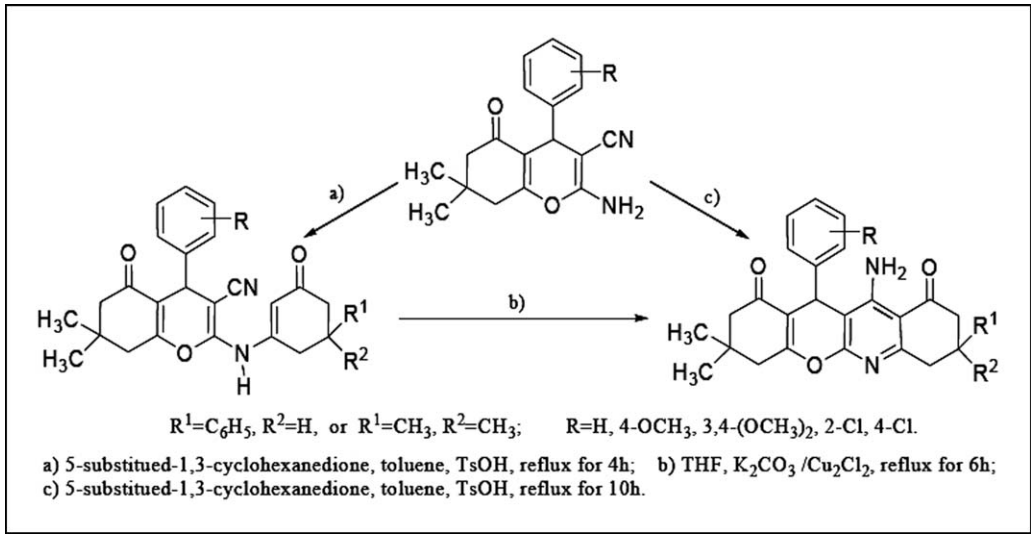


A series of novel 11-amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-hexahydro-2*H*-benzopyran[2,3-*b*]quinoline-1,10-dione derivatives **4** were synthesized by 2-amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran **2** with 5-substituted-1,3-cyclohexanedione using *p*-toluenesulfonic acid, $K_2CO_3$, and $Cu_2Cl_2$ as catalysts. The compounds **2** as easily accessible precursors were obtained from 5,5-dimethyl-1,3-cyclohexanedione by Michael addition with β-dicyanostyrenes **1**, prepared by Knoevenagel condensation of different aromatic aldehydes and malononitrile. The synthesis of the title compounds **4** completed by one-pot reaction of 4-aryl-4*H*-benzopyran derivatives with 5-substituted-1,3-cyclohexanediones by refluxing in toluene using TsOH as catalyst. The structures of all compounds were characterized by elemental analysis, IR, MS, and $^1$H NMR spectra.

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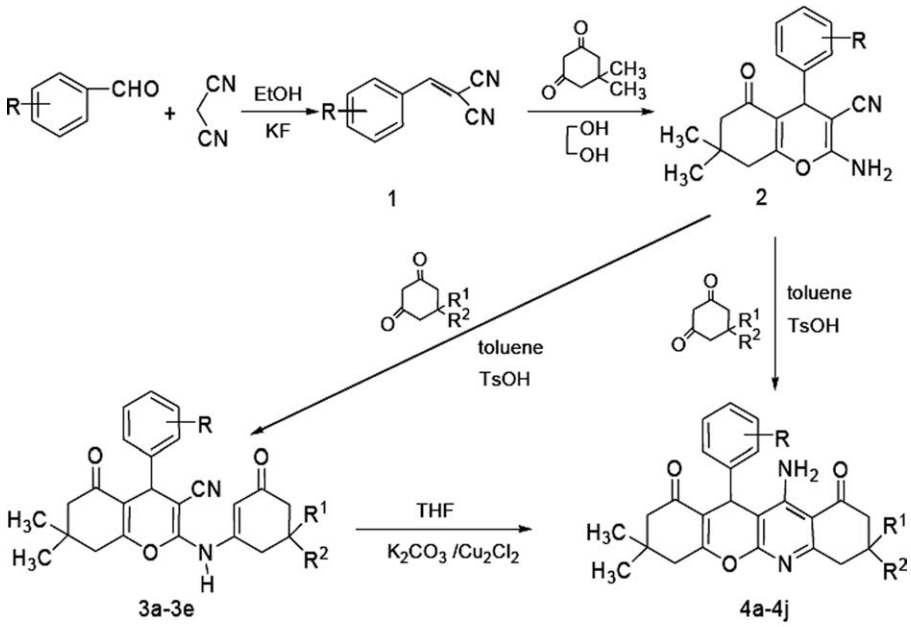
## INTRODUCTION

Many of the multirings occurring products containing simultaneously oxygen and nitrogen atoms on their carbon frameworks display various pharmacological activities [1]. Tacrine, a potent and reversible AChE inhibitor, was the first drug approved in the United States for the palliative treatment of Alzheimer's disease [2]. Jose [2] reported some new multipotent tetracyclic tacrine analogs, which had the similar structure with the title compounds and these tacrine analogs are modest AChE inhibitors but proved to be very selective. And some of them show a significant neuroprotective effect on neuroblastoma cells subjected to $Ca^{2+}$ overload or free radical induced toxicity. In addition, these compounds bind AChE to the peripheral anionic site of AChE. And, consequently, are potential agents that can prevent the aggregation of *b*-amyloid.

Among which benzopyran[2,3-*b*]quinolinone not only possesses the structure of benzopyran but also contains a quinoline ring. Benzopyran, as the parent ring of many natural products, are widely found in the nature. Their derivatives have been approved to possess good biological activity, and also exhibit antitumor activity. In addition, benzopyran derivatives could serve as the moderator for the potassium ion channel [3–5]. Quinoline belongs to the class benzopyridines (a class with six-membered nitrogened heterocyclic-fused polycyclic rings). The compounds of quinoline with aromatic or heterocyclic compounds have rigid planar with a conjugated structure. These compounds exhibit strong fluorescence properties as well as a variety of biological activities. They can be used by DNA and other biological macromolecules to embed into the body, and also can be served as the fluorescent probes and synthetic drugs. They have been widely used in the medical and molecular biology [6]. Nitrogen-containing

**Scheme 1**




3a: $R^1$=$C_6H_5$, $R^2$=H, R=H; 3b: $R^1$=$C_6H_5$, $R^2$=H, R=4-$OCH_3$;
3c: $R^1$=$C_6H_5$, $R^2$=H, R=3,4-$(OCH_3)_2$; 3d: $R^1$=$CH_3$, $R^2$=$CH_3$, R=4-$OCH_3$;
3e: $R^1$=$CH_3$, $R^2$=$CH_3$, R=4-Cl;
4a: $R^1$=$C_6H_5$, $R^2$=H, R=H; 4b: $R^1$=$C_6H_5$, $R^2$=H, R=4-$OCH_3$;
4c: $R^1$=$C_6H_5$, $R^2$=H, R=3,4-$(OCH_3)_2$; 4d: $R^1$=$CH_3$, $R^2$=$CH_3$, R=4-$OCH_3$;
4e: $R^1$=$CH_3$, $R^2$=$CH_3$, R=4-Cl; 4f: $R^1$=$C_6H_5$, $R^2$=H, R=4-Cl;
4g: $R^1$=$C_6H_5$, $R^2$=H, R=2-Cl; 4h: $R^1$=$CH_3$, $R^2$=$CH_3$, R=H;
4i: $R^1$=$CH_3$, $R^2$=$CH_3$, R=3,4-$(OCH_3)_2$; 4j: $R^1$=$CH_3$, $R^2$=$CH_3$, R=2-Cl.

heterocyclic compounds have shown a strong trend of development and broad application prospects in the fields of sterilization, anti-malaria, and anti-malignant tumor [7].

To search for medicinal compounds, and enrich the tetracyclic compounds, we first synthesized a series of new six-membered tetracyclic compounds, benzopyran [2,3-*b*]quinolinone derivatives with oxygen and nitrogen atoms inlaying in the ring.

## RESULTS AND DISCUSSION

11-Amino-12-aryl-2,3,4,7,8,9,10,12-octahydro-3,3-dimethyl-1*H*-chromeno[2,3-*b*]quinoline-1-one derivatives have been synthesized by 4-aryl-4*H*-chromenes and cyclohexanone using $AlCl_3$ as catalyst in 1,2-dicholonethane [2]. Pyrano[2,3-*b*]pyridines were achieved by the Friedlander reaction of 2-amino-3-cyano-4*H*-pyrans with cyclopentanone/cyclohexanone using $SnCl_2{\cdot}2H_2O$ under solvent-free condition [8]. Both methods have been tried in our investigation, but they are found to suffer from several drawbacks, such as low yield, no reaction, more byproducts, and long reaction time. Compared with these methods, our method has many advantages, such as higher yield, shorter reaction time, less side reaction and so on. In this study, β-dicyanostyrene **1** were prepared as building block from aromatic aldehyde, malononitrile in dry ethanol with $KF{\cdot}2H_2O$ as catalyst. And 4-aryl-4*H*-benzopyran derivatives **2** were synthesized by β-dicyanostyrene and 5,5-dimethyl-1,3-cyclohexanedione in ethylene glycol. The intermediate enamines **3** were obtained by condensation reaction of compounds **2** with 5-substituted-1,3-cyclohexanedione using *p*-toluenesulfonic acid as catalyst in toluene. 11-Amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-tetrahydro-2*H*-benzopyran[2,3-*b*]quinoline-1,10-dione derivatives **4** were synthesized by cyclization of the intermediate enamines **3** in the presence of $K_2CO_3$ and $Cu_2Cl_2$ [9,10]. Meanwhile, these series of novel compounds **4** could also be obtained via a one-step reaction by 4-aryl-4*H*-benzopyran **2** with 5-substituted-1,3-cyclohexanedione, using *p*-toluenesulfonic acid as catalyst in toluene. The synthetic pathway was shown in Scheme 1.

Each of compounds **4a–c**, **4f–g** should be as a diastereomeric mixture. It was speculated from the $^1$H NMR spectrum that the yields of the major product was above 90%. The diastereomeric were difficult to be isolated by silica gel flash chromatography, and therefore, the major product was purified by multiple-step crystallizing. As

**Table 1**

Synthesis of 2-*N*-(5-Substituted-3-oxo-1-cyclohexanyl)-amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-5-oxo-benzopyran (compounds **3**).

| Entry | $R^1$ | $R^2$ | R | Yield (%) |
|---|---|---|---|---|
| **3a** | $C_6H_5$ | H | H | 60.2 |
| **3b** | $C_6H_5$ | H | 4-$OCH_3$ | 45.3 |
| **3c** | $C_6H_5$ | H | 3,4-$(OCH_3)_2$ | 64.8 |
| **3d** | $CH_3$ | $CH_3$ | 4-$OCH_3$ | 48.5 |
| **3e** | $CH_3$ | $CH_3$ | 4-Cl | 50.6 |

shown in the $^1$H NMR spectrum, it was a single peak for the C12—H. The specific stereostructure of the main product need to be further studied.

The data of $^1$H NMR, MS, and IR shown in the experimental section are in accordant with the chemical structures of the target compounds. In the $^1$H NMR spectrum of compound **3a**, the broad single proton peaks at δ 6.38 was the characteristic absorption proton peak of the amino group. The single peak at δ 5.84 was the typical proton peak of the vinyl group. In the $^1$H NMR spectrum of compound **4a**, two broad single peaks at δ 5.07 and δ 9.14 were observed. They disappeared after $D_2O$ exchange, and therefore, were attributed to the two N—H of the amino group. Because of the existing of intramolecular hydrogen bond between one proton of the amino group and the oxygen atom of the carbonyl group nearby, its proton peak was drifted to δ 9.14. The structures of these compounds were further supported by their IR spectra. Server typical absorption bands at 2204 $cm^{-1}$ for **3a** (C≡N), 1655 $cm^{-1}$ for **4a** (C—O), and 3410 $cm^{-1}$ for (N—H) were observed, respectively.

## CONCLUSIONS

During our investigate, it is found that the toluene, TSOH, and raw materials are drier, the corresponding yields are more excellent and the side reactions are less; and when the ratio of 4-aryl-4*H*-benzopyran derivatives and 5-substituted-1,3-cyclohexanedione is 1:1.2, it can give the corresponding products in best yields. It is also found that the intermediate enamines **3** can be obtained using 4-aryl-4*H*-benzopyran derivatives and 5-substituted-1,3-cyclohexanedione in water with catalytic amount of HCl, and the corresponding yields are also relatively high, however, the side reactions are more. Therefore, using this method to synthesize our target compounds need to be further investigated.

In summary, during the synthesis of benzopyran[2,3-*b*]quinolinone derivatives, we used two methods and both could obtain the target compounds. Compared with the two methods, the method B extended the first step reaction time based on the method A. But we achieved one-step ring closure, reduced the kinds of catalysts and organic solvents, and shortened the total reaction time. Both the method and the benzopyran[2,3-*b*]quinolinone derivatives have not been reported. The purpose to enrich the tetracyclic heterocyclic compounds was achieved. These compounds contain atoms and groups that they can be modified according to the need, which can conduct further reaction.

## EXPERIMENTAL

Melting points were determined on an electrothermal apparatus and the temperature was not calibrated. Microanalysis was performed by the Perkin-Elmer 2400 Microanalytical Service. Infrared spectra were recorded as thin films on KBr using a Perking-Elmer 1700 spectrophotometer. The NMR spectra were recorded by a Bruker ARX-300 spectrometer. Sample solutions were prepared in $CDCl_3$ or DMSO containing TMS as an internal reference. Mass spectra were recorded by JMS-DX300 at 70 eV. All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled. 5-Substituted-1,3-cyclohexanedione were obtained from aromatic aldehyde, acetone and diethyl malonate according to the literature [1] method with slightly modification.

**General method for the synthesis of β-dicyanostyrene(1).** To a solution of the corresponding aldehyde (1 equiv) in dry ethanol (1 mL/mmol), malonodinitrile (1 equiv), and a catalytic amount of $KF{\cdot}2H_2O$ [11] were added. The mixture was stirred at 60°C for 2–4 h. Then, the reaction mixture was cooled to rt. To this mixture was added 100 mL water and the precipitated solid was isolated by filtration, washed with cold ethanol, recrystallized from 95% ethanol.

**General method for the synthesis of 2-Amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran(2).** To a solution of the corresponding β-dicyanostyrene (1 equiv) in ethylene glycol (1 mL/mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 equiv) were added. The mixture was stirred at 80°C for 2–4 h. Then, the resultant mixture was cooled to rt. To this mixture was added 100 mL water and the precipitated solid was isolated by filtration, washed with water, recrystallized from methanol.

**General method for the synthesis of 2-*N*-(5-substituted-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydro-5-oxo-4*H*-benzopyran (3a–3e).** 2-Amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran (1 equiv) and 5-substituted-1,3-cyclohexanedione (1.2 equiv) were suspended in toluene (1 mL/mmol) containing *p*-

**Table 2**

Synthesis of 11-amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-hexahydro-2*H*-benzopyran[2,3-*b*]quinoline-1,10-dione (compounds **4**).

| Entry | $R^1$ | $R^2$ | R | Yield (%) |
|---|---|---|---|---|
| **4a** | $C_6H_5$ | H | H | 59.6 |
| **4b** | $C_6H_5$ | H | 4-$OCH_3$ | 57.6 |
| **4c** | $C_6H_5$ | H | 3,4-$(OCH_3)_2$ | 40.8 |
| **4d** | $CH_3$ | $CH_3$ | 4-$OCH_3$ | 54.5 |
| **4e** | $CH_3$ | $CH_3$ | 4-Cl | 73.5 |
| **4f** | $C_6H_5$ | H | 4-Cl | 65.5 |
| **4g** | $C_6H_5$ | H | 2-Cl | 62.3 |
| **4h** | $CH_3$ | $CH_3$ | H | 59.6 |
| **4i** | $CH_3$ | $CH_3$ | 3,4-$(OCH_3)_2$ | 56.8 |
| **4j** | $CH_3$ | $CH_3$ | 2-Cl | 55.4 |

toluenesulfonic acid monohydrate (0.2 equiv). The mixture was refluxed for 4 h and the water was collected in a Dean-Stark water separator. At the end of the reaction, the reaction mixture was chilled to rt and the compound was filtered off. The yellow powder was recrystallized from ethyl acetate.

**General method for the synthesis of 11-amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-tetrahydro-2*H*-benzopyran [2,3-*b*]quinoline-1,10-dione(4a–4j).** ***Method A.*** 2-*N*-(5-Substituted-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-5-oxo-4*H*-benzopyran (1 equiv) was added to tetrahydrofuran (1 mL/mmol) containing potassium carbonate (0.5 equiv) and cuprous chloride (0.25 equiv). The reaction mixture was refluxed for 6 h and the hot mixture was filtered into hexane (2 mL/mmol). The precipitated was filtered off and washed with ethanol. The yellow powder was purified by silica gel flash chromatography using ethyl acetate/hexane mixture(1:2) as eluent to give purecompounds. The compounds **4a–4e** were synthesized by this method.

***Method B.*** In this study, we discovered that these series of novel compounds **4** could also be obtained via a one-step reaction by 4-aryl-4*H*-benzopyran **2** with 5-substituted-1,3-cyclohexanedione, using *p*-toluenesulfonic acid as catalyst in toluene refluxed for 10 h. Then, the hot mixture was filtered into hexane (2 mL/mmol). The precipitated was filtered off and washed with ethanol. The yellow powder was purified by silica gel flash chromatography using ethyl acetate/hexane mixture (1:2) as eluent to give pure compounds. The compounds **4f–j** were synthesized by this method. Data of compounds are shown below.

*2-N-(5-phenyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-pheny-7, 7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3a**).* Yield: 60.2%, m.p. 214–216°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.03(s, 3H, $CH_3$), 1.15(s, 3H, $CH_3$), 2.51–2.82(m, 6H, 8-, 4′-, and 6′-H), 3.38–3.41(m, 1H, 5′-H), 4.50(s, 1H, 4-H), 5.84(s, 1H, 2′-H), 6.38(br s, 1H, NH), 7.21–7.40(m, 10H, Ph-H); IR (KBr) υ: 3464(NH), 1687(C=O), 2204(C≡N); MS (70 eV) *m*/*z* (%): 465.0 (M+1, 100); *Anal*. calcd. for $C_{30}H_{28}N_2O_3$: C 77.56, H 6.08, N 6.03; found C 77.50, H 5.98, N 6.15.

*2-N-(5-phenyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(4-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8- tetrahydro-4H-benzopyran (**3b**).* Yield: 55.3%, m.p. 224–226°C; $^1$H NMR (DMSO, 300 MHz) δ: 1.03(s, 3H, $CH_3$), 1.13(s, 3H, $CH_3$), 2.07–2.22(m, 4H, 6-, and 8-H), 2.27–2.49(m, 4H, 4′-, and 6′-H), 3.34–3.45(m, 1H, 5′-H), 3.71(s, 3H, $OCH_3$), 4.41(s, 1H, 4-H), 4.85(s, 1H, 2′-H), 5.84(br s, 1H, NH), 6.83–7.11(m, 8H, Ph-H); IR (KBr) υ: 3399(NH), 1719(C=O), 2254(C≡N); MS (70 eV) *m*/*z* (%): 495.2 (M + 1, 100).

*2-N-(5-phenyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(3,4-dimethoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3c**).* Yield**:** 64.8%, m.p. 188–190°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.07(s, 3H, $CH_3$), 1.15(s, 3H, $CH_3$), 2.27–2.58(m, 2H, 8-H), 2.61–2.76(m, 6H, 6-, 4′-, and 6′-H), 3.42–3.45(m, 1H, 5′-H), 3.84(s, 3H, $OCH_3$), 3.86(s, 3H, $OCH_3$), 4.44(s, 1H, 4-H), 5.83(s, 1H, 2′-H), 5.87(br s, 1H, NH), 6.71–7.40(m, 8H, Ph-H); IR (KBr) υ: 3442(NH), 1682(C=O), 2205(C≡N); MS (70eV) *m*/*z* (%): 525.3 (M + 1, 100); *Anal*. calcd. for $C_{32}H_{32}N_2O_5$: C 73.26, H 6.15, N 5.34; found C 73.39, H 6.22, N 5.20.

*2-N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(4-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3d**).* Yield: 48.5%, m.p. 192–194°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.04(s, 3H, $CH_3$), 1.10(s, 6H, 2 × $CH_3$), 1.26(s, 3H, $CH_3$), 2.18–2.31(m, 6H, 8-, 4′-, and 6′-H), 2.54(s, 2H, 6-H), 3.78(s, 3H, $OCH_3$), 4.45(s, 1H, 4-H), 5.79(s, 1H, 2′-H), 6.45(br s, 1H, NH), 6.82–7.18(m, 5H, Ph-H); IR (KBr) υ: 3460(NH), 1672(C=O), 2210(C≡N); MS (70 eV) *m*/*z* (%): 447.2 (M + 1, 100); *Anal*. calcd. for $C_{27}H_{30}N_2O_4$: C 72.62, H 6.77, N 6.27; found C 72.50, H 6.69, N 6.35.

*2-N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(4-chlorine-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3e**).* Yield: 50.6%, m.p. 194–196°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.04(s, 3H, $CH_3$), 1.12(s, 6H, 2 × $CH_3$), 1.14(s, 3H, $CH_3$), 2.19–2.32(m, 6H, 8-, 4′-, and 6′-H), 2.56(s, 2H, 6-H), 4.48(s, 1H, 4-H), 5.82(s, 1H, 2′-H), 6.21(br s, 1H, NH), 7.17–7.32(m, 5H, Ph-H); IR (KBr) υ: 3385(NH), 1719(C=O), 2238(C≡N); MS (70 eV) *m*/*z* (%): 449.9 ($M^+$, 100).

*11-amino-3,3-dimethyl-8,12-diphenyl-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4a**).* Yield: 59.6% .m.p. 244–246°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.96(s, 3H, $CH_3$), 1.10(s, 3H, $CH_3$), 2.17–2.30(m, 2H, 4-H), 2.57(s, 2H, 2-H), 2.75–2.92(m, 2H, 9-H), 3.09–3.29(s, 2H, 7-H), 3.39–3.50(m, 1H, 8-H), 4.85 (s, 1H, 12-H), 5.07(br s, 1H, NH),7.17–7.38(m, 10H, Ph-H), 9.14(br,s, 1H, N-H); IR (KBr) υ: 3410, 1655, 1167, 1125 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 465.2 (M + 1, 100); *Anal*. calcd. for $C_{30}H_{28}N_2O_3$: C 77.56, H 6.08, N 6.03; found C 77.44, H 6.15, N 5.96.

*11-amino-3,3-dimethyl-8-phenyl-12-(4-methoxy-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4b**).* Yield: 57.6 % , m.p. 210–212°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.98(s, 3H, $CH_3$), 1.10(s, 3H, $CH_3$), 2.17–2.30(m, 2H, 4-H), 2.56(s, 2H, 2-H), 2.75–2.93(m, 2H, 9-H), 3.09–3.31(m, 2H, 7-H), 3.39–3.51(m, 1H, 8-H), 3.75(s, 3H, $OCH_3$), 4.81(s, 1H, 12-H), 5.10(br s, 1H, NH),6.79–7.39(m, 9H, Ph-H), 9.16(br s, 1H, NH); IR (KBr) υ: 3450, 1654, 1182, 1029 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 495.2 (M + 1, 100); *Anal*. calcd. for $C_{31}H_{30}N_2O_4$: C 75.28, H 6.11, N 5.66; found C 75.21, H 6.21, N 5.58.

*11-amino-3,3-dimethyl-8-phenyl-12-(3,4-dimethoxy-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4c**).* Yield: 40.8%, m.p. 216–218°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.03(s, 3H, $CH_3$), 1.11(s, 3H, $CH_3$), 2.16–2.30(m, 2H, 4-H), 2.56(s, 2H, 2-H), 2.76–2.95(m, 2H, 9-H), 3.09–3.30(m, 2H, 7-H), 3.37–3.51(m, 1H, 8-H), 3.75(s, 3H, $OCH_3$), 3.80(s, 3H, $OCH_3$),4.81(s, 1H, 12-H), 5.16(br s, 1H, NH), 6.89–7.38(m, 8H, Ph-H), 9.26(br s, 1H, NH); IR (KBr) υ: 3430, 1640, 1180, 1025$cm^{-1}$;MS (70 eV) *m*/*z* (%): 525.3 (M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-(4-methoxy-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4d**).* Yield: 54.5%, m.p. 230–232°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.00(s, 6H, 2 × $CH_3$), 1.10(s, 6H, 2 × $CH_3$), 2.14–2.27(m, 4H, 4-H, 7-H), 2.46(s, 4H, 2-H, 9-H), 3.74(s, 3H, $OCH_3$), 4.70(s, 2H, 12-H), 5.15(br s, 1H, NH), 6.74–7.22(m, 4H, Ph-H), 9.13(br s, 1H, NH); IR (KBr) υ: 3448, 1668, 1195, 1137 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 447.2 (M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-(4-chlorine-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4e**).* Yield: 73.5%, m.p. 236–238°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.96(s, 3H, $CH_3$), 1.08(s, 3H, $CH_3$), 1.09(s, 3H, $CH_3$), 1.10(s, 3H, $CH_3$), 2.16–2.29(m, 2H, 4-H), 2.45(s, 2H, 2-H), 2.56(s, 2H, 9-H), 2.83(s, 2H, 7-H), 4.82(s, 1H, 12-H), 5.09(br s, 1H, NH), 7.22–7.30(m, 4H, Ph-H), 9.10(br s, 1H, NH); IR (KBr) υ: 3484, 1654, 1184, 1126 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 449.9 ($M^+$, 100).

*11-amino-3,3-dimethyl-8-phenyl-12-(4-chlorine-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4f**)*. Yield: 65.5%, m.p. 230–232°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.97(s, 3H, $CH_3$), 1.11(s, 3H, $CH_3$), 2.17–2.30(m, 2H, 4-H), 2.57(s, 2H, 2-H), 2.82–2.88(m, 2H, 9-H), 3.14–3.24(m, 2H, 7-H), 3.44–3.47(m, 1H, 8-H), 4.84(s, 1H, 12-H), 5.10(br s, 1H, NH), 7.23–7.39(m, 9H, Ph-H), 9.17(br s, 1H, NH); IR (KBr) υ: 3484, 1656, 1216, 1168 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 499.2(M + 1, 100); *Anal*. calcd. for $C_{30}H_{27}N_2O_3Cl$: C 72.21, H 5.45, N 5.61; found C 72.13, H 5.36, N 5.70.

*11-amino-3,3-dimethyl-8-phenyl-12-(2-chlorine-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4g**)*. Yield: 62.3%, m.p. 184–186°C; $^1$H NMR ($CDCl_3$, 300MHz) δ: 1.01(s, 3H, $CH_3$), 1.13(s, 3H, $CH_3$), 2.17–2.32(m, 2H, 4-H), 2.63(s, 2H, 2-H), 2.82–2.88(m, 2H, 9-H), 3.08–3.25(m, 1H, 8-H), 3.37–3.50(m, 2H, 7-H), 5.26(s, 1H, 12-H), 5.73(br s, 1H, NH), 7.15–7.36(m, 9H, Ph-H), 9.39(br s, 1H, NH); IR (KBr) υ:3476, 1655, 1169,1138 $cm^{-1}$; MS (70eV) *m*/*z* (%): 499.2(M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-phenyl-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4h**)*. Yield: 59.6%, m.p. 246–248°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.98(s, 6H, 2 × $CH_3$), 1.10(s, 6H, 2 × $CH_3$), 2.22–2.24(m, 2H, 4-H), 2.44(s, 2H, 2-H), 2.59(s, 2H, 9-H), 2.86(s, 2H, 7-H), 4.83(s, 1H, 12-H), 5.09(br s, 1H, NH),7.17–7.36(m, 5H, Ph-H), 9.10(br s, 1H, NH); IR (KBr) υ: 3422, 1660, 1195,1152 $cm^{-1}$; MS (70 eV) *m*/*z* (%): 417.1 (M + 1, 100); *Anal*. calcd. for $C_{26}H_{28}N_2O_3$: C 74.97, H 6.78, N 6.73; found C 74.93, H 6.72, N 6.82.

*11-amino-3,3,8,8-tetramethyl-12-(3,4-dimethoxy-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4i**)*. Yield: 56.8%, m.p. 266-268°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.01(s, 6H, 2 × $CH_3$), 1.11(s, 6H, 2 × $CH_3$), 2.15–2.28(m, 4H, 4-H, 7-H), 2.46(s, 4H, 2-H, 9-H), 3.80(s, 3H, $OCH_3$), 3.86(s, 3H, $OCH_3$) 4.71(s, 2H, 12-H), 5.18(br s, 1H, NH), 6.74–6.91(m, 3H, Ph-H), 9.12(br s, 1H, NH); IR (KBr) υ: 3415, 1649, 1186,1125 $cm^{-1}$; MS (70 eV) *m*/*z* (%):477.2 (M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-(2-chlorine-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4j**)*. Yield: 55.4%, m.p.174–176°C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.12(s, 6H, 2 × $CH_3$), 1.15(s, 6H, 2×$CH_3$), 2.35(s, 2H, 2-H), 2.54–2.61(m, 2H, 4-H), 2.87(s, 2H, 9-H), 2.93–2.99(m, 2H, 7-H), 4.75(s, 1H, 12-H), 5.18(br s, 1H, NH), 6.89–7.19(m, 4H, Ph-H), 9.10(br s, 1H, NH); IR (KBr) υ: 3484, 1654, 1184, 1126$cm^{-1}$; MS (70 eV) *m*/*z* (%): 449.9 ($M^+$, 100).

## REFERENCES AND NOTES

[1] Han, G. F.; Wang, J. J.; Jiang, G. J. Chin J Org Chem 2003, 23, 1004 (in Chinese).

[2] Jose, M. C.; Rafael, L.; Cristobal, R.; Antonio, G. G.; Manuela, G. L.; Mercedes, V. Bioorg Med Chem 2006, 14, 8176.

[3] Isabelle, K.; Marc, H.; Stephane, C. Eur J Med Chem 2008, 43, 2735.

[4] Siegfriend, E.; Drewes, F.; Fatima, K.; Alvaro, K. Eur J Med Chem 2005, 66, 1812.

[5] Franco, C.; Bruna, B.; Adriana, B. Photosynth Res 2006, 41, 208.

[6] Noble, S.; Fauldsd, A. Drugs 1998, 31, 115.

[7] Hoock, C.; Reichert, J.; Schmidtke, M. Molecule 1999, 4, 264.

[8] Selvam, N. P.; Babu, T. H.; Perumal, P. T. Tetrahedron 2009, 65, 8524.

[9] Han, G. F.; Wang, R. H.; Zhang, W. T. Synth Commun 2009, 39, 2492.

[10] Shutske, G. M.; Pierrat, F. A.; Kapples, K. J.; Cornfeldt, M. L.; Szewczak, M. R.; Huger, F. P.; Bores, G. M.; Haroutunian, V.; Davis, K. L. J Med Chem 1989, 32, 1805.

[11] Dai, G. Y.; Shi, D. Q.; Zhou, L. H. Chinareagent 1996, 18, 39.

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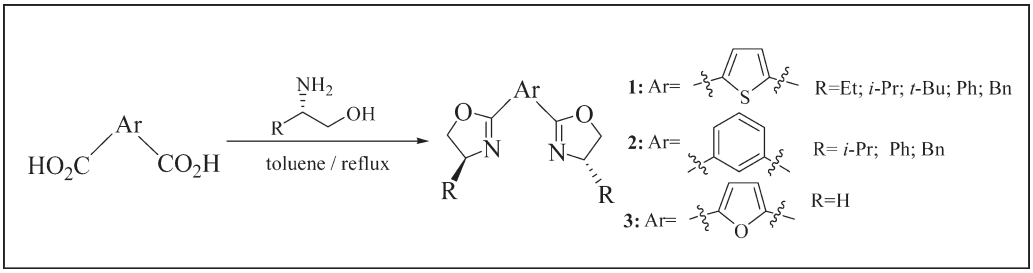


Thiophene-2,5-dicarboxylic acid, benzene-1,3-dicarboxylic acid, or furan-2,5-di-carboxylic acid, respectively, reacted with various β-amino alcohols in toluene under reflux within 24 h, to form nine bis(oxazoline)s (**1**–**3**) in good yields through water deprivation *via* a one-pot reaction. The synthetic method is facile and efficient and deserves great application potentials in the research and development in the area of bis(oxazoline)s.

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## INTRODUCTION

Since Butula *et al*. prepared the first optically active bis(oxazoline) in 1976, the design and development of effective chiral bis(oxazoline) ligands have played a significant role in advancement of asymmetric catalysis and have attracted a great deal of attention because they hold special structural characters and provide high enantioselectivities in a variety of asymmetric catalytic reactions [1–6]. Chiral bis(oxazoline) ligands have widespread uses in asymmetric hydrosilylation [7], cyclopropantion reaction [8], Friedel-Crafts reaction [9], Diels-Alder reaction [10], Aldol addition [11], Michael reaction [12], Henry reaction [13], allylic oxidation [14], 1,3-dipolar cycloaddition [15], and so on.

Chiral bis(oxazoline)s have various structures, which determine the diversity of their synthetic methods. At present, two general synthetic routes are summarized from various synthesis [2,3,16]: (a) Reaction of dintriles with chiral amino alcohol or diols afford the target compound *via* a one or multiple-step reaction in the presence of Lewis acid or base. (b) Dicarboxylic acids or their derivatives (diacyl halide, diacylamide or diesters) react with chiral amino alcohol, *via* the corresponding bis(β-hydroxylamide)s as the successive intermediates, that cyclize to produce the target compounds. The latter method requires activating agents, with thionyl chloride, also cyclizing agent being the most commonly used, which results in more side reactions and low yields. Therefore, a simpler and more efficient synthesis approach should be explored to meet the needs of bis(oxazoline) ligands.

In this article, we report the results of the reaction of dicarboxylic acids with β-amino alcohols under reflux through water deprivation to obtain chrial bis(oxazoline)s **1a**–**1e**, **2a**–**2c**, and a novel achiral bisoxazoline **3** (Fig. 1 and Scheme 1–3) *via* a one-pot reaction. This method afforded high yields with simple workup procedure.

## RESULTS AND DISCUSSION

Gao *et al*. reported that chiral bis(oxazoline)s **1a**–**1e** were synthesized from thiophene-2,5-dicarboxylic acid by sequential amidation with a chiral ethanolamine, conversion of hydroxyl to chloro group, and base-promoted oxazoline ring formation [17,18]. Kanazawa *et al*. described the synthetic procedure of chiral 1,3-bis[4′-substitutedoxazolin-2′-yl]benzene including bis(oxazoline)s **2a**–**2c**, which isophthaloyl dichloride reacted with chiral β-amino alcohols at 0°C to form the corresponding diamide-dialcohols as the successive intermediates and then cyclized to obtain the target compounds in the presence of methanesulfonyl chloride at 0°C [19]. As described above, the syntheses of chiral bis(oxazoline)s involve multistep reactions, which result in more side reactions and low yields.

To address above issues, we successfully developed a new, facile, and efficient method for the synthesis of

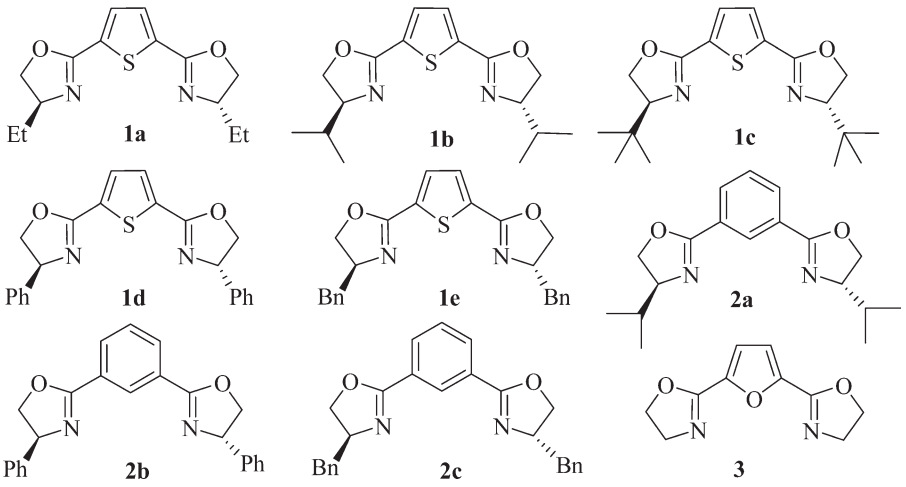



**Figure 1.** Chemical structures of bis(oxazoline)s.

bis(oxazoline)s starting from dicarboxylic acids. With this convenient method, bis(oxazoline)s **1** or **2** were readily synthesized in high yields from thiophene-2,5-dicarboxylic acid (TDA) or benzene-1,3-dicarboxylic acid (BDA) and β-amino alcohols (Scheme 1 and 2). Briefly, a mixture of dicarboxylic acid and β-amino alcohol was refluxed in toluene through water deprivation for 24 h. After cooling to ambient temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the desired product in high yield. The conditions and results of reaction of carboxylic acids with β-amino alcohols have been listed in Table 1 (entries 1–8).

Instead of thiophene-2,5-dicarboxylic acid (TDA) or benzene-1,3-dicarboxylic acid (BDA), furan-2,5-dicarboxylic acid (FDA) reacted with 2-aminoethanol to afford a new achiral bis(oxazoline) **3** in high yield under the same reaction condition (Scheme 3 and Table 1, entry 9).

In conclusion, a facile one-pot synthetic method of bis(oxazoline)s (**1**–**3**) was described, which is simple and efficient, deserving great application potentials in the research and development in the area of bis(oxazoline)s.

## EXPERIMENTAL

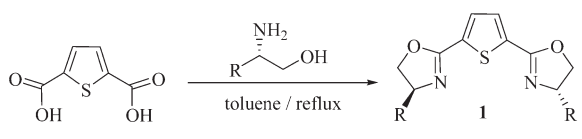
**General.** Melting points were determined by the capillary method and are uncorrected. $^1$H-NMR spectra were measured on a Varian UNITY INOVI-500 NMR spectrometer, a Bruker Avance DPX300 NMR spectrometer or a Bruker DRX-400 NMR spectrometer, using TMS as internal standard. Mass spectra were taken on a MDS Sciex API 2000 LC/GC/MS instrument. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer. Optical rotation values were measured on a POLARTRONIC HNQW 5 polarimeter.

All solvents used for the synthesis were of analytical grade and were dried and freshly distilled under a nitrogen atmosphere prior to use. Chiral β-amino alcohols, furan-2,5-dicarboxylic acid, and benzene-1,3-dicarboxylic acid were purchased from Fluka Chemical Co. Thiophene-2,5-dicarboxylic acid was synthesized in our own laboratory. Other reagents were all of analytical grade.

**General procedure for the synthesis of 2,5-bis[4′(*S*)-substituted-oxazolin-2′-yl]thiophene (1a–1e).** Thio-phene-2,5-dicarboxylic acid (100.0 mg, 0.58 mmol), chiral β-amino alcohol (1.16 mmol), and toluene (20 mL) were added to a three-neck flask with a water segregator, a reflux condenser, and a magnetic stirring bar. The mixture was refluxed and dehydrated for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with dichloromethane and ethanol (50:1) as eluent to give the pure title compound.

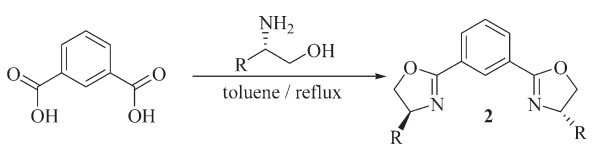
***(−)-2,5-Bis[4′(S)-ethyloxazolin-2′-yl]thiophene(1a).*** This compound was obtained as colorless solid; yield 96%; mp 90–91°C ([18] 89–90°C); $[\alpha]_D^{20} = -95.3$ ($c$ 1.0, $CH_2Cl_2$); $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.99 (t, $J$ = 7.4Hz, 6H, $CH_3$), 1.58–1.65 (m, 2H, $CH_2$), 1.67–1.74 (m, 2H, $CH_2$), 4.06 (dd, $J$ = 7.4, 10.2 Hz, 2H, $OCH_2$), 4.19–4.28 (m, 2H, NCH), 4.50 (dd, $J$ = 8.4, 10.2 Hz, 2H, $OCH_2$), 7.56 (s, 2H, thiophene-H).

**Scheme 1**



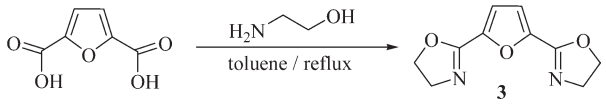

a: R=Et; b: R=*i*-Pr; c: R=*t*-Bu
d: R=Ph; e: R=Bn

**Scheme 2**




a: R= *i*-Pr; b: R=Ph; c: R=Bn

**Scheme 3**




ESI-MS: *m/z* ($MH^+$) 279. Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.23; H, 6.54; N, 10.02.

***(−)-2,5-Bis[4′(S)-isopropyloxazolin-2′-yl]thiophene(1b).*** This compound was obtained as colorless solid; yield 91; mp 66–67°C ([18] 66–68°C); $[\alpha]_D^{20} = -29.7$ (*c* 0.5, $CH_3COCH_3$); $^1$H-NMR (500 MHz, $CDCl_3$): δ 0.91 (d, *J* = 7.0 Hz, 6H, $CH_3$), 1.15 (d, *J* = 7.0 Hz, 6H, $CH_3$), 1.84–1.91 (m, 2H, CH), 4.08–4.15 (m, 4H, $OCH_2$), 4.39 (dd, *J* = 8.0, 9.0 Hz, 2H, NCH), 7.57 (s, 2H, thiophene-H). ESI-MS: *m/z* ($MH^+$) 307. Anal. Calcd. for $C_{16}H_{22}N_2O_2S$: C, 62.71; H, 7.24; N, 9.14. Found: C, 62.55; H, 7.26; N, 9.11.

***(+)-2,5-Bis[4′(S)-tert-butyloxazolin-2′-yl]thiophene(1c).*** This compound was obtained as colorless solid; yield 89%; mp 119–120°C ([17] 120–121°C); $[\alpha]_D^{20} = +5.9$ (*c* 0.6, $CH_3COCH_3$); $^1$ H-NMR (500 MHz, $CDCl_3$): δ 0.98 (s, 18H, $CH_3$), 4.02 (dd, *J* = 7.5, 10.0 Hz, 2H, $OCH_2$), 4.24 (dd, *J* = 8.0, 8.5 Hz, 2H, NCH), 4.35 (dd, *J* = 8.5, 10.0 Hz, 2H, $OCH_2$), 7.53 (s, 2H, thiophene-H). ESI-MS: *m/z* ($MH^+$) 335. Anal. Calcd. for $C_{18}H_{24}N_2O_2S$: C, 64.64; H, 7.84; N, 8.38. Found: C, 64.41; H, 7.86; N, 8.35.

***(+)-2,5-Bis[4′(S)-phenyloxazolin-2′-yl]thiophene(1d).*** This compound was obtained as colorless solid; yield 93%; mp 127–128°C; $[\alpha]_D^{20} = +59.5$ (*c* 0.4, $CH_2Cl_2$); $^1$ H-NMR (500 MHz, $CDCl_3$): δ 4.32 (dd, *J* = 8.0, 16.0 Hz, 2H, NCH), 4.78 (dd, *J* = 8.5, 10.0 Hz, 2H, $OCH_2$), 5.39 (dd, *J* = 8.0, 10.0 Hz, 2H, $OCH_2$), 7.27–7.36 (m, 10H, Ph-H), 7.68 (s, 2H, thiophene-H). ESI-MS: *m/z* ($MH^+$) 375. Anal. Calcd. for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.46; H, 4.84; N, 7.46.

***(+)-2,5-Bis[4′(S)-benzyloxazolin-2′-yl]thiophene(1e).*** This compound was obtained as colorless solid; yield 93%; mp 108–110°C ([18] 107–109°C); $[\alpha]_D^{20} = +91.5$ (*c* 0.3, $CH_3COCH_3$); $^1$ H-NMR (500 MHz, $CDCl_3$): δ 2.74 (dd, *J* = 8.5, 13.5 Hz, 2H, $CH_2$-Ph), 3.21 (dd, *J* = 5.0, 13.5 Hz, 2H, $CH_2$-Ph), 4.14 (dd, *J* = 7.0, 9.0 Hz, 2H, $OCH_2$), 4.37 (dd, *J* = 8.5, 9.0 Hz, 2H, $OCH_2$), 4.58–4.61 (m, 2H, NCH), 7.22–7.31 (m, 10H, Ph-H), 7.52 (s, 2H, thiophene-H). ESI-MS: *m/z* ($MH^+$) 403. Anal. Calcd. for $C_{24}H_{22}N_2O_2S$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.34; H, 5.53; N, 6.94.

**General procedure for the synthesis of 1,3-bis[4′(*S*)-substitutedoxazolin-2′-yl]benzene (2a–2c).** Benzene-1,3-dicarboxylic acid (100.0 mg, 0.60 mmol), chiral β-amino alcohol (1.20 mmol), and toluene (20 mL) were added to a three-neck flask with a water segregator, a reflux condenser, and a magnetic stirring bar. The mixture was refluxed and dehydrated for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with dichloromethane and ethanol (50:1) as eluent to give the pure title compound.

***(−)-1,3-Bis[4′(S)-isopropyloxazolin-2′-yl]benzene(2a).*** This compound was obtained as colorless solid; yield 93%; mp 58–60°C; $[\alpha]_D^{20} = -141.5$ (*c* 0.3, $CHCl_3$); $^1$ H-NMR (500 MHz, $CDCl_3$): δ 0.94 (d, *J* = 7.0 Hz, 6H, $CH_3$), 1.06 (d, *J* = 7.0 Hz, 6H, $CH_3$), 1.87–1.94 (m, 2H, CH), 4.11–4.19 (m, 4H, $OCH_2$), 4.38–4.45 (m, 2H, NCH), 7.45–8.51 (m, 4H, benzene-H). ESI-MS: *m/z* ($MH^+$) 301. Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.75; H, 8.08; N, 9.31.

***(−)-1,3-Bis[4′(S)-phenyloxazolin-2′-yl]benzene(2b).*** This compound was obtained as colorless solid; yield 94%; mp 122–124°C ([19] 120–124°C); $[\alpha]_D^{20} = -73.1$ (*c* 0.3, $CH_2Cl_2$); $^1$ H-NMR (500 MHz, $CDCl_3$): δ 4.42 (dd, *J* = 8.0, 8.5 Hz, 2H, $OCH_2$), 4.92 (dd, *J* = 8.0, 10.0 Hz, 2H, $OCH_2$), 5.48 (dd, *J* = 7.0, 10.0 Hz, NCH), 7.27–7.41 (m, 10H, Ph-H), 7.57 (t, *J* = 7.5 Hz, 1H, benzene-H), 8.39 (dd, *J* = 1.5, 7.5 Hz, 2H, benzene-H), 8.76 (t, *J* = 1.5 Hz, 1H, benzene-H). ESI-MS: *m/z* ($MH^+$) 369. Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.01; H, 5.49; N, 7.58.

***(−)-1,3-Bis[4′(S)-benzyloxazolin-2′-yl]benzene(2c).*** This compound was obtained as colorless solid; yield 94%; mp 105–107°C ([19] 106–107°C); $[\alpha]_D^{20} = -4.1$ (*c* 0.5, $CHCl_3$); $^1$ H-NMR (300 MHz, $CDCl_3$): δ 2.73–3.28 (m, 4H, $CH_2Ph$), 4.17 (dd, *J* = 7.5, 8.5Hz, 2H, $OCH_2$), 4.37–4.41 (m, 2H, $OCH_2$), 4.58–4.63 (m, 2H, NCH), 7.10–7.36 (m, 10H, Ph-H), 7.50–8.49 (m, 4H, benzene-H). ESI-MS: *m/z* ($MH^+$) 397. Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.52; H, 6.12; N, 7.05.

**Synthesis of 2,5-bis(oxazolin-2′-yl) furan (3).** Furan-2,5-dicarboxylic acid (100.0 mg, 0.64 mmol), 2-aminoethanol (78.3 mg, 1.28 mmol), and toluene (20 mL) were added to a three-neck flask with a water segregator, a reflux condenser, and a magnetic stirring bar. The mixture was refluxed and dehydrated for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with

**Table 1**

The conditions and results of dicarboxylic acid reacted with β-amino alcohol in toluene through water deprivation.[a]

| Entry | Dicarboxylic acid | β-Amino alcohol | Bis(oxazoline) | Yield (%) |
|---|---|---|---|---|
| 1 | TDA | (*S*)-2-aminobutan-1-ol | **1a** | 96 |
| 2 | TDA | L-leucinol | **1b** | 91 |
| 3 | TDA | L-tert-leucinol | **1c** | 89 |
| 4 | TDA | L-phenylglycinol | **1d** | 93 |
| 5 | TDA | L-phenylalaninol | **1e** | 93 |
| 6 | BDA | L-leucinol | **2a** | 93 |
| 7 | BDA | L-phenylglycinol | **2b** | 94 |
| 8 | BDA | L-phenylalaninol | **2c** | 94 |
| 9 | FDA | 2-aminoethanol | **3** | 88 |

[a] Dicarboxylic acid/β-amino alcohol = 1/2 (mole ratio). Reaction time: 24 h.

dichloromethane and ethanol (50:1) as eluent to give the pure title compound as colorless liquid; yield 88%; $^1$ H-NMR (400 MHz, DMSO-$d_6$): δ 2.94 (t, $J$ = 5.2 Hz, 4H, $NCH_2$), 3.62 (t, $J$ = 5.2 Hz, 4H, $OCH_2$), 6.73 (s, 2H, furan-H). $^{13}$ C-NMR (400 MHz, DMSO-$d_6$): 41.5, 57.9, 113.5, 151.1, 163.3. ESI-MS: $m/z$ ($MK^+$) 245. Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.14; H, 4.91; N, 13.57.

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## REFERENCES AND NOTES

[1] Butula, I.; Karlovic, G. Liebigs Ann Chem 1976, 7–8, 1455.

[2] Ghosh, A. K.; Mathivanan, P.; Cappiello, J. Tertahedron Asymmetry 1998, 9, 1.

[3] Desimon, G.; Faita, G.; Quadrellip, P. Chem Rev 2003, 103, 3119.

[4] Desimoni, G.; Faita, G.; Jørgensen, K. A. Chem Rev 2006, 106, 3561.

[5] Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. J Am Chem Soc 2005, 127, 6972.

[6] Denmark, S. E.; Nakajima, N.; Stiff, C. M.; Nicaise, O. J. C.; Kranza, M. Adv Synth Catal 2008, 350, 1023.

[7] Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. J Org Chem 1992, 57, 4308.

[8] (a) Werner, H.; Herrerías, C. I.; Glos, M.; Gissibl, A.; Fraile, J. M.; Pérez, I.; Mayoral, J. A.; Reisera, O. Adv Synth Catal 2006, 348, 125; (b) Bayardon, J.; Holczknecht, O.; Pozzib, G.; Sinou, D. Tetrahedron Asymmetry 2006, 17, 1568; (c) Burguete, M. I.; Cornejo, A.; García-Verdugo, E.; García, J.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayorald, J. A.; Sokolova, M. Green Chem 2007, 9, 1091; (d) Fraile, J. M.; Garc, J. I.; Gissibl, A.; Mayoral, J. A.; Pires, E.; Reiser, O.; Roldán, M.; Villalba, I. Chem Eur J 2007, 13, 8830.

[9] (a) Yang, H.; Hong, Y.-T.; Kim, S. Org Lett 2007, 9, 2281; (b) Singh, P. K.; Bisai, A.; Singh, V. K. Tetrahedron Lett 2007, 48, 1127.

[10] (a) Yeom, C.-E.; Kim, H. W.; Shin, Y. J.; Kim, B. M. Tetrahedron Lett 2007, 48, 9035; (b) Tanaka, S.; Tada, M.; Iwasawa, Y. J Catal 2007, 245, 173; (c) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. J Org Chem 2007, 72, 240.

[11] (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. J Am Chem Soc 1996, 118, 5814; (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. J Am Chem Soc 1997, 119, 7893; (c) Inoue, H.; Kikuchi, M.; Ito, J.; Nishiyama, H. Tetrahedron 2008, 64, 493.

[12] Nishiyama, H.; Ishikawa, J.; Shiomi, T. Tetrahedron Lett 2007, 48, 7841.

[13] (a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. J Am Chem Soc 2003, 125, 12692; (b) Ginotra, S. K.; Singh, V. K. Org Biomol Chem 2007, 5, 3932.

[14] (a) Clariana, J.; Comelles, J.; Moreno-Mañas, M.; Vallribera, A. Tetrahedron Asymmetry 2002, 13, 1551; (b) Andrus, M. B.; Zhou, Z. J Am Chem Soc 2002, 124, 8806; (c) Ginotra, S. K.; Singh, V. K. Org Biomol Chem 2006, 4, 4370.

[15] (a) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. J Org Chem 1998, 63, 5483; (b) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. J Org Chem 1999, 64, 2353.

[16] (a) Gomez, M.; Muller, G.; Rocamora, M. Coord Chem Rev 1999, 193–195, 769; (b) Glorius, F.; Pfaltz, A. Org Lett 1999, 1, 141; (c) Mazet, C.; Gade, L. H. Chem Eur J 2002, 8, 4308; (d) Corey, E. J.; Imai, N.; Zhang, H. Y. J Am Chem Soc 1991, 113, 728; (e) Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. J Org Chem 1996, 61, 9629; (f) Andrus, M. B.; Asgari, D. Tetrahedron 2000, 56, 5775; (g) Ammar, H. B.; Notre, L. J.; Salem, M.; Kaddachi, M. T.; Dixneuf, P. H. J Organomet Chem 2002, 662, 63; (h) Bayardon, J.; Sinou, D. Tetrahedron Lett 2003, 44, 1449; (i) Kato, K.; Tanaka, M.; Yamamura, S.; Yamamoto, Y.; Akita, H. Tetrahedron Lett 2003, 44, 3089; (j) Boulch, R.; Scheurer, A.; Mosset, P.; Saalfrank, R. W. Tetrahedron Lett 2000, 41, 1023.

[17] Gao, M. Z.; Kong, D.; Clearfield, A.; Zingaro, R. A. Tetrahedron Lett 2004, 45, 5649.

[18] Gao, M. Z.; Wang, B.; Liu, H. B.; Xu, Z. L. Chin J Chem 2002, 20, 85.

[19] Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. Chem Eur J 2006, 12, 63.

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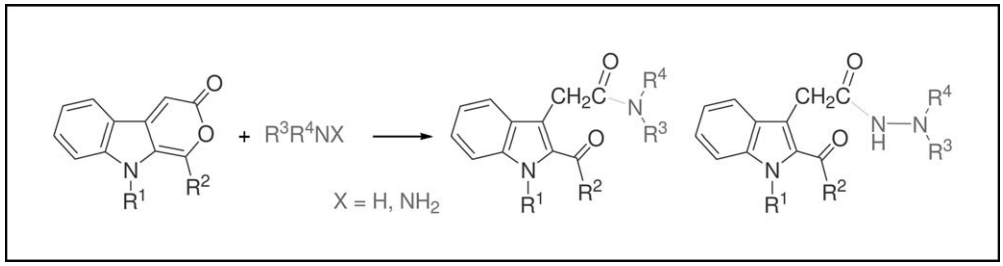


The synthesis of a number of indolylacetamides and indolylacetohydrazides in very good yields from the reaction of pyranoindolones with aliphatic amines and *N*,*N*-dimethylhydrazine, respectively, is described. The reactivity difference with aromatic amines but also with methylhydrazine and aromatic hydrazines is discussed.

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## INTRODUCTION

From the reaction between 1-methylpyranoindolone and aromatic amines in boiling bromobenzene, only Schiff bases **1** were isolated [1], whereas from the same reaction in boiling isopropanol, 2-acetyl-indoloacetic acid amides **2** were formed [2] (Fig. 1).

Concerning the reaction of pyranoindolones with aliphatic amines as nucleophiles only some scattered reports were found in the literature. Thus, by refluxing 1-methylpyranoindolone with ethanolic ammonia (2-acetyl-3-indolyl)acetamide was formed [3], whereas with methanolic dimethyl amine, the corresponding *N*,*N*-dimethylacetamide was isolated in 44% [4]. Recently, the synthesis of the *N*-benzyl-(2-acetyl-3-indolyl)acetamide was reported from the reaction of 1-methylpyranoindolone with benzylamine in boiling DMF, which was eventually cyclized to a β-carbolinone by reflux with triethylamine in acetic acid [5].

In addition, recently, we studied the reaction of pyranoindolones with bisnucleophiles, such as methylhydrazine, whereupon 1,2-diazepinoindoles were isolated [6], and also the reaction with aromatic hydrazines, such as phenyl- and benzoylhydrazine, leading to the synthesis of β-carbolinones [7].

## RESULTS AND DISCUSSION

In the light of the above results and in continuation of our research into the synthesis of compounds containing the indole ring [6,7], we embarked in a more detailed study of the reactions between pyranoindolones and aliphatic amines and also *N*,*N*-dimethylhydrazine.

Since the reaction of pyranoindolone **3a** with dimethylamine in protic solvents (boiling methanol) has been, as mentioned above, reported to give the *N*,*N*-dimethyl-2-acetyl-1*H*-indole-3-acetamide (**5a**) in 44% yield and since such reactions show a strong solvent effect, initially the pyranoindolones **3a**–**3f** were allowed to react with two molar equivalents of dimethylamine in refluxing bromobenzene for 20 min, whereupon the indole-3-acetamides **5a**–**5f** were isolated in much better yields (Table 1, Scheme 1).

The reaction proceeded smoothly also at lower temperatures (refluxing toluene or benzene for 4–6 h) and even at room temperature, though a longer reaction time (12 h) was necessary for the completion of the reaction (Table 1). Next, the reaction was repeated with another secondary amine morpholine, but also with the primary amine benzylamine at room temperature for 12 h, and in all cases, the corresponding indole-3-acetamides 6 and 7 were isolated as the only reaction products in very good yields (Table 1). Indolylacetohydrazides 8 were isolated, when *N*,*N*-dimethylhydrazine was used as nucleophile. Compounds 7 and 8 were isolated as a mixture of two rotamers, as was confirmed from their NMR spectra ranging from 10:1 (major to minor) in compound **7a** to 2:1 in compound **8d** (see Experimental). The molar ratio of the rotamers depends on their relative stability, which is based on the volume and the electronic properties of

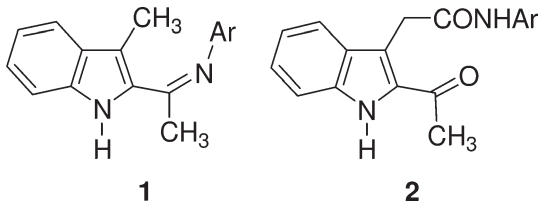


**Figure 1.** Products from the reaction of pyranoindolones with aromatic amines.

the substituents. The formation of the two rotamers is expected due to the high proportion of double bond character of the C—N amide bond resulting thus to hindered free rotation at low and ambient temperatures. As a result, in the case of different *N*-substituents, the NMR spectra of the two rotamers (in products 7 and 8) are practically different. In the case of two identical *N*-substituents (products 5 and 6), these substituents are in different magnetic environment and experience different chemical shifts.

Concerning the reaction mechanism for the formation of products **5–8** attack of the amines to the carbonyl carbon, being the strongest electrophilic center (Scheme 2) is observed in all cases. This result is not in agreement with the results previously obtained with aromatic amines, and also with the bisnucleophiles methylhydrazine, phenyl-, and benzoylhydrazine, where under the same reaction conditions, initial attack to the less electrophilic center, namely C-1 was always observed [1,6,7]. The different behavior can be explained by the enhanced nucleophilicity of the aliphatic amines thus attacking the strongest electrophilic center. All isolated products **5–8** are new, with exception of **5a** and **7a**.

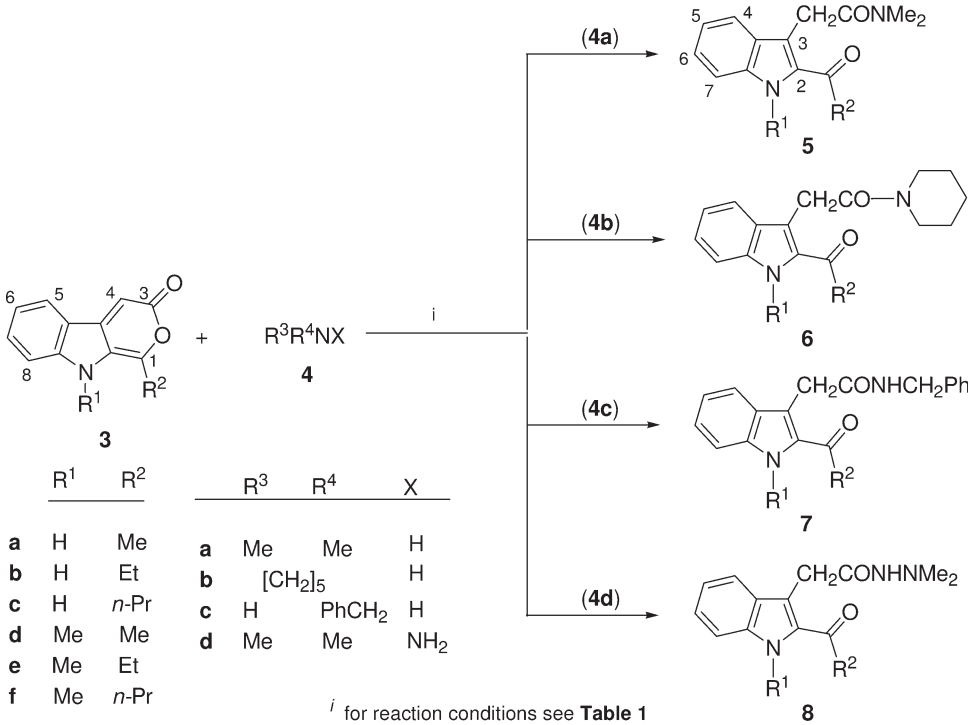
**Table 1**

Reaction conditions and products.

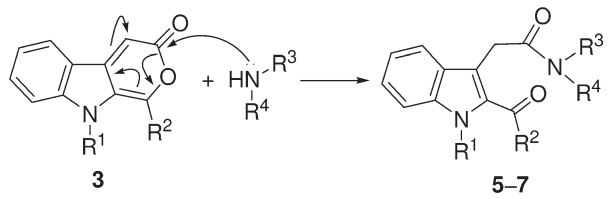
| Entry | Amine | Solvent | Temp (°C) | Time | Product | Yield (%) |
|---|---|---|---|---|---|---|
| **3a** | **4a** | PhBr | 156 | 20 min | **5a** | 69 |
| **3b** | **4a** | PhBr | 156 | 20 min | **5b** | 72 |
| **3c** | **4a** | PhBr | 156 | 20 min | **5c** | 65 |
| **3d** | **4a** | PhBr | 156 | 20 min | **5d** | 71 |
| **3e** | **4a** | PhBr | 156 | 20 min | **5e** | 69 |
| **3f** | **4a** | PhBr | 156 | 20 min | **5f** | 66 |
| **3e** | **4a** | PhMe | 111 | 4 h | **5e** | 60 |
| **3e** | **4a** | $C_6H_6$ | 80 | 6 h | **5e** | 78 |
| **3e** | **4a** | $C_6H_6$ | 25 | 12 h | **5e** | 65 |
| **3a** | **4b** | $C_6H_6$ | 25 | 12 h | **6a** | 71 |
| **3d** | **4b** | $C_6H_6$ | 25 | 12 h | **6d** | 68 |
| **3e** | **4b** | $C_6H_6$ | 25 | 12 h | **6e** | 82 |
| **3a** | **4c** | $C_6H_6$ | 25 | 12 h | **7a** | 61 |
| **3d** | **4c** | $C_6H_6$ | 25 | 12 h | **7d** | 65 |
| **3e** | **4c** | $C_6H_6$ | 25 | 12 h | **7e** | 97 |
| **3b** | **4d** | $C_6H_6$ | 25 | 12 h | **8b** | 53 |
| **3d** | **4d** | $C_6H_6$ | 25 | 12 h | **8d** | 51 |
| **3e** | **4d** | $C_6H_6$ | 25 | 12 h | **8e** | 47 |

The assigned molecular structures of all compounds **5–8** are based on rigorous spectroscopic analysis including IR, NMR ($^1$H, $^{13}$C, COSY, NOESY, HETCOR, and COLOC), MS, and elemental analysis data.

**Scheme 1**



**Scheme 2**



Regarding the structure of the isolated indole-3-acetamides **5–8**, the assignment of **5e** is described. The elemental analysis and mass spectra unequivocally established the reaction of one molecule of pyranoindolone **3e** with one molecule of dimethylamine with the loss of a water molecule, a fact that was also confirmed from the $^{13}C$ NMR spectrum, where 16 different signals were observed. Moreover, in the IR spectra, a carbonyl at 1657 $cm^{-1}$ was identified. In the $^1H$ NMR, the presence of the four indole aromatic protons resonating as a double doublet of doublets at δ 7.60 ($J$ = 8.0 Hz, $J$ = 1.0 Hz, and $J$ = 0.5 Hz), a double doublet of doublets at δ 7.12 ($J$ = 8.0 Hz, $J$ = 7.1 Hz, and $J$ = 1.1 Hz) [8], a multiplet at δ 7.33–7.34 for two protons with their carbons resonating at 120.4, 120.3, 125.3, and 110.2 ppm, respectively, was identified. The 3-position methylene protons appear as a singlet at δ 4.09, whereas in addition to the ethyl group, three *N*-methyl groups appeared at δ 3.00, 3.16, and 3.93 with their carbons resonating at 35.8, 37.4, and 32.6 ppm, respectively. Moreover, in addition to the characteristic COLOC correlations for the indole aromatic ring protons, the indole *N*-methyl group protons gave COLOC correlations with the quaternary carbons at 135.0 (C-2) and at 138.5 ppm (C-7a), whereas the 3-methylene protons correlated with the quaternary carbons at 135.0 (C-2) and at 126.9 (C-3a), 114.9 (C-3), and with the amide carbonyl carbon at 170.0 ppm, as depicted in Figure 2. In **8e**, the amide carbonyl carbon correlates as expected with the amide proton instead of the *N*-methyl protons.

In conclusion, a direct method for the systematic synthesis of a number of indolylacetamides and indolylacetohydrazides has been described. Moreover, the reaction of pyranoindolones with aliphatic amines and *N,N*-dimethylhydrazine does not show a solvent effect and proceeds with initial attack to the strongest electrophilic center, a result which is not in agreement with the results previously obtained with aromatic amines, and also with the bisnucleophiles methylhydrazine, phenyl-, and benzoylhydrazine, where initial attack to the less electrophilic center was always observed.

## EXPERIMENTAL

Melting points were measured on a Büchi apparatus and are uncorrected. Column chromatography was carried out using Fluka silica gel 60. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator $UV_{254}$ purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether–ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80°C. NMR spectra were recorded at room temperature on a Bruker AM 300 spectrometer at 300 MHz for $^1H$ and 75 MHz for $^{13}C$, respectively, using $CDCl_3$ as solvent. In the case of insoluble substances, 5–20% of DMSO-$d_6$ was added, whereas in one case, only DMSO-$d_6$ was used, as indicated. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for $^1H$ and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for $^{13}C$ NMR spectra; in the case of DMSO-$d_6$ solutions, the signal of the solvent at 39.7 ppm was used for calibration. Coupling constants $^nJ$ are reported in Hz. Second order $^1H$ NMR spectra were analyzed by simulation [8]. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers ($cm^{-1}$). Low-resolution electron impact mass spectra were recorded on a 6890N GC/MS system (Agilent Technology); in some cases, LC-MS (ESI, 1.65 eV) spectra were recorded on LCMS-2010 EV system (Shimadzu). Elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS, and NMR spectra ($^1H$, $^{13}C$, DEPT, COSY, NOESY, HETCOR, and COLOC).

**General procedure for the reaction of pyrano[3,4-b]indol-3(9H)-ones (3a–3f) with amines 4.** To a stirred and refluxing solution of pyranoindolone **3** (1.0 mmol) in bromobenzene (15 mL), amine **4a** (1.5 mmol) was added and refluxing and stirring was continued for 20 min. The solvent was distilled off under reduced pressure and the resulting residue was subjected to column chromatography on silica gel using petroleum ether–EtOAc (5:1) as eluent, slowly increasing the polarity up to 3:1 to give 2-(2-acyl-1H-indol-3-yl)-*N,N*-dimethylacetamide **5**.

The reaction conditions given in Table 1 are followed for the preparation of compounds **6–8**.

***From indolopyranones 3 and amine 4a.***

*2-(2-Acetyl-1H-indol-3-yl)-N,N-dimethylacetamide (5a).* 0.168 g, 69% Yield, yellow solid, mp 78–80°C (ethanol); IR (nujol) $\nu_{max}$: 3178, 1663, 1633 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 1.74 (s, 3H, 2-$CH_3$), 3.07 (s, 3H, 3-$NCH_3$), 3.21 (s, 3H, 3-$NCH_3$), 4.07 (s, 2H, 3-$CH_2$), 7.01 (ddd, $J$ = 8.0, 7.2, 1.2 Hz, 1H, 5-H), 7.06 (dd, $J$ = 7.8, 1.2 Hz, 1H, 7-H), 7.16 (dd, $J$ = 7.8, 7.2 Hz, 1H, 6-H), 7.49 (d, $J$ = 8.0 Hz, 1H, 4-H), 9.92 (s br, 1H, 1-H); $^{13}C$ NMR ($CDCl_3$): δ = 27.0 (2-$CH_3$), 30.1 (3-$CH_2$), 36.1 (N—$CH_3$), 37.7 (N—$CH_3$), 110.3 (C-7), 114.9 (C-3), 120.3 (C-5), 120.4 (C-4), 125.4 (C-6), 127.0 (C-3a), 135.1 (C-2), 138.6

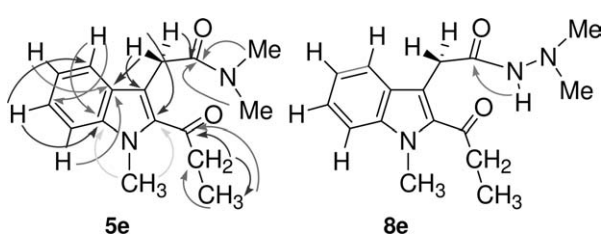


**Figure 2.** Diagnostic COLOC correlations between protons and carbons (via $^2J_{C-H}$ and $^3J_{C-H}$) in compounds **5e** and **8e**.

(C-7a), 171.7 (3-C=O), 191.6 (2-C=O); EIMS: *m*/*z* (%) 244 (45, $M^+$), 199 (35), 172 (100). Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60; N, 11.47%. Found: C, 69.05; H, 6.73; N, 11.35%.

*N,N-dimethyl-2-(2-propionyl-1H-indol-3-yl)acetamide (5b).* 0.186 g, 72% Yield, yellow solid, mp 145–147°C (ethanol); IR (nujol) $\nu_{max}$: 3202, 1670, 1634 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 0.77 (t, *J* = 7.1 Hz, 3H, 2-$CH_2CH_3$), 2.17 (q, *J* = 7.1 Hz, 2H, 2-$CH_2CH_3$), 3.15 (s, 3H, 3-$NCH_3$), 3.28 (s, 3H, 3-$NCH_3$), 4.14 (s, 2H, 3-$CH_2$), 7.07 (dd, *J* = 8.0, 7.2 Hz, 1H, 5-H), 7.13 (d, *J* = 8.0 Hz, 1H, 7-H), 7.22 (dd, *J* = 7.8, 7.2 Hz, 1H, 6-H), 7.56 (d, *J* = 7.8 Hz, 1H, 4-H), 9.98 (s br, 1H, 1-H). $^{13}C$ NMR ($CDCl_3$): δ = 7.3 (2-$CH_2CH_3$), 30.2 (3-$CH_2$), 36.1 (N—$CH_3$), 37.7 (N—$CH_3$), 113.4 (C-7), 115.8 (C-3), 120.0 (C-5), 120.3 (C-4), 125.5 (C-6), 128.2 (C-3a), 132.4 (C-2), 136.4 (C-7a), 171.7 (3-C=O), 194.3 (2-C=O). EIMS: *m*/*z* (%) 258 (35, $M^+$), 213 (45), 186 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84%. Found: C, 69.70; H, 6.93; N, 10.93%.

*2-(2-Butyryl-1H-indol-3-yl)-N,N-dimethylacetamide (5c).* 0.186 g, 65% Yield, yellow solid, mp 153–155°C (ethanol); IR (nujol) $\nu_{max}$: 3321, 3178, 1669, 1634 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3H, 2-$CH_2CH_2CH_3$), 1.39 (sextet, *J* = 7.4 Hz, 2H, 2-$CH_2CH_2CH_3$), 2.20 (t, *J* = 7.4 Hz, 2H, 2-$CH_2CH_2CH_3$), 3.13 (s, 3H, $CONCH_3$), 3.27 (s, 3H, $CONCH_3$), 4.15 (s, 2H, 3-$CH_2$), 7.06 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H, 5-H), 7.10–7.24 (m, 2H, 6-H, 7-H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H, 4-H), 9.82 (s, 1H, 1-H); $^{13}C$ NMR ($CDCl_3$): δ = 13.7 (2-$CH_2CH_2CH_3$), 17.0 (2-$CH_2CH_2CH_3$), 30.3 (3-$CH_2$), 36.1 ($CONCH_3$), 37.7 ($CONCH_3$), 41.4 (2-$CH_2CH_2CH_3$), 113.2 (C-7), 115.9 (C-3), 120.1 (C-5), 120.3 (C-4), 125.6 (C-6), 126.9 (C-3a), 132.3 (C-2), 136.3 (C-7a), 171.5 (3-CO), 193.8 (2-CO); EIMS: *m*/*z* (%) 286 ($M^+$, 37), 241 (25), 214 (100). Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.37; H, 7.76; N, 9.65%.

*2-(2-Acetyl-1-methyl-1H-indol-3-yl)-N,N-dimethylacetamide (5d).* 0.183 g, 71% Yield, yellow solid, mp 111–113°C (ethanol); IR (nujol) $\nu_{max}$: 1654, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 2.58 (s, 3H, 2-$CH_3$), 2.98 (s, 3H, $CONCH_3$), 3.15 (s, 3H, $CONCH_3$), 3.93 (s, 3H, 1-$CH_3$), 4.07 (s, 2H, 3-$CH_2$), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 5-H), 7.31–7.37 (m, 2H, 6-H, 7-H), 7.60 (dd, *J* = 8.0, 0.9 Hz, 1H, 4-H) [8]; $^{13}C$ NMR ($CDCl_3$): δ = 30.9 (3-$CH_2$ and 2-$CH_3$), 32.6 (1-$CH_3$), 35.9 ($CONCH_3$), 37.5 ($CONCH_3$), 110.4 (C-7), 116.0 (C-3), 120.4 (C-5), 120.6 (C-4), 125.8 (C-6), 127.0 (C-3a), 135.1 (C-2), 138.8 (C-7a), 170.0 (3-CO), 192.8 (2-CO); EIMS: *m*/*z* (%) = 258 (45, $M^+$), 213 (15), 186 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.31): C, 69.74; H, 7.02; N, 10.84%. Found: C, 70.14; H, 6.85; N, 10.45%.

*N,N-dimethyl-2-(2-propionyl-1-methyl-1H-indol-3-yl)-acetamide (5e).* 0.188 g, 69% Yield, yellow solid, mp 99–100°C (ethanol); IR (nujol) $\nu_{max}$: 1657 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3H, 2-$CH_2CH_3$), 2.91 (q, *J* = 7.2 Hz, 2H, 2-$CH_2CH_3$), 3.00 (s, 3H, $CONCH_3$), 3.16 (s, 3H, $CONCH_3$), 3.93 (s, 3H, 1-$CH_3$), 4.09 (s, 2H, 3-$CH_2$), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 5-H), 7.328 (ddd, *J* = 7.9, 1.1, 0.5 Hz, 1H, 7-H), 7.332 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, 6-H), 7.60 (ddd, *J* = 8.0, 1.0 Hz, 0.5 Hz, 1H, 4-H) [8]; $^{13}C$ NMR ($CDCl_3$): δ = 8.3 (2-$CH_2CH_3$), 30.8 (3-$CH_2$), 32.6 (1-$CH_3$), 35.7 (2-$CH_2CH_3$), 35.8 ($CONCH_3$), 37.4 ($CONCH_3$), 110.2 (C-7), 114.9 (C-3), 120.3 (C-5), 120.4 (C-4), 125.3 (C-6), 126.9 (C-3a), 135.0 (C-2), 138.5 (C-7a), 170.0 (3-CO), 196.4 (2-CO); EIMS: *m*/*z* (%) = 272 (42, $M^+$), 200 (100). Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29%. Found: C, 70.47; H, 7.33; N, 9.95%.

*2-(2-Butyryl-1-methyl-1H-indol-3-yl)-N,N-dimethylacetamide (5f).* 0.189 g, 66% Yield, yellow solid, mp 109–111°C (ethanol); IR (nujol) $\nu_{max}$: 1654, 1637 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3H, 2-$CH_2CH_2CH_3$), 1.77 (sextet, *J* = 7.3 Hz, 2H, 2-$CH_2CH_2CH_3$), 2.85 (t, *J* = 7.3 Hz, 2H, 2-$CH_2CH_2CH_3$), 2.98 (s, 3H, $CONCH_3$), 3.13 (s, 3H, $CONCH_3$), 3.90 (s, 3H, 1-$CH_3$), 4.06 (s, 2H, 3-$CH_2$), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 5-H), 7.31–7.35 (m, 2H, 6-H, 7-H), 7.62 (dd, *J* = 8.0, 1.0 Hz, 1H, 4-H); $^{13}C$ NMR ($CDCl_3$): δ = 13.9 (2-$CH_2CH_2CH_3$), 17.9 (2-$CH_2CH_2CH_3$), 31.0 (3-$CH_2$), 32.6 (1-$CH_3$), 35.9 ($CONCH_3$), 37.5 ($CONCH_3$), 44.8 (2-$CH_2CH_2CH_3$), 110.3 (C-7), 114.9 (C-3), 120.4 (C-5), 120.6 (C-4), 125.4 (C-6), 127.0 (C-3a), 135.3 (C-2), 138.6 (C-7a), 170.1 (3-CO), 196.2 (2-CO); EIMS: *m*/*z* (%) = 286 ($M^+$, 37), 241 (25), 214 (100). Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.57; H, 7.76; N, 9.55%.

***From indolopyranones 1 and amine 4b.***

*2-Acetyl-3-(2-oxo-2-piperidin-1-ylethyl)-1H-indole (6a).* 0.202 g, 71% Yield, yellow solid, mp 190–191°C (ethanol); IR (nujol) $\nu_{max}$: 3174, 1663, 1623 $cm^{-1}$; $^1H$ NMR: δ = 1.60–1.70 (m, 2H, 4′-H), 1.70–1.75 (m, 4H, 3′-H, 5′-H), 1.92 (s, 3H, 2-$CH_3$), 3.60–3.70 (m, 2H, 2′-H), 3.70–3.80 (m, 2H, 6′-H), 4.15 (s, 2H, 3-$CH_2$), 7.08 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H, 5-H), 7.15 (dd, *J* = 8.0, 1.2 Hz, 1H, 7-H), 7.23 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, 6-H), 7.57 (dd, *J* = 8.1, 1.0 Hz, 1H, 4-H), 10.09 (s br, 1H, 1-H); $^{13}C$ NMR ($CDCl_3$): δ = 24.7 (C-4′), 25.9 (C-3′), 26.4 (C-5′), 27.3 (2-$CH_3$), 30.0 (3-$CH_2$), 43.5 (C-6′), 47.1 (C-2′), 113.4 (C-7), 116.4 (C-3), 120.2 (C-4), 120.4 (C-5), 125.7 (C-6), 128.2 (C-3a), 132.6 (C-2), 136.4 (C-7a), 169.6 (3-C=O), 191.4 (2-C=O); EIMS: *m*/*z* (%) 284 (48, $M^+$), 199 (100), 172 (80), 143 (60), 130 (50), 112 (98). Anal. Calcd for $C_{17}H_{20}N_2O_2$ (284.35): C, 71.81; H, 7.09; N, 9.85%. Found: C, 71.75; H, 7.22; N, 9.82%.

*2-Acetyl-1-methyl-3-(2-oxo-2-piperidin-1-ylethyl)-1H-indole (6d).* 0.203 g, 68% Yield, yellow solid, mp 138–139°C (ethanol); IR (nujol) $\nu_{max}$: 1657, 1637 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 1.40–1.55 (m, 4H, 3′-H, 5′-H), 1.55–1.70 (m, 2H, 4′-H), 2.54 (s, 3H, 2-$CH_3$), 3.47–3.60 (m, 4H, 2′-H, 6′-H), 3.89 (s, 3H, 1-$CH_3$), 3.98 (s, 2H, 3-$CH_2$), 7.10 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H, 5-H), 7.30 (ddd, *J* = 8.1, 1.0, 0.8 Hz, 1H, 7-H), 7.32 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, 6-H), 7.57 (ddd, *J* = 8.2, 1.0, 0.8 Hz, 1H, 4-H); $^{13}C$ NMR ($CDCl_3$): δ = 24.3 (C-4′), 25.5 (C-3′), 26.3 (C-5′), 30.6 (3-$CH_2$), 30.7 (2-$CH_3$), 32.4 (1-$CH_3$), 43.0 (C-6′), 46.6 (C-2′), 110.1 (C-7), 116.2 (C-3), 120.1 (C-4), 120.4 (C-5), 125.5 (C-6), 126.8 (C-3a), 134.6 (C-2), 138.5 (C-7a), 167.9 (3-C=O), 192.5 (2-C=O); LCMS: *m*/*z* (%) 321 [100, $(M + Na)^+$], 298 ($M^+$, 20), 257 (5). Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39%. Found: C, 72.84; H, 7.22; N, 9.28%.

*1-Methyl-3-(2-oxo-2-piperidin-1-ylethyl)-2-propionyl-1H-indole (6e).* 0.256 g, 82% Yield, yellow solid, mp 111–113°C (ethanol); IR (nujol) $\nu_{max}$: 1655, 1635 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3H, 2-$CH_2CH_3$), 1.48–1.60 (m, 4H, 3′-H, 5′-H), 1.60–1.70 (m, 2H, 4′-H), 2.92 (q, *J* = 7.2 Hz, 2H, 2-$CH_2CH_3$), 3.52–3.63 (m, 4H, 2′-H, 6′-H), 3.94 (s, 3H, 1-$CH_3$), 4.10 (s, 2H, 3-$CH_2$), 7.13 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, 5-H),

7.35 (dd, $J$ = 8.0, 1.0 Hz, 1H, 7-H), 7.35 (ddd, $J$ = 8.0, 7.0, 1.0 Hz, 1H, 6-H), 7.63 (dd, $J$ = 8.1, 1.0 Hz, 1H, 4-H); $^{13}$C NMR: δ = 8.4 (2-$CH_2CH_3$), 24.6 (C-4′), 25.7 (C-3′), 26.5 (C-5′), 31.1 (3-$CH_2$), 32.7 (1-$CH_3$), 36.0 (2-$CH_2CH_3$), 43.3 (C-6′), 47.0 (C-2′), 110.3 (C-7), 115.2 (C-3), 120.4 (C-4), 120.6 (C-5), 125.5 (C-6), 127.1 (C-3a), 135.1 (C-2), 138.7 (C-7a), 168.4 (3-C=O), 196.6 (2-C=O); LCMS: *m/z* (%) 335 [100, (M + Na)$^+$], 312 (M$^+$, 20), 257 (5). Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05 H, 7.74; N, 8.97%. Found: C, 73.24; H, 7.37; N, 8.73%.

***From indolopyranones 1 and hydrazine 4c.***

*2-(2-Acetyl-1H-indol-3-yl)-N-benzylacetamide (7a).* 0.187 g, 61% Yield, yellow solid, mp 148–149°C (ethanol). IR (nujol) $\nu_{max}$: 3324, 1650, 1638 cm$^{-1}$. Because of amide partial double bond, two rotamers in a ratio of 10:1 were observed in the NMR spectra of compound **7a**. Major rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.61 (s, 3H, 2-$CH_3$), 4.08 (s, 2H, 3-$CH_2$), 4.35 (d, $J$ = 5.0 Hz, 2H, N—$CH_2$), 7.05–7.45 (m, 9H, 5-H, 6-H, 7-H, CONH and $C_6H_5$), 7.77 (d, $J$ = 8.2 Hz, 1H, 4-H), 10.95 (br s, 1H, 1-H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 28.1 (3-$CH_2$), 33.2 (2-$CH_3$), 43.0 (N—$CH_2$), 112.4 (C-7), 115.8 (C-3), 120.4 (C-5), 120.7 (C-4), 126.0 (C-6), 126.8 (C-4′), 127.0 (C-2′, C-6′), 127.6 (C-3a), 128.2 (C-3′, C-5′), 132.2 (C-2), 136.3 (C-7a), 138.2 (C-1′), 170.6 (3-C=O), 191.7 (2-C=O). Minor rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.62 (s, 3H, 2-$CH_3$), 4.08 (s, 2H, 3-$CH_2$), 4.35 (d, $J$ = 5.0 Hz, 2H, N—$CH_2$), 7.05–7.45 (m, 9H, 5-H, 6-H, 7-H, CONH and $C_6H_5$), 7.65 (d, $J$ = 7.8 Hz, 1H, 4-H), 10.50 (br s, 1H, 1-H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 28.2 (3-$CH_2$), 32.3 (2-$CH_3$), 43.0 (N—$CH_2$), 112.1 (C-7), 116.3 (C-3), 119.9 (C-5), 120.8 (C-4), 125.7 (C-6), 126.8 (C-4′), 128.0 (C-2′, C-6′), 127.6 (C-3a), 128.4 (C-3′, C-5′), 132.5 (C-2), 136.0 (C-7a), 138.2 (C-1′), 174.2 (3-C=O), 191.2 (2-C=O); GCMS: *m/z* (%) 306 (M$^+$, 5), 173 (80), 91 (100). Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.36): C, 74.49 H, 5.92; N, 9.14%. Found: C, 74.56; H, 5.83; N, 9.17%.

*2-(2-Acetyl-1-methyl-1H-indol-3-yl)-N-benzylacetamide (7d).* 0.208 g, 65% Yield, yellow solid, mp 129–131°C (ethanol); IR (nujol) $\nu_{max}$: 3285, 1652, 1637 cm$^{-1}$. Beacuse of amide partial double bond, two rotamers in a ratio of 3.5:1 were observed in the NMR spectra of compound **7d**. Major rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.62 (s, 3H, 2-$CH_3$), 3.96 (s, 3H, 1-$CH_3$), 4.04 (s, 2H, 3-$CH_2$), 4.38 (d, $J$ = 5.9 Hz, 2H, N—$CH_2$), 6.34 (br t, 1H, CONH), 7.05–7.45 (m, 8H, 5-H, 6-H, 7-H and $C_6H_5$), 7.74 (d, $J$ = 8.5 Hz, 1H, 4-H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 29.7 (3-$CH_2$), 31.1 (2-$CH_3$), 34.1 (1-$CH_3$), 43.5 (N—$CH_2$), 110.5 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.5 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.4 (C-2′, C-6′), 128.6 (C-3′, C-5′), 131.8 (C-2), 137.5 (C-7a), 138.9 (C-1′), 170.2 (3-C=O), 192.6 (2-C=O). Minor rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.62 (s, 3H, 2-$CH_3$), 3.85 (s, 3H, 1-$CH_3$), 3.90 (s, 2H, 3-$CH_2$), 4.32 (d, $J$ = 5.9 Hz, 2H, N—$CH_2$), 7.05–7.45 (m, 7H, 5-H, 7-H and $C_6H_5$), 7.47 (ddd, $J$ = 8.0, 8.0, 1.0 Hz, 1H, 6-H), 7.78 (d, $J$ = 7.8 Hz, 1H, 4-H), 8.34 (br t, 1H, CONH); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 31.3 (2-$CH_3$), 32.9 (3-$CH_2$), 33.8 (1-$CH_3$), 43.3 (N—$CH_2$), 109.2 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.6 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.5 (C-2′, C-6′), 128.7 (C-3′, C-5′), 132.2 (C-2), 136.4 (C-7a), 138.2 (C-1′), 172.4 (3-C=O), 192.5 (2-C=O); LCMS: *m/z* (%) 343 [100, (M + Na)$^+$]. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.39): C, 74.98 H, 6.29; N, 8.74%. Found: C, 74.84; H, 6.18; N, 8.73%.

*2-(1-Methyl-2-propionyl-1H-indol-3-yl)-N-benzylacetamide (7e).* 0.324 g, 97% Yield, yellow solid, mp 149–151°C (ethanol); IR (nujol) $\nu_{max}$: 3285, 1652, 1637 cm$^{-1}$. Beacuse of amide partial double bond, two rotamers in a ratio of 3.5:1 were observed in the NMR spectra of compound **7e**. Major rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.62 (s, 3H, 2-$CH_3$), 3.96 (s, 3H, 1-$CH_3$), 4.04 (s, 2H, 3-$CH_2$), 4.38 (d, $J$ = 5.9 Hz, 2H, N—$CH_2$), 6.34 (br t, 1H, CONH), 7.05–7.45 (m, 8H, 5-H, 6-H, 7-H and $C_6H_5$), 7.74 (d, $J$ = 8.5 Hz, 1H, 4-H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 29.7 (3-$CH_2$), 31.1 (2-$CH_3$), 34.1 (1-$CH_3$), 43.5 (N—$CH_2$), 110.5 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.5 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.4 (C-2′, C-6′), 128.6 (C-3′, C-5′), 136.4 (C-2), 138.9 (C-7a), 140.6 (C-1′), 170.2 (3-C=O), 192.6 (2-C=O). Minor rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.62 (s, 3H, 2-$CH_3$), 3.85 (s, 3H, 1-$CH_3$), 3.90 (s, 2H, 3-$CH_2$), 4.32 (d, $J$ = 5.9 Hz, 2H, N—$CH_2$), 7.05–7.45 (m, 7H, 5-H, 7-H, and $C_6H_5$), 7.47 (ddd, $J$ = 8.0, 8.0, 1.0 Hz, 1H, 6-H), 7.78 (d, $J$ = 7.8 Hz, 1H, 4-H), 8.34 (br t, 1H, CONH); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 31.3 (2-$CH_3$), 32.9 (3-$CH_2$), 33.8 (1-$CH_3$), 43.3 (N—$CH_2$), 109.2 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.6 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.5 (C-2′, C-6′), 128.7 (C-3′, C-5′), 137.5 (C-2), 138.2 (C-7a), 143.5 (C-1′), 172.4 (3-C=O), 192.5 (2-C=O); GCMS: *m/z* (%) 334 (30, M$^+$), 277 (5), 227 (10), 202 (90), 200 (100), 172 (75), 144 (42). Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.41): C, 75.42; H, 6.63; N, 8.38%. Found: C, 75.34; H, 6.55; N, 8.43%.

***From indolopyranones 1 and hydrazine 4d.***

*N′,N′-dimethyl-2-(2-propionyl-1H-indol-3-yl)acetohydrazide (8b).* 0.145 g, 53% Yield, yellow solid, mp 216–217°C (ethanol); IR (nujol) $\nu_{max}$: 3354, 3194, 1669, 1651, 1644 cm$^{-1}$. Beacuse of amide partial double bond, two rotamers in a ratio of 7:3 were observed in the NMR spectra of compound **8b**. Major rotamer: $^1$H NMR: δ = 1.18 (t, $J$ = 7.1 Hz, 3H, 2-$CH_2CH_3$), 2.49 (s, 6H, N($CH_3$)$_2$), 2.85 (q, $J$ = 7.1 Hz, 2H, 2-$CH_2CH_3$), 3.97 (s, 2H, 3-$CH_2$), 3.97 (s, 3H, 1-$CH_3$), 7.01 (brs, 1H, CONH), 7.13–7.18 (m, 1H, 5-H), 7.26–7.35 (m, 2H, 6-H and 7-H), 7.74 (d, $J$ = 8.3 Hz, 1H, 4-H), 9.51 (br s, 1H, 1-H). Minor rotamer: $^1$H NMR: δ = 1.13 (t, $J$ = 7.1 Hz, 3H, 2-$CH_2CH_3$), 2.61 (s, 6H, N($CH_3$)$_2$), 2.87 (q, $J$ = 7.2 Hz, 2H, 2-$CH_2CH_3$), 4.34 (s, 2H, 3-$CH_2$), 6.29 (br s, 1H, CONH), 7.08–7.12 (m, 1H, 5-H), 7.26–7.35 (m, 2H, 6-H and 7-H), 7.68 (d, $J$ = 8.0 Hz, 1H, 4-H), 9.34 (br s, 1H, 1-H); LCMS: *m/z* (%) = 296 [100, (M + Na)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01; N, 15.37%. Found: C, 65.97; H, 7.13; N, 15.45%.

*N′,N′-dimethyl-2-(1-methyl-2-acetyl-1H-indol-3-yl)acetohydrazide (8d).* 0.139 g, 51% Yield, yellow solid, mp 176–177°C (ethanol); IR (nujol) $\nu_{max}$: 3193, 1657, 1640 cm$^{-1}$. Because of amide partial double bond, two rotamers in a ratio of 2:1 were observed in the NMR spectra of compound **8d**. Major rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.40 (s, 6H, N($CH_3$)$_2$), 2.68 (s, 3H, 2-$CH_3$), 3.92 (s, 2H, 3-$CH_2$), 4.00 (s, 3H, 1-$CH_3$), 7.05 (brs, 1H, NH), 7.21 (ddd, $J$ = 8.0, 8.0, 1.2 Hz, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.74 (d, $J$ = 8.1 Hz, 1H, 4-H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 29.4 (3-$CH_2$), 30.9 (2-$CH_3$), 32.6 (1-$CH_3$), 47.1 (N($CH_3$)$_2$), 110.3 (C-7), 115.4 (C-3), 120.6 (C-5), 120.8 (C-4), 126.2 (C-6), 126.5 (C-3a), 134.9 (C-2), 138.6 (C-7a), 167.6 (3-C=O), 192.7 (2-C=O). Minor rotamer: $^1$H NMR ($CDCl_3$ + DMSO-$d_6$): δ = 2.49 (s, 6H, N($CH_3$)$_2$), 2.57 (s, 3H, 2-$CH_3$), 3.96 (s, 3H, 1-$CH_3$), 4.29 (s,

2H, 3-$CH_2$), 6.56 (br s, 1H, NH), 7.15 (ddd, $J$ = 8.0, 8.0, 1.2 Hz, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.71 (d, $J$ = 8.1 Hz, 1H, 4-H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): δ = 8.4 (2-$CH_2CH_3$), 30.7 (3-$CH_2$), 32.4 (2-$CH_3$), 32.7 (1-$CH_3$), 48.4 ($N(CH_3)_2$), 110.1 (C-7), 115.5 (C-3), 120.1 (C-5), 120.7 (C-4), 125.5 (C-6), 127.2 (C-3a), 134.7 (C-2), 138.5 (C-7a), 172.6 (3-C=O), 192.6 (2-C=O); LCMS: $m/z$ (%) = 296 [100, $(M + Na)^+$]. Anal. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01; N, 15.37%. Found: C, 65.86; H, 7.15; N, 15.30%.

*N′,N′-dimethyl-2-(1-methyl-2-propionyl-1H-indol-3-yl)acetohydrazide (8e).* 0.135 g, 47% Yield, yellow solid, mp 186–188°C (ethanol); IR (nujol) $\nu_{max}$: 3195, 1661, 1645 $cm^{-1}$. Beacuse of amide partial double bond, two rotamers in a ratio of 7:3 were observed in the NMR spectra of compound **8e**. Major rotamer: $^1$H NMR: δ = 1.25 (t, $J$ = 7.2 Hz, 3H, 2-$CH_2CH_3$), 2.47 (s, 6H, $N(CH_3)_2$), 2.95 (q, $J$ = 7.2 Hz, 2H, 2-$CH_2CH_3$), 3.93 (s, 2H, 3-$CH_2$), 3.98 (s, 3H, 1-$CH_3$), 6.80 (brs, 1H, NH), 7.22 (ddd, $J$ = 8.0, 8.0, 1.0 Hz, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.72 (dd, $J$ = 8.1, 1.0 Hz, 1H, 4-H); $^{13}$C NMR: δ = 8.4 (2-$CH_2CH_3$), 29.7 (3-$CH_2$), 33.1 (1-$CH_3$), 36.2 (2-$CH_2CH_3$), 47.3 ($N(CH_3)_2$), 110.5 (C-7), 114.5 (C-3), 120.7 (C-5), 121.1 (C-4), 126.2 (C-6), 126.7 (C-3a), 135.3 (C-2), 138.8 (C-7a), 167.8 (3-C=O), 196.55 (2-C=O). Minor rotamer: $^1$H NMR: δ = 1.24 (t, $J$ = 7.2 Hz, 3H, 2-$CH_2CH_3$), 2.55 (s, 6H, $N(CH_3)_2$), 3.02 (q, $J$ = 7.2 Hz, 2H, 2-$CH_2CH_3$), 3.91 (s, 3H, 1-$CH_3$), 4.27 (s, 2H, 3-$CH_2$), 6.16 (brs, 1H, NH), 7.12–7.17 (m, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.70 (dd, $J$ = 8.1, 1.0 Hz, 1H, 4-H); $^{13}$C NMR: δ = 8.4 (2-$CH_2CH_3$), 32.5 (3-$CH_2$), 32.9 (2-$CH_2CH_3$), 35.8 (1-$CH_3$), 48.7 ($N(CH_3)_2$), 110.3 (C-7), 114.3 (C-3), 120.3 (C-5), 120.8 (C-4), 125.4 (C-6), 127.2 (C-3a), 135.1 (C-2), 138.6 (C-7a), 172.8 (3-C=O), 196.62 (2-C=O); EIMS: $m/z$ (%) = 287 (42, $M^+$), 200 (100). Anal. Calcd for $C_{16}H_{21}N_3O_2$ (287.36): C, 66.88; H, 7.37; N, 14.62%. Found: C, 66.76; H, 7.23; N, 14.68%.

## REFERENCES AND NOTES

[1] Doitsides, N.; Mentzafos, D.; Mitkidou, S.; Terzis, A.; Stephanidou-Stephanatou, J. Synth Commun 1995, 25, 1411.

[2] Tolkunov, S. V.; Tolkunov, V. S.; Dulenko, V. I. Chem Heterocycl Compd 2004, 40, 481.

[3] Plieninger, H.; Müller, W.; Weinerth, K. Chem Ber 1964, 97, 667.

[4] Modi, S. P.; Archer, S. J Org Chem 1989, 54, 5189.

[5] Tolkunov, V. S.; Vysotsky, Y. B.; Gorban, O. A.; Shishkina, S. V.; Shishkin, O. V.; Dulenko, V. I. Chem Heterocycl Compd 2005, 41, 515.

[6] Hatzimimikou, D.; Livadiotou, D.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. Synlett 2008, 1773.

[7] Livadiotou, D.; Hatzimimikou, D.; Neochoritis, C.; Terzidis, M.; Tsoleridis, C.; Stephanidou-Stephanatou, J. Synthesis 2008, 3273.

[8] The multiplicities and chemical shifts of the aromatic protons have been confirmed after simulation with program SpinWorks, version 2.5, Available at: ftp://davinci.chem.umanitoba.ca/pub/marat/SpinWorks/.

# Syntheses of Potentially Bioactive [1,2,4]Oxadiazolo [5,4-*d*]benzothiazepines by 1,3-Dipolar Cycloaddition

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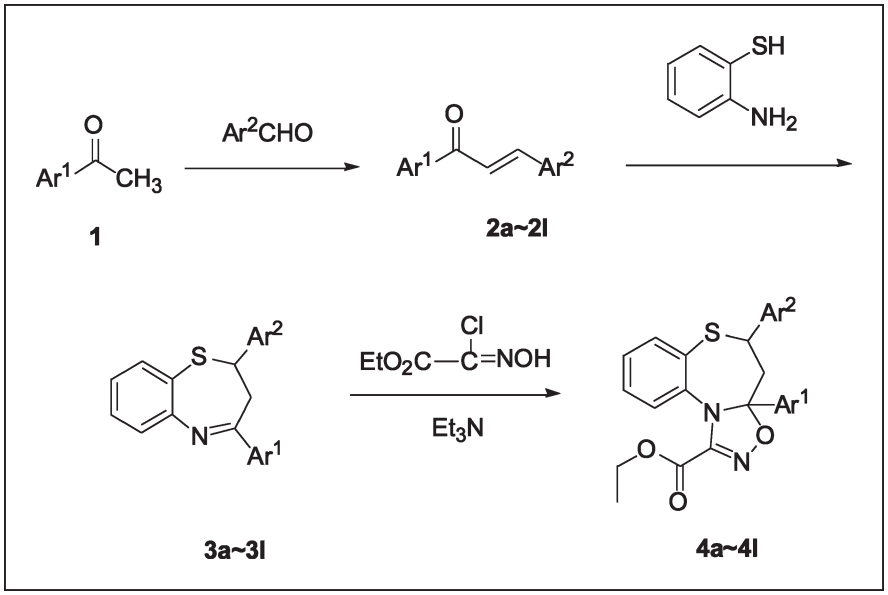


The chalcones, **2a-2l** reacted with *o*-aminobenzenthiol to give a series of 1,5-benzothiazepines, **3a-3l**. The [3+2] 1, 3-dipolar cycloaddition reactions of **3a-3l** with ethyl chlorooximidoacetate in the presence of $Et_3N$ afforded the target compounds, **4a-4l** possessing an additional 1,2,4-oxadiazole ring fused to the heptaatomic nucleus. The structures have been elucidated by spectral methods and X-ray crystallographic analysis.

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## INTRODUCTION

The Synthesis of benzothiazepine derivatives has attracted considerable attention of organic and medicinal chemists due to their broad spectrum of biological activity. The 1,5-benzothiazepine derivatives have been used as cardiovascular modulators [1], coronary vasodilators [2], elastase [3]/ACE inhibitors [4], anti-HIV [5], antihypertensives [6], anti-depressants [7], and anti-bacterial activity [8]. In recent years, a large number of 1,5-benzothiazepine derivatives containing anticancer activity [9,10], hemodynamic effects [11], antiulcer activity [12,13], and spasmolytic activities [14–18] have also been reported. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which include quetiapine fumarate and thiazesim [19–21].

Oxadiazoles are naturally occurring five-membered heterocycles with utility in synthetic and medicinal chemistry. They serve as the core components of a large number of substances that possess a wide range of interesting biological activities. The 1,2,4-oxadiazole scaffolds are associated with significant biological activities, such as anti-hypertensive [22], antikinetoplastid [23], antimicrobial and anti-inflammatory [24].

Recent work has demonstrated the interest to fix an additional heterocycle on 1,5-benzothiazepines. Pharmaceutical properties of such compounds are magnified when the heterocycle is bound to the heptatomic nucleus [25,26]. Keeping these observations in mind and in continuation of our interest to prepare a seven-membered ring [27,28], we report herein the reaction of 1,5-benzothiazepines **3a-3l** with ethyl chlorooximidoacetate through 1,3-dipolar cycloaddition to afford a new series of tricyclic system, [1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine derivatives, which might have useful biological and therapeutic activities (Table 1).

**Table 1**

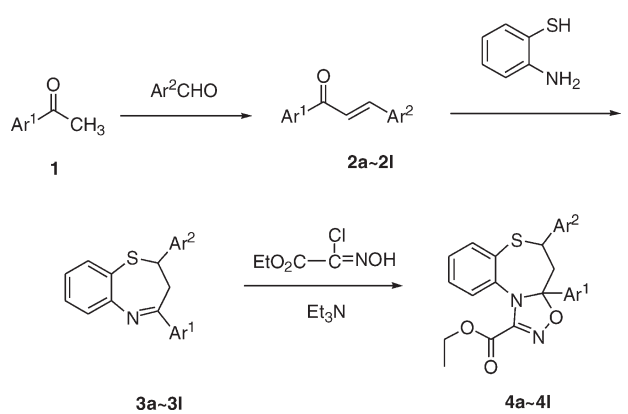
Physical and analytical data of compounds **4**.

| Comp. | $Ar^1$ | $Ar^2$ | mp(°C) | Yield % | Molecular formula | Analysis %(Calcd./found) C | H | *N* |
|---|---|---|---|---|---|---|---|---|
| **4a** | Ph | Ph | 177–178 | 34 | $C_{25}H_{22}N_2O_3S$ | 69.75 | 5.15 | 6.51 |
| | | | | | | 69.73 | 5.12 | 6.54 |
| **4b** | Ph | *p*-$ClC_6H_4$ | 174–175 | 35 | $C_{25}H_{21}ClN_2O_3S$ | 64.58 | 4.55 | 6.02 |
| | | | | | | 64.57 | 4.58 | 5.99 |
| **4c** | Ph | *p*-$CH_3OC_6H_4$ | 132–133 | 35 | $C_{26}H_{24}N_2O_4S$ | 67.81 | 5.25 | 6.08 |
| | | | | | | 67.83 | 5.24 | 6.07 |
| **4d** | Ph | *p*-$NO_2C_6H_4$ | 195–196 | 33 | $C_{25}H_{21}N_3O_5S$ | 63.15 | 4.45 | 8.84 |
| | | | | | | 63.12 | 4.46 | 8.83 |
| **4e** | *p*-$ClC_6H_4$ | Ph | 193–194 | 31 | $C_{25}H_{21}ClN_2O_3S$ | 64.58 | 4.55 | 6.02 |
| | | | | | | 64.59 | 4.53 | 6.01 |
| **4f** | *p*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | 165–166 | 30 | $C_{25}H_{20}Cl_2N_2O_3S$ | 60.12 | 4.04 | 5.61 |
| | | | | | | 60.14 | 4.02 | 5.63 |
| **4g** | *p*-$ClC_6H_4$ | *p*-$CH_3OC_6H_4$ | 143–144 | 23 | $C_{26}H_{23}ClN_2O_4S$ | 63.09 | 4.68 | 5.66 |
| | | | | | | 63.12 | 4.67 | 4.63 |
| **4h** | *p*-$ClC_6H_4$ | *p*-$NO_2C_6H_4$ | 232–233 | 25 | $C_{25}H_{20}ClN_3O_5S$ | 58.88 | 3.95 | 8.24 |
| | | | | | | 58.85 | 3.96 | 8.25 |
| **4i** | *p*-$CH_3OC_6H_4$ | Ph | 130–131 | 26 | $C_{26}H_{24}N_2O_4S$ | 67.81 | 5.25 | 6.08 |
| | | | | | | 67.80 | 5.28 | 6.04 |
| **4j** | *p*-$CH_3OC_6H_4$ | *p*-$ClC_6H_4$ | 213–214 | 32 | $C_{26}H_{23}ClN_2O_4S$ | 63.09 | 4.68 | 5.66 |
| | | | | | | 63.13 | 4.66 | 5.65 |
| **4k** | *p*-$CH_3OC_6H_4$ | *p*-$CH_3OC_6H_4$ | 173–174 | 36 | $C_{27}H_{26}N_2O_5S$ | 66.10 | 5.34 | 5.71 |
| | | | | | | 66.08 | 5.35 | 5.74 |
| **4l** | *p*-$CH_3OC_6H_4$ | *p*-$NO_2C_6H_4$ | 213–214 | 20 | $C_{26}H_{23}N_3O_6S$ | 61.77 | 4.59 | 8.31 |
| | | | | | | 61.74 | 4.60 | 8.34 |

## RESULTS AND DISCUSSION

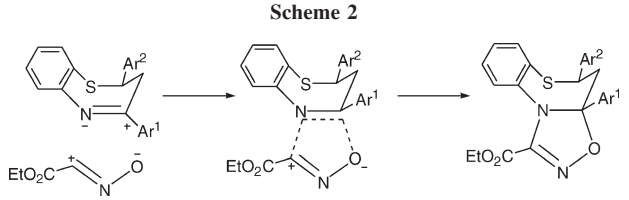
The title compounds were prepared according to the Scheme 1. The chalcones, **2a-2l** were readily prepared by condensation of aryl aldehydes with substituted acetophenones [29]. **2a-2l** were subsequently reacted with *o*-aminobenzenthiol in MeOH/AcOH to give the desired 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines, **3a-3l**. The formation of **3** may proceeded via two steps [30,31]. In the first step, nucleophilic attack by the sulfhydryl electrons of 2-aminobenzenethiol takes place on the activated β-carbon atom of the α, β-unsaturated carbonyl compounds to give Michael-adduct type intermediates, which simultaneously undergo dehydrative cyclization to give final products in the second step. Finally, the 1, 3-dipolar cycloaddition reaction between 1,5-benzothiazepine derivatives, **3a-3l** and nitrile oxide, generated *in situ* from ethyl chlorooximidoacetate and triethylamine, leads to the target compounds; 1,2,4-oxadiazolo[5,4-*d*]-1,5-benzothiazepine derivatives, **4a-4l** (Scheme 1) in which an oxadiazole ring is fused at the ''d'' edge of the heptatomic nucleus.

**Scheme 1**




The structures of title compounds have been characterized by IR, $^1$H-NMR, mass, and elemental analysis. The infrared spectra of these compounds show C=O absorption bands around 1740 $cm^{-1}$. In the nuclear magnetic resonance spectra, title compounds exhibited multiplet between δ 8.15–6.55ppm due to the aromatic protons, the signal for ethoxycarbonyl $CH_2$ and $CH_3$ appeared at δ 4.30–4.38 ppm and δ 1.29–1.31 ppm respectively, 3 distinct double doublets in the ABX pattern (a CH proton and 2 anisochronous protons of a $CH_2$) appeared at δ 3.60–2.50 ppm, as has been

**Scheme 2**



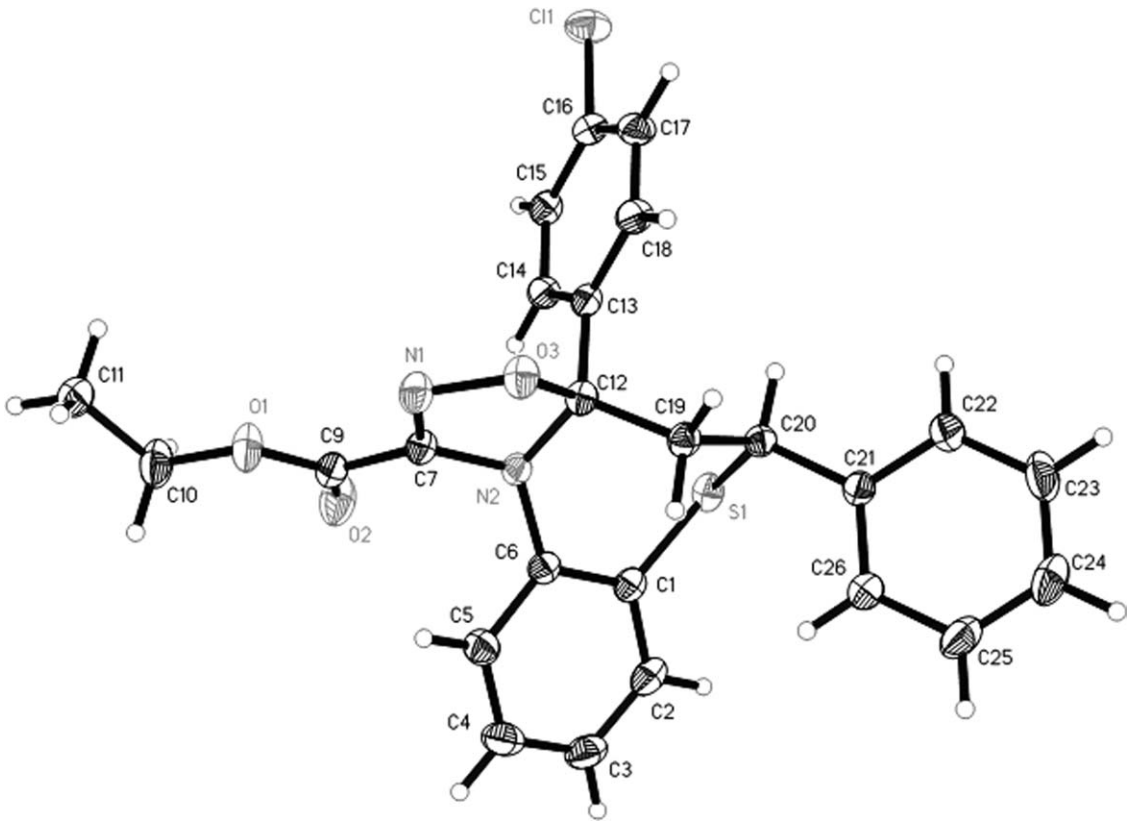



**Figure 1.** Molecular structure of **4e**.

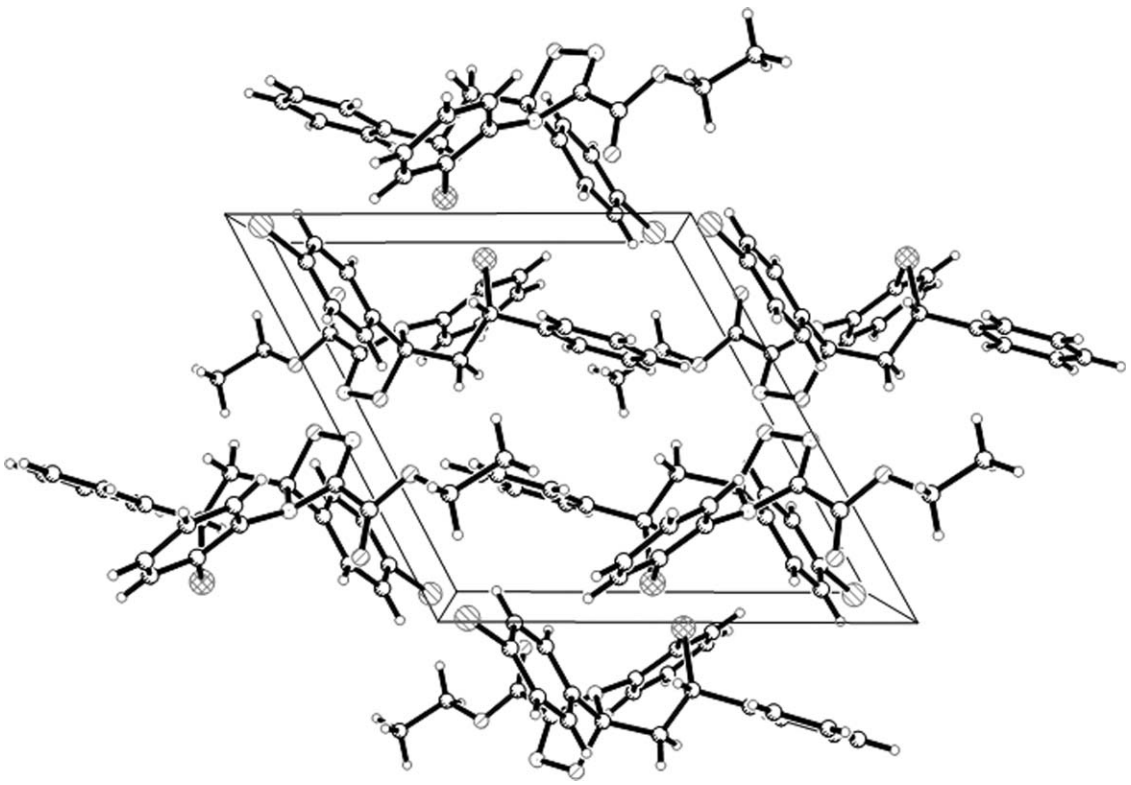


**Figure 2.** Packing of molecules in a unit cell of **4e**.

**Table 2**

Crystal data and structure refinement for compound **4e**.

| | | | |
|---|---|---|---|
| Empirical formula | $C_{25}H_{21}ClN_2O_3S$ | V, Å$^3$ | 1092.7(3) |
| Formula weight | 464.95 | Z | 2 |
| Temperature | 293(2) K | *D*c, mg/m$^3$ | 1.413 |
| Wavelength | 0.71073 A | Crystal size, mm | 0.55 × 0.45 × 0.35 |
| Crystal system | Triclinic | θ range, deg | 3.10–27.48 |
| Space group | P-1 | μ, mm$^{-1}$ | 0.302 |
| *a*, Å | 10.4744(13) | Reflections collected | 10,141 |
| *b*, Å | 10.9320(16) | Independent reflection | 4792 [*R*(int) = 0.0258] |
| *c*, Å | 10.971(2) | Data/restraints/parameters | 4792 / 0 / 290 |
| α, deg | 61.811(3) | Final *R* indices [$I > 2\sigma(I)$] | *R*1 = 0.0469, *wR*2 = 0.1397 |
| β, deg | 88.031(5) | *R* indices (all data) | *R*1 = 0.0568, *wR*2 = 0.1585 |
| γ, deg | 81.064(3) | | |

observed in 2,3-dihydro-1,5-benzothiazepines. In MS spectra, molecular ion peaks of all title compounds were obtained from EI-MS, but the intensities of molecular ion peaks were very weak.

A plausible intramolecular 1,3-diploar cycloaddition mechanism is proposed as shown in Scheme 2. According to the literatures [32], the conformations of the central heteroazepine ring in 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines adopt boat-like conformations and the 1,3-diploar cycloaddition reactions occurred in a concerted mechanism. In the presence of $Et_3N$, the nitrile oxide generated *in situ* and C═N double bond in benzothiazepine formed a cyclic transition state, then the σ-bonds of C─N and C─O were formed simultaneously to afford the 1,2,4-oxadiazole ring, the central thiazepine ring of the cycloadduct also adopts a boat-like conformation.

The X-ray crystallography of **4e** identified the structure of the desired products (Fig. 1). The higher occupancy in the 3-dimensional packing arrangement is shown in Figure 2. The crystal data and structure refinement of **4e** are listed in Table 2. Selected bond distances and angles of **4e** are tabulated in Table 3.

Figure 1 is the stereo structure of compound **4e**. There is a five-membered ring in the molecule, resulting from the cycloaddition reaction. All atoms [N(1), C(7), N(2), C(12), O(3)] in the ring are nearly coplanar with similar bond angles (N(1)─O(3) ─C(12) 106.32(14)°, O(3) ─C(12) ─N(2) 101.36(14)°, C(12) ─N(2) ─C(7) 102.60(14)°, N(2) ─C(7) ─N(1) 115.39(18)°, C(7) ─N(1) ─O(3) 105.94(16)°), indicating the ring is stable. The five-membered ring is characterized by the endocyclic torsion angles (enumerated clockwise and starting with O(3)─N(1)─C(7)─N(2)): −2.1(2)°, 19.7(2)°, −28.29(17)°, 25.87(17)°, −16.1(2)°. The five-membered ring plane adopts an envelope conformation with atom C(12) deviating from the plane defined by N(2), O(3), N(1), C(7) of 0.1684Å. The bond length of N(1)─C(7), 1.286(3)Å, indicates it is a double bond.

There is also a seven-membered ring in the molecule. 1,5-Benzothiazepine ring is characterized by the endocyclic torsion angles (enumerated clockwise and starting with S(1)─C(1)─C(6)─N(2)): 0.7(3)°, −53.6(3)°, −1.8(3)°, 82.5(2)°, −48.60(19)°, −35.20(15)°, 64.81(17)°. N(2), S(1), C(12) and C(20) are coplanar, while C(1), C(6) and C(19) are all above the plane. Therefore, the seven-membered ring adopts a boat-like conformation.

CCDC-768069 (for **4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html.

In conclusion, we have achieved an efficient one step synthesis of new [1,2,4]oxadiazolo[5,4-d][1,5]benzodiazepinones, **4a-4l** by way of highly regioselective 1,3-dipolar cycloaddition of ethyl chlorooximidoacetate to 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines, **3a-3l**.

## EXPERIMENTAL

All reagents were of commercial availability. Reactions were monitored by thin-layer chromatography (TLC). Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were determined as potassium bromide pellet on a Bruker Equinox 55 FTIR spectrophotometer. The $^1$H-NMR spectra were recorded on a Varian Inova-400 spectrophotometer using TMS as an internal standard. EI-ms spectra were recorded with an Agilent 5975 apparatus. X-ray crystal

**Table 3**

Selected bond lengths (Å) and angles (°) of compounds **4e**.

| | | | |
|---|---|---|---|
| S(1)─C(20) | 1.843(2) | N(1)─O(3)─C(12) | 106.32(14) |
| C(19)─C(20) | 1.522(3) | C(6)─N(2)─C(12) | 124.19(15) |
| O(3)─N(1) | 1.417(2) | N(1)─C(7)─N(2) | 115.39(18) |
| O(3)─C(12) | 1.469(2) | N(1)─C(7)─C(9) | 121.43(17) |
| N(2)─C(7) | 1.393(2) | O(2)─C(9)─O(1) | 126.2(2) |
| N(2)─C(6) | 1.428(2) | O(1)─C(9)─C(7) | 110.78(18) |
| N(2)─C(12) | 1.472(2) | O(3)─C(12)─C(13) | 106.65(14) |
| O(1)─C(10) | 1.448(3) | C(12)─C(19)─C(20) | 115.18(15) |
| O(1)─C(9) | 1.322(3) | N(2)─C(12)─C(19) | 114.91(15) |

**Table 4**

Yield (%) and mp (°C) of Compounds **3**.

| Comp | $Ar^1$ | $Ar^2$ | Yield | mp |
|---|---|---|---|---|
| **3a** | Ph | Ph | 86 | 113–115 |
| **3b** | Ph | p-$ClC_6H_4$ | 72 | 137–139 |
| **3c** | Ph | p-$CH_3OC_6H_4$ | 81 | 128–130 |
| **3d** | Ph | p-$NO_2C_6H_4$ | 43.2 | 201–202 |
| **3e** | *p*-$ClC_6H_4$ | Ph | 65.7 | 134–136 |
| **3f** | *p*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | 70.5 | 138–140 |
| **3g** | *p*-$ClC_6H_4$ | *p*-$CH_3OC_6H_4$ | 75.2 | 130–133 |
| **3h** | *p*-$ClC_6H_4$ | *p*-$NO_2C_6H_4$ | 47.3 | 195–196 |
| **3i** | *p*-$CH_3OC_6H_4$ | Ph | 44.6 | 124–125 |
| **3j** | *p*-$CH_3OC_6H_4$ | *p*-$ClC_6H_4$ | 65.3 | 128–130 |
| **3k** | *p*-$CH_3OC_6H_4$ | *p*-$CH_3OC_6H_4$ | 43.1 | 130–132 |
| **3l** | *p*-$CH_3OC_6H_4$ | *p*-$NO_2C_6H_4$ | 41.7 | 185–187 |

structure was obtained using R-AXIS SPIDER X-ray diffraction. The ethyl chlorooximidoacetate was obtained according to the known procedure [33–34].

**General procedure for the preparation of the 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines (3a-3l).** Chalcone **2** (6 mmol) and *o*-aminobenzenthiol (6 mmol) were dissolved in 25 ml containing glacial acetic acid methanol. After the mixture had cooled to room temperature, piperidine (5 drops) was added. Yellow floccule appeared in 0.5h, then a little methanol was added and the slurry was heated until all material dissolved. Glacial acetic acid (2 ml) was added and the mixture was allowed to stand overnight at a room temperature. The solid product was collected and recrystallized from anhydrous ethanol and benzene to give **3a-3l** as yellow crystals (Table 4).

**General procedure for the preparation of the 2,4-diaryl-2,3-dihydro-1,5-benzothiazepine derivatives containing 1,2,4-oxadiazole (4a-4l).** To a stirred solution of 1,5-benzothiazepine derivatives **3a-3l** (1 mmol) and ethyl chlorooximidoacetate (1.5 mmol) in $CH_2Cl_2$ (20 ml), a solution of triethylamine (0.5 ml) in the same solvent (5 ml) was added dropwise over a few minutes. The reaction mixture was kept under stirring at room temperature for 2 days. After the removal of the solvent at reduced pressure, ethyl acetate was added to the residue and the triethylamine hydrochloride was filtered. The solvent was then evaporated off and the residue subjected to silica gel column chromatography with ethyl acetate/light petroleum (V:V = 1:8). A series of compounds **4a-4l** were crystallized from ethyl acetate and light petroleum.

***Ethyl 3a,4-dihydro-3a,5-diphenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4a).*** This compound was obtained as colorless crystals in 34% yield, mp 177–178°C. IR(KBr): 3072 (Ar—H), 1736 (C=O), 761 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.21–6.78 (m, 14H, Ar—H), 4.34 (q, 2H, $CH_2$), 3.49 (dd, 1H, H-5x, $J_{bx}$ = 5.53 Hz, $J_{ax}$ = 10.01 Hz), 3.06 (dd, 1H, H-4b, $J_{bx}$ = 5.53 Hz, $J_{ab}$ = 14.90 Hz), 2.66 (dd, 1H, H-4a, $J_{ax}$ = 10.01 Hz, $J_{ab}$ = 14.90 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 430 ($M^+$). Anal. Calcd. for $C_{25}H_{22}N_2O_3S$: C, 69.75; H, 5.15; N, 6.51; Found: C, 69.73; H, 5.12; N, 6.54.

***Ethyl 3a,4-dihydro-3a-phenyl-5-(4-chlorophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4b).*** This compound was obtained as colorless crystals in 35% yield, mp 174–175°C. IR(KBr): 3046 (Ar—H), 1735 (C—O), 763 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.18–6.65 (m, 13H, Ar—H), 4.35 (q, 2H, $CH_2$), 3.46 (dd, 1H, H-5x, $J_{bx}$ = 6.53 Hz, $J_{ax}$ = 11.62 Hz), 3.02 (dd, 1H, H-4b, $J_{bx}$ = 6.53 Hz, $J_{ab}$ = 15.88 Hz), 2.60 (dd, 1H, H-4a, $J_{ax}$ = 11.62 Hz, $J_{ab}$ = 15.88 Hz), 1.31 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 464 ($M^+$). Anal. Calcd. for $C_{25}H_{21}ClN_2O_3S$: C, 64.58; H, 4.55; N, 6.02; Found: C, 64.57; H, 4.58; N, 5.99.

***Ethyl 3a,4-dihydro-3a-phenyl-5-(4-methoxyphenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4c).*** This compound was obtained as colorless crystals in 35% yield, mp 132–133°C. IR(KBr): 3032 (Ar—H), 1740 (C=O), 764 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 7.58–6.61 (m, 13H, Ar—H), 4.33 (q, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$), 3.45 (dd, 1H, H-5x, $J_{bx}$ = 6.72 Hz, $J_{ax}$ = 11.56 Hz), 3.01 (dd, 1H, H-4b, $J_{bx}$ = 6.72 Hz, $J_{ab}$ = 15.70 Hz), 2.60 (dd, 1H, H-4a, $J_{ax}$ = 11.56 Hz, $J_{ab}$ = 15.70 Hz), 1.29 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 460 ($M^+$). Anal. Calcd. for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08; Found: C, 67.83; H, 5.24; N, 6.07.

***Ethyl 3a,4-dihydro-3a-phenyl-5-(4-nitrophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4d).*** This compound was obtained as yellow crystals in 33% yield, mp 195–196°C. IR(KBr): 3041 (Ar—H), 1744 (C=O) 760 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.11–6.56 (m, 13H, Ar—H), 4.36 (q, 2H, $CH_2$), 3.40 (dd, 1H, H-5x, $J_{bx}$ = 5.76 Hz, $J_{ax}$ = 11.33 Hz), 3.02 (dd, 1H, H-4b, $J_{bx}$ = 5.76 Hz, $J_{ab}$ = 15.76 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.33 Hz, $J_{ab}$ = 15.76 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 475 ($M^+$). Anal. Calcd. for $C_{25}H_{21}N_3O_5S$: C, 63.15; H, 4.45; N, 8.84; Found: C, 63.12; H, 4.46; N, 8.83.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-phenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4e).*** This compound was obtained as colorless crystals in 31% yield, mp 193–194°C. IR(KBr): 3063 (Ar—H), 1744 (C=O), 760 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.10–6.68 (m, 13H, Ar—H), 4.35 (q, 2H, $CH_2$), 3.50 (dd, 1H, H-5x, $J_{bx}$ = 5.69 Hz, $J_{ax}$ = 10.11 Hz), 2.96 (dd, 1H, H-4b, $J_{bx}$ = 5.69 Hz, $J_{ab}$ = 13.01 Hz), 2.64 (dd, 1H, H-4a, $J_{ax}$ = 10.11 Hz, $J_{ab}$ = 13.01 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 464 ($M^+$). Anal. Calcd. for $C_{25}H_{21}ClN_2O_3S$: C, 64.58; H, 4.55; N, 6.02; Found: C, 64.59; H, 4.53; N, 6.01.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-(4-chlorophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4f).*** This compound was obtained as colorless crystals in 30% yield, mp 165–166°C. IR(KBr): 3057 (Ar—H), 1733 (C=O), 765 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.05–6.70 (m, 12H, Ar—H), 4.37 (q, 2H, $CH_2$), 3.48 (dd, 1H, H-5x, $J_{bx}$ = 5.19 Hz, $J_{ax}$ = 10.56 Hz), 2.92 (dd, 1H, H-4b, $J_{bx}$ = 5.19 Hz, $J_{ab}$ = 13.21 Hz), 2.55 (dd, 1H, H-4a, $J_{ax}$ = 10.56 Hz, $J_{ab}$ = 13.21 Hz), 1.31 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 498 ($M^+$). Anal. Calcd. for $C_{25}H_{20}Cl_2N_2O_3S$: C, 60.12; H, 4.04; N, 5.61; Found: C, 60.14; H, 4.02; N, 5.63.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-(4-methoxyphenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4g).*** This compound was obtained as colorless crystals in 23% yield, mp 143–144°C. IR(KBr): 3102 (Ar—H), 1736 (C=O), 763 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.09–6.68 (m, 12H, Ar—H), 4.34 (q, 2H, $CH_2$), 3.82 (s, 3H, $OCH_3$), 3.46 (dd, 1H, H-5x, $J_{bx}$ = 5.30 Hz, $J_{ax}$ = 10.77 Hz), 2.91 (dd, 1H, H-4b, $J_{bx}$ = 5.30 Hz, $J_{ab}$ = 13.72 Hz), 2.56 (dd, 1H, H-4a, $J_{ax}$ = 10.77 Hz, $J_{ab}$ = 13.72 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 494 ($M^+$). Anal. Calcd. for $C_{26}H_{23}ClN_2O_4S$: C, 63.09; H, 4.68; N, 5.66; Found: C, 63.12; H, 4.67; N, 4.63.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-(4-nitrophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4h).*** This compound was obtained as colorless crystals in 25% yield, mp 232–233°C. IR(KBr): 3116 (Ar—H), 1744 (C=O), 765 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.10–6.62 (m, 12H, Ar—H), 4.38 (q, 2H, $CH_2$), 3.50 (dd, 1H, H-5x, $J_{bx}$ = 5.32 Hz, $J_{ax}$ = 11.01 Hz), 2.92 (dd, 1H, H-4b, $J_{bx}$ = 5.32 Hz, $J_{ab}$ = 13.82 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.01 Hz, $J_{ab}$ = 13.82 Hz), 1.31 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 509 ($M^+$). Anal. Calcd. for $C_{25}H_{20}ClN_3O_5S$: C, 58.88; H, 3.95; N, 8.24; Found: C, 58.85; H, 3.96; N, 8.25.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-phenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4i).*** This compound was obtained as colorless crystals in 26% yield, mp 130–131°C. IR(KBr): 3107 (Ar—H), 1734 (C=O), 762 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.12–6.66 (m, 13H, Ar—H), 4.34 (q, 2H, $CH_2$), 3.81 (s, 3H, $OCH_3$), 3.42 (dd, 1H, H-5x, $J_{bx}$ = 6.38 Hz, $J_{ax}$ = 11.43 Hz), 2.99 (dd, 1H, H-4b, $J_{bx}$ = 6.38 Hz, $J_{ab}$ = 15.56 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.42 Hz, $J_{ab}$ = 15.56 Hz), 1.29 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 460 ($M^+$). Anal. Calcd. for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08; Found: C, 67.80; H, 5.28; N, 6.04.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-(4-chlorophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4j).*** This compound was obtained as colorless crystals in 32% yield, mp 213–214°C. IR(KBr): 3075 (Ar—H), 1736 (C=O), 762 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.02–6.65 (m, 12H, Ar—H), 4.35 (q, 2H, $CH_2$), 3.83 (s, 3H, $OCH_3$), 3.49 (dd, 1H, H-5x, $J_{bx}$ = 5.21 Hz, $J_{ax}$ = 10.32 Hz), 2.95 (dd, 1H, H-4b, $J_{bx}$ = 5.21 Hz, $J_{ab}$ = 13.44 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 10.32 Hz, $J_{ab}$ = 13.44 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 494 ($M^+$). Anal. Calcd. for $C_{26}H_{23}ClN_2O_4S$: C, 63.09; H, 4.68; N, 5.66; Found: C, 63.13; H, 4.66; N, 5.65.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-(4-methoxyphenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4k).*** This compound was obtained as colorless crystals in 36% yield, mp 173–174°C. IR(KBr): 3121 (Ar—H), 1739 (C=O), 762 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.11–6.60 (m, 12H, Ar—H), 4.30 (q, 2H, $CH_2$), 3.80 (s, 6H, $OCH_3$), 3.38 (dd, 1H, H-5x, $J_{bx}$ = 6.52 Hz, $J_{ax}$ = 11.89 Hz), 2.95 (dd, 1H, H-4b, $J_{bx}$ = 2.95 Hz, $J_{ab}$ = 15.62 Hz), 2.60 (dd, 1H, H-4a, $J_{ax}$ = 11.89 Hz, $J_{ab}$ = 15.62 Hz), 1.29 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 490 ($M^+$). Anal. Calcd. for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71; Found: C, 66.08; H, 5.35; N, 5.74.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-(4-nitrophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4l).*** This compound was obtained as yellow crystals in 20% yield, mp 213–214°C. IR(KBr): 3118 (Ar—H), 1738 (C=O), 761 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.04–6.69 (m, 12H, Ar—H), 4.37 (q, 2H, $CH_2$), 3.84 (s, 3H, $OCH_3$), 3.45 (dd, 1H, H-5x, $J_{bx}$ = 5.97 Hz, $J_{ax}$ = 11.65 Hz), 2.90 (dd, 1H, H-4b, $J_{bx}$ = 5.97 Hz, $J_{ab}$ = 15.71 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.65 Hz, $J_{ab}$ = 15.71 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 505 ($M^+$). Anal. Calcd. for $C_{26}H_{23}N_3O_6S$: C, 61.77; H, 4.59; N, 8.31; Found: C, 61.74; H, 4.60; N, 8.34.

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## REFERENCES AND NOTES

[1] Sato, M.; Nagao, T.; Yamaguchi, I.; Nakajima, H.; Kiyomoto, A. Arzneim–Forsch 1971, 21, 1338.

[2] Jiang, L.; Wan, X.-J.; Xu, H.; Bian, J.-J.; Han, W.-J.; Zhu, K.-M.; Deng, X.-M. J Med Coll PLA 2007, 22, 230.

[3] Skiles, J. W.; Sorcek, R.; Jacober, S.; Miao, C.; Mui, P. W.; McNeil, D.; Rosenthal, A. S. Bioorg Med Chem Lett 1993, 3, 773.

[4] Slade, J.; Stanton, J. J.; Ben-David, D.; Mazzenga, G. C.; J Med Chem 1985, 28, 1517.

[5] Grandolini, G.; Perioli, L.; Ambrogi, V. Eur J Med Chem 1999, 34, 701.

[6] Lévai, A. Pharmazie 1999, 54, 719.

[7] Darias, V.; Sánchez-Mateo, C. C.; Expósito-Orta, M. A.; Albertos, L. M.; Díaz, J. A.; Vega, S. Pharmazie 1999, 54, 783.

[8] Naik, V. R.; Naik, H. B. Asian J Chem 1999, 11, 661.

[9] Ahmed, N. K. Can. Pat. Appl CA 2,030,159 (1991); Chem Abstr 1991, 115, 198515f.

[10] Ahmed, N. K. Eur. Pat. Appl. EP 430,036 (1991); Chem Abstr 1992, 116, 717c.

[11] Kusukawa, R.; Kinoshita, M.; Shimono, Y.; Tomozana, G.; Hoshino, T. Arzneim–Forsch 1977, 27, 878.

[12] Yamamoto, H.; Asai, H. Chem Pharm Bull 1986, 34, 3844.

[13] Asano, T.; Okumura, T.; Hirano, K.; Adachi, T.; Sugiura, M. Chem Pharm Bull 1986, 34, 4238.

[14] Kendall, M. J.; Okopski, J. V. J Clin Hosp Pharm 1986, 11, 159.

[15] Narita, H.; Murata, S.; Yabana, H.; Kikkawa, K.; Sugawara, Y.; Akimoto, Y.; Nagao, T. Arzneim–Forsch 1988, 38, 515.

[16] Murata, S.; Yabana, H.; Kikkawa, K.; Sugawara, Y.; Akimoto, Y.; Nagao, T. Arzneim–Forsch 1988, 38, 521.

[17] Murata, S.; Kikkawa, K.; Nagao, T. Arzneim–Forsch 1988, 38, 526.

[18] Narita, H.; Gaino, M.; Suzuki, T.; Kurosawa, H.; Inoue, H.; Nagao, T. Chem Pharm Bull 1990, 38, 407.

[19] Geyer, H. M.; Watzman, N.; Buckley, J. P. J Pharm Sci 1970, 59, 964.

[20] Hopenwasser, J.; Mozayani, A.; Danielson, T. J.; Harbin, J.; Narula, H. S.; Posey, D. H.; Shrode, P. W.; Wilson, S. K.; Li, R.; Sanchez, L. A. J Anal Toxicol 2004, 28, 264.

[21] Bariwal, J. B.; Upadhyay K. D.; Manvar, A. T.; Trivedi, J. C.; Singh, J. S.; Jain, K. S.; Shah, A. K. Eur J Med Chem 2008, 43, 2279.

[22] Sakai, K.; Mizusawa, H.; Araki, H. Oyo Yakuri 1979, 18, 667.

[23] Cottrell, D. M.; Capers, J.; Salem, M. M.; DeLuca-Fradley, K.; Croft, S. L.; Werbovetz, K. L. Bioorg Med Chem 2004, 12, 2815.

[24] Srivastava, R. M.; de Almeida Lima, A.; Viana, O. S.; da Costa Silva, M. J.; Catanho, M. T. J. A.; de Morais, J. O. F. Bioorg Med Chem 2003, 11, 1821.

[25] Greco, G.; Novellino, E.; Fiorini, I.; Nacci, V.; Campiani, G.; Ciani, S. M. Garofalo, A.; Bernasconi, P.; Mennini, T. A. J Med Chem 1994, 37, 4100.

[26] Sarro, G. D.; Chimirri, A.; Sarro, A. D.; Gitto, R.; Grasso, S.; Zappala, M. Eur J Med Chem 1995, 30, 925.

[27] Liu, F.-M.; Wang, B.-L.; Li, Y.-P. Chem J Chin Univ 2002, 23, 2097.

[28] Yang, D.-B.; Liu, F.-M.; Xu, F.; Yang, C.; Ye, J.-W.; Shen, S.-W.; Zhou, Y.-L.; Li, W. Mol Divers 2008, 12, 103.

[29] Kohler, E. P.; Chadwell, H. M. Org Synth 1922, 2, 1.

[30] Stephens, W. D.; Field, L. J Org Chem 1959, 24, 1576.

[31] Pant, S.; Sharma, P.; Pant, U. C. Phosphorus Sulfur Silicon Relat Elem 2008, 183, 2974.

[32] Lu, Y. C.; Jin, S.; Xing, Q. Y. J Mol Struct (Theochem) 1988, 167, 253.

[33] Brenner, M.; Huber, W. Helv Chim Acta 1953, 36, 1109.

[34] Kozikowski. A. P.; Adamczyk, M. J Org Chem 1983, 48, 366.

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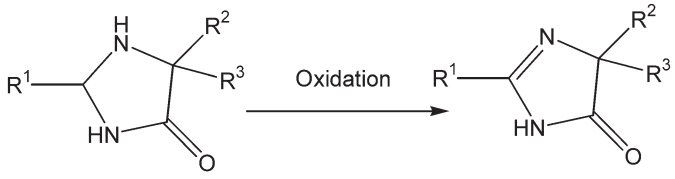


**1, 2a–i** **a**: $R^1 = CH_3(CH_2)_3$; **b**: $R^1 = C_6H_5$; **c**: $R^1 = 4\text{-}CH_3OC_6H_4$; **d**: $R^1 = 4\text{-}NO_2C_6H_4$; **e**: $R^1 = 2\text{-}HOC_6H_4$; **f**: 2-pyridyl; for $R^2 = R^3 = (CH_2)_4$ and **g**: $R^1$ = 2-pyridyl; for $R^2 = CH_3$; $R^3 = CH(CH_3)_2$

The reaction of aldehydes (pentanal, benzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, salicylaldehyde, pyridin-2-carbaldehyde) with 1-aminocyclopentancarboxamide or (*S*)-2-amino-2,3-dimethylbutanamide has been used to prepare substituted imidazolidin-4-ones **1a–g** (**a**: $R^1 = CH_3(CH_2)_3$; **b**: $R^1 = C_6H_5$; **c**: $R^1 = 4\text{-}CH_3OC_6H_4$; **d**: $R^1 = 4\text{-}NO_2C_6H_4$; **e**: $R^1 = 2\text{-}HOC_6H_4$; **f**: $R^1$ = 2-pyridyl; for $R^2 = R^3 = (CH_2)_4$), and **g**: $R^1$ = 2-pyridyl; for $R^2 = CH_3$; $R^3 = CH(CH_3)_2$) in the yields of 53–83%. Subsequent oxidations with various reagents gave the corresponding 4,5-dihydro-1*H*-imidazol-5-ones **2a–g**: Pd/C (72–93%), DDQ (25–80%), and $MnO_2$ (30–77%). Structure of the prepared compounds **1a–g** and **2a–g** was verified by $^1$H NMR and $^{13}$C NMR spectroscopy, EI-MS and elemental analysis. X-ray diffraction was performed in the case of compounds **1e** and **2e**.

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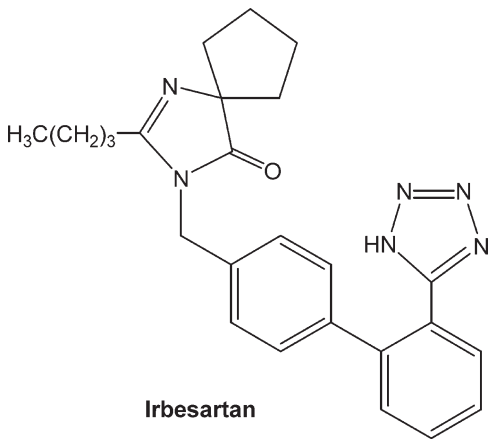
## INTRODUCTION

A number of substituted 4,5-dihydro-1*H*-imidazol-5-ones belong among still applied selective and non-toxic herbicides [1]. Our previous articles dealt with their synthesis, characterisation, and study of mechanism of their formation [2]. Other possible applications of 4,5-dihydro-1*H*-imidazol-5-ones lie in their use as ligands that form coordination compounds with selected metal ions [3]. Some of such complexes have been successfully adopted as catalysts of deallylation reactions of diallyl malonates [3b,f] in the Henry reaction [3c,e], or in allyl oxidation [3i]. Another example of application of this heterocyclic system is represented by 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one, which is an important starting compound for the synthesis of medical drug Irbesartan (2-butyl-3-[[2′-(1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]-nonen-4-on). Irbesartan is an antagonist of angiotensin II and is clinically applied in the treatment of hypertension [4].




The existing methods of synthesis of 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one use the acylation of amide or nitrile of 1-aminocyclopentancarboxylic acid with pentanoic acid chloride followed by ring closure reaction [5]. Another method of preparation of 2-butyl-1,3-

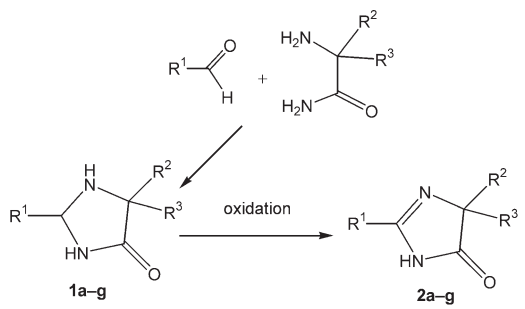
diazaspiro[4.4]non-1-en-4-one consists in acid catalyse condensation of ethyl 1-aminocyclopentancarboxylate with ethyl pentanimidate [6]. The third synthetic way described is based on the reaction of 1-aminocyclopentanecarboxamide with trimethyl orthopentanoate [7]. The described variant of synthesis of 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one is the reaction of pentanoic acid with 1-aminocyclopentannitrile [8]. The aim of the research described here is to elaborate a new alternative synthetic method for 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one and other substituted 4,5-dihydro-1*H*-imidazol-5-ones. This alternative adopts oxidation of substituted imidazolidin-4-ones to give 4,5-dihydro-1*H*-imidazol-5-ones.

## RESULTS AND DISCUSSION

The reaction of aldehydes (pentanal, benzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, salicylaldehyde, pyridin-2-carbaldehyde) with 1-aminocyclopentancarboxamide [5] or (*S*)-2-amino-2,3-dimethylbutanamide [1] was used to prepare cyclic aminals, *i.e.*, the corresponding imidazolidin-4-ones **1a–g** (**a**: $R^1 = CH_3(CH_2)_3$; **b**: $R^1 = C_6H_5$; **c**: $R^1 = 4\text{-}CH_3OC_6H_4$; **d**: $R^1 = 4\text{-}NO_2C_6H_4$; **e**: $R^1 = 2\text{-}HOC_6H_4$; **f**: $R^1 = 2$-pyridyl; for $R^2 = R^3 = (CH_2)_4$) and **g**: $R^1 = 2$-pyridyl; for $R^2 = CH_3$; $R^3 = CH(CH_3)_2$) (Scheme 1). The ring closure reaction was performed with acid catalysis (acetic acid) by heating the starting substances in methanol. Recrystallization gave the respective imidazolidin-4-ones **1a–i** in the yields of 53–83%. In the case of (5*S*)-4-isopropyl-4-methyl-2-(pyridin-2-yl)imidazolidine-4-one (**1g**), the reaction creates another chiral centre at the carbon atom at 2-position of the imidazolidin-4-one cycle. In this case, the reaction produces a diastereomeric mixture with the configurations 2*S*, 5*S* and 2*R*, 5*S*, in the ratio of 1:1, which resulted in doubling of signals in the NMR spectra.

The second reaction step leading to the substituted 4,5-dihydro-1*H*-imidazol-5-ones **2a-g** was the oxidation of the prepared imidazolidin-4-ones **1a–g** (Scheme 1). The following oxidizing agents were used for this oxidation reaction: palladium on carbon carrier (Pd/C), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and activated manganese (IV) oxide ($MnO_2$). The results presented in the following table show that the first method (Pd/C) gives the highest yields; however, in most cases the other two (cheaper) variants are also applicable (Table 1).

**Scheme 1**




**1, 2a–i** **a**: $R^1 = CH_3(CH_2)_3$; **b**: $R^1 = C_6H_5$; **c**: $R^1 = 4\text{-}CH_3OC_6H_4$; **d**: $R^1 = 4\text{-}NO_2C_6H_4$; **e**: $R^1 = 2\text{-}HOC_6H_4$; **f**: 2-pyridyl; for $R^2 = R^3 = (CH_2)_4$ and **g**: $R^1 = 2$-pyridyl; for $R^2 = CH_3$; $R^3 = CH(CH_3)_2$

**Table 1**

Oxidations 1 → 2, yields obtained with individual reagents.

| | | Catalyst/yield [%] | | |
|---|---|---|---|---|
| Entry | Product | Pd/C | DDQ | $MnO_2$ |
| 1 | **2a** | 80 | 25 | 65 |
| 2 | **2b** | 87 | 40 | 75 |
| 3 | **2c** | 83 | 73 | 77 |
| 4 | **2d** | 93 | 80 | 30 |
| 5 | **2e** | 72 | 77 | 67 |
| 6 | **2f** | 90 | 75 | 70 |
| 7 | **2g** | 72 | 38 | 64 |

Structures of the prepared products **1a–i and 2a–i** were verified by $^1$H NMR and $^{13}$C NMR spectroscopy, EI-MS and elemental analysis. In the case of 2-(4-nitrophenyl)-1,3-diazaspiro[4.4]non-1-en-4-one (**2d**), the NMR spectra revealed the presence of two tautomeric forms; a similar case was described and discussed in Ref. 2b,c. The structure of product 2-(2-hydroxyphenyl)-1,3-diazaspiro[4.4]nonan-4-one (**1e**) and its oxidation product 2-(2-hydroxyphenyl)-1,3-diazaspiro[4.4]non-1-en-4-one (**2e**) was also verified using X-ray diffraction. In molecule **1e** (Fig. 1), the bond distances in the central heterocyclic ring clearly show that all of them are single bonds. The only shortening of bond length is found in the case of N3—C1 bond, which can be attributed to the

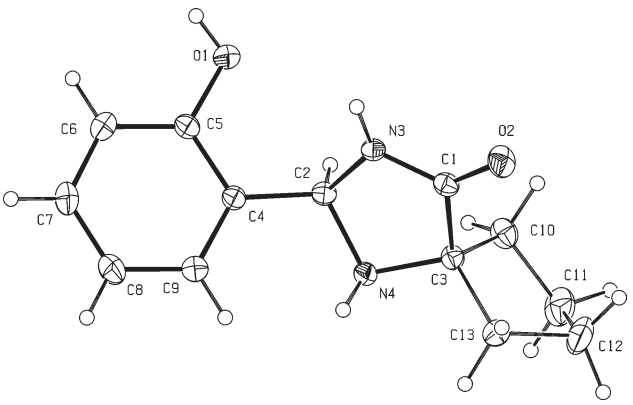



**Figure 1.** Molecular structure of **1e**, ORTEP 30% probability level. Selected interatomic distances [Å] and angles [°]: O(2)—C(1) 1.242(2), C(1)—C(3) 1.516(3), C(3)—N(4) 1.483(3), N(4)—C(2) 1.465(3), C(2)—N(3) 1.475(2), N(3)—C(1) 1.323(3), O(2)—C(1)—C(3) 124.91(19), C(1)—C(3)—N(4) 102.51(15), C(3)—N(4)—C(2) 105.38(14), N(4)—C(2)—N(3) 102.97(16), C(2)—N(3)—C(1) 111.82(17), N(3)—C(1)—C(3) 108.12(17), N(3)—C(1)—O(2) 126.94(18).

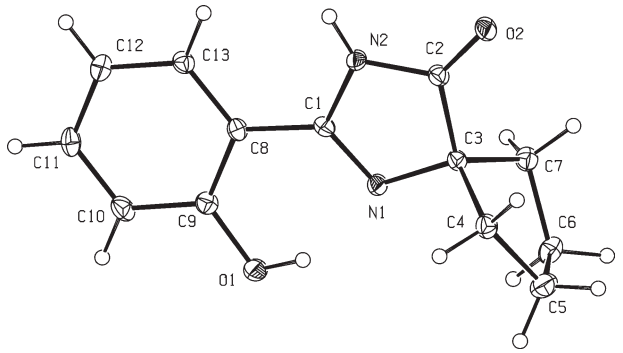



**Figure 2.** Molecular structure of **2e**, ORTEP 30% probability level. Selected interatomic distances [Å] and angles [°]:O(2)—C(2) 1.222(2), C(2)—C(3) 1.522(3), C(3)—N(1) 1.476(3), N(1)—C(1) 1.285(3), C(1)—N(2) 1.392(3), N(2)—C(2) 1.369(3), O(2)—C(2)—C(3) 128.50(19), C(2)—C(3)—N(1) 103,75(16), C(3)—N(1)—C(1) 107.77(17), N(1)—C(1)—N(2) 114.03(18), C(1)—N(2)—C(2) 108,72(17), N(2)—C(2)—C(3) 105.73(17), N(2)—C(2)—O(2) 125.8(2).

amido-character of the whole NH—C=O group. Also the C1—O2 interatomic distance corresponds to this character. From the values of bond angles and interplanar angles in this molecule is seen that the central ring is fairly deformed by a distortion of N4 atom from the ring core, and only five atoms (C1, C2, C3, N3, and O2) tend to lie in a plane.

Both molecules **1e** and **2e** are mutually similar. The main difference between them consists in the significant shortening of N1—C1 distance in the case of **2e** (Fig. 2), which corresponds to a typical double bond [9]. This fact the absence of the hydrogen atom at N1 atom and high degree of planarity of the central heterocyclic ring in this molecule are a proof of the oxidation of **1e**–**2e**.

The molecules of compound **1e** are interconnected to the layered supramolecular structure *via* H-bonding (Fig. 3). In the case of compound **2e**, two independent molecules were found in the crystal unit cell. The H-bonding in compound **2e** is slightly less extensive,

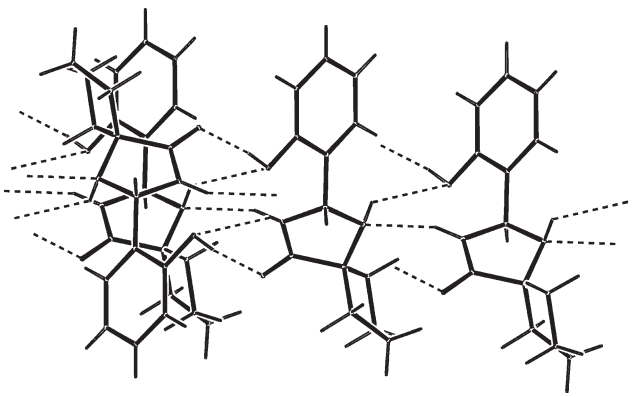


**Figure 3.** Crystal packing diagram of **1e** with hydrogen bonding system.

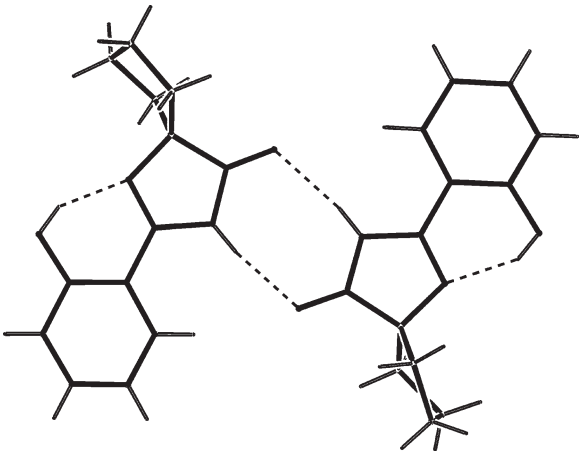


**Figure 4.** Crystal packing diagram of **2e** with hydrogen bonding system.

and only dimers are formed by the connection of amido group, and the imidazole nitrogen atom is connected to the O—H group *via* the intramolecular H-bond which fixed up the coplanarity of the aromatic ring (Fig. 4).

## EXPERIMENTAL

If not stated otherwise, the starting substances were purchased from Sigma-Aldrich. The melting point temperatures have not been corrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 500 instrument (500.13 MHz for $^1$H, and 125.77 MHz for $^{13}$C). Chemical shifts δ are referenced to solvent residual peak (2.50 ppm $^1$H, 39.43 ppm $^{13}$C for DMSO–$d_6$, and 7.26 ppm $^1$H, 77.00 ppm $^{13}$C for $CDCl_3$). The mass spectra were measured with a set of Agilent Technologies (gas chromatograph 6890 N with mass detector 5973 Network); (the samples were dissolved in dichloromethane or acetone). The elemental microanalysis was carried out using an apparatus of FISONS Instruments EA 1108 CHN. The optical rotation was measured on a Perkin–Elmer 341 instrument; the concentration *c* was given in g/100 mL (Optical rotatory power determination).

**Crystallography.** The X-ray data for colorless crystals of **1e** and **2e** were obtained at 150 K using an Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with Mo $K_\alpha$ radiation ($\lambda = 0.71073$ Å), a graphite monochromator, and the ϕ and χ scan mode. Data reductions were performed with DENZO-SMN [10]. The absorption was corrected by integration methods [11]. Structures were solved by direct methods (Sir92) [12] and refined by full matrix least-square based on $F^2$ (SHELXL97) [13]. Hydrogen atoms were mostly localized on a difference Fourier map; however, to ensure uniformity of treatment of crystal, all the hydrogen atoms were recalculated into idealized positions (riding model) and assigned temperature factors $H_{iso}$ (H) = 1.2 $U_{eq}$(pivot atom) or of 1.5 $U_{eq}$ for the methyl moiety with C—H = 0.96, 0.97, 0.98, and 0.93 Å for methyl, methylene, methane, and aromatic-ring hydrogen atoms, respectively; 0.86 Å or 0.93 Å for N—H, and 0.82 Å for O—H bonds. The crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 757,260 and 757,259

for **1e** and **2e**, respectively. [(Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.)] In Figure 2, there is a disordered cyclopentane ring. The disorder was treated by splitting of carbon atoms into two positions with similar occupancy.

**General method of preparation of imidazolidin-4-ones (1a–g).** A mixture of 1-aminocyclopentancarboxamide [5a] (4.35 g; 34 mmol) or (*S*)-2-amino-2,3-dimethylbutanamide [1] (4.40 g; 34 mmol) and the respective aldehyde (37 mmol), in methanol (20 mL) with a drop of acetic acid was refluxed 12 h. The mixture was evaporated, and the residue was recrystallized from the solvent given.

***2-Butyl-1,3-diazaspiro[4.4]nonan-4-one (1a).*** Yield: 6.3 g (96%); mp 72–74°C (hexane). $^1$H NMR ($CDCl_3$): δ 0.85–0.87 (m; 3H, $CH_3$), 1.25–1.32 (m; 4H, $(CH_2)_2$), 1.36–1.54 (m; 2H, $CH_2$), 1.55–1.64 (m; 6H, $(CH_2)_3$), 1.82–1.88 (m; 2H, $CH_2$), 4.23 (t; 1H; $J$ = 6 Hz; CH), 8.13 (s; 1H; NH). $^{13}$C NMR ($CDCl_3$, ppm): δ 13.7, 22.4, 25.1, 25.2, 26.7; 36.1; 36.5; 37.5; 68.5; 69.2; 182.0. Anal. Calcd. for $C_{11}H_{20}N_2O$ (196) (%): C, 67.31; H, 10.27; N, 14.27; found: C, 67.22; H, 10.38; N, 14.58.

***2-Phenyl-1,3-diazaspiro[4.4]nonan-4-one (1b).*** Yield 2.49 g (79%); mp 136–138°C (ethyl acetate/hexane); $^1$H NMR ($CDCl_3$): δ 1.49–1.76 (m, 7H), 1.81–1.90 (m, 1H), 3.13 (d, $J$ = 8.0 Hz, 1H, NH), 5.35 (d, $J$ = 8.0 Hz, 1H, CH), 7.30–7.44 (m, 5H, Ar), 8,55 (s, 1H, NHCO).$^{13}$C NMR ($CDCl_3$): δ: 25.1, 25.2, 36.4, 37.2, 68.9, 69.7, 127.0, 128.4, 128.5, 142.1, 180.3. EI-MS: *m/z* 216, 187, 173 (100%), 144, 106, 84. Anal. Calcd. for $C_{13}H_{16}N_2O_2$ (216) (%): C, 72.19; H, 7.46; N, 12.95; found: C, 72.01; H, 7.59; N, 13.12.

***2-(4-Methoxyphenyl)-1,3-diazaspiro[4.4]nonan-4-one (1c).*** Yield 1.47 g (81%); mp 182–183°C (ethyl acetate); $^1$H NMR ($CDCl_3$): δ 1.47–1.70 (m, 7H), 1.82–1.87 (m, 1H), 3.71 (s, 3H, $OCH_3$), 5.27 (s, 1H, CH), 6.88–6.90 (m, 2H, Ar), 7.29–7.31 (m, 2H, Ar), 8.44 (s, 1H, NHCO). $^{13}$C NMR ($CDCl_3$, ppm): δ: 24.9, 36.1, 36.7, 55.2, 68.7, 69.1, 113.7, 128.1, 133.7, 159.4, 180.0; EI-MS: *m/z* 246, 217, 203 (100%), 134, 121, 84. Anal. Calcd. for $C_{14}H_{18}N_2O_2$ (246) (%): C, 68.27; H, 7.37; N, 11.37; found: C, 68.45; H, 7.51; N, 11.50.

***2-(4-Nitrophenyl)-1,3-diazaspiro[4.4]nonan-4-one (1d).*** Yield 0.92 g (53%); mp 178–180°C (ethyl acetate); $^1$H NMR ($CDCl_3$): δ 1.39–1.42 (m, 1H), 1.58–1.76 (m, 7H), 3.54 (d, $J$ = 7.5 Hz, 1H, NH), 5.46 (d, $J$ = 7.5 Hz, 1H, CH), 7.64–7.66 (m, 2H, Ar), 8.21–8.22 (m, 2H, Ar), 8.71 (s, 1H, NHCO). $^{13}$C NMR ($CDCl_3$): δ 24.9, 25.0, 36.5, 37.6, 68.4, 68.5, 123.6, 128.2, 147.4, 150.0, 180.0; EI-MS: *m/z* 261, 232, 218 (100%), 151, 105, 84. Anal. Calcd. for $C_{13}H_{15}N_3O_3$ (261) (%): C, 59.76; H, 5.79; N, 16.08; found: C, 60.02; H, 5.95; N, 16.25.

***2-(2-Hydroxyphenyl)-1,3-diazaspiro[4.4]nonan-4-one (1e).*** Yield 3.15 g (83%); mp 179–181°C (ethyl acetate); $^1$H NMR($CDCl_3$) δ 4.48–1.56 (m, 1H), 1.59–1.80 (m, 6H), 1.85–1.90 (m, 1H), 5.60 (s, 1H, CH), 6.75–6.80 (m, 2H, Ar), 7.14 (t, $J$ = 7.5 Hz, 1H, Ar), 7.23 (d, $J$ = 7.5 Hz, 1H, Ar), 8.51 (s, 1H, NHCO), 10.96 (br, 1H, OH). $^{13}$C NMR ($CDCl_3$) δ 24.6, 24.8, 35.6, 36.8, 66.3, 67.9, 115.9, 118.6, 125.1, 127.7, 129.2, 156.4, 178.5. EI-MS: *m/z* 232, 188, 171 (100%), 113, 77, 44. Anal. Calcd. for $C_{13}H_{16}N_2O_2$ (232) (%): C, 67.22; H, 6.94; N, 12.06; found: C, 67.35; H, 7.11; N, 12.31.

***2-(2-Pyridyl)-1,3-diazaspiro[4.4]nonan-4-one (1f).*** Yield 1.62 g (80%); mp 109–111°C (ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) δ 1.48–1.55 (m, 1H), 1.62–1.72 (m, 6H), 1.87–1.91 (m, 1H), 5.38 (s, 1H, CH), 7.34–7.37 (m, 1H, ArH), 7.49 (d, $J$ = 7.69 Hz, 2H, Py), 7.82–7.85 (m, 1H, Py), 8.54–8.56 (m, 2H, Py + NH). $^{13}$C NMR ($CDCl_3$) δ 24.9, 36.7, 37.5, 68.4, 70.4, 121.7, 123.7, 137.3, 149.0, 159.9, 179.9; EI-MS: *m/z* 217, 188, 174 (100%), 145, 107, 79. Anal. Calcd. for $C_{12}H_{15}N_3O$ (217) (%): C, 66.34; H, 6.96; N, 13.34. Found: C, 66.21; H, 6.85; N, 13.22.

***(E + 2)(5S)-4-Isopropyl-4-methyl-2-(pyridin-2-yl)imidazolidin-4-one (1g).*** Yield 1.51 g (74%); mp 113–118°C (ethyl acetate/hexane); $[\alpha]_D$ −14.2 (c 1, $CH_3OH$) $^1$H NMR ($CDCl_3$) δ 0.80–0.99 (m, 12H, 2 × *i*.Pr), 1.20 (s, 3H, $CH_3$), 1.26 (s, 3H, $CH_3$), 1.83–1.91 (m, 2H, 2 × CH), 2.95 (br, 2H, NH), 5.48 (s, 1H, CH), 5.56 (s, 1H, CH), 7.15–7.18 (m, 2H, Py), 7.28 (d, $J$ = 7.6 Hz, 1H, Py), 7.43 (d, $J$ = 7.6 Hz, 1H, Py), 7.62–7.65 (m, 2H, Py), 8.25 (s, 1H, NHCO), 8.37 (s, 1H, NHCO), 8.45–8.48 (m, 2H, Py). $^{13}$C NMR ($CDCl_3$) δ 16.6, 16.7, 17.5, 17.6, 21.6, 23.2, 33.1, 34.5, 64.6, 64.7, 69.6, 71.1, 121.0, 123.3, 123.4, 136.8, 136.9, 148.9, 149.1, 158.7, 158.9, 180.5, 180.8. EI-MS: *m/z* 219, 204, 176 (100%), 133, 107, 92, 42. Anal. Calcd. for $C_{12}H_{17}N_3O$ (219) (%): C, 65.73; H, 7.81; N, 19.16; found: C, 65.38; H, 7.56; N, 19.51.

**General methods of preparation of 4,5-dihydro-1*H*-imidazol-5-ones (2a–g)**

***Method A (Pd/C).*** A mixture of the respective imidazolidin-4-one (5 mmol) and Pd/C (5%, 0.2 g) in methanol (50 mL) was refluxed 24 h. The final product was isolated after filtration, evaporation, and (sometimes) recrystallisation from the solvent given. In the case of isolation of compound **2d** the reaction mixture was evaporated, the residue was dissolved in NaOH solution (5%, 25 mL), the solution was filtered and the filtrate acidified to pH ∼ 7–8. The separated crystals of compound **2d** were collected by filtration and dried. The final product was recrystallized from DMF.

***Method B (DDQ).*** A mixture of the respective imidazolidin-4-one (5 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.3 g, 5.7 mmol) in dioxane (50 mL) was refluxed 10 min. The reaction mixture was filtered through a silica gel layer (2 cm), evaporated and (sometimes) recrystallized from the solvent given. In the case of isolation of compound **2d** the reaction mixture was evaporated, the residue was dissolved in NaOH solution (5%, 25 mL), the solution was filtered and the filtrate acidified to pH ∼ 7–8. The separated crystals of compound **2d** were collected by filtration and dried. The final product was recrystallized from DMF.

***Method C ($MnO_2$).*** A mixture of the respective imidazolidin-4-one (5 mmol) and activated manganese (IV) oxide (5 g, 91 mmol) in acetone (100 mL) was refluxed 24 h. The final product was isolated after filtration with kieselguhr, evaporation, and (sometimes) recrystallization from the solvent given. In the case of isolation of compound **2d,** the reaction mixture was evaporated, the residue was dissolved in NaOH solution (5%, 25 mL), the solution was filtered and the filtrate acidified to pH ∼ 7–8. The separated crystals of compound **2d** were collected by filtration and dried. The final product was recrystallized from DMF. The yields of individual compounds are presented in Table 1.

***2-Butyl-1,3-diazaspiro[4.4]non-1-en-4-one (2a).*** Colorless oil, TLC: (silika gel plates, Merck), chloroform/methanol 10:1, $R_F$ = 0.51; $^1$H NMR ($CDCl_3$) δ 0.90 (t, 3H, $CH_3$, $J$ = 7.3 Hz); 1.31–1.40 (m, 2H, $CH_2$); 1.58–1.66 (m, 2H, $CH_2$); 1.72–1.80 (m, 3H); 1.83–1.93 (m, 5H, $CH_2$); 2.42 (t, 2H, $CH_2$, $J$ = 7,4 Hz); 8.83 (bs, 1H, NHCO). $^{13}$C NMR ($CDCl_3$) δ 13.7; 23.1; 25.9; 27.9; 30.0; 37.2; 77.5; 190.2. Anal. Calcd. for

$C_{11}H_{18}N_2O$ (194) (%): C 68.01; H 9.34; N 14.42; Found: C 67.89; H 9.46; N 14.68.

***2-Phenyl-1,3-diazaspiro[4.4]non-1-en-4-one (2b).*** mp 202–203°C. $^1$H NMR (DMSO-$d_6$) δ 1.78–1.89 (m, 8H), 7.52–7.55 (m, 2H, Ar), 7.58–7.62 (m, 1H, Ar), 7.97–7.99 (m, 2H, Ar), 11.41 (br, 1H, NHCO). $^{13}$C NMR (DMSO-$d_6$) δ 25.6, 37.2, 77.6, 126.9, 128.7, 128.9, 131.5, 157.6, 188.1. EI-MS: *m/z* 214, 185, 171 (100%) 104, 83, 77, 54. Anal. Calcd. for $C_{13}H_{14}N_2O$ (214) (%): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.81; H, 6.52; N, 13.12.

***2-(4-Methoxyphenyl)-1,3-diazaspiro[4.4]non-1-en-4-one (2c).*** mp 236–237°C. $^1$H NMR ($CDCl_3$) δ 1.92–2.09 (m, 8H), 3.87 (s, 3H, $OCH_3$), 6.98–7.00 (m, 2H, Ar), 7.86–7.88 (m, 2H, Ar), 10.20 (br, 1H, NHCO). $^{13}$C NMR ($CDCl_3$) δ 25.6, 37.3, 55.6, 75.3, 114.3, 120.2, 129.6, 162.5, 162.7, 189.0. EI-MS: *m/z* 244, 215, 201, 134 (100%), 91, 83, 54. Anal. Calcd. for $C_{14}H_{16}N_2O_2$ (244) (%): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.52; N, 11.55.

***2-(4-Nitrophenyl)-1,3-diazaspiro[4.4]non-1-en-4-one (2d).*** mp >300°C (dec.); $^1$H NMR (DMSO-$d_6$) δ 1.72–1.96 (m, 16H), 8.09–8.49 (m, 8H, 2 × 2Ar), 11.48 (s, 1H, NHCO), 11.58 (s, 1H, NHCO). $^{13}$C NMR (TFA + DMSO-$d_6$) δ 28.9, 41.0, 77.4, 77.7, 124.0, 127.5, 130.0, 133.5, 133.9, 153.4, 156.5, 169.4, 169.7, 181.9, 182.1. Anal. Calcd. for $C_{13}H_{13}N_3O_3$ (259) (%): C, 60.23; H, 5.05; N, 16.21. Found: C, 60.15; H, 4.98; N, 16.29.

***2-(2-Hydroxyphenyl)-1,3-diazaspiro[4.4]non-1-en-4-one (2e).*** mp 232–233°C. $^1$H NMR ($CDCl_3$) δ 1.90–2.09 (m, 8H), 6.91 (t, $J$ = 7.50 Hz, 1H, Ar), 7.01 (d, $J$ = 8.00 Hz, 1H, Ar), 7.35 (t, $J$ = 8.00 Hz, 1H, Ar), 7.49 (d, $J$ = 7.50 Hz, 1H, Ar), 10.46 (vbs, 1H, NHCO), 12.46 (vbs, 1H, OH). $^{13}$C NMR ($CDCl_3$) δ 25.4 37.4, 76.1, 110.7, 117.3, 118.9, 127.7, 133.5, 160.3, 161.3, 185.5. EI-MS: *m/z* 230, 189, 173 (100%), 120, 102, 84, 54. Anal. Calcd. for $C_{13}H_{14}N_2O_2$ (230) (%): C, 60.81; H, 6.13; N, 12.17. Found: C, 60.78; H, 6.09; N, 12.24.

***2-(1,3-Diazaspiro[4.4]non-1-en-4-one-2-yl)pyridine (2f).*** mp 120–122°C. $^1$H NMR (DMSO-$d_6$ + TFA) δ 1.96–2.12 (m, 8H), 7.45 (t, $J$ = 5.5 Hz, 1H, Py), 7.85 (t, $J$ = 7.5 Hz, 1H, Py), 8.27 (d, $J$ = 7.50 Hz, 1H, Py), 8.67 (d, $J$ = 5.5 Hz, 1H, Py), 10.12 (s, 1H, NHCO).$^{13}$C NMR (DMSO-$d_6$ + TFA) δ 25.6, 37.1, 76.8, 122.7, 126.9, 137.6, 146.4, 149.4, 161.3, 187.4. EI-MS: *m/z* 215, 187 (100%), 159, 105, 78, 41. Anal. Calcd. for $C_{12}H_{13}N_3O$ (215) (%): C, 66.96; H, 6.09; N, 19.52. Found: C, 66.87; H, 6.02; N, 19.65.

***(S)-2-(4-Isopropyl-4-methyl-4,5-dihydro-1H-imidazol-5-one-2-yl)pyridine (2g).*** Colorless oil; $[\alpha]_D$ −17.4 (c 2, $CH_3OH$). $^1$H NMR (DMSO-$d_6$ + TFA) δ 0.85 (d, 3H, $J$ = 6.8 Hz *i*-Pr$CH_3$), 0.92 (d, 3H, $J$ = 6.8 Hz *i*-Pr$CH_3$), 1.23 (s, 3H, $CH_3$), 1.91 (m, 1H, *i*-Pr*CH*), 7.57 (m, 1H, Py), 7.87 (m, 1H, Py), 8.09 (d, 1H, $J$ = 7.4 Hz, Py), 8.18 (d, 1H, $J$ = 7.4 Hz, Py), 10.87 (bs, 1H, NHCO).$^{13}$C NMR (DMSO-$d_6$ + TFA) δ 16.8, 17.0, 21.4, 34.2, 74.6, 121.5, 126.5, 137.6, 147.4, 149.1, 159.0, 186.7. EI-MS: *m/z* 217, 202, 189, 174 (100%), 146, 105, 78. Anal. Calcd. for $C_{12}H_{15}N_3O$ (217) (%): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.15; H, 6.85; N, 19.30.

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## REFERENCES AND NOTES

[1] (a) Wepplo, P. J. Pestic Sci 1990, 31, 293; (b) Harris, J. E.; Gagne, J. A.; Fischer, J. E.; Sharma, R. R.; Traul, K. A.; Scot, J. D.; Hess, F. G. In The Imidazole Herbicides; Shaner, D. L.; O'Connor, S. L., Eds.; CRC Press: Boca Raton, FL, 1991; p 179.

[2] (a) Sedlák, M.; Halama, A.; Kaválek, J.; Macháček, V.; Štěrba, V. Collect Czech Chem Commun 1995, 60, 150; (b) Sedlák, M.; Halama, A.; Kaválek, J.; Macháček, V.; Mitaš, P.; Štěrba, V. Collect Czech Chem Commun 1996, 61, 910; (c) Sedlák, M.; Halama, A.; Mitaš, P.; Kaválek, J.; Macháček, V. J Heterocycl Chem 1997, 34, 1227; (d) Mitaš, P.; Sedlák, M.; Kaválek, J. Collect Czech Chem Commun 1998, 63, 85; (e) Sedlák, M.; Kaválek, J.; Mitaš, P.; Macháček, V. Collect Czech Chem Commun 1998, 63, 394; (f) Sedlák, M.; Hanusek, J.; Bína, R.; Kaválek, J.; Macháček, V. Collect Czech Chem Commun 1999, 64, 1629; (g) Sedlák, M.; Hanusek, J. Molecules 2000, 5, M177; (h) Sedlák, M.; Drabina, P.; Hanusek, J. Heterocycl Commun 2003, 9, 129.

[3] (a) Sedlák, M.; Drabina, P.; Císařová, I.; Růžička, A.; Hanusek, J.; Macháček, V. Tetrahedron Lett 2004, 45, 7723; (b) Turský, M.; Nečas, D.; Drabina, P.; Sedlák, M.; Kotora, M. Organometallics 2006, 25, 901; (c) Sedlák, M.; Drabina, P.; Keder, R.; Hanusek, J.; Císařová, I.; Růžička, A. J Organomet Chem 2006, 691, 2623; (d) Drabina, P.; Hanusek, J.; Jirásko, R.; Sedlák, M. Transition Met Chem 2006, 31, 1052; (e) Keder, R.; Drabina, P.; Hanusek, J.; Sedlák, M. Chem Pap 2006, 60, 324; (f) Nečas, D.; Drabina, P.; Sedlák, M.; Kotora, M. Tetrahedron Lett 2007, 45, 4539; (g) Mikysek, T.; Švancara, I.; Bartoš, M.; Vytřas, K.; Drabina, P.; Sedlák, M.; Klíma, J.; Urban, J.; Ludvík, J. Electroanalysis 2007, 19, 2529; (h) Sedlák, M.; Drabina, P.; Lánský, V.; Svoboda, J. J Heterocycl Chem 2008, 45, 859; (i) Drabina, P.; Sedlák, M.; Růžička, A.; Malkov, A.; Kočovský, P. Tetrahedron Asymmetry 2008, 19, 384.

[4] O'Neil, M. J. In The Merck Index—An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th ed.; O'Neil, M. J.; Smith, A.; Hackelman, P. E., Eds.; Merck & Co.: Rahway, NJ, 2001; p 914.

[5] (a) Kavitha, C. V.; Gaonkar, S. L.; Narendra Sharath Chandra, J. N.; Sadashiva, C. T.; Rangappa, K. S. Bioorg Med Chem 2007, 15, 7391; (b) Cousaert, N.; Willand, N.; Gesquière, J.-C.; Tartar, A.; Deprez, B.; Deprez-Poulain, R. Tetrahedron Lett 2008, 49, 2743.

[6] Xu, J.-Y.; Li, N.-G.; Wu, X.-M.; Hua, W.-Y.; Zhang, J.; Wang, Q.-J. Zhongguo Yaowu Huxae Zazhi 2003, 13, 311;Chem Abstr 2005, 144, 88216.

[7] Huszar, C.; Kis-Tamas, A.; Nemeth, A.; Gajary, A.; Pali, L. PCT Int Appl, WO 9905118, 1999; Chem Abstr 1999, 130, 168371.

[8] Huszar, C.; Kis-Tama, A.; Nemeth, A.; Gajary, A.; Kollar, E.; Aranyosi, P.; Gyure, K.; Meszaros, I.; Csetrine, H. Z.; Supic, A.; Dervalicsne, Z. I.; Dubovszki, K.; Pali, L.; Kunsztne, K. A.; Bognar, E. PCT Int Appl, WO 9905120 A1 19990204, 1999; Chem Abstr 1999, 130, 139344.

[9] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. J Chem Soc Perkin Trans 1987, 2, S1.

[10] Otwinowski, Z.; Minor, W. Methods Enzymol 1997, 276, 307.

[11] Coppens, P. In Crystallographic Computing; Ahmed, F. R.; Hall, S. R.; Huber, C. P., Eds.; Munksgaard: Copenhagen, 1970; p 255.

[12] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. J Appl Crystallogr 1993, 26, 343.

[13] Sheldrick, G. M. SHELXL-97; University of Göttingen: Göttingen, 1997.

# An Efficient Synthesis and Biological Testing of Novel 3-Chloro-4-aryl-1-(4-(phenyldiazenyl)phenyl)azetidin-2-ones



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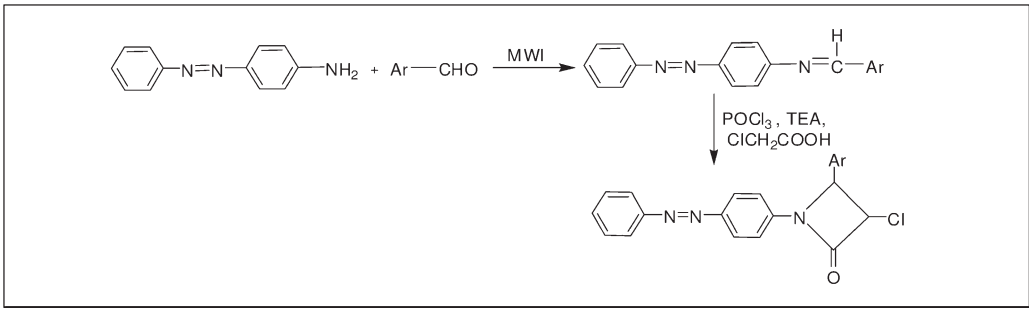


*N*-Benzylidene-4-(phenyldiazenyl)aniline (**Ia–Ij**) has been prepared from *p*-aminoazobenzene with different aromatic aldehydes under microwave irradiation, which on further treatment with chloro acetic acid and $POCl_3$ in the presence of triethyl amine gave the title compounds. The structure of the compounds has been confirmed by spectroscopic techniques (IR and $^1H$ NMR) and elemental analysis. These azetidinones analogues were screened for their antimicrobial activities against strains of different microorganisms. Some of the compounds displayed the promising antibacterial activities against some bacterial strains.

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## INTRODUCTION

The β-lactam skeleton is the key structural element of the most widely used family of antimicrobial agents to date, the β-lactam antibiotics, which includes as representative structural classes (Fig. 1) the Penams 1, Cephems 2, Penems 3, Monobactams 4, Carbapenems 5, and Trinems 6, among others [1]. The first member of this class of compounds was synthesized by Staudinger in 1907 [2]. An interesting group of β-lactams are the monocyclic β-lactams, which are molecules that do not contain another ring fused to the β-lactam. The development of several synthetic 2-azetidinone was due to the growing resistant of bacteria toward the β-lactam antibiotics and need for medicines with a more specific antibacterial activities [3,4]. A large number of monocyclic β-lactams reported to have some other types of biological activity such as antifungal, antitubercular, antitumor, anti-inflamatory, anticonvulsant, cholesterol absorption inhibition, and enzyme inhibition activity [5–10].

Because of such versatile applications, these moieties always attracted the interest of synthetic and medicinal organic chemists [11–14]. A large number of chemical methods for the production of β-lactams have been developed, and the topic has been amply documented and reviewed several times [15]. The hydroxamate cyclization [16], the metalloester enolate-imine condensation [17], the chromium carbene-imine reaction [18], the isocyanate-alkene cycloaddition [19], and the ketene-imine cycloaddition [20] are the approaches most often used for the construction of the azetidin-2-one ring. In particular, the most common method for the synthesis of 2-azetidinone is the Staudinger Ketene-imine cycloaddition, which involves the reaction of imine (Schiff Base) with acid chloride in the presence of tertiary base [21]. This reaction, however, depends on many factors including temperature and reaction time, which often needs to be optimized [22,23].

Hence, to further assess the pharmacological activities of these class of molecules, it was thought worthwhile to synthesize some new derivatives of β-lactam heterocycles by incorporating the *p*-aminoazobenzene and 2-azetidinone moieties in a single framework. We herein report a novel, convenient, and highly efficient method for the preparation of 3-chloro-4-(aryl)-1-(4-(phenyldiazenyl)phenyl)azetidin-2-one **IIa–IIj** in good yields involving two steps. It involves the formation of different Schiff's bases **Ia–Ij** of *p*-aminoazobenzene and aromatic aldehydes followed by the cycloaddition reaction

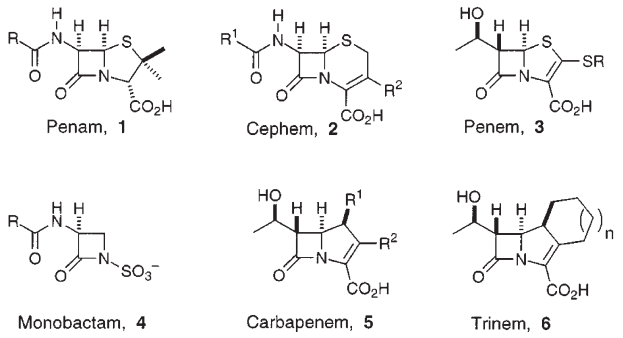


**Figure 1.** Some representative structural classes of β-lactam antibiotics.

of **Ia–Ij** with ketene, which is generated *in situ* from chloroacetic acid in presence of trimethylamine and $POCl_3$ (Scheme 1). The Schiff bases were also prepared by using microwave method [24].

However, the synthesis of Schiff bases **Ia–Ij** under the classical reaction was plagued by a number of serious disadvantages such as low yield of the product as given in Table 1. Therefore, to overcome the drawbacks of the classical method, modern version of this reaction by microwave superheating in solvent and solvent free condition has been adopted. All the synthesized compounds were characterized on the basis of different spectral analysis techniques such as IR and $^1$H NMR and elemental analysis techniques. Also in the present communication, we report the antibacterial activities of the titled compounds (**IIa–IIj**) against nine different bacterial strains.

## RESULTS AND DISCUSSION

As evident from data presented in Table 1, we were able to obtain *N*-arylbenzylidene-4-(phenyldiazenyl)aniline **Ia–Ij** in good yields by using neat conditions under microwave irradiation in presence of solvent and also in solvent free conditions when compared to that of conventional reflux reactions in ethanol. The comparison of isolated yields and reaction time of the three conditions used showed microwave-assisted solvent-free reactions as the most efficient synthetic method in terms of energy and time consumption. All the compounds synthesized were adequately characterized by their elemental analysis and spectral techniques such as IR, $^1$H NMR, and mass spectra.

**Antibacterial activity.** Antibacterial activities of all the compounds were studied against nine different bacterial strains (*E. coli* (mixed), *B. subtilis*, Pseudomonas sp., *S. aureus*, *P.vulageris*, Salmonella sp., *E. coli*(+ve strai,), Rhodococci, *B. stearothermophilus*) by measuring the zone of inhibition on agar plates. The compounds possess moderate to good activity against all strains in comparison with standard drug (Table 2). It can be observed from these results that compounds **IIa–IIj** have shown positive bacterial activity against different bacterial species, which are also known as human pathogenic bacteria. It was also observed that within the synthesized compound extracts, highest zone of inhibition recorded in 3-chloro-4-(furan-2-yl)-1-(4-(phenyl diazenyl) phenyl)azetidin-2-one **(IIe)** extract against the *P. vulageris* 22 mm, which is more than standard, *i.e.*, 17 mm zone of inhibition.

**Scheme 1.** Synthesis of Schiff base with different synthetic path and 3-chloro-4-aryl-1-(4-(phenyldiazenyl)phenyl)azetidin-2-one.

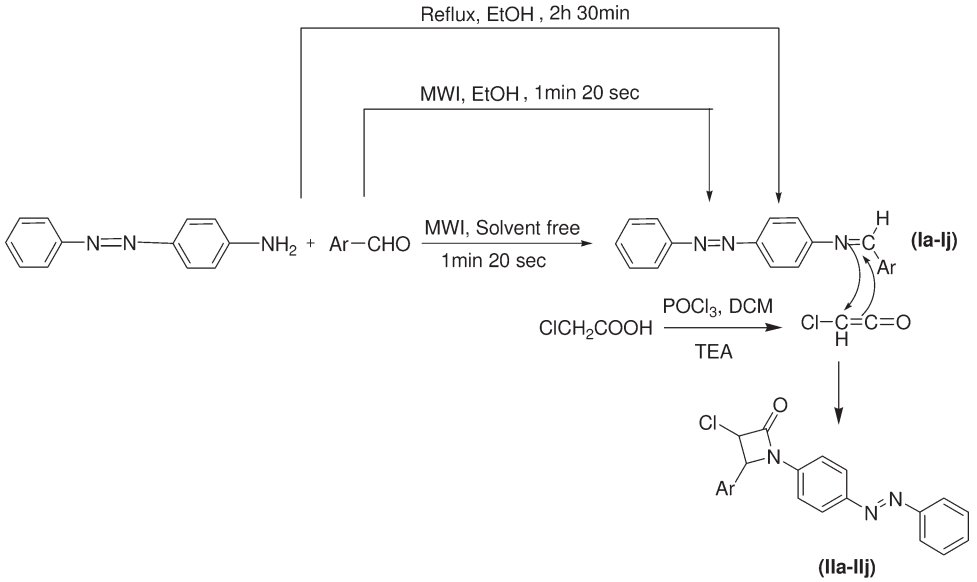

**Table 1**

Time and yield comparison between classical and MW irradiation.

| Compound | Ar | Reaction time (min/sec) | | | Yield (%)[a] | | |
|---|---|---|---|---|---|---|---|
| | | MWI, Solvent Free | MWI, EtOH | Classical, EtOH | MWI, Solvent Free | MWI, EtOH | Classical, EtOH |
| **Ia** | $C_6H_5$ | 1 min 20 sec | 1 min 20 sec | 150 min | 92 | 90 | 85 |
| **Ib** | 2-$OHC_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 90 | 85 | 80 |
| **Ic** | 2-$NO_2C_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 87 | 82 | 75 |
| **Id** | 3-$NO_2C_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 95 | 92 | 85 |
| **Ie** | $C_4H_3O$ | 1 min 20 sec | 1 min 20 sec | 150 min | 90 | 85 | 70 |
| **If** | 4-$OHC_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 85 | 80 | 65 |
| **Ig** | 4-$N(CH_3)_2C_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 92 | 87 | 80 |
| **Ih** | 2-$ClC_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 95 | 88 | 75 |
| **Ii** | 3-$BrC_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 97 | 95 | 85 |
| **Ij** | 4-$ClC_6H_4$ | 1 min 20 sec | 1 min 20 sec | 150 min | 88 | 80 | 60 |

[a] Isolated yields.

## EXPERIMENTAL

**General.** All the chemicals and solvents were obtained from E-Merck, India (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. The microwave assisted synthesis of Schiff base compounds were carried out in a CEM–908010, bench mate model, 300 watts laboratory microwave reactor. IR spectra were recorded on a Shimadzu Dr-8031 instrument. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. $^1$H NMR spectra of the synthesized compounds were recorded on a Bruker-Avance (300 MHz) and Varian-Gemini (200 MHz) spectrophotometer using $CDCl_3$ solvent and TMS as an the internal standard. EI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an EI source.

**Synthesis of Schiff base (Ia–Ij).** ***Microwave method without solvent.*** Equimolar amount of *p*-aminoazo benzene (0.001 mol) and aromatic aldehyde (0.001 mol) were thoroughly mixed in a glass tube, which was loosely closed. The reaction mixture was irradiated for 1min 20 sec with 100 W microwaves at 110°C in MW oven in the temperature control mode. The completion of the reaction was monitored by TLC. The crude product was recrystallized with methanol.

***Microwave method with solvent.*** Equimolar amount of *p*-aminoazobenzene (0.001 mol) and aromatic aldehyde (0.001 mol) and ethanol were taken in a glass tube which was loosely closed and irradiated in MW oven for 1min 20 sec. The completion of the reaction was monitored by TLC. The reaction mixture was allowed to attain room temperature. The solvent was removed, and the crude product was recrystallized with methanol.

**Classical method.** Equimolar amount of *p*-aminoazobenzene (0.001 mol), aromatic aldehyde (0.001 mol), and 10 mL of ethanol was refluxed for 2 hr 30 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set on one side to cool. Then, the reaction mixture was poured in ice cold water and the solid precipitate was separated out. The precipitate was filtered and collected crude product was recrystallized using methanol.

**Table 2**

Biological activities of compounds chloro-4-(aryl)-1-(4-(phenyldiazenyl) phenyl)azetidin-2-one (**IIa–IIj**).

| Bacterial strain | Zone of inhibition in mm along without well diameter (5 mm) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Chemical compounds | | | | | | | | | | |
| | **IIa** | **IIb** | **IIc** | **IId** | **IIe** | **IIf** | **IIg** | **IIh** | **IIi** | **IIj** | Standard Nystatin |
| *E. coil (mixed)* | 20 | 16 | 6 | 12 | – | 7 | 14 | 9 | 13 | 16 | 17 |
| *B. subtilis* | 3 | 5 | 2 | – | 3 | 2 | 8 | 6 | 9 | 2 | 6 |
| *Pseudomonas sp.* | 13 | 3 | 15 | 6 | 10 | 6 | 5 | 10 | 13 | 9 | 12 |
| *S. aureus* | – | – | 4 | 7 | 5 | 10 | 8 | 4 | 8 | 6 | 9 |
| *P. vulageris* | 15 | 11 | 9 | 13 | 22 | 16 | 8 | 14 | 10 | 5 | 17 |
| *Salmonella sp.* | 9 | 15 | 13 | 20 | 17 | 10 | 8 | 16 | 14 | 15 | 19.1 |
| *E. coil(+ve strain)* | – | – | 6 | 4 | 9 | 10 | 13 | 7 | – | 2 | 11 |
| *Rhodococci* | – | – | – | 4 | 2 | 5 | 3 | 3 | 2 | 1 | 6 |
| *B. stearothermopelus* | 5 | 2 | 4 | 6 | 2 | 5 | 3 | 4 | 10 | 6 | 7.2 |

"–" represent "not active."

***N-Benzylidene-4-(phenyldiazenyl)aniline (Ia).*** m. p.: 150°C, IR (KBr): 1410 $cm^{-1}$ (N=N), 1620.2 (—C=N—); $^1H$ NMR: δ = 6.80 (d, *J* = 8.4 Hz, 2H, Ar-CH); 7.20 (s, 1H, Ar-CH); 7.50–7.70 (m, 7H, Ar-CH); 7.80 (d, *J* = 8.7 Hz, 2H, Ar-CH); 8.00 (d, *J* = 8.2 Hz, 2H, Ar-CH); 8.60 (s, 1H, N=CH); Anal. Calcd. For $C_{19}H_{15}N_3$ : C, 79.98; H, 5.30; N, 14.73; Found: C, 79.50; H, 5.00; N, 14.50; Mass spectra, m/z = 285 (100%).

***2-((4-(Phenyldiazenyl)phenylimino)methyl)phenol (Ib).*** m. p.: 165°C, IR (KBr): 1430 $cm^{-1}$ (N=N), 1600 (—C=N—); $^1H$ NMR: δ = 6.70 (d, *J* = 8.8 Hz, 2H, Ar-CH); 7.0–7.60 (m, 9H, Ar-CH); 7.90 (d, J = 8.9 Hz, 2H, Ar-CH); 8.35 (s, 1H, —N=CH); 11.20 (s, 1H, Ar-OH); Anal. Calcd. For $C_{19}H_{15}ON_3$: C, 75.73; H, 5.02; N, 13.94; Found: C, 75.50; H, 5.00; N, 13.60; Mass spectra, m/z = 301 (100%).

***N-(2-Nitrobenzylidene)-4-(phenyldiazenyl)aniline (Ic).*** m. p.: 160°C, IR (KBr): 1420 $cm^{-1}$ (N=N), 1610 (—C=N—); $^1H$ NMR: δ = 6.50 (d, *J* = 8.1 Hz, 2H, Ar-CH); 7.20 (s, 1H, Ar-CH); 7.50–7.70 (m, 5H, Ar-CH); 7.80–8.00 (t, *J* = 7.9 Hz, 3H, Ar-CH); 8.20 (d, *J* = 8.8 Hz, 2H, Ar-CH); 8.64 (s, 1H, —N=CH); Anal. Calcd. For $C_{19}H_{14}N_4O_2$: C, 69.68; H, 4.27; N, 16.96; Found: C, 69.40; H, 4.10; N, 16.60; Mass spectra, m/z = 330.11 (100%).

***N-(3-Nitrobenzylidene)-4-(phenyldiazenyl)aniline (Id).*** m. p.: 175°C, IR (KBr): 1430 $cm^{-1}$ (N=N), 1650 (—C=N—); $^1H$ NMR: δ = 6.80 (d, *J* = 8.7 Hz,2H, Ar-CH); 7.20–8.30 (m, 10H, Ar-CH); 8.50 (s, 1H, Ar-CH); 8.60 (s, 1H, —N=CH); Anal. Calcd. For $C_{19}H_{14}N_4O_2$: C, 69.68; H, 4.27; N, 16.96; Found: C, 69.20; H, 4.00; N, 16.20 ; Mass spectra, m/z = 330 (100%).

***N-(Furan-2-ylmethylene)-4-(phenyldiazenyl)aniline (Ie).*** m. p.: 180°C, IR (KBr): 1460 $cm^{-1}$ (N=N), 1630 (—C=N—); $^1H$ NMR: δ = 6.50 (s, 1H, Ar-CH); 6.85 (d, *J* = 8.8 Hz, 2H, Ar-CH); 6.90 (s, 1H, Ar-CH); 7.20 (s, 1H, Ar-CH), 7.50 (s, 1H, —N=CH); 7.55–7.65 (m, 4H, Ar-CH); 7.70 (s, 1H, Ar-CH); 8.00 (d, *J* = 8.6 Hz, 2H, Ar-CH); Anal. Calcd. For $C_{17}H_{13}ON_3$: C, 74.17; H, 4.76; N, 15.26; Found: C, 74.00; H, 4.50; N, 15.00; Mass spectra, m/z = 275 (100%).

***4-((4-(Phenyldiazenyl)phenylimino)methyl)phenol (If).*** m. p.: 155°C, IR (KBr): 1450 $cm^{-1}$ (N=N), 1640 (—C=N—); $^1H$ NMR: δ = 6.85 (m, 4H, Ar-CH); 7.20 (s, 1H, Ar-CH); 7.55–7.60 (m, 4H, Ar-CH); 7.75–7.80 (d, *J* = 8.4 Hz, 2H, Ar-CH), 8.00 (d, *J* = 8.7 Hz, 2H, Ar-CH); 8.50 (s, 1H, —N=CH); 9.40 (s, 1H, Ar-OH); Anal. Calcd. For $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94; Found: C, 75.00; H, 4.90; N, 13.40; Mass spectra, m/z = 301.20 (100%).

***N,N-dimethyl-4-((4-phenyldiazenyl)phenylimino) methyl)aniline (Ig).*** m. p.: 180°C, IR (KBr): 1400 $cm^{-1}$ (N=N), 1620 (—C=N—); $^1H$ NMR: δ = 3.00 (s, 6H, —N(CH3)2); 6.80–6.85 (m, 4H, Ar-CH); 7.20 (s, 1H, Ar-CH); 7.50 (d, *J* = 8.6 Hz, 2H, Ar-CH); 7.60–7.68 (m, 4H, Ar-CH), 7.90 (d, *J* = 8.7 Hz, 2H, Ar-CH); 8.55 (s, 1H, —N=CH); Anal. Calcd. For $C_{21}H_{20}N_4$: C, 76.80; H, 6.14; N, 17.06; Found: C, 76.40; H, 6.00; N, 17.00; Mass spectra, m/z = 328 (100%).

***N-(2-Chlorobenzylidene)-4-(phenyldiazenyl)aniline (Ih).*** m. p.: 195°C, IR (KBr): 1420 $cm^{-1}$ (N=N), 1630 (—C=N—); $^1H$ NMR: δ = 6.80–7.50 (m, 4H, Ar-CH); 7.20–7.60(m, 7H, Ar-CH); 8.00 (d, *J* = 8.5 Hz, 2H, Ar-CH); 8.30(s, 1H, —N=CH); Anal. Calcd.For $C_{19}H_{14}N_3Cl$: C, 71.36; H, 4.41; N, 13.14; Found: C, 71.00; H, 4.20; N, 13.00; Mass spectra, m/z = 319 (100%).

***N-(3-Bromobenzylidene)-4-(phenyldiazenyl)aniline (Ii).*** m. p.: 170°C, IR (KBr): 1440 $cm^{-1}$ (N=N), 1650 (—C=N—); $^1H$ NMR: δ = 6.60–7.30 (t, *J* = 7.2 Hz, 3H, Ar-CH); 7.41 (s, 1H, Ar-CH); 7.25–7.80(m, 7H, Ar-CH); 8.20 (d, *J* = 8.8 Hz, 2H, Ar-CH); 8.70(s, 1H, —N=CH); Anal. Calcd.For $C_{19}H_{14}N_3Br$: C, 62.65; H, 3.87; N, 11.54; Found: C, 62.50; H, 3.60; N, 11.30; Mass spectra, m/z = 363.50 (100%).

***N-(4-Chlorobenzylidene)-4-(phenyldiazenyl)aniline (Ij).*** m. p.: 190°C, IR (KBr): 1470 $cm^{-1}$ (N=N), 1660 (—C=N—); $^1H$ NMR: δ = 6.80–7.45 (m, 4H, Ar-CH); 7.25–7.80(m, 7H, Ar-CH); 8.30 (d, *J* = 8.6 Hz, 2H, Ar-CH); 8.50(s, 1H, —N=CH); Anal. Calcd.For $C_{19}H_{14}N_3Cl$: C, 71.36; H, 4.41; N, 13.14; Found: C, 71.20; H, 4.30; N, 12.90; Mass spectra, m/z = 319 (100%).

**General procedure for the preparation of 3-chloro-4-aryl-1-(4-(phenyldiazenyl) phenyl) azetidin-2-one (IIa-IIj).** A mixture of Schiff base **Ia–Ij** (0.002 moles) and chloroacetic acid (0.002 moles) was dissolved in dichloromethane (10 mL) in stoppered conical flask, cooled, and stirred. In cold condition of the reaction mixture, triethylamine [TEA] (0.002 moles) was added in it, followed by dropwise addition of $POCl_3$ in dichloromethane (0.002 moles) with vigorous stirring. The reaction mixture was then stirred for additional 16 hr. The completion of the reaction was monitored by TLC. The reaction mixture was washed with water and dried over sodium sulphate. The products that were obtained after removing the solvent were purified from chloroform.

***3-Chloro-4-phenyl-1-(4-(phenyldiazenyl)phenyl)azetidin-2-one (IIa).*** Yield: 80%; m. p.: 210°C; IR (KBr, $cm^{-1}$): 1364 (C—N); 1460 (N=N); 1760 (C=O β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.10 (s, 1H, —N—CH), 5.40 (s, 1H, —CH—C=O), 6.80 (m, 4H, Ar-H); 7.25–7.40 (m, 6H, Ar-H); 7.60 (d, *J* = 8.4 Hz, 2H, Ar-H); 8.00 (d, *J* = 8.3 Hz, 2H, Ar-H). Anal. Calcd. for $C_{21}H_{16}N_3OCl$: C, 69.61; H, 4.41; N, 11.60; Found C, 69.50; H, 4.20; N, 11.40; Mass spectra, m/z = 361 (100%).

***3-Chloro-4-(2-hydroxyphenyl)-1-(4-(phenyldiazenyl)phe-nyl) azetidin-2-one (IIb).*** Yield: 91%; m. p.: 220°C; IR (KBr, $cm^{-1}$): 2973 (OH), 1360 (C—N); 1567 (N=N); 1765 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 5.16 (s, 1H, —N—CH), 5.35 (s, 1H, —CH—C=O), 6.80–6.95 (m, 4H, Ar-H); 7.20 (s, 1H, Ar-H); 7.65 (t, *J* = 7.2 Hz, 3H, Ar-H); 7.90 (d, *J* = 8.1 Hz, 2H, Ar-H); 8.30 (t, *J* = 7.3 Hz, 3H, Ar-H); 9.50 (s, 1H, Ar-OH). Anal. Calcd. for $C_{21}H_{16}O_2N_3Cl$: C, 66.66; H, 4.23; N, 11.11; Found: C, 66.40; H, 4.10; N, 11.00; Mass spectra, m/z = 377 (100%).

***3-Chloro-4-(2-nitrophenyl)-1-(4-(phenyldiazenyl)phenyl) azetidin-2-one (IIc).*** Yield: 95%; m. p.: 225°C; IR (KBr, $cm^{-1}$): 1340 (C—N); 1580 (N=N); 1755 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 5.00 (s, 1H, —N—CH), 5.30 (s, 1H, —CH—C=O), 6.90 (m, 4H, Ar-H); 7.10 (s, 1H, Ar-H); 7.40 (d, *J* = 8.1 Hz, 2H, Ar-H); 7.60 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.70 (d, *J* = 8.1 Hz, 2H, Ar-H); 8.00 (t, *J* = 7.6 Hz, 3H, Ar-H); 8.30 (t, *J* = 7.4 Hz, 3H, Ar-H). Anal. Calcd. for $C_{21}H_{19}N_4O_3Cl$: C, 61.91; H, 3.68; N, 13.75; Found: C, 61.00.; H, 3.60; N, 13.60; Mass spectra, m/z = 406 (100%).

***3-Chloro-4-(3-nitrophenyl)-1-(4-(phenyldiazenyl)phenyl) azetidin-2-one (IId).*** Yield: 90%; m. p.: 205°C; IR (KBr, $cm^{-1}$): 1330 (C—N); 1590 (N=N); 1740 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ (ppm) = 5.10 (s, 1H, —N—CH), 5.40 (s, 1H, —CH—C=O), 6.70 (d, *J* = 8.5 Hz, 2H, Ar-H); 7.20 (s, 1H, Ar-H); 7.60–7.68 (m, 4H, Ar-H); 8.00–8.08 (t, *J* = 7.1 Hz, 3H, Ar-H); 8.18 (s, 1H, Ar-H); 8.20 (d, *J* = 8.4 Hz, 2H, Ar-

H). Anal. Calcd. for $C_{21}H_{15}N_4O_3Cl$: C, 61.91; H, 3.68; N, 13.75; Found: C, 61.20; H, 3.40; N, 13.50; Mass spectra, m/z = 405.9 (100%).

***3-chloro-4-(furan-2-yl)-1-(4-(phenyldiazenyl)phenyl)az-etidin-2-one (IIe).*** Yield: 85%; m.p.: 225°C; IR (KBr, $cm^{-1}$): 1310 (C—N); 1560 (N=N); 1710 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 5.35 (s, 1H, —N—CH), 5.45 (s, 1H, —CH—C=O), 6.40–6.45 (t, *J* = 7.4 Hz, 3H, Ar-H); 6.80 (s, 1H, Ar-H); 7.10 (d, *J* = 8.1 Hz, 2H, Ar-H); 7.60 (d, *J* = 8.3 Hz, 2H, Ar-H); 7.70 (d, *J* = 8.2 Hz, 2H, Ar-H); 8.10 (d, *J* = 8.3 Hz, 2H, Ar-H). Anal. Calcd. for $C_{19}H_{14}O_2N_3Cl$: C, 64.77; H, 3.97; N, 11.93; Found: C, 64.60; H, 3.80; N, 11.80; Mass spectra, m/z = 351 (100%).

***3-chloro-4-(4-hydroxyphenyl)-1-(4-(phenyldiazenyl) phenyl) azetidin-2-one (IIf)*** Yield: 75%; m. p.: 230°C; IR (KBr, $cm^{-1}$): 1345 (C—N); 1600 (N=N); 1755 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 5.00 (s, 1H, —N—CH), 5.40 (s, 1H, —CH—C=O), 6.70–6.80 (m, 4H, Ar-H); 7.00 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.50 (d, *J* = 8.6 Hz, 2H, Ar-H); 7.90 (t, *J* = 7.6 Hz, 3H, Ar-H); 8.20 (d, *J* = 8.4 Hz, 2H, Ar-H); 9.30 (s, 1H, Ar-OH). Anal. Calcd. for $C_{21}H_{16}N_3O_2Cl$: C, 66.66; H, 4.23; N, 11.11; Found : C, 66.30; H, 4.20; N, 11.10 ; Mass spectra, m/z = 377 (100%).

***3-chloro-4-(4-(dimethylamino)phenyl)-1-(4-(phenyldiaz-enyl) phenyl)azetidin-2-one (IIg).*** Yield: 95%; m. p.: 220°C; IR (KBr, $cm^{-1}$): 1335 (C—N); 1620 (N=N); 1765 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 2.90 (s, 6H, $N(CH_3)_2$) 5.15 (s, 1H, —N—CH), 5.30 (s, 1H, —CH—C=O), 6.70 (d, *J* = 8.3 Hz, 2H, Ar-H); 6.80 (d, *J* = 8.2 Hz, 2H, Ar-H); 7.10 (d, *J* = 8.2 Hz, 2H, Ar-H); 7.20 (s, 1H, Ar-H); 7.55 (d, *J* = 8.5 Hz, 2H, Ar-H); 8.00 (d, *J* = 8.4 Hz, 2H, Ar-H); 8.40 (d, *J* = 8.2 Hz, 2H, Ar-H); Anal. Calcd. for $C_{23}H_{21}ON_4Cl$: C, 68.14; H, 5.18; N, 13.82; Found: C, 68.10; H, 5.10; N, 13.60; Mass spectra, m/z = 404 (100%).

***3-chloro-4-(2-chlorophenyl)-1-(4-(phenyldiazenyl) phenyl)-azetidin-2-one (IIh).*** Yield: 80%; m. p.: 240°C; IR (KBr, $cm^{-1}$): 1355 (C—N); 1660 (N=N); 1770 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 4.90 (s, 1H, —N—CH), 5.20 (s, 1H, —CH—C=O), 6.60 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.20–7.30 (m, 4H, Ar-H); 7.60–7.75 (t, *J* = 7.5 Hz, 3H, Ar-H); 7.80 (d, *J* = 8.1 Hz, 2H, Ar-H); 8.20 (d, *J* = 8.3 Hz, 2H, Ar-H); Anal. Calcd. for $C_{21}H_{15}ON_3Cl_2$: C, 63.63; H, 3.78, N, 10.60; Found: C, 63.50; H, 3.60; N, 10.50; Mass spectra, m/z = 395 (100%).

***4-(3-bromophenyl)-3-chloro-1-(4-(phenyldiazenyl) phenyl)-azetidin-2-one (IIi).*** Yield: 87%; m. p.: 245°C; IR (KBr, $cm^{-1}$): 1365 (C—N); 1630 (N=N); 1740 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 5.10 (s, 1H, —N—CH), 5.30 (s, 1H, —CH—C=O), 6.70 (d, *J* = 8.3 Hz, 2H, Ar-H); 7.20–7.30 (t, *J* = 7.6 Hz, 3H, Ar-H); 7.40–7.45 (d, *J* = 8.6 Hz, 2H, Ar-H); 7.60 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.90 (d, *J* = 8.4 Hz, 2H, Ar-H); 8.40 (d, *J* = 8.5 Hz, 2H, Ar-H); Anal. Calcd. for $C_{21}H_{15}ON_3BrCl$: C, 57.14; H, 3.40; N, 9.52; Found: C, 57.10; H, 3.30; N, 9.40; Mass spectra, m/z = 439 (100%).

***3-chloro-4-(4-chlorophenyl)-1-(4-(phenyldiazenyl) phenyl)-azetidin-2-one (IIj).*** Yield: 90%; m. p.: 250°C; IR (KBr, $cm^{-1}$): 1370 (C—N); 1650 (N=N); 1720 (C=O β-lactam); $^1H$ NMR ($CDCl_3$): δ(ppm) = 5.00 (s, 1H, —N—CH), 5.40 (s, 1H, —CH—C=O), 6.90 (d, *J* = 8.4 Hz, 2H, Ar-H); 7.20 (s, 1H, Ar-H); 7.40–7.50 (m, 4H, Ar-H); 7.60 (d, *J* = 8.2 Hz, 2H, Ar-H); 7.80 (d, *J* = 8.1 Hz, 2H, Ar-H); 8.50 (d, *J* = 8.3 Hz, 2H, Ar-H); Anal. Calcd. for $C_{21}H_{15}N_3OCl_2$: C, 63.63; H, 3.78; N, 10.60; Found: C, 63.40; H, 3.50; N, 10.30; Mass spectra, m/z = 395 (100%).

## CONCLUSIONS

A new method for the synthesis of Schiff base **Ia–Ij** using microwave irradiation offers significant improvements over existing procedures. Also, this simple and reproducible technique affords the products with short reaction times, excellent yields, and without formation of undesirable side products. From data of antimicrobial activity, it could be observed that compounds of the series **IIa–IIj** showing good comparable activity against standard drugs.

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### REFERENCES AND NOTES

[1] Palomo, C.; Aizpurua, J. M.; Ganboa, Inãki.; Oiarbide, M. Eur J Org Chem 1999, 8, 3223.

[2] Staudinger, H. Liebigs Ann Chem 1907, 61, 356.

[3] (a) O'Driscoll, M.; Greenhalgh, K.; Young, A.; Turos, E.; Dickey, S.; Lim, D. V. Bioorg Med Chem 2008, 16, 7832; (b) Bai, X.; Xu, X.; Fu, R.; Chen, J.; Chen, S. Bioorg Med Chem Lett 2007, 17, 101; (c) Turos, E.; Reddy, G. S. K.; Greenhalgh, K.; Ramaraju, P.; Abeylath, S. C.; Jang, S.; Dickey, S.; Lim, D. V. Bioorg Med Chem Lett 2007, 17, 3468; (d) Tozsera, J.; Sperka, T.; Pitlik, J.; Bagossia, P. Bioorg Med Chem Lett 2005, 15, 3086; (e) Banik, B. K.; Becker, F. F.; Banik, I. Bioorg Med Chem 2005, 13, 3611; (f) Nivsarkar, M.; Thavaselvam, D.; Prasanna, S.; Sharma, M.; Kaushik, M. P. Bioorg Med Chem Lett 2005, 15, 1371; (g) Sutton, J. C.; Bolton, S. A.; Harti, K. S.; Huang, M. H.; Jacobs, G.; Meng, W.; Zhao, G.; Bisacchi, G. S. Bioorg Med Chem Lett 2004, 14, 2233; (h) Marchand-Brynaert, J.; Dive, G.; Galleni, M.; Gerard, S. Bioorg Med Chem 2004, 12, 129; (i) Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L. Bioorg Med Chem Lett 1997, 7, 1689.

[4] Van der Steen, F. H.; Van Koten, G. Tetrahedron 1991, 47, 7503.

[5] Jubie, S.; Gowramma, B.; Muthal, N. K.; Gomathi, S.; Elango, K. Int J Chem Tech Res 2009, 1, 153.

[6] Kumar, A.; Gurtu, S.; Agrawal, J. C.; Sinha, J. N.; Bhrgava, K. P.; Shanker, K. J Indian Chem Soc 1983, LX, 608.

[7] Patel, R. B.; Desai, P. S.; Chikhalia, K. H. Indian J Chem 2006, 45B, 773.

[8] Toraskar, M. P.; Kadam, V. J.; Kulkarni, V. M. Int J Chem Tech Res 2009, 1, 1194.

[9] Halwe, A. K.; Bhadauria, R.; Dubey, R. N. Bioorg Med Chem Lett 2007, 17, 341.

[10] Priyadarshini, R.; Vijayraj, R.; Ravi, T. K. Indian J Heterocycl Chem 2004, 14, 165.

[11] (a) Singh, G. S. Tetrahedron 2003, 59, 7631; (b) Brown, M. J. Heterocycles 1989, 29, 2225; (c) Isaacs, N. S. Chem Soc Rev 1976, 5, 181; (d) Mihovilovic, M. D.; Spina, M.; Stanetty, P. Arkivoc 2005, 43; (e) Shirode, N. M.; Kulkarni, K. C.; Gumatse, V. K.; Deshmukh, A. R. A. S. Arkivoc 2005, 53.

[12] Singh, G. S. Mini-Rev Med Chem 2004, 4, 69.

[13] Singh, G. S. Mini-Rev Med Chem 2004, 4, 93.

[14] Reviews: (a) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswami, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. Curr Med Chem 2004, 11, 1889; (b) Alcaide, B.; Almendros, P. Curr Med Chem 2004, 11, 1921.

[15] For comprehensive general reviews, see: (a) Koppel, G. A. In Small Ring Heterocycles, Vol. 42; Hassner, A., Ed.; Wiley: New York, 1983; p 219; (b) Backes, J. In Houben- Weyl, Methoden der Orgnischen Chemie, Band E16B; Muller, E., Bayer, O., Eds.; Thieme: Stuttgart, 1991; p 31; (c) Dekimpe, N. In Comprehensive Heterocylic Chemistry II, Vol. 1B; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Padwa, A., Eds.; Pergamon: Oxford, 1996; p 507.

[16] Miller, M. J. Acc Chem Res 1986, 19, 49.

[17] (a) Hart, D. J.; Ha, D. C. Chem Rev 1989, 89, 1447; (b) Brown, M. J. Heterocycles 1989, 29, 2225; (c) Georg, G. I. In Natural Product Chemistry, Vol. 4; Rahman, A.-ur., Ed.; Elsevier: Amsterdam, 1989; p 431; (d) Fujisawa, T.; Shimizu, M. Rev Heteroatom Chem 1996, 15, 203; (e) Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. Pure Appl Chem 1990, 62, 605; (f) Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G.; Bandini, E. In Chemical Synthesis, Gnosis to Prognosis; Chatgilialoglu, C.; Snieckus, V., Eds.; Kluwer Academic: Amsterdam, 1996; p 25.

[18] (a) Hegedus, L. S. Acc Chem Res 1995, 28, 299; (b) Barrett, M. A.; Sturgess, M. A. Tetrahedron 1988, 44, 5615.

[19] Chmielewski, M.; Kaluza, Z.; Furman, B. Chem Commun 1996, 2689.

[20] Staudinger, H. Liebigs Ann Chem 1907, 356, 51.

[21] Singh, G. S.; Mbukwa, E.; Pheko, T. Arkivok 2007, 9, 80.

[22] (a) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswami, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. Curr Med Chem 2004, 11, 1889; (b) Alcaide, B.; Almendros, P. Curr Med Chem 2004, 11, 1921.

[23] Panday, V. K.; Gupta, V. D.; Upadhyay, M.; Singh, V. K.; Tandon, M. Indian J Chem SecB 2005, 44, 158.

[24] Thakre, W. B.; Meshram, J. S. Orient J Chem 2008, 24, 1123.

# Synthesis of 2-(*N*-Benzylpyrrolyl)-benzimidazoles Using Polyphosphoric Acid Prompted Cyclocondensation



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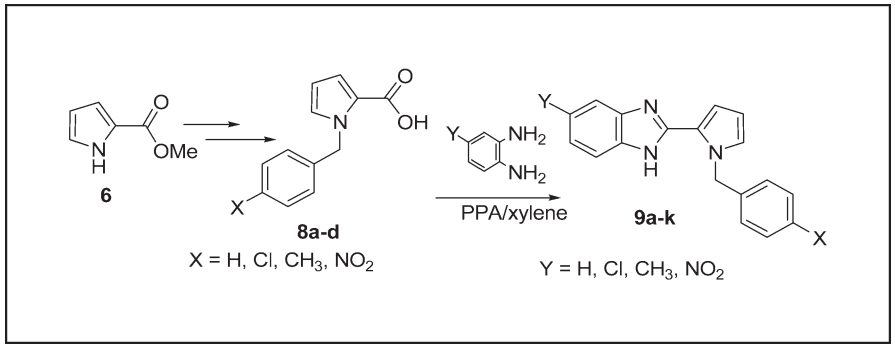


Synthesis of a series of 2-substituted benzimidazoles was carried out for screening anti-inflammatory activities. 2-(*N*-benzylpyrrolyl)-benzimidazoles **9a–k** were synthesized from *N*-benzyl-2-pyrrole carboxylic acids **8a–d** and 4-substituted-1,2-phenylenediamines by cyclocondensation utilizing polyphosphoric acid (PPA) as condensing agent. The *N*-benzyl-2-pyrrole carboxylic acids were prepared by standard method of *N*-benzylation of 2-pyrrole carboxylate using NaH/DMF and appropriately substituted benzyl halides followed by alkaline hydrolysis.

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## INTRODUCTION

Benzimidazole derivatives are known to possess varied biological activities. Substituted benzimidazole derivatives have been reported to possess anticancer, antiulcer, antiviral, antifungal, antimicrobial, and anti-inflammatory activities [1–6]. Prostaglandins and leukotriens from oxidative metabolism of arachidonic acid play established roles in the pathophysiology of inflammatory disorders [7,8]. Pharmacological interference with cyclooxygenase (COX) and 5-lipooxygenase (5-LOX), enzymes involved in production of prostaglandins and leukotriens is a hallmark feature of virtually all marked nonsteroidal anti-inflammatory drugs (NSAIDs). This property is believed to play an important role in their therapeutic effects and certain mechanism-based side effects including gastrointestinal bleeding, nephrotoxicity, and cardiovascular problems in the case of highly selective cyclooxygenase-2 inhibitors [9–14]. There have been remarkable efforts in developing new classes of compounds to minimize the side effects of the existing NSAIDs. Recent investigations on triazole, imidazole, pyrrole, benzimidazole, and indole derivatives Figure 1 have shown that these classes of heterocycles received much attention as potential NSAIDs [15–25]. Literature survey also revealed that when one bioactive heterocyclic system was coupled with another, a molecule with enhanced biological activity was produced [26–28]. Based on these considerations, in the course of research devoted to the development of new classes of anti-inflammatory agents [29–31], we have speculated that incorporating pyrrole ring into the 2-position of benzimidazole moiety result in compounds with single

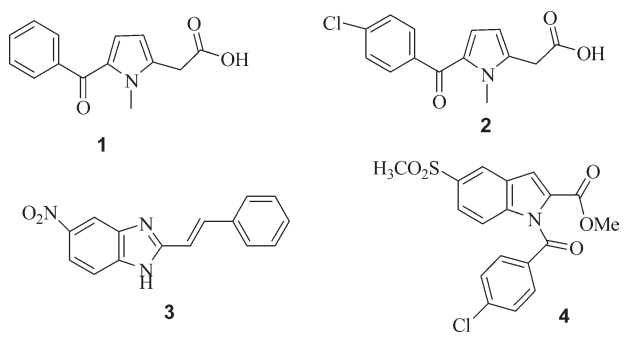



**Figure 1.** Structures of some pyrrole, benzimidazole, and indole derivatives with anti-inflammatory activity.

molecular scaffold that could enhance biological activities. Herein, we report the synthesis of this new class of compounds. The screening of anti-inflammatory activities of these compounds is underway.

## RESULTS AND DISCUSSION

The synthetic routes for the title compounds are outlined in Scheme 1. Pyrrolylbenzimidazoles, **9a–k** were synthesized starting from the commercially available 2-pyrrole carboxylic acid in four steps. Esterification of an acid by refluxing in thionylchloride/methanol mixture afforded the corresponding ester **6**. *N*-benzylation of **6** by treating with NaH/DMF followed by appropriately substituted benzyl halides afforded the corresponding *N*-benzyl-2-pyrrole carboxylates **7a–d**. Alkaline hydrolysis of **7** using 30% aqueous potassium hydroxide gave the carboxylic acids **8a–d**, as key intermediates for the preparation of the targeted benzimidazoles. Cyclocondensation of **8** with 4-substituted-1,2-phenylenediamine carried out utilizing polyphosphoric acid (PPA) as condensing agent afforded the titled compounds in fair to good yield. The chemical structures of all new compounds were established by infrared (IR), $^1$H NMR spectra as well as elemental analysis. The IR-spectral characteristics (all spectra taken in KBr) are quite similar and could be summarized as: ν (N—H): 3150–3185 cm$^{-1}$; ν (C—H) 2900 cm$^{-1}$; ν (—C=N—): 1620–1760 cm$^{-1}$. Detailed $^1$H NMR spectra of the targeted and intermediate compounds is given in the experimental section. The elemental analysis indicated by the symbols of the elements was within ±0.4% of theoretical values. Relevant physical data of the targeted compounds were collected and summarized in Table 1.

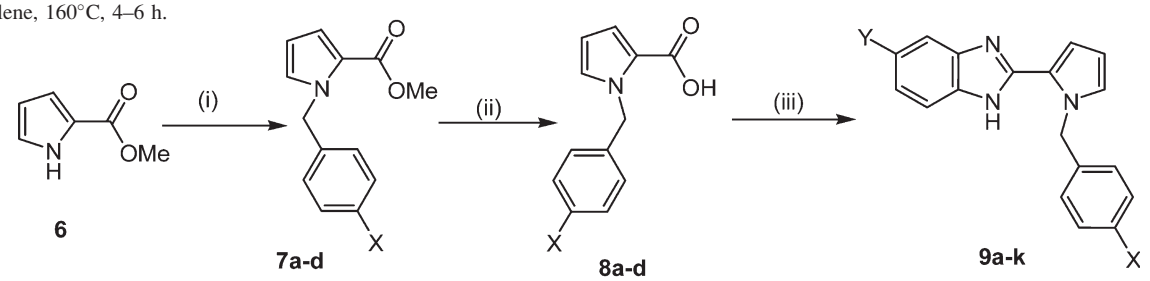
## EXPERIMENTAL

Melting points (mp) were determined on Gallenkamp melting point apparatus and are uncorrected. Reagents and solvents were purchased from Sigma-Aldrich Chemical Company (Milwaukee, WI) and used as received. The structures of the products described were confirmed by IR, $^1$H NMR, and elemental analysis data. The IR spectra were run with KBr pellets on Perkin-Elmer 1430 FT spectrometer and are reported in cm$^{-1}$. $^1$H NMR spectra were recorded on Varian Gemini HX-300 MHz spectrometer. All $^1$H chemical shifts (in ppm) are reported relative to tetramethylsilane as internal standard for solutions in DMSO-$d_6$ and $CDCl_3$ as the solvent unless otherwise specified. Elemental microanalysis was performed in Galbraith Laboratories (Knoxville, Tennessee). Analysis indicated by the symbols of the elements was within ±0.4% of the theoretical values. Analytical thin layer chromatography was performed on 250 μm-layer flexible plates. Spots were visualized under Ultraviolet illumination. Reaction products were purified, when necessary, by column chromatography on silica gel 60 (200–425 mesh), with the solvent system indicated. Solvents were evaporated *in vacuo*. Anhydrous sodium sulphate was used as drying agent.

**Preparation of *N*-benzyl-2-pyrrole carboxylates (7a–d); general procedure A.** To a cooled solution of methyl-2-pyrrol carboxylate **6** (1 equiv, 10 mmol), in 12 mL of DMF, NaH (1.5 equiv, 15 mmol) was added in small portions. The reaction mixture was stirred at 0°C for 20 min, the appropriately substituted benzyl halide (1 equiv, 10 mmol) in 0.6 mL DMF was added dropwise. The mixture was warmed to room temperature and stirred for 2 h. Excess hydride was decomposed with a small amount of methyl alcohol. After evaporation to dryness under reduced pressure, the crude residue was washed with water and extracted with ethyl acetate. The combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated *in vacuo*. The resulting solid was purified by column chromatography (ethyl acetate: hexane) to afford *N*-(4-substitutedbenzyl)-2-pyrrole carboxylates (**7a–d**).

***Methyl-N-benzylpyrrole-2-carboxylate (7a).*** Isolated as white crystalline solid, yield 1.86 g (86.5%); $^1$H NMR (300

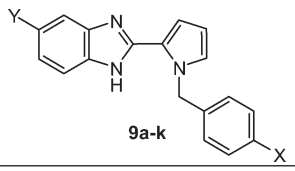
**Scheme 1.** Reagents and conditions: (i) NaH, DMF, $PhCH_2Br$, 0–65°C, 2–4 h, (ii) 30% KOH/MeOH, reflux, 1–2 h. (iii) *O*-phenylene diamine, PPA/xylene, 160°C, 4–6 h.




9a X = Y = H
9b X = H, Y = $CH_3$
9c X = H, Y = $NO_2$
9d X = H, Y = Cl
9e X = $CH_3$, Y = H
9f X = $CH_3$, Y = $NO_2$
9g X = Cl, Y = H
9h X = Cl, Y = $NO_2$
9i X = $NO_2$, Y = H
9j X = $NO_2$, Y = $CH_3$
9k X = $NO_2$, Y = Cl

**Table 1**

Physical and analytical data of *N*-benzyl-2-pyrrolylbenzimidazoles.




**9a-k**

| Entry | X | Y | Yield (%) | mp (°C) | M. Formula | Analysis (%) (Calc./Found) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **9a** | H | H | 77.4 | 121–123 | $C_{18}H_{15}N_3$ | 79.10 | 5.53 | 15.37 |
| | | | | | | 79.14 | 5.52 | 15.36 |
| **9b** | H | $CH_3$ | 80.1 | 133–134 | $C_{19}H_{17}N_3$ | 79.41 | 5.96 | 14.62 |
| | | | | | | 79.07 | 5.92 | 14.36 |
| **9c** | H | $NO_2$ | 67 | 151–153 | $C_{18}H_{14}N_4O_2$ | 67.91 | 4.43 | 17.60 |
| | | | | | | 67.87 | 4.52 | 17.44 |
| **9d** | H | Cl | 79 | 167–168 | $C_{18}H_{14}ClN_3$ | 70.24 | 4.58 | 13.65 |
| | | | | | | 70.07 | 4.52 | 13.36 |
| **9e** | $CH_3$ | H | 74 | 176–177 | $C_{19}H_{17}N_3$ | 79.41 | 5.96 | 14.62 |
| | | | | | | 79.15 | 5.98 | 14.76 |
| **9f** | $CH_3$ | $NO_2$ | 74.7 | 204–205 | $C_{19}H_{16}N_4O_2$ | 68.66 | 4.85 | 16.86 |
| | | | | | | 68.35 | 4.98 | 16.76 |
| **9g** | Cl | H | 78.8 | 233–235 | $C_{18}H_{14}ClN_3$ | 70.24 | 4.58 | 13.65 |
| | | | | | | 70.19 | 4.52 | 13.44 |
| **9h** | Cl | $NO_2$ | 61.9 | 239–241 | $C_{18}H_{13}ClN_4O_2$ | 61.28 | 3.71 | 15.88 |
| | | | | | | 61.15 | 3.88 | 15.74 |
| **9i** | $NO_2$ | H | 61.6 | 202–205 | $C_{18}H_{14}N_4O_2$ | 67.91 | 4.43 | 17.60 |
| | | | | | | 67.77 | 4.41 | 17.63 |
| **9j** | $NO_2$ | $CH_3$ | 63.8 | 246–248 | $C_{19}H_{16}N_4O_2$ | 68.66 | 4.85 | 16.86 |
| | | | | | | 68.35 | 4.98 | 16.76 |
| **9k** | $NO_2$ | Cl | 63.6 | 222–224 | $C_{18}H_{13}ClN_4O_2$ | 61.28 | 3.71 | 15.88 |
| | | | | | | 61.15 | 3.88 | 15.74 |

MHz, $CDCl_3$): δ 7.78 (d, $J$ = 7.6 Hz, 2H, $C_{3'}$,$C_{5'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.15–7.22 (m, 3H, $C_{2'}$, $C_{4'}$, $C_{6'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 4.98 (s, 2H, benzyl-$CH_2$), 3.77 (s, 3H, —$COOCH_3$).

***Methyl-N-(4-methylbenzyl)-pyrrole-2-carboxylate (7b).*** Isolated as light yellow oily liquid. Crystallized from absolute ethanol as white crystalline solid, yield 1.68 g (73.3%); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.0–7.4 (m, 4H, $C_{2'}$,$C_{3'}C_{5'}$,$C_{6'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_{4'}$H), 5.08 (s, 2H, benzyl-$CH_2$), 3.72 (s, 3H, —$COOCH_3$), 2.32 (s, 3H, Ar-$CH_3$).

***Methyl-N-(4-chlorobenzyl)-pyrrole-2-carboxylate (7c).*** Isolated as white solid, yield 1.52 g (60.8%); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, $J$ = 8.1 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.26 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.20 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, $C_{5'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_{4'}$H), 5.28 (s, 2H, benzyl-$CH_2$), 3.67 (s, 3H, —$COOCH_3$).

***Methyl-N-(4-nitrobenzyl)-pyrrole-2-carboxylate (7d).*** Isolated as white solid, yield 1.68 g (64.6%); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, $J$ = 8.1 Hz, 2H, $C_{3'}$,$C_{5'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.20 (d, 2H, $J$ = 8.4 Hz, $C_{2'}$, $C_{6'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.58 (s, 2H, benzyl-$CH_2$), 3.77 (s, 3H, —$COOCH_3$).

**Preparation of *N*-benzyl-2-pyrrole carboxylic acids (8a–d): general procedure B.** A suspension of the *N*-benzyl-pyrrole-2-carboxylates **7a–d** (1 equiv, 10 mmol) was dissolved in MeOH/$H_2O$ (3:1) and 30% KOH (4 equiv). The mixture was heated under reflux for 1–2 h. After cooling to room temperature, the reaction mixture was acidified using 2*N* HCl. The resulting precipitate was filtered and washed with water and petroleum ether to give the desired acids **8a–d**.

***N-benzyl-2-pyrrol carboxylic acid (8a).*** Isolated as white solid, yield 1.92 g (95.5%); $^1$H NMR (300 MHz, $CDCl_3$): δ 13.66 (br, s, 1H, —COOH), 7.7 (d, $J$ = 7.6 Hz, 2H, $C_{3'}$,$C_{5'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.25–7.32 (m, 3H, $C_{2'}$, $C_{4'}$, $C_{6'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 4.98 (s, 2H, benzyl-$CH_2$).

***N-(4-methylbenzyl)-2-pyrrole carboxylic acid (8b).*** Isolated as white solid, yield 2.07 g (96.2%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 13.78 (br, s, 1H, —COOH), 7.06–7,4 (m, 4H, $C_{2'}$,$C_{3'}$ $C_{5'}$, $C_{6'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 6.38 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.20 (m, 1H, pyrrole-$C_4'$H), 5.58 (s, 2H, benzyl-$CH_2$), 2.32 (s, 3H, Ar-$CH_3$).

***N-(4-chlorobenzyl)-2-pyrrole carboxylic acid (8c).*** Isolated as white solid, yield 2.18 g (93%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 13.80 (br, s, 1H, —COOH), 7.11 (d, $J$ = 8.1 Hz,

2H, $C_{3'}$,$C_{5'}$ Ar-H), 7.27 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.20 (d, 2H, $J$ = 8.4 Hz, $C_{2'}$, $C_{6'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.21 (m, 1H, pyrrole-$C_4'$H), 5.52 (s, 2H, benzyl-$CH_2$).

***N-(4-nitrobenzyl)-2-pyrrole carboxylic acid (8d).*** Isolated as white solid, yield 2.22 g (90.2%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 13.78 (br, s, 1H, —COOH), 7.96 (d, $J$ = 8.1 Hz, 2H, $C_{3'}$,$C_{5'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.20 (d, 2H, $J$ = 8.4 Hz, $C_{2'}$, $C_{6'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.58 (s, 2H, benzyl-$CH_2$).

**Preparation of *N*-benzylpyrrole-2-benzimidazoles (9a–k); general procedure C.** To a suspension of PPA (5.2 g) in xylene (15 mL) at 80°C, 4-substituted-1,2-phenylenediamine (1 equiv, 0.2 mmol) and the corresponding acid **(8a–d)** (1 equiv, 0.2 mmol) were added. The temperature was raised to 145°C and stirred for 4 h. The reaction mixture was cooled and diluted with hot water with stirring. The hot reaction mixture was filtered through a Buchner funnel and solid was isolated. The solid was taken in water (60 mL) and neutralized with $NaHCO_3$. The solid was filtered and washed with hot water (2 × 40 mL) and recrystallized from THF.

***2-(N-benzyl-2-pyrrolyl)-benzimidazole (9a).*** Isolated as white solid, yield 2.06 g (75.4%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.59 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_4$,$C_7$—H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.33 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_5$,$C_6$—H), 7.02–7.16 (m, 5H, Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.28 (s, 2H, benzyl-$CH_2$), 5.02 (br, s, 1H, NH).

***2-(N-benzyl-2-pyrrolyl)-5-methylbenzimidazole (9b).*** Isolated as white solid, yield 1.15 g (80.14%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.52 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_7$H), 7.34 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.13 (s, 1H, Bzi-$C_4$H), 7.05 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_6$H), 6.98–7.02 (m, 5H, Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.56 (s, 2H, benzyl-$CH_2$), 5.11 (br, s, 1H, NH), 2.30 (s, 3H, Bzi-$CH_3$).

***2-(N-benzyl-2-pyrrolyl)-5-nitrobenzimidazole (9c).*** Isolated as pale yellow solid, yield 1.06 g (67%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.59 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_7$H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.32 (s, 1H, Bzi-$C_4$H), 7.23 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_6$H), 6.98–7.11 (m, 5H, Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.39 (s, 2H, benzyl-$CH_2$), 5.06 (br, s, 1H, NH).

***N-benzyl-2-pyrrole-5-chlorobenzimidazole (9d).*** Isolated as yellow solid, yield 1.21 g (79%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.59 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_7$H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.33 (s, 1H, Bzi-$C_4$H), 7.23 (d, 1H, $J$ = 8.7Hz, Bzi-$C_6$H), 7.02–7.16 (m, 5H, Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.44 (s, 2H, benzyl-$CH_2$), 5.11 (br, s, 1H, NH).

***2-[N-(4-methylbenzyl)-2-pyrrolyl]-benzimidazole (9e).*** Isolated as white solid, yield 1.07 g (74%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.61 (d, J 7.6 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.59 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_4$,$C_7$—H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.33 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_5$,$C_6$—H), 7.22 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, $C_{5'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.43 (s, 2H, benzyl-$CH_2$), 5.0 (br, s, 1H, NH), 2.32 (s, 3H, Ar-$CH_3$).

***N-(4-methylbenzyl)-2-pyrrolyl-5-nitrobenzimidazole (9f).*** Isolated as white solid, yield 1.24 g (74.7%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.64 (d, $J$ 7.6 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.61 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_7$H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 7.33 (s, 1H, Bzi-$C_4$H), 7.23 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_6$H), 7.22 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, $C_{5'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 5.48 (s, 2H, benzyl-$CH_2$), 5.04 (br, s, 1H, NH), 2.42 (s, 3H, Ar-$CH_3$).

***N-(4-chlorobenzyl)-2-pyrrolylbenzimidazole (9g).*** Isolated as white solid, yield 1.21 g (78.8%). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.60 (d, $J$ 7.6 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.58 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_4$,$C_7$—H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.33 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_5$,$C_6$—H), 7.22 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, $C_{5'}$-Ar-H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 5.52 (s, 2H, benzyl-$CH_2$), 5.0 (br, s, 1H, NH).

***N-(4-chlorobenzyl)-2-pyrrolyl-5-nitrobenzimidazole (9h).*** Isolated as white solid, yield 1.09 g (61.9%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.61 (d, 2H, $J$ 7.6 Hz, $C_{2'}$,$C_{6'}$ Ar-H), 7.62 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_7$H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.31 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_4$H), 7.23 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_6$H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 7.22 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, $C_{5'}$-Ar-H), 5.49 (s, 2H, benzyl-$CH_2$), 5.06 (br, s, 1H, NH).

***N-(4-nitrobenzyl)-2-pyrrolylbenzimidazole (9i).*** Isolated as white solid, yield 0.98 g (61.6%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.02 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, $C_{5'}$-Ar-H), 7.59 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_4$,$C_7$—H), 7.54 (d, $J$ 7.6 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 7.33 (d, 2H, $J$ = 8.7 Hz, Bzi-$C_5$,$C_6$—H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_{4'}$H), 5.35 (s, 2H, benzyl-$CH_2$), 5.20 (br, s, 1H, NH).

***N-(4-nitrobenzyl)-2-pyrrolyl-5-methylbenzimidazole (9j).*** Isolated as white solid, yield 1.06 g (63.85%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.02 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$, 7.59 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_7$H), $C_{5'}$-Ar-H), 7.54 (d, $J$ 7.6 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 7.33 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_4$H), 7.23 (d, 1H, $J$ = 6 Hz, $C_6$H). 5.44 (s, 2H, benzyl-$CH_2$), 5.20 (br, s, 1H, NH), 2.51 (s, 3H, Ar-$CH_3$).

***N-(4-nitrobenzyl)-2-pyrrolyl-5-chlorobenzimidazole (9k).*** Isolated as white solid, yield 1.12 g (63.6%); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.02 (d, 2H, $J$ = 8.4 Hz, $C_{3'}$,$C_{5'}$-Ar-H), 7.59 (d,1H, $J$ = 8.7 Hz, Bzi-$C_7$H), 7.54 (d, $J$ 7.6 Hz, 2H, $C_{2'}$,$C_{6'}$ Ar-H), 7.37 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{5'}$H), 6.4 (d, 1H, $J$ = 1.5 Hz, pyrrole-$C_{3'}$H), 6.23 (m, 1H, pyrrole-$C_4'$H), 7.33 (d, 1H, $J$ = 8.7 Hz, Bzi-$C_4$H), 7.23 (d, 2H, $J$ = 6 Hz, $C_6$H). 5.51 (s, 2H, benzyl-$CH_2$), 5.18 (br, s, 1H, NH).

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## REFERENCES AND NOTES

[1] Jarak, I.; Kralij, M.; Piantanida, I.; Suman, L.; Zinic, M.; Pavelc, K.; Karminiski-Zamola, G. Bioorg Med Chem 2006, 16, 2859.

[2] Patil, A.; Ganguly, S.; Surana, S. Rasayan J Chem 2008, 1, 447.

[3] Ozden, S.; Atabey, D.; Yildiz, S.; Goker, H. Bioorg Med Chem 2005, 13, 1587.

[4] Edward, S. L.; Matteo, R. M.; Possanza, J. G. J Med Chem 1987, 30, 726.

[5] Ramla, M. M.; Omar, A. M.; El-Khamry, M. A.; El-Diwani, I. H. Bioorg Med Chem 2006, 14, 7324.

[6] Goker, H.; Kus, C.; Boykin, D. W.; Yildiz, S.; Altanlar, N. Bioorg Med Chem 2002, 10, 2589.

[7] Salmon, J. A.; Higgs, G. Br Med Bull 1987, 43, 285.

[8] Funk, C. D. Science 2001, 294, 1871.

[9] Rainsford, K. D. Am J Med 1999, 107, 27.

[10] Maarten, B. Lancet 2001, 357, 1222.

[11] Kalgutkar, A. S.; Zhao, Z. Curr Drug Targets 2001, 2, 79.

[12] Prasit, P.; Riendeau, D. Annu Rep Med Chem 1997, 32, 211.

[13] Talley, J. J. Prog Med Chem 1999, 36, 201.

[14] Richard, J.; Bing, M. L. J Am Coll Cardiol 2002, 39, 521.

[15] Turan-Zitouni, G.; Asim, K. Z.; Ozdemir, A.; Chevallet, P.; Kandilci, H. B.; Gumusel, B. Arch Pharm 2007, 340, 586.

[16] Latifeh, N.; Hooman, S.; Hamed, S.; Mohsen, A.; Ahmad, R. D.; Abbas, S. Bioorg Med Chem 2007, 15, 1976.

[17] Sondhi, S. M.; Singh, N.; Kumar, A.; Lozach, O.; Meijer, L. Bioorg Med Chem 2006, 14, 3758.

[18] Patel, V. M.; Bell, R.; Majest, S.; Henry, R.; Kolasa, T. J Org Chem 2004, 69, 7058.

[19] Terzioglu, N.; Rijn, R. M.; Bakker, R. A.; De Esch, I. J.; Leurs, R. Bioorg Med Chem Lett 2004, 14, 5251

[20] Paramashivappa, R.; Kumar, P. P.; Subba Rao, P. V.; Rao, A. S. Bioorg Med Chem Lett 2003, 13, 657.

[21] Hu, W.; Zongru, G.; Xiang, Y.; Changbin, G.; Fengming, C.; Guifang, C. Bioorg Med Chem 2003, 11, 5539.

[22] Sureyya, O.; Eiichi, A.; Dogu, N. Eur J Med Chem 2001, 36, 747.

[23] Danhardt, G.; Kiefer, W.; Kramer, S.; Maehrlein, U.; Fiebrich, B. N. J Med Chem Chim Ther 2000, 35, 5499.

[24] Khanna, I.; Weier, Y.; Collins, P. Y.; Miyashiro, J.; Koboldt, C.; Veenhuizen, A.; Currie, J.; Seibert, K.; Isakson, P. J Med Chem 1997, 40, 1619.

[25] Iglika, L.; Atanas, N.; Adriana, B.; Atanas, B. Farmaco 2005, 60, 209.

[26] Christopher, D. F.; Catherine, L.; Mark, W. Prog Med Chem 1999, 36, 91.

[27] Michaelidou, A. S.; Hadjipavlou-Litina, D. Chem Rev 2005, 105, 3235.

[28] Catherine, M.; Xavier de, L.; Fabien, J.; Jean-Michel, D.; Bernard, P.; Francois, D. Eur J Med Chem 2006, 41, 1446.

[29] Madhavi, G.; Redda, K. K. J Heterocycl Chem 2006, 43, 709.

[30] Yoon, K.; Wilson, T. L.; Ly, A. M.; Okoro, C. O.; Redda, K. K. Drugs Exp Clin Res 2000, 26, 73.

[31] Madhavi, G.; Redda, K. K. J Heterocycl Chem 2009, 46, 309.

# Chemoselective Synthesis of Quinoline *N*-Oxides from 3-(2-Nitrophenyl)-3-hydroxypropanones



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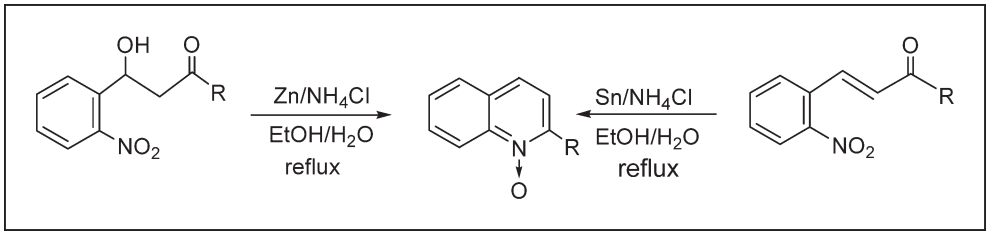


The reaction of 3-(2-nitrophenyl)-3-hydroxypropanones with $Zn/NH_4Cl$ gave the corresponding quinoline *N*-oxides in 80–90% yields. The reaction initiated the reduction of nitro group to afford the corresponding hydroxylamine, which intramolecularly condensed and followed by dehydration to give quinoline *N*-oxide. Although treatment of 2-nitrochalcone with $Zn/NH_4Cl$ in $EtOH/H_2O$ resulted in the formation of quinoline *N*-oxide in low yield, the reaction of 2-nitrochalcone with $Sn/NH_4Cl$ in refluxing $EtOH/H_2O$ afforded quinoline *N*-oxide in 80% yield.

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## INTRODUCTION

Quinoline ring framework can be found in many synthetic and natural compounds of biological importance. Especially, quinoline *N*-oxides (**1**) are important compounds because of their biological activity [1]. The quinoline *N*-oxide core unit has been found in drugs exerting microsomal Na, K-ATPase [2], antiviral [3], or antimalarian activities [4]. The synthetic method of quinoline *N*-oxide mainly devoted to the oxidation of the corresponding quinolines, which were synthesized from 2-aminochalcones or 2-nitrochalcones and Sn/HCl or with Pd/C hydrogenation and cyclization [5]. We have also reported the synthesis of quinolines by the reaction of 2-aminochalcones with NIS or $I_2$ [6]. Direct palladium-catalyzed arylation of quinoline *N*-oxides to 2-arylquinoline *N*-oxides was recently reported [7]. Although Baylis-Hilman adducts reacted with trifluoroacetic acid to give 3,4-substituted quinoline *N*-oxides in 49–82% yields [8], there are few reports on the direct synthesis of quinoline *N*-oxides from chalcones or 3-hydroxy ketones, which afforded mixtures of quinolines and quinoline *N*-oxides [9]. These results prompted us to investigate the direct synthesis of quinoline *N*-oxides from 3-hydroxy ketones (**2**) or 2-nitrochalcones. Herein, we would like to report a direct synthesis of quinoline *N*-oxides from easily available 3-hydroxy ketones **2** and 2-nitrochalcones.

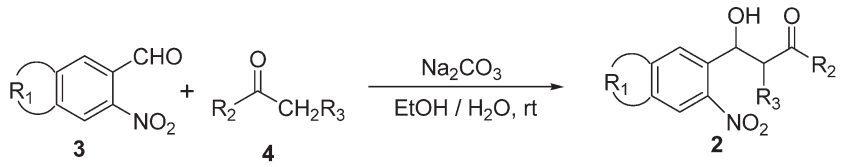
## RESULTS AND DISCUSSION

3-Hydroxy ketones **2** were synthesized by the reaction of 2-nitrobenzaldehydes (**3**) and acetophenones (**4**) in the presence of sodium carbonate by the method recently described by Wang et al. [10] (Scheme 1).

We first tried the metal mediated reductive cyclization of 3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one **2a** whether 2-phenylquinoline *N*-oxide **1a** or 2-phenylquinoline **5a** would be formed. The results were shown in Table 1. Treatment of **2a** with Sn/HCl resulted in the formation of *N*-oxide **1a** and **5a** in 26 and 60% yields, respectively (entry 1). When Zn/HCl was allowed to react with ketone **2a**, *N*-oxide **1a** was obtained in 46% yield (entry 2). When $Sn/NH_4Cl$ was treated with **2a** at 60°C for 12 h, *N*-oxide **1a** and quinoline **5a** were obtained in 7 and 6% yields, respectively (entry 4). Finally, when $Zn/NH_4Cl$ was used as reducing reagents at 60°C, *N*-oxide **1a** was exclusively obtained in 85% yield (entry 6).

As the optimum conditions (4 equiv Zn/ 3 equiv of $NH_4Cl$, $EtOH/H_2O$, 60°C) were determined, we then tried other 3-hydroxy ketones **2** to investigate the scope and limitation of this method. Treatment of 3-hydroxy-3-(2-nitrophenyl)-1-*p*-tolylpropan-1-one (**2b**) with $Zn/NH_4Cl$ in $EtOH/H_2O$ resulted in the formation of 2-(*p*-tolyl)quinoline *N*-oxide (**1b**) in 90% yield (entry 2). When methyl, methoxy, or chloro groups were substituted on aromatic ring (ketones **2c**–**e**), the corresponding

**Scheme 1**




**3a**: $R_1$ =H, H
**3b**: $R_1$ =$OCH_2O$

**4a**: $R_2$ = Ph, $R_3$ = H
**4b**: $R_2$ = 4-$MeC_6H_4$, $R_3$ = H
**4c**: $R_2$ = 3-$MeC_6H_4$, $R_3$ = H
**4d**: $R_2$ = 2-$MeC_6H_4$, $R_3$ = H
**4e**: $R_2$ = 4-$MeOC_6H_4$, $R_3$ = H
**4f**: $R_2$ = 4-$ClC_6H_4$, $R_3$ = H
**4g**: $R_2$ =2-naphthyl, $R_3$ = H
**4h**: $R_2$ = 2-OH, 5-Br $C_6H_3$, $R_3$ = H
**4i**: $R_2$ = Ph, $R_3$ =Br
**4j**: $R_2$ = Me, $R_3$ = H

**2a**: $R_1$ = H, $R_2$ = Ph, $R_3$ = H 72%
**2b**: $R_1$ = H, $R_2$ = 4-$MeC_6H_4$, $R_3$ = H 72%
**2c**: $R_1$ = H, $R_2$ = 3-$MeC_6H_4$, $R_3$ = H 57%
**2d**: $R_1$ = H, $R_2$ = 2-$MeC_6H_4$, $R_3$ = H 68%
**2e**: $R_1$ = H, $R_2$ = 4-$MeOC_6H_4$, $R_3$ = H 66%
**2f**: $R_1$ = H, $R_2$ = 4-$ClC_6H_4$, $R_3$ = H 74%
**2g**: $R_1$ = H, $R_2$ = naphthyl, $R_3$ = H 61%
**2h**: $R_1$ = H, $R_2$ = 2-OH, 5-$BrC_6H_2$, $R_3$ = H 74%
**2i**: $R_1$ = H, $R_2$ = Ph, $R_3$ = Br 52%
**2j**: $R_1$ = H, $R_2$ =Me, $R_3$ =H 66%
**2k**: $R_1$ =$OCH_2O$, $R_2$ = 4-Ph, $R_3$ = H 50%

*N*-oxides **1c–e** were obtained in high yields (entries 2–6). Naphthyl substituted ketone **2g** also afforded 2-naphtylquinoline *N*-oxide **1g** (entry 7). Interestingly, 4-hydroxy-4-(2-nitrophenyl)butan-2-one **2j** also reduced and cyclized to afford 2-methylquinoline *N*-oxide (**1j**) in 86% yield (entry 10). Other quinolines were obtained in high yields (Table 2). Thus, general synthesis of *N*-oxides **1** from easily available 3-hydroxy ketones **2** under mild conditions was achieved.

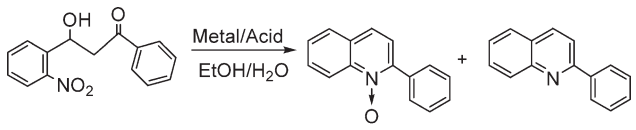
The reaction might proceed as follows: 3-hydroxy ketone **2a** was reduced by $Zn/NH_4Cl$ to give hydroxylamine **6a** which was easily cyclized under these conditions and dehydrated to give quinoline *N*-oxide **1a** (Scheme 2).

The present method has some advantage over direct Pd-catalyzed arylation of quinoline *N*-oxides [7], which requires $Pd(OAc)_2$ as a catalyst and refluxing toluene for 16 h in 55–91% yields. Additionally, 3 equiv of starting quinoline *N*-oxides were required. The present method requires shorter reaction time (5–6 h) and relatively lower temperature (60°C).

We then tried the reductive cyclization of 2-nitrochalcone (**7a**) whether *N*-oxide **1a** would be exclusively formed. Previously, Barros et al. [9] have reported the reductive cyclization of 2-nitrochalcones with $SnCl_2$/HCl, which led to the mixtures of 2-substituted quinoline *N*-oxides **1** and quinolines **5** in moderate yields. To the best of our knowledge, only one report on the practical synthesis of *N*-oxide **1** from chalcone **7** was appeared, whereas yields were low [11]. Thus, the method of exclusive formation of *N*-oxides **1** from **7** must be required. When chalcone **7a** was treated with Sn/HCl at RT for 1 h, quinoline **5a** was isolated in 80% yield (Table 3, entry 1). Treatment of chalcone **7a**, Pd/C (0.1 equiv), and $H_2$ gas in ethanol (5 h), followed by refluxing for 13 h resulted in the formation of quinoline

**Table 1**

Reaction of **2a** with metal and acid.



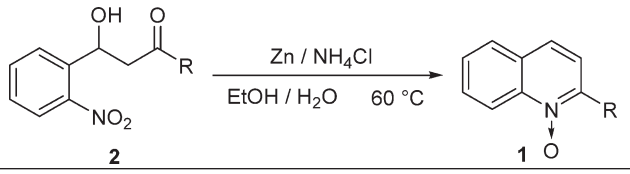

**2a** **1a** **5a**

| Entry | Metal (eq) | Acid (eq) | Temperature (°C) | Time (h) | **1a** Yield (%) | **5a** Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Sn (3) | HCl (4) | 60 | 1 | 26 | 60 |
| 2 | Zn (3) | HCl (4) | RT | 18 | 46 | 0[a] |
| 3 | Fe (3) | HCl (4) | RT | 12 | 61 | 14 |
| 4 | Sn (3) | $NH_4Cl$ (3) | 60 | 12 | 7 | 6[b] |
| 5 | Sn (3) | $NH_4Cl$ (3) | Reflux | 2 | 40 | 20[c] |
| 6 | Zn (4) | $NH_4Cl$ (3) | 60 | 5 | 85 | 0 |
| 7 | Fe (5) | $NH_4Cl$ (3) | Reflux | 24 | 0 | 0[d] |

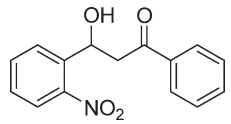
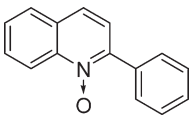
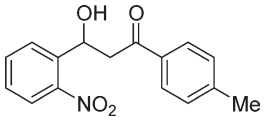
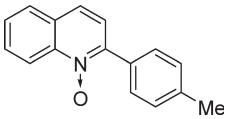
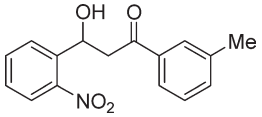
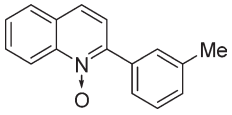
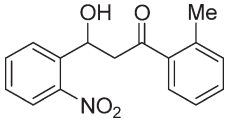
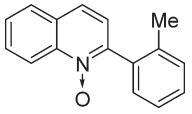
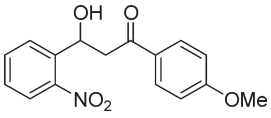
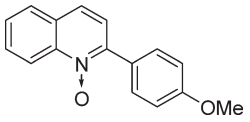
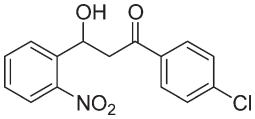
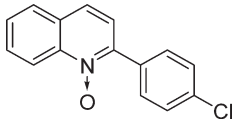
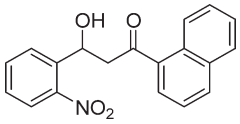
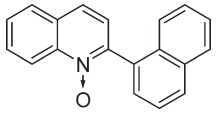
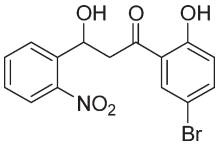
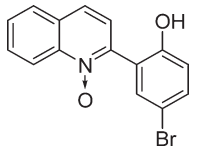
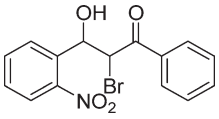
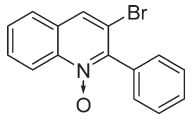
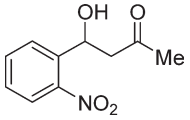
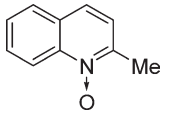
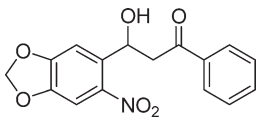
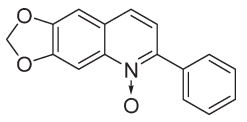
[a] Starting **2a** was recovered in 36% yield.
[b] Starting **2a** was recovered in 69% yield.
[c] Starting **2a** was recovered in 25% yield.
[d] Starting **2a** was recovered in 90% yield.

**Table 2**

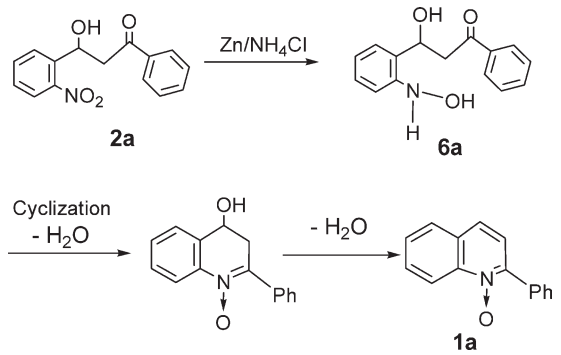
Reductive cyclization of 2-hydroxy ketones **2**.




**2** **1**

| Entry | Substrate | | Time (h) | Product | | Yield (%) |
|---|---|---|---|---|---|---|
| 1 |  | **2a** | 5 |  | **1a** | 85 |
| 2 |  | **2b** | 6 |  | **1b** | 90 |
| 3 |  | **2c** | 6 |  | **1c** | 88 |
| 4 |  | **2d** | 6 |  | **1d** | 90 |
| 5 |  | **2e** | 6 |  | **1e** | 89 |
| 6 |  | **2f** | 5 |  | **1f** | 82 |
| 7 |  | **2g** | 5 |  | **1g** | 80 |
| 8 |  | **2h** | 5 |  | **1h** | 89 |
| 9 |  | **2i** | 4 |  | **1i** | 89 |
| 10 |  | **2j** | 5 |  | **1j** | 86 |
| 11 |  | **2k** | 5 |  | **1k** | 85 |

**Scheme 2.** Reaction mechanism.




**5a** in 78% yield (entry 4). In both case, no quinoline *N*-oxide **1a** was obtained. When $Zn/NH_4Cl$ was treated with **7a** at 60°C, *N*-oxide **1a** was obtained in 21% yield along with 15% of starting chalcone **7a** (entry 5). When the reaction was carried in refluxing ethanol for 24 h by using $Sn/NH_4Cl$ as a reducing reagent, *N*-oxide **1a** and quinoline **5a** were obtained in 80% and 4% yields, respectively (entry 8). Prolonged heating resulted in the further reduction of **1a**–**5a** (entries 9–10). Other substituted nitrochalcones **7b–d** also afforded quinoline *N*-oxides **1** in good yields, however, small amount of starting chalcones **7b–d** were still remained unreacted (entries 11–13).

By using metal/HCl as reducing reagents, 2-nitrochalchone **7a** was reduced to give hydroxylamine **8a**. Since carbonyl moiety at trans position of hydroxylamine **8a** prevent intramolecular cyclization, part of which further reduced to give aniline **9a**, then cyclized to afford quinoline **5a** (entries 1–4). On the other hand, by using $Sn/NH_4Cl$, which have lower reducing ability than Sn/HCl, as reducing reagents, target quinoline *N*-oxides **1a** were obtained in acceptable yields, while careful tuning of the reaction time must be required (Scheme 3). Compared to the reductive cyclization of 3-hydroxy ketones **2** (Table 2), the reduction of 2-nitrochalcones required prolonged reaction time.

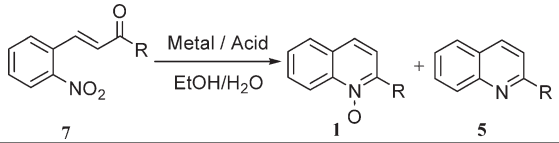
In summary, we have synthesized 2-substituted quinoline *N*-oxides by one-pot process from 3-hydroxylpropanones or 2-nitrochalcones. This procedure provides a general synthesis of quinoline *N*-oxides from easily available 3-hydroxypropanones or 2-nitrochalcones.

## EXPERIMENTAL

**General.** All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70-230 mesh). NMR spectra ($^1H$ at 400 MHz; $^{13}C$ at 100 MHz) were recorded in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal TMS ($\delta = 0.00$) and $CDCl_3$ ($\delta = 77.00$) for $^1H$- and $^{13}C$-NMR. Melting points were uncorrected.

**Table 3**

Hydroamination of 2-nitrochalcones with metal.

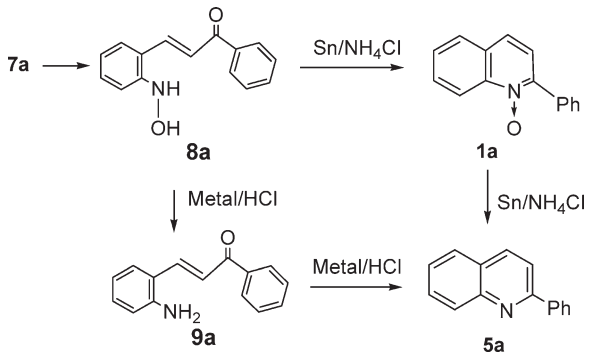



7 1 5

| Entry | R | Metal (equiv) | Acid | Temperature (°C) | Time (h) | Yield (%) 1 | Yield (%) 5 |
|---|---|---|---|---|---|---|---|
| 1 | Ph | Sn (3) | HCl | Rt | 1 | 0 | 80 |
| 2 | Ph | Zn (3) | HCl | Rt | 4 | 0 | 42 |
| 3 | Ph | Fe (3) | HCl | Rt | 24 | 0 | 0 |
| 4 | Ph | Pd/C (0.1) | – | reflux | 18 | 0 | 78 |
| 5 | Ph | Zn (3) | $NH_4Cl$ | 60 | 4 | 21 | 3 |
| 6 | Ph | Sn (3) | $NH_4Cl$ | 60 | 28 | 20 | 0 |
| 7 | Ph | Sn (3) | $NH_4Cl$ | reflux | 20 | 75[a] | 0 |
| 8 | Ph | Sn (3) | $NH_4Cl$ | reflux | 26 | 80 | 4 |
| 9 | Ph | Sn (3) | $NH_4Cl$ | reflux | 33 | 78 | 12 |
| 10 | Ph | Sn (3) | $NH_4Cl$ | reflux | 72 | 0 | 87 |
| 11 | 4-$MeC_6H_4$ | Sn (3) | $NH_4Cl$ | reflux | 24 | 82[b] | 0 |
| 12 | 4-$ClC_6H_4$ | Sn (3) | $NH_4Cl$ | reflux | 22 | 80[c] | 0 |
| 13 | 1-naphtyl | Sn (3) | $NH_4Cl$ | reflux | 24 | 82[d] | 0 |

[a] Starting chalcone **7a** was recovered in 5% yield.
[b] 1-(4-Methylphenyl)-3-(2-nitrophenyl)-2-en-1-one **7b** was recovered in 4% yield.
[c] 1-(4-Chlorophenyl)-3-(2-ntrophenyl)-2-en-1-one **7c** was recovered in 3% yield.
[d] 1-Naphtyl-3-(2-nitrophenyl)prop-2-en-1-one **7d** was recovered in 4% yield.

**Scheme 3**




**Materials.** Benzaldehydes **3a–3b** and ketones **4a–4j** were purchased from TCI and Aldrich. Zn powder (<50 nm) was purchased from Aldrich. Sn powder (200 mesh) was purchased from Wako.

**Preparation of 3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one (2a).** To a solution of acetophenone (1.20 g, 10.0 mmol) and sodium carbonate (0.55 g, 5.2 mmol) in water (60 mL) was added a solution of 2-nitrobenzaldehyde (1.51 g, 10.0 mmol) in ethanol (15 mL) in dropwise. After stirring for 17 h at RT, the reaction mixture was extracted with dichloromethane (10 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown solid, which was chromatographed over silica gel by elution with hexane-ethyl acetate (5:1) to afford green crystals of **2a** (1.95 g, 7.2 mmol). mp 106–107°C (ref. [11] mp 106–107°C). $^1$H-NMR ($CDCl_3$) δ = 8.00–7.96 (m, 4H), 7.71 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.60 (t, *J* = 7.4, 1.2 Hz, 1H), 7.45–7.50 (m 3H), 5.86 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.01 (d, *J* = 3.1 Hz, 1H), 3.73 (dd, *J* = 17.7, 2.4 Hz, 1H), 3.22 (dd, *J* = 17.7, 9.3 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 200.2, 147.5, 138.8, 138.6, 136.6, 134.1, 134.0, 129.0(2C), 128.7, 128.5(2C), 128.4, 124.7, 66.2, 46.7.

Other reactions were carried out in a similar manner.

**3-Hydroxy-1-(4-methylphenyl)-3-(2-nitrophenyl)propan-1-one (2b).** Yield: 72%. Deep green crystals. mp 70–71°C. $^1$H-NMR ($CDCl_3$) δ = 7.97–8.00 (m, 2H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.69 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 5.84 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.06 (br, 1H), 3.71 (dd, *J* = 17.6, 2.4 Hz, 1H), 3.17 (dd, *J* = 17.6, 9.4 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 199.9, 147.5, 145.1, 138.9, 134.1, 134.0, 129.7, 128.7(2C), 128.6(2C), 128.5, 124.7, 66.2, 46.5, 22.0. Calcd for $C_{16}H_{15}NO_4$; C, 67.36; H, 5.30; N, 4.91. Anal Found; C, 67.38; H, 5.36; N, 4.92.

**3-Hydroxy-1-(3-methylphenyl)-3-(2-nitrophenyl)propan-1-one (2c).** Yield: 57%. Deep green oil. $^1$H-NMR ($CDCl_3$) δ = 8.00–7.98 (m, 2H), 7.78–7.75 (m, 2H), 7.70 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.47 (ddd, *J* = 7.8, 7.6, 1.4 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 7.6, 7.5 Hz, 1H), 5.86 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.04 (br, 1H), 3.73 (dd, *J* = 17.6, 2.2 Hz, 1H), 3.20 (dd, *J* = 17.6, 9.3 Hz, 1H), 2.41(s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 191.0, 148.8, 143.0, 138.8, 137.7, 134.2, 133.9, 131.6, 130.6, 129.6, 129.5, 128.8, 127.8, 126.2, 25.2, 21.6. Calcd for $C_{16}H_{15}NO_4$(-$H_2O$); C, 71.90; H, 4.90; N, 5.24. Anal Found; C, 71.76; H, 5.12; N, 5.12.

**3-Hydroxy-1-(2-methylphenyl)-3-(2-nitrophenyl)propan-1-one (2d).** Yield: 68%, greenish brown crystals, mp 55–56°C. $^1$H-NMR ($CDCl_3$) δ = 8.00–7.96 (m, 2H), 7.72–7.66 (m, 2H), 7.46 (ddd, *J* = 7.7, 7.6, 1.2 Hz, 1H), 7.40 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.28–7.23 (m, 2H), 5.8 4(dd, *J* = 9.3, 2.0 Hz, 1H), 4.00 (br 1H), 3.64 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.15 (dd, *J* = 17.6, 9.3 Hz, 1H), 2.56(s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 203.9, 147.5, 139.1, 138.9, 137.0, 134.0, 132.4, 132.3, 129.2, 128.6, 128.5, 126.1, 124.7, 66.4, 49.2, 21.8. Calcd for $C_{16}H_{15}NO_4$ (-$H_2O$); C, 71.90; H, 4.90; N, 5.24. Anal Found; C, 71.84; H, 5.12; N, 5.11.

**3-Hydroxy-1-(4-metoxyphenyl)-3-(2-nitrophenyl)propan-1-one (2e).** Yield: 66%, pale yellow crystals, mp 128–129°C (ref. [12] mp 128–129°C). $^1$H-NMR ($CDCl_3$) δ = 8.00–7.93 (m, 4H), 7.69 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.46 (ddd, *J* = 7.6, 7.8, 1.4 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 2H), 5.83 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.20 (d, *J* = 2.6 Hz, 1H), 3.88 (s, 3H), 3.70 (d, *J* = 17.4, 2.4 Hz, 1H), 3.14 (dd, *J* = 17.4, 9.4 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 198.8, 164.4, 147.6, 138.9, 134.0, 130.9(2C), 129.6, 128.7, 128.5, 124.6, 114.1(2C), 66.4, 55.8, 46.1.

**1-(4-Chlorophenyl)-3-hydroxy-3-(2-nitrophenyl)propan-1-one (2f).** Yield: 74%, deep green crystals, mp 92–93°C. $^1$H-NMR ($CDCl_3$) δ = 7.99 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.98 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.70 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.49–7.43 (m, 3H), 5.85 (dd, *J* = 9.3, 2.2 Hz, 1H), 3.87 (d, *J* = 3.0 Hz, 1H), 3.68 (dd, *J* = 17.6, 2.2 Hz, 1H,) 3.19 (dd, *J* = 9.3, 17.6 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 198.8, 147.5, 140.6, 138.7, 134.9, 134.1, 129.9(2C), 129.3(2C), 128.6, 128.6, 124.7, 66.1, 46.8. Calcd for $C_{15}H_{12}ClNO_4$; C, 58.93; H, 3.96; N, 4.58. Anal. Found; C, 58.69; H, 4.11; N, 4.52.

**3-Hydroxy-1-naphthyl-3-(2-nitrophenyl)propan-1-one (2g).** Yield: 61%, greenish brown oil, $^1$H-NMR($CDCl_3$) δ = 8.73 (d, *J* = 8.6 Hz, 1H), 8.03–7.98 (m, 3H), 7.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.74 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 8.2, 1.2 Hz, 1H), 7.51–7.44 (m, 2H), 5.94 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.04 (d, *J* = 3.1 Hz, 1H), 3.82 (dd, *J* = 17.5, 2.2 Hz, 1H), 3.31 (dd, *J* = 175, 9.3 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 204.1, 147.5, 138.9, 134.9, 134.2, 134.1, 133.8, 130.4, 128.8, 128.8, 128.7, 128.6, 128.5, 126.9, 125.9, 124.7, 124.6, 66.7, 49.8. Calcd for $C_{19}H_{15}ClNO_4$ (+$H_2O$); C, 67.25; H, 5.05; N, 4.13. Anal Found; C, 67.49; H, 4.77; N, 4.04.

**1-(5-Bromo-2-hydroxyphenyl)-3-hydroxy-3-(2-nitrophenyl)propan-1-one (2h).** Yield: 74%, purple crystals, mp 92–93°C. $^1$H-NMR ($CDCl_3$) δ = 11.9 (s, 1H), 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.98 (d, *J* = 7.9, 1.3 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.73 (ddd, *J* = 7.9, 7.8, 1.3 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.50 (ddd, *J* = 7.9, 7.8, 1.4 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 5.90 (dd, *J* = 9.2, 2.1 Hz, 1H), 3.66 (dd, *J* = 17.8, 2.1 Hz, 1H), 3.41(br, 1H), 3.30(dd, *J* = 17.8, 9.2 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 204.7, 161.7, 147.4, 139.8, 138.4, 134.3, 132.4, 128.9, 128.6, 124.8, 120.9, 120.6, 111.0, 65.5, 46.9. Calcd for $C_{15}H_{12}NO_3$; C, 67.25; H, 5.05; N, 4.13. Anal. Found; C, 67.49; H, 4.77; N, 4.04.

**2-Bromo-3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one (2i).** Yield: 52%, colorless crystals, mp 103–104°C. $^1$H-NMR ($CDCl_3$) δ = 8.06 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.55 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.45–7.40 (m, 3H), 5.02 (d, *J* = 5.0 Hz, 1H), 4.83 (d, *J* = 5.0 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 191.4, 147.4, 135.2, 134.3, 134.2, 130.3, 129.8,

129.5, 129.0(2C), 128.5(2C), 124.9, 60.3, 58.1. Anal. Calcd for $C_{15}H_{12}NO_3$ (-HBr); C, 66.91; H, 4.12; N, 5.20. Found; C, 66.84; H, 4.38; N,5.24.

**4-Hydroxy-4-(2-nitrophenyl)butan-2-one (2j).** Yield: 66%, yellow crystals, mp 55–56°C (ref. [13] mp 52–55°C). $^1$H-NMR ($CDCl_3$) δ = 7.91 (d, *J* = 7.9 Hz, 1H), 7.68 (dd, *J* = 7.9, 7.7 Hz, 1H), 7.45 (dd, *J* = 8.1, 7.7 Hz, 1H), 5.69 (dd, *J* = 9.4, 2.0 Hz, 1H), 3.15 (dd, *J* = 17.8, 2.0 Hz, 1H), 2.73 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.24(s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 209.1, 147.4, 138.6, 134.1, 128.5, 128.4, 124.7, 65.9, 51.3, 30.7.

**3-Hydroxy-3-(*b*-nitrobenzo[1,3]dioxol-5-yl)-1-phenylpropan-1-one (2k).** Yield: 50%, pale yellow crystals, mp 96–97°C. $^1$H-NMR($CDCl_3$) δ = 7.96 (d, *J* = 7.4 Hz, 2H), 7.60 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.54 (s, 1H), 7.48 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.43 (s, 1H), 6.13 (s, 2H), 5.88 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.03 (d, *J* = 2.2 Hz, 1H), 3.72 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.11 (dd, *J* = 17.6, 9.2 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 200.3, 152.9, 147.4, 141.3, 136.8, 136.6, 134.0, 129.0(2C), 128.5(2C), 107.4, 105.4, 103.2, 66.4, 46.7. Anal. Calcd for $C_{16}H_{13}NO_6$; C, 60.95; H, 4.16; N, 4.44. Found; C, 60.67; H, 4.36; N, 4.40.

**Reductive cyclization of 2a by using tin and hydrochloric acid.** To a solution of **2a** (0.136 g, 0.5 mmol) and conc HCl (0.17 mL, 0.20 mmol) in EtOH (12 mL) was added Sn powder (0.178 g, 1.5 mmol) in one portion. After being stirred for 1h at 60°C, the reaction mixture was evaporated, washed with water, and extracted with $CH_2Cl_2$ (5 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale green oily solid, which was chromatographed over silica gel by elution with dichloromethane to afford 2-phenylquinoline *N*-oxide **1a** (0.029 g, 0.13 mmol) and 2-phenylquinoline **5a** (0.062 g, 0.30 mmol). mp 79–80°C (ref. [1] mp 78–79°C).

2-Phenylquinoline *N*-oxide **1a**: yield: 89%, pale yellow crystals, mp 74–75°C (ref. [14] mp 76°C). $^1$H-NMR ($CDCl_3$) δ = 8.87 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.80–7.75 (m 2H), 7.65 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.55–7.45 (m 4H). $^{13}$C-NMR ($CDCl_3$) δ = 144.9, 142.2, 133.5, 130.5, 129.6(2C), 129.5, 129.5, 128.4(2C), 128.3, 128.0, 125.2, 123.3, 120.2.

**Reductive cyclization of 2j by using zinc and ammonium chloride.** To a solution of 4-hydroxy-4-(2-nitropohenyl)-2-butanone **2j** (0.142 g, 0.50 mmol) and ammonium chloride (0.080 g, 1.5 mmol) in ethanol-water (1:1, 40 mL) was added zinc powder (0.098 g, 1.5 mmol) in one portion. After stirring for 6 h at 60°C, the reaction mixture was poured into water (20 mL), and extracted with dichloromethane (10 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale yellow solid, which was recrystallized from methanol to afford 2-methylquinoline *N*-oxide **1j** (0.094 g, 0.43 mmol) colorless crystals. mp 54–55°C (ref. [15] mp 76°C). $^1$H-NMR ($CDCl_3$) δ = 8.80 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.76 (dd, *J* = 8.6, 8.2 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.60 (dd *J* = 8.6, 8.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 2.73 (s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 146.0, 141.8, 130.5, 129.4, 128.2, 128.0, 125.4, 123.2, 119.8, 19.0.

Other reactions were carried out in a similar manner.

**2-(4-Methylphenyl)quinoline *N*-oxide (1b).** Yield: 90%, orange crystals, mp 112–113°C (ref. [7] mp 127–128°C). $^1$H-NMR ($CDCl_3$) δ = 8.86 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.77 (dd, *J* = 8.2, 7.8 Hz, 1H ), 7.73 (d, *J* = 9.0 Hz, 1H), 7.62 (dd *J* = 8.4, 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 145.4, 142.5, 139.9, 130.8, 129.9, 129.7(2C), 129.7(2C), 129.2, 128.5, 128.2, 125.5, 123.5, 120.5, 21.7.

**2-(3-Methylphenyl)quinoline *N*-oxide (1c).** Yield: 88%, orange crystals, mp 110–111°C. $^1$H-NMR ($CDCl_3$) δ = 8.87 (d, *J* = 8.8 Hz, 1H), 7.88–7.62 (m, 5H), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H ), 7.42 (dd *J* = 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 2.45(s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 145.5, 142.6, 138.2, 133.7, 130.8, 130.5, 130.3, 129.8, 128.6, 128.5, 128.2, 126.9, 125.3, 123.7, 120.6, 21.7. Anal. Calcd for $C_{13}H_{15}NO_4$; C, 81.86; H, 5.57; N, 5.95. Found; C, 81.52; H, 5.41; N, 5.78.

**2-(2-Methylphenyl)quinoline *N*-oxide (1d).** Yield: 90%, orange crystals, mp 109–110°C (ref. [7] mp 103–104°C).$^1$H-NMR ($CDCl_3$) δ = 8.85 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.82–7.71 (m, 2H), 7.66 (dd, *J* = 8.1, 8.1 Hz, 1H ), 7.43–7.29 (m, 5H), 7.62 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.27 (s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 146.7, 142.0, 137.7, 133.9, 130.4, 130.1, 129.9, 129.3, 129.1, 128.4, 128.0, 125.9, 124.6, 123.8, 120.3, 19.7.

**2-(4-Methoxylphenyl)quinoline *N*-oxide (1e).** Yield: 89%, pale yellow crystals, mp 123–124°C (ref. [7] mp 125–126°C). $^1$H-NMR ($CDCl_3$) δ = 8.86 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (ddd, *J* = 8.0, 8.0, 1.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.63 (ddd *J* = 8.4, 8.0, 1.2 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.89(s, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 160.7, 144.9, 142.5, 131.5(2C), 130.7, 129.5, 128.4, 128.1, 125.9, 125.4, 123.3, 120.4, 113.9(2C), 55.6.

**2-(4-Chlorophenyl)quinoline *N*-oxide (1f).** Yield: 82%, greenish yellow crystals mp 170–171°C. $^1$H-NMR ($CDCl_3$) δ = 8.84 (d, *J* = 8.8 Hz, 1H), 7.98–7.94 (m, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.52–7.48 (m, 3H). $^{13}$C-NMR ($CDCl_3$) δ = 144.1, 142.6, 135.8, 132.1, 131.2(2C), 131.0, 129.9, 128.9, 128.8(2C), 128.3, 125.6, 123.1, 120.5. Anal. Calcd for $C_{15}H_{10}ClNO_4$; C, 70.46; H, 3.94; N, 5.48. Found; C, 70.51; H, 4.18; N, 5.53.

**2-(1-Naphthyl)quinoline *N*-oxide (1g).** Yield: 80%, colorless crystals, mp 168–169°C (ref. [7] mp 168–169°C). $^1$H-NMR ($CDCl_3$) δ = 8.88 (d, *J* = 9.3 Hz, 1H), 8.02–7.91 (m, 3H), 7.85–7.77 (m, 2H), 7.69(ddd, *J* = 8.1, 6.8 and 1.2 Hz, 1H ), 7.60(d, *J* = 5.6 Hz, 2H), 7.60(d, *J* = 5.6 Hz 2H), 7.55–7.41(m, 4H). $^{13}$C-NMR ($CDCl_3$) δ = 145.6, 142.1, 133.4, 132.1, 130.7, 130.5, 130.1, 129.9, 128.6, 128.6, 128.1, 127.7, 126.9, 126.2, 125.4, 125.4, 124.7, 124.5, 20.4.

**2-(5-Bromo-2-hydroxyphenyl)-quinoline *N*-oxide (1h).** Yield: 89%, pale yellow crystals, mp 167–168°C (ref. [9] mp 167–168°C). $^1$H-NMR ($CDCl_3$) δ = 11.30 (s, 1H, OH), 8.91 (d, *J* = 8.8 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.92 (dd *J* = 8.5, 7.9 Hz, 1H), 7.75 (dd, *J* = 8.2, 7.9 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 159.4, 147.5, 141.1, 135.3, 133.6, 132.2, 129.9, 129.4, 129.2, 128.3, 124.2, 123.5, 122.7, 120.3, 112.0.

**3-Bromo-2-phenylquinoline *N*-oxide (1i).** Yield: 89%, yellow crystals mp 124–125°C (ref. [16] mp 125–127°C). $^1$H-NMR ($CDCl_3$) δ = 8.64 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.6

Hz, 1H), 7.60–7.52 (m, 4H), 7.52 (dd, $J$ = 7.8, 7.8 Hz, 2H), 7.44 (dd, $J$ = 7.4, 7.2 Hz, 1H), 7.27 (s, 1H). $^{13}$C-NMR ($CDCl_3$) δ = 130.1(2C), 129.9, 129.8, 129.7, 129.0, 128.7(2C), 128.6, 128.2, 128.0, 127.6, 127.1, 120.0, 111.3.

**6-Phenyl-[1,3]dioxolo[4,5-g]quinoline *N*-oxide (1k).** Yield: 85%, pale yellow crystals, mp 224–225°C. $^1$H-NMR ($CDCl_3$) δ = 8.22 (s, 1H), 7.91 (dd, $J$ = 8.2, 1.2 Hz, 2H), 7.58 (d, $J$ = 8.6 Hz, 1H), 7.52–7.44 (m, 3H), 7.35 (d, $J$ = 8.6 Hz, 1H), 7.09 (s, 1H), 6.17 (s, 2H). $^{13}$C-NMR ($CDCl_3$) δ = 152.2, 149.5, 133.9, 129.8(2C), 129.5, 129.4, 128.7, 128.4(2C), 127.0, 124.7, 121.9, 103.4, 102.6, 98.5. Anal. Calcd for $C_{16}H_{11}NO_3$; C, 72.45; H, 4.18; N, 5.28. Found; C, 72.28; H, 4.43; N, 5.27.

**Reductive cyclization of 2-nitrochalcone with Sn/HCl.** To a solution of 2-nitrochalchone **7a** (0.253 g, 1.0 mmol) and conc. HCl (0.33 mL, 4.0 mmol) in EtOH (15 mL) was added Sn powder (0.356 g, 3.0 mmol) in one portion. After stirring for 1h at RT, the reaction mixture was evaporated to afford dark solid, which was extracted with EtOAc (5 mL × 3), dried over sodium sulfate, filtered, and evaporated to afford yellow solid. Chromatographic separation of the solid ($SiO_2$, EtOAc:hexane = 1:1) gave 2-phenylquinoline **5a** (0.164 g, 0.80 mmol).

**Reductive cyclization of 2-nitrochalcone with Pd/C.** To a solution of 2-nitrochalcone **7a** (0.253 g, 1.0 mmol) in EtOH (15 mL) was added Pd/C (10%, 0.053 g, 0.05 mmol) in one portion. After stirring for 3 h under hydrogen atmosphere, the reaction mixture was refluxed for 8h, and evaporated to give dark brown oily crystals, which was chromatographed over silica gel by elution with EtOAc:Hexane (1:5) to give **5a** (0.160 g, 0.78 mmol).

**Reductive cyclization of 2-nitrochalcone with Sn/$NH_4Cl$.** To a solution of 2-nitrochalcone **7a** (0.127 g, 0.50 mmol) and ammonium chloride (0.080 g, 1.5 mmol) in ethanol-water (1:1, 40 mL) was added tin powder (0.178 g, 1.5 mmol) in one portion. After refluxing for 26 h, the reaction mixture was poured into water (20 mL), and extracted with dichloromethane (10 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale yellow crystals, which was chromatographed over silica gel to afford 2-phenyllquinoline *N*-oxide **1a** (0.088 g, 0.40 mmol) and 2-phenylquinoline **5a** (0.004 g, 0.02 mmol).

Other reactions were carried out in a similar manner.

2-(4-Methylphenyl)quinoline *N*-oxide **1b** (0.109 g, 0.41 mmol): mp 112–113°C. 2-(4-Chlorophenyl)quinoline *N*-oxide **1f** (0.115 g, 0.40 mmol): mp 170–171°C. 2-Naphtylquinoline *N*-oxide **1g** (0.124 g, 0.41 mmol): mp 168–169°C.

## REFERENCES AND NOTES

[1] (a) Fakhfakh, M. A.; Fournet, A.; Prina, E.; Mouscadet, J. -F.; Franck, X.; Hocquemiller, R.; Figadere, B. Bioorg Med Chem 2003, 11, 5013; (b) Banath, J. P.; Olive, P. L. Cancer Res 2003, 63, 4347; (c) Kanou, M.; Saeki, K.; Kato, T.; Takahashi, K.; Mizutani, T. Fund Clin Pharmacol 2002, 16, 513.

[2] Andreev, V. P.; Korvacheva, E. G.; Nizhnik, Y. P. Pharm Chem J 2006, 40, 347.

[3] Albrecht, T.; Spleelman, D. J.; Ramanujam, V. M. S.; Lund, H. W.; Legator, M. S.; Trieff, N. M. Terat Carcin Mut 1980, 1, 161.

[4] (a) Werbel, L. M.; Kersten, S. J.; Turner, W. R. Eur J Med Chem 1993, 28, 837; (b) Mouaddib, A.; Joseph, J.; Hasnaoui, A.; Merour, Y. -J. Synthesis 2000, 549.

[5] (a) Horino, H.; Inoue, N. Tetrahedron Lett 1979, 20, 329; (b) Horaguchi, T.; Hosokawa, N.; Tanemura, K.; Suzuki, T. J. Heterocycl Chem 2002, 39, 61.

[6] Okuma, K.; Yasuda, T.; Shioji, K.; Yokomori, Y. Bull Chem Soc Jpn 2007, 80, 1824.

[7] Campeau, L. C.; Stuart, D. R.; Leclerc, J. -P.; Bertrand-Laperte, M.; Villemure, E.; Sun, H. -Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. J. Am Chem Soc 2009, 131, 3291.

[8] Lee, K. Y.; Kim, J. M.. Kim, J. N. Tetrahedron 2003, 59, 385.

[9] (a) Barros, A. I. R. N. A.; Silva, A. M. S. Tetrahedron Lett 2003, 44, 5893; (b) Barros, A. I. R. N. A.; Dias, A. F.; Silva, A. M. S. Monatsh Chem 2007, 138, 585; (c) Muchowski, J. M.; Naddox, M. L. Can J Chem 2004, 82, 461.

[10] Wang, G. -W.; Zhang, Z.; Dong, Y. -W. Org Proc Res Dev 2004, 8, 18.

[11] Baik, W. K.; Kim, D. I.; Hyu, J.; Chung, W. -J.; Kim, B. H.; Lee, S. W. Tetrahedron Lett 1997, 38, 4579.

[12] Mei, K.; Zhang, S.; He, S.; Li, P.; Jin, M.; Xue, F.; Luo, G.; Zhang, H.; Song, L.; Duan, W.; Wang, W. Tetrahedron Lett 2008, 49, 2681.

[13] Chimni, S. S.; Mahajan, D. Tetrahedron 2005, 61, 5019.

[14] White, J. D.; Yager, K. M.; Stappenbeck, F. J. Org Chem 1993, 58, 3466.

[15] Bjorsvik, H. -R.; Gambarotti, C.; Jensen, V. R.; Gonzalez, R. R. J. Org Chem 2005, 70, 3218.

[16] Hayashi, E.; Miyashita, A. Yakugaku Zasshi 1976, 96, 968.

# Synthesis of Some New Pyrazole and Pyrazolopyrimidine Derivatives [1]



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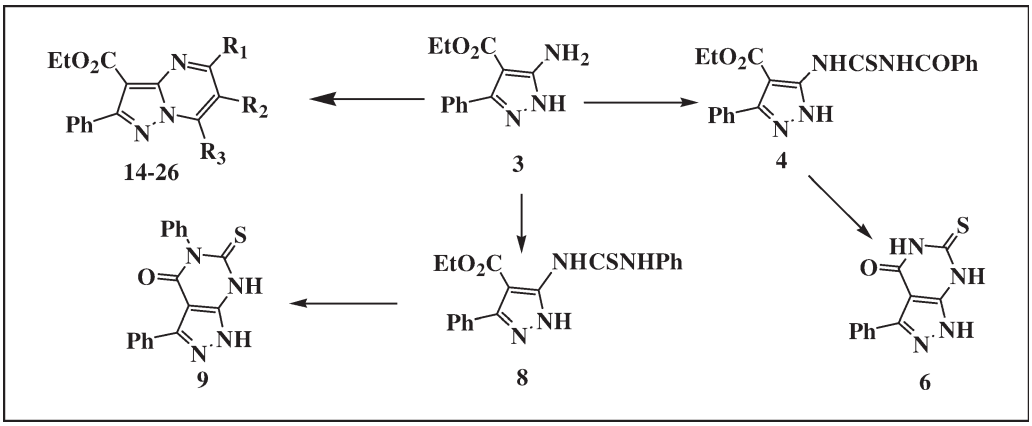


A series of pyrazolo [3,4-d] pyrimidine, pyrazolo [1,5-a] pyrimidine, and pyrazolyl triazoles have been prepared *via* reaction of ethyl 5-amino-3-phenylpyrazole-4-carboxylate with isothiocyanic esters, α,β-unsaturated nitriles, and some active methylene reagents.

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## INTRODUCTION

In the past decade, we have been involved in a program aiming at the synthesis of new heterocyclic compounds that may possess biologically active properties to be used as potential biodegradable agrochemicals [2–5]. In continuation of our earlier interest in 3(5)-aminopyrazole, we report here an efficient synthesis of the *hitherto* unreported ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **3** and its exploitation for the synthesis of some new fused pyrazole derivatives.

## RESULTS AND DISCUSSION

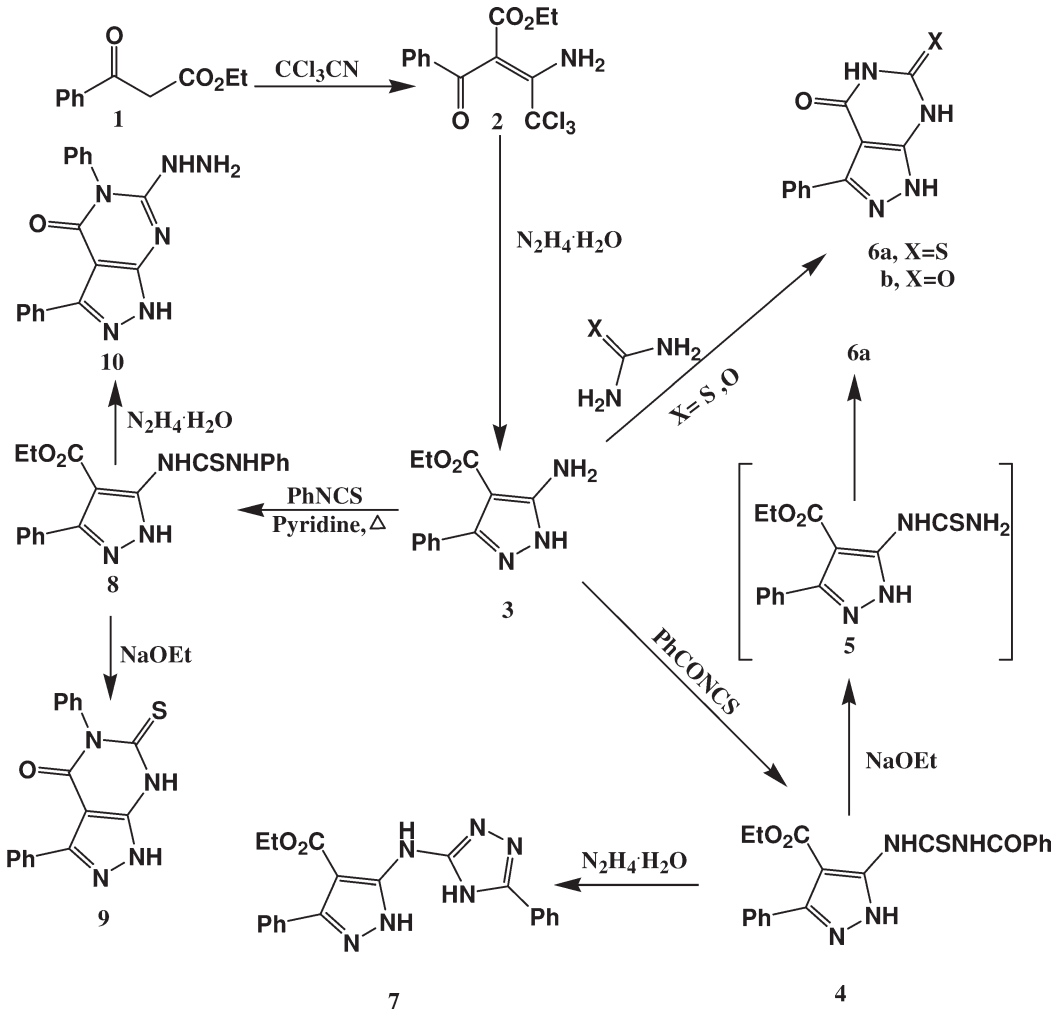
Thus, ethyl benzoylacetate **1** reacts with trichloroacetonitrile in ethanol catalyzed by sodium acetate to afford 1:1 adduct, which could be formulated as ethyl 3-amino-2-benzoyl-3-trichloromethyl acrylate derivative **2**. Structure **2** was assigned to this adduct on the basis of analytical and spectral data (cf. Experimental part). The reaction of **2** with hydrazine hydrate in refluxing pyridine afforded directly ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **3**. The formation of **3** is assumed to occur *via* nucleophilic attack of hydrazine $NH_2$ on **2** with elimination of chloroform followed by the condensation of the hydrazide $NH_2$ with the benzoyl-carbonyl group with elimination of water. This cyclization was expected to occur with elimination of ethanol; however, all spectral evidence showed the presence of the ester function.

Thus, IR spectrum of the product showed that absorption bands at $\upsilon_{max}$ = 1651, 3415, and 3365 $cm^{-1}$ attributable to carbonyl and amino groups. The $^1H$ NMR spectrum revealed a triplet at δ = 1.17–1.24 ppm ($J$ = 10.6 Hz) and quartet at δ = 4.12–4.23 ppm ($J$ = 10.6 Hz) characteristic for ethyl ester group, a singlet (2H, $D_2O$ exchangeable) at δ = 6.21 ppm for amino group, a multiplet (5H) at δ = 7.42–7.66 ppm for aromatic protons, and a broad singlet (1H) at δ = 12.05 ppm for the pyrazole NH. Moreover, the mass spectrum of the reaction product showed a strong absorption at $m/z$ = 231 (48%), which is compatible with the molecular formula $C_{12}H_{13}N_3O_2$ for compound **3**.

Aminopyrazoles are the most extensively utilized heterocyclic amines in heterocyclic synthesis due to their ready availability as well as their stability, which makes them useful precursors in dyes, pharmaceuticals, and agrochemical industries [6–13].

In conjunction with our interest in exploring the potential utility of functionally substituted pyrazoles

**Scheme 1.** Preparation of compounds **2**, **3**, **4**, **6a,b**, **7**, **8**, **9** and **10**.

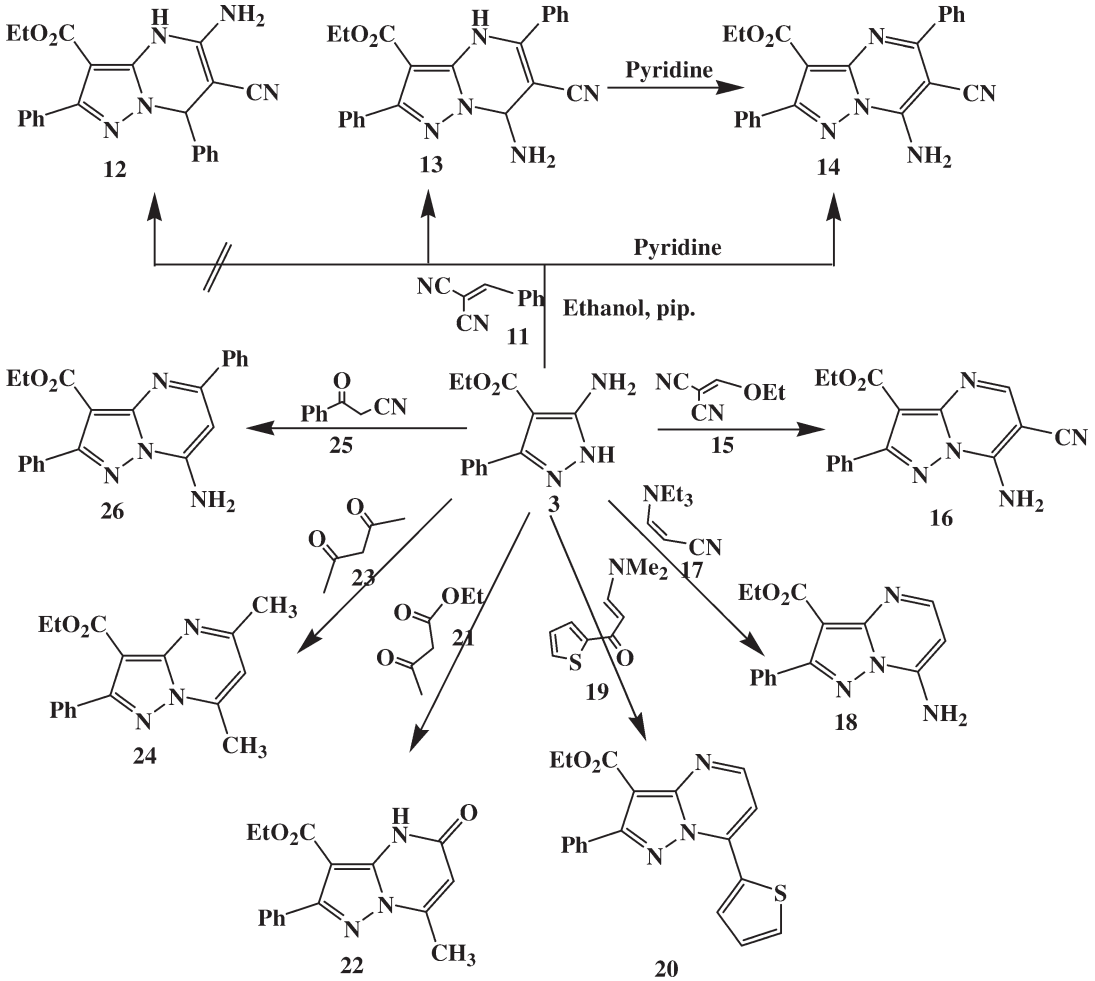



[14–16], we report here a simple and efficient synthesis of some new polyfunctionally substituted pyrazolopyrimidines of expected biological interest starting with our new pyrazole **3**.

Thus, ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **3** reacts with benzoyl isothiocyanate and phenyl isothiocyanate to afford the 1:1 adducts **4** and **8**, respectively, *via* electrophilic attack at the amino group, which was considered most likely for these adducts based on their stability under the conditions reported to effect decomposition of *N*-thiocarbamoyl pyrazoles [16–18]. Attempts to effect cyclization of both reaction products **4** and **8** by boiling in ethanolic sodium ethoxide has resulted in the formation of pyrazolo[3,4-d]pyrimidines **6a** and **9**, respectively. Structures **6a** and **9** are identified on the basis of analytical and spectral data, where the $^1$H NMR spectrum of **6a** revealed the presence of a multiplet at $\delta$ = 7.45–8.15 ppm (5H) for aromatic protons and three singlets at $\delta$ = 11.82, 12.99, and 13.88 ppm for NH-pyrazole and two NH-pyrimidine protons. The formation of **6a** from **4** seemed to proceed *via* alcoholysis with loss of the benzoyl moiety and the formation of the nonisolable intermediate **5**, which undergoes cyclization through ethanol elimination to give **6a** (Scheme 1). An authentic sample of **6a** has been obtained from the reaction of the pyrazole **3** with thiourea by fusion in an oil bath at 120°C (The same melting point, mixed melting point, and same analytical and spectral analyses). The loss of the benzoyl moiety in similar reaction is reported in [16–18].

The thiourea derivatives **4** and **8** reacted with hydrazine hydrate and afforded products for which structures **7** and **10** were assigned on the basis of analytical and spectral analyses, where the $^1$H NMR spectrum of **7** showed the presence of a triplet at $\delta$ = 1.13 ppm ($J$ = 7.2 Hz), a quartet at $\delta$ = 4.15 ppm ($J$ = 7.2 Hz), a

**Scheme 2.** Preparation of compounds **13**, **14**, **16**, **18**, **20**, **22**, **24** and **26**.




multiplet at δ = 7.45–8.15 ppm for 10 protons (aromatic protons), a singlet at δ = 9.20 ppm for Pyrazole-NH, and two singlets at δ = 11.90 and 13.05 ppm for both exocyclic NH and triazole-NH protons.

On the other hand, the $^{1}$H NMR of **10** revealed the presence of a singlet at δ = 5.56 ppm for the amino group protons, a multiplet at δ = 7.11–8.39 ppm integrated for 10H (2-Ph protons), a singlet at δ = 9.47 ppm for pyrazole-NH, and a singlet at δ = 13.18 ppm for hydrazine-NH. The $^{13}$C NMR spectrum of **10** revealed signals at 102.64 (C-4 pyrazolopyrimidine), 121.62, 123.60, 127.54, 128.18, and 128.62 (CH aromatic), 132.77 (C-9 pyrazolopyrimidine), 136.28, 138.25, and 147.12 (CH aromatic), 150.91 (C-3 pyrazolopyrimidine), 153.76 (C-7 pyrazolopyrimidine), and 157.59 (C-6 pyrazolopyrimidine) (CO).

The pyrazolo[3,4-*d*]pyrimidine-4,6-dione analogue **6b** has been obtained *via* reaction of the 5-aminopyrazole **3** with urea on fusion in oil bath at 120°C. Structure **6b** was assigned on the basis of elemental analysis and spectral data (cf. Experimental section).

Pyrazolo[1,5-*a*]pyrimidines are important due to their ability to inhibit 3′,5′-cyclic phosphodiestrase and their cardiotropic properties [19,20]. Moreover, the reported activities of pyrazolo[1,5-*a*]pyrimidines as antipyretics, anti-inflammatory, anticancer, and antischistosomal agents [21–23] prompted us to prepare some of their new derivatives *via* reacting our new 5-aminopyrazole derivative **3** with some α,β-unsaturated nitriles and active methylene reagents.

Thus, ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-caboxylate **3** reacts with the cinnamonitrile derivative **11** in refluxing ethanol with few drops of piperidine as a catalyst to afford products for which structures **12** or **13** seemed possible (cf. Scheme 2).

The spectral data of the reaction products suggested structure **13** to be assigned to this product rather than **12** (cf. Experimental section). Compound **13** was transformed into the fully aromatic pyrazolo[1,5-*a*]pyrimidine derivative **14** on reflux in pyridine. When the reaction of **3** with **11** was carried out in refluxing pyridine compound **14** was also obtained. The identity of the two

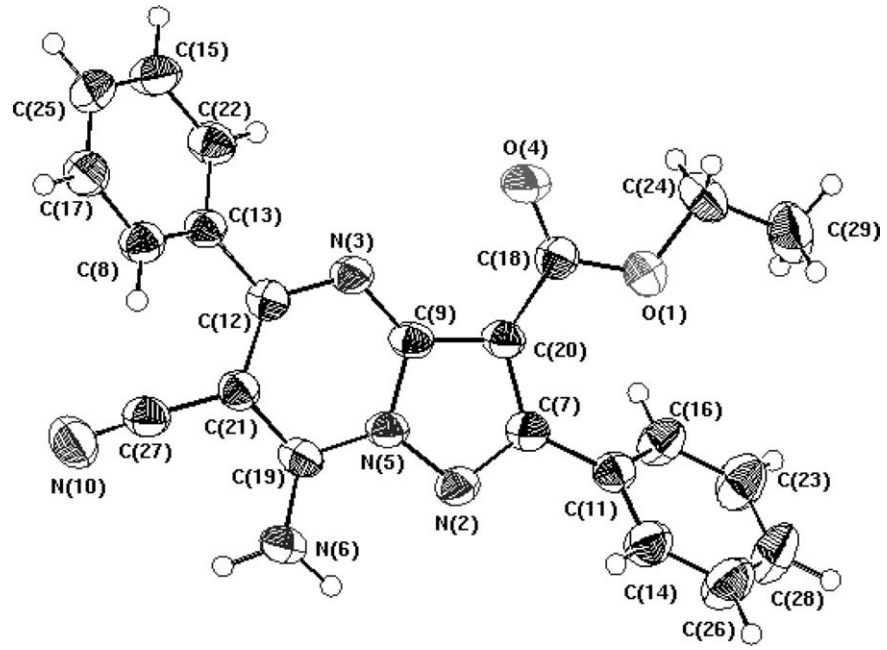



**Figure 1.** Single crystal X-ray structure of compound **14** [24–26].

products was inferred from melting points and spectral data. Structure **14** was assigned on the basis of the $^{13}C$ NMR and $^{1}H$ NMR spectra which revealed the disappearance of the pyrimidine-4-H signal and presence of a singlet at $\delta = 6.83$ ppm integrated for two protons ($NH_2$ protons) in addition to the other expected signals for aromatic and ethyl ester protons (cf. Experimental). The formation of **14** from **13** apparently takes place *via* auto-oxidation under the reaction conditions. Similar reactions have been reported [22,23].Structure **14** was unambiguously confirmed on the basis of the single crystal X-ray analysis [24–26] (cf. Fig. 1).

The aminopyrazole **3** reacted with ethoxy-methylene malononitrile **15** and afforded a product for which structure **16** is established based on analytical and spectral analyses.

On the other hand, when the 5-aminopyrazole **3** was condensed with both the enaminonitrile **17** and the enaminone **19**, it yielded the pyrazolo[1,5-*a*]pyrimidine derivatives **18** and **20**, respectively.

Structure **18** could be established on the basis of spectral analysis where the $^{1}H$ NMR spectrum revealed the amino group as a singlet at $\delta = 9.94$ ppm and the appearance of two doublets at $\delta = 6.56$ ppm ($J = 7.2$ Hz) and $\delta = 8.26$ ppm ($J = 7.2$ Hz) which may be attributed to H-5 and H-6.

5-Aminopyrazole-4-carboxylate **3** was also condensed with ethyl acetoacetate **21**, acetylacetone **23**, and benzoylacetonitrile **25** by fusion on oil bath at 100–120°C to yield products for which structures **22**, **24**, and **26** have been established, respectively, on the basis of analytical and spectral analyses. The IR spectrum of compound **22** revealed an absorption band at $\nu_{max} = 1712$ cm$^{-1}$ for carbonyl ester and another band at $\nu_{max} = 1662$ cm$^{-1}$ for amide carbonyl group.

The $^{1}H$ NMR spectrum of **24** showed two singlets at $\delta = 2.70$ and 2.80 ppm for the two methyl groups and a singlet at $\delta = 6.75$ ppm for pyrimidine-CH proton, beside the other expected signals for aromatic and ethyl ester protons. The formation of **26** apparently proceeds in a manner similar to the addition of the cinnamonitrile **11** shown above (cf. Scheme 2, Fig. 1, Experimental).

## EXPERIMENTAL

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-Vector 22 spectrophotometer. The $^{1}H$ and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ as solvent at 300 MHz and 75 MHz, respectively, on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in $\delta$ units (ppm). Mass spectra were measured on a Shimadzu GCMS - QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Micro analytical Center, Cairo University. The single crystal structure [24–26] was determined by X-ray unit at the National Research Center, Dokki, Giza, A. R. Egypt.

**3-Amino-2-benzoyl-4,4,4-trichloro-butyric acid ethyl ester (2).** To a solution of ethyl benzoylacetate **1** (1.92 g, 10 mmol) in absolute ethanol (50 mL) containing sodium acetate,

trichloroacetonitrile (1.44 g, 10 mmol) was added. Stirring lasted overnight at room temperature then the reaction mixture was poured into cold water. The resulting product obtained was filtered off, dried, and recrystallized from ethanol. White crystal (yield 80%), m.p. 107°C. $\nu_{max}$ $cm^{-1}$ = 3375, 3240 ($NH_2$), 1674, 1645 (CO). MS: *m/z* 336 ($M^+$). Anal. Calcd. for $C_{13}H_{12}Cl_3NO_3$ (336.05): C, 46.38; H, 3.59; N, 4.16; Cl, 31.59%. Found: C, 46.31; H, 3.52; N, 4.11; Cl, 31.53%.

**5-Amino-3-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (3).** To a suspension of **2** (3.36 g, 10 mmol) in ethanol was added the equivalent amount of hydrazine hydrate (0.50 mL, 10 mmol) and triethylamine as catalyst. The reaction mixture was refluxed for 5 h and then concentrated in *vacuo*. The solid product obtained upon cooling was isolated by filtration and recrystallized from a mixture of ethanol/dioxane. White crystal (yield 50%). m.p. 172°C. $\nu_{max}$ $cm^{-1}$ = 3415, 3365 ($NH_2$), 3245, 1651 (CO). MS: *m/z* 231 ($M^+$). $\delta_H$ = 1.17 (t, 3H, *J* = 10.6 Hz, $CH_3$), 4.12 (q, 2H, *J* = 10.6 Hz, $CH_2$), 6.21 (s, 2H, $NH_2$), 7.42–7.66 (m, 5H, Ar-H), 12.04 (s, 1H, NH-pyrazole). Anal. Calcd. for $C_{12}H_{13}N_3O_2$ (231.26): C, 62.32; H, 5.66; N, 18.17%. Found: C, 62.25; H, 5.60; N, 18.08%.

**5-(3-Benzoyl-thioureido)-3-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (4).** A solution of **3** (2.31 g, 10 mmol) and benzoyl isothiocyanate (1.63 g, 10 mmol) in dry acetone (50 mL) were refluxed for 5 h. The reaction mixture was evaporated under vacuo. The resulting solid was collected by filtration and crystallized from ethanol. White crystal (yield 50%), m.p. 158°C. $\upsilon_{max}$ $cm^{-1}$ = 3425, 3193 (NH), 1720, 1681 (CO). MS: *m/z* 394 ($M^+$). Anal. Calcd. for $C_{20}H_{18}N_4O_3S$ (394.45): C, 60.89; H, 4.59; N, 14.20; S, 8.12%. Found: C, 60.81; H, 4.53; N, 14.13; S, 8.08%.

**Synthesis of (6a). Method 1.** Compound **4** (10 mmol) was treated with ethanolic sodium ethoxide (0.23 g sodium in 50 mL ethanol), the reaction mixture was refluxed for 3 h and allowed to cool then poured into cold water and neutralized with dil. HCl. The resulting product was collected by filtration and crystallized from ethanol to afford **6a** in 72% yield.

**Synthesis of (6a, b).** Compound **3** (2.31 g, 10 mmol) was treated with thiourea (0.76 g, 10 mmol) or urea (0.60 g, 10 mmol) and the reaction mixture was heated in oil bath at 100–120°C for 2 h. The mixture was allowed to cool at room temperature. The formed solid product was crystallized from ethanol/dioxane to afford **6a** and **6b**, respectively.

***3-Phenyl-6-thioxo-1,5,6,7-tetrahydro-pyrazolo [3,4-d] pyrimidin-4-one (6a).*** Pale brown crystal (yield 65%), m.p > 300°C. $\upsilon_{max}$ $cm^{-1}$ = 3215, 3120 (NH), 1593 (CO). MS: *m/z* 244 ($M^+$). $\delta_H$ = 7.50–8.15 (m, 5H, Ar-H), 11.82 (s, 1H, NH-pyrazole), 12.99 (s, 1H, NH-pyrimidine), 13.88 (s, 1H, NH-pyrimidine). Anal. Calcd. for $C_{11}H_8N_4OS$ (244.27): C, 54.09; H, 3.30; N, 22.93; S, 13.34%. Found: C, 54.02; H, 3.27; N, 22.85; S, 13.29%.

***3-Phenyl-1,7-dihydro-pyrazolo [3,4-d] pyrimidine-4,6-dione (6b).*** Pale yellow crystal (yield 60%), m.p > 300°C. $\upsilon_{max}$ $cm^{-1}$ = 3430, 3223 (NH), 1730, 1640 (CO). MS: *m/z* 228 ($M^+$). $\delta_H$ = 7.43–8.14 (m, 5H, Ar-H), 10.65 (s, 1H, NH-pyrazole), 11.35 (s, 1H, NH-pyrimidine), 13.55 (s, 1H, NH-pyrimidine). Anal. Calcd. for $C_{11}H_8N_4O_2$ (228.21): C, 57.89; H, 3.53; N, 24.55%. Found: C, 57.81; H, 3.48; N, 24.49%.

**3-Phenyl-5-(3-phenyl-thioureido)-1*H*-pyrazole-4-carboxylic acid ethyl ester (8).** Phenyliso-thiocyanate (1.35 g, 10 mmol) was added to a solution of **3** (2.31 g, 10 mmol) in pyridine and were refluxed for 3 h and then allowed to cool at room temperature. The reaction mixture was poured into ice cold water and neutralized with dil. HCl. The resulting solid was collected by filtration and crystallized from ethanol. The product is identified as **8**. Pale yellow crystal (yield 50%), m.p. 218°C. $\upsilon_{max}$ $cm^{-1}$ = 3355, 3210 (NH), 1654 (CO). MS: *m/z* 366 ($M^+$). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (366.49): C, 62.26; H, 4.95; N, 15.28; S, 8.74%. Found: C, 62.21; H, 4.89; N, 15.23; S, 8.68%.

**3,5-Diphenyl-6-thioxo-1,5,6,7-tetrahydro-pyrazolo [3,4-*d*] pyrimidin-4-one (9).** Compound **8** (10 mmol) was treated with ethanolic sodium ethoxide solution (0.23 g sodium in 50 mL absolute ethanol). The reaction mixture was heated under reflux for 3 h, allowed to cool, then poured onto ice cold water and neutralized with dil. HCl. The resulting solid product is collected by filtration and crystallized from ethanol and identified as **9**. White crystal (yield 55%), m.p. > 300°C. $\upsilon_{max}$ $cm^{-1}$ = 3153, 3056 (NH), 1696 (CO). MS: *m/z* 320 ($M^+$). Anal. Calcd. for $C_{17}H_{12}N_4OS$ (320.37): C, 63.73; H, 3.77; N, 17.48; S, 10.00%. Found: C, 63.64; H, 3.69; N, 17.40; S, 9.92%.

**General method for preparation of (7) and (10).** Compound **4** or **8** (10 mmol) reacted with hydrazine hydrate (0.50 mL, 10 mmol) in pyridine (25 mL) and heated under reflux for 3 h, then allowed to cool at room temperature. The reaction mixtures were poured onto ice cold water and neutralized with dilute HCl. The resulting solids were collected by filtration and crystallized from ethanol.

***3-Phenyl-5-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-1H-pyrazole-4-carboxylic acid ethyl ester (7).*** Pale brown crystal (yield 70%), m.p. > 300°C. $\upsilon_{max}$ $cm^{-1}$ = 3325, 3175, 3150 (NH), 1676 (CO). MS: *m/z* 374 ($M^+$). $\delta_H$ = 1.13(t, 3H, *J* = 7.2 Hz, $CH_3$), 4.15 (q, 2H, *J* = 7.2 Hz, $CH_2$), 7.45–8.15 (m, 10H, 3Ar-H), 9.20 (s, 1H, NH-pyrazole). 11.90 (s, 1H, NH), 13.05 (s, 1H, NH-triazole). Anal. Calcd. for $C_{20}H_{18}N_6O_2$ (374.41): C, 64.42; H, 4.84; N, 22.44%. Found: C, 64.38; H, 4.80; N, 22.37%.

***6-Hydrazide-3,5-diphenyl-1,5-dihydro-pyrazolo [3,4-d] pyrimidin-4-one (10).*** White crystal (yield 50%), m.p. 295°C. $\upsilon_{max}$ $cm^{-1}$ = 3350, 3235 ($NH_2$), 3150 (NH). MS: *m/z* 318 ($M^+$). $\delta_H$ = 5.56 (s, 2H, $NH_2$), 7.11–8.39 (m, 10H, 2Ar-H), 9.47 (s, 1H, NH-pyrazole), 13.18 (s, 1H, NH-hydrazide). $\delta_C$ = 102.64 (C-4 pyrazolopyrimidine), 121.62, 123.60, 127.54, 128.18, and 128.62 (CH aromatic), 132.77 (C-9 pyrazolopyrimidine), 136.28, 138.25, and 147.12 (CH aromatic), 150.91 (C-3 pyrazolopyrimidine), 153.76 (C-7 pyrazolopyrimidine), 157.59 (C-5 pyrazolopyrimidine) (CO). Anal. Calcd. for $C_{17}H_{14}N_6O$ (318.34): C, 64.14; H, 4.43; N, 26.39%. Found: C, 64.09; H, 4.38; N, 26.31%.

**7-Amino-6-cyano-2,5-diphenyl-4,7-dihydro-pyrazolo[1,5-*a*] pyrimidine-3-carboxylic acid ethyl ester (13).** Compounds **11** (1.54 g, 10 mmol) were refluxed for 3 h with compound **3** (2.31 g, 10 mmol) in ethanol (50 mL) and few drops of piperidine as catalyst. The reaction mixture was then poured into ice-cold water and neutralized with dilute HCl. The resulting solid product was collected by filtration and crystallized from ethanol. White crystal (yield 65%), m.p. 220°C. $\upsilon_{max}$ $cm^{-1}$ = 3446, 3400 ($NH_2$), 3315 (NH), 2190 (CN), 1686 (CO). MS: *m/z* 385 ($M^+$). $\delta_H$ ($CDCl_3$) = 1.18 (t, 3H, *J* = 7.2 Hz, $CH_3$), 4.17 (q, 2H, *J* = 7.2 Hz, $CH_2$), 5.48 (s, 3H, $NH_2$, CH-pyrimidine), 6.72 (s, 1H, NH-pyrimidine), 7.39–7.70 (m, 10H, 2Ar-H). Anal. Calcd. for $C_{22}H_{19}N_5O_2$ (385.43): C, 68.55; H, 4.96; N, 18.17%. Found: C, 68.50; H, 4.92; N, 18.08%.

**7-Amino-6-cyanio-2,5-diphenyl-pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (14).** Compound **13** (3.85 g, 10 mmol) was dissolved in 25 mL pyridine (or 25 mL DMF) and heated under reflux for 3 h, then evaporated in vacuo and diluted with cold water (50 mL) then treated with few drops of dil. HCl. The resulting solid product is filtered off, washed well with cold water, and crystallized from ethanol/dioxane mixture. The solid product is identified as **14**. Brown crystal (yield 55%), m.p. 208°C. $\upsilon_{max}$ $cm^{-1}$ = 3415, 3365 ($NH_2$), 2219 (CN), 1685 (CO). MS: *m*/*z* 382 ($M^+$-1). $\delta_H$ = 1.31 (t, 3H, *J* = 7.2 Hz, $CH_3$), 4.34 (q, 2H, *J* = 7.2 Hz, $CH_2$), 6.83 (s, 2H, $NH_2$) 7.48–8.07 (m, 10H, 2Ar-H). $\delta_C$ = 14.11 ($CH_3$ ester), 60.55 ($CH_2$ ester), 75.27 (C-7 pyrazolopyrimidine), 106.23 (C-8 pyrazolopyrimidine), 115.41 (CN), 127.95, 128.59, 128.93, 129.59, 129.64, 131.07, 131.83, and 136.54 (CH aromatic), 148.69 (C-6 pyrazolopyrimidine), 150.55 (C-2 pyrazolopyrimidine), 159.99 (C-4 pyrazolopyrimidine), 160.79 (C-3 pyrazolopyrimidine), 162.69 (CO). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ (383.41): C, 68.91; H, 4.46; N, 18.26%. Found: C, 68.87; H, 4.37; N, 18.19%.

X-ray crystallographic data using *SIR*92 [25] program to solve structure: Yellow crystals, $C_{22}H_{17}N_5O_2$ ($M_r$ = 383.411 $gmol^{-1}$), orthorhombic prismatic, space group *Pna*-2(1), *a* = 8.8207(2) Å, *b* = 16.6408(4) Å, *c* = 25.7103(9) Å, α[°] = 90.00, β[°] = 90.00, γ[°] = 90.00; *V*[$Å^3$] = 3773.8(2). *Z* = 8, $D_x$ = 1.350 $Mgm^{-3}$, μ(Mo $K_\alpha$) = 0.09 $mm^{-1}$; Fine-focus sealed tube. Data were collected using KappaCCD. *T*[K] = 298, with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å), θ = 2.910–25.028°. Measured reflections 6613, Total independent reflections are 3780 were counted with observed reflections 1830. $R_{int}$ = 0.031. *R*(all) = 0.112, *R*(gt) = 0.042, wR(ref) = 0.078, and wR(all) = 0.097.

**General procedure for preparation of compounds (16), (18), and (20).** Compound **3** (2.31 g, 10 mmol) was added to a solution of **15**, **17**, or **19** (10 mmol) in pyridine (25 mL) and refluxed for 3 h. The reaction mixtures were evaporated under vacuo then poured onto ice cold water, and neutralized with diluted HCl. The resulting solids were collected by filtration and crystallized from dioxane/ethanol and identified as **16**, **18**, and **20**, respectively.

***7-Amino-6-cyano-2-phenyl-pyrazolo [1,5-a]pyrimidine-3-carboxylic acid ethyl ester (16).*** Brown crystal (yield 60%), m.p. 282°C. $\upsilon_{max}$ $cm^{-1}$ = 3406, 3220 ($NH_2$), 2221(CN), 1697, (CO). MS: *m*/*z* 307 ($M^+$). Anal. Calcd. for $C_{16}H_{13}N_5O_2$ (307.31): C, 62.53; H, 4.26; N, 22.79%. Found: C, 62.45; H, 4.19; N, 22.69%.

***7-Amino-2-phenyl-pyrazolo [1,5-a] pyrimidine-3-carboxylic acid ethyl ester (18).*** White crystal (yield 70%), m.p. 204°C. $\upsilon_{max}$ $cm^{-1}$ = 3427, 3372 ($NH_2$), 1671 (CO). MS: *m*/*z* 282 ($M^+$). $\delta_H$ = 1.21 (t, 3H, *J* = 7.2 Hz, $CH_3$), 4.28 (q, 2H, *J* = 7.2 Hz, $CH_2$), 6.56 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-5), 7.50–7.81 (m, 5H, Ar-H), 8.26 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-6), 9.94 (s, 1H, $NH_2$). Anal. Calcd. for $C_{15}H_{14}N_4O_2$ (282.31): C, 63.81; H, 4.99; N, 19.84%. Found: C, 63.72; H, 4.91; N, 19.79%.

***2-Phenyl-7-thiophen-2-yl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (20).*** Pale yellow crystal (yield 65%), m.p. 159°C. $\upsilon_{max}$ $cm^{-1}$ = 3062 (CH-Aromatic), 1697(CO). MS: *m*/*z* 349 ($M^+$). $\delta_H$ = 1.21(t, 3H, *J* = 6.9 Hz, $CH_3$), 4.27(q, 2H, *J* = 6.9 Hz, $CH_2$), 7.39–7.90 (m, 6H, Ar-H, thiophene-H-2), 7.95 (d, 1H, *J* = 3.9 Hz, thiophene-H-3), 8.14 (d, 1H, *J* = 3.9 Hz, thiophene-H-1), 8.57 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-6), 8.80 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-5). Anal. Calcd. for $C_{19}H_{15}N_3O_2S$ (349.41): C, 65.31; H, 4.33; N, 12.03; S, 9.18%. Found: C, 65.22; H, 4.38; N, 11.92; S, 9.05%.

**General procedure for preparation of compounds (22), (24), and (26).** Compound **3** (2.31 g, 10 mmol) and 10 mmol of either ethyl acetoacetate **21**, acetylacetone **23**, or benzoylacetonitrile **25** were reacted under thermal conditions in oil bath at 100–120°C for 2 h. The formed solid products were washed well with ethanol and crystallized from ethanol/dioxane to afford **22**, **24**, and **26**, respectively.

***7-Methyl-5-oxo-2-phenyl-4,5-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (22).*** White crystal (yield 70%), m.p 185°C. $\upsilon_{max}$ $cm^{-1}$ = 3200 (NH), 1712, 1662 (CO). MS: *m*/*z* 299 ($M^+$+2). $\delta_H$ = 1.17(t, 3H, *J* = 7.2 Hz, $CH_3$), 3.30 (s, 3H, $CH_3$), 4.22 (q, 2H, *J* = 7.2 Hz, $CH_2$), 5.87 (s, 1H, pyrimidine-H), 7.43–7.71 (m, 5H, Ar-H), 11.54 (s, 1H, NH-pyrimidine). Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (297.32): C, 64.63; H, 5.08; N, 14.13%. Found: C, 64.56; H, 4.98; N, 14.02%.

***5,7-Dimethy-2-phenyl-pyrazolo[1,5-a] pyrimidine-3-carboxylic acid ethyl ester (24).*** Yellow crystal (yield 50%), m.p. 124°C. $\upsilon_{max}$ $cm^{-1}$ = 3060 (CH-Aromatic), 1678 (CO). MS: *m*/*z* 295 ($M^+$). $\delta_H$ = 1.25 (t, 3H, *J* = 6.9 Hz, $CH_3$), 2.70 (s, 3H, $CH_3$), 2.80 (s, 3H, $CH_3$), 4.31 (q, 2H, *J* = 6.9 Hz, $CH_2$), 6.75 (s, 1H, pyrimidine-H) 7.44–7.77 (m, 5H, Ar-H). Anal. Calcd. for $C_{17}H_{17}N_3O_2$ (295.34): C, 69.13; H, 5.80; N, 14.22%. Found: C, 69.05; H, 5.75; N, 14.17%.

***7-Amino-2,5-diphenyl-pyrazolo[1,5-a] pyrimidine-3-carboxylic acid ethyl ester (26).*** Yellow crystal (yield 55%), m.p. > 300°C. $\upsilon_{max}$ $cm^{-1}$ = 3305, 3170 ($NH_2$), 1654 (CO). MS: *m*/*z* 358 ($M^+$). Anal. Calcd. for $C_{21}H_{18}N_4O_2$ (358.40): C, 70.37; H, 5.06; N, 15.63%. Found: C, 70.29; H, 4.97; N, 15.55%.

## REFERENCES AND NOTES

[1] This work is abstracted in part from the Ph.D. thesis of Mr. Khaled E. Azmy.

[2] Abdelrazek, F. M.; Ghozlan, S. A.; Michael, F. A. J Heterocycl Chem 2007, 44, 63.

[3] Ghozlan, S. A. S.; Hafez, E. A. A.; El-Bannany, A. A. Arch Pharm 1987, 320, 850.

[4] Ghozlan, S. A. S.; Hassanien, A. Z. A. Tetrahedron 2002, 58, 9423.

[5] Abdelrazek, F. M.; Metwally, N. H.; Kassab, N. A.; Sobhy, N. A. J Heterocycl Chem 2009, 46, 1380.

[6] Blass, B. E.; Srivastava, A.; Coburn, K. R.; Fanlkner, A. L.; Seibel, W. L. Tetrahedron Lett 2003, 44, 3009.

[7] Domagala, J. M.; Peterson, P. J Heterocycl Chem 1989, 26, 1147.

[8] Gilman, A. G.; Goodman, L. S. The Pharmaceutical Basis of Therapeutics; Macmillan: New York, 1985; p 1109.

[9] Fanger, F.; Nicklen, S.; Coulson, A. R. Proc Natl Acad Sci USA 1977, 74, 5463.

[10] Wellinga, K.; Grosscurt, A. C.; Van Hes, R. J Agric Food Chem 1977, 25, 987.

[11] Grosscurt, C.; Van Hes, R.; Wellinga, K. J Agric Food Chem 1979, 27, 406.

[12] Elbannany, A.; Ghozlan, S. A. S. Egypt J Chem 1988, 31, 587.

[13] Rzepecki, P.; Wehner, M.; Molto, O.; Zadmard, R.; Harms, K.; Schrader, T. Synthesis 2003, 1815.

[14] Abdallah, T. A.; Metwally, N. H.; Abdelrazek, F. M. Afinidad 2008, 65, 393.

[15] Abdelrazek, F. M.; Michael, F. A.; Mohamed, A. E. Arch Pharm Chem Life Sci (Weinheim) 2006, 339, 305.

[16] Zayed, E. M.; Ghozlan, S. A. S.; Ibrahim, A. A. H. Monatsh Chem 1984, 115, 431.

[17] Sigma, K.; Kobe, J.; Robins, R. K.; O'Brien, D. L. J Heterocycl Chem 1973, 12, 893.

[18] Vogel, A.; Troxler, F. Helv Chim Acta 1975, 58, 761.

[19] Makino, K.; Kim, H. S.; Kurasawa, Y. J Heterocycl Chem 1998, 35, 489.

[20] Bogza, S. D.; Ivanov, A. V.; Dulenko, V. I.; Kobrakov, K. I. Chem Heterocycl Compd 1997, 33, 69.

[21] Komykhov, S. A.; Ostras, K. S.; Kostanyn, A. R.; Desenko, S. M.; Orlov, V. D.; Meier, H. J Heterocycl Chem 2005, 42, 1111.

[22] Singa, K.; Brien, D. E.; Scholten, M. B.; Novenson, T.; Miller, J. P.; Robins, R. K. J Med Chem 1982, 25, 243.

[23] Senga, K.; Norenson, T.; Wilson, H. R.; Robrns, R. K. J Med Chem 1981, 24, 610.

[24] Crystallographic data (excluding structure factors) for the structure **8a** reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-755428. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

[25] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. J Appl Crystallogr 1994, 27, 435.

[26] Mackay, S.; Gilmore, C. J.; Edwards, C.; Stewart, N.; Shankland, K. MaXus Computer Program for the Solution and Refinement of Crystal Structures; Bruker Nonius: The Netherlands; MacScience: Japan; University of Glasgow: Glasgow, 1999.

# Synthesis of Substituted 1,3-Oxazines Using Sulfamic Acid as an Efficient and Eco-Friendly Catalyst

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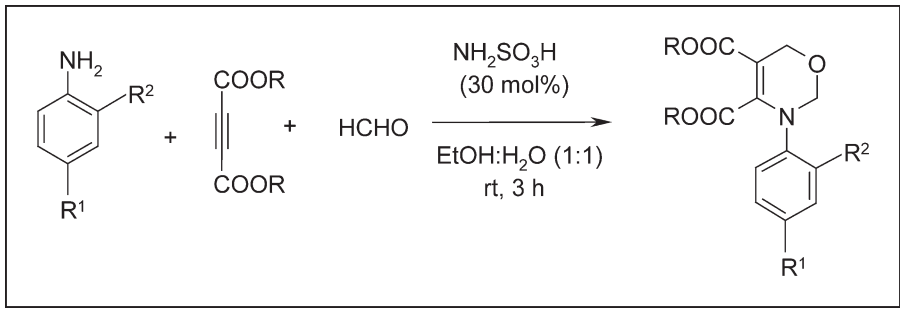


Sulfamic acid catalyzed the synthesis of substituted 1,3-oxazines by one-pot three-component reaction of aniline, alkynoates, and formaldehyde in excellent yields. The catalyst possesses distinct advantages shows ease of handling, good yields, cleaner reactions, nonhygroscopic, noncorrosive, and high activity. Sulfamic acid is a green alternative for metal-containing acidic materials, which are toxic and deleterious for human health and environmental protection.

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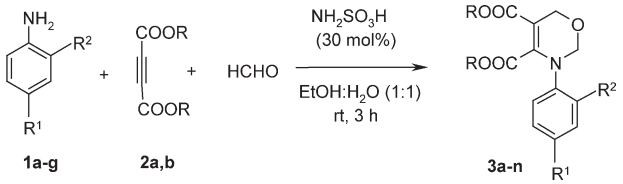
## INTRODUCTION

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. Domino reactions, which result from the combination of multiple transformations in a single pot, are highly efficient means for the improvement of reaction efficiency [1]. Hence, domino reactions and multicomponent reactions (MCRs) [2] involves three or more reactants in a single reaction flask to generate a product incorporating most of the atoms contained in the starting material. Because of intrinsic atom economy, simpler procedure, equipment, time, and energy saving MCRs are gaining much importance in both academia and industry [3]. In domino reactions, each new bond delivers a reactive species, which undergoes further steps without changing the reaction conditions. The main advantage of this strategy is that prefunctionalization of one or both coupling partners are not required; this simplifies the preparation of substrates, shortens the synthetic route, and therefore, minimizes waste production.

Sulfamic acid ($NH_2SO_3H$) has emerged as a substitute for conventional acidic catalysts and is a dry, nonvolatile, nonhygroscopic, odorless, and white crystalline solid with an outstanding stability. It possesses distinctive catalytic features related to its zwitterionic nature and displays an excellent activity over a vast array of acid catalyzed organic transformations, as witnessed by numerous reports published in the past years [4]. Subsequently, there are reports of sulfamic acid-catalyzed tetrahydropyranylation of hydroxy compounds [5], esterification of cyclic olefins with aliphatic acids under solvent-free conditions [6], and transesterification of β-ketoesters in ionic liquids [7], synthesis of quinoline [8], sulfamic acid is recyclable, easy to handle owing to its immiscibility with common organic solvents and it's intrinsic zwitter ionic property prompted us to explore further applications of $NH_2SO_3H$ as an acidic catalyst in other carbon-heteroatom forming reactions.

The synthesis of 1,3-oxazines has attracted attention in the past because of their potential as antibiotics [9], antitumor [10], analgesics [11], and anticonvulsants [12]. 1,3-Oxazines have generated great interest as antipsychotic agents and as possible effectors for serotonin and dopamine receptors [13]. The ring-chain tautomeric interconversion of N-unsubstituted 1,3-*N*-*O*-heterocycles and the corresponding hydroxyalkylimines can often be exploited advantageously in different areas of organic synthesis. Hence, synthesis of these derivatives is of considerable interest. The synthesis of dihydro-2*H*-1,3-oxazines was reported using hydrochloric acid as catalyst [14]. The disadvantage of this methodology is longer reaction time and hazardous acid catalyst. In a broad program of developing efficient eco-friendly synthetic method for pharmacologically important moieties, we

**Scheme 1.** Sulfamic acid-catalyzed synthesis of substituted 1,3-oxazines at room temperature.




explored an alternative procedure, which resulted in an operationally efficient process. More recently we have reported the synthesis of heterocyclic compounds promoted by sulfamic acid [15]. In our ongoing efforts on one-pot multicomponent synthesis [16] and organic synthesis using solid acid catalysts [17], herein we report the synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines using sulfamic acid as catalyst. The reactions proceeded in short reaction times. The catalytic activity of sulfamic acid showed enhanced effect in 1:1 mixture of ethanol and water.

## RESULTS AND DISCUSSION

The reactions were carried out using aniline **1a** (1 eq.), diethyl acetylenedicarboxylate **2a** (1 eq.), and formaldehyde (3 eq.) in the presence of 20 mol % sulfamic acid in 1:1 mixture of ethanol and water (Scheme 1). It was found that all the reactions proceeded rapidly and afforded the desired products in 70% yield. It was also found that increasing the amount of sulfamic acid (20–40 mol %.) increased the yield of the reaction. Further, increasing the amount of sulfamic acid (40–60 mol %) did not affect the rate of the reaction as well as yield. We tried using different acid catalysts, such as $KClO_4$, $Ce(SO_4)_2$, $Cd(OAc)_2$, tetrabutylammmoniumhydrogen suphate, and oxalic acid (Table 1) and found that sulfamic acid is the most effective catalyst in terms of reaction time as well as yield (80%) (Table 2), whereas in presence of other catalysts formed the products with varying yields (0–40%).

**Table 1**

Screening of different catalysts on the synthesis of substituted 1,3-oxazine **3a** at room temperature in EtOH/$H_2O$ (1:1).

| Entry | Catalyst | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | $NH_2SO_3H$ | 3 | 80 |
| 2 | $KClO_4$ | 12 | 20 |
| 3 | Oxalic acid | 12 | 40 |
| 4 | TBAHS | 12 | trace |
| 5 | $Ce(SO_4)_2$ | 12 | trace |
| 6 | $Cd(OAc)_2$ | 12 | No product |

**Table 2**

Solvent effect on the synthesis of substituted 1,3-oxazine **3a** catalyzed by sulfamic acid at room temperature.

| Entry | Solvent | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | EtOH/$H_2O$ (1:1) | 3 | 80 |
| 2 | EtOH | 12 | 70 |
| 3 | MeOH | 12 | 50 |
| 4 | $CH_3CN$ | 12 | 50 |
| 5 | Toluene | 12 | trace |
| 6 | $CHCl_3$ | 12 | 30 |
| 7 | DCM | 12 | 45 |

Also it has been observed that 1:1 mixture of ethanol and water is the best solvent for carrying out this reaction using sulfamic acid (30 mol %) (Table 3). For reaction of dimethyl acetylenedicarboxylate **2b**, aniline **1a** and formaldehyde, similar yields were obtained (Table 3, entries 1–7).

An evident electronic effect was observed on the yields of the products **(3a–n)**. The yield of the products decreased when electron donating groups were present on the phenyl ring. When diethyl acetylenedicarboxylate was used, there was no change in yields (Table 3, entries 8–14).

## CONCLUSIONS

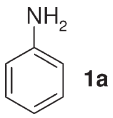
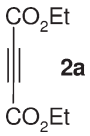
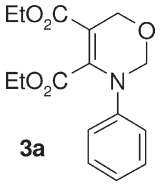
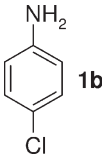
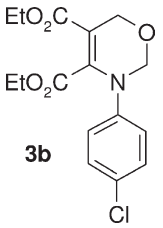
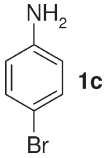
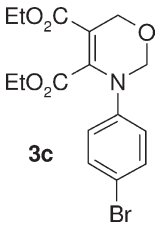
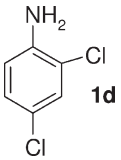
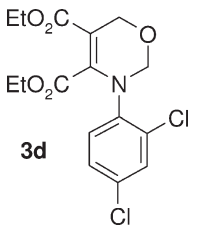
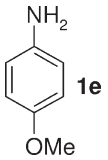
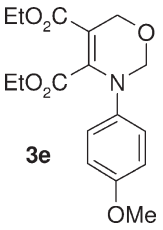
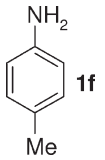
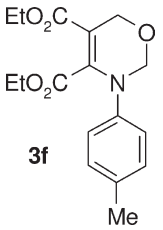
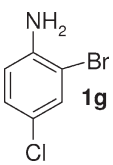
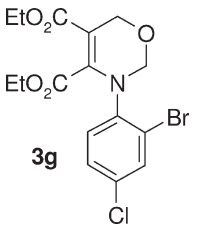
We have developed a novel and highly efficient method for the synthesis of 3,4,5-trisubstituted-1,3-oxazine from alkynoates, amines, and formaldehyde with a simple experimental workup procedure. Sulfamic acid has proved to be an efficient catalyst and green alternative for metal-containing acidic materials, which are toxic and deleterious for human health and environmental protection.

## EXPERIMENTAL

**Materials and methods.** $CDCl_3$ and DMSO-$d_6$ was purchased from Aldrich. IR measurements were done using Perkin Elmer Spectrum RXI FT-IR. The $^1H$ and $^{13}C$ NMR were recorded in $CDCl_3$ with JEOL 500 MHz high resolution NMR spectrometer. $CDCl_3$ was used as the solvent for the NMR spectral measurements and spectra were recorded in ppm with TMS as internal standard. The mass spectra were recorded by using an Electrospray Ionization method with Thermo Finnigan mass spectrometer and EI method with JEOL DX-303 mass spectrometer. Melting points were determined in capillary tubes and were uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer.

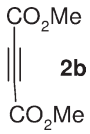
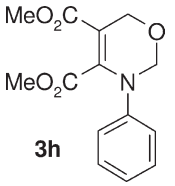
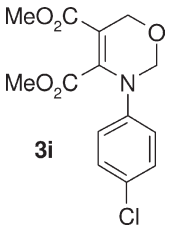
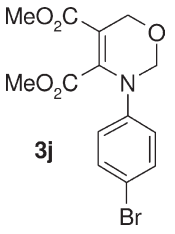
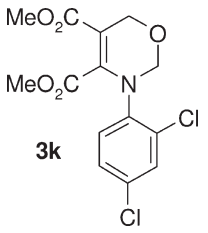
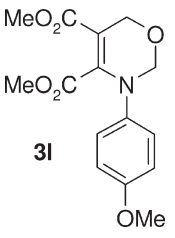
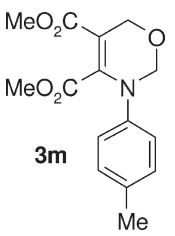
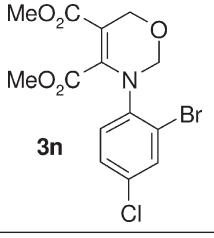
**Table 3**

Sulfamic acid-catalyzed synthesis of substituted 1,3-oxazines at room temperature.

| Entry | Aniline (**1**) | Alkynoates (**2**) | Product (**3**) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 80 |
| 2 |  **1b** | **2a** |  **3b** | 82 |
| 3 |  **1c** | **2a** |  **3c** | 85 |
| 4 |  **1d** | **2a** |  **3d** | 80 |
| 5 |  **1e** | **2a** |  **3e** | 72 |
| 6 |  **1f** | **2a** |  **3f** | 70 |
| 7 |  **1g** | **2a** |  **3g** | 82 |

(*Continued*)

**Table 3**
(*Continued*)

| Entry | Aniline (**1**) | Alkynoates (**2**) | Product (**3**) | Yield (%)[a] |
|---|---|---|---|---|
| 8 | **1a** |  **2b** |  **3h** | 70 |
| 9 | **1b** | **2b** |  **3i** | 78 |
| 10 | **1c** | **2b** |  **3j** | 80 |
| 11 | **1d** | **2b** |  **3k** | 80 |
| 12 | **1e** | **2b** |  **3l** | 76 |
| 13 | **1f** | **2b** |  **3m** | 70 |
| 14 | **1g** | **2b** |  **3n** | 85 |

[a] Isolated yield.

**Representative procedure for the synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines 3a–n.** To a mixture of diethyl acetylenedicarboxylate **2a** (1 mmol) and aniline **1a** (1 mmol), ethanol (3 mL) was added. The mixture was stirred at room temperature for 10 min. Subsequently, sulfamic acid (30 mmol %) and formaldehyde (3.5 mmol) were added. After 30 min, water (3 mL) was added and stirring was continued for 3 h. After completion of the reaction, the reaction mixture was extracted with diethyl ether (3 × 15 mL) and organic layer was separated and the combined extract was dried with anhydrous $Na_2SO_4$. Solvent was removed, and the residue was separated by column chromatography on silica gel (Merck, 100–200 mesh), ethyl acetatepetroleum ether (20:80) to obtain pure product **3a**. $^1$H NMR, $^{13}$C NMR, IR, and mass data of the products **3a–c**, **3e**, **3f**, **3h–j**, **3l**, and **3m** are in full agreement with those reported previously (Ref. 14).

***Diethyl 3,6-dihydro-3-phenyl-2H-1,3-oxazine-4,5-dicarboxylate 3a (Table 3, entry 1).*** Brown viscous oil; IR (neat): 2981, 2930, 1728, 1603, 1488, 1227 cm$^{-1}$. $^1$H NMR δ: 1.23 (t, 6H, $J$ = 6.9 Hz), 3.30 (s, 3H), 3.87 (d, 1H, $J$ = 9.1 Hz), 3.98 (d, 2H, $J$ = 9.1 Hz), 4.19–4.26 (m, 1H), 4.50 (d, 1H, $J$ = 10.4 Hz), 7.29 (t, 1H, d, 1H, $J$ = 6.9 Hz), 7.45 (t, 2H, $J$ = 8.4 Hz), 7.84 (d, 2H, $J$ = 8.4 Hz); $^{13}$C NMR δ: 14.0, 29.7, 49.0, 59.6, 63.0, 72.9, 119.6, 127.1, 129.4, 138.4, 156.4, 165.9, 193.5; ms (EI) $m/z$ = 306 ($M^+$); *Anal*. Calcd for $C_{16}H_{19}NO_5$: C 62.94, H 6.27, N 4.59 Found: C 62.80, H 6.31, N 4.65.

***Diethyl 3-(2,4-dichlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3d (Table 3, entry 4).*** Yellow solid. mp.: 78–80°C; IR (KBr): 2994, 2983, 1752, 1698, 1501, 890 cm$^{-1}$. $^1$H NMR δ: 1.28–1.38 (m, 6H), 3.47 (q, 2H, $J$ = 6.9 Hz), 4.13–4.21 (m, 5H), 4.47 (d, 1H, $J$ = 9.9 Hz), 7.38 (d, 1H, $J$ = 8.4 Hz), 7.56 (d, 1H, $J$ = 6.9 Hz), 7.74 (d, 1H, $J$ = 2.0 Hz); $^{13}$C NMR δ: 13.9, 14.3, 27.2, 52.0, 54.4, 60.3, 63.8, 119.0, 127.3, 129.1, 138.7, 153.9, 163.7, 187.7; ms (EI) $m/z$ = 374 ($M^+$), 376 ($M^{+2}$), 378 ($M^{+4}$); *Anal*. Calcd for $C_{16}H_{17}Cl_2NO_5$: C 51.35, H 4.58, N 3.74. Found: C 50.27, H 4.60, N 3.71.

***Diethyl 3-(2-bromo-4-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3g (Table 3, entry 7).*** Brown solid. mp 83–85°C. IR (KBr): 3024, 2970, 1766, 1694, 1501, 722 cm$^{-1}$. $^1$H NMR δ: 1.19–1.23 (m, 6H), 3.43 (q, 2H, $J$ = 6.9 Hz), 4.12–4.22 (m, 5H), 4.47 (d, 1H, $J$ = 9.9 Hz), 6.94 (d, 1H, $J$ = 9.2 Hz), 7.55 (d, 1H, $J$ = 8.4 Hz), 7.74 (d, 1H, $J$ = 1.7 Hz); $^{13}$C NMR δ: 14.1, 14.9, 31.4, 50.2, 59.5, 62.0, 70.9, 120.1, 127.0, 128.1, 137.2, 150.9, 165.4, 196.3; ms (EI) $m/z$ = 418 ($M^+$), 420 ($M^{+2}$), 422 ($M^{+4}$); *Anal*. Calcd for $C_{16}H_{17}BrClNO_5$: C 45.90, H 4.09, N 3.35. Found: C 45.86, H, 4.12, N 3.37.

***Dimethyl 3-(2,4-dichlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3k (Table 3, entry 11).*** Yellow soild. 77–79°C; IR (KBr): 3010, 2925, 1773, 1554, 1481, 1009 cm$^{-1}$. $^1$H NMR δ: 3.31 (s, 3H), 3.77 (s, 3H), 3.90 (d, 1H, $J$ = 9.2 Hz), 4.09 (d, 1H, $J$ = 9.5 Hz), 4.20 (d, 1H, $J$ = 10.8 Hz), 4.48 (d, 1H, $J$ = 10.4 Hz), 7.51 (d, 1H, $J$ = 8.6 Hz), 7.79 (d, 1H, $J$ = 8.8Hz), 7.88 (d, 1H, $J$ = 1.5 Hz); $^{13}$C NMR δ: 48.8, 52.3, 55.6, 59.5, 70.9, 119.0, 128.1, 138.7, 155.9, 164.4, 193.6; ms (EI) $m/z$ = 311 ($M^+$), 313 ($M^{+2}$), 315 ($M^{+4}$); *Anal*. Calcd for $C_{14}H_{13}Cl_2NO_5$: C 48.58, H 3.79, N 4.05. Found: C 48.66, H 3.75, N 4.02.

***Dimethyl 3-(2-bromo-4-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3n (Table 3, entry 14).*** Brown solid. mp 83–85°C; IR (KBr): 3031, 2985, 1706, 1677, 1481, 915 cm$^{-1}$. $^1$H NMR δ: 3.34 (s, 3H), 3.38 (s, 3H), 4.02 (d, 1H, $J$ = 9.2 Hz), 4.41 (d, 1H, $J$ = 9.2 Hz), 4.52 (d, 1H, $J$ = 10.6 Hz), 4.79 (d, 1H, $J$ = 10.2 Hz), 7.00 (d, 1H, $J$ = 6.8 Hz), 7.55 (d, 1H, $J$ = 7.2 Hz), 7.89 (d, 1H, $J$ = 1.6 Hz); $^{13}$C NMR δ: 47.8, 53.3, 55.6, 58.5, 71.9, 118.2, 127.1, 136.7, 156.9, 164.4, 194.0; ms (EI) $m/z$ = 390 ($M^+$), 392 ($M^{+2}$), 394 ($M^{+4}$); *Anal*. Calcd for $C_{14}H_{13}BrClNO_5$: C 43.05, H 3.35, N 3.59. Found: C 43.10, H 3.32, N, 3.61.

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## REFERENCES AND NOTES

[1] (a) Tietze, L. F. Domino Reactions in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2006; (b) Chapman, C. J.; Frost, C. G.; Synthesis 2007, 1; (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. Angew Chem Int Ed 2007, 46, 1570; (d) Tietze, L. F. Chem Rev 1996, 96, 115.

[2] (a) Multicomponent reactions; Zhu, J.; Bienayme, H. Eds.; Wiley-VCH: Weinheim, 2005; (b) Dömling, A. Chem Rev 2006, 106, 17; (c) Ramón, D. J.; Yus, M. Angew Chem Int Ed 2005, 44, 1602; (d) Simon, C.; Constantieux, T.; Rodriguez, J. Eur J Org Chem 2004, 4957; (e) Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471; (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. Chem Eur J 2000, 6, 3321; (g) Ulaczyk-Lesanko, A.; Hall, D. G. Curr Opin Chem Biol 2005, 9, 266.

[3] (a) Ugi, I.; Heck, S. Comb Chem High Throughput Screening 2001, 4, 1; (b) Weber, L.; IIIgen, K.; Almstetter, M. Synlett 1999, 366.

[4] (a) Jin, T. S.; Sun, G.; Li, Y. W.; Li, T. S. Green Chem 2002, 4, 255; (b) Wang, B.; Yang, L.; Suo, J. Synth Commun 2003, 3929; (c) Bo, W.; Ming, Y. L.; Shuan, S. J. Tetrahedron Lett 2003, 44 5037; (d) Li, J. T.; Han, J. F.; Yang, J. H.; Li, T. S. Ultrason Sonochem 2003, 10, 119; (e) Wang, B.; Gu, Y. L.; Luo, G. Y.; Yang, T.; Yang, L. M.; Suo, J. S. Tetrahedron Lett 2004, 45, 3369; (f) Nagarajan, R.; Magesh, C. J.; Perumal, P. T. Synthesis 2004, 69; (g) Sing, P. R.; Singh, D. U.; Samant, S. D. Synlett 2004, 1909; (h) Heydari, A.; Khaksar, S.; Pourayoubi, M.; Mahjoub, A. R. Tetrahedron Lett 2007, 48, 4059; (i) An, L.-T.; Zou, J.-P.; Zhang, L.-L.; Zhang, Y. Tetrahedron Lett 2007, 48, 4297.

[5] Wang, B.; Yang, L. M.; Suo, J. S. Synth Commun 2003, 33, 3929.

[6] Wang, B.; Gu, Y.; Yang, L.; Suo, J. S.; Kenichi, O. Catal Lett 2004, 96, 71.

[7] Wang, B.; Yang, L. M.; Suo, J. S. Tetrahedron Lett 2003, 44, 5037.

[8] Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, N. V.; Nagaiah, K.; Prasad, A. R. Tetrahedron Lett 2005, 46, 7249.

[9] (a) Haneishi, T.; Okazaki, T.; Hata, T.; Tamura, C.; Nomura, M.; Naito, A.; Seki, I.; Arai, M. J Antibiot 1971, 24, 797; (b) Sasaki, K.; Kusakabe, Y.; Esumi, S. J Antibiot 1972, 25, 151; (c) Kusakabe, Y.; Nagatsu, J.; Shibuya, M.; Kawaguchi, O.; Hirose, C.; Shirato, S. J Antibiot 1972, 25, 44.

[10] Wani, M. C.; Taylor, H. L.; Wall, M. E. Chem Soc Chem Commun 1973, 390.

[11] Urbáński, T.; Ghrne, D.; Szczerek, I.; Modaski, M. Polish Patent 1967, 54, 007.

[12] Mosher, H. S.; Frankel, M. B.; Gregory, M. J Am Chem Soc 1953, 75, 5326.

[13] Peglion, J. L.; Vian, J.; Gourment, B.; Despaux, N.; Audinot, V.; Millan, M. Bioorg Med Chem Lett 1997, 7, 881.

[14] Cao, H.; Jiang, H.-F.; Qi, C.-R.; Yao, W.-J.; Chen, H.-J. Tetrahedron Lett 2009, 50, 1209.

[15] (a) Kumar, R. S.; Ngarajan, R.; Perumal, P. T. Lett Org Chem 2005, 2, 458; (b) Panneer Selvam, N.; Saranya, S.; Perumal, P. T. Can J Chem 2008, 85, 32.

[16] (a) Shanmugam, P.; Damodiran, M.; Selvakumar, K.; Perumal, P. T. J Heterocycl Chem 2009, 46, 919; (b) Damodiran, M.; Muralidharan, D.; Perumal, P. T. Bio Org Med Chem Lett 2009, 19, 3611; (c) Damodiran, M.; Panneer Selvam, N.; Perumal, P. T. Tetrahedron Lett 2009, 50, 5474; (d) Thirumurugan, P.; Perumal, P. T. Tetrahedron Lett 2009, 50, 4145; (e) Thirumurugan, P.; Perumal, P. T. Tetrahedron 2009, 65, 7620; (f) Shanthi, G.; Perumal, P. T. Tetrahedron Lett 2009, 50, 3959; (g) Jayashree, P.; Shanthi, G.; Perumal, P. T. Synlett 2009, 917.

[17] (a) Karthik, M.; Magesh, C. J.; Perumal, P. T.; Palanichamy, M.; Arabindoo, B.; Murugesan, V. Appl Catal A: Gen 2005, 286, 137; (b) Magesh, C. J.; Nagarajan, R.; Karthik, M.; Perumal, P. T. Appl Catal A: Gen 2004, 266, 1.

# Synthesis of (±)-*trans*-Hexahydropyrrolo[3,4-*d*]oxazol-2-one and Its Derivatives by Using *N*-(*tert*-Butyloxycarbonyl)-3-pyrroline as Precursor



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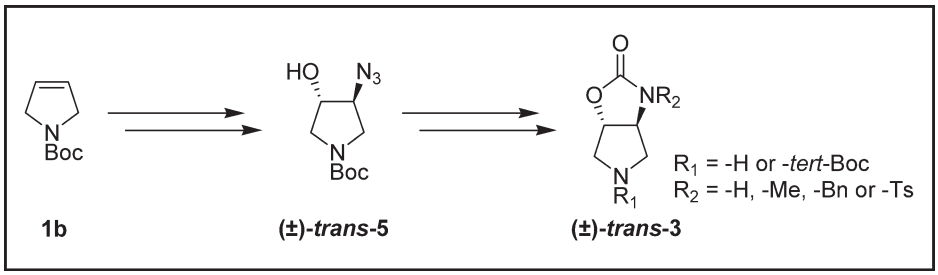


Synthetic method for the preparation of (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives has been developed. By one route, an efficient preparation of these fused heterobicyclic moieties could be achieved, which are prepared by using *N*-(*tert*-butyloxycarbonyl)-3-pyrroline as precursor. These fused heterobicyclic systems could be useful to develop a series of 2-oxazolidinone analogues.

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## INTRODUCTION

Diverse biological activities are encountered in fused heterocyclic systems containing the pyrrolidine and 2-oxazolidinone moieties [1]. In continuation of our interest in this field of 2-oxazolidinones [2], it was thought worthwhile to incorporate 2-oxazolidinone (**2**) to the 3-pyrroline ring by using *N*-(*tert*-butyloxycarbonyl)-3-pyrroilne (**1b**) as a precursor for building of newly fused heterobicyclic systems, (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives (**3**) (Fig. 1).

*N*-Substituted-3-pyrrolines are an important class of compounds which exhibit biological activity and serve as useful synthetic intermediates [3]. The alkene moiety of 3-pyrroline can serves as a handle for various functional group transformations.

The oxazolidinone family represents one of only two new chemical classes of antibiotics disclosed in the past 40 years [4]. Linezolid (Fig. 2), the first approved oxazolidinone, demonstrates good activity against all major pathogenic Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA*a*), vancomycin-resistant *Enterococcus faecium* (VREF), and penicillin-resistant *Streptococcus pneumoniae* [5]. However, not long after the commercial release of linezolid, oxazolidinone resistant strains of MRSA and VREF began to appear in the clinic [6], underscoring the increasingly urgent need for improved antibiotics that overcome bacterial resistance mechanisms. A particularly attractive goal would be a next-generation oxazolidinone with improved spectrum and binding affinity, while retaining properties for good oral exposure and safety [7].

Several SAR studies of the 2-oxazolidinones have demonstrated a high tolerance for structural variation at the 4-position of the phenyl ring [8], while the oxazolidinone ring is essential for biological activity [9]. These fused heterobicyclic systems could be useful to develop a series of oxazolidinone analogues where the morpholine moiety of linezolid could be replaced with these heterobicyclic systems such as RWJ-416457 [10] (Fig. 2).

## RESULTS AND DISCUSSION

The literature survey of the titled compound reveals the *cis* fusion of pyrrolidine and 2-oxazolidinone rings for the preparation of (±)-*cis*- and (3a*R*,6a*S*)-hexahydro-3-methylpyrrolo[3,4-*d*]oxazol-2-one only [11]. Furthermore, it is very important to find out a general methodology to synthesize (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives (**3**). The key challenge of the synthesis is the effective *trans* fusion of 2-oxazolidinone ring using alkene moiety between 3 and 4 positions of 3-pyrroline (**1a**). We required a general

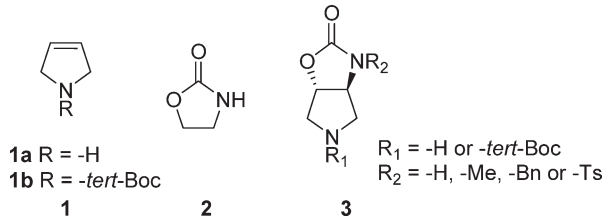
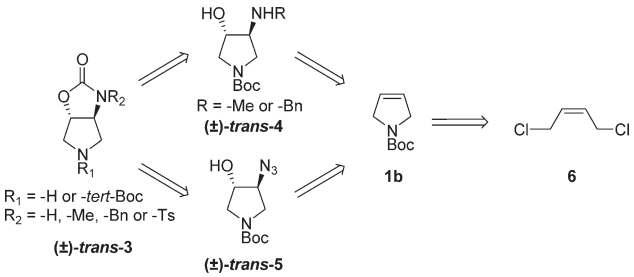



**Figure 1.** Chemical structures of 3-Pyrroline (**1a**), *N*-Boc-3-pyrroline (**1b**), 2-oxazolidinone (**2**), and (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives (**3**).

**Scheme 1.** Retrosynthetic analysis to prepare (±)-*trans*-**3**




method for the preparation of these *trans* fused heterobicyclic systems (**3**) which should be the most attractive in terms of practical and economical. Based on retrosynthetic analysis, we designed two synthetic routes to **3** and are shown in Scheme 1. Each synthetic route includes a key intermediate amino alcohol (**4**) or azido alcohol (**5**) which gives the targeted moieties (**3**).

To prepare these intermediates, *N*-(tert-butyloxycarbonyl)-3-pyrroline (**1b**) or *cis*-1,4-dichloro-2-butene (**6**) are regarded as a common starting material. Recently, **1b** was prepared by us with high purity in large scale starting from *cis*-1,4-dichloro-2-butene **6** *via* Delépine reaction [12] and subsequent *in situ* cyclization in the presence of potassium carbonate ($K_2CO_3$) followed by *N*-Boc protection with di-*tert*-butyldicarbonate ($Boc_2O$) in methanol [3]. This is an efficient and commercial viable synthetic method for *N*-(*tert*-butyloxycarbonyl)-3-pyrroline.

Reaction of **1b** with *N*-bromosuccinimide (NBS) in DMSO–$H_2O$ at room temperature afforded the racemic *trans* bromohydrin (**7**) [13]. The $^1$H NMR spectra of the latter product revealed disappearance the triplet corresponding to alkenyl protons at δ 5.78 ppm, whereas broad singlet for hydroxyl signal appeared at δ 2.8 ppm and also the mass spectrum showed in addition to molecular ion peak, bromine isotopic peak ($M^+$+2) at *m*/*z* 268.

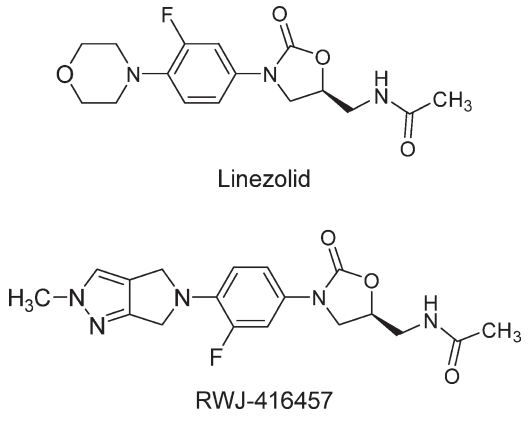



**Figure 2.** 2-Oxazolidinone antibacterials with different *N*-substitutents.

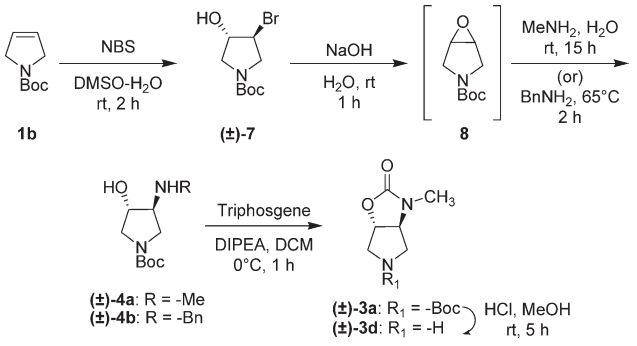
Under basic conditions (NaOH), the bromohydrin (±)-**7** was converted to the epoxide **8**, followed by treatment with methylamine or benzylamine furnished the desired intermediates **4a** or **4b**. However, the carbonyl insertion between β-amino alcohol of **4b** with various reagents, such as *N*,*N*′-carbonyldiimidazole (CDI), diethyl carbonate or triphosgene in different reaction conditions were not successful. Although in case of **4a**, after screening of several reaction conditions the required 2-oxazolidinone **3a** was obtained in low yield (36%) with triphosgene using *N*,*N*-diisopropylethylamine (DIPEA) as a base at 0°C. On treatment of **3a** with HCl in methanol, to remove the *N*-Boc protection, **3d** was obtained in good yield (Scheme 2).

On the other hand, **4b** on protection with $Boc_2O$ gives the di-*tert*-boc protected compound which on further treatment with mesyl chloride, tosyl chloride, or thionyl chloride, the corresponding fused 2-oxazolidinone was not achieved [14]. Thus, we have studied the scope of this approach by opening of epoxy compound **8** with different amines. We were not obtained the right results on the formation of 2-oxazolidinone heterobicyclic systems using different methodologies, such as direct carbonyl insertion or *tert*-boc protection of the amines **4** followed by reaction with mesyl chloride or tosyl chloride.

Finally, our attention was altered to another approach (Scheme 3). The major difference in this strategy is ring opening of epoxy compound **8** with sodium azide instead of amines. In the previous approach, the alkyl substituent on exo cyclic amine of **4** may hinders the formation of 2-oxazolidinone ring due to steric factor. Probably, by choosing alternative strategy, 2-oxazolidinone ring formation followed by alkylation, could be succeeded due to lower steric factor. The epoxide **8** was readily opened with sodium azide in AcOH—$H_2O$ at room temperature gave the corresponding azido alcohol, (±)-*trans*-**5**. The infra-red spectrum of **5** showed clearly a new band at $\upsilon = 2096\ cm^{-1}$ for $N_3$ group.

Azido alcohol (±)-**5** on further treatment with phenyl chloroformate using pyridine in dichloromethane at room temperature yielded the phenyl carbonate **9**. The $^1$H NMR spectra of the latter product **9** divulged a

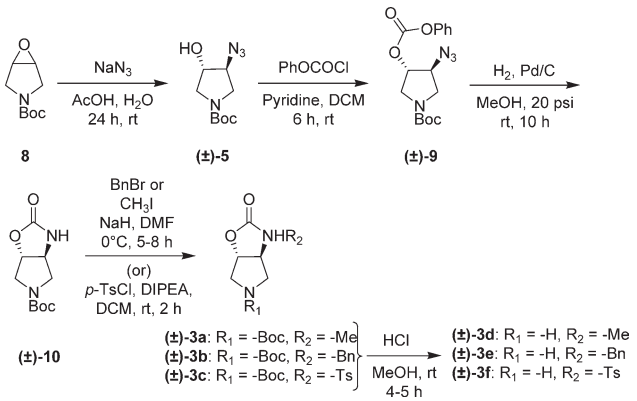
**Scheme 2**

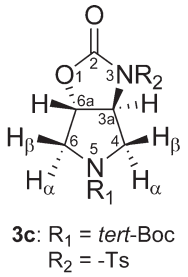



multiplet at δ 5.08–5.14 ppm due to deshielding of the $C_3$—H signal attached to phenyl carbonate and also two bands were appeared at ν = 1757, 1682 $cm^{-1}$ corresponding to carbonyl (C=O) groups in the infra-red spectrum. Reduction of azide in phenyl carbonate (±)-**9** could be achieved by hydrogenation (10% Pd/C, 20 psi, methanol) gave the corresponding amine which undergoes *in situ* cyclisation produced the required basic fused heterobicyclic compound (±)-**10**. Whereas the same reaction is performed in ethyl acetate instead of methanol, *in situ* cyclisation was not occurred. The spectral analysis of the latter product **10** showed the absence of phenyl protons in the $^1$H NMR spectrum and disappearance of azido absorption band at ν = 2122 $cm^{-1}$ in addition, two bands were appeared at ν = 1749, 1694 $cm^{-1}$ corresponding to carbonyl (C=O) groups in the infra-red spectrum. This heterobicyclic compound (±)-**10** was utilized to make derivatization with various substituents at 2-oxazolidinone site.

Compound (±)-**10** was alkylated with benzyl bromide or iodomethane using sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) at 0°C gave the related *tert*-butylhexahydro-3-alkyl-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate, **3a-b**. On the other hand, the alkylation of (±)-**10** with *p*-toluenesulfonyl chloride was attempted under similar conditions (NaH, DMF, 0°C), the reaction was very slow and also observed the incompletion of the reaction even at elevated temperatures. Finally, sulfonylation was achieved by the reaction of (±)-**10** with tosyl chloride using DIPEA in dichloromethane at 0°C.

**Scheme 3**




H-H interaction in NOE spectra (DMSO-d6)
H6a-$H_\beta$4: NOE (due to same spatial arrangement)
H6a-$H_\alpha$4: no NOE (due to different spatial arrangement)
$H_\beta$4-$H_\alpha$4: strong NOE (due to geminal coupling)
$H_\alpha$4-H3a: strong NOE (due to same spatial arrangement)
$H_\beta$4-H3a: minimal NOE
(due to different spatial arrangement)

**Figure 3.** H–H interaction of compound **3c** in NOE spectra (DMSO-*d*6).

Compounds **3a-c** are well characterized by spectral data. The $^1$H NMR spectrum of **3a-c** showed the corresponding alkylation peaks at *N*-3 site. Compound **3a-c** on *N*-*tert*-boc deprotection was achieved with HCl in methanol afforded the targeted hexahydro-3-alkylpyrrolo [3,4-*d*]oxazol-2-one **3e-f** in high yield (Scheme 3). Compounds **3d-f** have been characterized by spectral and elemental analyses.

The *trans* fusion of the two rings, pyrrolidine and 2-oxazolidinone, was assigned by using NOESY studies. To demonstrate the *trans* fusion of the synthesized compounds **3a-f**, the example chosen for NOESY experiments is **3c**. Upon irradiation of H-6a of compound **3c**, led to enhancement of the $H_\beta$-4 and no cross peak of $H_\alpha$-4, which suggested that both H-6a and $H_\beta$-4 are in the same spatial arrangement in addition H-6a and $H_\alpha$-4 are in different special arrangement. Whereas irradiation of $H_\alpha$-4 revealed that H-3a and $H_\alpha$-4 are in the same spatial arrangement (strong enhancement of H-3a signal). This indicates *trans* fusion at the ring junction, which was further confirmed by the very low NOE signal of H-3a upon irradiation of $H_\beta$-4 (Fig. 3). A similar spectral phenomenon was also observed in case of compound **9**.

As a conclusion, a simple and straightforward method was developed to synthesis (±)-*trans*-hexahydropyrrolo [3,4-*d*]oxazol-2-one and its derivatives. Further studies on the application of these compounds to prepare a series of 2-oxazolidinone analogues where the morpholine moiety of linezolid could be replaced with these

heterobicyclic systems are actively underway in our laboratories.

## EXPERIMENTAL

*N*-(*tert*-Butyloxycarbonyl)-3-pyrroline (**1b**) was synthesized in-house (purity >99%) [3]. All reagents and solvents used were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200°C, flame-dried, and flushed with dry nitrogen prior to use. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. TLC was performed on Kieselgel 60 $F_{254}$ silica-coated aluminium plates (Merck) and visualized by UV light ($\lambda = 254$ nm) or by spraying with a solution of ninhydrin. Organic extracts were dried over anhydrous $Na_2SO_4$. Flash chromatography was performed using Kieselgel 60 brand silica gel (230–400 mesh). The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FTIR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz ($^1$H) and at 75 MHz ($^{13}$C). Chemical shifts were given in ppm relative to trimethylsilane. Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

**Preparation of (±)-*trans-tert*-butyl 3-bromo-4-hydroxy pyrrolidine-1-carboxylate, 7 [13].** To a stirred solution of **1b** (60 g, 0.355 mol), DMSO (420 mL) and $H_2O$ (22 mL), NBS (75.3 g, 0.423 mol) was gradually added over 30 min at 0°C. After stirring at room temperature for 2 h, water (490 mL) was added and the mixture was extracted with AcOEt (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and the solvent removed under vacuum to leave a crude **7** as oil in 99.6% yield (94.0 g); $^1$H NMR ($CDCl_3$): δ 1.47 (s, 9H, *t*-butyl), 2.8 (br s, 1H, OH), 3.36–3.45 (m, 1H, $C_5$—H), 3.62–3.96 (m, 2H, $C_5$—H and $C_2$—H), 3.98–4.14 (m, 1H, $C_2$—H), 4.15–4.20 (m, 1H, $C_3$—H), 4.40–4.48 (m, 1H, $C_4$—H); APCI-MS: *m/z* (%) 266.0 (90, $M^+$+1), 268.0 (88, $M^+$+2), 533.1 (100, $2M^+$+3); IR (neat): ν 3387 (OH), 1655 (C=O) $cm^{-1}$.

**Preparation of (±)-*trans-tert*-butyl 3-hydroxy-4-(methyl amino)pyrrolidine-1-carboxylate, 4a.** A mixture of crude **7** (47.0 g, 0.177 mol) and aqueous NaOH (1N, 222 mL, 0.222 mol) was stirred at room temperature for 1 h. The mixture was treated with 40% methylamine-water (182 mL, 2.344 mol) and stirred at room temperature for 15 h. After evaporation of the solvent, the residue was triturated with *i*-$Pr_2O$ to give **4a** as white crystals in 71% yield relative to **1b** (27.2 g), mp 98–100°C; $^1$H NMR (DMSO-$d_6$): δ 1.40 (s, 9H, *t*-butyl), 2.38 (dd, 1H, $C_2$—H), 2.43 (s, 3H, $CH_3$), 3.1 (dd, 1H, $C_5$—H), 3.2 (m, 2H, $C_2$—H and $C_5$—H), 3.51 (br s, 2H, OH, and NH), 4.0 (m, 1H, $C_4$—H), 4.17 (m, 1H, $C_3$—H); ESI-MS: *m/z* (%) 161 (100), 217 (85, $M^+$+1); IR (KBr): ν 3309 (OH), 2972, 1694 (C=O) $cm^{-1}$.

**Preparation of (±)-*trans-tert*-butyl 3-(benzylamino)-4-hydroxypyrrolidine-1-carboxylate, 4b.** A mixture of crude **7** (47.0 g, 0.177 mol) and aqueous NaOH (1N, 222 mL, 0.222 mol) was stirred at room temperature for 1 h. The mixture was treated with benzylamine (47.2 g, 0.44 mol) and stirred at 65°C for 2 h, then cooled to 0°C. The resultant precipitates were collected by filtration, washed with water and *i*-$Pr_2O$ and dried to afford **4b** as white crystals in 60% yield relative to **1b** (31.1 g), mp 140–141°C; $^1$H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-butyl), 1.8 (br s, 2H, OH and NH) 3.10–3.30 (m, 3H, $C_2$—2H and $C_5$—H), 3.57–3.75 (m, 2H, $C_3$—H and $C_5$—H), 3.82 (d, 2H, $NCH_2$—Ph), 4.1 (m, 1H, $C_4$—H), 7.21–7.38 (m, 5H, ArH); ESI-MS: *m/z* (%) 291.2 (100, $M^+$−1), 293.2 (15, $M^+$+1); IR (KBr): ν 3255 (OH), 1694 (C=O) $cm^{-1}$.

**Preparation of (±)-*trans-tert*-butyl hexahydro-3-methyl-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate, 3a.** The amino alcohol **4a** (5.0 g, 0.023 mol) was dissolved in dichloromethane (30 mL) and the solution was cooled to 0°C. Triphosgene (8.23 g, 0.028 mol) was added followed by DIPEA (9.0 g, 0.07 mol) at 0°C. After 1 h, the mixture was washed with water, dried over anhydrous $Na_2SO_4$ and then concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate: hexane (1:1) to give **3a** as colourless liquid in 36% yield.

**Preparation of (±)-*trans-tert*-butyl 3-azido-4-hydroxy pyrrolidine-1-carboxylate, 5.** To a stirred mixture of **1b** (150 g, 0.89 mol), DMSO (1050 mL) and $H_2O$ (55 mL), NBS (188.3 g, 1.06 mol) was gradually added over 30 min at 0°C. After stirring at room temperature for 2 h, water (1225 mL) was added and the mixture was extracted with AcOEt (3 × 500 mL). The organic layer was washed with saturated NaCl, dried over anhydrous $Na_2SO_4$ and then concentrated under reduced pressure to give crude **7** as oil. To this crude **7**, aqueous NaOH (1N, 1110 mL, 1.11 mol) was added at room temperature. After 1 h, the reaction mixture was extracted with AcOEt (3 × 500 mL). The organic layer was washed with saturated NaCl solution, dried over anhydrous $Na_2SO_4$ and then concentrated under reduced pressure to give compound **8** as oil.

To a solution of sodium azide (274 g, 4.21 mol) and water (1250 mL), compound **8** was added at room temperature. To this solution, acetic acid (350 mL) was slowly added at room temperature over 40 min. After the reaction mixture was stirred at room temperature for 24 h, the mixture was extracted with AcOEt (3 × 500 mL). The organic layer was washed with saturated sodium bicarbonate followed by saturated NaCl solution, dried over anhydrous $Na_2SO_4$ and then concentrated under reduced pressure to give **5** as pale yellow color oil (162 g). This pale yellow color oil compound was proceeded to next step without further purification; $^1$H NMR ($CDCl_3$): δ 1.47 (s, 9H, *t*-butyl), 2.75 (br s, 1H, OH), 3.23–3.54 (m, 2H, $C_2$—H and $C_5$—H), 3.56–3.80 (m, 2H, $C_2$—H and $C_5$—H), 3.90–4.01 (m, 1H, $C_3$—H), 4.20–4.30 (m, 1H, $C_4$—H); ESI-MS: *m/z* (%) 229 (100, $M^+$+1); IR (neat): ν 3419 (OH), 2096 ($N_3$), 1668 (C=O) $cm^{-1}$.

**Preparation of (±)-*trans*-1-(*tert*-butoxycarbonyl)-4-azido pyrrolidin-3-yl phenyl carbonate, 9.** To a solution of **5** (50 g, 0.22 mol) in dichloromethane (500 mL), pyridine (50 mL) was added at 0°C. To this mixture, phenyl chloroformate (41 g, 0.262 mol) was slowly added at 0°C over 1 h. After the reaction mixture was stirred at room temperature for 6 h, the mixture was washed with water (250 mL) followed by saturated NaCl solution, dried over anhydrous $Na_2SO_4$ and then concentrated under vacuum. The residue was triturated with *n*-heptane and filtered to give **9** as a white solid in 80% yield

(61 g), mp 92–94°C; $^1$H NMR ($CDCl_3$): δ 1.43 (s, 9H, *t*-butyl), 3.42–3.80 (m, 4H, $C_2$—2H and $C_5$—2H), 4.20–4.24 (m, 1H, $C_4$—H), 5.08–5.14 (m, 1H, $C_3$—H), 7.18–7.42 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): δ 153.9, 150.7, 129.6, 126.4, 120.8, 80.4, 79.7, 78.9, 63.1, 62.3, 49.4, 49.0, 48.9, 48.5, 28.4; ESI-MS: *m*/z (%) 349.28 (100, $M^+$+1); IR (KBr): ν 2122 ($N_3$), 1757 (C=O), 1682 (C=O) cm$^{-1}$.

**Preparation of *tert*-butyl hexahydro-2-oxopyrrolo[3,4-*d*] oxazole-5-carboxylate, 10.** A solution of **9** (20 g, 0.057) in methanol (200 mL) was treated with palladium carbon (2 g, 10% palladium content) and hydrogenated at 20 psi for 10 h. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by column chromatography eluting with ethyl acetate: hexane (2:1) to give *tert*-butyl hexahydro-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate (**10**) as a colorless oil in 62% yield (8.1 g), $^1$H NMR ($CDCl_3$): δ 1.38 (s, 9H, *t*-butyl), 3.56–3.61 (m, 1H, $C_4$—H), 3.65–3.78 (m, 4H, $C_4$—H, $C_6$—2H and $C_{3a}$—H) 4.80–4.96 (m, 1H, $C_{6a}$—H), 8.02 (br s, 1H, NH); ESI-MS: *m*/z (%) 229.2 (100, $M^+$+1); IR (neat): ν 2972 (NH), 1749 (C=O), 1694 (C=O) cm$^{-1}$.

**General procedure for the preparation of *tert*-butyl hexa hydro-3-alkyl-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate, 3a-b.** To a solution of **10** (1.0 g, 0.0044 mol) in DMF (30 mL), sodium hydride (0.5 g, 60% dispersion in mineral oil) was added in one portion at room temperature. After 1 h, benzyl bromide or iodomethane (0.0044 mol) was added in a drop wise fashion. The reaction was left to stir for 5–8 h at room temperature. The reaction mixture was then poured into ice (20 mL) and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined dichloromethane layer was washed with water and dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum and the obtained residue was purified by column chromatography eluting with ethyl acetate: hexane (1:1) to give corresponding 2-oxazolidinone.

***tert*-Butyl hexahydro-3-methyl-2-oxopyrrolo[3,4-d]oxazole-5-carboxylate, 3a.** This compound was obtained as colorless liquid in 66% yield; $^1$H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-butyl), 3.20–3.30 (m, 1H, $C_4$—H), 3.4–3.7 (m, 4H, $C_4$—H, $C_6$—2H and $C_{3a}$—H), 3.82 (s, 3H, $CH_3$), 4.8 (m, 1H, $C_{6a}$—H); ESI-MS: *m*/z (%) 243.15 (100, $M^+$+1); IR (neat): ν 2975, 1695 (C=O), 1423 cm$^{-1}$.

***tert*-Butyl hexahydro-3-benzyl-2-oxopyrrolo[3,4-d]oxazole-5-carboxylate, 3b.** This compound was obtained as pale yellow color liquid in 55% yield; $^1$H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-butyl), 3.1–3.37 (m, 1H, $C_4$—H), 3.39–3.63 (m, 2H, $C_6$—H, and $C_4$—H), 3.6–3.82 (m, 2H, $C_6$—H, and $C_{3a}$—H), 4.56 (s, 2H, *N*$CH_2$—Ph), 4.8 (m, 1H, $C_{6a}$—H), 7.26–7.35 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): δ 154.7, 137.7, 128.5, 127.8, 127.7, 127.6, 83.7, 82.9, 79.4, 71.5, 55.5, 54.5, 51.8, 51.4, 50.5, 49.5, 48.6, 28.4; ESI-MS: *m*/z (%) 319 (100, $M^+$+1); IR (neat): ν 2973, 1690 (C=O), 1409 cm$^{-1}$.

**Preparation of tert-butyl hexahydro-2-oxo-3-tosylpyrrolo [3,4-d]oxazole-5-carboxylate, 3c.** To a solution of **10** (1.0 g, 0.0044 mol) in dichloromethane (30 mL), DIPEA (1.7 g, 0.013 mol) was added in one portion at room temperature. *p*-Toluene sulfonyl chloride (1.0 g, 0.005 mol) was slowly added to the reaction mixture at 0°C. After 2 h, the reaction mixture was diluted with water. The organic layer was washed with water and dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum and the obtained residue was purified by column chromatography eluting with ethyl acetate: hexane (1:1) to give **3c** as yellow viscous liquid in 69% yield (upon long standing in the refrigerator converted to semi-solid); $^1$H NMR (DMSO-$d_6$): δ 1.4 (s, 9H, *t*-butyl), 2.4 (s, 3H, $CH_3$), 3.05–3.1 (m, 1H, $C_4$—H), 3.22–3.33 (m, 2H, $C_6$—H and $C_4$—H), 3.52–3.61 (m, 1H, $C_6$—H), 3.7–3.73 (m, 1H, $C_{3a}$—H), 4.8–4.83 (m, 1H, $C_{6a}$—H), 7.4–7.45 (m, 2H, ArH), 7.78–7.80 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$): δ 154.5, 154.1, 143.8, 136.6, 129.8, 127.1, 80.4, 79.5, 78.1, 56.6, 55.7, 55.2, 50.0, 49.1, 48.5, 28.3, 21.5; IR (neat): ν 2973, 1753 (C=O), 1690 (C=O) cm$^{-1}$; ESI-MS: *m*/z (%) 193.14 (100), 383.26 (45, $M^+$+1).

**General procedure for the preparation of hexahydro-3-alkylpyrrolo[3,4-*d*]oxazol-2-one, 3d-f.** To a solution of **3a-c** (0.003 mol) in methanol (10 mL), 10% HCl in methanol (2.2 mL, 0.006 mol) was added slowly at 10°C. The reaction mixture was stirred at room temperature for 4–5 h. The solvent was removed under reduced pressure and the residue is diluted with saturated sodium bicarbonate solution. The mixture is extracted with dichloromethane, washed with saturated NaCl solution and dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum and the obtained residue was purified by column chromatography eluting with ethyl acetate: hexane (2:1) to give **3d-f**.

***Hexahydro-3-methylpyrrolo[3,4-d]oxazol-2-one, 3d.*** This compound was obtained as yellow color liquid in 92% yield; $^1$H NMR ($CDCl_3$): δ 2.8 (s, 3H, $CH_3$), 3.12–3.25 (m, 4H, $C_6$—2H and $C_4$—2H), 4.21–4.26 (m, 1H, $C_{3a}$—H), 4.81–4.86 (m, 1H, $C_{6a}$—H), 6.0 (br s, 1H, NH); IR (neat): ν 3223 (NH), 1690 (C=O) cm$^{-1}$; ESI-MS: *m*/*z* (%) 143.10 (100, $M^+$+1). *Anal*. *Calcd*. for $C_6H_{10}N_2O_2$: C 50.69; H 7.09; N 19.71. Found: C 50.42; H 6.88; N 19.92.

***Hexahydro-3-benzylpyrrolo[3,4-d]oxazol-2-one, 3e.*** This compound was obtained as yellow color liquid in 89% yield; $^1$H NMR ($CDCl_3$): δ 3.07–3.34 (m, 1H, $C_4$—H), 3.36–3.61 (m, 2H, $C_6$—H and $C_4$—H), 3.63–3.78 (m, 2H, $C_6$—H and $C_{3a}$—H), 4.5 (s, 2H, *N*$CH_2$—Ph), 4.68–4.72 (m, 1H, $C_{6a}$—H), 7.16–7.28 (m, 5H, ArH); IR (neat): ν 3310 (NH), 1692 (C=O) cm$^{-1}$; ESI-MS: *m*/*z* (%) 219.09 (100, $M^+$+1). *Anal*. *Calcd*. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 66.32; H 6.27; N 12.51.

***Hexahydro-3-tosylpyrrolo[3,4-d]oxazol-2-one, 3f.*** This compound was obtained as yellow color liquid in 87% yield (upon long standing in the refrigerator converted to semi-solid); $^1$H NMR (DMSO-$d_6$): δ 2.4 (s, 3H, $CH_3$), 2.43–2.77 (m, 1H, $C_4$—H), 2.95–3.0 (dd, 1H, $C_6$—H), 3.1–3.3 (m, 2H, $C_6$—H and $C_4$—H), 3.58–3.60 (m, 1H, $C_{3a}$—H), 4.81–4.84 (m, 1H, $C_{6a}$—H), 7.26–7.33 (d, 2H, ArH), 7.75–7.78 (d, 2H, ArH); IR (neat): ν 3305 (NH), 1694 (C=O) cm$^{-1}$; ESI-MS: *m*/*z* (%) 283.10 (100, $M^+$+1). *Anal*. *Calcd*. for $C_{12}H_{14}N_2O_4S$: C 51.05; H 5.00; N 9.92. Found: C 51.35; H 4.88; N 9.71.

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## REFERENCES AND NOTES

[1] (a) Liddell, J. R. Nat Prod Rep 1996, 13, 187; (b) Genin, M. J.; Barbachyn, M. R.; Hester, J. B.; Johnson, P. D. US Patent 6,387,896; Chem Abstr 1998, 134, 29408; (c) Staub, A.; Lampe, T.; Pernerstorfer, J.; Perzborn, E.; Pohlman, J.; Roehrig, S.; Schlemmer, K.-H. PCT Int Appl WO 2002-EP6237; Chem Abstr 2003, 138, 89797.

[2] (a) Madhusudhan, G.; Om Reddy, G.; Rajesh, T.; Ramanatham, J.; Dubey, P. K. Tetrahedron Lett 2008, 49, 3060; (b) Chinnam Naidu, K.; Ravi Babu, G.; Gangaiah, L.; Mukkanti, K.; Madhusudhan, G. Tetrahedron Lett 2010, 51, 1226.

[3] (a) Brandange, S.; Rodriguez, B. Synthesis 1988, 347; (b) Rajesh, T.; Abdul Azeez, S.; Naresh, E.; Madhusudhan, G.; Mukkanti, K. Org Process Res Dev 2009, 13, 638.

[4] (a) Moellering, R. C. Ann Intern Med 2003, 138, 135; (b) Wilcox, M. H. Expert Opin Pharmacother 2005, 6, 2315.

[5] Bozdogan, B.; Appelbaum, P. C. Int J Antimicrob Agents 2004, 23, 113.

[6] (a) Auckland, C.; Teare, L.; Cooke, F.; Kaufmann, M. E.; Warner, M.; Jones, G.; Bamford, K.; Ayles, H.; Johnson, A. P. J Antimicrob Chemother 2002, 50, 743; (b) Tsiodras, S.; Gold, H. S.; Sakoulas, G.; Eliopoulos, G. M.; Wennersten, C.; Venkataraman, L.; Moellering, R. C.; Ferraro, M. J. Lancet 2001, 358, 207.

[7] (a) Theuretzbacher, U. Int J Antimicrob Agents 2009, 34, 15; (b) Poce, G.; Zappia, G.; Porretta, G. C.; Botta, B.; Biava, M. Expert Opin Ther Pat 2008, 18, 97.

[8] (a) Weidner-Wells, M. A.; Boggs, C. M.; Foleno, B. D.; Wira, E.; Bush, K.; Goldschmidt, R. A.; Hlasta, D. J. Bioorg Med Chem Lett 2001, 11, 1829; (b) Sciotti, R. J.; Pliushchev, M.; Wiedman, P. E.; Balli, D.; Flamm, R.; Nilius, A. M.; Marsh, K.; Stolarik, D.; Jolly, R.; Ulrich, R.; Djuric, S. W. Bioorg Med Chem Lett 2002, 12, 2121.

[9] (a) Brickner, S. J. Curr Pharm Des 1996, 2, 175; (b) Barbachyn, M. R.; Cleek, G. J.; Dolak, L. A.; Garmon, S. A.; Morris, J.; Seest, E. P.; Thomas, R. C.; Toops, D. S.; Watt, W.; Wishka, D. G.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Adams, W. J.; Friis, J. M.; Slatter, J. G.; Sams, J. P.; Oien, N. L.; Zaya, M. J.; Wienkers, L. C.; Wynalda, M. A. J Med Chem 2003, 46, 284; (c) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. J Med Chem 2000, 43, 953.

[10] Foleno, B. D.; Abbanat, D.; Goldschmidt, R. M.; Flamm, R. K.; Paget, S. D.; Webb, G. C.; Wira, E.; Macielag, M. J.; Bush K. Antimicrob Agents Chemother 2007, 51, 361.

[11] (a) Andrew, J. J.; Christopher, B. D.; John, L. B.; Charlotte, N. J.; Rachel, T. J. PCT Int Appl WO-2009–153554; Chem Abstr 2009, 152, 97443; (b) Murabayashi, A.; Otsuka, S.; Tanimoto, N. JP 1993–5058995, Chem Abstr 1993, 119, 225810.

[12] (a) Warmus, J. S.; Dilley, G. J.; Meyers, A. I. J Org Chem 1993, 58, 270; (b) Delépine, M. Bull Soc Chim Fr 1922, 31, 108; (c) Delépine, M. Bull Soc Chim Fr 1897, 17, 290; (d) Delépine, M.; Hebd, C. R. Séances Acad Sci 1897, 124, 292; (e) Delépine, M.; Hebd, C. R. Séances Acad Sci 1895, 120, 501.

[13] Tsuzuki, Y.; Chiba, K.; Mizuno, K.; Tomita, K.; Suzuki, K. Tetrahedron Asymmetry 2001, 12, 2989.

[14] Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. Curr Org Synth 2007, 4, 81.

# Trichloroisocyanuric Acid-Catalyzed Reaction of Indoles: An Expeditious Synthesis of Bis-Indolyl, Tris-Indolyl, Di(bis-Indolyl), Tri(bis-Indolyl), and Tetra(bis-Indolyl)methane under Solid-State Conditions

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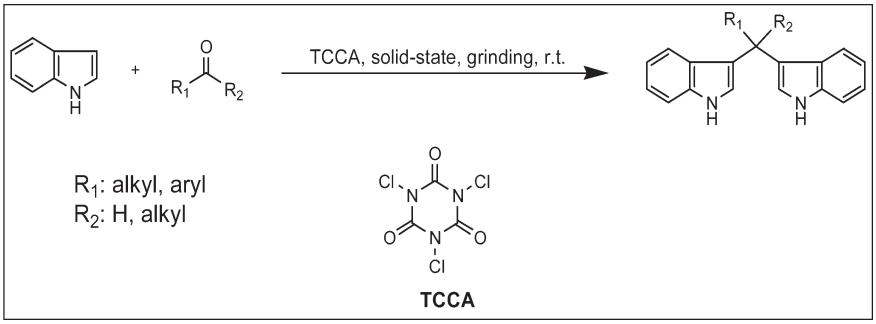


Trichloroisocyanuric acid is found to be an efficient catalyst for the electrophilic substitution reaction of indole with aldehydes/ketones to afford the corresponding bis-indolyl, tris-indolyl, di(bis-indolyl), tri(bis-indolyl), and tetra(bis-indolyl)methanes under solid-state conditions by pulverization-activation method at room temperature with excellent yields. The remarkable features of this new procedure are high conversions, shorter reaction times, cleaner reaction profiles, and simple experimental and work-up procedures.

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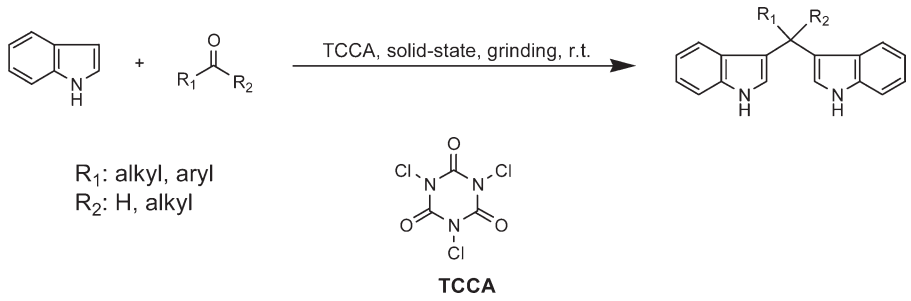
## INTRODUCTION

The development of bis(indolyl)alkane synthesis has been of considerable interest in organic synthesis because of their wide occurrence in various natural products possessing biological activity and usefulness for drug design [1]. Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism [2] and induce apoptosis in human cancer cell. Thus, the development of facile and environmentally friendly synthetic methods for the preparation of these compounds constitutes an active area of investigation in pharmaceutical and organic synthesis [3–5].

Synthetically the reaction of 1H-indole with aldehydes or ketones produces azafulvenium salts that react further with a second 1H-indole molecule to form bis(indol-3-yl)methanes [6]. In recent years, synthesis of this class of molecules under mild conditions have been reported, with promoters, such as montmorillonite clay K-10 [7], trichloro-1,3,5-triazine [8], $AlPW_{12}O_{40}$ [9], sodium dodecyl sulfate [10], $ZrCl_4$ [11], $H_2NSO_3H$ [12], $I_2$ [13], zeolites [14], bentonite [15], $In(OTf)_3$/ionic liquid [16], $CuBr_2$ [17], $Dy(OTf)_3$/ionic liquid [18], $HClO_4$-$SiO_2$ [19], $InCl_3$ [20], MW/Lewis acids ($FeCl_3$, $BiCl_3$, $InCl_3$, $ZnCl_2$, $CoCl_2$) [21], $NaHSO_4$ and Amberlyst-15 [22], sulfated zirconia [23], $ZrOCl_2/SiO_2$ [24], silica sulfuric acid [25], $TiO_2$ [26], $(NH_4)_2HPO_4$ [27], acidic ionic liquid [28], $NaBF_4$ [29], metal hydrogen sulfates [30], tetrabutylammonium tribromide [31], superacid $SO_4^{2-}/TiO_2$ [32], $NaHSO_4$/ionic liquid [33], NBS [34], $Ph_3CCl$ [35], $H_3PW_{12}O_{40}$ [36], $LiClO_4$ [37], Zr(DS)4 [38], and $Bi(NO_3)_3.5H_2O$ [39]. However, most of the existing methods involve toxic metal ions and solvent, high cost and cumbersome work-up procedures. Consequently, new procedures that address these drawbacks are desirable. Although TCCA has been produced on large scale for use in household and industry since the 1950s, it has never had a real breakthrough in organic chemistry laboratories. It also has not found its way into textbooks in

**Scheme 1**




organic chemistry and even books on heterocyclic chemistry fail to mention this very useful reagent. Also there is a nice article review by Tilstam [40] that they have shown that trichloroisocyanuric acid (TCCA) is a safe and efficient reagent, useful for chlorination and oxidation reactions.

## RESULTS AND DISCUSSION

In continuation of our interest in the application of N-halo reagents in organic synthesis [41–44], we report the use of TCCA as an catalyst in the electrophilic substitutions of indole with a variety of aldehydes and ketones under solid-state conditions to afford bis(indolyl)methanes by pulverization-activation method at room temperature with excellent yields (Scheme 1).

As TCCA contain chlorine atoms, which are attached to nitrogen atoms, it is also possible that it release $Cl^+$ *in situ*, which can act as Lewis acid to activate the carbonyl oxygen to form the bis-indole derivatives.

First, we examined the TCCA in the model reaction of indole with benzaldehyde in different reaction media to investigate the best conditions. The results are summarized in the Table 1 and show that under solvent-free conditions TCCA (0.1 mmol) led to the best result (Table 1, Entry 8). However, the solvent-free (grinding at solid-state condition) was found to be best for the catalytic reaction at room temperature in terms of yield, reaction time, and product isolation.

These results promoted us to investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions. As shown in Table 2, a series of aromatic, aliphatic and heterocyclic aldehydes underwent electrophilic substitution reaction with indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. The electron deficiency and nature of the substituents on the aromatic ring effect the conversion rate; aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 2, entries 10, 11) react slower than electron-donating groups (Table 2, entries 4, 8, 9, 12). Furthermore, unsaturated aldehydes, such as cinnamaldehyde, give the corresponding bis(indolyl)methanes without polymerization or halogenation under the above reaction conditions. Ketones required longer reaction times, which is most probably because of the electron-donating and steric effects of the methyl group.

This reaction was further explored for the synthesis of tri-indolylmethane (**3**), (**4**) by the condensation of indol-3-carbaldehyde (**1**) or isatin (**2**) with two equivalents of indole under similar conditions with our method in good yields (Scheme 2).

Selective condensation of a dialdehyde, that is, terephthaldialdehyde to the corresponding bis-indolyl methane was achieved by controlling the molar ratio of indole (Scheme 3). The results showed that addition of 2 equivalents of indole to terephthaldialdehyde, gives (**5**) in good yield (Scheme 3). Treatment of 4 equivalents of indole with terephthaldialdehyde gives the corresponding di(bis-indolyl methanes), (**6**) in excellent yield at room temperature under same conditions [38].

This reaction was further explored for the synthesis of tri(bis-indolyl)methane (**8**) and tetra(bis-indolyl)methanes (**10**) as new triarylmethanes, by the condensation of aldehyde (**7**) with 6 equivalents indole and aldehydes (**9**) with 8 equivalents indole under similar condition (solid-state, grinding) in high yields (Schemes 4 and 5).

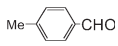
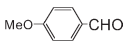
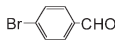
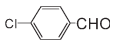
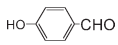
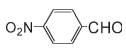
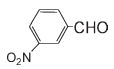
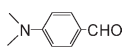
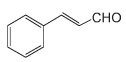
**Table 1**

Screening of the reaction conditions for the synthesis of bis(indolyl)methane by reaction of benzaldehyde and indole.

| Entry | Condition | Time | Yield (%) |
|---|---|---|---|
| 1 | MeCN/no reagent | 12 h | 0 |
| 2 | MeCN/(0.1 mmol) TCCA | 1 h | 95 |
| 3 | $CH_2Cl_2$/(0.1 mmol) TCCA | 2 h | 85 |
| 4 | $CHCl_3$/(0.1 mmol) TCCA | 2 h | 80 |
| 5 | EtOH/(0.1 mmol) TCCA | 1.5 h | 90 |
| 6 | MeCN/(0.2 mmol) TCCA | 1 h | 95 |
| 7 | Solvent-free/(0.05 mmol) TCCA/grinding | 5 min | 90 |
| 8 | Solvent-free/(0.1 mmol) TCCA/grinding | 1 min | 98 |
| 9 | Solvent-free/(0.2 mmol) TCCA/grinding | 1 min | 98 |

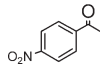
**Table 2**

Synthesis of bis(indolyl)methanes by the reaction of indole with aldehydes and ketones under solid-state conditions.

| Entry | Carbonyl compound | Time (min) | Yield (%)[a] | m.p. (°C) | m.p. (°C) [Lit.] |
|---|---|---|---|---|---|
| 1 |  | 1 | 98 | 124–125 | 124–125 [45] |
| 2 |  | 1.5 | 95 | 94–95 | 93–94 [10] |
| 3 |  | 1 | 98 | 134–136 | 133–135 [39] |
| 4 |  | 1.2 | 96 | 190–192 | 192–193 [45] |
| 5 |  | 3 | 90 | 110–112 | 112–113 [38] |
| 6 |  | 2 | 96 | 76–78 | 78–80 [45] |
| 7 |  | 1 | 98 | 70–72 | 70–71 [10] |
| 8 |  | 2 | 85 | >300 | >300 [10] |
| 9 |  | 3 | 90 | 123–125 | 123–125 [46] |
| 10 |  | 5 | 80 | 218–220 | 217–220 [10] |
| 11 |  | 4.5 | 85 | 258–260 | 260–261 [47] |
| 12 |  | 3 | 80 | 224–226 | 225–226 [39] |
| 13 |  | 3 | 85 | 98–100 | 98–99 [10] |
| 14 |  | 2.5 | 80 | 151–154 | 150–153 [10] |
| 15 |  | 5 | 75 | 121–123 | 122–124 [38] |

(*Continued*)

**Table 2**
(*Continued*)

| Entry | Carbonyl compound | Time (min) | Yield (%)[a] | m.p. (°C) | m.p. (°C) [Lit.] |
|---|---|---|---|---|---|
| 16 |  | 4 | 85 | 165–167 | 166–168[38] |
| 17 |  | 5 | 80 | 190–192 | 190–191 [38] |
| 18 |  | 5 | 75 | 115–116 | 114–116 [39] |

[a] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

3-Substituted indole was examined for this reaction under the above reaction conditions with aldehydes (Scheme 6). As the more active site (C-3) in indole was blocked in this case electrophilic substitution took place at C-2 in indole giving the corresponding bis(indolyl)-methane in high yield under solid-state conditions.

The chemo selectivity of the present method is also demonstrated by competitive reactions of indol with arylaldehydes in the presence of aliphatic ones and ketones. For example, when a 1:1 mixture of benzaldehyde and propionaldehyde was allowed to react with 2 equivalents of indole in the presence of TCCA under grinding conditions, it was found that the arylaldehydes was chemo selectively converted to the corresponding bis(indolyl)methane but the aliphatic ones was converted slightly. Also, in an equimolar mixture arylaldehyde and ketone, only arylaldehyde was converted to the corresponding bis(indolyl)methane, whereas ketone remained (Scheme 7). The reaction was clean and the products were obtained in high yields without the formation of any side products, such as N-alkylated products.

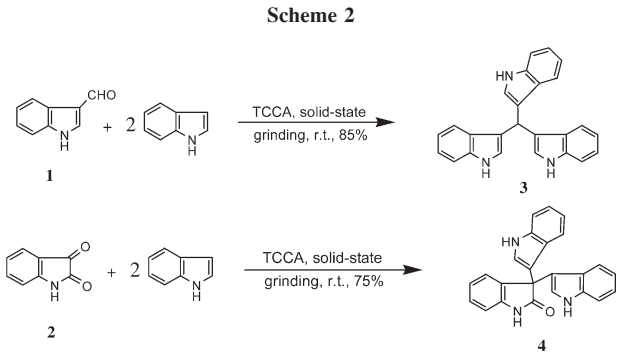
## CONCLUSIONS

In conclusion, we have introduced TCCA as a catalytic reagent for the efficient preparation of bis-indolyl, tris-indolyl, di(bis-indolyl), tri(bis-indolyl), and tetra(bis-indolyl)methanes from indole with various aldehydes and ketones under solid-state conditions by pulverization-activation method at room temperature with excellent yields. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic, α,β-unsaturated, heterocyclic substrates, and ketones. In addition, efficiency, mild reaction conditions, easy work up, simplicity and chemoselectivity of this protocol provide a fast, green, and low cost procedure for the synthesis of these compounds.

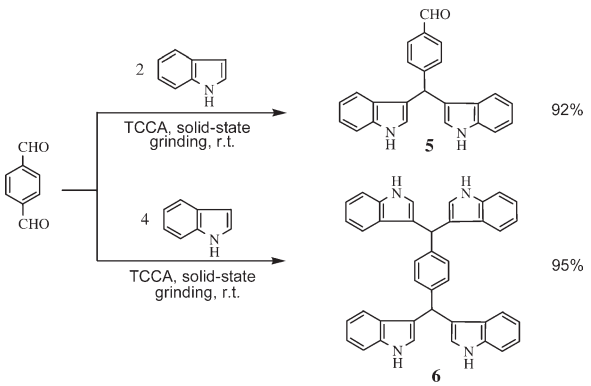
## EXPERIMENTAL

**Synthesis of bis(indolyl)methanes in solid-state grinding catalyzed by TCCA.** A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol), and TCCA (0.1 mmol) were

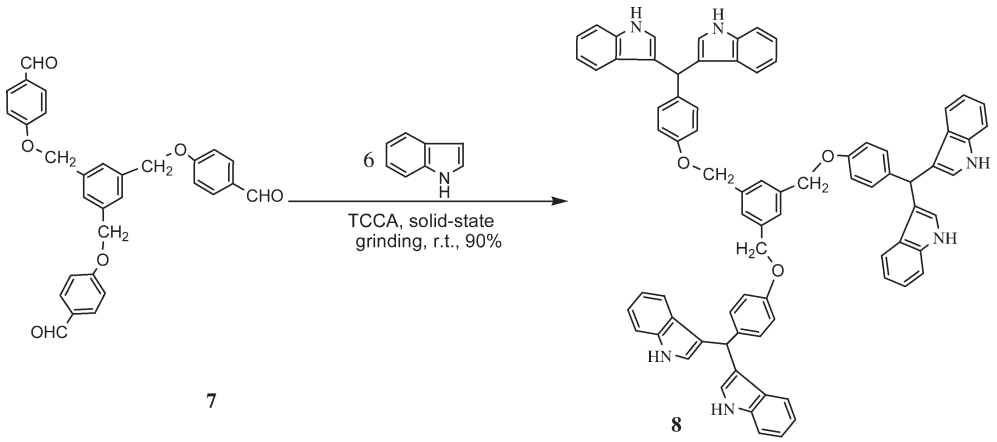
**Scheme 2**




**Scheme 3**



**Scheme 4**




added to a mortar and the mixture was pulverized with a pestle. A spontaneous reaction took place [1–5 min, Table 2, monitored by TLC (4:1, hexane/ acetone)]. After completion of the reaction, $CH_2Cl_2$ (10 mL) was added, and insoluble reagents were removed by filtration. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by recrystallization from ethanol-water to afford pure products.

***3,3′-Bisindolyl-phenylmethane (Table 2, entry 1)*** Pink solid, m.p.: 124–125°C; IR (KBr): 3402, 3050, 2986, 1615, 1600, 1455, 1112 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.88 (s, 1H), 6.68 (s, 2H), 7.13–7.45 (m, ArH, 13H), 7.95 (br s, NH, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta_c$ (ppm) 31.6, 110.9, 111.9, 118.4, 119.5, 1121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2; MS: *m*/*z* 322.

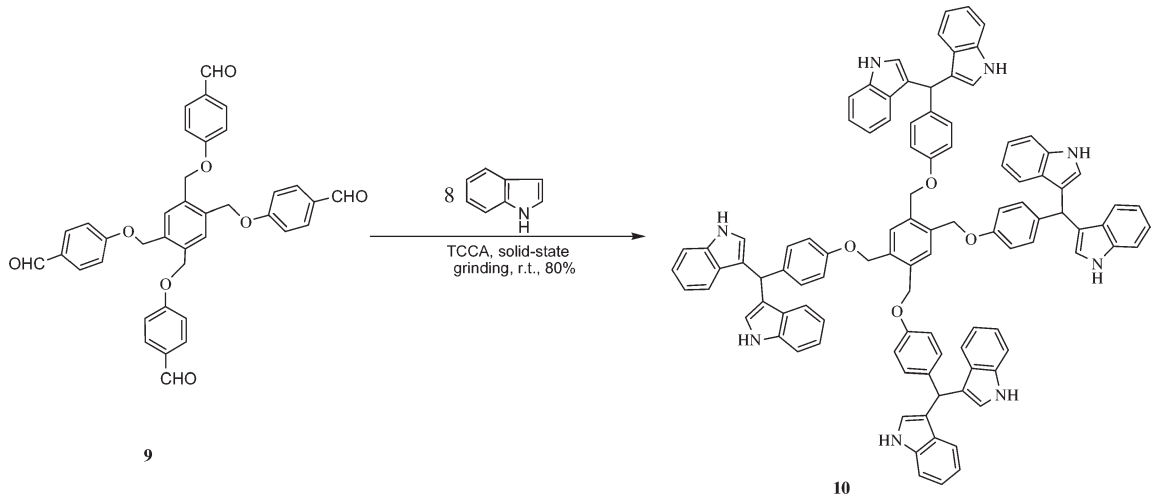
***3,3′-Bisindolyl-4-methylphenylmethane (Table 2, entry 2)*** Pinkish solid, m.p.: 94–95°C; IR (KBr): 3452, 3112, 3045, 2950, 1604, 1523, 1210, 1052, 765 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 2.38 (s, 3H), 5.85 (s, 1H), 6.70–7.55 (m, ArH, 14H), 7.85 (br s, NH, 2H); MS: *m*/*z* 336; *Anal*. Calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.45; H, 5.88; N, 8.14.

***3,3′-Bisindolyl-2-methoxylphenylmethane (Table 2, entry 3)*** Red solid, m.p.: 134–136°C; IR (KBr): 3408, 3056, 2932, 1597, 1486, 1450, 1335, 1102, 745 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.82 (s, 3H), 6.32 (s, 1H), 6.61 (s, 2H), 6.81–7.40 (m, ArH, 12H), 7.80 (br s, NH, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta_c$ (ppm) 32.3, 56.0, 110.0, 110.8, 111.1, 119.2, 119.8, 120.2, 120.6, 121.9, 123.7, 127.2, 129.9, 132.5, 136.9, 157.1; *Anal*. Calcd. for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.24; H, 5.45; N, 7.86.

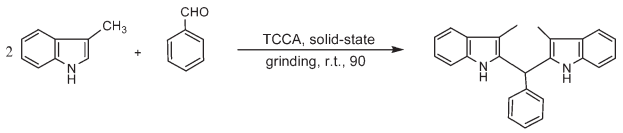
***3,3′-Bisindolyl-4-methoxyphenylmethane (Table 2, entry 4)*** Pinkish solid, m.p. 190–192°C; $^1H$ NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.84 (s, 3H), 5.90 (s, 1H), 6.64–7.65 (m, ArH, 14H), 7.80 (br s, NH, 2H); $^{13}C$ NMR (ppm): 39.7, 55.6, 111.5, 114.0, 119.6, 120.4, 120.4, 122.3, 123.9, 127.5, 130.0, 136.7, 137.1, 158.3.

***3,3′-Bisindolyl-4-bromophenylmethane (Table 2, entry 5)*** Pink solid, m.p.: 110–112°C; IR (KBr): 3410, 3054, 1487, 1455, 1089 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 6.66

**Scheme 5**



**Scheme 6**




**11**

(s, 2H), 7.02–7.45 (m, ArH, 12H), 7.85 (br s, NH, 2H); MS: *m*/*z* 361.

***3,3′-Bisindolyl-4-chlorophenylmethane (Table 2, entry 6)*** Pink solid, m.p.: 76–78°C; IR (KBr): 3409, 2958, 1456, 1488; $^1$H NMR (300 MHz, acetone-$d_6$) δ(ppm): 5.90 (s, 1H), 6.82 (s, 2H), 6.89–7.39 (m, 12H), 9.99 (s, 2H, N—H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ(ppm): 40.8, 112.1, 119.2, 120.1, 120.3, 121.9, 124.5, 128.1, 129.2, 138.0, 143.4.

***3,3′-Bisindolyl-2-chlorophenylmethane (Table 2, entry 7)*** Pinkish solid, m.p.: 70–72; $^1$H NMR ($CDCl_3$): 7.89 (br s, 2H), 7.07–7.51 (m, 12H), 6.53 (s, 2H), 6.36 (s, 1H); $^{13}$C NMR ($CDCl_3$): (36.9, 110.1, 111.3, 119.3, 119.8, 122.0, 124.0, 126.7, 127.0, 128.3, 30.4, 130.7, 135.3, 136.7, 141.5.

***3,3′-Bisindolyl-2-furylmethane (Table 2, entry 8)*** Pale red solid, m.p.: >300; $^1$H NMR ($CDCl_3$): 7.74 (br s, 2H), 7.32–7.63 (m, 9H), 7.09 (s, 2H), 6.21–6.35 (m, 2H), 5.82 (s, 1H); $^{13}$C NMR ($CDCl_3$): d 41.2, 102.1, 110.3, 111.8, 112.6, 119.4, 120.3, 121.5, 122.6, 131.0, 136.4, 141.2, 152.0.

***3,3′-Bisindolyl-4-hydroxyphenylmethane (Table 2, entry 9)*** Pink solid, m.p.: 123–125°C; IR (KBr): 3420, 3239, 1455, 1511, 1616 cm$^{-1}$; $^1$H NMR (DMSO): 7.58 (br s, 2H), 6.69–7.24 (m, 13H), 6.67 (s, 2H), 5.85 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ(ppm): 31.12, 111.89, 115.28, 118.58, 119.19, 119.71, 121.30, 123.89, 127.17, 129.66, 135.71, 136.93, 137.10, 155.79.

***3,3′-Bisindolyl-4-nitrophenylmethane (Table 2, entry 10)*** Red solid, m.p.: 218–220; $^1$H NMR ($CDCl_3$): 8.19 (d, 2H, *J* = 7.81), 7.76 (br s, 2H), 7.40–7.58 (m, 10H), 7.03 (s, 2H), 6.05 (s, 1H); $^{13}$C NMR ($CDCl_3$): d 44.5, 110.0, 112.1, 119.6, 119.8, 120.9, 121.3, 121.9, 130.2, 133.8, 136.2, 143.1, 145.2.

***3,3′-Bisindolyl-3-nitrophenylmethane (Table 2, entry 11)*** Pinkish solid, m.p.: 258–260; $^1$H NMR ($CDCl_3$): 8.46 (br s, 2H), 7.02–7.87 (m, 12H), 6.61 (s, 2H), 5.34 (s, 1H); $^{13}$C NMR ($CDCl_3$): d 34.9, 111.5, 111.6, 119.5, 120.7, 121.9, 122.2, 124.3, 126.8, 129.6, 131.2, 132.6, 134.2, 136.8, 149.7.

***3,3′-Bisindolyl-4-(N,N-dimethyl)phenylmethane (Table 2, entry 12)*** Pinkish solid, m.p.: 224–226; $^1$H NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.28 (s, 6H), 5.75 (s, 1H), 6.76–7.84 (m, ArH, 14H), 7.82 (br s, NH, 2H); MS: *m*/*z* 365.

***3,3′-Bisindolyl-1-(2-phenylethylene)methane (Table 2, entry 13)*** Pinkish solid, m.p.: 98–100; $^1$H NMR (90 MHz, $CDCl_3$): 5.92–6.07 (m, 2H), 5.76 (m, 1H), 6.71 (s, 2H), 6.89–7.68 (m, 15H), 8.02 (br s, 2H, NH); MS: *m*/*z* 348.

***3,3′-Bisindolyl-[2]thienylmethane (Table 2, entry 14)*** Brown solid, m.p.: 151–154°C; IR (KBr): 3412, 1715, 1452, 1260, 1105 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 6.18 (s, 1H), 6.87 (s, 2H), 6.92–7.48 (m, ArH, 11H), 7.98 (br s, NH, 2H); *Anal*. Calcd. for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 76.52; H, 5.10; N, 8.35.

***3,3′-Bisindolyl-1-butylmethane (Table 2, entry 15)*** Pale red solid, m.p.: 121–123; $^1$H NMR (90 MHz, $CDCl_3$): 0.80 (t, *J* = 6.7 Hz, 3H), 1.25–1.29 (m, 6H), 4.62 (t, *J* = 6.7 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 2H), 6.89–7.68 (m, 8H), 8.12 (br s, 2H, NH); MS: *m*/*z* 302.

***3,3′-Bisindolyl-1-methyl-1-phenylmethane (Table 2, entry 16)*** Pinkish solid, m.p.: 165–167°C; $^1$H NMR (90 MHz, $CDCl_3$): 2.40 (s, 3H), 6.67 (s, 2H), 6.95–7.43 (m, 13H), 7.91 (br s, 2H, NH); MS: *m*/*z* 336.

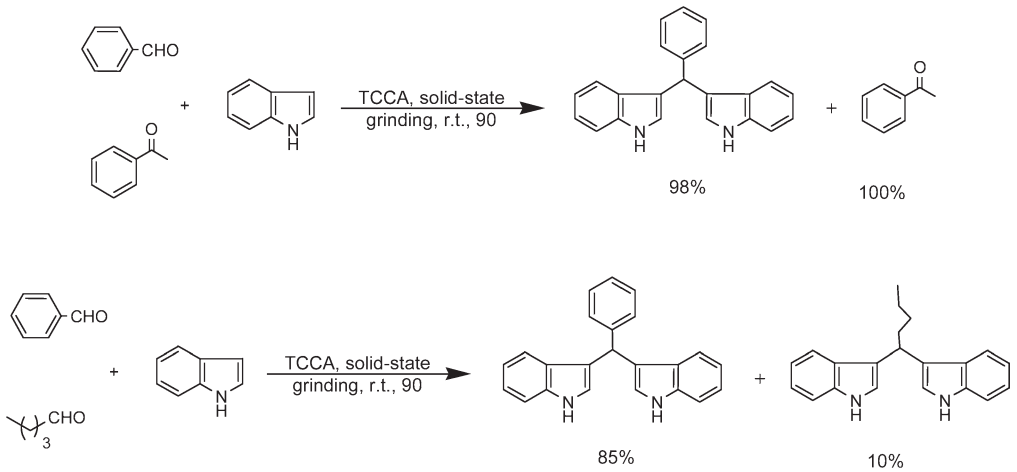
***3,3′-Bisindolyl-1-methyl-1-(4-nitro)phenylmethane (Table 2, entry 17)*** Pink solid, m.p.: 190–192; $^1$H NMR (90 MHz, $CDCl_3$): 2.46 (s, 3H), 6.78 (s, 2H), 6.79–7.68 (m, 12H), 7.98 (br s, 2H, NH); MS: *m*/*z* 381.

***3,3′-Bisindolyl-[1,1]cyclohexane (Table 2, entry 18)*** Red solid, m.p.: 115–116°C; IR (KBr): 3478, 3020, 2935, 1603, 1522, 1421, 1335, 1216, 1099, 1017, 758, 699 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$): $\delta_H$ (ppm) 1.56 (m, 6H), 2.48 (m, 4H), 6.81 (s, 2H), 7.03–7.65 (m, 8H), 7.84 (br s, NH, 2H).

**Analytical data for compound tri-indolylmethane (3).** Pale yellow solid, m.p.: 255–257°C (Lit. 256—258°C [48]); $^1$H NMR (90 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 9.67 (br s, 2H), 6.24 (s, 3H), 6.27–6.87 (m, 12H), 5.47 (s, 1H); IR (KBr): 3403, 3043, 2918 cm$^{-1}$; MS: *m*/*z* 361.

**Analytical data for compound (4).** White solid, m.p.: >300°C (Lit. >300°C [49]); $^1$H NMR (90 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 9.98 (br s, 2H), 9.81 (br s, 1H), 6.45 (m, 2H), 6.52–

**Scheme 7**



6.93 (m, 12H); $^{13}$C NMR (90 MHz, DMSO-$d_6$): $\delta_c$ (ppm) 200.8, 160.5, 137.4, 136.8, 125.5, 124.4, 123.9, 121.0, 120.5, 118.3, 117.7, 117.0, 113.9, 111.7, 111.5; MS: *m*/*z* 364.

**Analytical data for compound (6).** Pink solid, m.p.: 194–195°C; FTIR (KBr): 3405, 3049, 1622, 1455, 1216 cm$^{-1}$; $^1$H NMR (90 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 5.75 (s, CH, 1H), 6.29 (s, 4H), 7.05–7.40 (m, CH aromatic, 20H), 7.31 (br s, NH, 4H); $^{13}$C NMR (90 MHz, DMSO-$d_6$): $\delta_c$ (ppm) 142.5, 136.7, 128.1, 126.8, 123.6, 120.9, 119.2, 118.4, 118.3, 111.5, 29.1; MS: *m*/*z* 566.200.

**Analytical data for compound (8).** Light red solid, m.p.: 208–210°C; IR (KBr): 3421, 2950, 2900, 1635, 1506, 1457, 1377, 1216, 1173, 1082, 742 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 5.01 (s, $CH_2$ benzylic, 6H), 5.72 (s, CH, 3H), 6.74–7.50 (m, CH aromatic, 46H), 10.71 (s, NH, 6H); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta_c$ (ppm) 40.08, 69.48, 111.85, 114.67, 115.24, 118.54, 118.82, 119.58, 121.25, 123.87, 127.05, 129.66, 137.03, 137.73, 138.15, 156.91; *Anal*. Calcd. for $C_{78}H_{60}N_6O_3$: C, 82.95; H, 5.35; N, 7.44. Found: C, 82.52; H, 5.21; N, 7.36.

**Analytical data for compound (10).** Red solid, m.p.: 250–251°C d; IR (KBr): 3417, 2926, 2854, 1609, 1506, 1456, 1413, 1338, 1218, 1172, 1127, 1012, 743 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 5.08 (s, $CH_2$ benzylic, 8H), 5.76 (s, CH, 4H), 6.82–7.65 (m, CH aromatic, 60H), 10.70 (s, NH, 8H); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta_c$ (ppm) 41.05, 70.40, 111.45, 114.52, 115.12, 117.85, 118.85, 119.26, 120.85, 122.82, 126.65, 129.26, 136.76, 137.43, 138.63, 157.43; *Anal*. Calcd. for $C_{102}H_{78}N_8O_4$: C, 82.79; H, 5.31; N, 7.57. Found: C, 82.12; H, 5.20; N, 7.35.

**2,2′-Bisindolyl-phenylmethane (11).** $^1$H NMR (90 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 7.94 (br s, 2H), 7.22–7.66 (m, 13H), 6.04 (s, 1H), 2.23 (s, 6H); *Anal*. Calcd. for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.43; H, 5.95; N, 7.68; MS: *m*/*z* 350.

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## REFERENCES AND NOTES

[1] Sundberg, R. J. The Chemistry of Indoles; Academic Press: New York, 1996.

[2] Zeligs, M. A. J Med Food 1998, 1, 67.

[3] Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. Tetrahedron Lett 2002, 43, 4075.

[4] (a) Bandgar, B. P.; Shaikh, K. A. Tetrahedron Lett 2003, 44, 1959; (b) Ramanatham, V. K.; Kotha, V. S. R. S. K.; Kotarkonda, R. G. J Heterocycl Chem 2005, 42, 153.

[5] Reddy, A. V.; Ravinder, K.; Reddy, V. L. N.; Venkateshwer Goud, T.; Ravikanth, V.; Venkateswarlu, Y. Synth Commun 2003, 33, 3687.

[6] Remers, W. A. In Heterocyclic Compounds; Houlihan, W. J., Ed.; Interscience Publishers: New York, 1972, 1.

[7] Maiti, A. K.; Bhattacharyya, P. J Chem Res 1997, 424.

[8] Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. Tetrahedron Lett 2004, 45, 7729.

[9] Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. J Mol Catal A Chem 2005, 244, 168.

[10] Deb, M. L.; Bhuyan, P. J. Tetrahedron Lett 2006, 47, 1441.

[11] Zhang, Z.-H.; Yin, L.; Wang, Y.-M. Synthesis 2005, 1949.

[12] Li, J.-T.; Dai, H.-G.; Xu, W.-Z.; Li, T.-S. Ultrasonics Sonochem 2006, 13, 24.

[13] Bandgar, B. P.; Shaikh, K. A. Tetrahedron Lett 2003, 44, 1959.

[14] Karthik, M.; Tripathi, A. K.; Gupta, N. M.; Palanichamy, M.; Murugesan, V. Catal Commun 2004, 5, 371.

[15] Penieres-Carrillo, G.; García-Estrada, J. G.; Gutiérrez-Ramírez, J. L.; Alvarez-Toledano, C. Green Chem 2003, 5, 337.

[16] Ji, S.-J.; Zhou, M.-F.; Gu, D.-G.; Wang, S.-Y.; Loh, T.-P. Synlett 2003, 2077.

[17] Mo, L.-P.; Ma, Z.-C.; Zhang, Z.-H. Synth Commun 2005, 35, 1997.

[18] Mi, X.; Luo, S.; He, J.; Cheng, J.-P. Tetrahedron Lett 2004, 45, 4567.

[19] Kamble, V. T.; Kadam, K. R.; Joshi, N. S.; Muley, D. B. Catal Commun 2007, 8, 498.

[20] Pradhan, P. K.; Dey, S.; Giri, V. S.; Jaisankar, P. Synthesis 2005, 1779.

[21] Xia, M.; Wang, S. H.; Yuan, W. B. Synth Commun 2004, 34, 3175.

[22] Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. Adv Synth Catal 2003, 345, 557.

[23] Reddy, B. M.; Sreekanth, P. M.; Lakshmanan, P. J Mol Catal A Chem 2005, 237, 93.

[24] Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. J Mol Catal A Chem 2006, 253, 249.

[25] (a) Pore, D. M.; Desai, U. V.; Thopate, T. S.; Wadgaonkar, P. P. Arkivoc 2006, 12, 75; (b) Zolfigol, M. A.; Salehi, P.; Shiri, M.; Sayadi, A.; Abdoli, A.; Keypour, H.; Rezaeivala, M.; Niknam, K.; Kolvari, E. Mol Divers 2008, 12, 203.

[26] Hosseini-Sarvari, M. Acta Chim Slovenica 2007, 54, 354.

[27] Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Vakilzadeh, Y.; Kiani, S. Monatshefte for Chemie 2007, 138, 595.

[28] Hagiwara, H.; Sekifuji, M.; Hoshi, T.; Qiao, K.; Yokoyama, C. Synlett 2007, 1320.

[29] Kamble, V. T.; Bandgar, B. P.; Bavikar, S. N. Chin J Chem 2007, 25, 13.

[30] Niknam, K.; Zolfigol, M. A.; Sadabadi, T.; Nejati, A. J Iran Chem Soc 2006, 3, 318.

[31] Lin, X. F.; Cui, S. L.; Wang, Y. G. Synth Commun 2006, 36, 3153.

[32] Zeng, X. F.; Ji, S. J. Lett Org Chem 2006, **3**, 374.

[33] Zhang, L. P.; Li, Y. Q.; Zhou, M. Y. Chin Chem Lett 2006, 17, 723.

[34] Koshima, H.; Matsuaka, W. J Heterocycl Chem 2002, 1089.

[35] Khalafi-Nezhad, A.; Parhami, A.; Zare, A.; Moosavi Zare, A. R.; Hasaninejad, A.; Panahi, F. Synthesis 2008, 617.

[36] Azizi, N.; Torkian, L.; Saidi, M. R. J Mol Catal A Chem 2007, 275, 109.

[37] Mehrazma, S.; Azizi, N.; Saidi, M. R. Lett Org Chem 2006, 3, 161.

[38] Zolfigol, M. A.; Salehi, P.; Shiri, M.; Tanbakouchian, Z. Catal Commun 2007, 8, 173.

[39] Khodaei, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R.; Khosropour, A. R.; Nikofar, K.; Ghanbary, P. J Heterocycl Chem 2008, 45, 1.

[40] Tilstam, U.; Weinmann, H. Org Proc Res Develop 2002, **6**, 384.

[41] Ghorbani-Vaghei, R.; Zolfigol, M. A.; Chegeny, M.; Veisi, H. Tetrahedron Lett 2006, 47, 4505.

[42] Ghorbani-Vaghei, R.; Shahbazee, E; Veisi, H. Mendeleev Commun 2005, 207.

[43] Veisi, H.; Hemmati, S.; Veisi, H. J Chin Chem Soc 2009, 56, 240.

[44] Ghorbani-Vaghei, R.; Veisi, H. Mol Divers, to appear.

[45] Srinivasa, A.; Nandeshwarappa, B. P.; Kiran, B. M.; Mahadevan, K. M. Phosphorus Sulfur Silicon 2007, 182, 2243.

[46] Sadaphal, S. A.; Shelke, K. F.; Sonar, S. S.; Shingare, M. S. Cent Eur J Chem 2008, 6, 622.

[47] Sheng, S. -R.; Wang, Q. -Y.; Ding, Y.; Liu, X. -L.; Cai, M. -Z. Catal Lett 2009, 128, 418.

[48] Wang, S. -Y.; Ji, S. -J. Tetrahedron 2006, 62, 1527.

[49] Sekiya, M.; Yanaihara, C.; Suzuki, J. Chem Pharm Bull 1969, 17, 752.

# An Efficient and Scalable Synthesis of (2*R*,α*S*)-3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)-phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol: A Potent CETP Inhibitor

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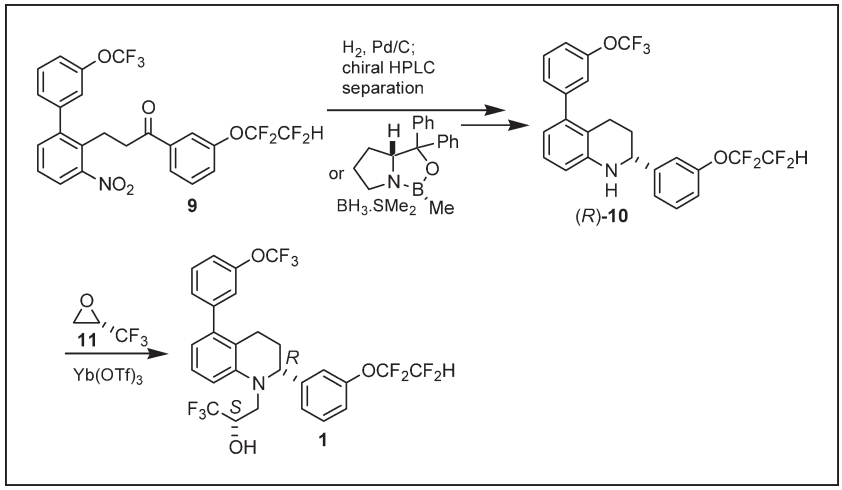


An efficient and scalable synthesis of the potent CETP inhibitor, (2*R*,α*S*)-3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol **1**, is described. One of the important intermediates, tetrahydroquinoline **10**, was readily prepared by reductive cyclization of nitroketone **9** in high yield. Asymmetric synthesis of **10** with high enantiomeric excess (>80% ee) was also developed.

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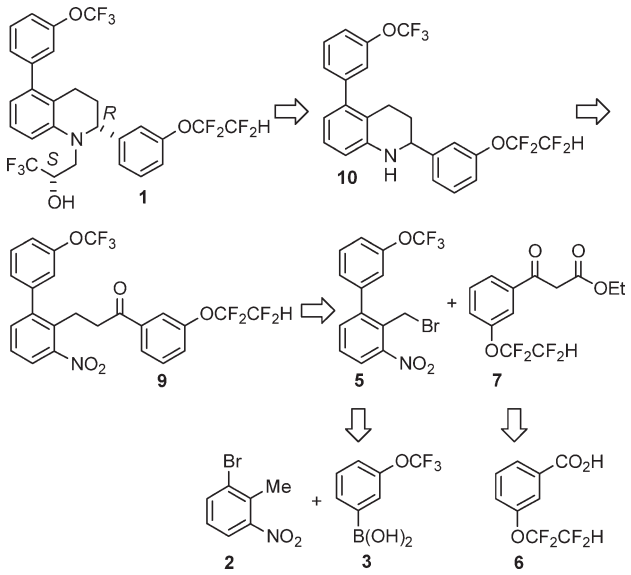
## INTRODUCTION

Low levels of high density lipoprotein-cholesterol (HDL-C) and high levels of low density lipoprotein-cholesterol (LDL-C) are independent risk factors for the development of atherosclerosis and eventually coronary heart disease (CHD), which remain the leading cause of death in the developed countries [1–3]. HDL-C plays important role in removal of excess cholesterol from peripheral cells to the liver for metabolic degradation in a reverse cholesterol transport (RCT) process [4–6]. Therefore, the increase in HDL-C level offers a new and promising therapeutical principle for treatment of CHD [7]. Plasma protein cholesteryl ester (CE) transfer protein (CETP) mediates the transfer of CE from HDL to very low density lipoprotein (VLDL) and LDL in exchange for triglyceride [8,9]. As a result, the disadvantage of this action is a reduction in HDL-C level and with increase in VLDL-C and LDL-C levels. Inhibition of CETP has been proposed as a strategy to raise HDL-C level [10], thus increases the efficiency of RCT.

Compound **1** has been identified as a potent CETP inhibitor [11]. It showed $IC_{50}$ in 34–44 n*M* range and increased HDL-C in human CETP transgenic mice. The original preparation of **1** [11c] was lengthy and involved the use of some highly toxic and potentially explosive chemicals. To supply a large quantity of material **1** for further *in vivo* and toxicity studies, an efficient and scalable synthesis was required. In this article, we describe the chemical synthesis that was used successfully in the preparation of multigram quantities of compound **1**.

As illustrated by the retrosynthetic analysis in Scheme 1, the feature of our strategy involved efficient construction of the piperidine ring. We envisioned that transforming nitroketone **9** to tetrahydroquinoline **10** would be the key step in achieving our goal. This could be realized by reductive cyclization of nitroketone **9** to a racemic mixture of **10** from which the (*R*)-enantiomer

**Scheme 1.** Retrosynthetic analysis



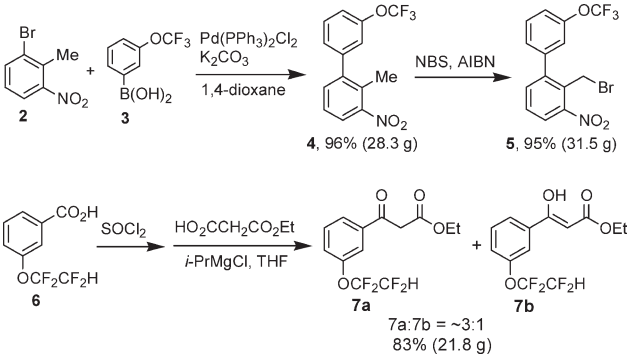
could be isolated by chiral HPLC separation. (*R*)-**10** might also be prepared in a stepwise fashion by asymmetric reductive cyclization of **9**. The nitroketone **9** could be derived from benzyl bromide **5** and β-keto ester **7** by alkylation and decarboxylation. The synthons **5** and **7** should be easily assembled from commercially available 5-bromo-6-methylnitrobenzene **2**, 3-(trifluoromethoxy)phenyl-boronic acid **3**, and 3-tetrafluoroethoxybenzoic acid **6**, respectively.

The preparation of benzyl bromide **5** and β-keto ester **7** is shown in Scheme 2, and the reaction scale is given in parentheses. Suzuki reaction [12] of 5-bromo-6-methylnitrobenzene **2** with 3-(trifluoromethoxy)phenylboronic acid **3** provided 28 g of **4** in 96% yield. In a solvent-free system, bromination [13] of **4** (26 g) with *N*-bromosuccimide and AIBN at 90°C for 5 h gave benzyl bromide **5** in 95% yield. The β-keto ester **7** was synthesized by acylation of ethyl hydrogen malonate with 3-tetrafluoroethoxybenzoyl chloride, followed by decarboxylation during acidic work-up procedure [14]. The product was a mixture of β-keto ester **7a** and its tautomer enol **7b** in ~3:1 ratio.

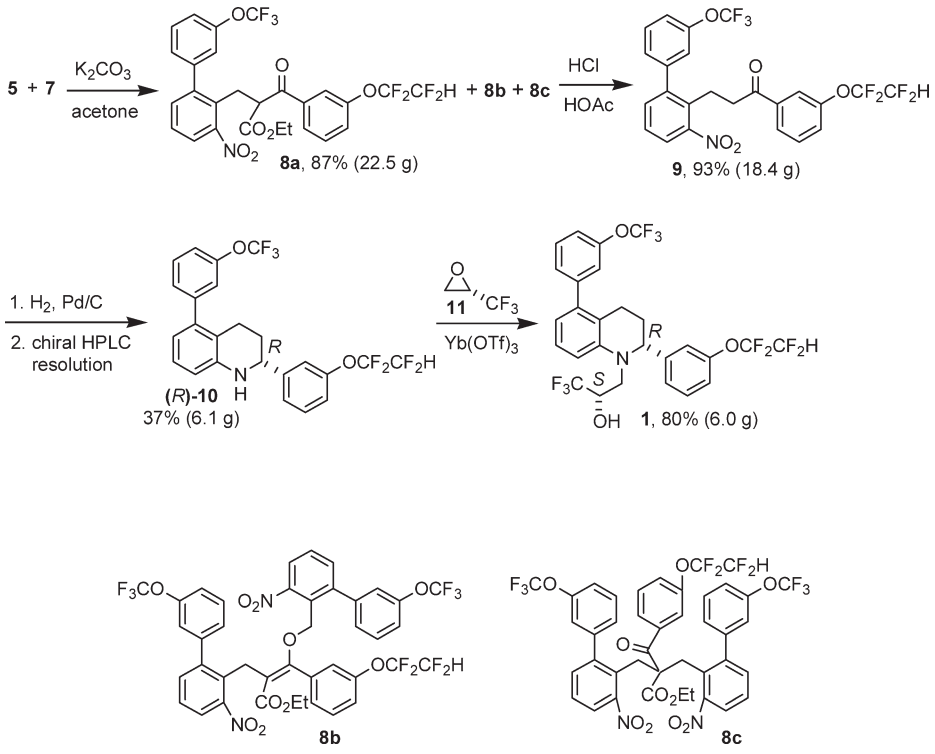
With both building synthons **5** and **7** available, the stage was set to generate the important intermediate **8a** by alkylation of β-keto ester **7** with benzyl bromide **5** (Scheme 3). However, the reaction was complicated by the formation of **8a**, *C*,*O*-dialkylation compound **8b**, and α,α-dialkylation by-product **8c**. Different reaction conditions were explored by varying a variety of bases (such as $NaN(SiMe_3)_2$, NaH, *n*-BuLi, $Cs_2CO_3$, and $K_2CO_3$), solvents (such as THF, DMF, $CH_3CN$, and acetone), reaction temperature, the order of reagent addition. It was found that using $K_2CO_3$ in acetone was the best conditions tried to give the desired product **8a** in 87% yield, along with 5% of *C*,*O*-dialkylation by-product **8b**. Without separation of the two compounds, the mixture was converted to the same nitroketone **9** upon treatment with hydrochloric acid in hot acetic acid [15]. Under normal catalytic hydrogenation conditions, reductive cyclization of nitroketone **9** occurred to form tetrahydroquinoline **10** in essentially quantitative yield. The (*R*)-**10** was collected by chiral HPLC resolution of the racemic mixture. The *R* configuration at the 2 position of the tetrahydroquinoline ring of (*R*)-**10** was known by comparing its optical rotation, $[\alpha]_D^{20}$ –13.3° (*c*1.0, $CHCl_3$), with that of (*R*)-**10**, $[\alpha]_D^{20}$ –12.9° (*c* 1.0, $CHCl_3$), obtained from an asymmetric synthesis shown below in Scheme 4. In the presence of catalytic amount of Lewis acid ytterbium trifluoromethanesulfonate, N-alkylation of (*R*)-**10** with commercially available ~90% enriched (*S*)-1,1,1-trifluoro-2,3-epoxypropane **11** occurred to produce the target **1** in 80% yield [16]. Under these conditions, the ring opening of the epoxide proceeded with complete regioselectivity.

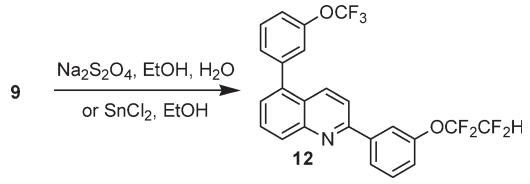
Although this route is attractive due to its simplicity and rapid access to **1**, it suffers from the obvious need for resolution of racemic tetrahydroquinoline **10** and economy of synthesis. We then turned our attention toward the development of an asymmetric approach to (*R*)-**10**. It was hoped that by controlling reaction conditions, the hydrogenation of nitroketone **9** could stop at aminoketone or cyclic-imine stage, and both of the materials could be reduced to (*R*)-**10** in high enantiomeric purity by subjecting to chiral sodium triacyloxyborohydride [17] as demonstrated in our syntheses of similar analogues [18]. However, preliminary investigation by changing $H_2$ pressure, solvents, and catalysts only yielded a mixture of starting material **9** and partially reduced intermediates. The strategy of stepwise reduction of nitroketone **9** to aminoketone and subsequently enantioselective reductive cyclization of which to (*R*)-**10** was also attempted by using inorganic reducing reagents such as $Na_2S_2O_4$, $SnCl_2$, and $FeSO_3$. Unfortunately, it only resulted in the formation of quinoline **12** (eq. 1):

**Scheme 2**



**Scheme 3**

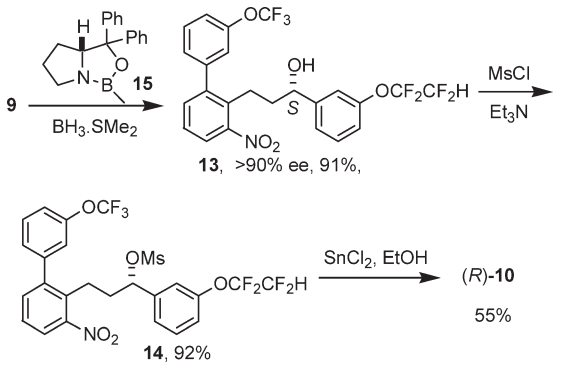



(1)

Alternatively, the required stereocenter was introduced by utilizing Corey's oxazaborolidine-borane methodology [19]. Using the *R*-Me CBS oxazaborolidine reagent **15**, nitroketone **9** was enantioselectively reduced to (*S*)-alcohol **13** in 91% yield and >90% enantiomeric excess (% ee) [20] (Scheme 4). The *S* configuration of alcohol **13** was assigned based upon the precedent illustrated in Corey and Helal's article [19]. The hydroxyl group in **13** was then converted to a good leaving group mesylate **14**. Upon treatment of **14** with $SnCl_2$ in ethanol, the nitro group was reduced to amino functionality [21] and followed by spontaneous intramolecular displacement of the mesylate to yield the ring closed (*R*)-**10** in 80–85% ee [20]. During this transformation, the inversion of the original stereocenter occurred to give the *R* absolute configuration at the 2 position of the tetrahydroquinoline ring of **10**. A small erosion of ee was observed during the cyclization step due to a competitive ionization pathway.

**Scheme 4**




In conclusion, we have developed a very efficient, scalable, and high yielding synthesis of (2*R*,α*S*)-3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol **1**. This method provides access to **1** in multigram quantities reliably.

## EXPERIMENTAL

**2-Methyl-3-nitro-3′-trifluoromethoxy-biphenyl (4).** A mixture of 2-bromo-6-nitrotoluene **2** (21.5 g, 99.5 mmol), 3-trifluoromethoxylbenzeneboronic acid **3** (27.0 g, 131.1 mmol), $Pd(PPh_3)_2Cl_2$ (3.50 g, 5.0 mmol), and 2.0*M* $K_2CO_3$ (120 mL, 240 mmol) in dioxane (330 mL) was degassed with $N_2$ and then heated at 100°C for 3 h. After cooling to room temperature, the reaction mixture was passed through Celite and partitioned between EtOAc and brine. The combined organic

phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (1–10% EtOAc in hexane) to give 28.27 g (96%) of **4** as a light yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, $J$ = 7.8 Hz, 1 H), 7.74–7.38 (m, 3 H), 7.31–7.23 (m, 2 H), 7.19 (s, 1 H), 2.37 (s, 3 H).

**2-Bromomethyl-3-nitro-3′-trifluoromethoxy-biphenyl (5).** A mixture of **4** (26.1 g, 87.8 mmol), NBS (20.3 g, 114 mmol), and AIBN (1.44 g, 8.77 mmol) was degassed with $N_2$ and then heated at 85°C. After 20 min, it began to react vigorously. After 2 h, the temperature was raised to 90°C, and the mixture was heated for 3 more hours. After cooling to room temperature, the reaction mixture was diluted with hexane. The solid was filtered off, and the filtrate was concentrated to give 31.47 g (95%) of **5** as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, $J$ = 2.0, 2.0, 1 H), 7.58–7.49 (m, 3 H), 7.41–7.28 (m, 3 H), 4.69 (s, 2 H).

**3-Oxo-3-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-propionic acid ethyl ester (7).** To an ice-cooled solution of 3-tetrafluoroethoxy-benzoic acid **6** (40.0 g, 0.168 mol) was added $SOCl_2$ (59.0 mL, 0.809 mol) dropwise. After addition, the ice-bath was removed, and the mixture was stirred at room temperature for 3 h followed by heating at 50°C for 2 h and 75°C for 3 h. The reaction mixture was left stirring at room temperature overnight. After removing of $SOCl_2$ *in vacuo*, to the residue was added dry toluene and concentrated (20 mL × 3). After on high vacuum line for 5 h, the acyl chloride was obtained as a clear oil (41.0 g, 95%).

To a solution of $EtOCOCH_2CO_2H$ (16.1 g, 0.122 mol) in THF (120 mL) at –78°C was added *i*-PrMgCl (2.0*M* in THF, 122 mL, 0.244 mol) dropwise through an additional funnel. After stirring at –78°C for 1 h, the above prepared acyl chloride (20.9 g, 0.0815 mol) in THF (80 mL) was added via an addition funnel. The reaction mixture was stirred at –78°C for 1 h and RT for 2 h. The reaction flask was cooled in an ice-bath, and ∼100 mL of 1*N* HCl was added dropwise until pH < 1. Upon addition of 1*N* HCl, some precipitate formed and stirring became difficult. The precipitated solid gradually dissolved during further addition of 1*N* HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried, concentrated, and purified by flash column chromatography (5–10% EtOAc in hexane) to give 21.8 g (83%) of **7** as a yellow oil.

***7a.*** $^1$H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 1 H), 7.80 (s, 1 H), 7.56–7.51 (m, 1 H), 7.48–7.45 (m, 1 H), 5.95 (tt, $J$ = 53.0, 2.5 Hz, 1 H), 4.23 (q, $J$ = 7.2 Hz, 2 H), 3.98 (s, 2 H), 1.27 (t, $J$ = 7.2 Hz, 3 H); MS (ES) $m/z$: 331 ($M+Na^+$); HRMS (ESI) calcd for $C_{13}H_{12}F_4O_4$ ($M + H^+$) $m/z$ 309.0750, found $m/z$ 309.0751.

***7b.*** $^1$H NMR (300 MHz, $CDCl_3$) δ 12.6 (s, 1 H), 7.71–7.68 (m, 1 H), 7.63 (s, 1 H), 7.45–7.42 (m, 1 H), 7.34–7.31 (m, 1 H), 5.94 (tt, $J$ = 53.0, 2.5 Hz, 1 H), 5.68 (s, 1 H), 4.29 (q, $J$ = 7.2 Hz, 2 H), 1.35 (t, $J$ = 7.2 Hz, 3 H); MS (ES) $m/z$: 331 ($M+Na^+$).

**2-(3-Nitro-3′-trifluoromethoxy-biphenyl-2-ylmethyl)-3-oxo-3-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-propionic acid ethyl ester (8a).** To a mixture of β-keto ester **7** (13.5 g, 43.8 mmol) and benzyl bromide **5** (15.7 g, 41.7 mmol) in 270 mL of acetone was added $K_2CO_3$ (8.66 g, 62.6 mmol). After stirring at room temperature for 1 h, TLC (15% EtOAc in hexane) showed the completion of reaction. The reaction mixture was filtered through Celite and the solid was washed with EtOAc. The filtrate was concentrated and purified by flash column chromatography (5–15% EtOAc in hexane) to give 22.5 g (87%) of **8a** as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, $J$ = 6.5, 2.7 Hz, 1 H), 7.59–7.54 (m, 2 H), 7.48–7.36 (m, 5 H), 7.26–7.21 (m, 2 H), 7.14 (s, 1 H), 5.92 (tt, $J$ = 53.0, 2.5 Hz, 1 H), 4.21 (t, $J$ = 7.0 Hz, 1 H), 4.02–3.82 (m, 2 H), 3.74–3.59 (m, 2 H), 0.96 (t, $J$ = 7.1 Hz, 3 H); MS (ES) $m/z$: 626 ($M+Na^+$). Anal. Calcd for $C_{27}H_{20}F_7NO_7$: C, 53.74; H, 3.34; N, 2.32. Found: C, 54.00; H, 3.02; N, 2.36.

**3-(3-Nitro-3′-trifluoromethoxy-biphenyl-2-yl)-1-[3-(1, 1,2,2-tetrafluoro-ethoxy)-phenyl]-propan-1-one (9).** A solution of **8a** (22.5 g, 37.3 mmol) in concentrated HCl (85 mL) and HOAc (140 mL) was heated at 100°C for 9 h. TLC (20% EtOAc in hexane) showed the completion of reaction. After cooling down to room temperature, HOAc was evaporated through a rotary evaporator. The residue was diluted with water (200 mL) and cooled in an ice-bath. To the mixture was added 6*N* NaOH (∼80 mL) until basic judged by pH paper. The aqueous solution was extracted with EtOAc (×3), and the combined organic layers were dried ($Na_2SO_4$), concentrated, and purified by flash column chromatography (10–20% EtOAc in hexane) to give 18.4 g (93%) of **9** as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90–7.84 (m, 1 H), 7.71–7.64 (m, 2 H), 7.50–7.37 (m, 5 H), 7.28–7.22 (m, 2 H), 7.17 (s, 1 H), 5.91 (tt, $J$ = 53.0, 2.7 Hz, 1 H), 3.21–3.08 (m, 4 H); MS (ES) $m/z$: 554 ($M+Na^+$); HRMS (ESI) calcd for $C_{24}H_{16}F_7NO_5$ ($M + H^+$) $m/z$ 532.0995, found $m/z$ 532.0989. Anal. Calcd for $C_{24}H_{16}F_7NO_5$: C, 54.25; H, 3.01; N, 2.64. Found: C, 54.38; H, 2.59; N, 2.89.

**2-[3-(1,1,2,2-Tetrafluoro-ethoxy)-phenyl]-5-(3-trifluoromethoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (10).** A mixture of **9** (5.70 g, 10.7 mmol) and 10% Pd/C (615 mg) in EtOAc (∼100 mL) was shaken in a par-shaker under 50 psi $H_2$ for 19 h. The reaction mixture was filtered through Celite and the solid was washed with EtOAc. The filtrate was concentrated and dried under vacuum to give 5.20 g (100%) of **10** as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 3 H), 7.28–7.23 (m, 2 H), 7.20–7.05 (m, 4 H), 6.61 (d, $J$ = 7.8 Hz, 2 H), 5.92 (tt, $J$ = 53.0, 2.8 Hz, 1 H), 4.50 (dd, $J$ = 8.9, 3.3 Hz, 1 H), 2.75 (ddd, $J$ = 16.4, 10.6, 5.1 Hz, 1 H), 2.51 (dt, $J$ = 16.5, 4.9 Hz, 1 H), 2.10–2.02 (m, 1 H), 1.91–1.81 (m, 1 H); MS (ES) $m/z$: 486 ($M+H^+$). Anal. Calcd for $C_{24}H_{18}F_7NO_2$: C, 59.39; H, 3.74; N, 2.89. Found: C, 59.80; H, 3.50; N, 2.80.

**(2*R*)-1,2,3,4-Tetrahydro-2-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-5-[3-(trifluoromethoxy)phenyl]quinoline (10).** Chiral HPLC resolution of racemate (±)-**10**: 16.5 g of (±)-**10** was separated by using Chiralcel OJ eluting with 80% heptane–20% ethanol at 80 mL/min and wavelength 220 nm. A total of 6.46 g of (*R*)-**10** and 5.91 g of (*S*)-**10** were obtained in 99.99% and 99.5% ee, respectively. (*R*)-**10**: $[\alpha]_D^{20}$ –13.3° (*c*1.0, $CHCl_3$).

Cyclization of (*S*)-**14**: A solution of **14** (105 mg, 0.172 mmol) and EtOH (2 mL) was degassed under vacuum and then filled with $N_2$ for three times. To the solution $SnCl_2{\cdot}2H_2O$ (244 mg, 1.08 mmol) was added and the reaction mixture was stirred at room temperature under $N_2$ for 4.5 h. After removal of EtOH under vacuum, to the residue were added $CH_2Cl_2$ and saturated $NH_4OH$. The precipitated solid was filtered through Celite, and rinsed with $CH_2Cl_2$ and EtOAc. The filtrate was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried, concentrated *in vacuo*, and purified by flash column chromatography (10–15% EtOAc in hexane) to give 46 mg (55%) of (*R*)-**10** as an oil. $^1$H NMR (400 MHz, $CDCl_3$) δ

7.42–7.30 (m, 3 H), 7.29–7.23 (m, 2 H), 7.21–7.07 (m, 4 H), 6.61 (d, $J$ = 7.8 Hz, 2 H), 5.91 (tt, $J$ = 53.1, 2.8 Hz, 1 H), 4.51 (dd, $J$ = 9.0, 3.4 Hz, 1 H), 4.20 (brs, 1 H), 2.76 (ddd, $J$ = 16.3, 10.6, 5.2 Hz, 1 H), 2.53 (dt, $J$ = 16.6, 5.0 Hz, 1 H), 2.11–2.04 (m, 1 H), 1.93–1.83 (m, 1 H); MS (ES) $m/z$: 486 ($M+H^+$); HRMS (ESI) calcd for $C_{24}H_{18}F_7NO_2$ $m/z$ 485.1226, found $m/z$ 485.1219. $[\alpha]_D^{20}$ –12.9° ($c$ 1.0, $CHCl_3$). A total of 80–85% ee was analyzed by chiral HPLC (Chiralcel OJ; isocratic elution 10/90 isopropanol/hexane, 0.8 mL/min, area integration at 210 nm).

**(α*S*)-3-Nitro-α-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-3′-(trifluoromethoxy)-[1,1′-biphenyl]-2-propanol (13).** To a solution of THF (0.2 mL) and 1.0*M* (*R*)-2-methyl-CBS-oxazaborolidine (0.186 mL, 0.186 mmol) in toluene was added 2.0*M* $BH_3{\cdot}SMe_2$ (0.137 mL, 0.274 mmol) in THF. After stirring at room temperature for 15 min, the mixture was cooled to –25°C and to which a solution of **9** (132 mg, 0.249 mmol) in THF (2 mL) was added. The reaction mixture was stirred from –20°C to –10°C for 3.5 h and then quenched with a few drops of MeOH followed by a few drops of 1*N* HCl. The reaction mixture was partitioned between $CH_2Cl_2$ and water. The organic layer was dried, concentrated, and purified by flash column chromatography (10–20% EtOAc in hexane) to provide 114 mg (86%) of **13** as an oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.88–7.77 (m, 1 H), 7.43–7.37 (m, 3 H), 7.28–7.23 (m, 2 H), 7.14–6.99 (m, 5 H), 5.90 (tt, $J$ = 53.1, 2.8 Hz, 1 H), 4.54 (brs, 1 H), 2.89–2.79 (m, 1 H), 2.73–2.63 (m, 1 H), 1.92–1.76 (m, 2 H), 1.73 (brs, 1 H); MS (ES) $m/z$: 556 ($M+Na^+$). Anal. Calcd for $C_{24}H_{18}F_7NO_5$: C, 54.04; H, 3.40; N, 2.63. Found: C, 54.10; H, 2.89; N, 2.50. $[\alpha]_D^{20}$ –10.6° ($c$ 1.0, $CHCl_3$). A total of >90% ee was determined by chiral HPLC (Chiralcel OJ; isocratic elution 10/90 isopropanol/hexane, 0.8 mL/min, area integration at 210 nm).

**(α*S*)-3-Nitro-α-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-3′-(trifluoromethoxy)-[1,1′-biphenyl]-2-propanol methanesulfonate (14).** To a solution of **13** (220 mg, 0.413 mmol) and $CH_2Cl_2$ (3 mL) was added methanesulfonyl chloride (0.040 mL, 0.52 mmol) and $Et_3N$ (0.086 mL, 0.62 mmol). After stirring at room temperature for 2 h, water was added and the mixture was acidified with 1*N* HCl until acidic by pH paper. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried and concentrated to give 250 mg (99%) of **14** as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 1 H), 7.49–7.45 (m, 1 H), 7.42 (d, $J$ = 4.6 Hz, 2 H), 7.36–7.29 (m, 2 H), 7.20–7.15 (m, 2 H), 7.09–7.07 (m, 2 H), 7.03 (s, 1 H), 5.92 (tt, $J$ = 53.0, 2.7 Hz, 1 H), 5.38 (dd, $J$ = 7.3, 5.8 Hz, 1 H), 2.85 (td, $J$ = 12.6, 4.8 Hz, 1 H), 2.72 (s, 3 H), 2.67 (dd, $J$ = 13.1, 4.8 Hz, 1 H), 2.18–1.98 (m, 2 H); MS (ES) $m/z$: 634 ($M+Na^+$).

**(2*R*,α*S*)-3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol (1).** To a mixture of (*R*)-**10** (6.10 g, 10.2 mmol) and 1,1,1-trifluoro-2,3-epoxypropane **11** (5.71 g, 51.0 mmol) in $CH_2Cl_2$ (60 mL) under $N_2$ was added $Yb(OTf)_3$ (1.58 g, 2.55 mmol). The reaction mixture was heated at 50°C for 48 h and then cooled to ambient temperature. EtOAc was added and the mixture was washed with saturated $NaHCO_3$, $H_2O$ and brine, dried, concentrated and purified by flash column chromatography (5–15% EtOAc in hexane) to give 6.00 g (80%) of **1** as an oil. $^1$H NMR (400 MHz, $CDCl_3$) d 7.40–7.34 (m, 2 H), 7.25–7.12 (m, 6 H), 7.05 (s, 1 H), 6.74 (d, $J$ = 8.1 Hz, 1 H), 6.68 (d, $J$ = 7.3 Hz, 1 H), 5.89 (tt, $J$ = 53.1, 2.8 Hz, 1 H), 4.90 (t, $J$ = 4.4 Hz, 1 H), 4.46–4.41 (m, 1 H), 3.92 (d, $J$ = 15.4 Hz, 1 H), 3.32 (dd, $J$ = 15.4, 9.6 Hz, 1 H), 2.49 (dt, $J$ = 16.2, 4.6 Hz, 1 H), 2.41–2.34 (m, 2 H), 2.19–2.10 (m, 1 H), 2.00–1.94 (m, 1 H); MS (ES) $m/z$: 598 ($M+H^+$); HRMS (ESI) calcd for $C_{27}H_{21}F_{10}NO_3$ $m/z$ 597.1362, found $m/z$ 597.1378. Anal. Calcd for $C_{27}H_{21}F_{10}NO_3$: C, 54.28; H, 3.54; N, 2.34. Found: C, 54.10; H, 3.40; N, 1.99. $[\alpha]_D^{20}$ –112.0° ($c$1.0, $CHCl_3$).

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## REFERENCES AND NOTES

[1] Assmann, G.; Schulte, H.; von Eckardstein, A.; Huang, Y. Atherosclerosis 1996, 124, S11.

[2] Castelli, W. P.; Garrison, R. J.; Wilson, P. W.; Abbott, R. D.; Kalousdian, S.; Kannel, W. B. J Am Med Assoc 1986, 256, 2835.

[3] Kannel, W. B. Am J Cardiol 1995, 76, 69C.

[4] Bruce, C.; Chouinard, R. A., Jr.; Tall, A. R. Annu Rev Nutr 1998, 18, 297.

[5] Yamashita, S.; Sakai, N.; Hirano, K.-I.; Ishigami, M.; Maruyama, T.; Nakajima, N.; Matsuzawa, Y. Front Biosci 2001, 6, D366.

[6] Krause, B. R.; Auerbach, B. J. Curr Opin Invest Drugs 2001, 2, 375.

[7] Assmann, G.; Nofer, J. R. Annu Rev Med 2003, 54, 321.

[8] Tall, A. R. J Lipid Res 1993, 34, 1255.

[9] Lagrost, L. Biochem Biophys Acta 1994, 1215, 209.

[10] Sikorski, J. A.; Connolly, D. T. Curr Opin Drug Discov Dev 2001, 4, 602.

[11] (a) Kuo, G.-H.; Rano, T.; Pelton, P.; Demarest, K. T.; Gibbs, A. C.; Murray, W. V.; Damiano, B. P.; Connelly, M. A. J Med Chem 2009, 52, 1768; (b) Rano, T. A.; Sieber-McMaster, E.; Pelton, P. D.; Yang, M.; Demarest, K. T.; Kuo, G-H. Bioorg Med Chem Lett 2009, 19, 2456; (c) Rano, T. A.; Kuo, G-H. Org Lett 2009, 11, 2812; (d) Rano, T.; Kuo, G.-H.; Sieber-McMaster, E.; Demarest, K. T.; Pelton, P.; Wang, A. U.S. Pat Appl Publ US 2007265304 A1 20071115, 2007; (e) Sorgi, K. L.; Liu, F.; Chen, Y.; Chen, H.; Patel, M. N.; Li, X.; Wang, A.; Ballentine, S. A.; Beauchamp, D. A.; Macphee, J.-M.; Rammeloo, T. J. L.; Vanhoegaerden, T. J. PCT Int Appl WO 2008141077 A1 20081120, 2008.

[12] Miyaura, N.; Suzuki, A. Chem Rev 1995, 95, 2457.

[13] Togo, H.; Hirai, T. Synlett 2003, 5, 702.

[14] Renau, T. E.; Sanchez, J. P.; Domagala, J. M. J Heterocycl Chem 1996, 33, 1407.

[15] Balasankar, T.; Gopalakrishnan, M.; Nagarajan, S. Eur J Med Chem 2005, 40, 728.

[16] Reinhard, E. J.; Wang, J. L.; Durley, R. C.; Fobian, Y. M.; Grapperhaus, M. L.; Hickory, B. S.; Massa, M. A.; Norton, M. B.; Promo, M. A.; Tollefson, M. B.; Vernier, W. F.; Connolly, D. T.; Witherbee, B. J.; Melton, M. A.; Regina, K. J.; Smith, M. E.; Sikorski, J. A. J Med Chem 2003, 46, 2152.

[17] Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. J Heterocycl Chem 1991, 28, 329.

[18] Wang, A.; Prouty, C. P.; Pelton, P. D.; Yong, M.; Demarest, K. T.; Murray, W. V.; Kuo, G.-H. Bioorg Med Chem Lett 2010, 20, 1432.

[19] Corey, E. J.; Helal, C. J. Angew Chem Int Ed 1998, 37, 1986.

[20] Enantiomeric excess was determined by chiral HPLC (Chiralcel OJ; isocratic elution 10/90 isopropanol/hexane, 0.8 mL/min, area integration at 210 nm).

[21] Bellamy, F. D.; Ou, K. Tetrahedron Lett 1984, 25, 839.

# One-Pot Synthesis and Antimicrobial Activity of Novel Quinolone Heterocyclic Derivatives



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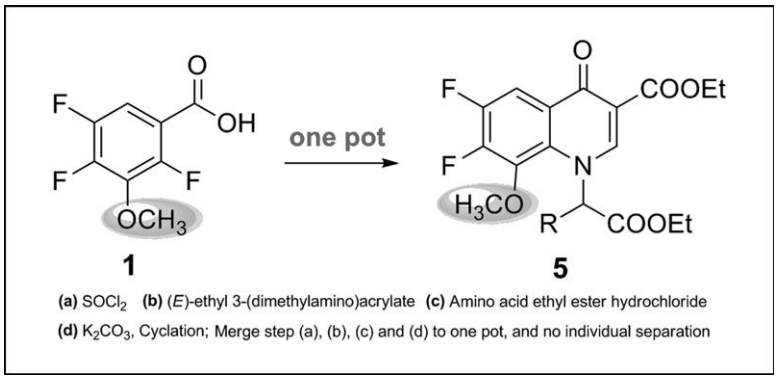


A series of novel quinolone heterocyclic derivatives from natural amino acid were synthesized in one-pot method, which is very beneficial for the industrial operation to save manufacturing costs. These new compounds were characterized by $^{1}$H NMR, $^{13}$C NMR, infrared spectrum, mass spectrum, and elemental analysis. The preliminary bioassays results revealed that they had certain antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*.

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## INTRODUCTION

Interests in heterocycle compounds [1], especially quinolone heterocyclic compounds, have flourished for many years, largely as a result of the wide spread use on anti-asthmatic, anti-bacterial, anti-malarial, tyrosine-kinase PDGF-RTK inhibitor agent, etc. [2]. Because of such a wide range of applicability in medicine and bioorganic chemistry, there has been increasing interests in exploring new quinolone heteocyclic compounds to enrich this domain [3]. Enlightened and encouraged by the bioactivity of quinolone heterocyclic compounds and the abundant existence of amino acid in nature, we attempt to introduce amino acid piece into quinolone heterocycle and wish to discover some new bioactive compounds.

Generally, there are several steps and much complicated post-treatment and purification process to synthesize the quinolone and fluoroquinolone derivatives, such as 4-oxoquinoline, 8-nitrofluoro-quinolone, and other quinolone derivatives [4–7]. Therefore, we wish to develop a concise route with simple post-treatment to synthesize a series of novel quinolone heterocyclic compounds. Fortunately, when we use one-pot method to synthesize compounds **5** from compound **1**, the whole reaction goes well and smoothly. This method is very beneficial for the industrial operation to save time and manufacturing costs. Herein a series of novel quinolone heterocyclic derivatives from natural amino acid salts were designed and prepared according to this method. The title compounds were characterized by $^{1}$H NMR, $^{13}$C NMR, infrared spectrum, mass spectrum, and elemental analysis. To investigate their preliminary antimicrobial bioactivities, these compounds were screened by *Bacillus subtilis*, *Staphylococcus aureus*, *Aspergillus fumigatus*, and *Candida albicans*. The preliminary bioassays results revealed that they had certain bactericidal activity against *Bacillus subtilis* and *Staphylococcus aureus*. The synthetic routes are shown in Figure 1.

## RESULTS AND DISCUSSION

**Chemistry.** As part of our ongoing interests to find new quinolone heterocyclic derivatives, we try to obtain the quinolone compounds *via* intramolecular cyclization reaction, which contain natural amino acid piece at N1-position of quinolone heterocyclic ring. We selected the 2,4,5-trifluoro-3-methoxybenzoic acid **1** as started materials to synthesize quinolone derivatives **6**. At first, we synthesized compounds **6** step by step from **1** to **5** with complicated post-treatment and purification in each step. Interestingly, when we attempt to synthesize compounds **5** from compound **1** in one-pot to cut off much troublesome separation and purification in the middle process we found the whole reaction goes well. So a facile and simple rout

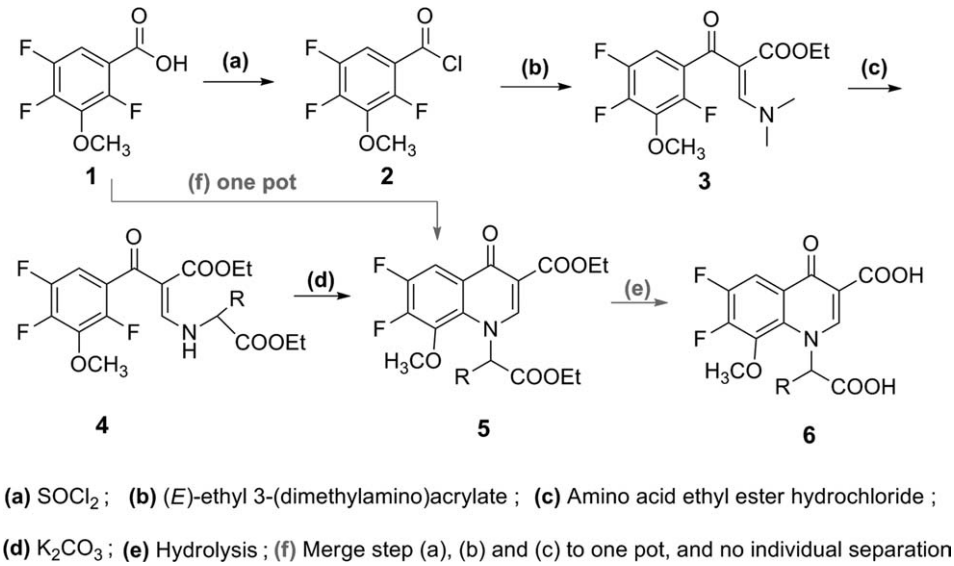



**Figure 1.** (a) $SoCl_2$; (b) (E)-ethyl 3-(dimethylamino)acrylate; (c) Amino acid ethyl ester hydrochloride; (d) $K_2CO_3$; (e) Hydrolysis; (f) Merge step (a), (b), and (c) to open-pot, and no individual separation.

for the synthesis of compound **5** in one-pot way without any separation was developed, which is very beneficial for the industrial operation to save manufacturing costs.

The structures of quinolone heterocyclic compounds of **6a–6f** were confirmed by IR, $^1$H NMR, $^{13}$C NMR, MS, and elemental analysis. The infrared spectra of all compounds showed easily distinguishable carboxylic group stretching at 1789–1799 $cm^{-1}$ and 1721–1747 $cm^{-1}$ because of the two kind of carboxylic groups. In $^1$H NMR spectrum, two kind of carboxylic group signals appear between 13.42–13.73 ppm and 14.42–14.58 ppm, which demonstrate the existence of amino acids and quinolone cycle. In $^{13}$C NMR spectrum, the typical signals of carboxylic group and aromatic ring appear between 164.47–176.71 ppm and 102.85–158.97 ppm, which reveal the existence of the quinolone cycle.

**Biological activities.** All the title compounds were tested preliminarily for their antibacterial and antifungal activity. From the screening results, all the title compounds have certain activity against *Bacillus subtilis* and *Staphylococcus aureus* and nearly have no activity against *Aspergillus fumigatus* and *Candida albicans*. The detail results are listed in Table 1.

From the preliminary biological results, all the new compounds have certain antibacterial and antifungal bioactivity, which intrigued us to study its QSAR further and synthesize higher activity compound, the in-depth research work is undergoing.

In conclusion, we have developed a simple one-pot way of preparing quinolone heterocyclic compounds and synthesized a series of novel quinolone heterocyclic derivatives from natural amino acid. This method facilitates the industrial operation to save manufacturing costs. The preliminary bioassays results reveal that they have certain antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*.

## EXPERIMENTAL

All the reagents were purchased commercially and used without further purification. The melting point was determined

**Table 1**

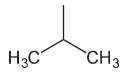
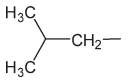
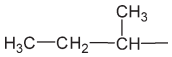
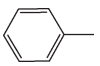
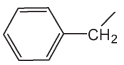
The preliminary antimicrobial activity of title compounds.

| | Conc. (mg/mL) | 6a | 6b | 6c | 6d | 6e | 6f |
|---|---|---|---|---|---|---|---|
| *Bacillus subtilis* | 1 | 0.95[a] | 0.75 | 0.85 | 0.80 | 0.90 | 1.25 |
| | 0.2 | 0.60 | 0.65 | 0.65 | 0.65 | 0.75 | 0.60 |
| | 0.2 | –[b] | – | – | – | 0.60 | – |
| *Staphylococcus aureus* | 1 | 0.85 | 0.70 | 0.70 | 1.20 | 1.10 | 0.95 |
| | 0.2 | 0.60 | 0.60 | – | 0.75 | 1.00 | 0.65 |
| | 0.1 | – | – | – | – | 0.85 | – |

[a] Diameter of inhibition zone (cm).
[b] No inhibition.

**Table 2**

Chemical structure, yields, and melt point of the synthesized compounds.

| Compound | R | Yield (%) | M. P (°C) |
|---|---|---|---|
| **6a** | H | 52 | 258–260 |
| **6b** |  | 52 | 251–253 |
| **6c** |  | 50 | 310–312 |
| **6d** |  | 49 | 284–286 |
| **6e** |  | 52 | 162–164 |
| **6f** |  | 48 | 195–197 |

using a XT-4 melting-point apparatus and uncorrected. IR spectra were recorded on a Bruker Equinox-55 spectrophotometer using KBr discs in the 4000–400 $cm^{-1}$ region. The $^1H$ NMR and $^{13}C$ NMR data were obtained on a Bruker AC-400 (400 MHz) instrument in DMSO-$d_6$ using TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. Mass spectra were obtained on a Agilent 5973N mass spectrometer operating at 70 eV by electron ionization technique (EI/MS). Elemental analyses were performed on an EA-1110 instrument.

General synthesis procedure of compound **6a** is described below and other compounds were synthesized in similar way. The chemical structure, yields, and melt points of the synthesized compounds are listed in Table 2.

**1-(Carboxymethyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6a).** 2,4,5-trifluoro-3-methoxybenzoic acid 4.12 g (0.02 mol) was dissolved in thionyl chloride 22 mL in a 50 mL round-bottomed flask, stirring and reflux for 3 h, removing the superfluous $SOCl_2$ on a rotary evaporator. (E)-ethyl-3-(dimethylamino) acrylate 2.86 g (0.02 mol) was added dropwise to the toluene solution of above leavings with stirring at 40–50°C, monitoring with TLC [PE/EA = 1/1 (v/v)] to the end of reactants, adding amino acid ethyl ester hydrochloride (0.02 mol) directly and stirring for about 5–8 h at room temperature, checking the reaction *via* TLC, then potassium carbonate 4.14 g (0.03 mol) was added and stirring for 8–10 h at 100°C. When the reaction was complete (determined by TLC), the mixture was acidified with diluted hydrochloride acid (5%) to PH = 2–3. The reaction mixture was poured into separatory funnel and separated. The organic layer was concentrated under reduced pressure and the residual was chromatographed on silica gel (PE/EA=2/1 (v/v)) to give compound **5**, which was added to the 20% sulfuric acid solution, refluxing for about 6–8 h, cooled to room temperature and filter. The filter cake was crystallized using 20% alcohol aqueous solution to afford compounds **6a**. IR (KBr) *v*: 3493, 2981, 2809, 1799, 1746, 1632, 1581, 1484, 1348, 1215, 1062 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 4.02 (s, 3H, $OCH_3$), 5.37 (s, 2H, $CH_2$), 8.03–8.07 (m, 1H, ArH), 9.01 (s, 1H, C=CH), 13.42 (br s, 1H, COOH), 14.55 (br s, 1H, COOH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 59.33, 63.59, 107.56, 107.21 (d, $^2J_{C-F}$ = 17.8 Hz), 122.90 (d, $^3J_{C-F}$ = 7.20 Hz), 131.86 (d, $^3J_{C-F}$ = 3.39 Hz), 140.64 (d, $^2J_{C-F}$ = 11.7 Hz), 147.45 (dd, $^1J_{C-F}$ = 107.2 Hz, $^2J_{C-F}$ = 15.4 Hz), 149.96 (dd, $^1J_{C-F}$ = 104.1 Hz, $^2J_{C-F}$ = 15.6 Hz), 153.57, 165.50, 169.37, 176.43; MS (70 eV): *m/z* (%) = 313 ($M^+$); Anal. Calcd. for $C_{13}H_9F_2NO_6$: C, 49.85; H, 2.90; N, 4.47; Found: C, 50.01; H, 4.45; N, 4.51.

**1-(1-Carboxy-2-methylpropyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6b).** IR (KBr) *v*: 3488, 2981, 2898, 1795, 1726, 1631, 1573, 1499, 1378, 1216, 1058 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 0.82 (d, J = 7.20 Hz, 6H, $CH_3$), 2.11–2.14 (m, 1H, CH), 3.68–3.70 (m, 1H, CH), 4.21 (s, 3H, $OCH_3$), 8.01–8.04 (m, 1H, ArH), 9.12 (s, 1H, C=CH), 13.73 (br s, 1H, COOH), 14.52 (br s, 1H, COOH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 21.71, 22.18, 29.42, 61.56, 68.51, 108.22, 109.43 (d, $^2J_{C-F}$ = 15.6 Hz), 121.75 (d, $^3J_{C-F}$ = 5.62 Hz), 132.13 (d, $^3J_{C-F}$ = 4.2 Hz), 141.21 (d, $^2J_{C-F}$ = 14.6 Hz), 146.13 (dd, $^1J_{C-F}$ = 108.3 Hz, $^2J_{C-F}$ = 14.3 Hz), 148.68 (dd, $^1J_{C-F}$ = 107.5 Hz, $^2J_{C-F}$ = 15.1 Hz), 152.98, 164.67, 169.66, 175.13; MS (70 eV): *m/z* (%) = 355 ($M^+$); Anal. Calcd. for $C_{16}H_{15}F_2NO_6$: C, 54.09; H, 4.26; N, 3.94; Found: C, 54.12; H, 4.19; N, 4.01.

**1-(1-Carboxy-3-methylbutyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6c).** IR (KBr) *v*: 3482, 2959, 2852, 1789, 1721, 1631, 1557, 1499, 1348, 1210, 1078 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 0.87 (d, *J* = 7.20 Hz, 6H, $CH_3$), 1.36–1.42 (m, 1H, CH), 2.11–2.15 (m, 1H, $CH_2$), 3.81–3.83 (m, 1H, CH), 4.36 (s, 3H, $OCH_3$), 8.63–8.67 (m, 1H, ArH), 9.07 (s, 1H, C=CH), 13.62 (br s, 1H, COOH), 14.58 (br s, 1H, COOH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 22.25, 23.19, 26.22, 29.57, 62.96, 71.55, 102.73, 107.60 (d, $^2J_{C-F}$ = 15.8 Hz), 128.08 (d, $^3J_{C-F}$ = 4.2 Hz), 139.11 (d, $^3J_{C-F}$ = 4.8 Hz), 142.94 (d, $^2J_{C-F}$ = 15.2 Hz), 145.39 (dd, $^1J_{C-F}$ = 108.3 Hz, $^2J_{C-F}$ = 14.6 Hz), 148.84 (dd, $^1J_{C-F}$ = 108.1 Hz, $^2J_{C-F}$ = 14.2 Hz), 153.29, 165.82, 171.79, 176.71; MS (70 eV): *m/z* (%) = 369 ($M^+$); Anal. Calcd. for $C_{17}H_{17}F_2NO_6$: C, 55.29; H, 4.64; N, 3.79; Found: C, 55.38; H, 4.52; N, 3.92.

**1-(1-Carboxy-2-methylbutyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6d).** IR (KBr) *v*: 3491, 2965, 2851, 1798, 1742, 1656, 1581, 1498, 1346, 1213, 1078 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 0.74–0.79 (m, 6H, $CH_3$), 0.88–0.95 (m, 2H, $CH_2$), 2.01–2.05 (m, 1H, CH), 3.89–3.92 (m, 1H, CH), 4.23 (s, 3H, $OCH_3$), 8.00–8.05 (m, 1H, ArH), 9.18 (s, 1H, C=CH), 13.53 (br s, 1H, COOH), 14.49 (br s, 1H, COOH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 11.74, 13.77, 25.55, 38.01, 65.82, 67.97, 102.85 (d, $^2J_{C-F}$ = 19.1 Hz), 109.68, 129.76 (d, $^3J_{C-F}$ = 5.6 Hz), 139.05 (d, $^3J_{C-F}$ = 6.4 Hz), 142.12 (d, $^2J_{C-F}$ = 17.1 Hz), 147.92 (dd, $^1J_{C-F}$ = 108.2 Hz, $^2J_{C-F}$ = 12.2 Hz), 149.15 (dd, $^1J_{C-F}$ = 109.1 Hz, $^2J_{C-F}$ = 14.8 Hz), 158.97, 165.62, 171.12, 176.55; MS (70 eV): *m/z* (%) = 369 ($M^+$); Anal. Calcd. for $C_{17}H_{17}F_2NO_6$: C, 55.29; H, 4.64; N, 3.79; Found: C, 55.31; H, 4.59; N, 3.77.

**1-(Carboxy(phenyl)methyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6e).** IR (KBr) *v*: 3495, 2926, 2809, 1796, 1746, 1632, 1581, 1484, 1348, 1259, 1105 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 4.11 (s, 3H, $OCH_3$), 4.33 (s, 1H, CH), 7.49–7.54 (m, 5H, ArH), 8.06–8.08 (m, 1H, ArH), 9.05 (s, 1H, C=CH), 13.56 (br s, 1H, COOH),

14.42 (br s, 1H, COOH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 62.75, 69.83, 107.31 (d, $^2J_{C-F}$ = 18.2 Hz), 109.78, 123.34, 129.39, 130.21 (d, $^3J_{C-F}$ = 5.7 Hz), 131.22, 132.44, 133.03, 133.41, 140.78 (d, $^3J_{C-F}$ = 5.2 Hz), 141.06 (d, $^2J_{C-F}$ = 16.4 Hz), 148.12 (dd, $^1J_{C-F}$ = 108.8 Hz, $^2J_{C-F}$ = 13.6 Hz), 149.47 (dd, $^1J_{C-F}$ = 107.6 Hz, $^2J_{C-F}$ = 12.2 Hz), 150.69, 165.14, 168.89, 176.32; MS (70 eV): *m*/*z* (%) = 389 ($M^+$); Anal. Calcd. for $C_{19}H_{13}F_2NO_6$: C, 58.62; H, 3.37; N, 3.60; Found: C, 58.71; H, 3.39; N, 3.71.

**1-(1-Carboxy-2-phenylethyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoli-ne-3-carboxylic acid (6f).** IR (KBr) *v*: 3495, 2958, 2868, 1798, 1747, 1617, 1568, 1474, 1353, 1279, 1110 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.23–3.27 (m, 2H, $CH_2$), 3.89–3.92 (m, 1H, CH), 4.21 (s, 3H, $OCH_3$), 7.31–7.42 (m, 5H, ArH), 8.11–8.14 (m, 1H, ArH), 9.02 (s, 1H, C=CH), 13.42 (br s, 1H, COOH), 14.58 (br s, 1H, COOH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 36.89, 74.09, 106.78 (d, $^2J_{C-F}$ = 16.8 Hz), 107.94, 123.14, 127.08, 127.24, 128.74, 129.33, 129.71, 129.89 (d, $^3J_{C-F}$ = 5.2 Hz), 136.91, 140.05 (d, $^3J_{C-F}$ = 6.1 Hz), 145.32 (d, $^2J_{C-F}$ = 15.6 Hz), 148.16 (dd, $^1J_{C-F}$ = 107.4 Hz, $^2J_{C-F}$ = 15.6 Hz), 150.41 (dd, $^1J_{C-F}$ = 108.1 Hz, $^2J_{C-F}$ = 14.7 Hz), 154.03, 165.16, 172.41, 176.15; MS (70 eV): *m*/*z* (%) = 403 ($M^+$); Anal. Calcd. for $C_{20}H_{15}F_2NO_6$: C, 59.56; H, 3.75; N, 3.47; Found: C, 59.62; H, 3.69; N, 3.51.

All of the synthesized compounds were tested for their antibacterial and antifungal activity *in vitro* by broth dilution method with some bacteria *Bacillus subtilis*, *Staphylococcus aureus*, *Aspergillus fumigatus*, and *Candida albicans* according to the literature [8]. The antimicrobial discs (diameter, 0.55 cm) were prepared at concentrations of 1, 0.2, and 0.1 mg/mL and applied to each of the culture plates previously seeded with the test bacteria. These culture plates were then incubated at 37°C for 24 h. The preliminary antimicrobial activity was determined by the diameter of inhibition zone. For each compound, three replicate trials were conducted against each organism.

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## REFERENCES AND NOTES

[1] (a) Enguehard, C. G.; Gueiffier, A. Mini-Rev Med Chem 2007, 7, 888; (b) Chrisman, W.; Knize, M. G.; Tanga, M. J. J Heterocycl Chem 2008, 45, 1641; (c) Abdelhamid, A. O. J Heterocycl Chem 2009, 46, 680.

[2] (a) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. J Med Chem 2001, 44, 2374; (b) Silva, A. D.; Almeida, M. V.; Souza, M. V. N.; Couri, M. R. C. Curr Med Chem 2003, 10, 21; (c) Beek, D. V.; Wijdicks, E. F. M.; Vermeij, F. H.; Haan, R. J.; Prins, J. M.; Spanjaard, L.; Dippel, D. W. J.; Nederkoorn, P. J. Arch Neuro 2009, 66, 1076.

[3] (a) Murugesan, D.; Palaniappan, S.; Perumal, Y.; Arnab, C.; Valakunja, N.; Dharmarajan, S. Bioorg Med Chem Lett 2008, 18, 1229; (b) Chai, Y.; Wan, Z. L.; Wang, B.; Guo, H. Y.; Liu, M. L. Eur J Med Chem 2009, 44, 4063.

[4] Harbeson, S. L. PCT WO 2009/035662, 19 March 2009.

[5] Al-Hiari, Y. M.; Al-Mazari, I. S.; Shakya, A. K.; Darwish, R. M.; Abu-Dahab, R. Molecules 2007, 12, 1240.

[6] Okada, T.; Tsuji, T.; Tsushima, T.; Yoshida, T.; Matsuura, S. J Heterocycl Chem 1991, 28, 1061.

[7] Kimura, Y.; Atarashi, S.; Kawakami, K.; Sato, K.; Hayakawa, I. J Med Chem 1994, 37, 3344.

[8] (a) Kong, W. J.; Zhao, Y. L.; Xiao, X. H.; Li, Z. L.; Jin, C.; Li, H. B. J Appl Microbiol 2009, 107, 1072; (b) Andre, S.; Patrick, J. K. Plant Cell Tissue Organ Culture 1984, 3, 111.

# Synthesis, Characterization, and Antimicrobial Activity of 3′-(4-(2-Substituted thiazol-4-yl)phenyl)spiro [indoline-3,2′-thiazolidine]-2,4′-diones



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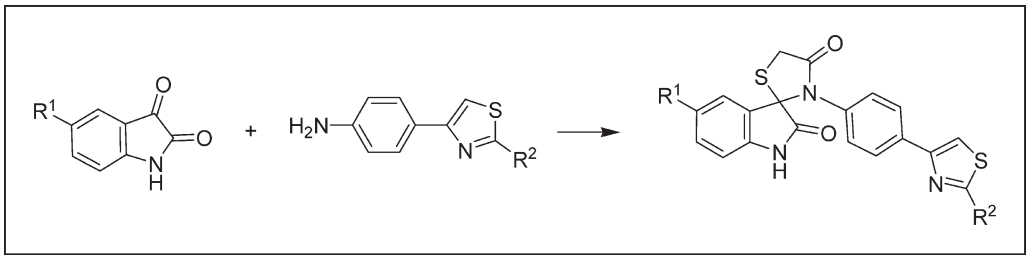

A series of 3′-(4-(2-methyl/phenyl/benzylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-diones was synthesized. The structures of the synthesized compounds were evaluated by analytical and spectral (IR, $^1$H NMR, $^{13}$C NMR, LC-MS, and elemental analysis) methods. All the synthesized compounds were screened for qualitative (Zone of inhibition) and quantitative antimicrobial activities (MIC). Most of the derivatives showed good activity towards Gram-positive and Gram-negative bacteria.

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## INTRODUCTION

The chemistry of spiro derivatives of isatin continues to draw attention of synthetic organic chemists due to their varied biological activities [1–4]. Of these, spiro[indol-thiazolidenes] has attracted our attention because they show a broad spectrum of pharmacological properties [5,6]. On the basis of these observations it was thought that it would be worthwhile to design and synthesize some new isatin based spirothiazolidine derivatives derived by coupling spiro[indol-thiazolidenes] with biologically active thiazole nucleus. Hence, we have synthesized several 3′-(4-(2-substituted thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-diones **13–32** and screened for their antimicrobial activity.

## RESULTS AND DISCUSSION

The synthesis of 3′-(4-(2-methyl/phenyl/benzylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-diones **13–32** is illustrated and outlined in Figure 1. The starting materials 2-methyl-4-(4-aminophenyl)thiazole **3**, 2-aryl-4-(4-aminophenyl)thiazole **4–6**, 2-benzyl-4-(4-aminophenyl)thiazole **7–12**, were prepared according to reported procedure [7]. The spiro compounds were synthesized by the reported procedure [8–13]. All the compounds were purified by column chromatography or recrystallized from hexane: ethyl acetate (9:1). The structures of the compounds were established by IR, $^1$H NMR, $^{13}$C NMR, LCMS, and elemental analysis and the results are presented in the experimental section. The spectral data of compounds **13–32** were in accordance with the assumed structures. The mass spectra of all the compounds revealed the molecular ion peak $M^+$ and M+2 ion peak due to S, Br, and/or Cl. The IR spectra showed presence of characteristic absorption peaks at 3200–3400 cm$^{-1}$ (>NH), 1730 and 1695 cm$^{-1}$ (C=O) indicating that cyclocondensation has occurred which was confirmed by its $^1$H NMR and $^{13}$C NMR data. The $^1$H NMR spectra revealed a double doublet integrating for two geminal protons of thiazolidine nucleus. $^{13}$C NMR spectra showed all expected characteristic peaks in the aromatic and aliphatic region along with δ 110–111 (spiro carbon atom) [13]. As a representative case, the IR spectrum of compound **27** showed peaks at 3238 cm$^{-1}$(>NH), 1735 and 1694 cm$^{-1}$ (C=O), 1619 cm$^{-1}$ (C=N) indicating that the cycloaddition has occurred. This was further confirmed by its $^1$H NMR spectrum which revealed an AB quartet of thiazolidine methylene at δ 3.75 and 4.42 with $J$ = 15 Hz. The benzylic methylene protons appeared at δ 4.18. All the aromatic protons appeared between δ 6.88 and 7.67. The lactam N—H appeared at δ 10.17. Further the $^{13}$C NMR spectrum of **27** revealed two signals at δ 33.00 and 38.8 for

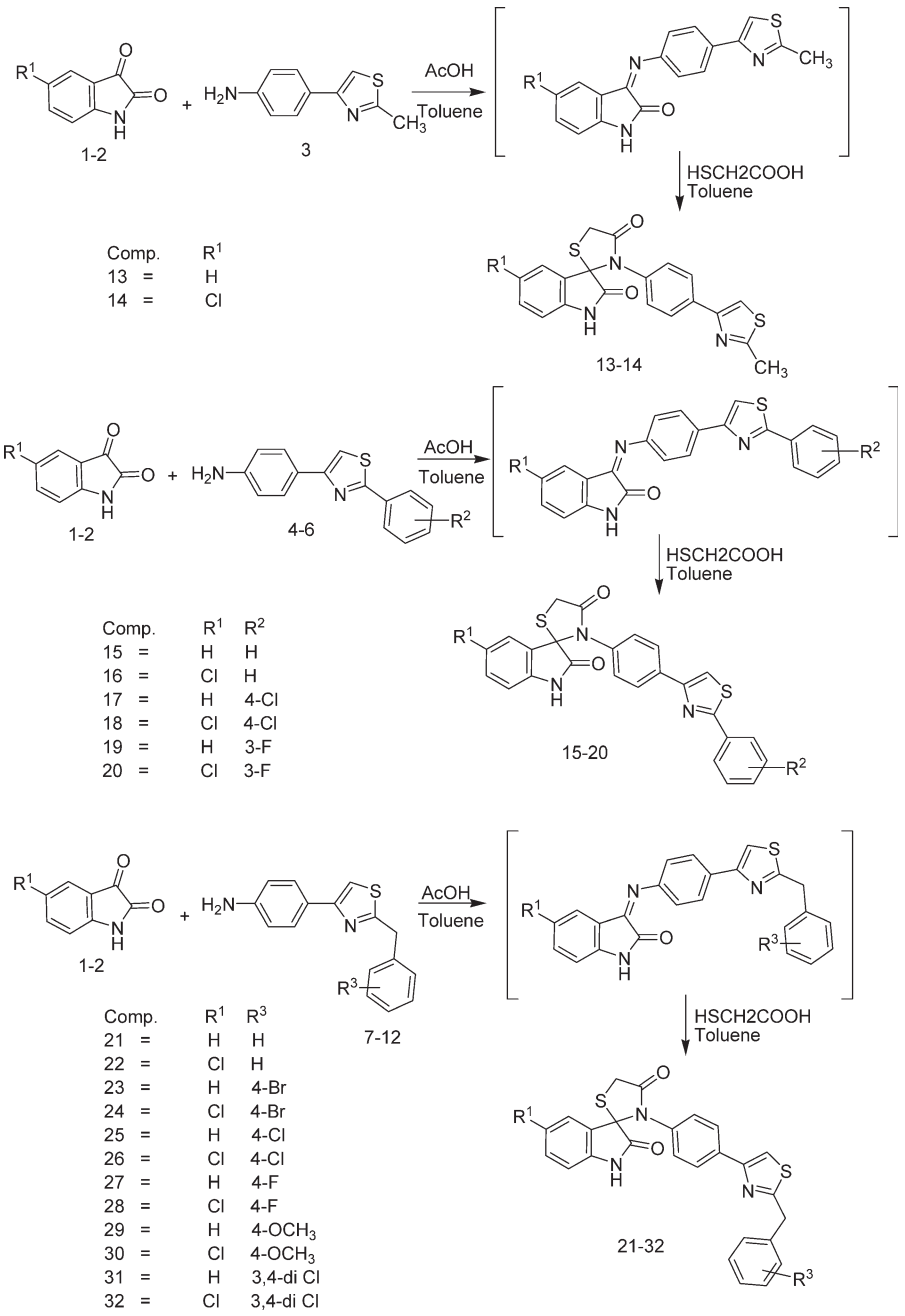


**Figure 1.** Synthetic pathway for the formation of the compounds **13–32**.

benzylic and thiazolidine methylene carbons, in addition the spiro carbon appeared at δ 110.9. The aromatic ipso carbon attached to fluorine appeared as doublet with $^1J$ = 246.8 Hz (C—F). The ortho and the meta carbon atoms in the same ring also appeared as doublets with $^2J$ = 21.5 Hz and $^3J$ = 8.3 Hz. All other aromatic carbon atoms appeared between δ 113–119 and 163.8 and the two carbonyl carbons appeared downfield at δ 172.6 and 176.8. The mass spectrum showed a molecular ion peak $M^+$ at *m/z* 427. The elemental analysis C (63.71), H (3.93), N (9.06), and S (12.87) was within ±0.4% of the calculated.

**Antimicrobial evaluation.** The *in vitro* antibacterial activity was performed against Gram-positive bacteria including *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2250), and Gram-negative bacteria including *Escherichia coli* (NCIM 2109). The antifungal activity was against fungi including *Candida albicans*

**Table 1**

Antimicrobial screening of synthesized compounds **13–32**.

| Compounds[a] | Microorganisms | | | | |
|---|---|---|---|---|---|
| | *B. subtilis* | *S. aureus* | *E. coli* | *C. albicans* | *A. niger* |
| 13 | 15.64 | 12.52 | – | – | – |
| 14 | – | 16.00 | 14.97 | – | – |
| 15 | 11.95 | 10.11 | – | – | – |
| 16 | 13.78 | 9.00 | – | – | – |
| 17 | 12.88 | 12.13 | 11.80 | – | – |
| 18 | 9.76 | 8.00 | – | – | – |
| 19 | – | 11.65 | 10.12 | – | – |
| 20 | 11.50 | 10.28 | – | – | – |
| 21 | 15.06 | 11.23 | – | 10.12 | 9.80 |
| 22 | – | 12.88 | – | – | – |
| 23 | – | 10.47 | – | – | – |
| 24 | 10.97 | – | 11.74 | – | – |
| 25 | 12.79 | 11.90 | 8.34 | – | – |
| 26 | 10.38 | 10.04 | – | – | – |
| 27 | – | 12.71 | – | – | – |
| 28 | – | 9.52 | 9.36 | – | – |
| 29 | 10.20 | 12.94 | 11.98 | – | – |
| 30 | 9.88 | 11.04 | 10.34 | – | – |
| 31 | – | 10.02 | – | – | – |
| 32 | – | 8.60 | – | – | – |
| Ciprofloxacin[a] | 26 | 28 | 25 | NA | NA |
| Nystatin[a] | NA | NA | NA | 20.5 | 22.1 |

Zone diameter of growth inhibition in mm.
NA, not applicable; –, inactive.
[a] Ciprofloxacin (10 μg/disc) and Nystatin (100 U/disc) were used as reference; synthesized compounds (100 μg/disc).

(NCIM 3471) and *Aspergillus niger* (NCIM 545). To evaluate the activity of the synthesized compounds against bacteria, the zone of inhibition and minimum inhibitory concentrations (MICs) were determined. Known antibiotic Ciprofloxacin (the reference for antibacterial drugs) and Nystatin (the reference antifungal drug) were used for comparison. The zone of inhibition and MIC against micro organisms tested is reported in (Tables 1 and 2), respectively.

The results of the antibacterial activity showed that the tested compounds are effective against the Gram-positive bacteria *S. aureus and B. subtilis* and Gram-negative bacteria *E. coli*. The investigation showed moderate inhibitory effects, with the majority of the compounds with the MIC values between 50 and 100 μg/mL. As shown in Table 2, all the compounds were active against *S. aureus* except compound **24**. The 4-methoxy substituted compounds **29** and **30** were active against all the three species. In general, compound with methyl group and the benzyl ring at 2 position of thiazole moiety showed enhanced activity.

The results of antifungal activity showed that all the compounds were inactive except compound **21**, which showed moderate activity against *C. albicans and A. niger*.

**Table 2**

Antibacterial activity of compounds **13–32**.

| Compounds | Microorganisms | | |
|---|---|---|---|
| | *B. subtilis* | *S. aureus* | *E. coli* |
| 13 | – | 50 | 60 |
| 14 | – | 50 | 60 |
| 15 | 100 | 90 | – |
| 16 | 100 | 100 | – |
| 17 | 90 | 85 | 85 |
| 18 | 100 | 100 | – |
| 19 | | 80 | 100 |
| 20 | 100 | 90 | – |
| 21 | 60 | 60 | – |
| 22 | – | 50 | – |
| 23 | – | 85 | – |
| 24 | 70 | – | 80 |
| 25 | 90 | 100 | 90 |
| 26 | 100 | 100 | – |
| 27 | – | 90 | – |
| 28 | – | 100 | 100 |
| 29 | 100 | 80 | 80 |
| 30 | 100 | 90 | 90 |
| 31 | – | 80 | – |
| 32 | – | 100 | – |
| Ciprofloxacin | 4 | 4 | 4 |

MIC in μg/mL.

## EXPERIMENTAL

Melting points were determined in an open capillary using Veego melting point apparatus and are uncorrected. The purity of the compounds was checked on silica gel-G plates. Infrared spectra ($cm^{-1}$) were recorded in KBr on a Shimadzu Model FTIR-435 spectrophotometer. $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ solution on a Varian Mercury YH-300 spectrometer operating at 300 MHz or on BRUKER ADVANCE II 400 spectrometer operating at 400 MHz for $^1H$ and 75 MHz for $^{13}C$. Chemical shifts are expressed relative to tetramethylsilane (TMS) and were reported as δ (ppm). LCMS measurements were made on a Jeol-JMS-DX 303 mass spectrometer. The elemental analysis was performed on FLASH EA 1112 analyzer.

**General procedure for compounds (13–32).** To a solution of isatin **1** (0.37 g, 2.5 mmol) in glacial acetic acid (1 mL) and dry toluene (30 mL), 2-methyl-4-(4-aminophenyl)thiazole, **3** (0.48 g, 2.5 mmol) was added. The mixture was refluxed using a Dean-Stark apparatus for 5–8 h to obtain the Schiff's base. After the completion of the reaction as monitored on TLC, thioglycolic acid (3.0 mmol) was added and mixture was further refluxed for 7–10 h. The solvent was removed under reduced pressure and the residue was treated with saturated solution of $NaHCO_3$ to remove the unreacted acid. The product was extracted with ethyl acetate, washed with water, brine and dried ($Na_2SO_4$). The solvent was removed under vacuum, the thick liquid thus obtained was added dropwise to a stirred solution of hexane to obtain crystalline solid.

***3′-(4-(2-Methylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (13)*** Yield: 67%; mp 200–202°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3221 (NH); 3118, 3020 (CH, Ar-H); 1730 (CO); 1695 (CO); 1609 (C=N); $^1H$ NMR ($CDCl_3$): δ 2.71 (s, 3H, $-CH_3$); 3.87 (d, 1H, $J$ = 15.6 Hz, Thiazolidine); 4.37 (d, 1H, $J$ = 15.6 Hz, Thiazolidine); 6.67–7.74 (m, 8H, Ar-H); 7.39 (s, 1H, Thiazole) ppm; ms: $m/z$ 394.0 ($M^+$) Anal. Calcd. for $C_{20}H_{15}N_3O_2S_2$: C, 60.05; H, 3.84; N, 10.86; S, 16.30. Found: C, 59.97; H, 3.78; N, 10.58; S, 15.95.

***5-Chloro-3′-(4-(2-methylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (14)*** Yield: 62%; mp 193–195°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3437, 3224 (NH); 3123, 3022 (CH, Ar-H); 1730 (CO); 1694 (CO); 1607 (C=N); $^1H$ NMR ($CDCl_3$): δ 2.77 (s, 3H, $CH_3$); 3.88 (d, 1H, $J$ = 15 Hz, Thiazolidine); 4.36 (d, H, $J$ = 15.6 Hz, Thiazolidine); 6.71–7.82 (m, 7H, Ar-H); 7.48 (s, 1H, Thiazole) ppm; ms: $m/z$ 429.0 ($M^+$), 431(M+2). Anal. Calcd. for $C_{20}H_{14}ClN_3O_2S_2$: C, 56.13; H, 3.30; N, 9.82; S, 14.99. Found: C, 56.30; H, 3.38; N, 9.93; S, 15.12.

***3′-(4-(2-Phenylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (15)*** Yield: 67%; mp 66°C dec., recrystallized from hexane–ethyl acetate (9.5:0.5); IR (KBr, $cm^{-1}$) 3435, 3224 (NH); 3115, 3024 (CH, Ar-H); 1730 (CO); 1694 (CO); 1607 (C=N); $^1H$ NMR ($CDCl_3$): δ 3.88 (d, 1H, $J$ = 16 Hz, Thiazolidine); 4.38 (d, H, $J$ = 16 Hz, Thiazolidine); 6.71–7.98 (m, 13H, Ar-H); 7.40 (s, 1H, Thiazole); ms: $m/z$ 456.1 ($M^+$). Anal. Calcd. For $C_{25}H_{17}N_3O_2S_2$: C, 65.91; H, 3.76; N, 9.22; S, 14.08. Found: C, 65.58; H, 3.55; N, 9.46; S, 14.31.

***5-Chloro-3′-(4-(2-phenylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (16)*** Yield: 72%; mp 84°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3440, 3221 (NH); 3118, 3021 (CH, Ar-H); 1731 (CO); 1695 (CO); 1612 (C=N); $^1H$ NMR (DMSO): δ 4.05 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 4.17 (d, H, $J$ = 15.4 Hz, Thiazolidine); 6.76–8.00 (m, 12H, Ar-H); 8.15 (s, 1H, Thiazole); 10.94 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 490.0 ($M^+$), 492.0 (M+2). Anal. Calcd. for $C_{25}H_{16}ClN_3O_2S_2$: C, 61.28; H, 3.29; N, 8.58; S, 13.09. Found: C, 60.80; H, 3.55; N, 8.41; S, 12.81.

***3′-(4-(2-(4-Chlorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (17)*** Yield: 74%; mp 222°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3436, 3216 (NH); 3118, 3011 (CH, Ar-H); 1730 (CO); 1694 (CO); 1605 (C=N); $^1H$ NMR (DMSO): δ 4.02 (d, 1H, $J$ = 15.2 Hz, Thiazolidine); 4.18 (d, 1H, $J$ = 15.2 Hz, Thiazolidine); 6.75–8.01 (m, 12H, Ar-H); 8.16 (s, 1H, Thiazole); 10.80 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 490.0 ($M^+$), 492.0 (M+2). Anal. Calcd. for $C_{25}H_{16}ClN_3O_2S_2$: C, 61.28; H, 3.29; N, 8.58; S, 13.09. Found: C, 61.40; H, 3.45; N, 8.50; S, 13.21.

***5-Chloro-3′-(4-(2-(4-chlorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (18)*** Yield: 74%; mp 230°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3442, 3227 (NH); 3115, 3016 (CH, Ar-H); 1731 (CO); 1694 (CO); 1615 (C=N); $^1H$ NMR ($CDCl_3$): δ 4.04 (d, 1H, $J$ = 15.6 Hz, Thiazolidine); 4.17 (d, H, $J$ = 15.6 Hz, Thiazolidine); 6.76–8.02 (m, 11H, Ar-H); 8.18 (s, 1H, Thiazole); 10.94 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 524.0 ($M^+$), 525.9 (M+2). Anal. Calcd. for $C_{25}H_{15}Cl_2N_3O_2S_2$: C, 57.25; H, 2.88; N, 8.01; S, 12.23. Found: C, 57.39; H, 2.98; N, 9.19; S, 12.44.

***3′-(4-(2-(3-Fluorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (19)*** Yield: 64%; mp 86–87°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3440, 3222 (NH); 3121, 3008 (CH, Ar-H); 1731 (CO); 1696 (CO); 1609 (C=N); $^1H$ NMR ($CDCl_3$): δ 3.89 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.10 (d, H, $J$ = 15.3 Hz, Thiazolidine); 6.75–7.75 (m, 12H, Ar-H); 8.67 (s, 1H, Thiazole); $^{13}C$ NMR ($CDCl_3$): δ 33.2 ($CH_2$, Thiazolidine); 111.12 (Spiro C); 113.14–164.57 (21C-Ar-C, Thiazole-C); 172.7 (CONH); 177.1 (CONH); ms: $m/z$ 473.6 ($M^+$). Anal. Calcd. for $C_{25}H_{16}FN_3O_2S_2$: C, 63.41; H, 3.41; N, 8.87; S, 13.54. Found: C, 63.35; H, 3.82; N, 8.27; S, 11.35.

***5-Chloro-3′-(4-(2-(3-fluorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (20)*** Yield: 62%; mp 140°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3442, 3219 (NH); 3122, 3021 (CH, Ar-H); 1731 (CO); 1697 (CO); 1611 (C=N); $^1H$ NMR ($CDCl_3$): δ 3.92 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.30 (d, H, $J$ = 15.3 Hz, Thiazolidine); 6.77–7.82 (m, 11H, Ar-H); 8.65 (s, 1H, Thiazole); ms: $m/z$ 508.6 ($M^+$), 510.2 (M+2). Anal. Calcd. for $C_{25}H_{15}ClFN_3O_2S_2$: C, 59.11; H, 2.98; N, 8.27; S, 12.62. Found: C, 59.41; H, 3.17; N, 8.12; S, 13.01.

***3′-(4-(2-Benzylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (21)*** Yield: 72%; mp 194°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3443, 3200 (NH); 3109, 3026 (CH, Ar-H); 1736 (CO); 1697 (CO); 1617 (C=N); $^1H$ NMR ($CDCl_3$): δ 3.88 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 4.31 (s, 2H, $CH_2$); 4.37 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 6.71–7.75 (m, 13H, Ar-H); 8.05 (s, 1H, Thiazole); $^{13}C$ NMR ($CDCl_3$): δ 33 ($CH_2$, Thiazolidine); 39.7 ($CH_2$, Benzyl); 110.82 (Spiro C); 113.85–154 (21C, Ar-C Thiazole-C); 170.7 (CONH); 172.5 (CONH); ms: $m/z$ 469.0 ($M^+$).

Anal. Calcd. for $C_{26}H_{19}N_3O_2S_2$: C, 66.50; H, 4.08; N, 8.95; S, 13.66. Found: C, 66.20; H, 4.01; N, 9.11; S, 13.78.

***3′-(4-(2-Benzylthiazol-4-yl)phenyl)-5-chlorospiro[indoline-3,2′-thiazolidine]-2,4′-dione (22)*** Yield: 72%; mp 112°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3411, 3248 (NH); 3108, 3030 (CH, Ar-H); 1737 (CO); 1697 (CO); 1618 (C=N); $^1$H NMR ($CDCl_3$): δ 3.88 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.30 (s, 2H, $CH_2$); 4.35 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 6.65–7.79 (m, 12H, Ar-H); 7.92 (s, 1H, Thiazole); 9.5 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 503.0 ($M^+$), 505.0 (M+2). Anal. Calcd. for $C_{26}H_{18}ClN_3O_2S_2$: C, 61.96; H, 3.60; N, 8.34; S, 12.72. Found: C, 62.06; H, 3.79; N, 8.86; S, 11.56.

***3′-(4-(2-(4-Bromobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (23)*** Yield: 72%; mp 204–207°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3411, 3205 (NH); 3111, 3052 (CH, Ar-H); 1731 (CO); 1694 (CO); 1606 (C=N); $^1$H NMR ($CDCl_3$): δ 3.87 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.25 (s, 2H, $CH_2$); 4.36 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 6.70–7.75 (m, 12H, Ar-H); 7.98 (s, 1H, Thiazole); $^{13}$C NMR ($CDCl_3$): δ 33 ($CH_2$, Thiazolidine); 39.05 ($CH_2$, Benzyl); 110.76 (Spiro C); 113.9–164.1 (21C, Ar-C, Thiazole-C); 171 (CONH); 173.2 (CONH); ms: $m/z$ 547.5 ($M^+$), 549.6 (M+2). Anal. Calcd. for $C_{26}H_{18}BrN_3O_2S_2$: C, 56.94; H, 3.31; N, 7.66; S, 11.69. Found: C, 57.06; H, 3.36; N, 8.07; S, 11.85.

***3′-(4-(2-(4-Bromobenzyl)thiazol-4-yl)phenyl)-5-chlorospiro[indoline-3,2′-thiazolidine]-2,4′-dione (24)*** Yield: 65%; mp 190–192°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3411, 3236 (NH); 3110, 3039 (CH, Ar-H); 1731 (CO), 1695 (CO); 1614 (C=N); $^1$H NMR ($CDCl_3$): δ 3.88 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 4.27 (s, 2H, $CH_2$); 4.36 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 6.64–7.78 (m, 11H, Ar-H); 7.68 (s, 1H, Thiazole); ms: $m/z$ 581.9 ($M^+$), 583.9 (M+2), 585.9 (M+4). Anal. Calcd. for $C_{26}H_{17}BrClN_3O_2S_2$: C, 53.48; H, 3.11; N, 7.20; S, 10.98. Found: C, 53.78; H, 3.33; N, 7.51; S, 11.17.

***3′-(4-(2-(4-Chlorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (25)*** Yield: 70%; mp 56°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3414, 3240 (NH); 3118, 3022 (CH, Ar-H); 1731 (CO); 1694 (CO); 1612 (C=N); $^1$H NMR ($CDCl_3$): δ 3.87 (d, 1H, $J$ = 15.2 Hz, Thiazolidine); 4.28 (s, 2H, $CH_2$); 4.37 (d, 1H, $J$ = 15.2 Hz, Thiazolidine); 6.70–7.75 (m, 12H, Ar-H); 7.45 (s, 1H, Thiazole); ms: $m/z$ 504.0 ($M^+$), 506.0 (M+2). Anal. Calcd. for $C_{26}H_{18}ClN_3O_2S_2$: C, 61.96; H, 3.60; N, 8.34; S, 12.72. Found: C, 61.99; H, 3.82; N, 8.46; S, 11.28.

***5-Chloro-3′-(4-(2-(4-chlorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (26)*** Yield: 65%; mp 99°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3418, 3239 (NH); 3120, 3014 (CH, Ar-H); 1732 (CO); 1695 (CO); 1612 (C=N); $^1$H NMR ($CDCl_3$): δ 3.76 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 4.28 (s, 2H, $CH_2$); 4.34 (d, 1H, $J$ = 15.4 Hz, Thiazolidine); 6.70–7.75 (m, 11H, Ar-H); 7.68 (s, 1H, Thiazole); $^{13}$C NMR ($CDCl_3$): δ 33 ($CH_2$, Thiazolidine); 39.04 ($CH_2$, Benzyl); 111 (Spiro C); 113.4–165.6 (21C, Ar-C, Thiazole-C); 172.7 (CONH); 175.4 (CONH); ms: $m/z$ 538.0 ($M^+$), 540.0 (M+2), 542.1 (M+4). Anal. Calcd. for $C_{26}H_{17}Cl_2N_3O_2S_2$: C, 56.99; H, 3.18; N, 7.8; S, 11.91. Found: C, 57.23; H, 3.26; N, 7.96; S, 12.13.

***3′-(4-(2-(4-Fluorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (27)*** Yield: 60%; mp 133–135°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3439, 3228 (NH); 3101(CH, Ar-H); 1735 (CO); 1694 (CO); 1619 (C=N); $^1$H NMR ($CDCl_3$): δ 3.75 (d, 1H, $J$ = 15 Hz, Thiazolidine); 4.18 (s, 2H, $CH_2$); 4.22 (d, 1H, $J$ = 15 Hz, Thiazolidine); 6.56–7.67 (m, 12H, Ar-H); 7.21 (s, 1H, Thiazole); 10.17 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 487.6 ($M^+$). Anal. Calcd. for $C_{26}H_{18}FN_3O_2S_2$: C, 64.05; H, 3.72; N, 8.62; S, 13.15. Found: C, 63.71; H, 3.93; N, 9.06; S, 12.87.

***5-Chloro-3′-(4-(2-(4-fluorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (28)*** Yield: 66%; mp 139–140°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3404, 3257 (NH); 3113, 3043 (CH, Ar-H); 1730 (CO); 1694 (CO); 1609 (C=N); 864 (Ar-Cl); $^1$H NMR ($CDCl_3$): δ 3.71 (d, 1H, $J$ = 7.6 Hz, Thiazolidine); 4.20 (s, 2H, $CH_2$); 4.28 (d, 1H, $J$ = 7.6 Hz, Thiazolidine); 6.56–7.67 (m, 11H, Ar-H); 7.35 (s, 1H, Thiazole); 10.42 (s, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR ($CDCl_3$): δ 33 ($CH_2$, Thiazolidine); 38($CH_2$, Benzyl); 111.7 (Spiro C); 113.9–160.2 (21C, Ar-C, Thiazole-C); 172.2 (CONH); 175.9 (CONH); ms: $m/z$ 521.2 ($M^+$), 523.3 (M+2). Anal. Calcd. for $C_{26}H_{17}ClFN_3O_2S_2$: C, 59.82; H, 3.28; N, 8.05; S, 12.29. Found: C, 60.05; H, 3.51; N, 8.26; S, 11.97.

***3′-(4-(2-(4-Methoxybenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (29)*** Yield: 58%; mp 62°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3440, 3230 (NH); 3118(CH, Ar-H); 1732 (CO); 1696 (CO); 1609 (C=N); $^1$H NMR ($CDCl_3$): δ 3.80 (d, 1H, $J$ = 15 Hz, Thiazolidine); 4.18 (s, 2H, $CH_2$); 4.27 (d, 1H, $J$ = 15 Hz, Thiazolidine); 4.33 (s, 3H, $CH_3$); 6.66–7.74 (m, 12H, Ar-H); 7.68 (s, 1H, Thiazole); 10.17 (s, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR ($CDCl_3$): δ 33.1 ($CH_2$, Thiazolidine); 38.4 ($CH_2$, Benzyl); 58.4 (O—$CH_3$); 111.4 (Spiro C); 113.4–164.4 (21C, Ar-C, Thiazole-C); 171.4 (CONH); 176.2 (CONH); ms: $m/z$ 499.6 ($M^+$). Anal. Calcd. for $C_{27}H_{21}N_3O_3S_2$: C, 64.91; H, 4.24; N, 8.41; S, 12.84. Found: C, 65.11; H, 4.36; N, 8.52; S, 13.11.

***5-Chloro-3′-(4-(2-(4-methoxybenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (30)*** Yield: 60%; mp 41°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3412, 3252 (NH); 3121, 3033 (CH, Ar-H); 1734 (CO); 1696 (CO); 1612 (C=N); 864 (Ar-Cl); $^1$H NMR ($CDCl_3$): δ 3.82 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.20 (s, 2H, $CH_2$); 4.28 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.36 (s, 3H, $CH_3$); 6.68–7.88 (m, 11H, Ar-H); 7.76 (s, 1H, Thiazole); 10.42 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 533.2 ($M^+$), 535.6 (M+2). Anal. Calcd. for $C_{27}H_{20}ClN_3O_3S_2$: C, 60.72; H, 3.77; N, 7.87; S, 12.01. Found: C, 60. 81; H, 3.89; N, 8.04; S, 12.23.

***3′-(4-(2-(3,4-Dichlorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-dione (31)*** Yield: 65%; mp 97°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3414, 3246 (NH); 3103, 3048 (CH, Ar-H); 1729 (CO); 1695 (CO); 1613 (C=N); 864 (Ar-Cl); $^1$H NMR ($CDCl_3$): δ 3.88 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.35 (d, 1H, $J$ = 15.3 Hz, Thiazolidine); 4.37 (s, 2H, $CH_2$); 6.70–7.73 (m, 11H, Ar-H); 7.40 (s, 1H, Thiazole); 8.6 (s, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR ($CDCl_3$): δ 33 ($CH_2$, Thiazolidine); 36.5 ($CH_2$, Benzyl); 110.97 (Spiro C); 113.9–168.1 (21C, Ar-C, Thiazole-C); 172.6 (CONH); 176.9 (CONH); ms: $m/z$ 537.7 ($M^+$), 539.7 (M+2), 541.8 (M+4). Anal. Calcd. for $C_{26}H_{17}Cl_2N_3O_2S_2$: C, 57.99; H, 3.18; N, 7.80; S, 11.91. Found: C, 58.23; H, 3.29; N, 8.02; S, 12.21.

***5-Chloro-3′-(4-(2-(3,4-dichlorobenzyl)thiazol-4-yl)phenyl)-spiro[indoline-3,2′-thiazolidine]-2,4′-dione (32)*** Yield: 65%; mp 198–202°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr, $cm^{-1}$) 3409, 3233 (NH); 3113, 3041 (CH, Ar-H); 1730 (CO); 1696 (CO); 1610 (C=N); 860 (Ar-Cl); $^1H$ NMR ($CDCl_3$): δ 3.88 (d, 1H, $J$ = 15 Hz, Thiazolidine); 4.34 (d, 1H, $J$ = 15.Hz, Thiazolidine); 4.41 (s, 2H, $CH_2$); 6.63–7.77 (m, 10H, Ar-H); 8.03 (s, 1H, Thiazole); 8.9 (s, 1H, NH, $D_2O$ exchangeable); ms: $m/z$ 571.9 ($M^+$), 573.9 (M+2), 575.9 (M+4), 577.8 (M+6). Anal. Calcd. for $C_{26}H_{16}Cl_3N_3O_2S_2$: C, 54.51; H, 2.81; N, 7.33; S, 11.19. Found: C, 54.65; H, 2.93; N, 7.46; S, 11.51.

**Antimicrobial activity.** Compounds **14–32** were screened for their *in vitro* antimicrobial activity against the standard strains *B. subtilis, S. aureus*, and *E. coli* by the disk diffusion method [14,15]. Disks measuring 6 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 disks were dispensed to each screw-caped bottle and sterilized by dry heat at 145°C for 1 h. The test compounds were prepared with 100 μg/mL concentration in dimethyl sulfoxide. Disks of each concentration were placed in nutrient agar medium inoculated with fresh bacteria strains separately. The incubation was carried out at 37°C for 48 h. Ciprofloxacin was used as standard drugs at a concentration of 10 μg/mL. Solvent and growth controls were kept and zones of inhibition were noted.

The two-fold dilution technique [16] was followed to determine the minimum inhibitory concentration (MIC) of the synthesized compounds. The test compounds were dissolved in dimethyl sulfoxide and then diluted with culture medium (Mueller-Hinton agar medium) at the required final concentration 150–155 μg/mL. A plate containing only the culture medium and DMSO in the same dilution was used as negative control. The MIC values were recorded after incubation at 37°C for a period of 24 h. The lowest concentration of the test substance that completely inhibited the growth of the microorganism was reported as MIC expressed in terms of μg/mL.

The compounds were screened for their antifungal activity against *C. albicans* (MTCC 1637) *and A. niger* (AIIMS) in DMSO by disc diffusion method under standard conditions using Sabourad Dextrose Agar medium as described by NCCLS [17]. Sterile filter paper discs (6 mm diameter) containing specific amount of anti fungal agent (100 μg for the synthesized compounds) were placed on the surface of an agar plate inoculated with the standardized suspension of microorganisms tested. The plates were incubated at 37°C for 7 days for evaluating antifungal activity. The diameters of inhibition zones (in mm) were measured. Nystatin was used as standard drug at a concentration of 10 μg/mL.

## CONCLUSIONS

In conclusion, a series of new 3′-(4-(2-methyl/phenyl/benzylthiazol-4-yl)phenyl)spiro[indoline-3,2′-thiazolidine]-2,4′-diones **13–32** was synthesized. The pharmacological studies were undertaken to evaluate the effects of substituents on the antimicrobial activities. Most of the synthesized compounds exhibited moderate activity towards Gram-positive and Gram-negative bacteria. These compounds, however, did not show any promising antifungal activity except compound **21**. Compounds with methyl group and benzyl ring at 2-position of thiazole nucleus showed enhanced antibacterial activity.

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## REFERENCES AND NOTES

[1] Wolf, M.; Masciffi, A. A. US Pat. 3,395,156, 1968; Chem Abstr 1988, 69, 96504r.

[2] Rohm, Hoss Co. Brit. Pat. 913,937, 1962; Chem Abstr 1963, 59, 577f.

[3] Winters, G.; Mola, N. D. Ger. Pat. 2,442,667, 1975; Chem Abstr 1975, 83, 28096.

[4] Kornet, N. J.; Thio, A. P. J Med Chem 1976, 19, 892.

[5] Joshi, K. C.; Dandia, A.; Bhajat, S. J. Fluor Chem 1990, 48, 169.

[6] Popp, F. D.; Rajopadhye, M. J Heterocycl Chem 1985, 22, 93.

[7] Rindhe, S. S.; Mane, R. A.; Ingle, D. B. J Ind Chem Soc 1985, 62, 334.

[8] Mashelkar, U. C.; Rane, D. M. Ind J Chem 2005, 44B, 1937.

[9] Joshi, K. C.; Dandia, A.; Bhajat, S. Ind J Chem 1990, 29B, 766.

[10] Bhambi, D.; Sharma, C.; Sharma, S.; Salvi, V. K.; Talesara, G. L. Ind J Chem 2009, 48B, 1006.

[11] Rajopadhye, M.; Popp, F. D. J Heterocycl Chem 1984, 21, 289.

[12] Mogilaiah, K.; Rao, R. B. Ind J Chem 1998, 37B, 894.

[13] Jain, S. C.; Sinha, J.; Bhagat, S.; Errington, W.; Olsen, C. E. Syn Commun 2003, 33, 563.

[14] Cruickshank, R.; Duguid, J. P.; Marion, B. P.; Swain, R. H. A. Medicinal Microbiology, 12th ed.; Vol. 2, Churchil Livingstone: London, 1975, p 196.

[15] Collins, H. A. Microbiological Methods, 2nd ed.; Butterworth: London, 1976.

[16] Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. NCCLS Approval Standard Document M7-A6. National Committee for Clinical Laboratory Standards: Wayne, PA, 2003.

[17] NCCLS Approval Standard Document M2-A7. National Committee for Clinical Laboratory Standards: Vilanova, PA, 2000.

# An Efficient One-Pot Solvent-Free Synthesis of 2,3-Dihydroquinazoline-4(1H)-ones *via* $Al/Al_2O_3$ Nanoparticles



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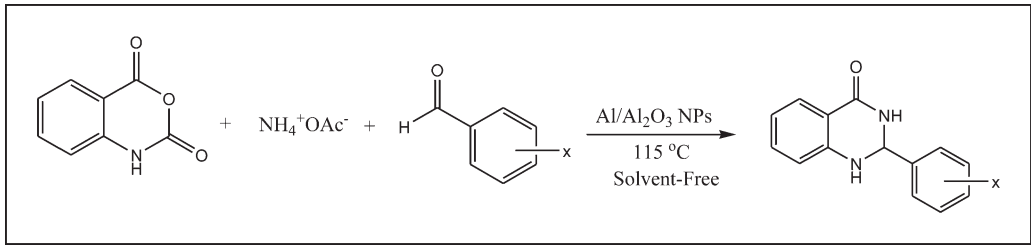


An efficient one-pot, solvent-free method is reported for the synthesis of 2-phenyl-2,3-dihydroquinazoline-4(1H)-one as well as its *o*-Cl, *o*-OMe, *m*-Br, *m*-$NO_2$, *p*-OH, *p*-$NO_2$, *p*-CN, *p*-$PhCH_2O$, *p*-Cl, *p*-F, *p*-Br, *p*-Me, and *o,m*-dichloro derivatives, using our ''as-prepared'' arc discharge fabricated $Al/Al_2O_3$ nanoparticles. Compared with our previous report and other known methods, this route gives higher yields with shorter reaction times, whereas its green catalyst appears recyclable at least four times-with minor decrease in its catalytic activity, under mild conditions.

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## INTRODUCTION

Dihydroquinazolinones and their derivatives are important heterocyclic compounds, which influence numerous cellular processes. They are analgesic, diuretic, and vasodilating agents, displaying a broad range of biological, medicinal, and pharmacological properties [1–10]. Also, they are constituents of antitumor, antibiotic, antidefibrillatory, antipyretic, antihypertonic, antihistamine, and antidepressant drugs. In addition, these compounds can easily be oxidized to their quinazolin-4(3H)-one analogues [11], which also include important pharmacologically active compounds [12]. Several routes, including our recent method, using iodine as the catalyst, have been reported for the synthesis of 2,3-dihydroquinazolinones [13–19]. Yet, development of a green, simple, efficient, and general method for the synthesis of these widely used organic compounds, from readily available reagents, remains one of the major challenges in organic synthesis. In this manuscript, we have made use of the novel, recently reported metal and metal oxide nanoparticles, which exhibit high-surface/volume ratio, quantum size, and quanta tunnel effects [20–23]. We think our new procedure is cleaner and more environment friendly than our previous one, where we used the relatively toxic iodine catalyst [19]. Specifically, we employ small amounts of novel, recyclable, nontoxic, and inexpensive $Al/Al_2O_3$ nanocatalyst with a high-surface/volume ratio in, a three-component one-step synthesis of 2,3-dihydroquinazolin-4(1H)-ones (Scheme 1).

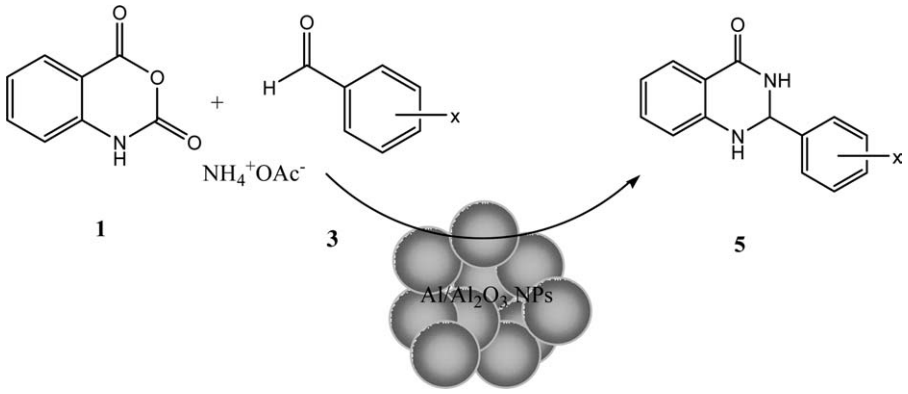
## RESULTS AND DISCUSSION

After demonstrating the impact of media and current on the arc fabrication of Al nanoparticles [24], we wondered if we could substitute $Al/Al_2O_3$ nanoparticles for iodine in the preparation of 2,3-disubstituted quinazolin-4(3H)-ones through multicomponent reactions, which we had already reported [19]. The reason was our immense desire to adopt rather green and economical reaction conditions, since the vapor of iodine was toxic at high-temperatures, and to remove the excess iodine we had to use saturated $Na_2S_2O_3$. Also the previous catalyst was not reusable.

The scanning electron microscopy (SEM) images showed spherical arc fabricated $Al/Al_2O_3$ NPs with a size range of 30 – 40 nm (Fig. 1).

The X-ray diffraction (XRD) pattern confirmed the formation of $Al/Al_2O_3$ NPs with similar average grain size range estimated *via* Scherer's equation [25], using the maximum peak (111) was used (Fig. 2). At a scanning speed of 2°/min from 20° to 80° (2θ), the XRD pattern showed five peaks, which were characteristic of

**Scheme 1.** Three-component one-step synthesis of 2,3 dihydroquinazolin-4(1H)-ones.




aluminum ($2\theta$ = 38.56°; 44.84°; 65.25°; 78.33°, and 82.59°), corresponding to Miller indices (111), (200), (220), (311), and (111), revealing the formation of face-centered cubic (fcc) Al NPs. Besides, it illustrated the lines (110), (104), and (220) at $2\theta$ = 45.93°; 66.98°; 85.09°, respectively, for $\gamma$-$Al_2O_3$.

Catalytic amounts of this as-prepared $Al/Al_2O_3$ NPs was added to a well-stirred mixture of isatoic anhydride (**1**), an aromatic aldehyde (**3**, either with electron-donating or electron-withdrawing groups), and ammonium acetate. It gave the corresponding 2,3-dihydroquinazolin-4(1H)-ones (**5a – o**) in 65 – 98% yields, at 115°C, under solvent-free conditions (Table 1).

Reactions were completed under smooth conditions within 8 – 30 min, and the products were isolated by a simple workup procedure. Thus an easy and rather green method for the synthesis of a novel class of the quinazolinone family was found. However, no simple relationship was observed between the electronic properties of the aryl groups and the corresponding quinazolinone products. Specifically, the amount of the catalyst ($Al/Al_2O_3$ NPs) for this condensation reaction was probed at 0.00, 0.06, 0.012, 0.036, and 0.048 g against isatoic anhydride (0.163 g, 1.0 mmol), ammonium acetate, and 4-chlorobenzaldehyde (0.14 g, 1.0 mmol), under solvent-free condition, at 115°C (Table 2).

The best results were obtained using 0.036 g of catalyst (yield = 94%). Increasing the amount of catalyst higher than 0.048 g did not affect the reaction time and yield. The absence of the catalyst required considerably higher reaction time giving the lowest yield (75%).

To check the reusability of our catalyst, the prepared $Al/Al_2O_3$ NPs (0.036 g) was stirred for 2 min with isatoic anhydride (0.163 g, 1 mmol), aromatic aldehyde (0.14 g, 1 mmol), and ammonium acetate, at room temperature. Then the mixture was heated in a paraffin bath at 115°C, for different periods of time (Table 1). After completion of the reaction excess ammonium acetate was washed away by water (5 mL). Subsequently, the hydroquinazolinone products were extracted by ethanol (50 mL). The solid residue was our catalyst, which was dried and reused for at least four cycles (Fig. 3).

The question is how this catalyst works? Evidently, the $Al/Al_2O_3$ NPs function as a good Lewis acid, which attracts and activates the carbonyl and imine groups involved and provides a surface on which the reactions

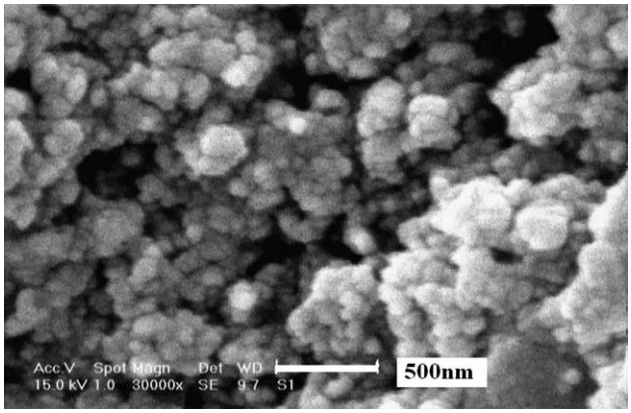



**Figure 1.** The SEM image of the as-prepared $Al/Al_2O_3$ nanoparticles.

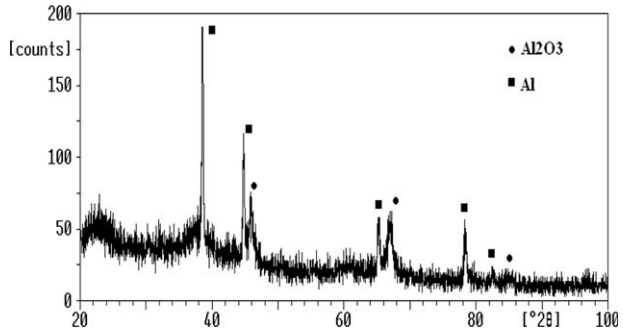



**Figure 2.** The XRD pattern of the as-prepared $Al/Al_2O_3$ nanoparticles.

**Table 1**

The reaction time and the % yield of hydroquinazolin product.

| Product | Ar | Time (min) | Yield (%)[a] | M.P (°C) Found | M.P (°C) Reported |
|---|---|---|---|---|---|
| 5a | 4-$OHC_6H_4$ | 8 | 91 | 285 – 287 | 278 – 280 [19] |
| 5b | 4-$NO_2C_6H_4$ | 8 | 78 | 300 – 302 | 310 – 312 [19] |
| 5c | 4-$CNC_6H_4$ | 15 | 75 | 350 – 351 | 350 – 351 [19] |
| 5d | 4-$PhCH_2$–O–$C_6H_4$ | 15 | 98 | 238 – 240 | 238 – 240 [19] |
| 5e | 4-$ClC_6H_4$ | 15 | 94 | 207 – 208 | 207 – 208 [19] |
| 5f | 4-$FC_6H_4$ | 30 | 89 | 279 – 280 | 279 – 280 [19] |
| 5g | 4-$BrC_6H_4$ | 10 | 80 | 195 – 197 | 195 – 197 [19] |
| 5h | 2-$ClC_6H_4$ | 12 | 79 | 230 – 231 | 230 – 231 [19] |
| 5i | 2-$OMeC_6H_4$ | 10 | 82 | 173 – 175 | 173 – 175 [19] |
| 5j | 3-$BrC_6H_4$ | 15 | 95 | 229 – 230 | 229 – 230 [19] |
| 5k | 2,3-$Cl_2C_6H_3$ | 5 | 90 | 232 – 233 | 232 – 233 [19] |
| 5l | 4-$MeOC_6H_4$ | 8 | 80 | 183 – 184 | 183 – 184 [19] |
| 5m | $C_6H_5$ | 15 | 88 | 225 – 226 | 225 – 226 [19] |
| 5n | 4-$MeC_6H_4$ | 15 | 92 | 228 – 230 | 229 – 231 [19] |
| 5o | 3-$NO_2C_6H_4$ | 30 | 65 | 180 – 182 | 180 – 182 [19] |

[a] Isolated yield.

occur sequentially leading to the desired products (Scheme 2).

Specifically, decarboxylation of **1** occurs through its condensation with ammonium acetate in the presence of $Al/Al_2O_3$ NPs, affording antranylamide intermediate **2**, which reacts with the aromatic aldehyde **3** and gives the imine intermediate **4** that cyclizes to yield the corresponding hydroquinazolinone **5**.

## CONCLUSION

We have employed $Al/Al_2O_3$ NPs as an effective catalyst in the one-pot multicomponent synthesis of 2,3-dihydroquinazolin-4(1H)-ones. This catalyst is highly efficient, easily available, economical, operationally simple, and requires mild reaction conditions. Also the products were formed in excellent yields with short reaction times. This method offers several advantages, such as omitting toxic solvents or catalyst, very simple workups, and needs no chromatographic method for purification of the products. The starting materials are also inexpensive and commercially available.

**Table 2**

The reaction time and the yield of hydroquinazolin product as a function of the amount of the employed catalyst ($Al/Al_2O_3$ NPs).

| Entry | Amount of Catalyst (g) | Temperature (°C) | Reaction Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | 0.000 | 115 | 55 | 75 |
| 2 | 0.006 | 115 | 30 | 81 |
| 3 | 0.012 | 115 | 25 | 82 |
| 4 | 0.024 | 115 | 20 | 84 |
| 5 | 0.036 | 115 | 15 | 94 |
| 6 | 0.048 | 115 | 15 | 95 |

[a] Isolated yield

## EXPERIMENTAL

**General remarks.** Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker DRX-300 spectrometer, at 300 and 75 MHz, using TMS as an internal standard. Chemical shifts (δ) were reported relative to TMS, and coupling constants (*J*) were reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70-eV ionization potential. Elemental analyses of new compounds were performed using a Vario EL III 0 Serial No.11024054 instrument. The particle shape and morphology were characterized by SEM of a Holland Philips XL30 microscope with an accelerating voltage of 20 kV. A Holland

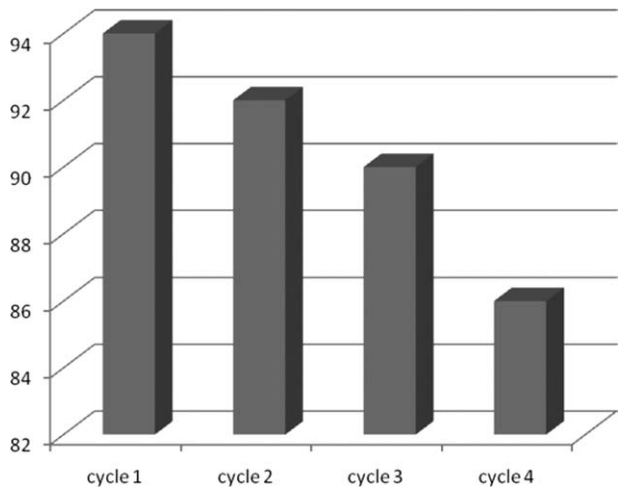
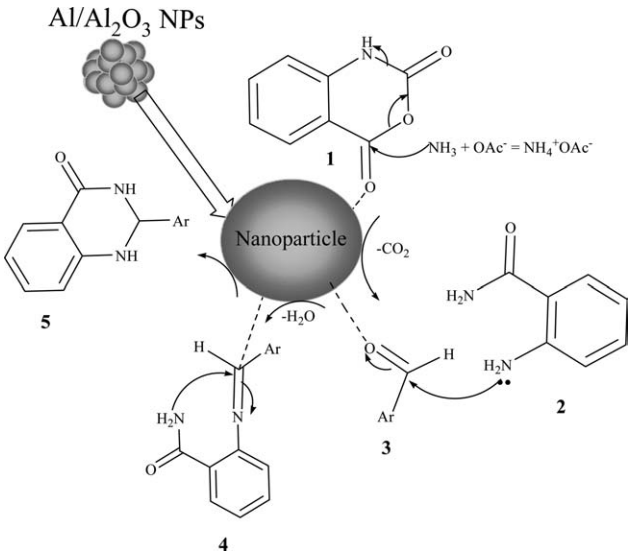



**Figure 3.** Catalytic recyclability of $Al/Al_2O_3$ NPs.

**Scheme 2.** A provisional mechanism for the synthesis of dihydroquinazoline in the presence of $Al/Al_2O_3$ NPs.




Philips X-pert X-ray powder diffraction (XRD) diffractometer was employed for characterization of nanoparticles.

**Fabrication of $Al/Al_2O_3$ NPs.** Nanoparticles used in this work were fabricated through arc discharge. The electrodes were customized by cutting commercial 2 mm diameter rather pure aluminum rods (95.50%) into 40 mm length segments. A current of 100 A was passed through the electrodes in ethylene glycol, until visible explosions occurred (0.01 – 1s). To maintain a stable current discharge, with an average voltage of 25 V, the cathode-anode gap was set at $\sim$ 1 mm with an angle of 85°.

**General procedure for the synthesis of hydroquinazolinone.** Prepared $Al/Al_2O_3$ NPs (0.036 g) was stirred for 2 min with isatoic anhydride (0.163 g, 1 mmol), aromatic aldehyde (1 mmol), and ammonium acetate at room temperature. Then the mixture was heated in a paraffin bath at 115°C for different periods of time (Table 1). After completion of the reaction (monitored by thin-layer chromatography, TLC; *n*-hexane and EtOAc, 2:1), excess ammonium acetate was washed away by water (5 mL). Subsequently the hydroquinazolinone products were crystallized from ethanol.

**Spectral data for some compounds.** ***4-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)benzonitrile (5c).*** This compound was obtained as a white crystalline solid, mp 350 – 351°C (Lit. mp 350 – 351 [19]), IR: 1602, 1677, 2225, 3027, 3124, 3169 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 5.84 (s, 1H, CH), 7.55 (t, $J$ = 6.0 Hz, CH), 7.76 (d, $J$ = 6.0 Hz, 1H, CH), 7.87 (m, 1H, CH), 8.02 (d, $J$ = 6.0 Hz, 2H, CH), 8.16 (d, $J$ = 6.0 Hz, 1H, CH), 8.32 (d, $J$ = 6.0 Hz, 2H, CH), 12.7 (s, 1H, NH); $^{13}C$ NMR (75 MHz, DMSO-*d6*): $\delta$ = 65.5, 113.6, 118.3, 121.2, 125.9, 127.2, 127.7, 128.6, 132.5, 134.7, 136.9, 150.9, 162.1; MS (EI): $m/e$ = 249 ($M^+$), 247, 119, 92, 50.

***2,3-dihydro-2-(3-nitrophenyl)quinazolin-4(1H)-one (5o).*** This compound was obtained as an yellow crystalline solid, mp 180–182°C (Lit. mp 180 – 182 [19]), IR: 1608, 2910, 3050, 3245, 3350 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 6.66 (t, 1H, $J$ = 6.0 Hz, CH), 6.77 (d, 1H, $J$ = 6.0 Hz, CH), 7.26 (d, t, $J_1$ = 1.2 *Hz*, $J_2$ = 9.0 Hz, 1H, CH), 7.33 (s, 1H, NH), 7.59 (d, 1H, $J$ = 9.0 Hz, CH), 7.69 (t, $J$ = 6.0 Hz, 1H, CH), 7.83 (m, 1H, CH), 7.92 (d, 1H, $J$ = 9.0 Hz, CH), 8.19 (d, 1H, $J$ = 6.0 Hz, 8.34 (s, 1H, CH), 8.54 (s, 1H, NH); $^{13}C$ NMR (75MHz, DMSO-*d6*): $\delta$ = 65.1, 114.6, 114.9, 117.5, 121.6, 122.7, 123.3, 125.9, 127.4, 131.3, 133.4, 133.6, 134.7, 144.3, 144.3, 147.3, 147.7, 163.3; MS (EI): $m/e$ = 269 ($M^+$), 221, 147, 120, 92, 65, 39.

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## REFERENCES AND NOTES

[1] Yale, H. L.; Kalkstein, M. J Med Chem 1967, 10, 334.
[2] Neil, G. L.; Li, L. H.; Buskirk, H. H.; Moxlcy, T. E. Cancer Chemother 1972, 56, 163.
[3] Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. J Med Chem 1968, 11, 1136.
[4] Bolger, J. W. (Rexall Drug Co.) US Pat. 3,257,397 (1966); Chem Abstr 1966, 66, 8933b.
[5] Boehringer Sohn, C. H. Fr Pat. M 2588 (1964); Chem Abstr 1964, 61, 16075h.
[6] Alaimo, R. J.; Russel, H. E. J Med Chem 1972, 15, 335.
[7] Cohen, E.; Klarberg, B.; Vaughan, J. R. J Am Chem Soc 1959, 81, 5508.
[8] Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. J Med Chem 1968, 11, 348.
[9] Instituto De Angeli S. P. A, French Patent M 1893, 1964; Chem Abstr 1964, 60, 3956.
[10] Levin, J. I.; Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M. Bioorg Med Chem Lett 1994, 4, 1141.
[11] Abdel-Jalil, R. J.; Volter, W.; Saeed, M. Tetrahedron Lett 2004, 45, 3475.
[12] Liu, J. F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. Tetrahedron Lett 2005, 46, 1241.
[13] Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webster, W. J Org Chem 1969, 34, 887.
[14] Su, W.; Yang, B. Aust J Chem 2002, 55, 695.
[15] Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Hu, H. Tetrahedron Lett 2003, 44, 3199.
[16] Sadanandam, Y. S.; Reddy, K. R. M.; Rao, A. B. Eur J Org Chem 1987, 22, 169.
[17] Reo, V. B.; Ratnam, C. V. Indian J Chem 1979, 18B, 409.
[18] Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. Angew Chem Int Ed Engl 2009, 48, 908.
[19] Rostamizadeh, S.; Amani, A. M.; Aryan, R.; Ghaieni, H. R.; Shadjou, N. Synth Commun 2008, 38, 3567.
[20] Gleiter, H. Nanostruct Mater 1992, 1, 1.
[21] Chen, B. J.; Sun, X. W.; Xu, C. X. Physica E 2004, 21, 103.
[22] Zhang, W. W.; Cao, Q. Q. J Colloid Interface Sci 2003, 257, 237.
[23] Cui, Z. L.; Dong, L. F.; Hao, C. C. Mater Sci Eng A 2000, 286, 205.
[24] Kassaee, M. Z.; Buazar, F. J Manufac Proc 2009, 11, 31.
[25] Birks, L. S.; Friedman, H. J Appl Phys 1946, 16, 687.

# A Novel and Short Synthesis of Naturally Occurring 5-(3′-Indolyl)oxazoles



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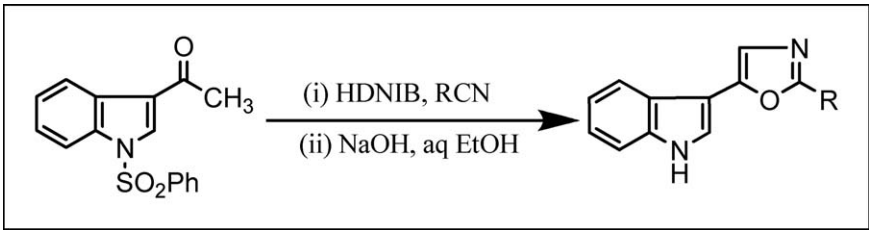


A novel, concise, and convenient synthesis of 5-(3′-indolyl)oxazoles using relatively benign reagent [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benezene has been described. The advantages of this procedure include operational simplicity, good yield, and avoidance of the use of toxic metal.

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## INTRODUCTION

The 5-(3′-indolyl)oxazole is a naturally occurring an important heterocyclic motif of immense medicinal and therapeutic potential. Many 5-(3′-indolyl)oxazoles have been isolated from different microorganisms and are known to display interesting biological activities [1]. The 2,5-disubstituted (3′-indolyl)oxazoles, such as pimprinine (2-methyl-5-(3′-indolyl)oxazole); pimprinethine (2-ethyl-5-(3′-indolyl)oxazole), and pimprinaphine (2-benzyl-5-(3′-indolyl)oxazole) were isolated from *Streptoverficillium oliva reticuli*. The pimprinine is known to inhibit monoamine oxidase and showed antiepileptic effects [1a]. Analogs WS-30581 A and B isolated from *Streptoverticillium waksmanii* are shown to display potent inhibitory effects of platelet aggregation [1b]. Recently isolated, the Labradorin 1 (2-isobutyl-5-(3′-indolyl)oxazole) and Labradorin 2 (2-*n*-pentyl-5-(3′-indolyl)oxazole) from *Pseudomonas syringae pv. coronafaciens* are reported to exhibit very good inhibitory activity against various human cancer cells [1c].

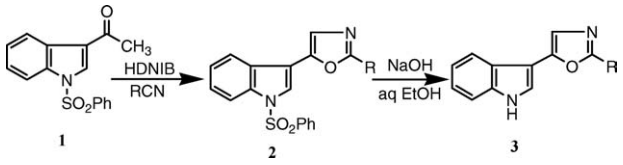
Many procedures are reported for the synthesis of 5-(3′-indolyl)oxazoles, however, straightforward and simple methods are quite limited [2]. Direct synthesis of 5-(3′-indolyl)oxazoles involve rhodium catalyzed reaction of diazoacetylindole with nitriles [2a] and aza-Wittig-type reaction of iminophosphorane derived from 3-azidoacetyl-1-methylindole with isocyanates and acid chlorides [2b]. In general, most of the methods involve multiple synthetic steps, which often require harsh reagents and reaction conditions and afford products in moderate yields. Thus, it is desirable to develop a simple and direct method for the synthesis of 5-(3′-indolyl)oxazoles that can be achieved under milder reaction conditions from readily available starting material.

Hypervalent iodine reagents have found broad utility in organic synthesis due to their low toxicity, ready availability, and ease of handling [3]. The α-[(2,4-dinitrobenzene)sulfonyl]oxyketones are very useful intermediate in organic synthesis, and can be easily prepared from the reaction of enolizable ketone with [hydroxy(2,4-dinitrobenzene-sulfonyloxy)iodo]benzene (PhI(ODNs)OH, HDNIB) [4]. More recently, we have reported a multistep synthesis of 5-(3′-indolyl)oxazoles involving preparation of key intermediate α-aminoketones and cyclization of acylamidoketones using *p*-toluenesulfonic acid [5]. To further improve synthesis of 5-(3′-indolyl)-oxazoles, and to continue our efforts to explore hypervalent iodine reagents in the syntheses of biological important heterocyclic compounds [6], we report herein HDNIB mediated one-pot conversion of 3-acetyl-1-benzenesulfonylindole **1** into naturally occurring 5-(3′-indolyl)oxazoles **3**.

## RESULTS AND DISCUSSION

The reaction of 3-acetyl-1-benzenesulfonylindole **1** with 2-(pyridin-3-yl)acetonitrile in presence of HDNIB at 100°C produced pure 5-(1′-benzenesulfonylindol-3′-yl)-2-(3′-pyridinylmethyl)oxazole (**2a**) in 63% yield (Scheme 1). The benzenesulfonyl moiety of oxazole **2a** was removed by treatment with sodium hydroxide to obtain pure 2-(3′-pyridinylmethyl)-5-(3′-indolyl)oxazole **3a** in quantitative yield. Similarly, analogs 5-(3′-indolyl)oxazoles **2b–h** were obtained and removal of benzenesulfonyl group led to the corresponding 5-(3′-indolyl) oxazoles **3b–h** (Table 1). The spectral data of 5-(3′-indolyl)]oxazoles **3a–h** are in agreement with the proposed structures.

**Scheme 1**




In the reaction of 3-acetyl-1-benzenesulfonylindole **1** with HDNIB in 2-(pyridin-3-yl)acetonitrile, two additional spots on TLC were initially observed, probably corresponding to the 3-α-(2,4-dinitrobenzenesulfonyloxy)-acetylindole and **2a**, which upon further heating converted exclusively to a single spot, that is, **2a**. The 3-acetyl-1-benzenesulfonylindole **1** reacted equally well with benzonitrile, alkylnitriles, and heteroaryl nitriles to afford corresponding oxazoles **2**. Attempts to isolate probable intermediate 3-α-(2,4-dinitrobenzenesulfonyloxy)acetyl indole could not be successful because of its instability. It is, however, to be noted that the reaction of 3-acetylindole with HDNIB in acetonitrile generated a complex mixture.

It is proposed that initial nucleophilic addition of enol **I** on HDNIB forms species **II**, which subsequently loses iodobenzene and water to afford intermediate 3-[α-(2,4-dinitrobenzenesulfonyloxy)]acetyl indole **III** (Scheme 2). The nucleophilic displacement of ODNs in **III** by nitrile, results in the formation of species **IV**, which finally cyclizes to oxazole **2**. Apparently, ODNs being a better leaving group may be responsible for the efficient cyclization, but reaction fails to proceed with the intermediacy of 3-[α-(tosyloxy)]acetylindole obtained from the reaction of 3-acetyl-1-benzenesulfony-lindole **1** with [hydroxy(tosyloxy)iodo]benzene.

## CONCLUSIONS

We have introduced a novel, short, and efficient protocol for the preparation of naturally occurring 5-(3′-indolyl)-oxazoles from readily available 3-acetylindole **1** using metal free [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benezene. This protocol should be complementary to other approaches in the synthesis of 5-(3′-indolyl)oxazoles described.

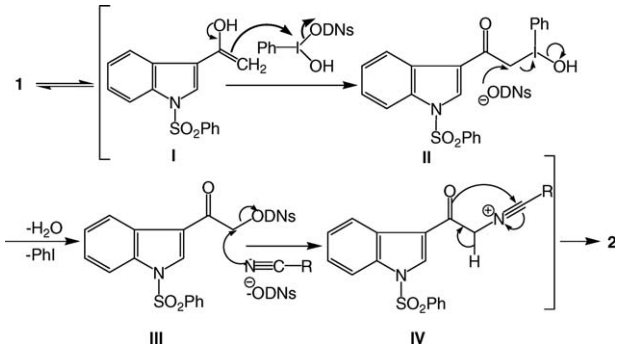
**Table 1**

Synthesis of 5-(3′-indolyl)oxazoles **2** and **3**.

| Entry | R | Yield (%)[a] (**2a–h**) | Overall Yield (%)[b] (**3a–h**) |
|---|---|---|---|
| **a** | 3-Pyridinylmethyl | 63 | 60 |
| **b** | $C_6H_5$ | 65 | 61 |
| **c** | $CH_3$ | 66 | 60 |
| **d** | $CH_3CH_2CH_2$ | 65 | 60 |
| **e** | $(CH_3)_2CHCH_2$ | 65 | 59 |
| **f** | $C_6H_5CH_2$ | 71 | 65 |
| **g** | $CH_3CH_2CH_2CH_2$ | 70 | 66 |
| **h** | 3-Pyridinyl | 65 | 61 |

[a] Isolated yields.
[b] Combined isolated yields of both the steps.

**Scheme 2**




## EXPERIMENTAL

Melting points were recorded on EZ-Melt automated melting point apparatus (Stanford Research Systems, USA) and are uncorrected. IR spectra were recorded on Jasco IR-Report-100 using KBr pellet. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance II (400 MHz) and Bruker (200 MHz) spectrophotometer using $CDCl_3$ and DMSO as solvent. Mass spectra were taken on a Agilent Mass spectrometer using FAB mode. All the reagents and solvents were commercially purchased and further purified according to the standard procedures.

**General procedure for the preparation of 2-substituted-5-(1′-benzenesulfonylindol-3′-yl)oxazoles (2a–h).** A mixture of 3-acetyl-1-benzenesulfonylindole **1** [7] (0.150 g, 0.501 mmol), HDNIB (0.281 g, 0.602 mmol) and appropriate nitrile (2.51 mmol) were heated at 100°C for 18 h. After completion of the reaction, the crude reaction mixture was percolated through a silica-gel column using ethyl acetate-hexane elution system.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-(3′-pyridinylmethyl)oxazole (2a)*** m.p. 185°C; $^1$H NMR (200 MHz, $CDCl_3$): δ = 4.40 (s, 2H, $CH_2$), 7.25–7.55 (m, 10H, Ar-H), 7.90–8.04 (m, 5H, Ar-H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 39.73, 113.63, 113.67, 118.06, 121.09, 123.78, 124.43, 125.02, 126.84, 127.20, 128.40, 128.80, 129.09, 129.28, 133.89, 135.37, 137.67, 137.99, 148.09, 170.43; HRMS for $C_{23}H_{17}N_{3a}O_3S$, calcd. $(M)^+$: 415.0991; found: 415.1201 $(M)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-phenyloxazole (2b).*** m.p. 153–156°C (Lit. [5] m.p. 156°C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.59 (m, 9H, Ar-H), 7.83 (dd, 1H, *J* = 1.2, 8.0 Hz, Ar-H), 7.95–7.97 (m, 2H, Ar-H), 7.99 (s, 1H, Ar-H), 8.06 (dd, 1H, *J* = 1.2, 7.6 Hz, Ar-H), 8.13–8.15 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 103.86, 111.63, 119.20, 119.94, 120.20, 121.87, 122.35, 123.47, 123.52, 125.26, 127.15, 128.24, 129.26, 129.73, 133.90, 134.63, 136.27, 145.00, 158.42; MS(EI) for $C_{23}H_{16}N_2O_3S$, calcd. $(M + H)^+$: 401.0; found: 401.0 $(M + H)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-methyloxazole (2c).*** m.p. 145°C (Lit. [5] m.p. 143°C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H, $CH_3$), 7.18 (s, 1H, Ar-H), 7.26–7.49 (m, 5H, Ar-H), 7.50 (m, 2H, Ar-H), 7.54 (s, 1H, Ar-H), 7.75–7.82 (m, 2H, Ar-H); MS(EI) for $C_{18}H_{14}N_2O_3S$, calcd. $(M + H)^+$: 339.1; found: 339.1 $(M + H)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-propyloxazole (2d).*** m.p. 135°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.05 (t, 3H, *J* = 6.9 Hz, $CH_3$), 1.88 (m, 2H, $CH_2$), 2.82 (t, 2H, *J* = 7.1 Hz, $CH_2$), 7.14 (s, 1H, Ar-H), 7.48–7.53 (5H, m, Ar-H), 7.61 (s, 1H, Ar-H), 7. 69 (m, 2H, Ar-H), 7.83 (m, 2H, Ar-H); HRMS for $C_{20}H_{18}N_2O_3S$, calcd. $(M + H)^+$: 367.1116; found: 367.1162 $(M + H)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-(i-butyl)oxazole (2e).*** m.p. 182–184°C (Lit. [5] m.p. 185°C); $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.13 (d, 6H, *J* = 6.6 Hz, $2CH_3$), 2.26 (m, 1H, CH), 2.70 (d, 2H, *J* = 7.6 Hz, $CH_2$), 7.17 (s, 1H, Ar-H), 7.26–7.39 (m, 5H, Ar-H), 7.52 (s, 1H, Ar-H), 7.83 (dd, 2H, *J* = 1.2, 8.0 Hz, Ar-H), 7.95–7.97 (dd, 2H, *J* = 1.2, 7.6 Hz, Ar-H); MS(EI) for $C_{21}H_{20}N_2O_3S$, calcd. $(M + H)^+$: 381.1, found: 381.0 $(M + H)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-benzyloxazole (2f).*** m.p. 140°C (Lit. [5] mp 138–142°C); $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 3.28 (s, 2H, $CH_2$), 7.16 (s, 1H, Ar-H), 7.26–7.59 (m, 10H, Ar-H), 7.58 (s, 1H, Ar-H), 7.83 (dd, 2H, *J* = 1.2, 8.0 Hz, Ar-H), 8.06 (dd, 2H, *J* = 1.2, 7.6 Hz, Ar-H); MS(EI) for $C_{24}H_{18}N_2O_3S$, calcd. $(M + H)^+$: 415.1, found: 415.2 $(M + H)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-butyloxazole (2g).*** m.p. 148°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 0.96 (t, 3H, *J* = 6.8 Hz, $CH_3$), 1.43 (m, 2H, $CH_2$), 1.77 (m, 2H, $CH_2$), 2.83 (t, 2H, *J* = 6.7 Hz), 7.15 (s, 1H, Ar-H), 7.24–7.29 (m, 5H, Ar-H), 7.55–7.82 (5H, m, Ar-H); HRMS for $C_{21}H_{20}N_2O_3S$, calcd. $(M + H)^+$: 381.1273; found: 381.1285 $(M + H)^+$.

***5-(1′-Benzenesulfonylindol-3′-yl)-2-(pyridin-3″-yl)oxazole (2h).*** m.p. 194°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.24 (s, 1H, Ar-H), 7.32–7.36 (m, 5H, Ar-H), 7.45 (d, 1H, *J* = 7.56 Hz, Ar-H), 7.51 (dd, 2H, *J* = 1.7, 8.0 Hz, Ar-H), 7.55–7.59 (m, 4H, Ar-H), 7.76 (dd, 2H, *J* = 1.8, 7.6 Hz, Ar-H); HRMS for $C_{22}H_{15}N_3O_3S$, calcd. $(M)^+$: 401.0834; found: 401.1001 $(M)^+$.

**General procedure for the preparation of 2-substituted-5-(3′-indolyl)oxazoles 3.** A stirred solution of oxazole **2** (0.19 mmol) and sodium hydroxide (0.02 g, 0.50 mmol) in aqueous ethanol (6 mL) was refluxed for 2 h. After removal of ethanol under vacuum, the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum.

***2-(3′-Pyridinylmethyl)-5-(3′-indolyl)oxazole (3a).*** Yield 95%; m.p. 195–198°C; $^1$H NMR (200 MHz, $CDCl_3$): δ = 4.39 (s, 2H, $CH_2$), 7.15–7.40 (m, 7H, Ar-H), 7.69 (s, 1H, Ar-H), 8.00 (s, 1H, Ar-H), 8.61 (s, 1H, Ar-H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 39.68, 110.28, 111.49, 112.51, 119.95, 120.48, 122.40, 123,79, 125.04, 127.08, 128.72, 129.11, 136.49, 137.92, 150.41, 169.82; HRMS for $C_{17}H_{13}N_3O$, calcd. $(M)^+$: 275.1059; found: 275.1123 $(M)^+$.

***2-(Phenyl)-5-(3′-indolyl)oxazole (3b).*** Yield 81%; m.p. 213–216°C (Lit. [5] m.p. 216°C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.26 (m, 2H, Ar-H), 7.42–7.52 (m, 4 H, Ar-H), 7.58 (s, 1H, Ar-H), 7.67 (d, 1H, *J* = 2.8 Hz, Ar-H), 7.87–7.89 (m, 1H, Ar-H), 8.09–8.11 (m, 2H, Ar-H), 11.03 (s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 103.86, 111.63, 119.00, 119.91, 120.16. 121.87, 122.43, 123.47, 125.26, 127.15, 128.27, 129.26, 136.15, 147.97, 158.38; MS(EI) for $C_{17}H_{12}N_2O$, calcd. $(M + H)^+$: 261.1; found: 261.1 $(M + H)^+$.

***2-(Methyl)-5-(3′-indolyl)oxazole (3c).*** Yield 83%; m.p. 201°C (Lit. [8] mp 204–205°C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H, $CH_3$), 7.10 (s, 1H, Ar-H), 7.17–7.25 (m, 2H, Ar-H), 7.44 (d, 1H, *J* = 7.60 Hz, Ar-H), 7.50 (d, 1H, *J* = 2.56 Hz, Ar-H), 7.80 (d, 1H, *J* = 7.64 Hz, Ar-H), 10.12 (s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.39, 104.53, 111.27, 118.89, 119.07, 119.76, 121.50, 121.86, 123.47, 135.95, 147.18, 158.34; MS(EI) for $C_{12}H_{10}N_2O$, calcd. $(M + H)^+$: 199.1; found: 199.1 $(M + H)^+$.

***2-(Propyl)-5-(3′-indolyl)oxazole (3d).*** Yield 81%; m.p. 124°C (Lit. [1b] m.p. 128–130°C); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ = 1.05 (t, 3H, *J* = 6.9 Hz, $CH_3$), 1.88 (m, 2H, $CH_2$), 2.82 (t, 2H, *J* = 7.1 Hz, $CH_2$), 7.12–7.53 (5H, m, Ar-H), 7.83 (m, 1H, Ar-H), 9.58 (s, 1H, NH); HRMS for $C_{20}H_{18}N_2O_3S$, calcd. $(M + H)^+$: 367.1116; found: 367.1162 $(M + H)^+$.

***2-(Isobutyl)-5-(3′-indolyl)oxazole(3e).*** Yield 74%; m.p. 143°C (Lit. [1c] m.p. 147–148°C); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ = 1.06 (d, 6H, *J* = 6.6 Hz, $2CH_3$), 2.27 (m, 1H, CH), 2.76 (d, 2H, *J* = 7.8 Hz, $CH_2$), 7.20 (s, 1H, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.44 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 1H, *J* = 2.93 Hz, Ar-H), 7.87 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.30 (s, 1H, NH); MS(EI) for $C_{15}H_{16}N_2O$, calcd. $(M + H)^+$: 241.1, found: 241.3 $(M + H)^+$.

***2-(Benzyl)-5-(3′-indolyl)oxazole (3f).*** Yield 79%; m.p. 174°C (Lit. [5] m.p. 172°C); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ = 3.24 (s, 2H, $CH_2$), 7.19 (s, 1H, Ar-H), 7.22–7.25 (m, 5H, Ar-H), 7.56 (d, 1H, *J* = 2.53 Hz, Ar-H), 7.79 (dd, 2H, *J* = 1.2, 8.0 Hz, Ar-H), 7.93 (dd, 2H, *J* = 1.2, 7.6 Hz, Ar-H), 9.82 (s, 1H, NH); MS(EI) for $C_{18}H_{14}N_2O$, calcd. $(M + H)^+$: 275.1, found: 275.0 $(M + H)^+$.

***2-(Butyl)-5-(3′-indolyl)oxazole (3g).*** Yield 84%; m.p. 119°C (Lit. [1b] m.p. 123–125°C); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ = 1.01 (t, 3H, *J* = 7.0 Hz, $CH_3$); 1.45 (m, 2H, $CH_2$), 1.80 (m, 2H, $CH_2$), 2.84 (t, 2H, *J* = 6.8 Hz), 7.15 (s, 1H, Ar-H), 7.53 (d, 1H, *J* = 2.52 Hz, Ar-H), 7.62–7.92 (4H, m, Ar-H), 9.10 (s, 1H, NH); HRMS for $C_{21}H_{20}N_2O_3S$, calcd. $(M + H)^+$: 381.1273; found: 381.1285 $(M + H)^+$.

***2-(Pyridin-3″-yl)-5-(3′-indolyl)oxazole (3h).*** Yield 79%, m.p. 142–144°C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ = 7.22 (s, 1H, Ar-H), 7.47 (d, 1H, *J* = 7.60 Hz, Ar-H), 7.53 (dd, 2H, *J* = 1.7, 8.0 Hz, Ar-H), 7.57–7.62 (m, 4H, Ar-H), 7.78 (dd, 2H, *J* = 1.8, 7.8 Hz, Ar-H), 9.58 (s, 1H, NH); HRMS for $C_{16}H_{11}N_3O$, calcd. $(M)^+$: 261.0902; found: 261.1102 $(M)^+$.

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## REFERENCES AND NOTES

[1] (a) Naik, S. R.; Harindran, J.; Varde, A. B. J Biotechnol 2001, 88, 1; (b) Umehara K.; Yoshida, K.; Okamoto, M.; Iwami, M.; Tanaka, H.; Kohsaka, M.; Imanaka, H. J Antibiot 1984, 37, 1153; (c) Pettit, G. R.; Knight, J. C.; Herald, D. L.; Davenport, R.; Pettit, R. K.; Tucker, B. E.; Schmidt, J. M. J Nat Prod 2002, 65, 1793; (d)

Takahashi, S.; Matsunaga, T.; Hasegawa, C.; Saito, H.; Fujita, D.; Kiuchi, F.; Tsuda, Y. Chem Pharm Bull 1998, 46, 1527.

[2] (a) Doyle, K. J.; Moody, C. J. Synthesis 1994, 1021; (b) Molina, P.; Fresneda, P. M.; Almendros, P. Synthesis 1993, 54.

[3] (a) Wirth, T., Ed. Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis; Topics in Current Chemistry Series 224; Springer: Berlin, 2003; (b) Zhdankin, V. V.; Stang, P. J. Chem Rev 2002, 102, 2523; (c) Wirth, T. Angew Chem Int Ed 2005, 44, 3656.

[4] (a) Lee, J. C.; Choi, J. H.; Lee, Y. C. Synlett 2001, 1563; (b) Lee, J. C.; Lee, Y. C. Bull Korean Chem Soc 2003, 24, 893.

[5] Kumar, D.; Sundaree, S.; Patel, G.; Rao, V. S. Tetrahedron Lett 2008, 49, 867.

[6] Nadipuram, A. K.; David, W. M.; Kumar, D.; Kerwin, S. M. Org Lett 2002, 4, 4543.

[7] Liu, S.-F.; Wu, Q.; Schmider, H. L.; Aziz, H.; Hu, N.-X.; Popovic, Z; Wang, S. J Am Chem Soc 2000, 122, 3671.

[8] Roy, S.; Haque, S.; Gribble, G. W. Synthesis 2006, 3948.

# A Novel, Facile, Simple and Convenient Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines to Pyridines Using Polymeric Iodosobenzene with KBr



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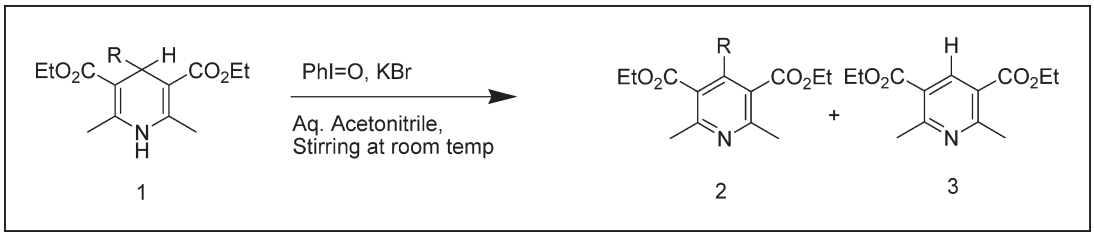


An easy, safe, effective and handy method for oxidative aromatization of Hantzsch 1,4-dihydropyridines catalyzed by hypervalent iodine (iodosobenzene) and potassium bromide to corresponding pyridine derivatives in high-yields and within short span of time was described. Dealkylation in case of 4-n-alkyl substituted 1,4-dihydropyridines was not obtained.

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## INTRODUCTION

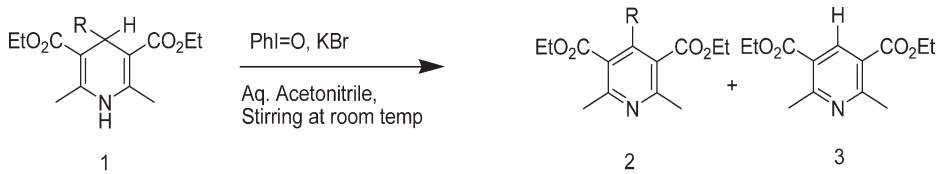
Hantzsch 1,4-dihydropyridines, six member nitrogen, containing heterocyclic compound, are often regarded as the class of the naturally reduced nicotinamine adenine dinucleotide [NADH] coenzyme that functions as redox reagent for biological reactions. 1,4-Dihydropyridines motif is found in a number of chemotherapeutic agents for the treatment of the cardiovascular disease [1,2] such as hypertension and angina pectoris, for example, amlodipine, felodipine, nifedipine, nicardipine, nimodipine, and nitrendipine. These compounds generally undergo oxidative metabolism in the liver by the action of cytochrome P450 to form the corresponding pyridine derivatives. Some representatives of this class show certain pharmacological activities such as acaricidal, insecticidal, bactericidal, and herbicidal activities [3]. Because of the relevance of this oxidative event to the biological NADH redox process [4–6], this transformation has attracted the attention of several research groups.

A variety of reagents have been utilized for this oxidative conversion: nitric acid [7], nitric oxide [8], urea nitrate [9], peroxodisulfate-Co(II) [9], clay-supported ferric and cupric nitrate[10], $BrCCl_3/h\nu$ [11], *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide [12], DDQ [13], $Zr(NO_3)_4$ [14], $Mn(OAc)_3$ [15], Pd/C [16], $I_2$/MeOH [17], manganese dioxide–bentonite clay [18], chromium trioxide [19], potassium permanganate [20], pyridinium chlorochromate [21], ceric ammonium nitrate (CAN) [22], clayfen [23], bismuth trinitrate [24], ruthenium trichloride [25], $Fe(ClO_4)_3$/HOAc [26], tert-butylhydroperoxide [27], silica gel supported ferric nitrate (silfen) [28], $MnO_2$ [29], and vanadium salts [30].

Despite a plethora of methods for this protocol, extended reaction times, poor yields and use of strong or toxic oxidant has led to the investigation of many alternative procedures. Therefore, development and introduction of convenient, milder, and efficient method for the oxidation of 1,4-dihydropyridines to the corresponding pyridines is of practical importance and is still in demand.

Iodosobenzene (PhIO) has wide synthetic application as a starting material in the preparation of numerous iodine (III) compounds and in oxidation reactions [31]. Because of poor solubility of polymerized iodosobenzene [(PhIO)n] in organic solvent, its oxidizing property is not much examined as compared with the other hypervalent organoiodanes. Activation is required to carryout the oxidation reaction with iodosobenzene. Literature review shows that the aromatization of Hantzsch 1,4-dihydropyridines by using hypervalent iodine (IBX, HTIB, PIFA, and IBD) has been reported earlier [32]. To my knowledge oxidative aromatization of 1,4-DHPs with iodosobenzene has not been reported in the literature. Although reported hypervalent iodine based aromatization of Hantzsch 1,4-dihydropyridines are efficient, but these methods suffer from relatively acidic by products [32], long reaction time[32(d)] and high-temperature [32(e)]. Therefore, the biological importance of 1,4-dihydropyridines oxidation and my ongoing attention to

**Scheme 1**




1 2 3

1. R= (a)H; (b) $CH_3$; (c)$C_2H_5$; (d) $(CH_3)_2CH$; (e)$C_6H_{13}$; (f)$C_6H_5CH_2$; (g)4-$NO_2C_6H_4$; (h) 3-$NO_2C_6H_4$; (i) 2-$NO_2C_6H_4$; (j) 4-$MeOC_6H_4$; (k) 3,4$(OCH_3)_2C_6H_3$; (l) 4-$CH_3C_6H_4$; (m) $C_6H_5$; (n)4-$ClC_6H_4$; (o)2,4-$Cl_2C_6H_3$; (p) 3-$BrC_6H_4$; (q)$C_6H_5CH$=CH; (r) 2-Furyl; (s) 3-Pyridyl

2. R= (a) $CH_3$; (b)$C_2H_5$; (c)$C_6H_{13}$; (d)4-$NO_2C_6H_4$; (e) 3-$NO_2C_6H_4$; (f) 2-$NO_2C_6H_4$; (g) 4-$MeOC_6H_4$; (h) 3,4$(OCH_3)_2C_6H_3$; (i) 4-$CH_3C_6H_4$; (j) $C_6H_5$; (k)4-$ClC_6H_4$; (l)2,4-$Cl_2C_6H_3$; (m) 3-$BrC_6H_4$; (n)$C_6H_5CH$=CH; (o) 2-Furyl; (p) 3-Pyridyl

the development of new methodology [32(b)], prompted me to investigate the aromatization of 1,4-DHPs by iodosobenzene with KBr in aqueous acetonitrile.

## RESULTS AND DISCUSSION

A long series of 1,4-DHP derivatives were synthesized to study their catalytic conversion to the analogous pyridines. I used iodosobenzene with KBr as catalyst to have an effect on these organic transformations. Iodosobenzene with KBr serves as an excellent oxidative catalyst for a variety of 4-substituted Hantzsch 1,4-DHPs system as shown in the generalized Scheme 1 and results are reported in Table 1. In a preliminary experiment, oxidative aromatization 4-phenyl substituted 1,4-DHP was carried out using iodosobenzene in aqueous acetonitrile at room temperature. It gave none or insignificant amount of the corresponding pyridine. However, when KBr is added in the reaction mixture, there is recognizable change in the yield of the oxidized product. The reaction is fast and gives quantitative yield. Reaction was smooth, clean, and occurred at room temperature with short span of time (less than 5 min). Therefore, I investigated the activation of PhI=O in this reaction with a variety of alkali metal salts. As a result, the addition of bromide ions such as LiBr, NaBr, and KBr was found to amazingly activate PhI=O to give **2e** in good yields [95% yield with KBr, 75% yield with NaBr and 62% with LiBr], whereas salts excluding bromide (LiCl, NaCl, KCl, NaF, NaOAc, NaI and KI) did not catalyze the reaction effectively. Therefore, the most economical alkali metal bromide, that is, KBr was chosen for further studies. The oxidation proceeds smoothly

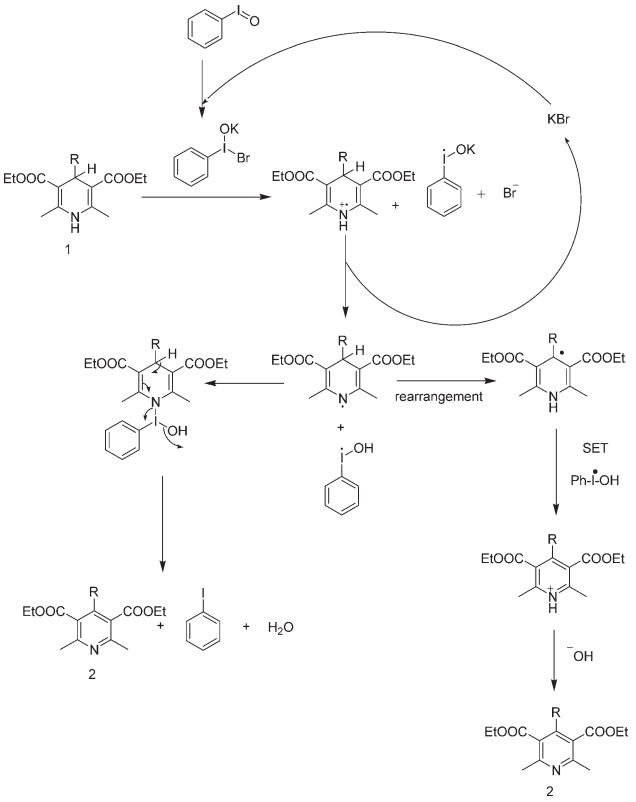
**Table 1**

Solvent-less synthesis of pyridines by oxidative aromatization or oxidative dealkylation of 1,4-DHP derivatives.

| Entry | Substrate R | Product | Reaction Time[a] t (min) | Yield[b] (%) | *M*p[c] (°C) | *M*p reported (°C) |
|---|---|---|---|---|---|---|
| 1 | H | 3 | 3 | 94 | 70 – 71 | 72-73 |
| 2 | $CH_3$ | 2a | 3 | 95 | oil | oil |
| 3 | $C_2H_5$ | 2b | 3 | 95 | oil | oil |
| 4 | $(CH_3)_2CH$ | 3 | 3 | 94 | 70 – 71[d] | 72 – 73 |
| 5 | $C_6H_{13}$ | 2c | 5 | 93 | oil | oil |
| 6 | $C_6H_5CH_2$ | 3 | 4 | 95 | 70 – 71[d] | 72 – 73 |
| 7 | 4-$NO_2C_6H_4$ | 2d | 5 | 94 | 112 – 113 | 115 – 116 |
| 8 | 3-$NO_2C_6H_4$ | 2e | 5 | 93 | 61 – 62 | 61.5 – 62.5 |
| 9 | 2-$NO_2C_6H_4$ | 2f | 5 | 95 | 73 – 75 | 73 – 75 |
| 10 | 4-$MeOC_6H_4$ | 2g | 4 | 94 | 51 – 52 | 49.5 – 50.5 |
| 11 | 3,4$(OCH_3)_2C_6H_3$ | 2h | 4 | 91 | 100 – 101 | 100 – 101 |
| 12 | 4-$CH_3C_6H_4$ | 2i | 4 | 94 | 71 – 72 | 71 – 72 |
| 13 | $C_6H_5$ | 2j | 4 | 95 | 62 – 63 | 62 – 63 |
| 14 | 4-$ClC_6H_4$ | 2k | 4 | 95 | 69 – 71 | 66 – 68 |
| 15 | 2,4-$Cl_2C_6H_3$ | 2l | 5 | 95 | 112 – 113 | 77.5 – 79.5 |
| 16 | 3-$BrC_6H_4$ | 2m | 5 | 95 | 70 – 72 | 70 – 72 |
| 17 | $C_6H_5CH$=CH | 2n | 5 | 93 | 161 – 162 | 161 – 162 |
| 18 | 2-Furyl | 2o | 5 | 92 | oil | oil |
| 19 | 3-Pyridyl | 2p | 5 | 92 | 84 – 86 | 84 – 86 |

[a] t: time for stirring.
[b] Yields are isolated.
[c] Melting points are uncorrected and compared with literature reports [32].
[d] Amount of KBr used in reaction is equivalent to iodosobenzene.

**Scheme 2.** Proposed mechanism for aromatization of 1,4-DHPs.




with 1,4-dihydropyridine substrates bearing substituents at the 4-position such as hydrogen, methyl, n-alkyl, aryl, and heterocyclic groups. However, in the case of oxidation of the 1,4-DHP with isopropyl and benzyl group at 4-poition underwent simultaneous dealkylation to give **3** as a sole product (Table 1). This may be because of either their electron donating ability of the corresponding radicals and these substituents are debarred with the formation of dealkylated products [15] or because of the stability of radical cation formed during the reaction via single electron mechanism [32(a)] (Scheme 2). The influence of various solvents on the yield of reaction was investigated using ethyl acetate, dichloromethane, chloroform, and aqueous acetonitrile. The reaction takes place smoothly in the aqueous acetonitrile may be because of solubility of iodosobenzene and KBr.

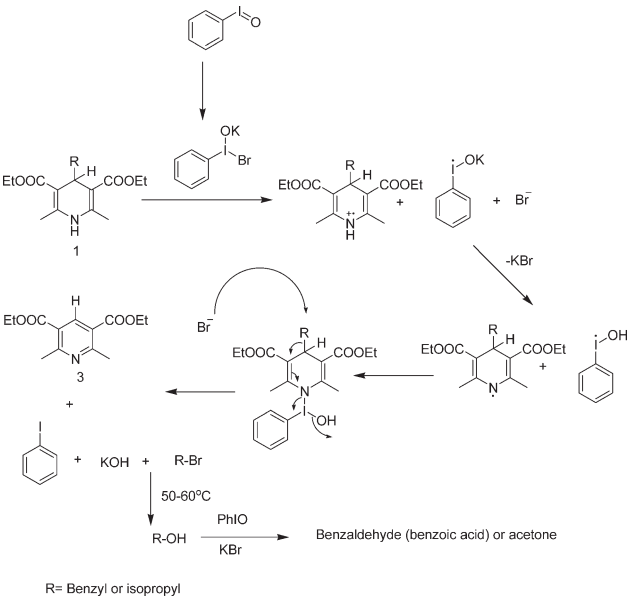
After that catalytic effect of KBr was investigated, and it was found that only 0.1 mmol of KBr is sufficient for 1.1 mmol of iodosobenzene (Scheme 3). However, in case of the 1,4-DHP with isopropyl and benzyl group at 4-poition oxidation depend upon the amount of KBr also as shown in Scheme 3. This is because of formation of isopropyl or benzyl bromide, and it is confirmed by GC. However, reaction mixture was found basic in nature and turn red litmus to blue when the reaction was carried out at 0°C. It is also observed that, when the temperature is raised to 60°C the reaction proceeds smoothly with catalytically amount of KBr (0.1 mmol). However, at elevated temperature, time required for these organic transformations is very short, but the amount of iodosobenzene required for this conversion is doubled. This is because of hydrolysis of benzyl bromide or isopropyl bromide with water to benzyl alcohol or isopropyl alcohol, which is oxidized to corresponding carbonyl derivatives.

In summary author have described a general and practical route for the oxidation of 1,4-dihydropyridines in excellent yields using catalytic amount KBr with iodosobenzene in aqueous acetonitrile. Aromatization is clean with this reagent, and the products are obtained in high-yield within short span of time. Novelty of this protocol is the reagents used in reaction are recovered as iodobenzene and KBr, which can be reused. Another salient feature of this method is that any acidic byproducts are not produced during reactions, which are toxic to the environment.

## EXPERIMENTAL

All chemicals used in this study were of the highest purity available and purchased from Lancaster, Merck, and Fluka companies (India). Melting points were determined on a buchi oil heated melting apparatus and are uncorrected. $^1$H NMR spectra were recorded in $CDCl_3$ on Brucker-300 Hz spectrometer using TMS as internal standard (chemical shift in δ, ppm). IR spectra were taken on a Perkin Elmer 1600, FTIR spectrophotometer using KBr pellets and peaks are reported in $cm^{-1}$. All the starting 1, 4-DHPs were prepared according to the literature procedure [33].

**Scheme 3.** Proposed mechanism for debenzylation or dealkylation.



**General procedure for oxidative aromatization of 1,4-dihydropyridines with iodosobenzene and KBr.** In a typical experimental procedure, the iodosobenzene (1.1 mmol) and KBr (0.1 mmol) were added to aqueous acetonitrile (15%, 20 mL), and mixture was stirred at room temperature for 5 min. To this reaction mixture an appropriate 1,4-dihydropyridine (1.0 mmol) was added and stirred at room temperature for time as indicated in Table 1. The progress of reaction was monitored by TLC. After completion of the reaction and the solvent was removed under vacuum to obtain the crude product, which was purified by column chromatography (ethyl acetate-hexane = 1:5).

**General procedure for oxidative aromatization of 4-isopropyl/4-benzyl-1,4-dihydropyridines.** The iodosobenzene (1.1 mmol) and KBr (1.1 mmol) were added to aqueous acetonitrile (15%, 20 mL), and mixture was stirred at room temperature for 5 min. Then 4-isopropyl/4-benzyl-1,4-dihydropyridines (1.0 mmol) was added and reaction mixture was stirred at room temperature for time indicated in Table 1. The progress of reaction was monitored by TLC. After completion of the reaction, added acetic acid (1 mL) and the solvent was removed under vacuum to obtain the crude product, which was purified by column chromatography (ethyl acetate-hexane = 1:7).

All compounds were fully characterized by mp, IR, and $^1$H NMR. These data are in full agreement with those previously reported in literature [32].

***Diethyl 2,6-dimethyl-4-methylpyridine-3,5-dicarboxylate (2a).*** IR (KBr): 2981, 2870, 1726, 1568, 1446, 1285, 1220, 1106, 1045, 871, 777 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 1.23 (t, $J$ = 7.10 Hz, 6H, $CH_3$), 2.19 (s, 3H, $CH_3$), 2.51 (s, 6H, $CH_3$), 4.25 (q, $J$ = 7.10 Hz, 4H, $OCH_2$). Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.23; H, 7.32; N, 5.01.

***Diethyl 2,6-dimethyl-4-ethylpyridine-3,5-dicarboxylate (2b).*** IR (KBr): 2992, 2879, 1731, 1576, 1438, 1286, 1112, 1045, 923, 847, 751 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 1.08 (t, $J$ = 7.5 Hz, 3H, $CH_3$), 1.25 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.49 (s, 6H, $CH_3$), 2.78(q, $J$ = 7.5 Hz, 2H, $CH_2$), 4.25 (q, $J$ = 7.11 Hz, 4H, $OCH_2$). Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.78; H, 7.78; N, 4.94.

***Diethyl 2,6-dimethyl-4-n-hexylpyridine-3,5-dicarboxylate (2c).*** IR (KBr): 2976, 2865, 1737, 1576, 1428, 1286, 1117, 1033, 926, 842, 755 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 1.06 (t, $J$ = 6.9 Hz, 3H, $CH_3$), 1.26 (t, $J$ = 7.10 Hz, 6H, $CH_3$), 1.33 – 1.43 (m, 8H), 2.49 (s, 6H, $CH_3$), 2.54 (t, $J$ = 6.9Hz, 2H, $CH_2$), 4.25 (q, $J$ = 7.11 Hz, 4H, $OCH_2$). Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.98; H, 8.78; N, 4.27.

***Diethyl-4-(4-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2d).*** IR (KBr): 3012, 2977, 1723, 1557, 1518, 1349, 1116, 865, 843, 745 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.20 (t, $J$ = 7.10 Hz, 6H, $CH_3$), 2.69 (s, 6H, $CH_3$), 4.27 (q, $J$ = 7.10 Hz, 4H, $OCH_2$), 7.41(d, $J$ = 8.2 Hz, 2H), 8.22 (d, $J$ = 8.2 Hz, 2H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.31; H, 5.36; N, 7.50.

***Diethyl-4-(3-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2e).*** IR (KBr): 3015, 2980, 1716, 1590, 1555, 1520, 1358, 1280, 1183, 870, 785, 715 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.21 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.70 (s, 6H, $CH_3$), 4.25 (q, $J$ = 7.11 Hz, 4H, $OCH_2$), 7.58 – 8.28 (m, 4H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.15; H, 5.49; N, 7.33.

***Diethyl-4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2f).*** IR (KBr): 3005, 2983, 1725, 1605, 1548, 1512, 1358, 1278, 1191, 762, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.19 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.70 (s, 6H, $CH_3$), 4.28 (q, $J$ = 7.11 Hz, 4H, $OCH_2$), 7.48 – 8.25 (m, 4H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.08; H, 5.22; N, 7.63.

***Diethyl-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2g).*** IR (KBr): 3030, 2973, 1729, 1614, 1557, 1291, 1107, 857, 835, 779 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.20 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 4.25 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 2.66 (s, 6H, $CH_3$), 3.82 (s, 3H, $OCH_3$), 6.89 (d, $J$ = 8.6 Hz, 2H), 7.10 (d, $J$ = 8.6 Hz, 2H). Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.05; H, 6.40; N, 3.88.

***Diethyl-4-(4-methylphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2i).*** IR (KBr): 3013, 2983, 1727, 1571, 1446, 1239, 1033, 821, 856, 775 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.23 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 2.37 (s, 3H, $CH_3$), 2.64 (s, 6H, $CH_3$), 4.29 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 7.11(d, $J$ = 6.8 Hz, 2H), 7.21 (d, $J$ = 6.8 Hz, 2H). Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.23; H, 6.56; N, 4.33.

***Diethyl-4-phenyl-2,6-dimethylpyridine-3,5-dicarboxylate (2j).*** IR (KBr): 3014, 2986, 1723, 1591, 1498, 1302, 1250, 1170, 791, 760 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.23 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 4.26 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 2.65 (s, 6H, $CH_3$), 7.18(m, 2H), 7.30 (m, 3H). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.83; H, 6.38; N, 4.32.

***Diethyl-4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2k).*** IR (KBr): 3025, 2984, 1729, 1580, 1231, 1104, 1044, 858, 658 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.24 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 4.27 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 2.69 (s, 6H, $CH_3$), 7.13(d, $J$ = 9.01 Hz, 2H), 7.32 (d, $J$ = 9.01 Hz, 2H). Anal. Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 62.97; H, 5.44; N, 4.03.

***Diethyl-4-(2, 4-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2l).*** IR (KBr): 3008, 2986, 1730, 1560, 1480, 1280, 1228, 1108, 856, 775, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.23 (t, $J$ = 7.13 Hz, 6H, $CH_3$), 4.33 (q, $J$ = 7.13 Hz, 4H, $OCH_2$), 2.67 (s, 6H, $CH_3$), 7.15–7.42 (m, 3H). Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.59; H, 4.83; N, 3.53. Found: C, 57.77; H, 5.00; N, 3.49.

***Diethyl-4-(3-bromophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2m).*** IR (KBr): 3026, 2986, 1726, 1561, 1278, 1230, 1108, 1035, 865, 787, 698 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.22 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 4.31 (q, $J$ = 7.11 Hz, 4H, $OCH_2$), 2.66 (s, 6H, $CH_3$), 7.20 – 7.44 (m, 4H). Anal. Calcd. for $C_{19}H_{20}BrNO_4$ C, 56.17; H, 4.96; N, 3.45. Found: C, 56.30; H, 5.10; N, 3.27.

***Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (3).*** IR (KBr): 2974, 1721, 1588, 1555, 1298, 1254, 1123, 1022, 777 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 1.35 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.74 (s, 6H, $CH_3$), 4.28 (q, $J$ = 7.11 Hz, 4H, $OCH_2$). Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.92; H, 7.02; N, 5.44.

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## REFERENCES AND NOTES


[1] (a) Flaim, S. F.; Zelis, R. Fed Proc 1981, 40, 2877; (b) Brewster, M. E.; Simay, A.; Czako, K.; Winwood, D.; Fatag, H.; Bodor, N. J Org Chem 1989, 54, 3721; (c) Friedols, F.; Knox, R. J Biochem Pharmacol 1992, 44, 631; (d) Janis, R. A.; Triggle, D. J. J Med Chem 1983, 25, 775.

[2] Triggle, D. J.; Janis, R. A. In Modern Methods in Pharmacology, Spectro, S.; Back, N., Eds.; Alan R.Liss: New York, 1984; Vol. 2, p 1.

[3] (a) Mason, R. P.; Mak, I. T.; Trumbore, M. W.; Mason, P. E. Am J Cardiol 1999, 84, 16; (b) Aruoma, O.; Smith, C.; Cecchini, R.; Evans, P.; Halliwell, B. Biochem Pharmacol 1991, 42, 735; (c) Peri, R.; Padmanabhan, S.; Rutledge, A.; Singh, S.; Triggle, Da.J. J Med Chem 2000, 43, 2906; (d) Khadikar, B.; Borkat, S. Synth Commun 1998, 28, 207.

[4] Stout D. M.; Meyers, A. I. Chem Rev 1982, 82, 223.

[5] Wei, X. Y.; Rutledge, A.; Triggle, D. J. J Mol Pharmacol 1989, 35, 541.

[6] Kill, R. J.; Widdowson, D. A. In Bioorganic Chemistry, E. E. Van Tamelen, Ed.; Academic Press: New York, 1978, Vol 4, p 239.

[7] Garcia, O.; Delgado, F.; Cano, A. C.; Alvarez, C. Tetrahedron Lett 1993, 34, 623.

[8] Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. J Org Chem 1997, 62, 3582.

[9] Anniyappan, M.; Murlidharan, D.; Perumal, P. T. Tetrahedron 2002, 58, 5069.

[10] (a) Balogh, M.; Hermecz, I.; Menszaros, Z.; Laszlo, P. Helv Chim Acta 1984, 67, 2270; (b) Maquestiau, A.; Mayence, A.; Vanden Eynde, J. J. Tetrahedron Lett 1991, 32, 3839.

[11] Kurz, J. L.; Hutton, R.; Westheimer, F. H. J Am Chem Soc 1961, 83, 584.

[12] Zhu, X.-Q.; Zhao, B.-J.; Cheng, J.-P. J Org Chem 2000, 65, 8158.

[13] Vanden Eynde, J. J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. Tetrahedron 1995, 51, 6511.

[14] Sabita, G.; Reddy, G. S. K. K.; Reddy, C. S.; Fatima, N.; Yadav, J. S. Synthesis 2003, 1267.

[15] Varma, R. S.; Kumar, D. Tetrahedron Lett 1999, 40, 21.

[16] (a) Nakamichi, N.; Kawashitta, Y.; Hayashi, M. Org Lett 2002, 4, 3955; (b) Kamal, A.; Ahmad, M.; Mohd, N.; Hamid, A. M. Bull Chem Soc Jpn 1964, 37, 610.

[17] Yadav, J. S.; Reddy, B. V. S.; Sabhita, G.; Reddy, G. S. K. K. Synthesis 2000, 1532.

[18] Delgado, F.; Alvarez, C.; Garcia, O.; Penieres, G.; Marquez, C. Synth Commun 1991, 21, 2137.

[19] Grinsteins, E.; Stankevics, B.; Duburs, G. Khim Geterotsikl Soedin 1967, 1118; Chem Abstr 1967, 69, 77095.

[20] (a) Eynde, J. J. V.; D'orazio, R.; Van, H. Y. Tetrahedron 1994, 50, 2479; (b) Fernandes, R. A. Synlett 2003, 741.

[21] Maquestiau, A.; Mayence, A.; Eynde, J. J. V. Tetrahedron 1992, 48, 463.

[22] Pfister, J. R. Synthesis 1990, 689.

[23] Balogh, M.; Hermecz, I.; Meszaros, Z.; Laszlo, P. Helv Chim Acta 1984, 64, 2270.

[24] Mashraqui, S. H.; Karnik, M. A. Synthesis 1998, 713 and references cited therein.

[25] Mashraqui; S. H.; Karnik, M. A. Tetrahedron Lett 1998, 39, 4895.

[26] Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. Tetrahedron Lett 2005, 46, 2775.

[27] Chavan, S. P.; Dantale, S. W.; Kalkote, U. R.; Jyothirmai, V. S.; Kharul, R. K. Synth Commun 1998, 28, 2789.

[28] Khadikar, B.; Borkar, S. Synth Commun 1998, 28, 207.

[29] Bagley, M. C.; Lubinu, M. C. Synthesis 2006, 1283.

[30] Litvic, M. F.; Litvic, M.; Vinkovic, V. Tetrahedron 2008, 64, 10912.

[31] (a) Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. J Am Chem Soc 1981, 103, 686; (b) Stang, P. J.; Zhdankin, V. V. Chem Rev 1996, 96, 1123; (c) Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Rani, N. J Chem Res(S) 1996, 9, 432; (d) Tohma, H.; Takizawa, S.; Watanabe, H.; Kita, Y. Tetrahedron Lett 1998, 39, 4547; (e) Ochiai, M.; Inenaga, M.; Nagao, Y.; Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. Tetrahedron Lett 1988, 29, 6917; (f) Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M.; Inenaga, M.; Nagao, Y. Tetrahedron Lett 1988, 29, 6913; (g) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. J Org Chem 1999, 64, 3519; (h) Adam, W.; Gelache, F. G.; Saha-Moller, C. R.; Stegmann, V. R. J Org Chem 2000, 65, 1915; (i) Ochiai, M.; Nakanishi, A.; Suefuji, T. Org Lett 2000, 2, 2923; (j) Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H. J Am Chem Soc 2001, 123, 7707; (k) Zhdankin, V. V.; Stang, P. J. Chem Rev 2002, 102, 2523; (l) McGarrigle, E. M.; Gilheany, D. G. Chem Rev 2005, 105, 1563; (m) Wolckenhauer, S. A.; Devlin, A. S.; Bois, J. D. Org Lett 2007, 9, 4363; (n) Zhdankin, V. V.; Stang, P. J. Chem Rev 2008, 108, 5299.

[32] (a) Lee, K. H.; KO, K. Y. Bull Korean Chem Soc 2002, 23, 1505; (b) Kumar, P. Chinese J Chem 2009, 27, 1487; (c) Varma, R. S.; Kumar, D. J Chem Soc Perkin Trans 1 1999, 1755; (d) Cheng, D. P.; Chen, Z. C. Synth Commun 2002, 32, 793; (e) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Baishya, G.; Narsaiah, A. V. Synthesis 2006, 451, 60.

[33] (a) Norcross, B. E.; Clement, G.; Weinstein, M. J Chem Education 1969, 46, 694; (b) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. Tetrahedron Lett 1995, 36, 8083; (c) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. Green Chem 2003, 5; (d) Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. Synthesis 2006, 55.

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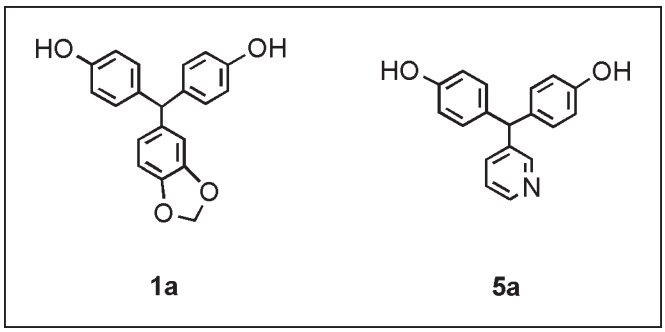


Some molecular modifications were attempted to find antiviral active compounds in the class of triarylmethanes against herpes simplex virus type 1 (HSV-1). All the synthesized compounds were evaluated for antiviral activity with HSV-1 by a plaque reduction assay. Some of the compounds showed significant antiviral activities.

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## INTRODUCTION

In our synthetic studies on antiviral compounds, we found that some triarylmethane derivatives showed significant activity against herpes simplex virus type 1 (HSV-1) in a plaque reduction assay [1–3]. Most of the compounds, which were synthesized previously, showed a wide range of activities against the HSV-1 virus. Molecular modifications of this class of compounds seemed interesting, and we therefore carried out further synthetic investigation and evaluation of this new class of derivatives.

In this series, we recently reported that the triarylmethane scaffold derivative **1a** showed a higher level of antiviral activity ($EC_{50}$ = 2.1 μM) and lower cytotoxicity ($IC_{50}$ = 79.3 μM) than those of the corresponding 4,4′-dihydroxytriphenylmethane derivative **2**, showing antiviral activity ($EC_{50}$ = 5.5 μM, $IC_{50}$ = 38.1 μM) [1]. Compound **1a** is composed of a heterocyclic methylenedioxy group instead of the 4-methoxyphenyl group in **2**. Phosphorylated aciclovir and many nucleoside phosphates have also shown significant antiviral activity [4–6]. A methane-based symmetrical tri-indolemethane **3** for enhancement of chemically induced HL-60 cell differentiation has recently been reported [7]. The corresponding tri-indolemethyl cation (turbomycin A) was isolated from soil microbial DNA, and it exhibited broad antibiotic activity against gram-negative and gram-positive organisms [8]. Therefore, the alteration of a phenyl ring to other heterocycles or the introduction of phosphoryl ester functionalities into the products has attracted our attention as a potential approach to find new antiviral active compounds.

We describe here, the preparation of some new heteroaryl (pyridine or pyrrole ring)-substituted triarylmethane derivatives. For the purpose of structural comparison nonheterocyclic 4,4′,4″-trihydroxytriphenylmethane **4a** was chosen. We also attempted the transformation of hydroxyl groups of products to phosphoryl ester functionalities. Results of plaque reduction assays to assess the anti-HSV-1 activities of these compounds are also presented.

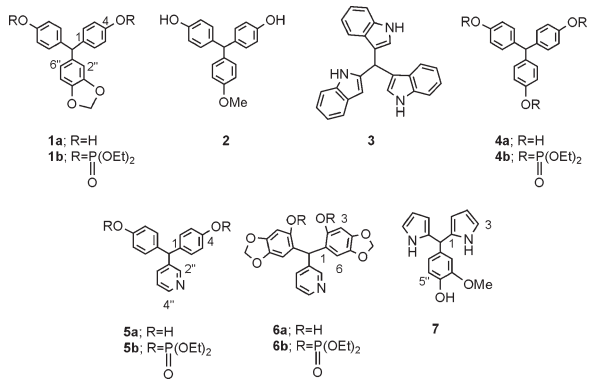
## RESULTS AND DISCUSSION

**Chemistry.** We have already reported [1] the procedure for synthesis of compound **1a** by condensation of phenol and aldehyde using various Brønsted acids. The reaction of phenol and aldehyde (piperonal) with sulfuric acid in the shade for **1a** improved the yield to 93%.

Heteroaryl-substituted triarylmethane derivatives **5a** or **7** containing pyridine or pyrrole rings were easily synthesized in excellent yield by the reaction of phenol and nicotinaldehyde or the reaction of pyrrole and vanillin using trifluoroacetic acid (TFA) as a Brønsted acid. For compound **6a**, the reaction of bromomagnesium phenolate of sesamol with nicotinaldehyde at a reaction

**Table 1**

Physical data of triarylmethane derivatives (**1** and **4–7**)




| Compound | mp (°C) (Recryst solvent) Appearance | Formula | Analysis (%) Calcd (Found) C | H | N | Formula, HR-MS *m/z* Calcd (Found) | IR ($cm^{-1}$) (KBr) |
|---|---|---|---|---|---|---|---|
| **1b** | Pale yellow oil | $C_{28}H_{34}O_{10}P_2$ · $1.5H_2O$ | 54.28 (54.36 | 6.02 6.29 | 0.00 0.00) | $C_{28}H_{35}O_{10}P_2$ $(M + H)^+$ 593.1705 (593.1705) | 3490 (OH) 1275 (P=O) 1030 (P—O) |
| **4b** | Pale yellow oil | $C_{31}H_{43}O_{12}P_3$ · $2.5H_2O$ | 49.94 (49.95 | 6.49 6.43 | 0.00 0.00) | $C_{31}H_{44}O_{12}P_3$ $(M + H)^+$ 701.2046 (701.2046) | 3500 (OH) 1270 (P=O) 1025 (P—O) |
| **5a** | 239–244 ($CH_3CN$-$H_2O$) colorless powder | $C_{18}H_{15}NO_2$ · $0.2H_2O$ | 76.96 (77.03 | 5.53 5.56 | 4.99 5.16) | $C_{18}H_{16}NO_2$ $(M + H)^+$ 278.1181 (278.1182) | 3240 (OH) 1260 (C—O) 1105 (C—O) |
| **5b** | Pale yellow viscous solid[a] | $C_{26}H_{33}NO_8P_2$ · $0.3H_2O$ | 56.28 (56.27 | 6.10 6.18 | 2.52 2.50) | $C_{26}H_{34}NO_8P_2$ $(M + H)^+$ 550.1760 (550.1757) | 3500 (OH) 1275 (P=O) 1030 (P—O) |
| **6b** | Yellow oil | $C_{28}H_{33}NO_{12}P_2$ · $0.8H_2O$ | 51.59 (51.63 | 5.35 5.34 | 2.15 2.11) | $C_{28}H_{34}NO_{12}P_2$ $(M + H)^+$ 638.1556 (638.1557) | 3495 (OH) 1275 (P=O) 1025 (P—O) |
| **7** | 117-120 (*iso*-PrOH) pale purple crystals | $C_{16}H_{16}N_2O_2$ | 71.62 (71.64 | 6.01 6.09 | 10.44 10.43) | $C_{16}H_{16}N_2O_2$ $(M^+)$ 268.1212 (268.1214) | 3420 (OH) 3320 (NH) 1230 (C—O) |

[a] Consistent and correct mp could not be obtained because this compound is a viscous material.

temperature of 30°C and a long reaction time (2 d) gave an excellent result (84% yield).

The phosphorylation of hydroxyl groups of tri- or dihydroxytriarylmethanes **1a** and **4–6b** gave tris- or bis- phosphoryl esters (**1b** and **4–6a**) by the reported procedures [9,10]. Thus, the phosphorylation of hydroxygroups was accomplished by a slight excess of $(EtO)_2POH$ in the presence of $Et_3N$ in $CCl_4$ from 0°C to room temperature overnight to give the products **1b** and **4–6b** in 11–89% yields. Compounds **5b** and **6b** were obtained under the conditions of a slight excess of $(EtO)_2POCl$ in the presence of NaH at room temperature for 1 h in 43% and 66% yields, respectively. In both methods, the yields of phosphorylated products depend on the solubility of the starting tri- or dihydroxytriarylmethanes. In fact, the addition of THF or DMF to improve the solubility of the reaction solvent resulted in better yields of the corresponding phosphorylated products (see experimental).

All of the structures of the new compounds synthesized were determined by using spectroscopic data and elemental analyses, and the signal assignments were confirmed by 2D-NMR analyses (Tables 1 and 2).

**Biological activities**

***Antiviral activities.*** The anti-HSV-1 activities of the synthesized compounds were estimated by using plaque reduction assays in Vero cells [11]. The results of the assays are summarized in Table 3 together with the data for the original compounds **1a** [1] and **6a** [1].

Substitution with a pyridine ring (compound **5a**) resulted in antiviral activity ($EC_{50}$ = 6.8 μM, $IC_{50}$ =

**Table 2**

$^{13}C$- and $^{1}H$-NMR data of triarylmethane derivatives (**1** and **4**—**7**) (δ ppm, *J* Hz).[a]

| | **1b** | | **4b** | | **5a** | | **5b** | | **6b** | | **7** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Position | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ |
| 1 | 140.41 | | 140.07 | | 133.60 | | 139.05 | | 123.89 d (8.3) | | 125.48 | |
| 2 | 130.42 | 7.04 d (8.5) | 130.48 | 7.02 d (8.85) | 129.66 | 6.89 d (8.5) | 130.40 | 7.04 d (8.7) | 142.79 d (7.2) | | | |
| 3 | 119.77 d (5.2) | 7.13 d (8.5) | 119.87 d (4.1) | 7.13 dd (8.85, 1.1) | 115.08 | 6.70 d (8.5) | 120.11 d (5.2) | 7.16 d (8.7) | 102.18 | 7.01 s | 108.29 | 6.61–6.64 m[b] |
| 4 | 149.24 d (7.2) | | 149.37 d (3.2) | | 155.65 | | 149.63 d (7.2) | | 144.65 or 147.27 | | 98.49 | 5.98 t (2.9) |
| 5 | 119.77 d (5.2) | 7.13 d (8.5) | 119.87 d (4.1) | 7.13 dd (8.85, 1.1) | 115.08 | 6.70 d (8.5) | 120.11 d (5.2) | 7.16 d (8.7) | 147.27 or 144.65 | | 97.81 | 5.72–5.74 m |
| 6 | 130.42 | 7.04 d (8.5) | 130.48 | 7.02 d (8.85) | 129.66 | 6.89 d (8.5) | 130.40 | 7.04 d (8.7) | 109.11 | 6.24 s | | |
| OH | | | | | | 9.24 s | | | | | | |
| —CH < | 55.05 | 5.40 s | 54.75 | 5.46 s | 51.69 | 5.41 s | 53.02 | 5.50 s | 41.47 | 6.12 s | 35.45 | 5.30 s |
| 1″ | 137.34 | | 140.07 | | 140.32 | | 138.98 | | 140.91 | | 127.00 | |
| 2″ | 109.71 | 6.55 d (1.8) | 130.48 | 7.02 d (8.85) | 149.94 | 8.33 d (1.8) | 150.53 | 8.40 br s | 149.20 | 8.57 s | 103.96 | 6.75 d (2.1) |
| 3″ | 147.77 | | 119.87 d (4.1) | 7.13 dd (8.85, 1.1) | | | | | | | 139.19 | |
| 4″ | 146.18 | | 149.37 d (3.2) | | 147.06 | 8.39 dm (4.9) | 147.86 | 8.48 br d (3.7) | 146.88 | 8.56 dd (5.5) | 136.47 | |
| 5″ | 108.03 | 6.71 d (7.9) | 119.87 d (4.1) | 7.13 dd (8.85, 1.1) | 123.20 | 7.30 dd (7.9, 4.9) | 123.34 | 7.23 m | 124.88 | 7.44 dd (7.9, 5.5) | 106.29 | 6.70 d (8.2) |
| 6″ | 122.37 | 6.52 ddd (7.9, 1.8, 0.6) | 130.48 | 7.02 d (8.85) | 136.01 | 7.43 dm (7.9) | 136.65 | 7.37 m | 140.20 | 7.68 d (7.9) | 112.58 | 6.61–6.64 m[b] |
| —$OCH_2O$— | 100.96 | 5.92 s | | | | | | | 101.94 | 5.95 s | | |
| | P—O—$CH_2CH_3$; 16.00 d (7.2) ($CH_3$), 64.60 d (6.2) ($CH_2$). | P—O—$CH_2CH_3$; 1.35 dt (7.0, 1.2) ($CH_3$), 4.21 ddq (8.2, 7.0, 2.7) ($CH_2$). | P—O—$CH_2CH_3$; 16.04 d (7.3) ($CH_3$), 64.55 d (6.2) ($CH_2$). | P—O—$CH_2CH_3$; 1.35 dt (7.0, 0.9) ($CH_3$), 4.21 ddq (8.2, 7.0, 2.7) ($CH_2$). | | | P—O—$CH_2CH_3$; 16.04 d (7.2) ($CH_3$), 64.57 d (6.2) ($CH_2$) | P—O—$CH_2CH_3$; 1.35 dt (7.0, 0.9) ($CH_3$), 4.22 ddq (8.2, 7.0, 2.7) ($CH_2$) | P—O—$CH_2CH_3$; 16.03 and 16.08 d (5.2) ($CH_3$), 64.88 and 64.92 d (11.3) ($CH_2$) | P—O—$CH_2CH_3$; 1.22 and 1.27 dt (7.0, 0.9) ($CH_3$), 4.03 m ($CH_2$) | OMe; 46.84 | OMe; 3.72 s |

[a] **1** and **4–6b** were measured in $CDCl_3$; **5a** and **7** were measured in DMSO-$d_6$ and $CD_3OD$, respectively.
[b] Two signals coincided.

**Table 3**

Antiviral activity ($EC_{50}$) and cytotoxicity ($IC_{50}$) against HSV-1.

| | $EC_{50}$ (μM) | I $C_{50}$ (μM) | $IC_{50}/EC_{50}$ |
|---|---|---|---|
| **1a**[a] | 2.1 | 79.3 | 38.2 |
| **1b** | >16 | 21.3 | <1.3 |
| **4a** | 22.6 | 127 | 5.6 |
| **4b** | 8.6 | 19.8 | 2.3 |
| **5a** | 6.8 | 54.1 | 7.9 |
| **5b** | >36 | 39.6 | <1.1 |
| **6a**[a] | 7.3 | >135 | >18.5 |
| **6b** | 49.1 | 87.6 | 1.8 |
| **7** | >150 | 190 | <1.3 |

[a] The data of the compounds from [1].

54.1 μM) similar to that of compound **6a** ($EC_{50}$ = 7.3 μM, $IC_{50}$ > 135 μM) previously reported [1]; however, its cytotoxicity was increased to that of 2,2′-dihydroxytriarylmethane **6a**. The introduction of two pyrrole rings with an N—H group (compound **7**) resulted in no significant antiviral activity at a concentration of 150 μM. Thus, two hydroxyl groups on the triphenylmethane scaffold might be necessary to show significant antiviral potency.

The phosphorylation of hydroxyl groups of **1a**, **5a**, and **6a** resulted in increased cytotoxicity in both transformations into **1b**, **5b**, and **6b**, respectively. Transformation of nonheterocyclic derivative **4a** into **4b** also showed a similar tendency. Phosphorylated triphenylmethane derivative **4b** showed a higher level of antiviral activity than that of original compound **4a**, but antiviral activities of both heteroaryl-substituted derivatives **5b** and **6b** were lower than those of the corresponding **5a** and **6a**, respectively. With reference to the phosphorylated hetero-ring substituted derivative **1b**, its antiviral activity was also lower than that of the corresponding nonphosphorylated original compound **1a**. Compounds synthesized in this study showed inhibitory concentrations ($EC_{50}$) ranging from 6.8 to > 150 μM. Among these compounds, we found that **5a** has the highest level of activity against HSV-1 ($EC_{50}$ = 6.8 μM), but its selectivity index was 7.9.

In this study on modification of triarylmethanes by alteration of heteroaryl rings and transformation into phosphorylated derivatives, unfortunately, we could not find more potent antiviral compounds than the 4,4′-dihydroxytriarylmethane **1a** reported previously [1]. Throughout this work, however, it is notable that compounds **5a** and **6a** containing a heteroaryl group (pyridine) showed higher levels of antiviral activity than that of $C_3$ symmetrical 4,4′,4″-trihydroxytriphenylmethane **4a** ($EC_{50}$ = 22.6 μM), and the $C_3$ symmetry structure of both compounds (a prochiral symmetrical molecule) was destroyed by introducing a different heteroaryl ring in the molecule. To elucidate these phenomena, further molecular modifications of triarylmethanes and evaluation of their activity against HSV-1 are underway.

## EXPERIMENTAL

Melting points were determined using a micro melting point apparatus (Yanagimoto MP-S3) without correction. IR spectra were measured by a Shimadzu FTIR-8100 IR spectrophotometer. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained by a JEOL JMS HX-110 double-focusing model equipped with a FAB ion source interfaced with a JEOL JMA-DA 7000 data system. $^1$H- and $^{13}$C-NMR spectra were obtained by JEOL JNM A-500. Chemical shifts were expressed in δ ppm downfield from an internal tetramethylsilane signal for $^1$H-NMR and the carbon signal of the corresponding solvent [$CDCl_3$ (77.00 ppm), $CD_3OD$ (39.50 ppm), and dimethyl sulfoxide (DMSO)-$d_6$ (39.50 ppm)] for $^{13}$C-NMR. Microanalyses were performed with a Yanaco MT-6 CHN corder. Routine monitoring of reactions was carried out using precoated Kieselgel $60F_{254}$ plates (E. Merck). Centrifugal or flash column chromatography was performed on silica gel (Able-Biott or Fuji Silysia FL60B, respectively) with a UV detector. Preparation of compounds (**1a** [1], **4a** [1], and **6a** [4]) have already been reported. Commercially available starting materials including **4a** were used without further purification.

**4,4′-(1,3-Benzodioxol-5-ylmethylene)bisphenol (1a) [1].** To a solution of phenol (755 mg, 8.0 mmol) and 3,4-methylenedioxybenzaldehyde (600 mg, 4.0 mmol) in AcOH (2.3 mL) was added conc. $H_2SO_4$ (0.43 mL, 8.0 mmol). In the shade, the solution was stirred for 20 h at room temperature. The reaction mixture was poured into ice water (50 mL) and extracted from AcOEt (100 mL × 3). The organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was purified by centrifugal chromatography on silica gel (1% EtOH/$CH_2Cl_2$) to give **1a** (1.192 g, 3.7 mmol, 93% yield). Recrystallization from water/*iso*PrOH gave pale reddish crystals.

**General procedure of phosphorylation for preparation of 4,4′-(1,3-benzodioxol-5-ylmethylene)bisphenylphosphoric acid tetraethyl ester (1b).** This compound was prepared according to the method reported by Huffman *et al*. [9]. Thus, diethyl phosphite (3.6 mmol) was added to a stirred solution of **1a** (1.5 mmol) in $CCl_4$ (5 mL) at 0°C, followed by the addition of $Et_3N$ (4.2 mmol) dropwise. The reaction mixture was stirred overnight at 0°C to room temperature for 18 h. After dilution with $CH_2Cl_2$, the resulting mixture was washed with water, 10% aqueous HCl, and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was purified by centrifugal chromatography ($SiO_2$: 30–40% AcOEt in *n*-hexane), which gave **1b** (0.281 mmol, 19% yield) as a pale yellow oil.

**4,4′,4″-Methylidynetriphenyl-phosphoric acid hexaethyl ester (4b).** In a manner similar to that for the preparation of **1b**, after reaction of **4a** (2.0 mmol) in $CCl_4$ (3 mL), diethyl phosphite (7.4 mmol) and $Et_3N$ (8.2 mmol) at temperatures in the range of 0°C to room temperature for 17 h, purification by flash chromatography ($SiO_2$: 2–10% EtOH in $CH_2Cl_2$) gave **4b** (1.78 mmol, 89% yield) as a pale yellow oil.

**4,4′-(3-Pyridinylmethylene)bisphenol (5a).** A mixture of phenol (941 mg, 10.0 mmol) and nicotinaldehyde (536 mg, 5.0 mmol) and TFA (3.85 mL, 50 mmol) was stirred in the shade at room temperature for 20 h. After evaporation, purification by centrifugal chromatography (50–70% AcOEt in *n*-hexane) gave **5a** (1.380 g, 5.0 mmol) as a colorless solid quantitatively. Recrystallization from $CH_3CN$—$H_2O$ gave an analytically pure colorless powder **5a**.

**4,4′-(3-Pyridinylmethylene)bisphenylphosphoric acid tetraethyl ester (5b)**

***[Method A].*** In a manner similar to that for the preparation of **1b**, after the reaction of **5a** (1.0 mmol) in $CCl_4$ (3 mL), diethyl phosphate (3.7 mmol), and $Et_3N$ (4.1 mmol) in the range of 0°C to room temperature for 18 h, purification by centrifugal chromatography ($SiO_2$: 3–5% EtOH in $CH_2Cl_2$) gave **5b** (0.281 mmol, 11% yield) as a pale yellow viscous solid.

***[Method B].*** According to the method reported by Asaad *et al* [10], NaH (60% in oil, 10 mmol) was added to a stirred solution of **5a** (1.0 mmol) in dry THF-$CH_2Cl_2$ (1, 3 mL) at room temperature under an $N_2$ atmosphere. After stirring for 0.5 h, diethyl chlorophosphate (3.0 mmol) in dry $CH_2Cl_2$ (2 mL) was added to the reaction mixture dropwise for 20 min and then stirred for more 1 h. The reaction mixture was then poured into a saturated $NaHCO_3$ solution (40 mL) and extracted with $CH_2Cl_2$ (30 mL × 2), and its organic layer was washed with water, dried over $MgSO_4$, and evaporated. The resulting products were purified by centrifugal chromatography ($SiO_2$: 5% EtOH in $CH_2Cl_2$) to give **5b** (0.432 mmol, 43% yield).

**6,6′-(3-Pyridinylmethylene)bis-1,3-benzodioxol-5-ol (6a) [1].** Under $N_2$ atmosphere, a solution of sesamol (2.76 g, 20.0 mmol) in dry ether ($Et_2O$; 50 mL) was added dropwise to a solution of 3 M EtMgBr (6.7 mL, 20 mmol) in dry $Et_2O$ (60 mL) with stirring at room temperature, and the mixture was kept for 10 min, then the solvent was removed in vacuo. After addition of dry $CH_2Cl_2$ (300 mL) to the residue, a solution of nicotinaldehyde (536 mg, 5.0 mmol) in dry $CH_2Cl_2$ (50 mL) was added with stirring under $N_2$ atmosphere. The resulting mixture was sonicated at 30°C for 2 days. The reaction was quenched with saturated aqueous $NH_4Cl$ (100 mL), and the mixture was extracted with AcOEt (100 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the solid. The residue was recrystallized from MeOH to give **6a** as a pale green powder (1.53 g, 4.2 mmol) in 84% yield.

**Preparation of 6,6′-(3-pyridinylmethylene)bis-1,3-benzodioxol-5-ylphosphoric acid tetraethyl ester (6b)**

***[Method A].*** In a manner similar to that of the preparation of **1b**, after reaction of **6a** (1.0 mmol) in $CCl_4$ (3 mL), diethyl phosphite (3.7 mmol), and $Et_3N$ (4.1 mmol) at temperatures in the range of 0°C to room temperature for 18 h, purification by centrifugal chromatography ($SiO_2$: 3–5% EtOH in $CH_2Cl_2$) gave **6b** (0.505 mmol, 51% yield) as a yellow oil.

***[Method B].*** In a manner similar to that for the preparation of **5b**, after the reaction of **6a** (1.0 mmol) in dry THF-$CH_2Cl_2$-DMF (3, 3, 2 mL) and 60% NaH (2.6 mmol) with diethyl chlorophosphate (2.4 mmol) in dry $CH_2Cl_2$ (2 mL) for 1.5 h, the reaction mixture was poured into a saturated $NaHCO_3$ solution (50 mL) and extracted with AcOEt (40 mL × 3). Centrifugal chromatography ($SiO_2$: 70–100% AcOEt in *n*-hexane) gave **6b** (0.663 mmol, 66% yield) as a yellow oil.

**2,2′-[(4-Hydroxy-3-methoxy-phenyl)methylene]bis-1*H*-pyrrol (7).** A mixture of pyrrole (16.4 mL, 240 mmol) and vanillin (912 mg, 6.0 mmol) and TFA (94 μL, 1.2 mmol) was stirred in the shade at room temperature for 20 h. After evaporation, purification by flash chromatography (5% AcOEt in $CHCl_3$) gave **7** (1.288 g, 4.8 mmol) as a colorless solid in 80% yield. Recrystallization from *iso*-PrOH gave analytically pure pale violet crystals **7**.

**Antiviral activity assay and cytotoxicity of target compounds.** The antiviral activities of synthesized compounds were measured using a plaque reduction assay [11] as described in our previous article [1]. Results of antiviral activity ($EC_{50}$) and cytotoxicity values ($IC_{50}$) with Vero cells are summarized in Table 3.

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## REFERENCES AND NOTES

[1] Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. Chem Pharm Bull 2005, 53, 1171.

[2] Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. Chem Pharm Bull 2003, 51, 1325.

[3] Mibu, N.; Sumoto, K. Chem Pharm Bull 2000, 48, 1810.

[4] Yamanaka, G.; Tuomari, A. V.; Hagen, M.; McGeever-Rubin, B.; Terry, B.; Haffey, M.; Bisacchi, G. S.; Field, A. K. Mol Pharmacol 1991, 40, 446.

[5] Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. Proc Natl Acad Sci USA 1977, 74, 5716.

[6] De Clercq, E.; Andrei, G.; Balzarini, J.; Leyssen, P.; Naesens, L.; Neyts, J.; Pannecouque, C.; Snoeck, R.; Ying, C.; Hockova, D.; Holy, A. Nucleos Nucleot Nucl 2005, 24, 331.

[7] Noguchi-Yachide, T.; Tetsuhashi, M.; Aoyama, H.; Hashimoto, Y. Chem Pharm Bull 2009, 57, 536.

[8] Gillespie, D. E.; Brady, S. F.; Bettermann, A. D.; Cianciotto, N. P.; Liles, M. R.; Rondon, M. R.; Clardy, J.; Goodman, R. M.; Handelsman. J. Appl Environ Microbiol 2002, 68, 4301.

[9] Huffman, J. W.; Miller, J. R. A.; Liddle, J.; Yu, S.; Thomas, B. F.; Wiley, J. L.; Martin, B. R. Bioorg Med Chem 2003, 11, 1397.

[10] Asaad, N.; Kirby, A. J. J Chem Soc Perkin Trans 2 2002, 1708.

[11] Schinazi, R. F.; Peters, J.; Williams, C.; Chance, D.; Nahmias, A. Antimicrob Agents Chemother 1982, 22, 499.

# A Simple and Efficient Synthesis of Some Novel Thiazolidine-4-one Derivatives



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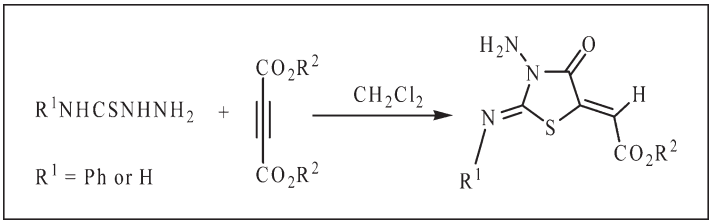


Reaction of 4-phenylthiosemicarbazide with dialkyl acetylenedicarboxylate in $CH_2Cl_2$ at 0°C lead to construction of alkyl 3-amino-2-phenyliminothiazolidine-4-one-5-ylidene acetate in a few minutes and good yields. Alternatively, the use of thiosemicarbazide has given the corresponding 3-amino-2-imino-thiazolidine-4-one-5-ylidene acetate, while application of di-*t*-butylacetylenedicarboxylate in these reactions has not entailed with cyclization.

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## INTRODUCTION

Thiazolidine-4-ones are important building blocks in variety of pharmaceutical agents and biologically active products [1]. Several substituted thiazolidinones have been found to possess hypnotic, anesthetic, sedative, anticonvulsant, and microbiological activities [2–4]. Some thiazoline derivatives show interesting anti-HIV or anticancer activities and can inhibit cell division [5–10]. Because of the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared and several new methods for the preparation of substituted thiazolidine-4-one have been recently reported [11,12]. Despite the synthetic importance of these methods, they commonly suffer from the need to elevated temperatures and also from long reaction times. Therefore, it is reasonable that development of mild and efficient methods for their synthesis still is more desired. In this context, we present here a mild and expedient method for synthesis of 2-iminothiazolidine-4-one-5-ylidene acetate derivatives in fairly good yields.

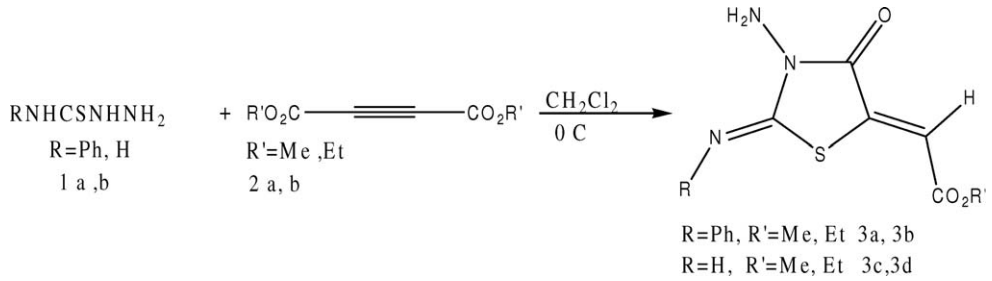
## RESULTS AND DISCUSSION

As is shown in Scheme 1, the synthesis of 2-imino-thiazolidine-4-one-5-ylidene acetate was simply effected by a two component reaction between thiosemicarbazide and an acetylenic ester. The reaction proceeds smoothly without using any catalyst by mixing the two reactants in dry $CH_2Cl_2$ media at room temperature and needs no more care on controlling the temperature or using special techniques of activation. Only the thiazolidine products were formed and separated from the reaction mixture. An attracting feature of this reaction is the synthesis of a multifunctionalized complex heterocycle from simple starting materials.

Thus, 4-Phenylthiosemicarbazide **(1a)** and dimethyl acetylenedicarboxylate undergo a smooth reaction in dry $CH_2Cl_2$ at 0°C to produce methyl 3-amino-2 phenylimino-thiazolidine-4-one-5-ylidene acetate **(3a)** in 94% yield (Scheme 1). In a similar manner, thiazolidine-4-ones **(3c,d)** were formed on reaction between thiosemicarbazide and the corresponding acetylenic ester in excellent yields (Scheme 1). Surprisingly, di-*tert*-butyl acetylenedicarboxylate showed up a different behavior as instead of cyclocondensation with thiosemicarbazide their reaction lead to addition of the two components and solely formation of thiosemicarbazone derivatives (Scheme 2).

Structures of all the compounds were deduced from their IR, $^1$H NMR, $^{13}$C NMR, and mass spectral data as well as elemental analyses. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The $^1$H NMR spectrum of **3a**, for example, in $CDCl_3$ showed three singlet peaks arising from resonances of methoxy δ 3.48, amino δ 4.89, and olefinic protons δ 7.00, along with multiplets at δ 7.03–7.42 ppm for the aromatic protons. The $^{13}$C NMR

**Scheme 1**




spectrum of **3a** showed 10 signals in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section. The $^{1}$H- and $^{13}$C NMR spectra of **3b–3d** are very similar to those of **3a**, except for the ester and aryl moieties, which exhibit characteristic signals at appropriate chemical shift.

On the basis of well established chemistry of electrophilic acetylenes [10], it is reasonable to assume that the synthesis proceeds through initial conjugate addition of the sulfur atom of **1** onto the acetylenic ester following cyclocondensation of the thus formed 1:1 adduct [13,14] to yield the products **3** (Scheme 3).

In the cases of using di-*t*-butyl acetylenedicarboxylate, the reactions are prevented from proceeding through above mechanism due to steric hindrance of bulky alkyl groups, so are unable to give the desired thiazolidine products.

In conclusion, we have made a contribution to the synthesis of thiazolidine-4-one compounds [13,14] by using the reaction between 4-phenylthiosemicarbazide or thiosemicarbazide with a dialkyl acetylenedicarboxylate to produce some novel thiazolidine-4-one derivatives. The method carries the advantage that is not only the reaction performed under neutral conditions but also the substrates can react by mixing without any activation or modification.

## EXPERIMENTAL

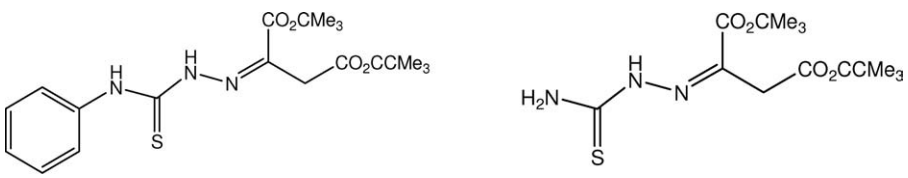
Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. $^{1}$H and $^{13}$C NMR spectra were recorded by a Bruker DRX-300 AVANCE instrument with deuteriochloroform as solvent at 300 and 75 MHz, respectively. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. 4-Phenylthiosemicarbazide, thiosemicarbazide, dimethyl acetylenedicarboxylate, and diethyl acetylenedicarboxylate were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

**Typical procedure for the preparation of compounds 3.** To a stirred solution of **1** (2 mmol) in 10 mL of dichloromethane was added dropwise a mixture of **2** (2 mmol) in 2 mL dichloromethane at 0°C over 1 min. The reaction quickly went to complete, as monitored by tlc on silica-gel 60 using 1:1 solution of ethyl acetate:petroleum ether, and the solid product precipitate. After 5 min, the solid was filtered and recrystallized from diethyl ether to afford the pure products.

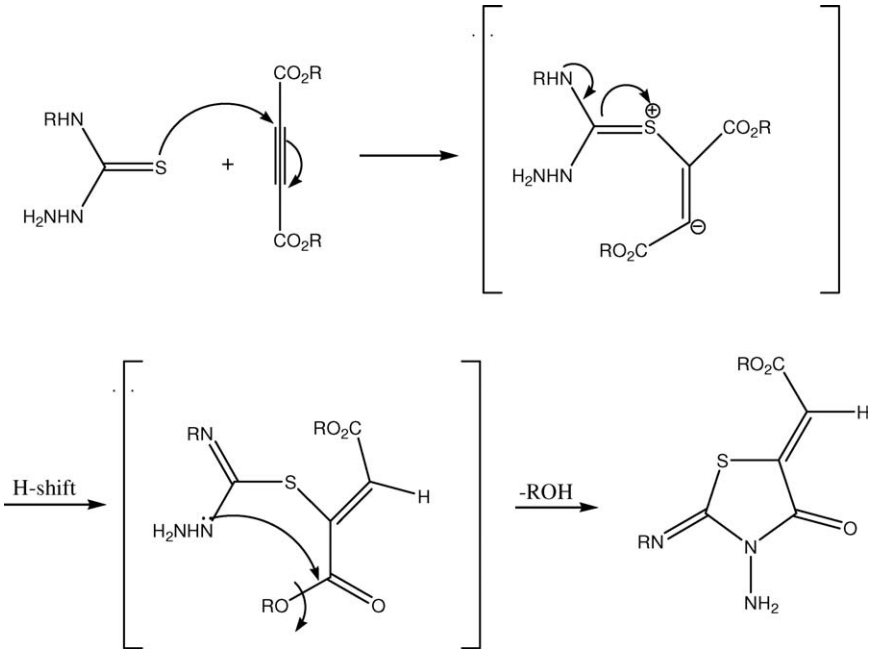
***Methyl 3-amino-2-phenylimino-4-oxo-1,3-thiazolan-5-ylideneacetate (3a).*** Pale yellow crystals; yield: 0.55g (99%), mp 161–162°C; IR (KBr): $\bar{\nu}$ = 3306, 3145 ($NH_2$), 1731, 1645 (C=O), 1694 (C=C), 1608 (C=N) cm$^{-1}$; $^{1}$H NMR: δ = 3.84 (3H, s, MeO), 4.89 (2H, s, $NH_2$), 7.0 (1H, s, CH), 7.03–7.42 (5H, m, Ph) ppm; $^{13}$C NMR: δ = 166.6, 161.8 (C=O), 149.6 (C=N), 146.8 (C), 139.8 (C), 129.9 (2CH), 126.0 (CH), 121.5 (2CH), 117.3 (CH), 53.0 ($CH_3$—O) ppm; ms: m/z (%) 277 (28, $M^+$), 160 (8), 142 (1), 117 (23), 85 (86), 77 (100), 58 (63), 44 (24). *Anal*. Calcd. for $C_{12}H_{11}N_3O_3S$ (277.24): C, 51.19; H, 3.96; N, 15.14%. Found: C, 51.33; H, 3.87; N, 15.05%.

***Ethyl 3-amino-2-phenylimino-4-oxo-1,3-thiazolan-5-ylideneacetate (3b).*** Pale yellow powder; yield: 0.57 g (98%), mp 160–163°C; IR (KBr): $\bar{\nu}$ = 3299, 3146 ($NH_2$), 1729, 1642 (C=O), 1688 (C=C), 1593 (C=N) cm$^{-1}$; $^{1}$H NMR: δ = 1.33 (3H, t, $^{3}J_{HH}$ = 7.1, Me), 4.28 (2H, q, $^{3}J_{HH}$ = 7.1, $CH_2O$), 4.88 (2H, br s, $NH_2$), 6.99 (1H, s, CH), 7.03–7.39 (5H, m, Ph) ppm; $^{13}$C NMR: δ = 166.2, 161.9 (2C=O), 149.7 (C=N), 146.9 (C), 139.5 (C), 129.9 (2CH), 126.0 (CH), 121.5 (2CH), 117.8 (CH), 62.3 ($CH_2O$), 14.5 ($CH_3$) ppm; ms: m/z (%) 291 (24,

**Scheme 2**



**Scheme 3**




$M^+$), 264 (4), 142 (23), 135 (26), 107 (40), 85 (66), 77 (100), 57 (20), 44 (54). *Anal*. Calcd. for $C_{13}H_{13}N_3O_3S$ (291.28): C, 53.55; H, 4.46; N, 14.01%. Found: C, 51.78; H, 4.83; N, 14.39%.

***Di-t-butyl succinal-2-ylidene-4-phenylthiosemicarbazone (4a).*** Greenish white powder; yield: 0.74 g (95%), mp 152–153°C; IR (KBr): $\bar{\nu}$ = 3286, 3271 (NH), 1721, 1685 (2 C=O), 1598 (C=N), 1584 (C=S) $cm^{-1}$; $^1H$ NMR: δ = 1.50 (9H, s, $3CH_3$), 1.57 (9H, s, $3CH_3$), 3.44 (2H, s, $CH_2$), 7.25–7.70 (5H, m, Ph), 9.31 (1H, s, NH), 12.55 (1H, s, NH) ppm;$^{13}C$ NMR: δ = 176.7 (C=S), 169.2, 161.2 (2C=O), 138.0 (C=N), 131.0 (C), 129.1 (2CH), 126.6 (C), 124.4 (2CH), 85.1 (C) 82.2 (C), 41.4 ($CH_2$), 28.5 ($3CH_3$), 28.30 ($3CH_3$) ppm; ms: m/z (%) 393 (8, $M^+$), 292 (70), 264 (28), 236 (100), 190 (18), 151 (18), 136 (44), 57 (88). *Anal*. Calcd. for $C_{19}H_{27}N_3O_4S$ (393.12): C, 58.01; H, 6.87; N, 10.68%. Found: C, 58.37; H, 6.89; N, 11.01%.

***Methyl3-amino-2-imino-4-oxo-1,3-thiazolan-5-ylideneacetate (3c).*** Yellow crystals; yield: 0.36 g (89%), mp 181–182°C; IR (KBr): $\bar{\nu}$ = 3302, 3147 ($NH_2$), 1732, 1646 (2 C=O), 1694 (C=C), 1608 (C=N) $cm^{-1}$; $^1H$ NMR: δ = 3.86 (s, MeO), 4.85 (s, $NH_2$), 5.2(s, NH), 7.01 (s, CH), ppm; $^{13}C$ NMR: δ = 166.2, 162.8 (2 C=O), 148.6 (C=N), 146.1 (C), 139.8 (C), 126.3 (CH), 52.3 (MeO) ppm; ms: m/z (%) 201 (38, $M^+$), 170 (8), 142 (5), 126 (25), 85 (86), 56 (100), 44 (24). *Anal*. Calcd. for $C_6H_7N_3O_3S$ (201.3): C, 35.82; H, 3.48; N, 20.89%. Found: C, 35.34; H, 3.27; N, 21.44%.

***Ethyl3-amino-2-imino-4-oxo-1,3-thiazolan-5-ylideneacetate (3d).*** Greenish yellow powder; yield: 0.39 g (91%), mp 170–173 °C; IR (KBr): $\bar{\nu}$ = 3291, 3143 ($NH_2$), 1727, 1643 (2 C=O), 1685 (C=C), 1591 (C=N) $cm^{-1}$; $^1H$ NMR: δ = 1.32 (t, $^3J_{HH}$ = 7.1, Me), 4.26 (q, $^3J_{HH}$ = 7.1, $CH_2O$), 4.88 (br s, $NH_2$),5.11(s, NH), 6.90 (s, CH) ppm;$^{13}C$ NMR: δ = 166.2, 161.9 (2 C=O), 149.7 (C=N), 146.9 (C), 139.5 (C), 126.0 (CH), 62.5 ($CH_2O$), 14.4 ($CH_3$) ppm; ms: m/z (%) = 215 (28, $M^+$), 170 (14), 142 (36), 135 (26), 107 (40), 85 (100), 57 (20), 44 (54). *Anal*. Calcd. for $C_7H_9N_3O_3S$ (215.21): C, 39.01; H, 4.18; N, 19.53%. Found: C, 38.88; H, 4.13; N, 20.11%.

***Di-t-butyl succinal-2-ylidenethiosemicarbazone (4b).*** White powder; yield: 0.54g (85%), mp 162–163°C; IR (KBr): $\bar{\nu}$ = 3286, 3273 (NH), 1724, 1685 (2 C=O), 1595 (C=N), 1584 (C=S) $cm^{-1}$; $^1H$ NMR: δ = 1.52 (9H, s, $3CH_3$), 1.55 (9H, s, $3CH_3$), 3.48 (2H, s, $CH_2$), 9.35 (2H, s, $NH_2$), 12.50 (1H, s, NH) ppm;$^{13}C$ NMR: δ = 176.7 (C=S), 169.2, 161.2 (2 C=O), 138.0 (C=N), 85.8 (C) 82.1 (C), 41.6 ($CH_2$), 28.9 (3 $CH_3$), 28.38 (3 $CH_3$) ppm; ms: m/z (%) 317 (18, $M^+$), 216 (77), 200 (22), 156 (100), 99 (18). *Anal*. Calcd. for $C_{13}H_{23}N_3O_4S$ (317.12): C, 49.21; H, 7.25; N, 13.24%. Found: C, 49.37; H, 7.89; N, 14.01%.

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## REFERENCES AND NOTES

[1] Newkome, G. R. Adv Heterocycl Chem 1979, 25, 83.

[2] Shah, S. J.; Shah, S. R.; Desai, N. C. J Indian Chem Soc 1984, 61, 648.

[3] Dave, M. P.; Patel, J. M.; Langalia, N. L. J Indian Chem Soc 1984, 61, 891.

[4] Boyce, R. J.; Mulqeen, G. C. Tetrahedron Lett 1994, 35, 5705.

[5] Wipf, P.; Fritch, P. C. Tetrahedron Lett 1994, 35, 5397.

[6] Lai, J. Y.; Yu, J.; Mekonnen, B. Tetrahedron Lett 1996, 37, 7167.

[7] Shih, M. H.; Ke, F. Y.; Bioorg Med Chem 2004, 2, 4633.

[8] Rao, A.; Carbone, A. II Farmaco 2002, 57, 747.

[9] Lakhan, R.; Singh, R. L. J Agric Food Chem 1991, 39, 580.

[10] Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Porshamsian, K.; Bagheri, M.; Ali-Asgari, S. Mol Divers 2007, 11, 81.

[11] Yavari, I.; Porshamsian, K.; Bagheri, M.; Ali-Asgari, S. J Sulfur Chem 2007, 28, 1.

[12] Sunduru, N.; Srivastava, K.; Rajakumar, S.; Puri, S. K. Bioorg Med Chem 2009, 19, 2570.

[13] Balázs, F.; Antal, C.; Tibor, Zs. N.; Mátyás, C.; Pál, S. J Organomet Chem 2009, 694, 3732.

[14] Yavari, I.; Hosseini, N.; Moradi, L. Monatsh Chem 2008, 139, 133.

# Phenylselenoetherification of Some $\Delta^4$-Alkenols Facilitated by Pyridine and Some Lewis Acids



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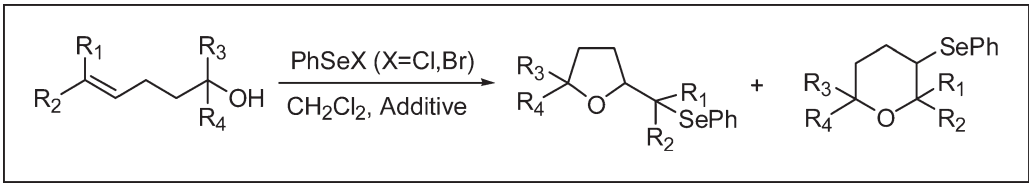


Studies on the phenylselenoetherification of some $\Delta^4$-alkenols in the presence of pyridine and some Lewis acids are described. All alkenols underwent intramolecular cyclization yielding corresponding tetrahydrofuran or tetrahydropyran derivatives. Yield and diastereomeric ratio of the cyclic products depend on counterion of selenylating reagent used. We found that external additives, such as pyridine and some Lewis acids coordinating to the electrophilic and/or nucleophilic species are used to control the course of cyclizations with high degrees of efficiency and improve the level of stereoinduction.

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## INTRODUCTION

Cyclization of unsaturated alcohols leading to cyclic ethers is well documented in a literature as convenient pathways in the synthesis of natural products and related compounds [1].

Substituted tetrahydrofuran and tetrahydropyran rings are common in many natural products and play important role as building blocks for the synthesis of various biologically active organic target molecules [2]. Stereoselective synthesis [3] of substituted cyclic ethers is important since cyclic ether units are frequently found in polyether antibiotics [4], C-glycosides [5], and polyene mycotoxins [6]. A number of these compounds exhibit remarkable antibiotic [4], neurotoxic [7], antiviral [8], and cytotoxic [9] effects, which have opened perspective for selected clinical applications [10]. This circumstance has brought about a growing demand for cyclic ethers in general. Since their supply cannot be covered from natural sources alone, the invention of methods for stereoselectively constructing the tetrahydrofuran and tetrahydropyran nucleus from unsaturated alcohols has received considerable attention [11].

Among the various kinds of ring-forming reactions, those based on the reaction of an electrophilic reagent with an alkene holding a suitably positioned hydroxyl group are certainly very useful. The term of cycloetherification is generally used to describe this kind of process which can be promoted by several electrophilic reagents [12]. The increasing popularity gained in recent years by selenium reagents induced ring closure reactions [13]. Different electrophilic selenium reagents and a variety of reaction conditions have been used and recent reviews are highlighting the broad scope of this general process [14]. Scheme 1 illustrates the possible modes of cyclization depending on the relative position of hydroxyl group and the double bond in the starting alkene.

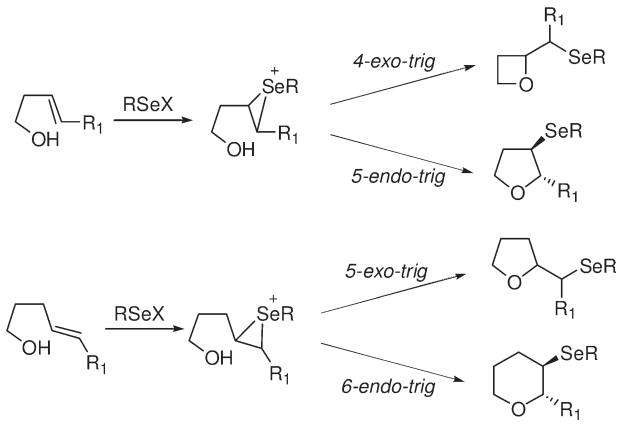
Outcome of this reaction is influenced by the nature of selenium reagent used, and the reactivity of the selenium electrophile also depends on the nature of counterion. Although standard conditions can be used for these cyclizations, the interactions between the selenium electrophile, counterion, the solvent, and the substrate are not fully understood, and we describe herein our recent investigations toward these cyclizations.

Lewis acids are widely used as catalysts and mediators in many organic reactions [15] and stereoselective synthesis [16]. However, PhSeCl in combination with equimolar amount of $ZnCl_2$ is known as strong chlorophenilselenilating reagent for olefins [17]. These findings prompt us to extend the use of Lewis acids to phenylselenoetherification of some $\Delta^4$-alkenols. Now, we are interested in the behavior toward additives such as Lewis acids and pyridine in the reaction conditions to study reactivity and regiochemical and stereochemical outcome of the cyclization.

## RESULTS AND DISSCUSION

In recent years, we have studied intramolecular cyclization of some $\Delta^4$- and $\Delta^5$-alkenols by means of phenylselenyl

**Scheme 1**




halides, PhSeX (X = Cl, Br) [18]. Intramolecular heterocyclization is the main reaction in the case of all investigated primary and secondary alkenols, while tertiary alkenols, under the same experimental conditions, are not converted into cyclic products at all by PhSeBr and in a small amount with PhSeCl. Although the additional products are expected, we have found that all investigated tertiary alkenols in the reaction with PhSeBr afforded γ- and δ-bromoalkanols in high yields [19].

Recently, we found that cyclizations of $\Delta^5$-alkenols can be facilitated in the presence of pyridine, $Ag_2O$, and some Lewis acids as catalysts [18d]. In this article, we wish to present the extension of the method to $\Delta^4$-alkenols. These alkenols envisage to the *5-exo* and/or *6-endo* cyclizations. Prompted by this fact, we considered it synthetically interested to study the influence of additives, pyridine, and some Lewis acids ($ZnCl_2$ and $FeCl_3$) on reactivity and regioselectivity and stereoselectivity in selenocyclization reaction.

The reactions are performed with two selenylating reagents, PhSeCl and PhSeBr, and equimolar amount of additives, in dichloromethane as solvent, at room temperature. All reactions proceeded to form five- and/or six-membered oxygen heterocycles bearing the phenylseleno moiety. The results of our investigation are shown in Scheme 2 and Table 1.

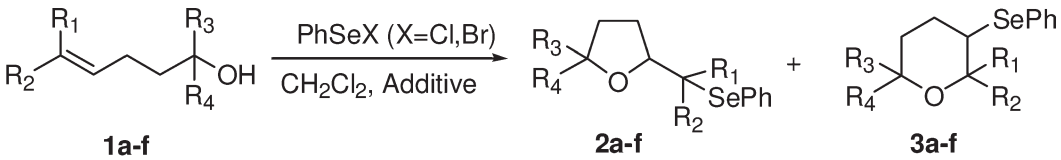
Primary **1a** and secondary **1c** alkenols gave expected tetrahydropyran-type cyclic ether products, while tertiary alkenols **1d–f** gave anti-Markovnikoff tetrahydrofuran-type products predominantly due to stereoelectronic effects.

Cyclization is facilitated by the presence of pyridine and Lewis acids. It became clear that phenylselenyl halides in combination with these additives usually gave rise to cleaner reactions and improved yields compared with phenylselenyl halides alone. Also, the additives increased the reaction rate dramatically. In the case of tertiary alkenols with larger substituents **1d**,**f**, the yields of products decreased regarding to the effects of steric hindrance. Depending on mechanism, this can indeed be expected. As it can be seen from Table 1, pyridine gave the best results, conversion to cyclic products was quantitative in all cases. It appears that the presence of pyridine is beneficial to the cyclizations process due to its basic properties. Function of external base was to neutralize hydrohalogenic acid generated on cyclizations. In the absence of external base, the halide counterion must fulfill this role and an undesired acid-promoted reaction was competitive. All additives could enhance the nucleophilicity of the hydroxyl group of the alkenol and also mediate the stabilization of oxonium ion intermediates.

Although phenylselenoetherification with nonhiral selenium reagents is generally known to give low stereoselectivity [20], very good results were obtained in the cyclizations of $\Delta^3$-alkenols [21]. However, in all cases, stereoselectivity of the ring closure reaction was strongly influenced by the presence and the nature of allylic substituent in the starting alkenol.

In this context, we initiated our study of phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols **1b** under kinetic conditions using both selenium reagents and pyridine, in dichloromethane at temperature ranging from −78°C to room temperature. *cis*-Alcohol is envisage to facilitate the *5-exo*-favored cyclization, while *trans*-isomer facilitate the *6-endo*-unfavored cyclizations by the

**Scheme 2**




**1a-f** **2a-f** **3a-f**

a) $R_1=R_2=R_3=R_4=H$
b) $R_1=R_3=R_4=H$, $R_2=Me$
c) $R_1=R_2=R_3=Me$, $R_4=H$
d) $R_1=R_2=R_3=R_4=Me$
e) $R_1=R_2=R_3=Me$, $R_4=$ethenyl
f) $R_1=R_3=Me$, $R_2=$isoprenyl, $R_4=$ethenyl

**Table 1**

Phenylselenoetherification of $\Delta^4$-Alkenols in the presence of pyridine, $ZnCl_2$, and $FeCl_3$.

| | Yields (%) PhSeCl | | | | Yields (%) PhSeBr | | | |
|---|---|---|---|---|---|---|---|---|
| Alkenol | No additives | Py | $FeCl_3$ | $ZnCl_2$ | No additives | Py | $FeCl_3$ | $ZnCl_2$ |
| 1a | 69 | 100 | 96 | 92 | 63 | 100 | 100 | 98 |
| 1b (*E*) | 81 | 100 | 90 | 92 | 65 | 100 | 96 | 95 |
| 1b (*Z*) | 72 | 100 | 98 | 96 | 75 | 100 | 99 | 98 |
| 1c | 56 | 100 | 78 | 81 | 18 | 100 | 74 | 76 |
| 1d | 37 | 100 | 71 | 75 | 0 | 100 | 60 | 62 |
| 1e | 46 | 100 | 58 | 62 | 0 | 100 | 52 | 55 |
| 1f | 23 | 100 | 53 | 58 | 0 | 100 | 48 | 52 |

Baldwin's rules, yielded regioselectively tetrahydrofurans **2b** (*threo* and *erythro*) and tetrahydropyrans **3b** (*trans* and *cis*), respectively (Scheme 3).

The experimental results, summarized in Table 2, show that more electrophilic PhSeCl was used to drive reaction more completely and maintain better stereoselectivity but the poorer electrophile, PhSeBr, gave reversal stereoselectivity. The results reveal the effect of reaction temperature, which drove the reaction further toward completion and better stereoselectivity. Superior results are obtained with pyridine. Conversion to cyclic ethers was quantitative with increased and reversal stereoselectivity regardless to reagent used. (*E*)-Hex-4-en-1-ol affords six-membered *cis*-izomer predominantly, while (*Z*)-hex-4-en-1-ol affords five-membered *erythro*-isomer as unique product.

We also studied the reactivity and stereoselectivity of these reactions in the presence of equimolar amount of some Lewis acids, which were considered as the perspective candidates. $ZnCl_2$, $FeCl_3$, and $AlCl_3$ were tested at room temperature. As it can be seen from the results obtained, Lewis acids also promoted cyclization process (Table 3). In all cases, reactions were high yielded. Diastereomeric ratio was improved and reversal stereoselectivity in the reactions with PhSeBr was not noticed. (*Z*)-Hex-4-en-1-ol affords five-membered *threo*-isomer, while (*E*)-hex-4-en-1-ol affords six-membered *trans*-isomer predominantly. In the presence of Lewis acids, reactivity of selenium electrophile is independent of nature of counterion.

All used additives can bound counter ion from reagent, increase electrophilicity of PhSe group, and eliminate $X^-$ as a concurrent of hydroxyl group in cyclization step. They could also enhance the nucleophilicity of hydroxyl group of the alkenol and also mediate the stabilization of the oxonium ion intermediates.

In summary, we found that external additives, such as pyridine and Lewis acids coordinating to the electrophilic species are used to control the course of cyclizations with high degrees of efficiency and improve the level of stereoinduction. The course of cyclization can be directed as desired by the choice of the electrophile and the additives used in the reaction.

## EXPERIMENTAL

Gas chromatography/mass spectrometry analyses were obtained with an Agilent Technologies instrument, model 6890 N with HP-5NS columns. $^1H$ and $^{13}C$ NMR spectra were run in $CDCl_3$ on Varian Gemini 200-MHz NMR spectrometer. IR spectra were obtained with Perkin-Elmer FTIR spectrophotometer model Spectrum one. Microanalyses were performed by ''Dornis and Colbe'' and found to be in good agreement with the calculated values. Thin layer chromatography was carried out on 0.25-mm E. Merck precoated silica gel plates (60F-254)

**Scheme 3**

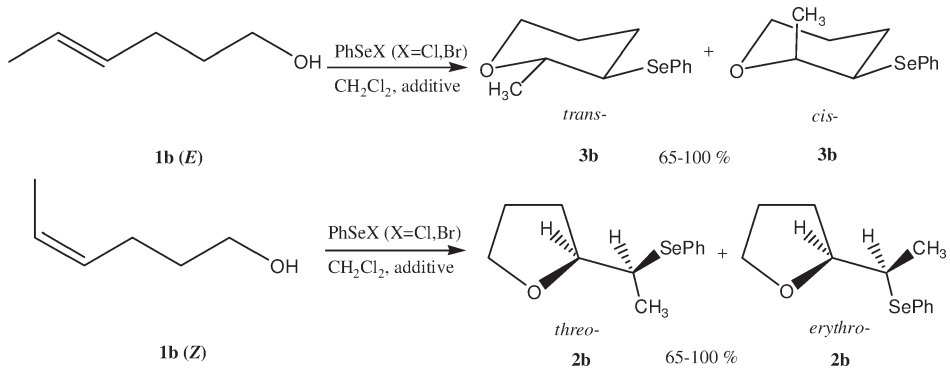


**Table 2**

Phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-ols at different temperature and in the presence of pyridine.

| | Yield and ratio of cyclic products/% | | |
|---|---|---|---|
| Reagent | −78°C | 0°C | Room temperature |
| (*E*)-hex-4-en-1-ol | | | |
| PhSeCl | 85 (87:13) | 83 (75:25) | 81 (69:31) |
| PhSeCl/Py | 100 (95:5) | 100 (74:26) | 100 (24:76) |
| PhSeBr | 77 (80:20) | – | 65 (65:35) |
| PhSeBr/Py | 100 (92:8) | 100 (86:14) | 100 (20:80) |
| (*Z*)-hex-4-en-1-ol | | | |
| PhSeCl | 78 (98:2) | 75 (85:15) | 72 (70:30) |
| PhSeCl/Py | 100 (23:77) | 100 (5:95) | 100 (0:100) |
| PhSeBr | 83 (33:67) | – | 75 (30:70) |
| PhSeBr/Py | 100 (14:86) | 100 (8:92) | 100 (0:100) |

**Table 3**

Phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols in the presence of Lewis acids ($ZnCl_2$, $FeCl_3$, and $AlCl_3$).

| | Yield and ratio of cyclic products/% | | | |
|---|---|---|---|---|
| Substrate | No additives | $ZnCl_2$ | $FeCl_3$ | $AlCl_3$ |
| PhSeCl | | | | |
| (*E*)-1b | 81 (69:31) | 92 (98:2) | 89 (76:24) | 91 (72:18) |
| (*Z*)-1b | 72 (70:30) | 96 (97:3) | 98 (86:14) | 89 (93:7) |
| PhSeBr | | | | |
| (*E*)-1b | 65 (65:35) | 95 (95:5) | 96 (82:18) | 99 (97:3) |
| (*Z*)-1b | 75 (30:70) | 98 (96:4) | 99 (95:5) | 95 (92:8) |

using UV light for visualization. For column chromatography, E. Merck silica gel (60, particle size 0.063–0.200 mm) was used. Alkenols used as substrates are commercially available. Reagents (PhSeCl and PhSeBr) were used as supplied by Aldrich. Dichloromethane was distilled from calcium hydride.

**General procedure.** All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of 1 mmol of alkenol and 1 mmol of additive (0.162 g $FeCl_3$, 0.136 g $ZnCl_2$, or 0.134 g $AlCl_3$) in 5-mL dry dichloromethane was added 0.212 g solid PhSeCl (1.1 mmol) or 0.260 g PhSeBr (1.1 mmol) at room temperature until the solid dissolved. The reaction went to completion virtually instantaneously. Solution was washed with saturated $NaHCO_3$ aqueous solution and brine. Organic layer was dried over $Na_2SO_4$, concentrated, and chromatographed. The products were obtained after the elution of the traces of diphenyl diselenide on a silica gel–dichloromethane column. All the products were characterized and identified on the basis of their spectral data. Cyclic ether products were known compounds and their spectral data have been presented previously [18a].

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## REFERENCES AND NOTES

[1] Mugesh, G.; Du Mont, W. W.; Sies, H. Chem Rev 2001, 101, 2125.

[2] Lord, M. D.; Negri, J. T.; Paquette, L. A. J Org Chem 1995, 60, 191.

[3] (a) Angle, S. R.; White, S. L.; Tetrahedron Lett 2000, 41, 8059; (b) Harmange, J.-C.; Figadere, B.; Tetrahedron: Asymmetry 1993, 4, 1711.

[4] (a) Wesley, J. W. Polyether Antibiotics Naturally Occurring Ionophores; Marcel Dekker: New York, 1982; (b) Boivin, T. L. B.; Tetrahedron 1987, 43, 3309; (c) Bartlett, P. A. Tetrahedron 1980, 36, 2.

[5] Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. J Am Chem Soc 2000, 122, 11348.

[6] (a) Sakabe, N.; Goto, T.; Hirata, Y. Tetrahedron 1977, 33, 3077; (b) Niwa, M.; Endo, T.; Ogiso, S.; Furukava, H.; Yamamura, S. Chem Lett 1981, 1285; (c) Rebuffat, S.; Davoust, D.; Molho, L.; Molho, D. Phytochemistry 1980, 19, 427.

[7] (a) Shimizu, Y. Marine Natural Products: Academic Press: New York, 1978; Vol. 1; (b) Ellis, S. Toxicon 1985, 23, 469.

[8] Sakemi, S.; Higa, T.; Jefford, C. W.; Bernandinelli, G. Tetrahedron Lett 1986, 27, 4287.

[9] (a) Suzuki, T.; Suzuki, A.; Furusaki, T.; Matsumoto, A.; Kato, A.; Imanaka, Y.; Kurosawa, A. Tetrahedron Lett 1985, 26, 1329; (b) Corley, D. G.; Herb, R.; Moore, E.; Scheuer, P. J.; Paul, V. J. J Org Chem 1988, 53, 3644.

[10] Faul, M. M.; Huff, B. E. Chem Rev 2000, 100, 2407.

[11] Postema, M. H. D. Tetrahedron 1992, 48, 8545.

[12] (a) Mark, E. C.; Williams, E. J Chem Soc Perkin Trans 1 2001, 2303; (b) Wolfe, J. P.; Hay, M. B. Tetrahedron 2007, 63, 261; (c) Cardillo, G.; Orena, M. Tetrahedron 1990, 44, 3321.

[13] (a) Beaulieu, P. L.; Désiel, R. In Organoselenium Chemistry; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; (b) Wirth, T. Tetrahedron 1999, 55, 1.

[14] (a) Tiecco, M. Top Curr Chem 2000, 208, 7; (b) Petragnani, N.; Stefani, H. A.; Valduga, C. J. Tetrahedron 2001, 57, 1411; (c) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. Tetrahedron 2004, 60, 5273.

[15] Yamamoto, H.; Ishihara, K. Acid Catalysis in Modern Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2008.

[16] Santelli, M.; Pons, J.-M. Lewis Acids and Selectivity in Organic Synthesis: CRC Press: Boca Raton, Florida, 1996.

[17] D'Onofrio, F.; Parlanti, L.; Piantacelli, G. Tetrahedron Lett 1995, 36, 1929.

[18] (a) Konstantinovic, S.; Bugarcic, Z.; Milosavljevic, S.; Schroth, G.; Mihailovic, M. Lj. Liebigs Ann Chem 1995, 34, 354; (b) Mojsilovic, B. M.; Bugarcic, Z. M. Heteroat Chem 2001, 12, 475; (c) Bugarcic, Z. M.; Dunkic, J. D.; Mojsilovic, B. M. Heteroat Chem 2004, 15, 468; (d) Bugarcic, Z. M.; Mojsilovic, B. M. Heteroat Chem 2004, 15, 146; (e) Bugarcic, Z. M.; Mojsilovic, B. M.; Divac, V. M. J Mol Catal A 2007, 272, 288; (f) Divac, V. M.; Rvovic, M. D.; Bugarcic, Z. M. Monatsh Chem 2008, 139, 1373.

[19] Petrovic, Z.; Mojsilovic, B.; Bugarcic, Z. J Mol Catal A 1999, 142, 393.

[20] Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III, J Org Chem 1987, 52, 4191.

[21] (a) Landais, Y.; Planchenault, D.; Weber, V. Tetrahedron Lett 1995, 36, 2987; (b) Landais, Y.; Planchenault, D. Synlett 1995, 1191; (c) Tiecco, M.; Testaferi, L.; Santi, C. Eur J Org Chem 1999, 797; (d) Lipshutz, B. H.; Gross, T. J Org Chem 1995, 60, 3572.

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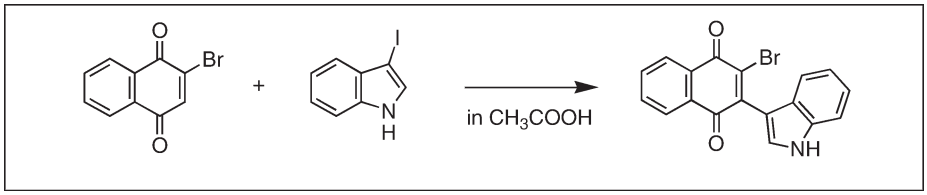


The usefulness of 3-iodoindole available for introduction of an indole unit is presented. The reaction of 3-iodoindole with 2-bromo(or methyl)-1,4-naphthoquinone in acetic acid gave 2-bromo(or methyl)-3-(3-indolyl)-1,4-naphthoquinone. On the other hand, the reaction of 3-iodoindole with 2-bromo-1,4-naphthoquinone in the presence of cesium carbonate in acetonitrile produced 2-(1-indolyl-3-iodo)-1,4-naphthoquinone.

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## INTRODUCTION

An indole unit naturally occurs in indole alkaloids and many of the naturally occurring compounds have physiologically important activities [1]. Some reports have appeared concerning the reaction of indoles with the 1,4-naphthoquinones. For example, Bu'Lock and Mason [2] reported that the reaction of indole (**1**) with 1,4-naphthoquinone (**2**) gave 2-(3-indolyl)-1,4-naphthoquinone (**3**) in acetic acid at room temperature for 7 days without describing the yield. Prota and coworkers [3] found that the reaction of **1** with **2** afforded **3** in acidic ethanol at room temperature for 1 h in the moderate yield.

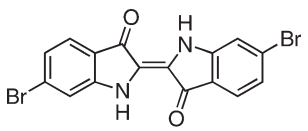
In previous articles [4,5], we reported the syntheses of Tyrian purple (**4**) (Fig. 1) [6] and its related compounds using 3-iodoindoles. Moreover, we have revealed the usefulness of 3- iodoindoles available for introduction of an indole unit [7]. The 3-iodoindole compounds are labile, therefore, not commercially available. However, the compounds are easily synthesized from the corresponding indoles. This article describes the reaction of 3-iodoindole with 1,4-naphthquinones.

## RESULTS AND DISCUSSION

The reaction of 3-iodoindole (**5**) with 2-bromo-1,4-naphthoquinone (**6**) in acetic acid at room temperature for 3 days gave the 2-bromo-3-(3-indolyl)-1,4-naphthoquinone (**7**) in 72% yield. The mass spectrum of the product (**7**) exhibits the molecular ion peak at *m*/*z* 351 and 353 in the ratio of 1 to 1. The $^1$H NMR spectrum of **7** shows a doublet peak ($J$ = 2.8 Hz) at $\delta$ = 8.24 due to H-2′.

On the other hand, the same reaction was carried out in the presence of cesium carbonate in acetonitrile at room temperature for 1 day to give 2-(1-indoly-3-iodo)-1,4-naphthoquinone (**8**) in 19% yield with **7** in 5% yield (Scheme 1). The structure of the product (**8**) was mainly based on the NMR spectral data and MS spectral data. The $^1$H NMR spectrum shows signals at $\delta$ = 7.17 (singlet) and 7.68 (singlet) due to H-3 and H-2′, respectively. The $^{13}$C NMR spectrum shows a signal at $\delta$ = 64.28 due to C-I. The mass spectrum clearly exhibits a molecular ion peak at *m*/*z* 399.

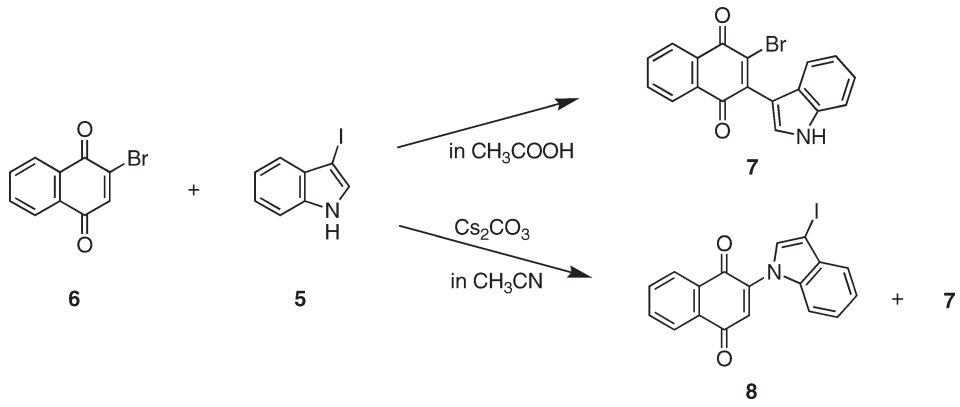
We have already reported the reaction of **5** with **2** in acetic acid at 90°C for 40 min to give **3** in 74% yield [7]. The same reaction was carried out in the presence




**4**

**Figure 1.** Tyrian purple.

**Scheme 1**




of cesium carbonate in acetonitrile at room temperature for 1 day, but the iodo compound (**8**) was not obtained (Scheme 2).

We next applied the reaction of Scheme 1 to 2-methyl-1,4-naphthoquinone (**9**) (Scheme 3). The treatment of **5** with **9** in acetic acid at room temperature for 4 days gave 2-methyl-3-(3-indolyl)-1,4-naphthoquinone (**10**) in 62% yield.

The structure of the product (**10**) was mainly determined on the basis of the NMR spectral data and MS spectral data. The $^1$H NMR spectrum shows signals at $\delta = 2.21$ (singlet) and $\delta = 7.43$ (singlet) due to $CH_3$ and H-2′, respectively. The $^{13}$C NMR spectrum shows a signal at $\delta = 15.76$ due to $CH_3$. The mass spectrum clearly exhibited a molecular ion peak at *m*/*z* 287. The same reaction was carried out in the presence of cesium carbonate in acetonitrile at room temperature for a day, but the compound (**10**) instead of the iodo compound was obtained in 23% yield.

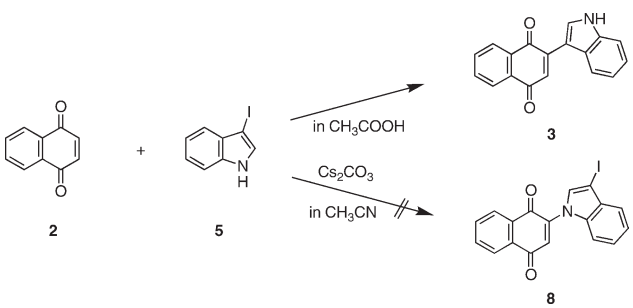
## EXPERIMENTAL

The $^1$H NMR and $^{13}$C NMR spectra were obtained using a JEOL JNM-A500 (500 MHz) spectrometer at room temperature. The chemical shifts are given in ppm relative to tetramethylsilane as an internal reference standard. The EI mass spectra were performed using a JEOL JMS-SX 102A mass spectrometer. The infrared spectra were recorded using a Shimadzu IR 470 spectrometer in potassium bromide pellets. The melting points were obtained using a Yanaco MS-S3 micro melting point apparatus (hotplate type). For the preparative column chromatography, Wakogel C-200 silica gel was employed. Thin-layer chromatography (TLC) was accomplished on precoated plates of silica gel 60 $F_{254+366}$ (Merck). 2-Bromo-1,4-naphthquinone and 2-methyl-1,4-naphthoquinone were purchased from Aldrich (USA) and Tokyo Kasei Kogyo Co. (Tokyo, Japan), respectively.

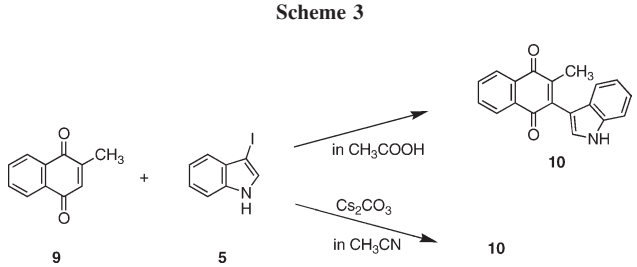
**3-Iodoindole (5).** 3-Iodoindole was prepared using a modified procedure of Arnold's method [8]. To a solution of indole (**1**) (100 mg, 0.85 mmol) in methanol (10 mL) was added sodium hydroxide (34 mg, 0.85 mmol). After the mixture was stirred at room temperature for 10 min, iodine (217 mg, 0.85 mmol) and an aqueous solution (1 mL) of potassium iodide (142 mg, 0.85 mmol) was added. The mixture was further stirred at room temperature for 10 min and the water was then added. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo* to obtain **5** (167 mg), which was used for the following reaction without its purification because of its lability.

**2-Bromo-3-(3-indolyl)-1,4-naphthoquinone (7).** A solution of 3-iodoindole (**5**) (149 mg, 0.61 mmol) and 2-bromo-1,4-naphthoquinone (**6**) (145 mg, 0.61 mmol) in acetic acid (10 mL) was stirred at room temperature for 3 days. After the mixture was concentrated under reduced pressure, the residue was chromatographed on silica gel with chloroform to give **7** (62 mg) in 29% yield with the starting material **6** (86 mg). The yield based on the amount of the consumed quinone was 72%. The product **7** was recrystallized with ethyl acetate–hexane (1:1), mp 202–205°C; ir (potassium bromide): 3335 (NH), 1661, 1588, 1547, 1421, 1269, 745, 717 cm$^{-1}$; $^1$H NMR

**Scheme 2**




**Scheme 3**



($CDCl_3$): δ 7.30 (m, 1H, H-5′), 7.46 (m, 2H, H-6′, 7′), 7.76 (m, 2H, H-4′, 6), 7.99 (m, 1H, H-7), 8.13 (m, 1H, H-8), 8.17 (m, 1H, H-5), 8.24 (d, 1H, $J$ = 2.8 Hz, H-2′), 8.74 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$): δ 109.00, 111.92, 113.29, 117.48, 120.44, 121.90, 123.37, 125.89, 126.89, 129.73, 130.98, 132.24, 133.31, 136.32, 142.03, 144.47, 178.39 (C=O), 182.06 (C=O); MS (EI) *m/z* (relative intensity) 353 (M+2, 52%), 351 ($M^+$, 47), 274 (57), 273 (100), 272 (63), 217 (62), 216 (45), 189 (37); HRMS (EI) calcd. for $C_{18}H_{10}O_2NBr$, $M^+$ 350.9895, found 350.9884.

**2-(1-Indolyl-3-iodo)-1,4-naphthoquinone (8).** A mixture of 3-iodoindole (**5**) (142 mg, 0.58 mmol), 2-bromo-1,4-naphthoquinone (**6**) (139 mg, 0.58 mmol), and cesium carbonate (190 mg, 0.58 mmol) in acetonitrile (10 mL) was stirred at room temperature for 1 day. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel with chloroform, followed by chromatography of TLC (silica gel; $CHCl_3$: $CH_3CN$ = 20:1) to give **8** (44 mg) in 19% yield along with **7** (11 mg) in 5% yield. The product **8** was recrystallized with ethyl acetate–hexane (3:1), mp 196–198°C; ir (potassium bromide): 1670, 1654, 1609, 1603, 1591, 1573, 1448, 1287, 1204, 732, 717 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 7.17 (s, 1H, H-3), 7.31–7.38 (m, 2H, H-5′, 6′), 7.51 (dd, 1H, $J$ = 1.0, 7.5 Hz, H-7′), 7.56 (dd, 1H, $J$ = 1.0, 7.5 Hz, H-4′), 7.68 (s, 1H, H-2′), 7.80–7.86 (m, 2H, H-6, 7), 7.17 (dd, 1H, $J$ =1.0, 7.5 Hz, H-5), 8.22 (dd, 1H, $J$ = 1.0, 7.5 Hz, H-8); $^{13}$C NMR ($CDCl_3$): δ 64.28 (C-I), 112.03, 122.15, 123.10, 124.57, 125.95, 126.28, 127.34, 131.54, 131.77, 132.12, 132.84, 134.04, 134.69, 135.45, 141.95, 181.05 (C=O), 184.32 (C=O); MS (EI) *m/z* (relative intensity) 399 ($M^+$, 100%), 272 (59), 244 (21), 216 (36), 136 (20); HRMS (EI) calcd. for $C_{18}H_{10}O_2NI$, $M^+$ 398.9756, found 398.9760.

**2-Methyl-3-(3-indolyl)-1,4-naphthoquinone (10).** A solution of 3-iodoindole (**5**) (167 mg, 0.69 mmol) and 2-methyl-1,4-naphtoquinone (**9**) (118 mg, 0.69 mmol) in acetic acid (10 mL) was stirred at room temperature for 4 days. After the mixture was concentrated under reduced pressure, the residue was chromatographed on silica gel with chloroform, followed by TLC (silica gel; $CHCl_3$: $CH_3CN$ = 20:1) to give **10** (31 mg) in 16% yield with the starting material **9** (77 mg). The yield based on the amount of the consumed quinone was 62%. The product **10** was recrystallized with ethyl acetate–hexane (2:1), mp 252–254°C; ir (potassium bromide): 3340 (NH), 1653, 1594, 1288, 746, 718 $cm^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.21 (s, 3H, $CH_3$), 7.15–7.18 (m, 1H, H-5′), 7.22–7.26 (m, 1H, H-6′), 7.32 (d, 1H, $J$ = 8.2 Hz, H-7′), 7.43 (s, 1H, H-2′), 7.46 (d, 1H, $J$ = 8.2 Hz, H-4′), 7.74 (m, 2H, H-6, 7), 8.16 (m, 2H, H-5, 8), 9.38 (broad, 1H, NH); $^{13}$C NMR ($CDCl_3$): δ 15.76 ($CH_3$), 108.28, 111.69, 111.74, 120.37, 120.42, 122.30, 126.19, 126.70, 127.22, 132.48, 132.52, 133.46, 133.53, 135.80, 140.43, 143.30,184.76 (C=O), 185.99 (C=O); MS (EI) *m/z* (relative intensity) 287 ($M^+$, 100%), 270 (56), 230 (16), 154 (10); HRMS (EI) calcd. for $C_{19}H_{13}O_2N$, $M^+$ 287.0946, found 287.0973.

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## REFERENCES AND NOTES

[1] Toyota, M.; Ihara, N. Nat Prod Rep 1998, 15, 327.

[2] Bu'Lock, J. D.; Harley – Mason, J. J Chem Soc 1951, 703.

[3] Corradini, M. G.; Costantini, C.; Prota, G.; Schultz, T. M. Gazz Chim Ital 1989, 119, 153.

[4] Tanoue, Y.; Terada, A.; Sakata, K.; Hashimoto, M.; Morishita, S.; Hamada, M.; Kai, N.; Nagai, T. Fish Sci 2001, 67, 726.

[5] Tanoue, Y.; Sakata, K.; Hashimoto, M.; Hamada, M.; Kai, N.; Nagai, T. Dyes Pigm 2004, 62, 101.

[6] McGovern, P. E.; Michel, R. H. Acc Chem Res 1990, 23, 152.

[7] Tanoue, Y.; Hamada, M.; Kai, N.; Sakata, K.; Hashimoto, M.; Nagai, T. J Heterocycl Chem 2005, 42, 1195.

[8] Arnold, R. D.; Nutter, W. M.; Stepp, W. L. J Org Chem 1959, 24, 117.

# Synthesis of Novel Carbazolyl-Oxazolone Derivatives and Their Spectroscopic Properties

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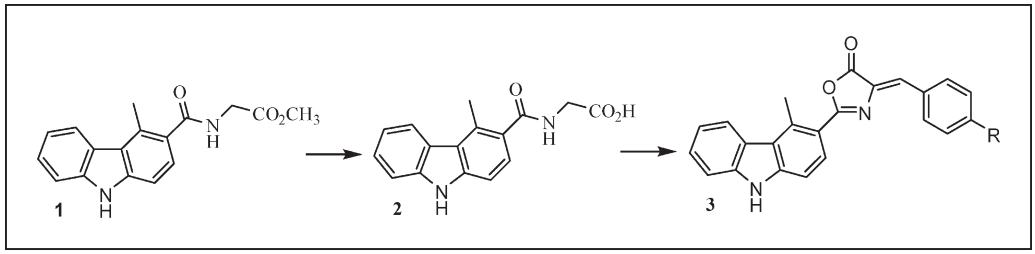


Novel carbazolyl-oxazolones, **3a–d**, were synthesized with 3-[*N*-(2-hydroxycarbonylmethyl)-carboxamide]-4-methyl-9*H*-carbazole and several aryl aldehydes for the first time. Photo physical characterization of synthesized 2-carbazolyl-4-arylidene-5-oxazolones (**3a–d**) in dichloromethane, chloroform, and toluene was performed.

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## INTRODUCTION

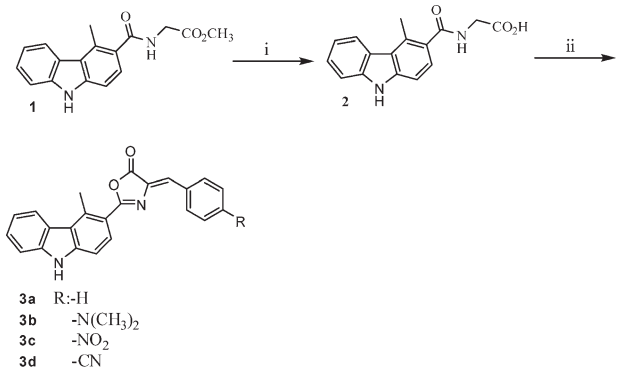
Carbazole [1–6] and oxazolone [7,8] moieties have received great attention by chemist not only because of their biological properties, but also for their technological importance. Oxazolones that are internal anhydrides of acyl amino acids are important class of five-membered heterocycles. They are highly versatile intermediates used for the synthesis of several organic molecules, including amino acids, peptides, antimicrobial or antitumor compounds, immunomodulators, heterocyclic precursors, for biosensors coupling, and/or photosensitive composition devices for proteins. They can be easily prepared from *N*-acyl amino acids by dehydration. 5-Oxazolones also have a wide range of applications including their use in semiconductor devices because of their promising photophysical and photochemical activities [9]. Carbazole derivatives are important optical materials due to their special photorefractive, electrical, and chemical properties [2–6].

2-Aryl-4-carbazolyliden-5-oxazolones were first synthesized *via* an Erlenmeyer reaction of the carbazole aldehyde derivatives with several *N*-benzoyl glycine derivatives and their optical properties were studied [10,11]. We recently synthesized several 5-oxazolone derivatives and investigated their basic photophysical and sensor characteristics by using UV-vis and fluorescence spectroscopy [12–18]. Herein, we prepared novel 2-carbazolyl-4-arylidene-5-oxazolones (**3a–d**) with a carbazole glycine derivative for the first time. This work also describes the photophysical characterization of 2-carbazolyl-4-arylidene-5-oxazolones (**3a–d**) in dichloromethane, chloroform, and toluene. We also examined the correlation between the molecular structures and their fluorescent properties.

## RESULTS AND DISCUSSION

We synthesized novel 2-carbazolyl-4-arylidene-5-oxazolones (3a–d) with a carbazole glycine derivative for the first time (Fig. 1). Thus, we aimed to combine the advantages of carbazole structures and 5-oxazolone derivatives. We used a carbazole glycine ester 1 derivative as a starting material, which was synthesized previously by our group [19]. Then, the hydrolysis of carbazole glycine ester 1 in basic conditions gave the glycine derivative of carbazole 2 [20]. Finally, 2-carbazolyl-4-arylidene-5-oxazolones were synthesized with carbazole glycine derivative 2 and several aryl aldehydes by an Erlenmeyer reaction.

Also, the absorption and emission spectral properties of (**3a–d**) were also investigated in dichloromethane, chloroform, and toluene (Table 1). The results obtained show that the nature of the substituent groups on the aryl moiety influences the absorption and fluorescence emission maxima. The absorption maxima of **3a–d** derivatives were observed between 393 and 470 nm (Table 1, Fig. 2). The excitation wavelengths were chosen as 410, 473, 442, and 441 nm for **3a–d**, respectively, and the emission spectra were recorded.




**Reagent and Conditions: i)** $LiOH.H_2O$, ethanol; **ii)** NaOAc, $Ac_2O$, ArCHO

**Figure 1.** The synthesis route and structural formulas of **3a–d**.

Emission and related excitation spectra of **3c** in dichloromethane are shown in Figure 3. The excitation spectral data were acquired by exciting the molecule at its emission maximum. The chromophore system is affected by the electron donor group (carbozolyl groups) and electron acceptor groups (4-nitrophenyl and cyanophenyl) of **3c** and **3d** derivatives. Thus, the emission maxima are red shifted for **3c** and **3d** in comparison to **3a**. As the nitro group is a stronger electron acceptor than a cyano group, **3c** has a longer emission wavelength maximum. A bathocromic shift was also observed for **3b**, which has an *N*,*N*-dimethylamino moiety, a strong electron donor group. The Stokes' shift values were calculated for all derivatives and the highest Stokes' shift values were obtained for **3c** and **3d**. For all derivatives studied, the Stokes shift values are higher in chloroform and dichloromethane, in comparison to the values obtained in toluene. This result indicates that as the solvents polarity decreases, the Stokes shift values decrease as well.

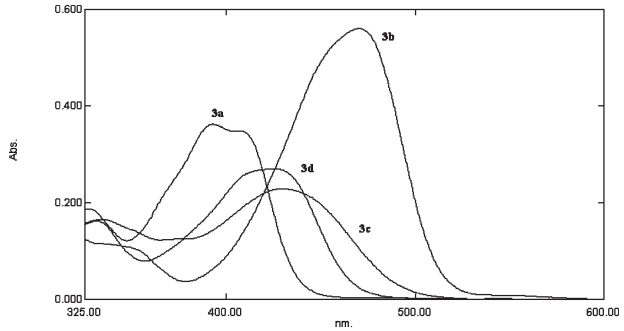



**Figure 2.** Absorption spectra of compounds **3a–3d** measured in dichloromethane ($1 \times 10^{-5}$ *M*).

HPTS was used as reference quantum yield standard $\lambda_{ex} = 400$ nm, quantum yield = 1, in acidic water for 3a; and $\lambda_{ex} = 470$ nm, quantum yield = 1, in basic water for **3c–d**. Fluorescence quantum yields ($\Phi_F$) were determined by the formula [21]:

$$\Phi = \Phi_{std} \times (FA_{std}\eta^2)/(FA_{std}\eta_{std}^2)$$

where $F$ and $F_{std}$ are the areas under the fluorescence emission curves of the samples and the standard, respectively. $A$ and $A_{std}$ are the respective absorbance of the samples and standard at the excitation wavelength, respectively, and $\eta$ and $\eta_{std}$ the refractive indexes of solvents used for the samples and standard, respectively. **3c** and **3d** in toluene exhibited the highest quantum yield values of 0.7675 and 0.9323, respectively. This can be explained by the charge transfer efficiency of the molecules in the excited state. Electron accepting 4-nitro and cyano substituents increase π-electron mobility much more than the electron donating 4-dimethylamino substituent at the same position resulting in high charge separation properties of **3c** and **3d**. This can also be attributed to the fact that, more polar solvents provide

**Table 1**

Absorption and fluorescence emission data for compounds **3a–d** (λ, nm and ε, l $mol^{-1}$ $cm^{-1}$), stokes shifts, Δλ (nm), singlet energy, $E_s$ (kcal $mol^{-1}$), and fluorescence quantum yield, Φ in solutions.

| Compound | Solvent | $\lambda_{max}^{ab}$ | $\varepsilon_{max}$ | $\lambda_{max}^{f}$ | Δλ | $E_s$ | Φ |
|---|---|---|---|---|---|---|---|
| 3a | Chloroform | 412 | 9600 | 484 | 72 | 69.2 | 0.2462 |
| 3b | | 462 | 18000 | 514 | 52 | 61.7 | 0.0025 |
| 3c | | 439 | 11600 | 565 | 126 | 64.9 | 0.0535 |
| 3d | | 432 | 34000 | 522 | 90 | 66.0 | 0.2274 |
| 3a | Toluene | 414 | 33000 | 438 | 24 | 68.8 | 0.3374 |
| 3b | | 467 | 14400 | 496 | 29 | 61.0 | 0.0056 |
| 3c | | 453 | 5000 | 508 | 55 | 62.9 | 0.7675 |
| 3d | | 436 | 9200 | 475 | 39 | 65.4 | 0.9323 |
| 3a | Dichloromethane | 393 | 36000 | 479 | 86 | 72.6 | 0.3710 |
| 3b | | 470 | 56000 | 520 | 50 | 60.7 | 0.0026 |
| 3c | | 430 | 22000 | 592 | 162 | 66.3 | 0.0300 |
| 3d | | 423 | 27000 | 523 | 100 | 65.5 | 0.1172 |

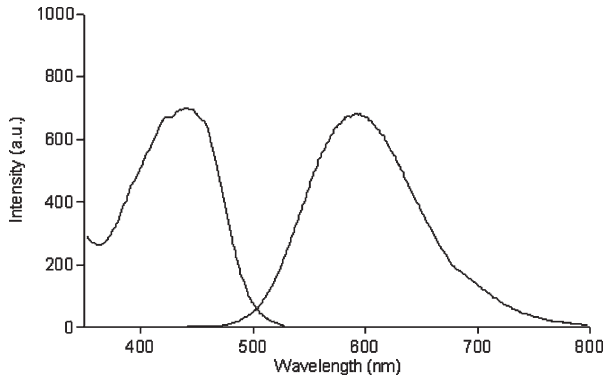



**Figure 3.** Emission and excitation spectra of **3c** in dichloromethane.

**3c** and **3d** freedom to rotate and vibrate which serve as the nonradiative transitions.

The photostabilities of **3a–d** derivatives were recorded with a steady-state spectrofluorimeter in dichloromethane, chloroform, and toluene (Fig. 4). The data were acquired at their maximum emission wavelengths after exposure to xenon arc lamp for 1 h of monitoring. All derivatives exhibited excellent photostability in three of the solvents studied.

## CONCLUSION

Four different carbazolyl–oxazolones derivatives were synthesized for the first time. All derivatives displayed emission maxima in the range of 438–592 nm and excellent photostabilities. The highest quantum yield value was determined for 3d in toluene, 0.9323, which is quite promising. Considering the absorption and fluorescence emission maxima, 3c and 3d are expected to be good probes for biological applications. Our next goal is to investigate their performance as ion sensors for biological applications.

## EXPERIMENTAL

All solvents were of analytical grade and purchased from Merck (Darmstadt, Germany), Fluka (Buchs, Switzerland), and Riedel (Seelze, Germany). All melting points were measured in sealed tubes using an electrothermal digital melting points apparatus (Southend, UK) and are uncorrected. Infrared spectra were recorded on a Perkin Elmer (Massachusetts, USA) FTIR infrared spectrometer (spectrum BX-II). $^1$H NMR spectra were obtained on a high resolution fourier transform Bruker WH-400 NMR spectrometer (Coventry, UK) with tetramethylsilane as an internal standard. Mass spectra were determined on the electron impact mode by direct insertion at 70 eV with a Micromass UK Platform II LC-MS spectrometer (Manchester, UK). Combustion analysis of compounds was obtained on a CHNS-932-LECO (St. Joseph, MI). Analytical and preparative thin layer chromatographies (TLC) were carried out using silica gel 60 $F_{254}$ (Merck). Column chromatography was carried out by using 70–230 mesh silica gel (0.063–0.2 mm, Merck). UV/visible absorption spectra were recorded with Schimadzu UV-1601 spectrophotometer (Tokyo, Japan). All fluorescence measurements were undertaken by using Varian-Carry Eclipse spectrofluorimeter (Mulgrave, Australia). 1-hydroxypyrene-3,6,8-trisulfonate trisodium salt (HPTS) purchased from Fluka was used as reference standard for fluorescence quantum yield calculations of **3a–d**.

**3-[*N*-(2-Hydroxycarbonylmethyl)-carboxamide]-4-methyl-9H-carbazole (2).** A solution of 1 (1.5 g, 5 mmol) and lithium hydroxide monohydrate (0.21 g, 5 mmol) in 25 mL of ethanol was stirred for 2 h. The solvent was removed under reduced pressure and the residue was diluted with water and acidified with concentrated hydrochloric acid. The solution was extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the resulting residue was recrystallized from ether to afford 1.30 g (91%) of 2 as a white solid, mp 273°C; ir (potassium bromide): ν 3403(NH), 3260 (NH), 2921 (CH), 1703 (ester C=O), 1631 (amide C=O) cm$^{-1}$; $^1$H NMR ($d_6$-dimethyl sulfoxide): δ 2.88 (s, 3H, $CH_3$), 3.92 (d, 2H, CONHC$H_2$, $J$ = 6.0 Hz), 7.18 (d, 1H, $J$ = 8.0 Hz, ArH), 7.33 (d, 1H, $J$ = 8.4 Hz, ArH), 7.37–7.44 (m,1H, ArH) 7.50 (d, 1H, $J$ = 8.4 Hz, ArH), 8.18 (d, 1H, $J$ = 8.4 Hz, ArH), 8.42 (t, 1H, $J$ = 6.0 Hz, CON$H$CH$_2$), 11.40 (s, 1H, NH), 12.50 (bs,1H, OH); ms (70 eV): *m*/*z*% 284 (7.7), 283 (65), 209 (13.1), 208 (100), 73 (26.7). Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.03; H, 5.38; N, 10.91.

**General methods for the synthesis of phenyl carbazole oxazolones (3a–d).** Aldehyde (6 mmol), 3-[*N*-(2-hydroxycarbonylmethyl)-carboxamide]-4-methyl-9*H*-carbazole (6 mmol), acetic anhydride (2.49 mL, 12 mmol), and sodium acetate (0.87 g, 6 mmol) was heated until the mixture just liquefied, and then heating was continued for further 2 h. After completion of the reaction (determined by thin layer chromatography), ethanol (25 mL) was added and mixture was kept at room temperature for 18 h. The solid product thus obtained was purified by washing with cold ethanol, hot water, and small amount of hexane. The solid was recrystallized from hot ethanol to afford carbazolyl-oxazolone.

***2-(4-Methyl-9H-carbazol-3-yl)-4-benzylidene-oxazol-5(4H)-one (3a).*** mp: 152°C; ir (potassium bromide): ν 3365 (NH), 1770 (—*O*—*C*=*O*), 1644(—*C*=*N*—), 1167(—*O*—*C*=*O*) cm$^{-1}$; $^1$H NMR ($d_6$-dimethyl sulfoxide): δ 3.39 (s, 3H, $CH_3$), 7.19 (s, 1H, Ar-CH=C), 7.24 (t, 1H, $J$ = 7.2 Hz, ArH), 7.43–7.56 (m, 6H, ArH), 8.00 (d, 1H, $J$ = 8.4 Hz, ArH), 8.24–8.29 (m, 3H, ArH), 11.8 (s, 1H, NH); ms (70 eV): *m*/*z* % 354 (26.9),

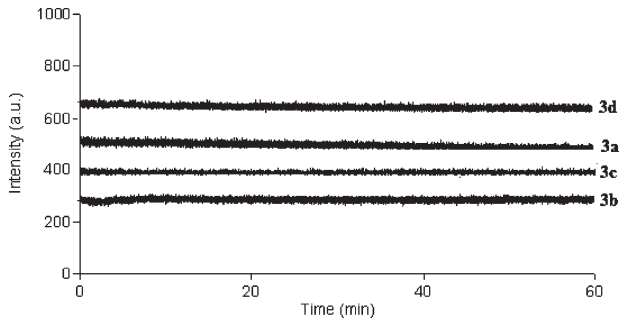



**Figure 4.** The photostability test result of **3a–d** in toluene after 1 h of monitoring.

353 (100), 314 (24.9), 286 (28.6), 284 (24.4), 258 (19.9), 256 (12), 230 (11.2), 208 (71.1), 73 (51.1). Anal. Calcd. for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.23; H, 4.52; N, 8.04.

***2-(4-Methyl-9H-carbazol-3-yl)-4-(4-(dimethylamino)benzylidene)-oxazol-5(4H)-one (3b).*** mp 139°C; ir (potassium bromide): ν 3269 (NH), 1747 (—O*C*=*O*), 1620 (—*C*=*N*—), 1162 (—*O*—*C*=O) $cm^{-1}$; $^1H$ NMR ($d_6$-dimethyl sulfoxide): δ 3.11 (s, 6H, $N(CH_3)_2$), 3.40 (s, 3H, $CH_3$), 6.77 (d, 2H, $J$ = 8 Hz, ArH), 7.13 (s, 1H, Ar-CH=C), 7.24–7.52 (m, 6H, ArH), 8,14 (d, 2H, $J$ = 8 Hz, ArH), 11.9 (s, 1H, NH); ms (70 eV): *m*/*z*% 397 (16), 396 (100), 356 (8.0), 340 (7.1), 334 (4.9), 304 (11.5), 236 (18.5), 214 (75.7), 198 (69.1). Anal. Calcd. for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63. Found: C, 75.71; H, 5.41; N, 10.69.

***2-(4-Methyl-9H-carbazol-3-yl)-4-(4-nitrobenzylidene)-oxazol-5(4H)-one (3c).*** mp 143°C; ir (potassium bromide): ν 3419 (NH), 1784 (—O*C*=*O*), 1650 (—*C*=*N*—), 1539 and 1508 (-$NO_2$), 1171 (—*O*—*C*=O) $cm^{-1}$; $^1H$ NMR ($d_6$-dimethyl sulfoxide): δ 3.34 (s, 3H, $CH_3$), 7.25 (s, 1H, Ar-CH=C), 7.45–7.51 (m, 4H, ArH), 7.57 (d, 1H, $J$ = 8.0 Hz, ArH), 8.05 (d, 1H, $J$ = 8.8 Hz, ArH), 8.30 (d, 2H, $J$ = 8.8 Hz, ArH), 8.47 (d, 2H, $J$ = 8.4 Hz, ArH), 11.9 (s, 1H, NH); ms (70 eV): *m*/*z*% 398 (4.8), 397 (30.1), 396 (100), 314 (14.5), 286 (16.7), 258 (19), 230 (77), 208 (7.5), 73 (36.7). Anal. Calcd. for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10.57. Found: C, 69.40; H, 3.73; N, 10.63.

***2-(4-Methyl-9H-carbazol-3-yl)-4-(4-cyanobenzylidene)-oxazol-5(4H)-one (3d).*** mp 138°C; ir (potassium bromide): ν 3340 (NH), 2227 (CN), 1793(—O*C*=*O*), 1644(—*C*=*N*—), 1165 (—*O*—*C*=O) $cm^{-1}$; $^1H$ NMR ($d_6$-dimethyl sulfoxide): δ 3.24 (s, 3H, $CH_3$), 7.11 (s, 1H, Ar—CH=C), 7.22 (t, 1H, $J$ = 7.6 Hz, ArH), 7.42 (d, 2H, J=8.4 Hz, ArH), 7.52 (d, 1H, $J$ = 8.0 Hz, ArH), 7.84 (d, 2H, $J$ = 8.0 Hz, ArH), 7.96 (d, 1H, $J$ = 8.4 Hz,ArH), 8.22 (d, 1H, $J$ = 8.0 Hz, ArH), 8.28(d, 2H, $J$ = 8.4 Hz, ArH), 11.8 (s, 1H, NH); ms (70 eV): *m*/*z*% 378 (0.9), 377 (0.2), 360 (8.9), 315 (24), 314 (100), 286 (78.7), 258 (72.3), 230 (96), 73 (80.6). Anal. Calcd. for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.13. Found: C, 76.51; H, 4.06; N, 11.04.

## REFERENCES AND NOTES


[1] Knölker, H. J.; Reddy, K. R. Chem Rev 2002, 102, 4303.

[2] Yoon, K. R.; Ko, S. O.; Lee S. M.; Lee, H. Dyes Pigm 2007, 75, 567.

[3] Ying, Q. Dyes Pigm 2008, 76, 277.

[4] Xing, Y.; Xu, X.; Zhang, P.; Tian, W.; Yu, G.; Lu, P.; Liu Y.; Zhu, D. Chem Phys Lett 2005, 408, 169.

[5] Mishra, A. K.; Jacob J.; Müllen, K. Dyes Pigm 2007, 75, 1.

[6] Bai, G.; Li, J.; Li, D.; Dong, C.; Han X.; Lin, P. Dyes Pigm 2007, 75, 93.

[7] Grigoras M.; Antonoaia, N. C. Eur Polym J 2005, 41, 1079.

[8] Khan, K. M.; Mughal, U. R.; Khan, M. T. H.; Ullah, Z.; Perveenb S.; Choudhary, M. I. Bioorg Med Chem 2006, 14, 6027.

[9] Ozturk, G.; Alp S.; Ertekin, K. Dyes Pigm 2007, 72, 150.

[10] Dıaz, J. L.; Villacampa, B.; Lopez-Calahorraa, F.; Velascoa, D. Tetrahedron Lett 2002, 43, 4333.

[11] Dıaz, J. L.; Villacampa, B.; Lopez-Calahorra, F.; Velasco, D. Chem Mater 2002, 14, 2240.

[12] Ozturk, G.; Alp S.; Ergun, Y. Tetrahedron Lett 2007, 48, 7347.

[13] Icli, S.; Doroshenko, A. O.; Alp, S.; Abmanova, N. A.; Egoorova, S. I.; Astley, S. T. Spectrosc Lett 1999, 32, 553.

[14] Icli, S.; Icil, H.; Alp, S.; Koc, H.; McKillop, A. Spectrosc Lett 1994, 27, 1115.

[15] Ertekin, K.; Alp, S.; Karapire, C.; Yenigül, B.; Henden, E.; Icli, S. J Photochem Photobiol A Chem 2000, 137, 155.

[16] Ertekin, K.; Karapire, C.; Alp, S.; Yenigul, B.; Icli, S. Dyes Pigm 2003, 56, 125.

[17] Ertekin, K.; Cinar, S.; Aydemir, T.; Alp, S. Dyes Pigm 2005, 67, 133.

[18] Ertekin, K.; Alp, S.; Yalcın, I. Dyes Pigm 2005, 65, 33.

[19] Ergün, Y.; Gülle, S.; Çagdas, A. B.; Göçmentürk, M.; Okay, G. Asian J Chem 2010, 22, 1853.

[20] Sharma, V.; Lansdell, T. A.; Jin, G.; Tepe, J. J. J Med Chem 2004, 47, 3700.

[21] Ozturk, G.; Förstel, M.; Ergun, Y.; Alp, S.; Rettig, W. J Fluoresc 2008, 18, 1007.

# Toward a Novel Approach to Bis-β-Lactam Synthesis Using Vilsmeier Reagent as an Efficient Entity *via* Staudinger Cycloaddition Reaction



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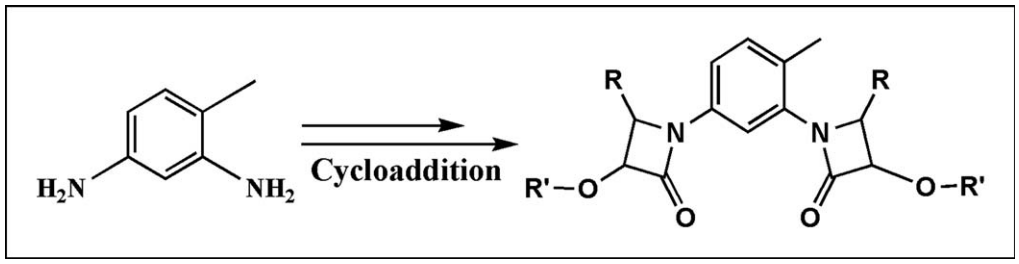


A facile synthesis of bis-β-lactams has been executed using chloromethylenedimethylammonium chloride (Vilsmeier reagent), prepared easily from *N*,*N*-dimethylformamide and phosphorus oxychloride. It works out as a versatile acid activator reagent for the direct [2 + 2] ketene–imine cycloaddition of substituted acetic acid and bis-imines in one-pot synthesis under mild conditions. Thus, this method has been proved as a high yielding, efficient, and cheap protocol for bis-β-lactam synthesis.

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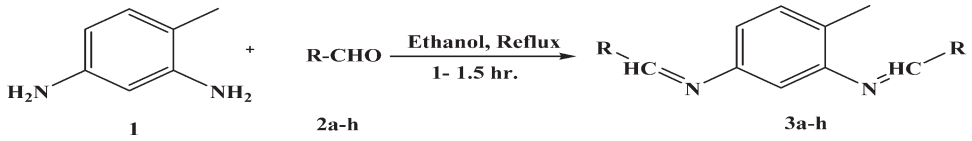
## INTRODUCTION

The β-lactam skeleton is the key structural unit of the most widely employed β-lactam antibiotics [1]. The constant need for new drugs displaying broader antibacterial activity and the necessity for new β-lactam antibiotics to combat the microorganisms that have built up resistance against the most traditional drugs [2] have maintained the interest of organic chemists in β-lactams for decades. In addition to its use in the synthesis of variety of β-lactam antibiotics, the β-lactam skeleton has been recognized as a useful building block by exploiting its strain energy associated with four member ring [3]. Efforts have been made in exploring such new aspects of β-lactam chemistry using pure β-lactams as versatile intermediates for organic syntheses [4]. Ojima *et al*. [5] have shown the utility of bis-β-lactams for the synthesis of peptides. The synthesis of bis-β-lactams, in general, has been reported by a step-wise construction of β-lactam rings [6]. In continuation of our work on synthesis of bis-β-lactams [7], we were interested in building bis-β-lactams from bis-imines using the Staudinger cycloaddition reaction.

Among the various methods available for the synthesis of β-lactams, the Staudinger cycloaddition reaction (ketene–imine cycloaddition reaction) is the most widely used [8] mainly because of the simplicity in reaction procedures. This method has been used for the synthesis of a large number of monocyclic, bicyclic, tricyclic, and spirocyclic β-lactams [9]. The ketenes are commonly generated *in situ* from acyl halides in the presence of tertiary amines [10]. In addition to the utilization of acyl halides, a variety of other methods have been described to activate carboxylic acids [11]. These methods are conventionally useful when the acid halides are not commercially available, difficult to prepare or when they are unstable. Some acid activating agents include 1,1-carbonyldi-imidazole [12], triphosgene [13], ethyl chloroformate [14], trifluoroacetic anhydride [15], p-toluenesulfonyl chloride [16], phosphorus-derived reagents [17], cyanuric chloride [18], the Mukaiyama reagent [19], and acetic anhydride [20].

Herein this communication, we report the synthesis of bis-β-lactams using Vilsmeier reagent. Chloromethylenedimethylammonium chloride (Vilsmeier reagent) has been known as a formylating agent [21]. It has also emerged as an efficient synthetic auxiliary for the synthesis of some important class of organic compounds. This white solid is easily synthesized by reaction of *N*,*N*-dimethylformamide (DMF) and chlorinating agents such as $POCl_3$ or $SOCl_2$ [22]. But in our methodology, we have generated this reagent *in situ* using DMF and $POCl_3$ in dichloromethane as reported [23]. This reagent was reported for the synthesis of monobactams by Jarrahpour and Zarei [24]. We have extended its applicability in the synthesis of bis β-lactams by generating it *in situ*. In this article, we wish to describe the versatility and utility of the Vilsmeier reagent for the activation of carboxylic acids in bis-β-lactam synthesis under simple

**Scheme 1.** Synthesis of bis-imines **2a–h**.




**2a,3a** R=$C_6H_5$ , **2e,3e** R=3-$NO_2C_6H_4$,
**2b,3b** R=2-$OHC_6H_4$, **2f,3f** R=4-N,N-$C_6H_3(CH_3)_2$
**2c,3c** R=4-$OHC_6H_4$, **2g,3g** R=2-$ClC_6H_4$
**2d,3d** R=2-$NO_2C_6H_4$, **2h,3h** R=4-$ClC_6H_4$

and mild conditions. It has proved to be a high yielding protocol for the synthesis.

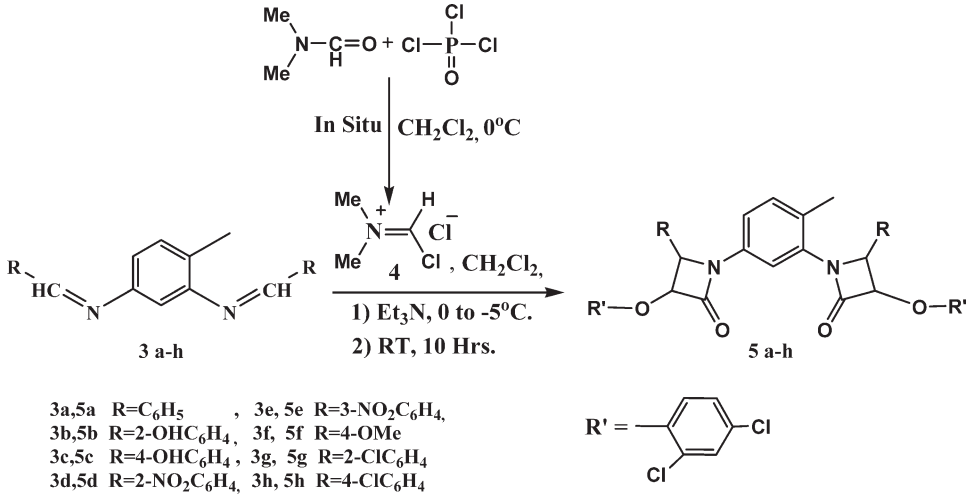
## RESULTS AND DISCUSSION

We selected toluene-2,4-diamine for the preparation of various bis-imines from different aldehydes and this imine were used for the construction of bis-β-lactams. The bis-imines **3a–h** were prepared by refluxing toluene-2,4-diamine with 2 mol equivalent of aldehydes (benzaldehyde, 2-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 2-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-methoxybenzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, and 4-methoxy-benzaldehyde in ethanol for about 1 to 1.5 h as shown in Scheme 1 according to known method [23]. Crude bis-imines were recrystallized with hot methanol.

Chloromethylenedimethylammonium chloride **4** was prepared from DMF and phosphorus oxychloride in dry $CH_2Cl_2$. We have successfully employed the Vilsmeier reagent for the one-step cycloaddition reaction of various imines **3a–h** and substituted phenoxyacetic acid to obtain bis-β-lactams **5a–h** (Scheme 2). Solution of Chloromethylenedimethylammonium chloride **4** was added to a solution of mixture of acid, imines, and triethylamine in $CH_2Cl_2$ between 0 and −5°C, and the reaction mixture was stirred at room temperature for 10 h. The usual work-up and then crystallization from hot methanol gave pure bis-β-lactams **5a–h** in high yields. We found that this method was very efficient, simple, and clean. The DMF and triethylammonium salt are two by-products, which were removed by simple aqueous work-up. In all cases the cycloaddition afforded only *cis*, *cis* bis-β-lactams **5a–h**.

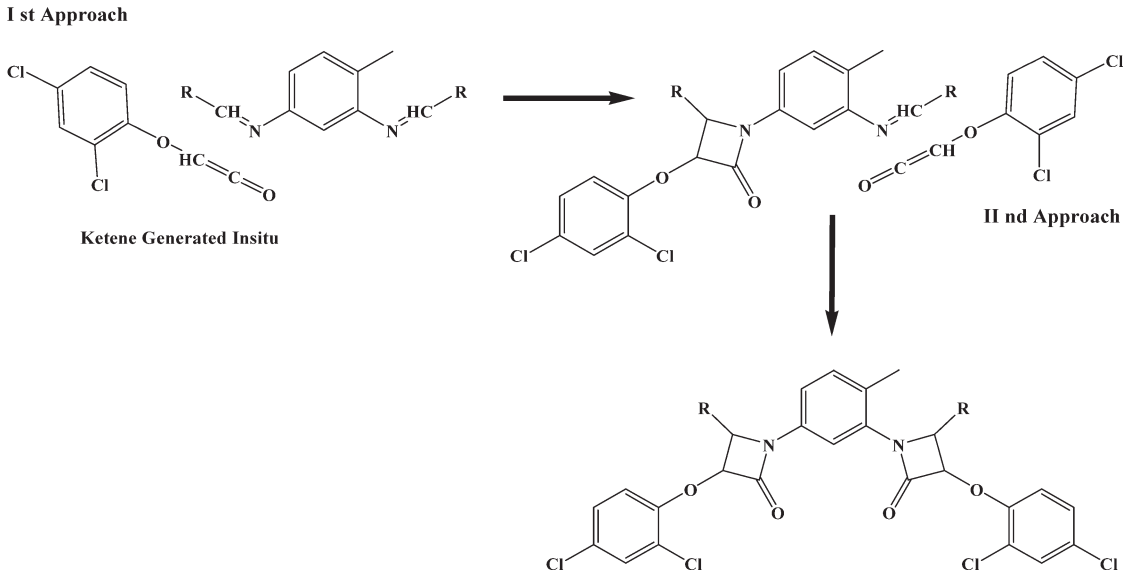
The *cis* steriochemistry for bis-β-lactam **5a–h** was assigned on the basis of $^1$H NMR spectral analysis. The $^1$H NMR spectra showed two doublets between 5.24 and 5.56 ppm for cis-β-lactam ring protons ($J$ = 4.6 to 4.8 Hz for *cis* β-lactam protons). The absence of —CH=N protons in **5a–h** show the azetidinone ring formation. The IR spectra of the bis-imines **3a–h** were compared with those of the bis-β-lactams to draw conclusion on cycloaddition. There were some guide peaks in the spectrum of the bis-imines and bis-lactams, which were helpful in achieving this goal. The position and the intensities of these peaks are expected to change upon cycloaddition. In the spectrum of bis-imines, the characteristic absorption around 1618–1650 $cm^{-1}$ can be assigned to (—C=N) azomethine linkage, which

**Scheme 2.** General synthesis of bis-β-lactam products **5a–h**.




**3a,5a** R=$C_6H_5$ , **3e, 5e** R=3-$NO_2C_6H_4$,
**3b,5b** R=2-$OHC_6H_4$, **3f, 5f** R=4-OMe
**3c,5c** R=4-$OHC_6H_4$, **3g, 5g** R=2-$ClC_6H_4$
**3d,5d** R=2-$NO_2C_6H_4$, **3h, 5h** R=4-$ClC_6H_4$

**Scheme 3.** Approaches in the formation of *cis, cis* bis-β-lactam.




disappears in the spectrum of the bis-β-lactams confirming the cycloaddition. In the spectrum of bis-lactams, the characteristic absorption around 1750–1700 $cm^{-1}$ can be assigned to (—C=O) linkage. The mass spectra of these compounds displayed a molecular ion peak at their respective *m/z* values, which are corresponding well with the respective molecular mass. All the compounds have given the satisfactory elemental analysis.

We believe that mono-β-lactam is initially formed by the reaction of the most stable bis-imine (I approach) with ketene. The approach of the ketene in the Staudinger cycloaddition reaction is such that the steric interaction between the aryl group of the imine and phenoxy group of the ketene is minimum in the transition state (Scheme 3) resulting in the formation of *cis*-β-lactam. However, the formation of trans-β-lactam is unfavorable due to severe steric interaction between the aryl group of imine and phenoxy group of ketene in the transition state. The mono β-lactam further undergoes cycloaddition reaction with the second molecule of ketene to give bis-β-lactam (Scheme 3). The approach of the second ketene towards the imine is from the opposite site of the preformed azetidinone ring to give bis-β-lactam **5a**. In this approach, the ketenes are generated directly from the carboxylic acid using Vilsmeier reagent instead of acid chloride. Thus, the Staudinger reaction of imines with carboxylic acids using Vilsmeier reagent **4** as an activator proceeded smoothly under milder reaction conditions. As acid chlorides are usually unstable, this approach is quite practical as starting carboxylic acid can be easily handled and stored as compared to respected acid chloride.

## EXPERIMENTAL

The solvents and reagents used in the synthetic work were of analytical grade obtained from Qualigens India and were purified by distillation or crystallization, where necessary and their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. $^1H$ NMR spectra were recorded on a Perkin Elmer FT NMR Cryo-magnet Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-$d_6$ as a solvent. Chemical shifts are given in parts per million (ppm). Infrared spectra were recorded on Schimadzu-IR Prestige 21. Mass spectra were recorded on a Waters Micromass Q-T of Micro spectrometer. The reactions were monitored, and the purity of products was checked out on pre-coated TLC plates (Silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber.

**General procedure for the preparation of bis-imines 3a–h.** A mixture of freshly distilled benzaldehyde (2.78 g, 26.3 mmol) and toluene-2,4-diamine (2.20 g, 17.5 mmol) in ethanol (30 mL) was refluxed for 1–1.5 h. The completion of the reaction was monitored by thin layer chromatography. After disappearance of the starting materials, the reaction mixture was allowed to attain the room temperature during which solid precipitated out. It was filtered out and recrystallized from hot methanol to afford **3a** as yellow crystalline solid. Following this procedure, bis-imines **3b–h** were prepared in excellent yield. All the bis-imines are well known in the refs. 25–27 and identified by comparison of their physical and spectral data.

**A typical procedure for the preparation of bis-β-lactams 5a–h.** In a 100 mL Round Bottom Flask, (1.0 g, 3.35 mmol) bis-imine **3a** was charged followed by (10 mL) dichloromethane. To it (1.48 g, 6.70 mmol), 2,4-dichlorophenoxyacetic acid followed by (1.35 g, 13.40 mmol) triethylamine was charged. It was chilled to −5°C. To a separate 50 mL Round Bottom Flask, (1.2 g, 8.04 mmol), $POCl_3$ in (10 mL) dichloromethane was charged. The solution was cooled to 10°C and a

solution of DMF (0.50 g, 6.7 mmol) in 5 mL dichloromethane was added over 10 min maintaining the temperature between 10 and 15°C. When the addition was complete, the mixture was allowed to stir at room temperature for 30 min. This Vilsmeier solution was then added gradually to the above prepared bis-imine solution over 15 min, maintaining the temperature between 0 and −5°C. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 10 h. The reaction mixture was then washed with water (2 × 20 mL), saturated sodium bicarbonate solution (20 mL) and saturated brine solution (20 mL). The organic layer was then dried over anhydrous $Na_2SO_4$ and concentrated to give the crude bis-β-lactams. It was recrystallized from hot methanol to give pure bis-β-lactams. Following this procedure other β-lactams **5b–h** were prepared.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-phenylazetidin-1-yl)-4-methyl phenyl)-4-phenylazetidin-2-one 5(a).*** This compound was obtained as white solid, 81%, m.p. 193–194°C, IR (KBr): 3120, 2965, 2970, 1755, 1365 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.34 (s, 3H, —$CH_3$), 6.80–7.62 (m, 19H, Ar), 5.25 (d, 1H, $J$ = 4.7 Hz), 5.51 (d, 1H, $J$ = 4.7 Hz), 5.26 (d, 1H, $J$ = 4.6 Hz), 5.56 (d, 1H, $J$ = 4.6 Hz). MS: $m/z$: 704 ($M^+$, 100%), 702 (71%), 706 (52%). Anal. Calc. for $C_{37}H_{26}Cl_4N_2O_4$: C, 63.09; H, 3.72; Cl, 20.13; N, 3.98; O, 9.09. Found: C, 63.12; H, 3.75; Cl, 20.10; N, 3.96; O, 9.12.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(2-hydroxyphenyl)azetidin-1-yl)-4-methyl phenyl)-4-(2-hydroxyphenyl)azetidin-2-one 5(b).*** This compound was obtained as light yellow solid, 79%, m.p. 201–203°C, IR (KBr): 3300, 3122, 2960, 2965, 1760, 1368 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.33 (s, 3H, —$CH_3$), 5.25 (d, 1H, $J$ = 4.7 Hz), 5.51 (d, 1H, $J$ = 4.7 Hz), 5.26 (d, 1H, $J$ = 4.6 Hz), 5.56 (d, 1H, $J$ = 4.6 Hz), 6.85–7.72 (m, 17H, Ar), 12.10–12.20 (s, 2H, —OH). MS: $m/z$: 736 ($M^+$, 100), 737 (68%), 738 (30%). Anal. Calc. for $C_{37}H_{26}Cl_4N_2O_6$: C, 60.35; H, 3.56; Cl, 19.26; N, 3.80; O, 13.0. Found: C, 60.38; H, 3.53; Cl, 19.29; N, 3.83; O, 13.10.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(4-hydroxyphenyl)azetidin-1-yl)-4-methyl phenyl)-4-(4-hydroxyphenyl)azetidin-2-one 5(c).*** This compound was obtained as light yellow solid, 82%, m.p. 185–186°C, IR (KBr): 3300, 3120, 2962, 2964, 1758, 1366 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.33 (s, 3H, —$CH_3$), 5.24 (d, 1H, $J$ = 4.7 Hz), 5.54 (d, 1H, $J$ = 4.7 Hz), 5.26 (d, 1H, $J$ = 4.6 Hz), 5.60 (d, 1H, $J$ = 4.6 Hz), 6.83–7.74 (m, 17H, Ar), 12.12 (s, 1H, —OH). MS: $m/z$: 736 ($M^+$, 100), 737 (73%), 738 (42%). Anal. Calc. for $C_{37}H_{26}Cl_4N_2O_6$: C, 60.35; H, 3.56; Cl, 19.26; N, 3.80; O, 13.0. Found: C, 60.38; H, 3.53; Cl, 19.29; N, 3.83; O, 13.10.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(2-nitrophenyl)azetidin-1-yl)-4-methyl phenyl)-4-(2-nitrophenyl)azetidin-2-one 5(d).*** This compound was obtained as yellow solid, 75%, m.p. 190–191°C, IR (KBr): 3122, 2975, 2970, 1756, 1366 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.12 (s, 3H, —$CH_3$), 6.79–8.03 (m, 17H, Ar), 5.26 (d, 1H, $J$ = 4.7 Hz), 5.51 (d, 1H, $J$ = 4.7 Hz), 5.26 (d, 1H, $J$ = 4.6 Hz), 5.55 (d, 1H, $J$ = 4.6 Hz). MS: $m/z$: 794 ($M^+$, 100%), 795 (62%), 796 (26%). Anal. Calc. for $C_{37}H_{24}Cl_4N_4O_8$: C, 55.94; H, 3.05; Cl, 17.85; N, 7.05; O, 16.11. Found: C, 55.92; H, 3.10; Cl, 17.83; N, 7.08; O, 16.13.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(3-nitrophenyl)azetidin-1-yl)-4-methyl phenyl)-4-(3-nitrophenyl)azetidin-2-one 5(e).*** This compound was obtained as yellow solid, 72%, m.p. 214–215°C, IR (KBr): 3118, 2971, 2969, 1765, 1365 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.13 (s, 3H, —$CH_3$), 6.75–8.10 (m, 17H, Ar), 5.26 (d, 1H, $J$ = 4.7 Hz), 5.51 (d, 1H, $J$ = 4.7 Hz), 5.26 (d, 1H, $J$ = 4.6 Hz), 5.55 (d, 1H, $J$ = 4.6 Hz). MS: $m/z$: 794 ($M^+$, 100%), 795 (65%), 796 (32%). Anal. Calc. for $C_{37}H_{24}Cl_4N_4O_8$: C, 55.94; H, 3.05; Cl, 17.85; N, 7.05; O, 16.11. Found: C, 55.90; H, 3.11; Cl, 17.83; N, 7.09; O, 16.16.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(4-methoxyphenyl)azetidin-1-yl)-4-methyl phenyl)-4-(4-methoxyphenyl)azetidin-2-one 5(f).*** This compound was obtained as brown solid, 69%, m.p. 206–208°C, IR (KBr): 3120, 2965, 2970, 1755, 1365, 1040 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.25 (s, 3H, —$CH_3$), 3.85 (s, 3H, —$OCH_3$), 6.93–7.60 (m, 17H, Ar), 5.45 (d, 1H, $J$ = 4.7), 5.50 (d, 1H, $J$ = 4.7 Hz), 5.28 (d, 1H, $J$ = 4.6 Hz), 5.66 (d, 1H, $J$ = 4.6 Hz). MS: $m/z$: 764 ($M^+$, 100%), 765 (61%), 766 (23%). Anal. Calc. for $C_{39}H_{30}Cl_4N_2O_6$: C, 61.27; H, 3.96; Cl, 18.55; N, 3.66; O, 12.56. Found: C, 61.25; H, 3.86; Cl, 18.40; N, 3.90; O, 12.60.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(2-chlorophenyl)azetidin-1-yl)-4-methyl phenyl)-4-(2-chlorophenyl)azetidin-2-one 5(g).*** This compound was obtained as white solid, 71%, m.p. 189–190°C, IR (KBr): 3122, 2965, 2970, 1765 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.20 (s, 3H, —$CH_3$), 6.78–7.60 (m, 17H, Ar), 5.25 (d, 1H, $J$ = 4.7), 5.50 (d, 1H, $J$ = 4.7 Hz), 5.27 (d, 1H, $J$ = 4.6 Hz), 5.56 (d, 1H, $J$ = 4.6 Hz). MS: $m/z$: 773 ($M^+$, 100%), 774 (73%), 776 (30%). Anal. Calc. for $C_{37}H_{24}Cl_6N_2O_4$: C, 57.43; H, 3.13; Cl, 27.51; N, 3.52; O, 28.09. Found: C, 57.45; H, 3.15; Cl, 27.52; N, 3.50; O, 28.10.

***3-(2,4-Dichlorophenoxy)-1-(3-(3-(2,4-dichlorophenoxy)-2-oxo-4-(4-chlorophenyl)azetidin-1-yl)-4-methyl phenyl)-4-(4-chlorophenyl)azetidin-2-one 5(h).*** This compound was obtained as white solid, 76%, m.p. 211–212°C, IR (KBr): 3130, 2971, 2975, 1768 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 2.22 (s, 3H, —$CH_3$), 6.78–8.10 (m, 17H, Ar), 5.24 (d, 1H, $J$ = 4.7 Hz), 5.54 (d, 1H, $J$ = 4.7 Hz), 5.30 (d, 1H, $J$ = 4.6 Hz), 5.58 (d, 1H, $J$ = 4.6 Hz). MS: $m/z$: 773 ($M^+$, 100%), 774 (76%), 776 (34%). Anal. Calc. for $C_{37}H_{24}Cl_6N_2O_4$: C, 57.43; H, 3.13; Cl, 27.51; N, 3.52; O, 28.09. Found: C, 57.50; H, 3.21; Cl, 27.55; N, 3.61; O, 28.15.

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## REFERENCES AND NOTES

[1] (a) Durkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. Angew Chem Int Ed Engl 1985, 24, 180; (b) Morin, R. B.; Gorman, M., Eds. Chemistry and Biology of β-Lactam Antibiotics; Academic Press: New York, 1982; Vols. 1–3; (c) Southgate, R. Contemp Org Synth 1994, 1, 417.

[2] Page, M. I., Ed. The Chemistry of β-Lactams; Chapman & Hall: London, 1992.

[3] (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. Heterocycles 1976, 5, 669; (b) Manhas, M. S.; Wagle, D. R.; Chiang, J. Heterocycles 1988, 27, 1755.

[4] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Curr Med Chem 2004, 11, 1837.

[5] (a) Ojima, I.; Hatanaka, N.; Yoda, N.; Abe, R.; Yatabe, M.; Yanashita, M. In Peptide Chemistry; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, 1983; p 29; (b) Yamashita, M.; Abe, R.; Hatanaka, N.; Ojima, I. In Peptide Chemistry; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, 1983; p 85.

[6] (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. J Org Chem 1991, 56, 526; (b) Ojima, I.; Nakahashi, K.; Branstadter, S. M.; Hatanaka, N. J Am Chem Soc 1987, 109, 1798.

[7] Parvez, A.; Jyotsna, M.; Hamid, Y.; Taibi, H. Phosphorus Sulfur Silicon Relat Elem, to appear.

[8] (a) Staudinger, H. Liebigs Ann Chem 1907, 356, 51; (b) George, G. I.; Ravikumar, V. T. In The Organic Chemistry of β-Lactams; George, G. I., Ed.; VCH: New York, 1993; p 295; (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Eur J Org Chem 1999, 3223.

[9] (a) Morin, R. B.; Gorman, M. Chemistry and Biology of β-Lactam Antibiotics; Academic Press: New York, NY, 1982; (b) Jarrahpour, A. A.; Shekarriz, M.; Taslimi, A. Molecules 2004, 9, 29; (c) Hakimelahi, G. H.; Jarrahpour, A. A. Helv Chim Acta 1989, 72, 1501.

[10] (a) Van der Steen, F. H.; Van Koten, G. Tetrahedron 1991, 47, 7503; (b) Jarrahpour, A.; Alvand, P. Iran J Sci Technol Trans A 2007, 31, 17; (c) Jarrahpour, A. A.; Shekarriz, M.; Taslimi, A. Molecules 2004, 9, 939.

[11] George, G. I., Ed. The Organic Chemistry of β-Lactams; VCH: New York, NY, 1993.

[12] Nahmany, M.; Melman, A. J Org Chem 2006, 71, 5804.

[13] Deshmukh, A. R. A. S.; Krishnaswamy, D.; Govande, V. V.; Bhawal, B. M.; Gumaste, V. K. Tetrahedron 2002, 58, 2215.

[14] Bose, A. K.; Manhas, M. S.; Amin, S. G.; Kapur, J. C.; Kreder, J.; Mukkavilli, L.; Ram, B.; Vincent, J. E. Tetrahedron Lett 1979, 2771.

[15] Bose, A. K.; Kapur, J. C.; Sharma, S. D.; Manhas, M. S. Tetrahedron Lett 1973, 2319.

[16] (a) Jarrahpour, A.; Zarei, M. Molecules 2007, 12, 2364; (b) Miyake, M.; Tokutake, N.; Kirisawa, M. Synthesis 1983, 833.

[17] (a) Bhalla, A.; Venugopalany, P.; Bari, S. S. Tetrahedron 2006, 62, 8291; (b) Farouz-Grant, F.; Miller, M. J. Bioorg Med Chem Lett 1993, 3, 2423; (c) Cossio, F. P.; Lecea, B.; Palomo, C. J Chem Soc Chem Commun 1987, 1743.

[18] Manhas, M. S.; Bose, A. K.; Khajavi, M. S. Synthesis 1981, 209.

[19] (a) Matsui, S.; Hashimoto, Y.; Saigo, K. Synthesis 1998, 1161; (b) George, G. I.; Mashava, P. M.; Guan, X. Tetrahedron Lett 1991, 32, 581.

[20] Croce, P. D.; La Rosa, C. Tetrahedron Asymmetry 1999, 10, 1193.

[21] Campaigne, E.; Archer, W. L. J Am Chem Soc 1953, 75, 141.

[22] Eilingsfeld, H.; Seefelder, M.; Weidenger, H. Angew Chem 1969, 72, 836.

[23] Dyer, U. C.; Henderson, D. A.; Tiffin, P. D. Org Process Res Dev 2002, 6, 311.

[24] Jarrahpour, A.; Zarei, M. Tetrahedron lett 2007, 48, 8712.

[25] Mederos, A.; Manrique, F.; Medina, A. An Quim B 1980, 76, 33.

[26] Roman, B. Coord Chem Rev 2004, 248, 757.

[27] Meshram, J.; Parvez, A.; Tiwari, V. Green Chem Lett Rev, to appear.